Pocket Medicine

Fourth Edition

Edited by
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The Massachusetts General Hospital
Handbook of Internal Medicine

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Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo
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*Mary Berlik Rice, Kathryn A. Hibbert, Atul Malhotra*

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*Louis J. Cohen, Andrew S. de Lemos, Lawrence S. Friedman*

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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
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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 fourth edition come several major improvements including: a thorough updating of every topic; the addition of several new topics (including acute aortic syndromes, sepsis, obstructive sleep apnea, hepatic vascular disease, optimal use of diuretics, viral respiratory infections, infections in susceptible hosts, intensive glycemic control, approach to the patient with joint pain, and alcohol withdrawal); incorporation of references to the most recent reviews and important studies published through the middle of 2010; and the addition of high-resolution chest radiographs, chest and abdominal CTs, and echocardiograms, and photomicrographs of peripheral blood smears and urinalyses. 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, Denny Ausiello, Larry Friedman, Nesli Basgoz, Mort Swartz, Eric Isselbacher, Bill Dec, Mike Fifer, and Roman DeSanctis, as well as the late Charlie McCabe and Peter Yurchak. 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, brady) and **rhythm** (relationship between P and QRS)
- **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 V1–V6, ST ↑/↓, or T-wave Δs)

**Left axis deviation (LAD)**

- **Definition**: axis beyond –30° (S > R in lead II)
- **Etiologies**: HTN, AS/AI, HCMP, coarctation of aorta
  - **Left ventricular hypertrophy (LVH)**
  - **QT varies with HR**
  - **QT measured from beginning of QRS complex to end of T wave (measure longest QT)**
  - **Prolonged QT interval**
  - **Bifascicular block: RBBB/H001**

- **Right axis deviation (RAD)**

  - **Definition**: axis beyond +90° (S > R in lead I)
  - **Etiologies**: RVH, PE, COPD
  - **Left posterior fascicular block: RAD (90–180°)**

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

- **Normal**
  - Initial depolarization is left-to-right across the septum (r in V1 & q in V6, nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depolarization later and visible in RBBB).
  - 1. QRS > 120 msec (110–119 in complete)
  - 2. rSR’ in R precordial leads (V1, V5)
  - 3. Wide S wave in I and V4
  - 4. ± ST or TWI in R precordial leads

- **RBBB**

  - 1. QRS > 120 msec (110–119 in complete)
  - 2. Broad, slurred, monophasic R in I, aVL, V5–V6
  - 3. Absence of Q in I, V5, and V6 (may have narrow q in aVL)
  - 4. Displacement of ST & TW opposite major QRS deflection
  - 5. ± PRWP, LAD, Qw's in inferior leads

- **LBBB**

  - 1. QRS > 120 msec (110–119 in complete)
  - 2. rS in I & aVL
  - 3. qR in III & aVF
  - 4. No other cause of LAD (eg, IMI)

**Prolonged QT interval** (JAMA 2003;289:2120; NEJM 2004;350:1013; www.torsades.org)

- **QT measured from beginning of QRS complex to end of T wave (measure longest QT)**
- **Formula**: QTc = QT/√RR (in sec)
- **Formula**: inaccuracy at very high and low HR (nl QTc = Accurate)
- **Etiologies**:
  - **Antiarrhythmics**: class 1a (procainamide, disopyramide), class III (amiodarone, sotalol)
  - **Psych drugs**: antipsychotics (phenothiazines, haloperidol, atypicals), Li, SSRI, TCA
  - **Antimicrobials**: macrolides, quinolones, voriconazole, pentamidine, atovaquone
  - **Electrolyte disturbances**: hypoCa, hypoK, hypoMg
  - **Autonomic dysfunction**: ICH (deep TWI), stroke, carotid endarterectomy, neck dissection
  - **Congenital**: long QT syndrome
  - **Misc**: CAD, CMP, bradyarrhythmia, high-grade AVB, hypothyroidism, hypothermia

**Left Atrial Abnormality (LAA)** (Circ 2009;119:e251)

- **Left ventricular hypertrophy (LVH)**
  - **Etiologies**: HTN, AS/AI, HCMP, coarctation of aorta
  - **Criteria** (all w/ Se <50%, Sp >85%)
    - Romhilt-Estes point-score system: 4 points = probable, 5 points = definite
    - Amplitude (any of the following): largest R or S in limb leads ≥20 mm or S in V1 or V2 ≥30 mm or R in V5 or V6 ≥30 mm (3 points)
ECG

-2

• Etiologies:
• Definition:

• Intracranial bleed ("cerebral T waves," usually w/ electrolyte, digoxin, PaO2, PaCO2, pH, or core temperature disturbances
• Post-tachycardia or post-pacing
• Repolarization abnl in a/w LVH/RVH ("strain pattern"), BBB
• T wave inversion

• Definition: loss of anterior forces w/o frank Q waves (V1–V6)

• Etiologies: cor pulmonale, congenital (tetralogy, TGA, PS, ASD, VSD), MS, TR
• RVH (delayed RWP with prominent S wave in lead I)

• Definition: Acute MI (upward convexity)

• ST elevation

• Acute MI (upward convexity) or prior MI with persistent STE
• Coronary spasm (Prinzmetal's angina; transient STE in a coronary distribution)
• Myopericarditis (diffuse, upward concavity STE; a/w PR, δ wave, ↑ QRS)
• RVH, COPD (small R wave and prominent S wave in lead I)

• Pathologic Q waves

• Definition: ≥30 msec or >25% height of the R wave in that complex
• Small (septal) q waves in I, aVL, V5 & V6 are normal, as can be isolated Qw in III, aVR, V1

• ST depression

• Myocardial ischemia (↑ T wave) or acute true posterior MI (V1–V6)
• Digitalis effect (downsloping ST)
• Hypokalemia (↑ U wave)
• Repolarization abnl in a/w LBBB or LVH (usually in leads V5, V6, aVL)

• T wave inversion

• Definition: ≥1 mm; deep if ≥5 mm

• ST depression

• Myocardial ischemia (↑ T wave abnl) or acute true posterior MI (V1–V6)
• Digitalis effect (downsloping ST ± T wave abnl, does not correlate w/ dig levels)
• Hypokalemia (↑ U wave)
• Repolarization abnl in a/w LBBB or LVH (usually in leads V5, V6, aVL)

• Low voltage

• QRS amplitude (R + S) ≤5 mm in all limb leads & ≤10 mm in all precordial leads
• Etiologies: COPD (precordial leads only), pericardial effusion, myxedema, obesity, pleural effusion, restrictive or infiltrative CMP, diffuse CAD
CHEST PAIN

Cardiac Causes

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<th>Typical Characteristics &amp; Diagnostic Studies</th>
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<td>Unstable angina</td>
<td>Subternal pressure → neck, jaw, L arm; ≤30°; ≤ Dyspnea, diaphoresis, N/V, ↑ w/ exertion; ↓ w/ NTG or rest; however, relief by NTG in ED not reliable indicator of angina (Knebel EM 2005:43:381); ≤ ECG Δs (ST ↑, TWI).</td>
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<tr>
<td>MI</td>
<td>Same as angina but ↑ intensity &amp; duration. ≥ troponin or CK-MB.</td>
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<tr>
<td>Pericarditis &amp; Myopericarditis</td>
<td>Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ≥ Pericardial friction rub. ECG Δs (diffuse STE &amp; PR ↓). ≥ Pericardial effusion.</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Abrupt onset severe tearing, knife-like pain (absence ≥LR 0.3), ant or post mid-scapular. HTN or HoTN. ≥ Asymmetric (&gt;20 mmHg) BP or pulse deficit (≥LR 5.7), focal neuro deficit (≥LR &gt;6), AI, widened mediastinum on CXR (absence ≥LR 0.3); false lumen on imaging. (JAMA 2002;287:2262)</td>
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Pulmonary Causes

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<th>Disorder</th>
<th>Typical Characteristics &amp; Diagnostic Studies</th>
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<tr>
<td>Pneumonia</td>
<td>Pleuritic; dyspnea, fever, cough, sputum. ↑ RR, crackles. CXR infiltrate.</td>
</tr>
<tr>
<td>PTX</td>
<td>Sudden onset, sharp pleuritic pain. Hyperresonance, ↓ BS. PTX on CXR.</td>
</tr>
<tr>
<td>PE</td>
<td>Sudden onset pleuritic pain. ↑ RR &amp; HR. ↓ SO2, ECG Δs (RAD, RBBB, TWI↑–V4, occ STE V1–V4), ⊕ CTA.</td>
</tr>
<tr>
<td>PHT</td>
<td>Exertional pressure, dyspnea. ↓ SO2, loud P2, right-sided S3 and/or S4.</td>
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GI Causes

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<th>Disorder</th>
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<td>Esophageal reflux</td>
<td>Subternal burning, acid taste in mouth, water brash. ↑ by meals, recumbency; ↓ by antacids. EGD, manometry, pH monitoring.</td>
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<tr>
<td>Esoph spasm</td>
<td>Intense substernal pain. ↑ by swallowing, ↓ by NTG/CCB. Manometry.</td>
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<tr>
<td>Mallory-Weiss syndrome</td>
<td>Precipitated by vomiting. EGD.</td>
</tr>
<tr>
<td>Boerhaave syndrome</td>
<td>Precipitated by vomiting. Severe pain, ↑ w/ swallowing. Palpable SC emphysema; mediastinal air on chest CT.</td>
</tr>
<tr>
<td>PUD</td>
<td>Epigastric pain, relieved by antacids. ≥ GIB. EGD, ≥ H. pylori test.</td>
</tr>
<tr>
<td>Biliary dis.</td>
<td>RUQ pain, nausea/vomiting. ↑ by fatty foods. RUQ US, LFTs.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Epigastric/back discomfort. ↑ amylase &amp; lipase; abd CT.</td>
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Muscculoskeletal and Miscellaneous Causes

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<th>Typical Characteristics &amp; Diagnostic Studies</th>
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<td>Chostochondritis</td>
<td>Localized sharp pain. ↑ w/ movement. Reproduced by palpation.</td>
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<tr>
<td>Herpes zoster</td>
<td>Intense unilateral pain. Dermatogenous rash &amp; sensory findings.</td>
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<tr>
<td>Anxiety</td>
<td>“Tightness”</td>
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Initial approach

- Focused history: quality & severity of pain; location & radiation; provoking & palliating factors; duration, frequency & pattern; setting in which it occurred; associated sx

- Targeted exam: VS (including BP in both arms), cardiac gallops, murmurs, or rubs; signs of vascular disease (carotid or femoral bruits, ↓ pulses); signs of heart failure; lung & abdominal exam; chest wall exam for reproducibility of pain

- 12-lead ECG: obtain w/in 10 min; c/w priors & obtain serial ECGs; consider posterior leads (V7–V9) to reveal isolated posterior MI if hx c/w ACS but ECG unrevealing

- Cardiac biomarkers (Tn, CK-MB): serial testing at presentation, 6–12 h after sx onset troponin (II/T): most Se & Sp marker; level ≥99th %ile in appro clinical setting is dx of MI detectable 3–6 h after injury; peaks 24 h, may remain elevated for 7–10 d in STEMI high-sens. assays: 90–95% Se & Sp; 85% Se w/in 3 h of sx onset (NEJM 2009:361:858, 868) “false ⊕” (non-ACS myonecrosis): myocarditis/toxic CMP, severe CHF, HTN crisis, PE or severe resp. distress, cardiac trauma/cardioversion, sepsis, SAH, demand ischemia; ↑ renal failure (↑ clearance, skeletal myopathy vs. true microinfarctions)

- CK-MB: less Se & Sp (skel. muscle, tongue, diaphragm, intestine, uterus, prostate)

- CXR: other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing

- Coronary CT angiography: ½ free of CAD → 0% w/ ACS; ½ w/ plaque → 17% w/ ACS; even with signif stenosis, only 35% w/ ACS (JACC 2009:53:1642). ≥ good for r/o not r/i
### NONINVASIVE EVALUATION OF CAD

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETT (w/ ECG only)</td>
<td>60%</td>
<td>75%</td>
<td>Exercise capacity; no radiation; low cost</td>
<td>Limited Sens (&lt;50% for 1VD, but 85% for 3VD/LM)</td>
</tr>
<tr>
<td>SPECT/PET</td>
<td>85%</td>
<td>90%</td>
<td>Localizes ischemia; LV fxn</td>
<td>Radiation; cost</td>
</tr>
<tr>
<td>Echo</td>
<td>85%</td>
<td>95%</td>
<td>Localizes ischemia; LV fxn &amp; valve data, no radiation</td>
<td>Operator dependent; cost</td>
</tr>
<tr>
<td>CT Angio</td>
<td>90%</td>
<td>88%</td>
<td>High NPV to r/o CAD</td>
<td>Radiation; contrast; cost</td>
</tr>
</tbody>
</table>

### Exercise tolerance test (stress test) (NEJM 2001;344:1840)

- **Indications:** dx CAD, evaluate if known CAD & \( \Delta \) in clinical status, risk stratify s/p ACS, evaluate exercise tolerance, localize ischemia (imaging required)

- **Contraindications**
  - **Absolute:** AMI w/in 48 h, high-risk UA, acute PE, severe AS, uncontrolled CHF, uncontrolled arrhythmias, myopericarditis, acute aortic dissection
  - **Relative:** left main CAD, mod valvular stenosis, severe HTN, HCMP, high-degree AVB, severe electrolyte abnl, inability to exercise

- **Exercise:** standard Bruce (↑ speed/incline q3min), modified Bruce (begins w/o treadmill incline), submax (if <3 wk post-MI), or sx-limited; hold antianginals if trying to dx CAD, give if assessing if Pt ischemic on meds

- **Pharmacologic:** if unable to exer., low exer. tol or recent MI. Se & Sp = exercise; Preferred if LBBB. Requires imaging since ECG not specific in this setting. Coronary vasodilators (will reveal CAD, but not tell you if Pt ischemic): regadenoson, dipyridamole, or adenosine (may precipitate tachyarrhythmias).

- **Imaging:** used if uninterpretable ECG (paced, LBBB, resting ST ↑, 1 mm, dig., LVH, WPW), after indeterminate ECG test, pharmacologic tests, or localization of ischemia

#### Test results

- **HR** (must achieve >85% of max predicted HR [220-age] for exercise test to be dx), **BP response,** peak double product (**HR × BP**), HR recovery (**HRpeak**–HRmin later than HR ↓ -12)

- **Max exercise capacity** achieved (**METs** or min)

- **Occurrence of symptoms** (at what level of exertion and similarity to presenting sx)

- **ECG changes:** downsloping or horizontal **ST ↑** (≥1 mm) predictive of CAD (but distribution of ST ↑ do not localize ischemic territory); STE highly predictive

- **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; false \( \oplus \): breast → ant “defect” and diaphragm → inf “defect”

#### High-risk test results (PPV ~50% for LM or 3VD, \( \sim \) consider coronary angiography)

- **ECG:** ST ↑ ≥2 mm or ≥1 mm in stage 1 or in ≥5 leads or ≥5 min in recovery; ST ↑ ↑ VT
- **Physiologic:** 1 BP exercise <4 METS, angina during exercise, Duke score ≤-11; EF <35%
- **Radionuclide:** ≥1 g or ≥2 mod. reversible defects, transient LV cavity dilation, ↑ lung uptake

#### Myocardial viability

- **Goal:** identify hibernating myocardium that could regain fxn after revascularization

- **Options:** MRI (Se >95%, Sp ~70%), PET (Se ~90%, Sp ~75%), dobutamine stress echo (Se ~70%, Sp ~85%); rest-redistribution thallium (Se ~90%, Sp ~55%)

#### CT & MR coronary angiography (NEJM 2008;359:1; Circ 2010;121:2509)

- **Image quality best at slower & regular HR (give \( \beta \)B if possible, goal HR 55–60)
- **Calcium generates artifact for CT angiography**
- **MRI** being studied: angiography, perfusion, LV fxn, hyperenhancement (Circ 2009;119:1671)

#### Coronary artery calcium score (CACS, NEJM 2008;358:1336; JAMA 2010;303:1610)

- **Quantitative evaluation of extent of calcium and thus estimate of plaque burden**
- **Not able to assess % stenosis of coronary arteries (no IV contrast)**
- \( \sim \) value in asx Pts w/ intermediate Framingham risk score (10–20% 10-y risk) w/ CACS of 0, 1–100, 101–300, and >300 corresponding to low, average, moderate, and high risk
- **May be of value as screening test to r/o CAD in sx Pt (CACS <100 → 3% probability of signif CAD; but high scores have poor specificity)**
CORONARY ANGIOGRAPHY AND REVASCULARIZATION

Indications for coronary angiography in stable CAD or axS Pts

• CCS class III-IV angina despite medical Rx or angina + systolic dysfxn
• High-risk stress test findings (see prior topic)
• Uncertain dx after noninvasive testing (& compelling need to determine dx), occupational need for definitive dx (eg, pilot), or inability to undergo noninvasive testing
• Systolic dysfxn with unexplained cause
• Survivor of SCD, polymorphic VT, sustained monomorphic VT
• Suspected spasm or nonatherosclerotic cause of ischemia (eg, anomalous coronary)

Pre-cath checklist

• Document peripheral arterial exam (femoral, DP, PT pulses; femoral bruits); NPO
• CBC, PT, & Cr; give IVF (bicarb, acetylcysteine; see "CIAKI"); blood bank sample
• ASA 325 mg; consider clopidogrel prRx (300–600 mg)

Coronary revascularization in stable CAD (JACC 2004;44:e213 & 2006;47:e1)

• CABG: ↓ mortality c/w med Rx (albeit pre stents & ACEI/ARB) in Pts w/ 3VD, LM, or 2VD w/ critical prox LAD, and espec. if ↓ EF (but viable myocardium); ↓ repeat revascularization & trend toward ↓ D/MI but ↑ stroke c/w PCI in LM/3VD (NEJM 2009;360:961); CABG vs. PCI being studied in FM (FREEDOM trial)
• PCI: ↓ angina c/w med Rx; does not ↓ D/MI (COURAGE, NEJM 2007;357;1503); prompt repeat revascularization (PCI or CABG) did not ↓ mortality vs. med Rx in DM (NEJM 2009;360:2503)
• PCI comparable to CABG in Pts w/o 3VD, w/o DM, and NL EF (Lancet 2009;373:1190)
• For stable CAD w/o critical anatomy and w/o ↓ EF, initial focus on optimal med Rx
• If revascularisation 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
• Fractional flow reserve (ratio of maximal flow (induced by IV or IC adenosine) distal vs. proximal to a stenosis): PCI only if <0.8 – 1.0 stents & ↓ D/MI/revascular (NEJM 2009;360:213)

PCI

• Balloon angioplasty (POBA): effective, but c/b dissection & elastic recoil & neointimal hyperplasia → restenosis; now reserved for small lesions & some SVG lesions
• Bare metal stents (BMS): ↓ elastic recoil → 33–50% ↓ restenosis & repeat revascularization (to ~10% by 12 mos) c/w POBA; requires ASA lifelong & clopidogrel × >4 wks
• Drug-eluting stents (DES): ↓ neointimal hyperplasia → ~75% ↓ restenosis, ~50% ↓ repeat revascular (to <5% by 1 yr), no ↑ D/MI c/w BMS (NEJM 2008;359:1330); 2nd gen. everolimus DES promising (NEJM 2010;362;1728); require ASA lifelong & clopidogrel × >1 yr (Gra 2007;115:813)
• Anticoagulant: UFH (short-acting, rapidly reversible, but need to ↓ PTT/ACT), LMWH (no need for monitoring, but 110–120 h), bivalirudin (i bleeding, but ↓ MI; NEJM 2009;359:488)

Post-PCI complications

• Postprocedure vascular access site, distal pulses, ECG, CBC, Cr, CK-MB
• Bleeding
  • hematomat/overt bleeding: manual compression, reverse/stop anticoag
  • retroperitoneal bleed: may present with ↓ Hct + back pain; ↑ HR & ↓ BP late
  • Dx: abd/pelvic CT (‘?’); Rx: reverse/stop anticoag, IVF/PRBC as required if bleeding uncontrolled, consult performing interventionalist or surgery
• Vascular damage
  • pseudoaneurysm: triad of pain, expandable mass, systolic bruit; Dx: U/S; Rx: manual compression, U/S-directed compression or thrombin injection, or surgical repair
  • AV fistula: continuous bruit; Dx: U/S; Rx: surgical repair
  • ↑ perfusion to LE (embolization, dissection, thrombus): loss of distal pulse; Dx: angio;
  • Rx: percutaneous or surgical repair
• Peri-procedural MI: ~3–5% of CK-MB occurs in 5–10%; Qw MI in <1%
• Renal failure: contrast-induced manifests w/in 24 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. Often due to mechanical prob. (stent underexpansion or unrecognized dissection, typically presents early) or d/c of antiplt Rx (espec if d/c both ASA & ADP blocker; JAMA 2005;293:2126). Risk of late stent thrombosis may be higher with DES than BMS (JACC 2006;48:2584).
• 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

Myocardial ischemia typically due to atherosclerotic plaque rupture → coronary thrombosis

<table>
<thead>
<tr>
<th>Spectrum of Acute Coronary Syndromes</th>
<th>UA</th>
<th>NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary thrombosis</td>
<td>Subtotal</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>angina that is new-onset, crescendo, or at rest; usually ≤ 30 min</td>
<td>angina at rest usually ≥ 30 min</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>± ST depression and/or TWI</td>
<td>ST elevations</td>
<td></td>
</tr>
<tr>
<td>Troponin/CK-MB</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- Nonatherosclerotic coronary artery disease
  - Spasm: Prinzmetal’s variant, cocaine-induced (6% of CP + cocaine use r/i for MI)
  - Dissection: spontaneous (vasculitis, CTD, pregnancy), aortic dissection with retrograde extension (usually involving RCA → IMI), or mechanical (catheter, surgery, trauma)
  - Embolism: endocarditis, prosthetic valve, mural thrombus, myxoma; thrombosis
  - Vasculitis: Kawasaki syndrome, Takayasu arteritis, PAN, Churg-Strauss, SLE, RA
  - Congenital: anomalous origin from aorta or PA, myocardial bridge (intramural segment)

- Fixed CAD but ↑ myocardial O2 demand (eg, ↑ HR, anemia, AS) → “demand” ischemia
- Myocarditis (myocardial necrosis, but not caused by CAD); toxic CMP; cardiac contusion

Clinical manifestations (JAMA 2005;294:2623)

- Typical angina: retrosternal pressure/pain/tightness → radiation to neck, jaw, or arms precip. by exertion, relieved by rest or NTG; in ACS, new-onset, crescendo, or at rest
- Associated symptoms: dyspnea, diaphoresis, N/V, palpitations, or lightheadedness
- Many MIs (≥20% in older series) are initially unrecognized b/c silent or atypical sx

Physical exam

- Signs of ischemia: S4, new MR murmur → papillary muscle dysfxn, paradoxical S2
- Signs of heart failure: ↑ JVP, crackles in lung fields, S3, HoTN, cool extremities
- Signs of other areas of atherosclerotic disease: carotid or femoral bruits, distal pulses

Diagnostic studies

- ECG: ST deviation (depression or elevation), TWI, LBBB not known to be old Qw or PRWP suggest prior MI and CAD
- Cardiac biomarkers (Tn or CK-MB): serial testing at presentation, 6–12 h after sx onset; rise to 99th %ile of reference limit in approp. clinical setting dx of MI (see “Chest Pain”)
- CT angiography: only 35% PPV (JACC 2009;53:1642)
- Echocardiogram: new wall motion abnormality (operator & reader dependent)
- Cocaine-induced vasospasm: avoid β-blockers; d/c smoking

Localization of MI

<table>
<thead>
<tr>
<th>Anatomic Area</th>
<th>ECG Leads w/ STE</th>
<th>Coronary Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal</td>
<td>V1–V2</td>
<td>Proximal LAD</td>
</tr>
<tr>
<td>Anterior</td>
<td>V3–V4</td>
<td>LAD</td>
</tr>
<tr>
<td>Apical</td>
<td>V5–V6</td>
<td>Distal LAD, LCx, or RCA</td>
</tr>
<tr>
<td>Lateral</td>
<td>I, aVL</td>
<td>LCx</td>
</tr>
<tr>
<td>Inferior</td>
<td>II, III, aVF</td>
<td>RCA (~85%), LCx (~15%)</td>
</tr>
<tr>
<td>RV</td>
<td>V1–V3, V5–R (most Se)</td>
<td>Proximal RCA</td>
</tr>
<tr>
<td>Posterior</td>
<td>ST depression V1–V3</td>
<td>RCA or LCx</td>
</tr>
</tbody>
</table>

If ECG non-dx and suspicion high, consider additional (posterior) leads (V4–V6) to further assess LCx territory. Check right-sided precordial leads in patients w/ IMI to help detect RV involvement (STE in V3R, most Se).

Cardiac biomarkers (Tn or CK-MB): serial testing at presentation, 6–12 h after sx onset; rise to ≥99th %ile of reference limit in approp. clinical setting dx of MI (see “Chest Pain”); nb, in Pts w/ ACS & ↓ CrCl, ↑ Tn → poor prognosis (NEJM 2002;346:2047)

CT angiography: only 35% PPV (JACC 2009;53:1642)

Echocardiogram: new wall motion abnormality (operator & reader dependent)

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, focal spasm w/ hyperventilation, acetylcholine
- Treatment: high-dose CCB, nitrates (SL NTG prn), α-blockers; d/c smoking
- Cocaine-induced vasospasm: avoid β as unopposed α-stimulation can worsen spasm
Approach to triage

- If remain nl & Pt pain-free, have r/o MI, but
- If remain nl and low likelihood of ACS, search for alternative causes of chest pain
- If hx and initial ECG & biomarkers non-dx, repeat ECG & biomarkers

Antiplatelet Therapy

Aspirin

50–70% ↓ D/MI (NEJM 1988;319:1105)
If ASA allergy, use clopidogrel instead (and desensitize to ASA)

Clopidogrel (ADP receptor blocker)

300 mg x 1 → 75 mg/d
Give in addition to ASA. 20% ↓ CVD/MI/stroke
↑ benefit if given upstream prior to PCI
but need to wait >5 d after d/c clopi prior to CABG (NEJM 2001;345:494; Lancet 2001;358:257)
~30% pop have ↓ f/x CYP2C19 allele → ↓ plt inhib & ↑ ischemic events (NEJM 2009;360:354)

Prasugrel (ADP receptor blocker)

60 mg x 1 → 10 mg/d
(↑ 5 mg/d if <60 kg)
More rapid (~30 min) and potent plt inhib c/w clopi. 19% ↓ CVD/MI/stroke in ACS w/ planned PCI vs clopi, but ↑ bleeding (NEJM 2007;359:2003)
Particularly efficacious in DM (Circ 2008;118:1626).
Avoid if >75 yr; contraind. if h/o TIA/CVA.

Ticagrelor (ADP receptor blocker)

180 mg x 1 → 90 mg bid reversible (~nl plt f/xn after 72 h)
More rapid (~30 min) and potent plt inhib c/w clopi. 16% ↓ CVD/MI/stroke & 22% ↓ death c/w clopi, but with ↑ non-CABG bleeding (NEJM 2009;361:1045).
↑ frequency of dyspnea.

GP Ib/IIa inhibitors (GPI)

abciximab; eptifibatide; tirofiban infusions given 2–24 h post-PCI
May be given in addition to oral antiplt Rx(s)
No clear benefit for starting GPI prior to PCI and ↑ risk of bleeding (NEJM 2009;360:2176)
Anticoagulant Therapy

**UFH**
- 60 U/kg IVB (max 4000 U)
- 12 U/kg/h (max 1000 U/h)
- 24% ↓ D/MI (JAMA 1996;276:811)
- Titrate to aPTT 1.5–2x cntl (~50–70 sec)

**Enoxaparin** (low-molecular-weight heparin)
- 1 mg/kg SC bid × 2–8 d (≤ 30 mg IVB)
- (qd if CrCl < 30)
- Consider instead of UFH.
- 60 U/kg IVB (max 4000 U)
- titrate to aPTT 1.5–2x cntl (~50–70 sec)
- 12 U/kg/h (max 1000 U/h)

**Bivalirudin** (direct thrombin inhibitor)
- Use instead of heparin for Pts w/ HIT.
- 0.75 mg/kg IVB at time of PCI

**Fondaparinux** (Xa inhibitor)
- C/w enox, 17% Tm mortality & 38% T bleeding by 2.5 mg SC qd 30 d (NEJM 2006;354:1464).
- However, ↓ risk of cath thromb.; must supplement w/ UFH if PCI.

**Coronary angiography** (Circ 2007;116:e148 & 2009;120:2271)
- **Conservative approach** – selective angiography
  - medical Rx with pre-d/c stress test; angio only if recurrent ischemia or strongly ◁ ETT
- **Early invasive approach** – routine angiography w/in 24–48 h
  - Indicated if high risk; recurrent ischemia, ◁ Tn, ST,·Δ, TRS ≥ 3, CHF, ↓ EF, recent PCI <6 mos, sustained VT, prior CABG, hemodynamic instability
  - 32% ↓ rehospt for ACS, nonsignif 16% ↓ MI, no Δ in mortality c/w cons. (JAMA 2008;300:271)
  - ↓ peri-PCI MI counterbalanced by ↓ in spont. MI
  - Long-term mortality benefit likely only if c/w cons. strategy with low rate of angio/PCI ↓ D/Mi/refractory ischemia if cath w/in 24 h c/w 36 h (NEJM 2009;360:165);
  - ↓ reasonable to cath high-risk Pts (GRACE score > 140) w/ 12–24 of admission

**TIMI Risk Score for UA/NSTEMI** (JAMA 2000;284:2052)
- **Calculation of Risk Score**
  - Historical
  - Age ≥65 y
  - ≥3 Risk factors for CAD
  - Known CAD (stenosis ≥50%)
  - ASA use in past 7 d
  - Presentation
  - Severe angina (≥2 episodes w/in 24 h)
  - ST deviation ≥0.5 mm
  - ◁ cardiac marker (troponin, CK-MB)
- **Application of Risk Score**
  - Score
  - D/Mi/UR by 14 d
  - Total points (0–7)

**Figure 1-2** Approach to UA/NSTEMI

**LOW RISK**
- ◁ Tn, no ST ↓, and TRS 0–2, ◁ CHF
- ASA & clopidogrel
  - ENOX, fonda, or UFH
- Med Rx
- **CONS strategy**
- Stress test once stabilized and before d/c
- **HIGH RISK**
- ◁ Tn, ST ↓ ≥0.5 mm, TRS ≥3, s/s CHF
- ASA; clopidogrel (upstream or at time of PCI)
  - UFH, ENOX, or bival (depending on pref of cath lab)
  - ± GP IIb/IIIa inhibitor
- Med Rx
  - W/in ~24 h
  - **INV strategy**
  - Angiography
  - Med Rx
  - PCI (w/ MPI unless bival; consider prasugrel vs. dopi)
  - CABG
  - Long-term medical Rx

**Calculation of Risk Score Application of Risk Score**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Point</th>
<th>Score</th>
<th>D/Mi/UR by 14 d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Historical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>1</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>≥3 Risk factors for CAD</td>
<td>1</td>
<td>3</td>
<td>13%</td>
</tr>
<tr>
<td>Known CAD (stenosis ≥50%)</td>
<td>1</td>
<td>4</td>
<td>20%</td>
</tr>
<tr>
<td>ASA use in past 7 d</td>
<td>1</td>
<td>5</td>
<td>26%</td>
</tr>
<tr>
<td>Presentation</td>
<td>6–7</td>
<td></td>
<td>41%</td>
</tr>
<tr>
<td>Severe angina (≥2 episodes w/in 24 h)</td>
<td>1</td>
<td>Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH, GP IIb/IIIa</td>
<td></td>
</tr>
<tr>
<td>ST deviation ≥0.5 mm</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>◁ cardiac marker (troponin, CK-MB)</td>
<td>1</td>
<td>inhibitors, and early angiography</td>
<td></td>
</tr>
</tbody>
</table>
### STEMI

**Reperfusion**
- 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)*
- Superior to lysis: 27% ↓ death, 65% ↓ reMI, 54% ↓ stroke, 95% ↓ ICH *(Lancet 2003;361:13)*
- Thrombus aspiration during angio prior to stenting ↓ mortality *(Lancet 2008;371:1915)*
- Transfer to center for 1° PCI may also be superior to lysis *(NEJM 2003;349:733)*, see below

### Fibrinolysis vs. Hospital Transfer for Primary PCI

**Assess Time and Risk**
1. **Time required for transport to skilled PCI lab:** door-to-balloon <90 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

**Fibrinolysis**
- Indications: sx <12 h and either STE =0.1 mV (=1 mm) in ≥2 contig. leads or LBBB not known to be old; benefit if sx >12 h less clear; reasonable if persistent sx & STE
- 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 groups include elderly (~2% if >75 y), women, low wt
- Although age not contraind., ↑ risk of ICH in elderly (~75 y) makes PCI more attractive

#### Contraindications to Fibrinolysis

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior ICH</td>
<td>Hx of severe HTN or SBP &gt;180 or DBP &gt;110 on presentation (? absolute contra. if low-risk MI)</td>
</tr>
<tr>
<td>Intracranial neoplasm, aneurysm, AVM</td>
<td>Ischemic stroke &gt;3 mos prior</td>
</tr>
<tr>
<td>Nonhemorrhagic stroke or closed head trauma w/in 3 mo</td>
<td>Prolonged CPR (~10 min)</td>
</tr>
<tr>
<td>Active internal bleeding or known bleeding diathesis</td>
<td>Trauma or major surgery w/in 3 wk</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
<td>Recent internal bleed (w/in 2–4 wk); active PUD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonprimary PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilitated PCI: upstream lytic, GPI, or GPI + ½ dose lytic before PCI of no benefit</td>
</tr>
<tr>
<td>Rescue PCI if shock, unstable, failed reperfusion or persistent sx <em>(NEJM 2005:353:2758)</em></td>
</tr>
<tr>
<td>Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/Revasc <em>(Lancet 2004;364:1045)</em> and w/in 6 h ↓ reMI, recurrent ischemia &amp; CHF c/w w/in 2 wk <em>(NEJM 2009;360:2705)</em>; ↓: if lysed at non-PCI capable hospital, consider transfer to PCI-capable hospital ASAP espec if high-risk presentation (eg, anterior MI, inferior MI w/ low EF or RV infarct, extensive STE or LBBB, HF, ↓ BP or ↑ HR)</td>
</tr>
<tr>
<td>Late PCI (median day 8) of occluded infarct-related artery: no benefit <em>(NEJM 2006:355:2395)</em></td>
</tr>
</tbody>
</table>

**Antiplatelet Therapy**

| Aspirin 162–325 mg (crushed/chewed) | 23% ↓ in death *(Lancet 1988;i:349)* |
| ADP receptor blocker | Lysis: clopidogrel 41% ↑ in patency, 7% ↓ mort., no Δ in major bleed or ICH *(NEJM 2005:352:1179)*; Lancet 2005;366:1607); no data for prasugrel or ticagrelor |
| Clopidogrel: 600 mg pre-PCI, 300 mg if lysis (not if >75 y) → 75 mg/d | PCI: prasugrel and ticagrelor ↓ CV events c/w clopi |
| Prasugrel & ticagrelor as above | | |
| GP IIb/IIIa inhibitors | Lysis: no indication *(Lancet 2001:357:1905)* |
| abciximab, eptifibatide, tirofiban | | |
| Peri-PCI: 60% ↓ D/MI/UR *(NEJM 2001:344:1895)* |

Adapted from ACC/AHA 2009 STEMI Guidelines Focused Update *(Circ 2009;120:2271)*
### Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>60 U/kg IVB (max 4000 U) / 12 U/kg/h (max 1000 U/h)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>30 mg IVB x 1 → 1 mg/kg SC bid (–75 y: no bolus, 0.75 mg/kg SC bid)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>0.75 mg/kg IVB → 1.75 mg/kg/hr IV</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg SC QD</td>
</tr>
</tbody>
</table>

No demonstrated mortality benefit
† patency with fibrin-specific lytics
Titrated to aPTT 1.5–2x cntl (–50–70 sec)
Lysis: 17%↓ DI/MI w/ ENOX x 7 d vs. UFH x 2 d (NEJM 2006;354:1447)
P CI: acceptable alternative to UFH (age & CrCl adjustments untested in 1° PCI)
P CI: ↓ death & ↓ bleeding but ↑ acute stent thrombosis c/w heparin + GPI (NEJM 2008;358:2218)
Lysis: superior to placebo & to UFH, with less bleeding (JAMA 2006;295:1519)
P CI: risk of cath thromb.: should not be used

### Immediate Adjunctive Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>eg, metoprolol 25 mg PO q6h titrate to HR 55–60 Iv only if HTN &amp; no s/s CHF</td>
</tr>
<tr>
<td>Nitrates</td>
<td>SL or IV</td>
</tr>
<tr>
<td>β-blockers</td>
<td>−20%↓ arrhythmic death or reMI, 30%↓ cardiogenic shock, &amp; no ∆ overall mortality when given to Pts incl those w/ mod CHF (Lancet 2005;366:1622)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>−5%↓ mortality (Lancet 1994;343:1115;1995;345:649)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Use for relief of sx control of BP or Rx of CHF</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>eg, captopril 6.25 mg tid, titrate up as tolerated</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Greatest benefit in ant. MI, EF &lt;40%, or prior MI</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Contraindicated in severe hypotension or renal failure</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Use if necessary to keep S O₂ &gt; 90%</td>
</tr>
<tr>
<td>Morphine</td>
<td>Relieves pain, ↓ anxiety, venodilation → ↓ preload</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>eg, captopril 6.25 mg tid, titrate up as tolerated</td>
</tr>
<tr>
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</tr>
<tr>
<td>Oxygen</td>
<td>Contraindicated in severe hypotension or renal failure</td>
</tr>
<tr>
<td>ARBs</td>
<td>Appear = ACE (VALIANT, NEJM 2003;349:20)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Treat hyperglycemia &gt;180 mg/dl while avoiding hypoglycemia, no clear benefit for intensive control</td>
</tr>
</tbody>
</table>

Adapted from ACC/AHA 2007 STEMI Guidelines Focused Update (Circ 2008;117:296)

**LV failure (~25%)**
- Diurese to achieve PCWP 15–20 → ↓ pulmonary edema, ↓ myocardial O₂ demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O₂ demand
- can use IV NTG or nitroprusside (risk of coronary steal) → short-acting ACEI
- Inotropes if CHF despite diuresis & ↓ afterload; use dopamine, dobutamine, or milrinone
- Cardiogenic shock (~7%) → MAP <60 mmHg, CI <2 L/min/m², PCWP >18 mmHg
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**IMI complications** (Circ 1990;81:401; Annals 1995;123:509)
- Heart block (~20%, occurs because RCA supplies AV node)
- Cardiogenic shock (~7%) → MAP <60 mmHg, CI <2 L/min/m², PCWP >18 mmHg
- Cardiogenic shock (~7%) → MAP <60 mmHg, CI <2 L/min/m², PCWP >18 mmHg
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**Mechanical complications** (incid.<1% for each; typically occur a few days post-MI)
- Free wall rupture: ↑ risk w/ fibrinolysis, size of MI, age; p/w PEA or hypo-TN, pericardial sx, tamponade; Rx: volume resusc, ↑ periocardiocentesis, 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, pers. closure
- Papillary muscle rupture: small MI; more likely in IMI → PM pap. muscle (supplied by PDA) than AMI → AL pap. muscle (supplied by diags & OMs); 50% w/ new murmur, rarely a thrill, ↑ v wave in PCWP tracing; asymmetric pulmonary edema, Rx: diuretics, vasodilators, IABP, surgery

**Arrhythmias post-MI**
- Treat as per ACLS for unstable or symptomatic bradycardias & tachycardias
- AF (10–16% incidence): β-blocker, amiodarone, digoxin (particularly if CHF), heparin
• VT/VF: lido or amio × 6–24 h, then reassess; ↑ β as tol., replete K & Mg, r/o ischemia; early monomorphic (<48 h post-MI) does not carry bad prognosis
• Accelerated idioventricular rhythm (AIVR): slow VT (<100 bpm), often seen after successful reperfusion; typically self-terminates and does not require treatment
• 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 under fluoro guidance)

<table>
<thead>
<tr>
<th>Other Post-MI Complications</th>
<th>Clinical features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV thrombus</td>
<td>~30% incid. (esp. lg antero-apical MI)</td>
<td>Anticoagulate × 3–6 mo</td>
</tr>
<tr>
<td>Ventricular aneurysm</td>
<td>Noncontractile outpouching of LV; 8–15% incid.; persistent STE.</td>
<td>Surgery if recurrent CHF, thromboemboli, arrhythmia</td>
</tr>
<tr>
<td>Ventricular pseudoaneurysm</td>
<td>Rupture → sealed by thrombus and pericardium</td>
<td>Surgery</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>10–20% incid.; 1–4 d post-MI ⊕ pericardial rub; ECG Δs rare</td>
<td>High-dose aspirin, NSAIDs Minimize anticoagulation</td>
</tr>
<tr>
<td>Dressler’s syndrome</td>
<td>&lt;4% incid.; 2–10 wk post-MI</td>
<td>Fever, pericarditis, pleuritis</td>
</tr>
</tbody>
</table>

Prognosis
• In registries, in-hospital mortality is 6% w/ reperfusion Rx (lytic or PCI) and ~20% w/o
• Predictors of mortality: age, time to Rx, anterior MI or LBBB, heart failure (Girc 2000;102:2031)

<table>
<thead>
<tr>
<th>Killip Class</th>
<th>Definition</th>
<th>Mort.</th>
<th>Forrester Class Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>no CHF</td>
<td>6%</td>
<td>PCWP (mmHg)</td>
</tr>
<tr>
<td>II</td>
<td>S3 and/or basilar rales</td>
<td>17%</td>
<td>≤2.2</td>
</tr>
<tr>
<td>III</td>
<td>pulmonary edema</td>
<td>30–40%</td>
<td>≤2.2</td>
</tr>
<tr>
<td>IV</td>
<td>cardiogenic shock</td>
<td>60–80%</td>
<td>≤2.2</td>
</tr>
</tbody>
</table>

**PredischARGE CheckIst and Long-Term Post-ACS MANAGEMENT**

Risk stratification
• Stress test if anatomy undefined or significant residual CAD after PCI of culprit vessel
• Echocardiogram to assess EF; EF ↑ ~6% in STEMI over 6 mos (JACC 2007;50:149)

Medications (barring contraindications)
• Aspirin: 162–325 mg/d for 1 mo (BMS) or 3–6 mos (DES); 75–162 mg/d thereafter
• ADP receptor blocker (eg, clopidogrel): ≥12 mos (! longer if DES); some PPIs may interfere with biotransformation of clopidogrel and ∴ pt inhibition, but no convincing evidence to date of impact on clinical outcomes (Lancet 2009;374:989; COGENT, TCT 2009)
• β-blocker: 23% ↓ mortality after acute MI
• Statin: high-intensity lipid-lowering (eg, atorvastatin 80 mg, NEJM 2004;350:1495)
• ACEI: life-long if CHF; EF; HTN; DM; 4–6 wks or at least until hosp. d/c in all STEMI 
• long-term benefit in CAD w/o CHF (NEJM 2000;342:145 & 2004;351:2058; Lancet 2003;362:782)
• Aldosterone antagonist: if EF <40% & signs of HF (see “Heart Failure”)
• Nitrates: standing if symptomatic; SL NTG prn for all
• Oral anticoagulants: beyond indic. for AF and LV thrombus, comb. of warfarin (goal INR 2–2.5) + ASA + D/MI/CVA c/w ASA alone, but ↑ bleeding (NEJM 2002;347:969); addition of oral Xa or lla inhibitors post-ACS under study (Lancet 2009;374:269)

ICD (NEJM 2008;359:2245)
• If susvt VT/VF: ~2 d post-MI not due to reversible ischemia
• 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
• Low chol. (<200 mg/dl) & low fat (<7% saturated) diet; LDL goal ≤70 mg/dl; fish oil (BMJ 2008;337:b2931)
• BP <140/90 mmHg, ≤130/80 if diabetes or chronic kidney disease, consider <120/80
• Smoking cessation
• If diabetic, HbA1c ≤7% (avoid TZDs if CHF) 
• Exercise (~30 mins 3–4 × per wk); Weight loss with BMI goal 18.5–24.9 kg/m²
• Influenza vaccination (Girc 2006;114:1549)
PA CATHETER AND TAILORED THERAPY

Rationale
- Cardiac output (CO) = SV × HR; SV depends on LV end-diastolic volume (LVEDV)
  - manipulate LVEDV to optimize CO while minimizing pulmonary edema
- Balloon at tip of catheter inflated → floats into “wedge” position. Column of blood extends from tip of catheter, through pulmonary circulation, to a point just proximal to LA. Under conditions of no flow, PCWP = LA pressure – LVEDP, which is proportional to LVEDV.
- Situations in which these basic assumptions fail:
  1) Catheter tip not in West lung zone 3 (and .) PCWP = alveolar pressure = LA pressure; clues include lack of a & v waves and if PA diastolic pressure < PCWP
  2) PCWP > LA pressure (eg, mediastinal fibrosis, pulmonary VOD, PV stenosis)
  3) Mean LA pressure > LVEDP (eg, MR, MS)
  4) Δ LVEDP-LVEDV relationship (ie, abnl compliance, . “nl” LVEDP may not be optimal)

Indications
- Diagnosis and evaluation
  Ddx of shock (cardiogenic vs. distributive; espec. if trial of IVF failed / high-risk) and of pulmonary edema (cardiogenic vs. not; espec. if trial of diuretic failed / high-risk)
  Evaluation of CO, intracardiac shunt, pulmonary HTN, MR, tamponade
- Therapeutics
  Tailored therapy to optimize PCWP, SV, S.O2 in heart failure/shock
  Guide to vasodilator therapy (eg, inhaled NO, nifedipine) in pulmonary HTN
  Guide to perioperative management in some high-risk Pts, pre-transplantation
- Contraindications
  Absolute: right-sided endocarditis, thrombus, or mechanical R-sided valve
  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
- No benefit to routine PAC in high-risk surgery or ARDS (NEJM 2006;354:2213)
- No benefit in decompensated CHF (JAMA 2005;294:1625;): untested in cardiogenic shock
- But: ~½ of CO & PCWP clinical estimates incorrect; CVP & PCWP not well correl.; use PAC to (a) answer hemodynamic ? and then remove, or (b) manage cardiogenic shock

Placement
- 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
- Deflate the balloon when withdrawing and at all other times
- CXR should be obtained after bedside placement to assess for catheter position and PTX
- If catheter cannot be successfully floated (typically if severe TR or RV dilatation) or if another relative contraindication exists, consider fluoroscopic guidance

Complications
- Central venous access: pneumo/hemothorax (1–3%), arterial puncture, air embolism
- Advancement: atrial or ventricular arrhythmias (3% VT), RBBB (5%), catheter knotting, cardiac perforation/tamponade, PA rupture
- Maintenance: infection (especially if catheter >3 d old), thrombus, pulmonary infarction (~1%), PA rupture/pseudoaneurysm (esp. 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 (convert cmH2O to mmHg by × ⅓).
- PCWP: LV preload best estimated at a wave; risk of pulmonary edema from avg PCWP

Cardiac output
- Thermodilution: saline injected in RA. Δ in temp in over time measured at thermistor (in PA) is integrated ~ 1/CO. Inaccurate if ↓ CO, sev TR, or shunt.
- Fick method: O2 consumption (L/min) = CO (L/min) × arteriovenous O2 difference. CO derived by dividing O2 consumption by observed AV O2 difference [10 × 1.34 ml O2/g Hb × Hb g/dl × (S.O2 – S.O2)] Can estimate O2 consumption using wt-based formula, but best to measure (espec if ↑ metabolism, eg, sepsis).
- If S.O2 >80%, consider wedged (ie, pulm vein) sat. L→R shunt, impaired O2 utilization (severe sepsis, cyanide, carbon monoxide), ↑↑ O2 delivery.
**PA Catheter Waveforms**

<table>
<thead>
<tr>
<th>Location</th>
<th>RA</th>
<th>RV</th>
<th>PA</th>
<th>PCWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>-20 cm</td>
<td>-30 cm</td>
<td>-40 cm</td>
<td>-50 cm</td>
</tr>
<tr>
<td>Pressure (mmHg)</td>
<td>mean = 6</td>
<td>syst 15–30 diast 1–8</td>
<td>syst 15–30 diast 6–12</td>
<td>mean = 12</td>
</tr>
</tbody>
</table>

**Waves**

- **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

**Comment**

- RVEDP occurs right before upstroke and is 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 = RV distolic unless there is a gradient (eg, PS).
- Similar to RA except dampened and delayed.

**Hemodynamic Profiles of Various Forms of Shock**

<table>
<thead>
<tr>
<th>Type of shock</th>
<th>RA (JVP)</th>
<th>PCWP (CXR)</th>
<th>CO (UOP)</th>
<th>SVR (Cap refill)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>nl or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Distributive</td>
<td>variable</td>
<td>variable</td>
<td>usually ↑</td>
<td>↓</td>
</tr>
<tr>
<td>(but can be ↓ in sepsis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Infarct / Massive PE</td>
<td>↑</td>
<td>nl or ↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Tamponade</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

(Surrogates for hemodynamic parameters shown below parameter in parentheses.)

**Tailored therapy in cardiogenic shock** *(Gicz 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 (higher levels may be tolerated in chronic HF)
- **Optimize preload** = LVEDV = LVESP = LAP = PCWP *(NEJM 1973;289:1263)*
  - goal PCWP 14–18 in acute MI, 10–14 in chronic heart failure
  - 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)]
  - MAP = MAP + SVR = (MAP – CVP / CO); goals: MAP >60, SVR >1000
  - vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or weak pressors
  - MAP >60 & SVR ↑ & CO ↓: temporize w/ pressors until can ↑ CO (see below)
  - MAP >60 & SVR low/nl: vasopressors (eg, norepinephrine [α, β], dopamine [D, α, β], phenylephrine [x], or vasopressin [V1] if refractory)
- **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 (moderate inotrope & mild vasodilator), milrinone (strong inotrope & vasodilator, incl pulmonary artery), both proarrhythmic, or epinephrine (strong inotrope and vasopressor); also consider mechanical assistance with IABP or percutaneous or surgical LVAD = RVAD
HEART FAILURE

HF 114

Definitions (Braunwald's Heart Disease, 8th ed., 2008)
• Failure of heart to pump blood forward at sufficient rate 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)

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 2002;287:628)
• Congestion (“dry” vs. “wet”)
  ↑ JVP (~80% of the time JVP >10 → PCWP >22; J Heart Lung Trans 1999;18:1126)
  hepatojugular reflux: >1 cm ↑ in JVP for ≥15 sec with abdominal pressure
  73% Se & 87% Sp for RA; 80% Se & 83% Sp for PCWP >15 (AJC 1990;66:1002)
  Valsalva square wave (↑ SBP thru strain) (JAMA 1996;275:630)
  S4 (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 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)
  pulsus alternans, cool & pale extremities, ↓ UOP, muscle atrophy
  ± Other: Cheyne-Stokes resp., abnl PMI (diffuse, sustained, or lifting depending on cause of HF), S4 (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
• BNP / NT-proBNP: can help exclude HF as cause of dyspnea if low; predicts risk of rehosp
• Evidence of ↓ perfusion to vital organs: ↑ BUN, ↑ Cr, ↓ serum Na, abnormal LFTs
• Echo (see inserts): ↑ EF & ↑ chamber size → systolic dysfxn; hypertrophy, abnl MI inflow, abnl tissue Doppler → ↑ diastolic dysfxn; abnl valves or pericardium; estimate RVSP
• PA catheterization: ↑ PCWP, ↓ CO and ↓ SVR (low-output failure)


### Evaluation of the causes of heart failure
- ECG: evidence for CAD, LVH, LAE, heart block or low voltage (infiltrative CMP/DCMP)
- Coronary angiography (or CT coronary angiography)
- If no CAD, w/u for nonischemic DCMP, HCM, or RCM (see "Cardiomyopathies")

### Precipitants of acute heart failure
- Myocardial ischemia or infarction: myocarditis
- Renal failure (acute, progression of CKD, or insufficient dialysis) → ↑ preload
- Hypertensive crisis (incl. from RAS), worsening AS → ↑ left-sided afterload
- Dietary indiscretion or medical nonadherence
- Drugs (β-blockers, ACEIs, ARBs, potassium sparing diuretics, aldosterone antagonists)
- Anemia, systemic infection, thyroid disease
- Myocardial ischemia or infarction
- Arrhythmias; acute valvular dysfunction (e.g., endocarditis), especially mitral or aortic regurgitation
- Cardiac transplantation:
  1. For assessing degree of congestion & adequacy of perfusion
  2. To treat advanced heart failure

### Treatment of acute decompensated heart failure
- Assess degree of congestion & adequacy of perfusion

#### For congestion: "LMNOP"
- Lasix w/ monitoring of UOP; high-dose (IVB 2.5 × PO dose) vs. low-dose (IVB 1 × PO dose) → ↑ UOP but transient
- In renal dysfunction; clear diff between cont. vs. intermittent (DOSE, ACC 2010)
- Morphine (1 sx, venodilator, i afterload)
- Nitrates (venodilator)
- Oxygen ± noninvasive ventilation ("Mechanical Ventilation")
- Position (sitting up & legs dangling over side of bed → ↓ preload)
- For low perfusion, see below

### Treatment of advanced heart failure
- Tailored Rx w/ PAC (qv): goals of MAP > 60, CI ≥ 2.2 (MVO2 > 60%), SVR < 800, PCWP < 18
- IV vasodilators: NTG, nitrprosulide (risk of coronary steal in pts w/ CAD)
- Prolonged use → cyanide/thiocyanate toxicity; nesiritide (BNP) → PCWP & sx, but may ↑ Cr & mortality (JAMA 2002;287:1531 & 2005;293:1900)
- Inotropes (properties in addition to ↑ inotropy listed below)
  - Dobutamine: vasodilation at doses ≥ 5 μg/kg/min; mild ↓ PVR; desensitization over time
  - Dopamine: splanchnic vasodilation
  - Milrinone: prominent systemic & pulmonary vasodilation; ↓ dose by 50% in renal failure
- Ultrafiltration: > 1 L fluid loss at 48 h and ~ 50% ↓ in rehospitalization (JACC 2007;49:675)
- Mechanical circulatory support
  - Intraaortic balloon pump (IABP): deflates in diastole & inflates in systole to ↓ impendence to LV ejection of blood & ↑ coronary perfusion
  - Ventricular assist device (LVAD ± RVAD): as bridge to recovery (NEJM 2006;355:1873) or as destination therapy (45–50% ↓ mortality vs. med Rx; NEJM 2001;345:1435 & 2009;361:2241)
- Cardiac transplantation: 15–20% mortality in 1st y, median survival 10 y

### Recommended Chronic Therapy by CHF Stage

<table>
<thead>
<tr>
<th>Stage (Not NYHA Class)</th>
<th>Pt Characteristics</th>
<th>Therapy</th>
</tr>
</thead>
</table>
| A                      | High risk for HF  
Structural heart dis.  
Asx                      | HTN, DM, CAD  
Cardiotoxic exposure  
FHX of CMP               | Treat HTN, lipids, DM, SVT  
Stop smoking, EtOH  
Encourage exercise  
ACEI if HTN, DM, CVD, PAD |
| B                      | Structural heart dis.  
Asx                      | Prior MI, ↓ EF, LVH  
Or asx valvular dis.    | All measures for stage A  
ACEI & β if MI/CAD or ↓ EF |
| C                      | Structural heart dis.  
Symptoms of HF  
(prior or current)      | Overt HF            | All measures for stage A  
ACEI, β, diuretics, Na restrict  
Consider aldactone, ICD, CRT  
Consider nitrates/lydral, digoxin |
| D                      | Refractory HF  
requiring specialized interventions | Sx despite maximal medical Rx  
4 yr mortality > 50% | All measures for stage A–C  
IV inotropes, VAD, transplant  
End-of-life care |

(Circ 2009;119:e391)

- No clear evidence that BNP-guided Rx results in superior clinical outcomes outside of encouraging intensification of established therapies (JAMA 2009;301:183)
- Implantable PA pressure sensor may ↓ risk of hosp (CHAMPION, HF Congress 2010)
Treatment of Chronic Heart Failure with Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>Diet, exercise</th>
<th>Na &lt; 2 g/d, fluid restriction, exercise training in ambulatory Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>↓ mortality: 40% in NYHA IV, 16% in NYHA III, 20% in asx, post-MI, EF ≤ 40% (NEJM 1987;316:1429, 1991;325:293, 1992;327:669) 20% ↓ rehosp for HF (amt of benefit w/ ↑ renal function) 30% ↓ HF in asx Pts w/ EF ≤ 35% (SOLVD-P, NEJM 1992;327:685) High-dose ACEI more efficacious than low-dose Watch for azotemia, ↑ K (can ameliorate by low-K diet, diuretics, kayexalate), cough, angioedema</td>
</tr>
<tr>
<td>AT1 receptor blockers (ARBs)</td>
<td>Consider as alternative if cannot tolerate ACEI (eg, b/c cough) Noninferior to ACEI (VALIANT, NEJM 2003;349:1893) Good alternative if ACEI intoler (CHARM-Alternative, Lancet 2003;362:772) As with ACEI, higher doses more efficacious (Lancet 2009;374:1840) ↑ HF (Val-HEFT, NEJM 2001;345:1667) and ↓ mort. when added to ACEI (CHARM-Added, Lancet 2003;362:767), but ↑ risk of ↑ K and ↑ Cr</td>
</tr>
<tr>
<td>Hydralazine + nitrates</td>
<td>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) Carvedilol superior to low-dose metoprolol (Lancet 2003;362:7)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>EF will transiently ↓, then ↑. Contraind. in uncompensated HF. 35% ↓ mort. &amp; 40% ↓ rehosp. in NYHA II–IV (JAMA 2002;287:88) Carvedilol superior to low-dose metoprolol (Lancet 2003;362:7)</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Consider if HF severe or post-MI, adeq. renal fxn; watch for ↑ K 30% ↓ mort. in NYHA III/IV &amp; EF ≤ 35% (RALES, NEJM 1999;341:709) 15% ↓ mort. in HF post-MI, EF ≤ 40% (EPHESUS, NEJM 2003:348:1309)</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy (CRT)</td>
<td>Consider if EF ≤ 35%, QRS = 120 ms, and symptomatic 36% ↓ mort. &amp; ↑ EF in NYHA III–IV (CARE-HF, NEJM 2005;352:1539) ↓ HF if EF ≤ 30% &amp; NYHA III, esp. if QRS ≥ 150 ms, no Δ in mortality (NEJM 2009;361:1329) No single measure of dyssynchrony on echo improves Pt mortality (NEJM 2009;361:1329)</td>
</tr>
<tr>
<td>ICD</td>
<td>Use for 1st prevention if sx &amp; EF ≤ 35% or for 2nd prevention ↓ mort. in Pts w/ MI &amp; EF ≤ 30% (NEJM 2002;346:877); no Δ mort. early post-MI (NEJM 2004;351:2481; 2009;361:1427); wait ≥ 40 d 23% ↓ mort. in all DCMP, EF ≤ 35% (SCD-HeFT, NEJM 2005;352:225) ↓ arrhythmic death in nonisch DCMP (DEFINITE, NEJM 2004:350:2151)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Loop ± thiazide diuretics (sx relief; no mortality benefit)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>23% ↓ HF hosp., no Δ mortality (NEJM 1997;336:525) ↑ mortality in women, ↑ related to ↑ levels (NEJM 2002;347:1403) ↑ optimal dig concentration 0.5–0.8 ng/mL (JAMA 2003;289:871)</td>
</tr>
<tr>
<td>Ω-3 fatty acids</td>
<td>9% ↑ mortality (Lancet 2008;372:1223)</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Consider if AF, LV thrombus, large akinetic LV segment, EF &lt; 30% For sx AF, pulm vein isolation improves sx c/w AVN ablation &amp; CRT (NEJM 2008;359:1778)</td>
</tr>
</tbody>
</table>

Heart failure with preserved EF (“Diastolic HF”) (JACC 2009;53:905)
- 40–60% of Pts w/ HF have normal or only min. impaired systolic fnx (EF ≥ 40%) (NEJM 2006;355:251, 260), w/ mortality rates similar to those w/ systolic dysfnn
- ~30% of population ≥ 45 y w/ diastolic dysfnn on echo, ~20% mild, < 10% mod/sev, but only 50% of severe and 5% of moderate cases were symptomatic (JAMA 2003;289:194)
- Etiologies (impaired relaxation and/or ↑ passive stiffness): ischemia, prior MI, LVH, HCM, infiltrative CMP, RCM, 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 (↓ preload → ↓ stroke volume)
- Dx w/ clinical s/s of HF w/ preserved systolic and impaired diastolic fnx on echo: abnormal MV inflow: E/A reversal and Δs in E wave deceleration time ↓ myocardial relax.: ↓ isovol relax. time & ↓ early diastole tissue Doppler vel LVH, LAE
Dilated Cardiomyopathy (DCMP)

Definition and epidemiology (Circ 2006;113:1807)
- Ventricular dilatation and ↓ contractility ↓ wall thickness,
- Incidence: 5–8 cases/100,000 population per y; prevalence: 1 in 2500

Etiologies (NEJM 1994;331:1564 & 2000;342:1077)
- Ischemia: systolic dysfxn & dilation out of proportion to CAD (poor remodeling post-MI)
- Valvular disease: systolic dysfxn due to chronic volume overload in MR & AI
- Familial (~25%): mutations in cytoskeletal, nuclear, and filament proteins (NEJM 1992;362:777)
- Idiopathic (~25% of DCMP; undiagnosed infectious, alcoholic, or genetic cause)
- Infectious myocarditis (10–15%, autoimmune response to infxn; NEJM 2009;360:1526)
  
  Viruses (coxackie, adenov, echovirus, CMV): ranging from subacute (dilated LV w/ mild-moder dysfxn) to fulminant (nondilated, thickened, edematous LV w/ severe dysfxn)

  Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB)
  HIV: ~8% of asx HIV due to HIV vs. other viruses vs. meds (NEJM 1998;339:1093)

    Chagas: apical aneurysm ± thrombus, RBBB, megasphagous or colon (NEJM 1993;329:639)

- Toxic
  Alcohol (5%) typically 7–8 drinks/d × >5 y, but much interindividual variability

    Anthracyclines (risk ↑ >550 mg/m², may manifest late), cyclophosphamide, trastuzumab

    Cocaine, antiretrovirals, lead, carbon monoxide poisoning, radiation

- Infiltrative (5%): often mix of DCMP + RCM (qv) w/ thickened wall amyloidosis, sarcoidosis, hemochromatosis, tumor

- Autoimmune
  Collagen vascular disease (3%): polymyositis, SLE, scleroderma, PAN, RA, Wegener’s

  Peripartum (last month → 5 mo postpartum): <0.1% of preg; ↑ risk w/ multiparity & ↑ age; ~50% will improve; ? ↑ risk w/ next preg, (JAMA 2000;283:1183)

  Idiopathic giant cell myocarditis (GCM): avg age 42 y, fulminant, VT (NEJM 1997;336:1860)

    Eosinophilic (variable peripheral eosinophilia): hypersensitivity (mild CHF) or acute necrotizing (ANEM; STE, effusion, severe CHF)

- Stress-induced (Takotsubo apical ballooning): mimics MI (pain, ± STE & ↑ Tn; deep TWI & ↑ QT; mid/apical dyskinesis; ? Rx w/ ACEI; usually improves over wks (NEJM 2005;352:539)

- Tachycardia-induced: likelihood proportional to rate and duration

- Arrhythmogenic right ventricular cardiomyopathy (ARVC): fibrofatty replacement of RV → dilation (dx w/ MRI); ECG: ± RBBB, TWI → V, e wave; risk VT (Circ 2004;110:1879)

- Metabolic & other: hypothyroidism, acromegaly, pheo, thiamine, sleep apnea

Clinical manifestations
- Heart failure: both congestive & poor forward flow sx; signs of L- & R-sided HF

  - diffuse, lat.-displaced PMI, S, ± MR or TR (annular dilat., displaced pap. muscle)
  - Embolic events (~10%), arrhythmias & palpitations
  - Chest pain can be seen w/ some etiologies (eg, myocarditis)

Diagnostic studies and workup
- CXR: moderate to marked cardiomegaly, ± pulmonary edema & pleural effusions
- ECG: may see PRWP, Q waves, or BBB; low voltage; AF (20%) (NEJM 2005;352:26)
- Echocardiogram: LV dilatation, ↓ EF; regional or global LV HK, ↓ RV HK, ± mural thrombi
- Laboratory evaluation: TFS, iron studies, HIV, SERP, ANA; others per clinical suspicion
- Family hx (20–35% w/ familial dis.), genetic counseling ± genetic testing (JAMA 2009;302:2471)
- Stress test: completely test useful to r/o ischemic etiology (low false rate), but test does not rule in ischemic etiology (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 2005;50:1914): yield 10% (of these, 75% myocarditis, 25% systemic disease); 40% false rate (patchy dis.) & false (necrosis → inflammation)
  
  no proven Rx for myocarditis: ↓ biopsy if: acute & hemody compromise (r/o GCM, ANEM); arrhythmia or RCM features (r/o infiltrative); or suspect toxic, allergic, tumor

  Cardiac MRI: detect myocarditis or infiltrative disease, but nonspecific (EHJ 2005;26:1461)

Treatment (see “Heart Failure” for standard HF Rx)
- Implantation of devices may be tempered by possibility of reversibility of CMP
- Immunosuppression for giant cell myocarditis (prednisone + AZA), collagen vascular disease, peripartum (? IVlg), & eosinophilic; no proven benefit for viral myocarditis
- Prognosis differs by etiology (NEJM 2000;342:1077): postpartum (best), ischemic (worst)
Hypertrophic Cardiomyopathy (HCMP)

Definition and epidemiology
- LV (usually ≥15 mm) and/or RV hypertrophy disproportionate to hemodynamic load
- Prevalence: 1 case/500 population; 50% sporadic, 50% familial
- Differentiate from 2° LVH: hypertension (espec. elderly women; NEJM 1985;312:277), AS, elite athletes (wall thickness usually <13 mm & symmetric and nil/rates of tissue Doppler diastolic relaxation; NEJM 1991;324:295), Fabry dis. († Cr, skin findings)

Pathology
- Autosomal dominant mutations in cardiac sarcomere genes (eg, β-myosin heavy chain)
- Myocardial fiber disarray with hypertrophy
- Morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical

Pathophysiologic
- Subaortic outflow obstruction: narrowed tract 2° hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (may be fixed, variable, or nonexist.) and papillary muscle displacement. Gradient (V) worse w/ ↑ contractility (digoxin, β-agonists), ↑ preload, or ↓ afterload.
- Mitral regurgitation: due to SAM (mid-to-late, post.-directed regurg. jet) and abnormal 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 ↑ LVESP, MR, and diastolic dysfunction
- Angina (25%) even w/o epicardial CAD; microvasc dysfn (NEJM 2003;349:3-1027)
- Arrhythmias (AF in 20–25%;VT/VF) → palpitations, syncope, sudden cardiac death

Physical exam
- Sustained PMI, S2, paradox. split if severe outflow obstruction, S4 (occ. palpable)
- Systolic crescendo-decrescendo murmur at LLSB: ↑ w/ Valsalva & standing
- ≤ mid-to-late or holosystolic murmur of MR at apex
- Bifurcated 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
- CXR: cardiomegaly (LV and LA)
- ECG: LVH, anterolateral and inferior pseudo-Qw, apical variant
- Echo: no absolute cutoffs for degree of LVH but septum / post wall ≥13 suggestive, as is septum >15 mm; other findings include dynamic outflow obstruction, SAM, MR
- MRI: hypertrophy + patchy delayed enhancement (useful for dx & prognosis)
- Cardiac cath: subaortic pressure V; Brockenbrough sign = ↓ pulse pressure post-extrasystolic beat (in contrast to AS, in which pulse pressure ↑ postextrasystole)

Treatment (NEJM 2004;350:1320)
- Heart failure
  - If refractory to drug therapy and there is obstructive physiology (V >50 mmHg):
    a) Alcohol septal ablation (NEJM 2002;347:1326)
      - trifasic V response: acute ↓ to ≤ partial ↑ to back to 50% of baseline ↓ over months by 1 y resting ≤ 15 mmHg & stress-induced ≤ 31 mmHg (Interv Card 2006;19:319)
      - complications: transient (& occ. delayed) 3° AVB w/ 10–20% req. PPM; VT
    b) Surgical myectomy: long-term sx improvement in 90% (JACC 1997;29:435; Circ 1999;99:2927)
  - Dual-chamber pacing, but largely placebo effect (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 with β-blockers, maintain SR with disopyramide, amiodarone
  - Sudden cardiac death: ICD (JACC 2003;42:1687; Major risk factors include history of VT/VF, FHx SCD, unexplained syncope, NSVT, ↓ SBP or relative HoTN († SBP < 20 mmHg) w/ exercise, LV wall ≥30 mm; risk 4%/y in high-risk Pts (JAMA 2007;298:405)
  - Counsel to avoid dehydration, extreme exertion
  - Endocarditis prophylaxis no longer recommended (Circ 2007;16:1736)
  - First-degree relatives: periodic screening w/ echo (as timing of HCMP onset variable)
RESTRICTIVE CARDIOMYOPATHY (RCMP)

Definition
• Impaired ventricular filling due to ↓ compliance in absence of pericardial disease

Etiology (NEJM 1997;336:267; JACC 2010;55:1769)
• Myocardial processes
  autoimmune (scleroderma, polymyositis-dermatomyositis)
  infiltrative diseases (see primary entries for extracardiac manifestations, Dx, Rx)
  amyloidosis (JACC 2006;51:1022): age at presentation ~60 y; male:female ~ 3:2
  AL (MM, light-chain, MGUS,WM); familial (transthyretin, TTR); AA/senile (TTR, ANP)
  ECG: ↓ QRS amplitude (50%), pseudoinfarction pattern (Qw), AVB (10–20%),
    hemiblock (20%), BBB (5–20%)
  Echo: biventricular wall thickening, granular sparkling texture (30%), biatrial
    enlargement (40%), thickened atrial septum, valve thickening (65%), diastolic
    dysfxn, small effusion
  normal voltage & normal septal thickness has NPV ~ 90%
  MRI: distinct late gadolinium enhancement pattern (JACC 2008;51:1022)
  sarcoidosis: age at present ~30 y; more common in blacks, N. Europeans, women
    5% of those with sarcoid w/ overt cardiac involvement; cardiac w/o systemic in
    10% ECG:AVB (75%), RBBB (20–60%), VT
  Echo: regional WMA (particularly basal septum) with thinning or mild hypertrophy
    nuclear imaging: gallium uptake in areas of sestaMIBI perfusion defects
  hemochromatosis: presents in middle-aged men (particularly N. European)
  storage diseases: Gaucher’s, Fabry, Hurler’s, glycogen storage diseases
  diabetes mellitus
• Endomyocardial processes
  chronic eosinophilic: Löffler’s endocarditis (temperate climates; ↑ eos.; mural thrombi
    that embolize); endomyocardial fibrosis (tropical climates; var. eos.; mural thrombi)
  toxins: radiation, anthracyclines
  serotonin: carcinoid, serotonin agonists, ergot alkaloids
  metastatic cancer

Pathology & pathophysiology
• Path: normal or ↑ wall thickness ± infiltration or abnormal deposition
• ↓ myocardial compliance → ↓ 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 (classically seen in constrictive pericarditis)
• Cardiac: ± S3 and S4, ± 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, bialtrial enlarge., ± mural thrombi, ± cavity oblct.
  w/ diast dysfxn: ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio, ↓ decel. time
• Cardiac MRI: may reveal inflammation or evidence of infiltration (although 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 and RV pressure peaks during respiratory cycle (vs. discordance in constrictive pericarditis; Circ 1996;93:2007)
• Endomyocardial biopsy if suspect infiltrative process
• 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 and maintain SR (important for diastolic filling). Dig proarrhythmic 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, ↑ cholesterol, ESRD
- Congenital (ie, bicuspid AoV w/ premature calcification): cause in 50% of pts <70 y
- Rheumatic heart disease (AS usually accompanied by AI and MV disease)
- AS mimickers: subvalvular (HCMP, subaortic membrane), supravalvular

Clinical manifestations (usually indicates AVA <1 cm² or concomitant CAD)
- Angina: ↑ O₂ demand (hypertrophy) + ↓ O₂ supply (↓ cor perfusion pressure) < CAD
- Syncope (exertional): peripheral vasodil. w/ fixed CO → ↓ MAP → ↓ cerebral perfusion
- Heart failure: outflow obstruct + diastolic dysfxn → pulm. edema; precip. by AF (↓ LV filling)
- Acquired von Willebrand disease (↓20% of sev. AS): destruction of vWF (NEJM 2003;349:343)
- Natural hx: usually slowly progressive (AVA ↓ ~0.1 cm² per 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 examination
- Midsystolic crescendo-decrescendo murmur at RUSB, harsh, high-pitched, radiates to carotids, apex (holosystolic = Gullardian effect) ↑ w/ passive leg raise, ↓ w/ standing & Valsalva
- In contrast, dynamic outflow obstruction (eg, HCMP) ↓ w/ passive leg raise & ↑ w/ standing & Valsalva
- Ejection click after S1 sometimes heard with bicuspid AoV
- Signs of severity: late-peakng murmur; paradoxically split S₂ or inaudible A₂, small and delayed carotid pulse (“pulsus parvus et tardus”), LV heave, S₃ (occasionally palpable)

Diagnostic studies
- ECG: LVH, LAE, LBBB, AF (in late disease)
- CXR: cardiomegaly, AoV calcification, poststenotic dilation of ascending Ao, pulmonary congestion
- Echo: valve morphology, estim pressure gradient & calculate AVA, EF
- Cardiac cath: pressure gradient (ΔV) across AoV, AVA, ratio CAD (in ~50% of calcific AS)
- Dobutamine challenge during echo or cath if low EF and ΔV <30 to differentiate: afterload mismatch: 20% ↑ SV & ↑ ΔV, no Δ AVA (implies contractile reserve & ↑ EF post-AVR) pseudostenosis: 20% ↑ SV, no Δ in ΔV, ↑ AVA (implies low AVA artifact of LV dysfxn) limited contractile reserve: no Δ SV, ΔV, or AVA (implies EF prob. will not improve w/ AVR)

Pathophysiology of Heart Disease, 4th ed., 2006, for this and subseq. graphics.

<table>
<thead>
<tr>
<th>Classification of Aortic Stenosis</th>
<th>Mean Gradient (mmHg)</th>
<th>Jet Vel. (m/s)</th>
<th>AVA (cm²)</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>1</td>
<td>&gt;1.5</td>
<td>normal</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;25</td>
<td>&lt;3</td>
<td>&gt;1.5</td>
<td>normal</td>
</tr>
<tr>
<td>Moderate</td>
<td>25–40</td>
<td>3–4</td>
<td>1.0–1.5</td>
<td>normal</td>
</tr>
<tr>
<td>Severe, compensated</td>
<td>&gt;40</td>
<td>&gt;4</td>
<td>&lt;1.0</td>
<td>normal</td>
</tr>
<tr>
<td>Severe, uncompensated</td>
<td>Variable</td>
<td>Variable</td>
<td>&lt;1.0</td>
<td>↓</td>
</tr>
</tbody>
</table>

AVA index (AVA relative to BSA) <0.6 cm²/m² also qualifies for severe AS.

- Management decisions are based on symptoms: once they develop surgery is needed.
- If asx, HTN can be cautiously Rx’d; statins have not been proven to ↓ progression.
- AVR: only effective Rx for severe AS. Indicated in sx AS (almost invariably severe; if not, look for another cause of sx) & asx sev. AS & EF <50%. Consider if asx sev. AS and AVA <0.6 cm², mean gradient >60 mmHg, aortic jet >5 m/s. ↓ BP w/ exercise (can carefully exercise asx AS to uncover sx, do not exercise sx AS), high likelihood of rapid prog. or asx mod sx AS and undergoing CV surgery.
- Medical therapy: used in sx pts who are not operative candidates carefu diuresis, control HTN, maintain SR; digoxin if low EF or AF avoid venodilators (nitrates) and β blockers (CCB) in severe AS avoid vigorous physical exertion once AS moderate-severe ↓ nitroprusside if p/w CHF w/ sev. AS, EF <35%, CI <2.2, & nl BP (NEJM 2003;348:1756)
- IABP: stabilization, bridge to surgery
- Balloon Ao valvotomy (BAV): 50% ↑ AVA & ↓ peak V, but 50% restenosis by 6–12 mo & ↑ risk of peri-PAV stroke/AI (NEJM 1988;319:125), ↓ bridge to AVR or palliation
- Transcatheter AoV implantation (TAVI): bioprosthetic valve mounted on balloon-expandable stent (JACC 2009;53:1829); AVA ↑ ~1 cm² (JACC 2010;55:1080); RCTs ongoing
AORTIC INSUFFICIENCY (AI)

**Etiology** (Circ 2006;114:422)
- **Valve disease** (43%)
  - Rheumatic heart disease (usually mixed AS/AI and concomitant MV disease)
  - Bicuspid AoV: natural hx: 1/3 → normal, 1/3 → AS, 1/6 → AI, 1/6 → endocarditis → AI
  - Infective endocarditis
  - Valvulitis: RA, SLE, anorectics (fen/phen) & other serotoninergics (NEJM 2007;356:29,39)
- **Root disease** (57%)
  - HTN
  - Hypertensive aortic aneurysm or dissection, annuloaortic ectasia, Marfan syndrome
  - Aortic inflammation: giant cell, Takayasu's, ankyllosing 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 examination**
- **Early diastolic decrescendo murmur at LUSB** (RUSB if dilated Ao root); ↑ sitting forward, expir, handgrip; severity of AI/ duration of murmur (except in acute and severe late); Austin Flint murmur: mid-to-late diastolic rumble at apex (AI jet interfering w/ mitral inflow)
- **Wide pulse pressure** due to ↑ stroke volume, hyperdynamic pulse → many of classic signs (see table); pulse pressure narrows in late AI with ↓ LV fxn; bisferiens (twice-beating) arterial pulse
- **PMI diffuse and laterally displaced; soft S1** (early closure of MV); Z T EF but rather just volume overload in AI

<table>
<thead>
<tr>
<th>Sign Description</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water hammer pulse (ie, rapid rise/fall or distention/collapse)</td>
<td>Corrigan’s pulse</td>
</tr>
<tr>
<td>Popliteal SBP – brachial SBP &gt; 60 mmHg</td>
<td>Hill’s sign</td>
</tr>
<tr>
<td>To-and-fro murmur heard over femoral artery w/ light compression</td>
<td>Duroziez’s sign</td>
</tr>
<tr>
<td>Pistol shot sound heard over femoral artery</td>
<td>Pistol shot sounds</td>
</tr>
<tr>
<td>Double sound heard over femoral artery when compressed distally</td>
<td>Traube’s sound</td>
</tr>
<tr>
<td>Systolic pulsations of the uvula</td>
<td>de Musset’s sign</td>
</tr>
<tr>
<td>Subungual capillary pulsations (low Sp)</td>
<td>Quincke’s pulses</td>
</tr>
</tbody>
</table>

**Diagnostic studies**
- **ECG:** LVH, LAD, abnl repolarization; CXR: cardiomegaly ± ascending Ao dilatation
- **Echo:** severity of AI (severe → width of regurgitant jet > 65% LVOT, vena contracta > 0.6 cm, regurg fraction ≥ 50%, regurg orifice ≥ 0.3 cm², flow reversal in descending Ao); LV size & fxn

**Treatment** (Circ 2008;118:e523)
- **Acute decompensation** (consider ischemia and endocarditis as possible precipitants)
  - Surgery usually urgently needed for acute severe AI which is poorly tolerated by LV
  - LV afterload reduction (nitroprusside) and inotropic support (dobutamine)
  - Chronotropic support (↑ HR → ↓ diastole → ↓ time for regurgitation)
  - Pure vasoconstrictors and IABP contraindicated
  - In chronic AI, management decisions based on LV size and fxn (and before sx occur)
- **Surgery (AVR, replacement or repair if possible)**
  - sx (if equivocal, consider stress test) severe AI (if not severe, unlikely to be cause of sx)
  - asx severe AI and EF < 50% or LV dilation (end syst. diam. > 55 mm or end diast. diam. > 75 mm, or > 50 & > 70, respectively, if progression) or undergoing cardiac surgery
  - Medical therapy: **vasodilators** (nifedipine, ACEI, hydralazine) if severe AI w/ sx or LV dysfxn & Pt not operative candidate or to improve hemodynamics before AVR;
  - no clear benefit on clinical outcomes or LV fxn when used to try to prolong compensation in asx severe AI w/ mild LV dilation & nl LV fxn (NEJM 2005:353:1342)
MITRAL REGURGITATION (MR)

Etiology (Lancet 2009;373:1382)
- Leaflet abnormalities: myxomatous degeneration (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs
- Functional: inferoapical papillary muscle displacement due to ischemic LV remodeling or other causes of DCMP; LV annular dilatation due to LV dilation
- Ruptured chordae tendineae: myxomatous, endocarditis, spontaneous, trauma
- Acute papillary muscle dysfunction due to ischemia or rupture during MI [usu. posteromedial papillary m. (supplied by PDA only) vs. anterolateral (suppl. by diags & OMs)]
- HCM (see “Cardiomyopathy”)

Clinical manifestations
- Acute: pulmonary edema, hypotension, cardiogenic shock (NEJM 2004;351:1627)
- Chronic: typically sx 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 examination
- 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)
- Lat. displ. hyperdynamic PML, obscured S1, widely split S2
- Ant. leaflet abnl → post. jet heard at spine
- Post. leaflet abnl → ant. jet heard at sternum
- Lat. disp. hyperdynamic PML, obscured S1, widely split S2
- A2 early b/c ↓ LV afterload; P2 late if PHT; ± S3
- Carotid upstroke brisk (vs. diminished and delayed in AS)

Diagnostic studies
- ECG: LAE, LVH, ± atrial fibrillation
- CXR: dilated LA, dilated LV, ± pulmonary congestion
- Echo: MV anatomy (ie, cause of MR); MR severity: jet area (can underestimate eccentric jets), jet width at origin (“vena contracta”), or effective regurgitant orifice (ERO; predicts survival, NEJM 2005;352:875); LV fxn (EF should be supranormal if compensated, ↓ EF <60% w/ sev. MR → LV dysfxn). TEE if TTE inconclusive or pre/intraop to guide repair vs. replace
- Cardiac cath: prominent PCWP cv waves (not spec. for MR), LVgram for MR severity & EF

<table>
<thead>
<tr>
<th>Classification of Mitral Regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
</tbody>
</table>

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

Treatment (Circ 2008;118:e523; NEJM 2009;361:2261)
- Acute decompensation (consider ischemia and endocarditis as precipitants)
- LV afterload reduction (nitroprusside), ± inotropes (dobutana), IABP, avoid vasoconstrictors surgery usually needed for acute severe MR as prognosis is poor w/o MVR
- Surgery (repair [preferred if feasible] vs. replacement w/ preservation of mitral apparatus) for asx severe MR, asx severe MR and EF 30–60% or LV sys. diam. > 40 mm
- Consider MV repair for asx severe MR w/ preserved EF, esp. if new AF or PHT
- In AF, Maze procedure or pulm vein isolation may → NSR and prevent future stroke
- In Pts undergoing CABG w/ mod/sev fnxal ischemic MS, consider annuloplasty ring placed in coronary sinus (Circ 2006;113:851) under study
- Medical: β benefit (incl ACEI) in asx Pts; indicated if sx but not an operative candidate, ↓ preload (i CHF and MR by ↓ MV orifice): diuretics, nitrates (espec if ischemic/fxnl MR) if LV dysfxn: ACEI, βB (carvedilol), ± biv pacing; maintain SR

MITRAL STENOSIS (MS)

Etiology
- Rheumatic heart disease (RHD): fusion of commissures → “fish mouth” valve from autoimmune rexn to β strep infxn; seen largely in developing world today
- Mitral annular calcification (MAC): encroachment upon leaflets → functional MS
- Congenital, infectious endocarditis w/ large lesion, myxoma, 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, especially 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 examination
• Low-pitched mid-diastolic rumble at apex w/ presystolic accentuation (if not in AF); best
  heard in L lat decubitus position during expiration, c w/ exercise; severity proportional to
duration (not intensity) of murmur
• Opening snap (high-pitched early diastolic sound at apex) from fused leaflet tips;
  MVA proportional to S2–OS interval (tighter valve Sc LA pressure Sc shorter interval)
• Loud S1 (unless MV calcified)

Diagnostic studies
• ECG: LAE (“P mitrale”), ± AF, ± RVH
• CXR: dilated LA (straightening of left heart border, double density on right, left
  mainstem bronchus elevation)
• Echocardiography: estimate pressure gradient (V), RVSP, valve area, valve echo score (0–16, based on
  leaflet mobility & thickening, subvalvular thickening, Ca: exercise TTE if discrepancy
  between sx and severity of MS at rest; TEE to assess for LA thrombus before PMV
• Cardiac cath: V from simultaneous PCWP & LV pressures, calculated MVA; LA
  pressure tall a wave and blunted y descent; PA pressures

Classification of Mitral Stenosis
<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean gradient (mmHg)</th>
<th>MV area (cm²)</th>
<th>PA Systolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>4–6</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Mild</td>
<td>&lt;5</td>
<td>1.5–2</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Moderate</td>
<td>5–10</td>
<td>1–1.5</td>
<td>30–50</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;10</td>
<td>&lt;1</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

Treatment (Circ 2008;118:e523)
• Medical: Na restriction, cautious diuresis, β-blockers, sx-limited physical stress
• Anticoagulation if AF, prior embolism, LA thrombus, or large LA
• Indications for mechanical intervention: heart failure sx w/ MVA ≤1.5 or
  heart failure sx w/ MVA >1.5 but ↑ PASP, PCWP, or MV V w/ exercise, or
  asx Pts w/ MVA ≤1.5 and PHT (PASP >50 or >60 mmHg w/ exercise) or new-onset AF
• Percutaneous mitral valvotomy (PMV): preferred Rx if RHD; MVA doubles, ↓ by 50%;
  ↓MVR if valve score <8, ± mild MR, Ø AF or LA clot (NEJM 1994;331:961; Circ 2002;105:1465)
• Surgical (MV repair if possible, o/w replacement): consider in sx Pts w/ MVA ≤1.5
  if PMV unavailable or contraindicated (mod. MR, LA clot), or valve morphology unsuitable
• Pregnancy: if NYHA class III/IV → PMV, o/w medical Rx w/ low-dose diuretic & βB

MITRAL VALVE PROLAPSE (MVP)
Definition and Etiology
• Billowing of MV leaflet ≥2 mm above mitral annulus in parasternal long axis echo view
• Leaflet redundancy from myxomatous proliferation of spongiosa of MV apparatus
• Idiopathic, familial, and a/w connective tissue diseases (eg, Marfan’s, Ehlers-Danlos)
• Prevalence 1–2.5% of gen. population, ±< (NEJM 1999;341:1), most common cause of MR

Clinical manifestations (usually asymptomatic)
• MR (from leaflet prolapse or ruptured chordae); infective endocarditis; embolic events
• Arrhythmias, rarely sudden cardiac death

Physical exam
• High-pitched, midsystolic click ± mid-to-late systolic murmur
  ↓ LV volume (standing) → click earlier; ↑ LV volume or afterload → click later, softer

Treatment
• Endocarditis prophylaxis no longer recommended (Circ 2007;116:1736)
• Aspirin or anticoagulation if prior neurologic event or atrial fibrillation
**Prosthetic Heart Valves**

**Mechanical (60%)**
- Bileaflet (eg, St. Jude Medical); tilting disk; caged-ball
- Characteristics: very durable (20–30 y), but thrombogenic and require anticoagulation
  - consider if age <~65 y or if anticoagulation already indicated (JACC 2010;55:2413)

**Bioprosthetic (40%)**
- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft
- Characteristics: less durable, but minimally thrombogenic
  - consider if age >~65 y, lifespan <20 y, or contraindication to anticoagulation

**Physical examination**
- Normal: crisp sounds, soft murmur during forward flow (normal to have small ∇)
  - Abnormal: regurgitant murmurs, absent mechanical valve closure sounds

**Anticoagulation** (Circ 2008;118:e523)
- Warfarin
  - low-risk mech AVR: INR 2–3 (consider 2.5–3.5 for 1st 3 mo)
  - mech MVR or high-risk (defined below) mech AVR: INR 2.5–3.5
  - high-risk bioprosthetic: INR 2–3 (and consider for 1st 3 mo in low-risk)
  - high-risk features: prior thromboembolism, AF, EF, hypercoagulable
- ASA (75–100 mg) indicated for all Pts with prosthetic valves; avoid adding to warfarin if h/o GIB, uncontrolled HTN, erratic INR, or >80 y

**Periprocedural “Bridging” of Anticoagulation in Pts with Mechanical Valve(s)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Warfarin Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR w/o risk factors</td>
<td>d/c warfarin 48–72 h before surg; restart 24 h after surg</td>
</tr>
<tr>
<td>MVR or AVR w/ risk factors</td>
<td>Preop: d/c warfarin, start UFH when INR &lt;2</td>
</tr>
<tr>
<td></td>
<td>4–6 h preop: d/c UFH; postop: restart UFH &amp; warfarin ASAP</td>
</tr>
</tbody>
</table>

Procedures include noncardiac surgery, invasive procedures, and major dental work (Circ 2008;118:e523)

**Correction of overanticoagulation** (Circ 2008;118:e626)
- Risk from major bleeding must be weighed against risk of valve thrombosis
- Not bleeding & INR <5: withhold warfarin, do not give vit K, serial INRs
- Not bleeding & INR 5–10: withhold warfarin, vit K 1–2.5 mg PO, serial INRs
- Bleeding or INR >10: FFP ± low-dose (1 mg) vit K IV

**Endocarditis prophylaxis** (see “Endocarditis”)
- Indicated for all prosthetic valves to ↓ IE risk during transient bacteremia

**Complications**
- Structural failure (r/o endocarditis): mechanical valves; rare except for Bjork-Shiley; bioprosthetic valves: up to 30% fail rate w/in 10–15 y, mitral > aortic
- Paravalvular leak (r/o endocarditis); small central jet of regurg is normal in mech. valves
- Obstruction from thrombosis or pannus ingrowth; TTE,TEE and/or fluoroscopy if ↓ clot significantly sx pannus ingrowth: remove w/ surgery
- Fibrinolytic Rx often ineffective for left-sided thrombosis & 12–15% risk of stroke; consider UFH ± lytic if mild sx and small clot burden or poor surg candidate; fibrinolytic therapy reasonable for right-sided thrombosis
- Infective endocarditis = valvular abscess and conduction system disruption
- Embolization (r/o endocarditis): risk ~1%/y w/ warfarin (vs. 2%/w ASA, or 4%/w meds) mech MVR 2× risk of embolic events vs. mech AVR (Circ 1994;89:635)
- Bleeding (from anticoag), hemolysis (especially w/ caged-ball valves or paravalvular leak)

**Heart Valves** (superior view, JAMA 1976;235:1603)
PERICARDIAL DISEASE

GENERAL PRINCIPLES

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

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

PERICARDITIS AND PERICARDIAL EFFUSION

Etiologies of Pericarditis (Lancet 2004;363:717)

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Viral: Coxsackie, echo, adeno, EBV, VZV, HIV, influenza</td>
</tr>
<tr>
<td></td>
<td>Bacterial (from endocarditis, pneumonia, or s/p cardiac surgery): S. pneumococcus, N. meningitidis, S. aureus, Borrelia (Lyme)</td>
</tr>
<tr>
<td></td>
<td>Tuberculous (extension from lung or hematogenous)</td>
</tr>
<tr>
<td></td>
<td>Fungal: Histoplasmosis, Coccidioides, Candida; Parasitic: Entamoeba, Echinococcus</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Common: metastatic (lung, breast, lymphoma, leukemia, renal cell)</td>
</tr>
<tr>
<td></td>
<td>Rare: primary cardiac &amp; serosal tumors (mesothelioma)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Connective tissue diseases: SLE, RA, scleroderma, Sjögren’s Vasculitides: PAN, Churg-Strauss, Wegener’s Drug-induced: procainamide, hydralazine, INH, CsA</td>
</tr>
<tr>
<td>Uremia</td>
<td>Develops in ~20% of pts, especially if on HD. May be transudative.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Acute transmural MI (5–20%); late post-MI (Dressler’s syndrome) Proximal aortic dissection (up to 45%) Chest trauma or s/p cardiac procedure or surgery</td>
</tr>
<tr>
<td>Radiation</td>
<td>&gt;4,000 cGy to mediastinum; acute or delayed; may be transudative.</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Most presumed to be undiagnosed viral</td>
</tr>
<tr>
<td>Effusions w/o pericarditis</td>
<td>CHF, cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis.; Transudative.</td>
</tr>
</tbody>
</table>

Clinical manifestations (NEJM 2004;351:2195)
• Pericarditis: chest pain that is pleuritic, positional (i.e. by sitting forward), radiates to trapezius; may be absent in tuberculous, neoplastic, post-XRT, and uremic pericarditis; ± fever; ± s/s of systemic etiologies
• Effusion: ranges from asx to tamponade (see below)

Physical exam
• Pericarditis: multiphasic friction rub best heard at LLSSB w/ diaphragm of stethoscope (leathery sound w/ up to 3 components: atrial contraction, ventricular contraction, and ventricular relaxation) that is notoriously variable and evanescent
• Effusion: distant heart sounds, dullness over left posterior lung field due to compressive atelectasis from pericardial effusion (Ewart’s sign)

Diagnostic studies (EHJ 2004;24:587; Circ 2006;113:1622)
• ECG: may show diffuse STE (concave up) & PR depression (except in aVR: ST ↓ & PR ↑). TwI; classically and in contrast to STE, TWI do not occur until STs normalize Stages: STE & PR ↓ (I); ST & PR normalize (II); diffuse TWI (III); Tw normalize (IV). May show evidence of large effusion w/ low voltage & electrical alternans (beat-to-beat Δ in QRS amplitude and/or axis).
• CXR: if large effusion (>250 mL of fluid) → ↑ cardiac silhouette w/ “water-bottle” heart and epicardial halo
• Echocardiogram: presence, size, & location of effusion; presence of tamponade physiology; pericarditis itself w/o spec. abnl (i.e. echo can be nl), although can see pericardial stranding (fibrin or tumor); can also detect asx myocarditis
• CT will reveal pericardial effusions, often appearing larger than on echocardiography
• CK-MB or troponin (↑ in ~30%, JACC 2003;42:2144) if myopericarditis

Workup for effusion
• r/o infxn: usually apparent from Hx & CXR; ± acute and convalescent serologies
• r/o noninfectious etiologies: BUN, Cr, ANA, RF, screen for common malignancies
• Pericardioceles if suspect infxn or malignancy or if effusion large (>-2 cm)
  ✔️ cell counts, TR LDH, glc, gram stain & Cx, AFB, cytology
  ADA, PCR for MTb, and specific tumor markers as indicated by clinical suspicion
  “exudate” criteria: TP > 3 g/dL, TP/serum LDH > 0.5, LDH/serum LDH > 0.6, or glc < 60 mg/dL
  high Se (~90%) but very low Sp (~20%); overall low utility (Chest 1997;111:1213)
  Pericardiocentesis if suspicion remains for malignancy or tuberculosis

**Treatment of pericarditis (EHJ 2004;25:387; Circ 2006;113:1622)**

- NSAIDs (eg, ibuprofen 600–800 mg tid) = colchicine 0.5 mg bid (Circ 2005;112:2012)
  sx usually subsides in 1–3 d, continue Rx for 7–14 d (JAMA 2003;289:1150)
- Steroids (usually systemic; occ. intrapericardial) for systemic rheum or autoimmune disorder; uremic, preg., contraindication to NSAID, or refractory idiopathic dis.
  Risks of steroids: ↑ rate of relapse, and ↑ osteoporosis, Cushing’s (Circ 2008;118:667).
  Avoid anticoagulants
- Infectious effusion → pericardial drainage (preferably surgically) + systemic antibiotics
- Acute idiopathic effusion self-limited in 70–90% of cases
- Recurrent effusion → consider pericardial window (percutaneous vs. surgical)

**Pericardial Tamponade**

**Etiology**

- Any cause of pericarditis but especially malignancy, uremia, idiopathic
  proximal aortic dissection with rupture, myocardial rupture
- Rapidly accumulating effusions most likely to cause tamponade as no time for pericardium to stretch (↑ compliance) and accommodate fluid

**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 → pulus 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.

**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 (JAMA 2007;297:1810)**

- Beck’s triad (present in minority): distant heart sounds, ↑ JVP, hypotension
- ↑ JVP (76%) w/ blunted y descent
- Reflex tachycardia (77%), hypotension (26%; occasionally hypertensive), cool extremities
- Pulus paradoxus (Se 82%, Sp 70%) = ↓ SBP ≥10 mmHg during inspiration
  ⊗ LR 3.3 (5.9 if pulsus >12), ⊗ LR 0.03
  Dx = PE, hypovolemia, severe obstructive lung disease, constriction (~1/3), CHF
  Can be absent if pre-existing ↑ LVEDP, cardiac arrhythmia, or regional tamponade
- Distant heart sounds (28%), ± pericardial fricition rub (30%)
- Tachypnea but clear lungs

**Diagnostic studies**

- ECG: ↓ voltage (seen in 42%), electrical alternans, ± signs of pericarditis
- CXR: ↑ cardiac silhouette (89%)
- Echocardiogram: ① 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.)
  post-surgical 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 post-pericardiocelesis ultimate proof of tamponade
  if RA pressure remains elevated after drainage, may have effusive-constrictive disease
  (NEJM 2004;350:469) or myocardial dysfxn (eg, from concomitant myocarditis)

**Treatment**

- Volume (but be careful as overfilling can worsen tamponade) and ② inotropes (avoid βB)
- Pericardiocelesis (except if due to aortic or myocardial rupture, in which cases consider removing just enough fluid to reverse PEA while awaiting surgery)
**Constrictive Pericarditis**

**Etiology**
- Any cause of pericarditis but especially postviral, radiation, uremia, TB, post-cardiac surgery, and idiopathic

**Pathophysiology**
- Rigid pericardium limits diastolic filling → ↑ 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’s 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**
- Right-sided > left-sided heart failure

**Physical exam**
- ↑ JVP with prominent y descent, ⊗ Kussmaul’s sign (Ddx:TS, acute cor pulmonale, RV infarct, RCMP)
- Hepatomegaly, ascites, peripheral edema
- PMI usually not palpable, pericardial knock, usually no pulsus paradoxus

**Diagnostic studies**
- ECG: nonspecific, AF common in advanced cases
- CXR: calcification (MTb most common cause), especially in lateral view (although does not necessarily/constriction)
- Echocardiogram: ± thickened pericardium, “septal bounce” – abrupt posterior displacement of septum during rapid filling in early diastole
- Cardiac catheterization:
  - Atria: Ms or Ws (prominent x and y descents)
  - Ventracles: dip-and-plateau or square-road sign (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
  - Discordance between LV & RV pressure peaks during respiratory cycle (Curr 1996;93:2007)
- CT or MRI: thickened pericardium (~4 mm on CT) with tethering

**Treatment**
- Diuresis for intravascular volume overload, surgical pericardiectomy

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### Constrictive Pericarditis vs. Restrictive Cardiomyopathy

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Constrictive pericarditis</th>
<th>Restrictive cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam</td>
<td>Kussmaul’s sign</td>
<td>± Kussmaul’s sign</td>
</tr>
<tr>
<td></td>
<td>Absent PMI</td>
<td>Powerful PMI, ⊗ S₃ and S₄</td>
</tr>
<tr>
<td></td>
<td>Pericardial knock</td>
<td>± Regurg murmurs of MR, TR</td>
</tr>
<tr>
<td>ECG</td>
<td>± Low voltage</td>
<td>Low voltage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± Conduction abnormalities</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Normal wall thickness</td>
<td>± ↑ wall thickness</td>
</tr>
<tr>
<td></td>
<td>Septal bounce during early diastole</td>
<td>Biventricular enlargement</td>
</tr>
<tr>
<td></td>
<td>Inspir. → ↑ flow across TV and ↓ flow across MV</td>
<td>Inspir. → ↓ flow across TV &amp; MV</td>
</tr>
<tr>
<td></td>
<td>E’ (tissue velocity) nl/↑</td>
<td>Slower peak filling rate</td>
</tr>
<tr>
<td></td>
<td>Expir. hepatic vein flow reversal</td>
<td>Longer time to peak filling rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E’ ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inspir. hepatic vein flow reversal</td>
</tr>
<tr>
<td>CT/MRI</td>
<td>Thickened pericardium</td>
<td>Normal pericardium</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td></td>
<td>LVEDP = RVEDP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prominent x and y descents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dip-and-plateau sign</td>
</tr>
<tr>
<td></td>
<td>RVSP &lt;55 (S90%, Sp 29%)</td>
<td>RVSP &lt;55 mmHg</td>
</tr>
<tr>
<td></td>
<td>RVEDP &gt;½ RVSP (S93%, Sp 46%)</td>
<td>RVEDP &lt;½ RVSP</td>
</tr>
<tr>
<td></td>
<td>Discordance of LV &amp; RV pressure peaks during respiratory cycle</td>
<td>Concordance of LV &amp; RV pressure peaks during respiratory cycle</td>
</tr>
<tr>
<td></td>
<td>Systolic area index (ratio of RV to LV pressure-time area in inspir vs. expir) &gt;1.1 (S97%, Sp 100%)</td>
<td>Systolic area index ≤1.1 (JACC 2008;51:315)</td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>Usually normal</td>
<td>± Specific etiology of RCMP</td>
</tr>
</tbody>
</table>
HYPERTENSION

JNC VII Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-HTN</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

BP should be determined by making ≥2 measurements separated by >2 min. Confirm stage 1 w/in 2 mo; can Rx stage 2 immediately. (JAMA 2003:289:2560; JNC VIII forthcoming)

Epidemiology (JAMA 2003:290:199)
- Prevalence 30% in U.S. adults; ~65 million affected (29% in whites, 33.5% in blacks)
- 60% of those w/ HTN are on Rx, only half of whom are adequately controlled

Etiologies
- Secondary: Consider if Pt <20 or >50 y or if sudden onset, severe, refractory or c HTN

Secondary Causes of Hypertension

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Suggestive Findings</th>
<th>Initial Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal renal parenchymal</td>
<td>h/o DM, polycystic kidney disease, glomerulonephritis</td>
<td>CrCl, albuminuria</td>
</tr>
<tr>
<td>Renovascular (1–2%)</td>
<td>ARF induced by ACEI/ARB</td>
<td>MRA (&gt;90% Se &amp; 5p), CTA, duplex U/S, angio, plasma renin (low Sp)</td>
</tr>
<tr>
<td>Pheochromocytoma (&lt;1%)</td>
<td>Paroxysmal HTN, H/A, palp.</td>
<td>See “Adrenal Disorders”</td>
</tr>
<tr>
<td>Myxedema (&lt;1%)</td>
<td>See Thyroid Disorders</td>
<td>TTFs</td>
</tr>
<tr>
<td>Hyperaldosterone Cushing (1–5%)</td>
<td>Hypokalemia, Metabolic alkalosis</td>
<td>ICa</td>
</tr>
<tr>
<td>Pheochromocytoma (&lt;1%)</td>
<td>Paroxysmal HTN, H/A, palp.</td>
<td>See “Adrenal Disorders”</td>
</tr>
<tr>
<td>Myxedema (&lt;1%)</td>
<td>See Thyroid Disorders</td>
<td>TTFs</td>
</tr>
<tr>
<td>Hypercalcemia (&lt;1%)</td>
<td>Polyuria, dehydration, Δ MS</td>
<td>ICa</td>
</tr>
<tr>
<td>Obstructive sleep apnea (qv)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medications: OCP, steroids, licorice; NSAIDs (espec. COX-2); Epo; cyclosporine

Complications of HTN
- Each ↑ 20 mmHg SBP or 10 mmHg DBP → 2 ↑ CV complications (Lancet 2002:360:1903)
- Neurologic: TIA/CVA, ruptured aneurysms
- Cardiac: CAD, LVH, CHF
- Vascular: aortic dissection, aortic aneurysm
- Renal: proteinuria, renal failure

Treatment (NEJM 2003:348:610)
- Goal: <140/90 mmHg; if DM or renal disease goal is <130/80 mmHg
- Treatment results in 50% ↓ CHF, 40% ↓ stroke, 20–25% ↓ MI (Lancet 2000:356:1955); benefits of Rx'ing stage II HTN extend to Pts >80 y (NEJM 2008:358:1887)
- Lifestyle modifications (each ↓ 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)
  - sodium restriction: ≤2.4 g/d and ideally ≤1.5 g/d (NEJM 2010:362:2102)
  - limit alcohol consumption: ≤2 drinks/d in men; ≤1 drink/d in women & lighter-wt Pts

Standard workup
- Goals: (1) identify CV risk factors or other diseases that would modify prognosis or Rx; (2) reveal 2 causes of hypertension; (3) assess for target-organ damage
- History: CAD, CHF, TIA/CVA, PAD, DM, renal insufficiency, sleep apnea; FHx for HTN
- Physical exam: BP in both arms; funduscopic, cardiac (LVH, murmurs), vascular, abdominal (masses or bruits), neurologic
- Laboratory tests: K, BUN, Cr, Ca, glc, Hct, U/A, lipids, TSH, ECG (for LVH), CXR, urinary albumin:creatinine (if appropriate)
• Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia

Treatment

• Metabolized to cyanide

• Tailor goals to clinical context (eg, more rapid lowering for Ao dissection)

• Sympathomimetics: cocaine, amphetamines, MAO inhibitors

• Endocrine: pheochromocytoma, Cushing’s

• Progression of essential HTN

Precipitants

• Hypertensive emergency

• Pregnancy: methyldopa, labetalol; other

Hypertensive urgency

• Cerebral injury (do

• Urgency:

Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

• Thiocyanate levels. Hydroxocobalamin or sodium thiosulfate infusion for treatment of cyanide toxicity.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside*</td>
<td>0.25–10 μg/kg/min</td>
<td>Captopril</td>
<td>12.5–100 mg tid</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>17–1000 μg/min</td>
<td>Labetalol</td>
<td>200–800 mg tid</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20 mg load → 20–80 mg IVB q10min or 0.5–2 mg/min</td>
<td>Clonidine</td>
<td>0.2 mg load → 0.1 mg qh</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10–20 mg q20–30min</td>
<td>Hydralazine</td>
<td>10–75 mg qid</td>
</tr>
<tr>
<td>Esmolol</td>
<td>500 μg/kg load → 25–300 μg/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.1–1.6 μg/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>5–15 mg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenotiamine</td>
<td>5–15 mg bolus q5–15min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 ANEURYSM

Definitions
- True aneurysm (involves all 3 layers of aorta) vs. false (rupture contained in adventitia)
- Location: root (annuloaortic ectasia), thoracic aortic aneurysm (TAA), thoracoabdominal aortic aneurysm, abdominal aortic aneurysm (AAA)
- Type: fusiform (circumferential dilation) vs. saccular (localized dilation)

Epidemiology (Circ 2005;111:1816 & 2008;117:242)
- Aortic aneurysms 13th leading cause of death in U.S. (~15,000 deaths/y from ruptures)
- TAA: ~1.7:1; usually involves root/asc Ao or descending Ao (arch & thoracoabdominal rare)
  - Risk factors: HTN, atherosclerosis, aortitis (Takayasu’s, GCA, spondyloarthropathies, syphilis); congenital (bicuspid AoV, Turner’s); connective tissue diseases (Marfan, Ehlers-Danlos type IV); familial; chronic Ao dissection; trauma
- AAA: 5% prev. in individuals >65 y; 5–10× more common in δ than γ; most infrarenal
  - Risk factors = risk factors for atherosclerosis: smoking, HTN, hyperlipidemia, age, FHx

Pathophysiology (NEJM 2009;361:1114; Not Med 2009:15-649)
- LaPlace’s law: tension across a cylinder ~ [(ΔP × r) / (wall thickness)]
- TAA: cystic medial necrosis (medial degeneration, mucoid infiltration, apoptosis)
- AAA: atherosclerosis & inflammation → matrix degeneration → medial weakening
- Inflammatory and infectious (“mycotic”) aneurysms rare

Screening (JAMA 2009;302:2015)
- TAA: no established population screening guidelines
- AAA: ✓ for pulsatile abdominal mass in all Pts; U/S for all men >60 y w/ FHx of AAA

Diagnostic studies (Circ 2005;111:816)
- Contrast CT: quick, noninvasive, good Se & Sp for all aortic aneurysms
- CXR: often abnormal, but not definitive in TAA
- Abdominal ultrasound: screening and surveillance test of choice for AAA
- TTE/TEE: useful for root and rest of TAA
- MRI: preferred for aortic root imaging for TAA, but also useful in AAA

Treatment (Circ 2006;113:e463; 2008;177:1883; 2010;121:1544)
- Risk factor modification: smoking cessation, LDL-C <70 mg/dL; β-blocker or tetracyclines (inhibit MMPs, anti-Chlamydia)
- BP control: β-blockers (↓ dP/dt) ↓ aneurysm growth (NEJM 1994;330:1335); ACEI a/w ↓ risk of rupture (Lancet 2006;368:659), ARB may ↓ rate of aortic root growth in Marfan (NEJM 2008;358:2787); no burst activity/exercise requiring Valsalva maneuvers (eg, heavy lifting)
- Surgery
  - TAA: symptomatic, ascending ≥5.5 cm; descending >6 cm; Marfan Pt ≥4.0–4.5 cm; growing >0.5 cm/y; aneurysm ≥4.5 cm and planned AoV surgery
  - AAA: ≤5 cm; rapidly growing; infrarenal/juxtarenal ≥5.5 cm (NEJM 2002;346:1437)
- Endovascular aneurysm repair (EVAR) (NEJM 2008;358:494)

Complications
- Pain: gnawing chest, back, or abdominal pain
- Rupture: risk ↑ w/ diameter, female sex, current smoking, HTN
  - TAA: ~2.5%/y if <6 cm vs. 7% if >6 cm; AAA: ~1%/y if <5 cm vs. 6.5% if 5–5.9 cm may be heralded by ↓ pain; once occurs, usually fatal or Pt may p/w severe constant pain and in hemorrhagic shock; 90% mortality
- Aortic Dissection (see following section)
- Thromboembolic ischemic events
- Compression of adjacent structures (eg, SVC, trachea, esophagus)

Follow-up
- Expansion rate ~0.1 cm/y for TAA, ~0.4 cm/y for AAA
- Serial imaging first 3, 6, 9, & 12 mo, then annually
- Screening for CAD, PAD, and aneurysms elsewhere, espec. popliteal. 25% of Pts w/ TAA will also have AAA.
ACUTE AORTIC SYNDROMES

Definitions (Circ. 2003;108:628)
• Classic dissection: intimal tear → extravasation of blood into aortic media
• Incomplete dissection: intimal-medial tear without significant intramural extravasation
• Intramural hematoma (IMH): vasa vasorum rupture → medial hemorrhage
• Penetrating ulcer: ulceration of plaque penetrating intima → medial hemorrhage

Classification
• Proximal: involves ascending Ao, regardless of origin (― Stanford A, DeBakey I & II)
• Distal: involves descending Ao only, distal to subclavian art. (― Stanford B, DeBakey III)

Risk factors
• Hypertension (h/o HTN in >70% of dissections); male sex (70% male)
• Connective tissue disease: Marfan (fibrillin); arachnodactyly, joint disloc., pectus, ectopia lentis, MVP; Ehlers-Danlos type IV (type III procollagen); translucent skin; bowel or uterine rupture; Loys-Dietz; annuloaortic ectasia, familial AoD; PCKD
• Congenital aortic anomaly: bicuspid aortic valve or coarctation (eg, in Turner’s)
• Aortitis: Takayasu’s, giant cell arteritis, Behçet’s, syphilis
• Pregnancy: typically in 3rd trimester; can also see spont. coronary artery dissections
• Trauma: blunt, IABP, cardiac or aortic surgery, cardiac catheterization

<table>
<thead>
<tr>
<th>Feature</th>
<th>Proximal</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Aortic” pain (often severe, tearing or ripping pain, maximal at onset [vs. crescendo for ACS])</td>
<td>94% (chest, back)</td>
<td>98% (back, chest, abd)</td>
</tr>
<tr>
<td>Syncope (often due to tamponade)</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>CHF (usually AI)</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>CVA</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35%</td>
<td>70%</td>
</tr>
<tr>
<td>Hypotension/shock (tamponade, AI, MI, rupture)</td>
<td>25%</td>
<td>4%</td>
</tr>
<tr>
<td>Pulse deficit</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>AI murmur</td>
<td>44%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Diagnostic studies (Circ 2005;112:3802)
• Check bilateral BP and radial pulses for symmetry
• CXR: abnormal in 60–90% (mediastinum, effusion), but cannot be used to r/o dissection
• CT: quick, noninvasive, good Se (80% for proximal; 90–95% for distal); multidetector CT may improve Se; however, if & high clin. suspicion → additional studies
• TEE: Se >95% for proximal, 80% for distal; can assess coronaries, pericardium, AI
• MRI: Se & Sp >98%, but time-consuming & not readily available
• Aortography: Se ~90%, time-consuming, cannot detect IMH; can assess branch vessels
• D-dimer: <500 ng/mL may help r/o dissection when sx <24 h (Circ 2009;119:2702)

Treatment (Lancet 2008;372:55; Circ 2010;121:1544)
• Medical: ↓ dP/dt targeting HR ~60 and SBP 100–120 first with IV β-blockers (eg, propranolol, esmolol, labelol) to blunt reflex ↑ HR & inotropy that will occur in response to vasodilators then ↓ SBP with IV vasodilators (eg, nitroprusside) control pain with MSO, prn
• Surgery proximal (root replacement): all acute; chronic if c/b progression, AI or aneurysm distal: if c/b progression, signif. branch artery involvement, uncontrolled HTN, aneurysm
• Endovascular options: covered stent to seal entry; bare-metal stent to restore flow down compromised branches; fenestration of false lumen

Complications
• Rupture: pericardial sac → tamponade (avoid pericardiocentesis unless shock/PEA); pleural space; mediastinum; retroperitoneum
• Obstruction of branch artery can be static (avulsed/thrombosed) or dynamic (Δs in pressure in true vs. false lumen) coronary → MI (usually RCA → IMI, since dissection often occurs along outer 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 → acute renal failure
• AI: due to annular dilatation or disruption or displacement of leaflet by false lumen
• Mortality: 1–2%/h × 48 h for acute proximal; 10% at 30 d for acute distal
ARRHYTHMIAS

BRADYCARDIAS, AV BLOCK, AND AV DISSOCIATION

Sinus bradycardia (SB) (NEJM 2000;342:703)
- Etiologies: meds (incl βB, CCB, amio, Li, dig), ↑ vagal tone (incl. athletes, sleep, IMI), metabolic (hypoxia, sepsis, myxedema, hypothermia, ↓ glc), OSA, ↑ ICP
- Treatment: usually none required; atropine 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

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Mobitz I</td>
<td>Prolonged PR (-200 ms), all atrial impulses conducted (1:1).</td>
</tr>
<tr>
<td>2° Mobitz II</td>
<td>Progressive ↑ PR until impulse not conducted (→ “grouped beating”). Abnl AV node due to ischemia (IMI), inflammation (myocarditis, 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). AVB usually worsens w/ carotid sinus massage, improves w/ atropine. Often paroxysmal/asx, no Rx required.</td>
</tr>
<tr>
<td>2° Mobitz III</td>
<td>Occasional or repetitive blocked impulses w/ consistent PR interval. Abnl His-Purkinje system due to ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation/AoV surgery. AVB usually improves w/ carotid sinus massage, worsens w/ atropine. Often progresses to 3° AVB. Pacing wire or PPM often required.</td>
</tr>
<tr>
<td>3° (complete)</td>
<td>No AV conduction. Escape, if present, narrow (jxnal) or wide (vent.)</td>
</tr>
</tbody>
</table>

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's non-conducting)

SUPRAVENTRICULAR TACHYCARDIAS (SVTs)

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia (ST)</td>
<td>Caused by pain, fever, hypovolemia, hypoxia, anemia, anxiety, β-agonists, etc.</td>
</tr>
<tr>
<td>SA node reentrant tachycardia (SANRT)</td>
<td>Rare. Reentrant loop w/in SA node, discern from ST by rapid onset &amp; termination.</td>
</tr>
<tr>
<td>Atrial tachycardia (AT)</td>
<td>Originate at site in atria other than SA node. Seen w/ CAD, COPD, ↑ catechols, EtOH, dig.</td>
</tr>
<tr>
<td>Multifocal atrial tachycardia (MAT)</td>
<td>↑ automaticity at multiple sites in the atria</td>
</tr>
<tr>
<td>Atrial flutter (AFL)</td>
<td>Macroleotropy, usually w/in tricuspid annulus</td>
</tr>
<tr>
<td>Atrial fibrillation (AF)</td>
<td>Wavelets irregularly passing down AVN, often originate from the pulmonary veins</td>
</tr>
<tr>
<td>AV nodal reentrant tach (AVNRT)</td>
<td>Reentrant circuit using dual pathways w/in AVN</td>
</tr>
<tr>
<td>Atrioventricular reciprocating tachycardia (AVRT)</td>
<td>Reentrant circuit using AVN and accessory pathway. Orthodromic (conducts down AVN; usually narrow QRS) vs. antidromic (conducts down accessory path; wide QRS).</td>
</tr>
<tr>
<td>Nonparoxysmal junctional tachycardia (NPJT)</td>
<td>↑ automaticity at AV junction May see retrograde P waves or AV dissociation Seen in myo/endocarditis, cardiac surg, IMI, dig.</td>
</tr>
</tbody>
</table>
**Treatment of SVT**

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Acute treatment</th>
<th>Long-term treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable</td>
<td>Cardioversion per ACLS</td>
<td>n/a</td>
</tr>
<tr>
<td>ST</td>
<td>Treat underlying stressor(s)</td>
<td>n/a</td>
</tr>
<tr>
<td>AT</td>
<td>β-blockers, CCB, or amiodarone</td>
<td>β-blockers or CCB, ± antiarrhythmics ± Radiofrequency ablation</td>
</tr>
<tr>
<td>AVNRT or AVRT</td>
<td>Vagal maneuvers</td>
<td>For AVNRT (see next section for AVRT): Radiofrequency ablation CCB or β-blockers (chronic or prn) ± Class IC antiarrhythmics (if nl heart)</td>
</tr>
<tr>
<td>NPJT</td>
<td>CCB, β-blockers, amiodarone</td>
<td>Rx underlying dis. (eg, dig tox, ischemia)</td>
</tr>
<tr>
<td>AF</td>
<td>β-blockers, CCB, digoxin, AAD</td>
<td>See “Atrial Fibrillation”</td>
</tr>
<tr>
<td>AFL</td>
<td>β-blockers, CCB, digoxin, AAD</td>
<td>Radiofrequency ablation β-blockers or CCB ± antiarrhythmics</td>
</tr>
<tr>
<td>MAT</td>
<td>CCB or β-blockers if tolerated</td>
<td>Treat underlying disease process</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± AVN ablation + PPM</td>
</tr>
</tbody>
</table>

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

- **Catheter ablation** has high overall success rate (AFL/AVNRT ~ 95%, AF ~ 80%)
- Complications: stroke, MI, bleeding, perforation, conduction block (JAMA 2007;290:2768)

**ACCESSORY PATHWAYS (WOLFF-PARKINSON-WHITE)**

- **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 MI); only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde then ECG will be normal during SR; “concealed” bypass tract)
- **WPW syndrome**: accessory pathway + paroxysmal tachycardia

---

**Diagnosis of SVT Type** (NEJM 2006;354:1039)

- **Onset**: Abrupt onset/offset suggests reentry (AVNRT, AVRT, SANRT)
- **Rate**: Not diagnostic as most SVTs can range from 140–250 bpm, but:
  - ST usually <150 bpm; AFL often conducts 2:1 → ventricular rate 150 bpm
  - AVNRT & AVRT are usually >150 bpm
- **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 V1)
    - AVRT: slightly after but usually distinct from QRS
  - Usually short RP interval (<1/2 RR), but can be long RP
  - Fibrillation or no P waves → AF
    - Saw-toothed “F” waves (best seen in inferior leads & V1) → AFL
- **Response to vagal stim. or adenosine**: ↑ automaticity rhythms (ST, AT, MAT) → slow rate or ↑ AV block
  - AVN reentry (AVNRT, AVRT) → abruptly terminate (classically with a P wave after last QRS) or no response
  - AFL → ↑ AV block → unmasking of “F” waves

---

**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 MI); only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde then ECG will be normal during SR; “concealed” bypass tract)
- **WPW syndrome**: accessory pathway + paroxysmal tachycardia
Tachycardias

- **Orthodromic AVRT**: narrow-complex SVT (typically), conducting ↓ AVN & ↑ accessory pathway; requires retrograde conduction and ↓ can occur w/ concealed bypass tracts
- **Antidromic AVRT**: wide-complex SVT, conducting ↓ accessory pathway & ↑ AVN; requires antegrade conduction and ↓ should see WPW pattern during SR
- **AF with rapid conduction down accessory pathway**: wide-complex irregular SVT; requires antegrade conduction and ↓ should see WPW pattern during SR

**Treatment**

- **AVRT**: vagal maneuvers, β-blockers and calcium channel blockers, caution w/ adenosine (can precip. AF); have defibrillator ready
- **AF/AFL** w/ conduction down accessory pathway: need to Rx arrhythmia and ↓ pathology refractoriness; use procainamide, ibutilide, flecainide or cardiovert; avoid CCB & β-blockers (ineffective) and digi/adenosine (can ↓ refractoriness of pathway → ↑ vent. rate → VF)
- **Long term**: Rx tachycardias w/ radiofrequency ablation or antiarrhythmics (IA, IC) consider pathway ablation if ax as yet AVRT or AF inducible on EPS (NEJM 2003;349:1803)

**Wide-Complex Tachycardias (WCTs)**

**Etiologies**

- **Ventricular tachycardia (VT)**
- **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 V1 – RBBB-type vs. downward – LBBB-type
- **Etiologies in a structurally abnormal heart**: prior MI (scar); CMP, myocardiitis, arrhythmogenic RV CMP (ARVC): incomplete RBBB, R wave (terminal notch in QRS) & TWI in V1,3 on resting ECG, LBBB-type VT, dx w/ MRI (Lancet 2009;373:1289)
- **Etiologies in a structurally normal heart**: RVOT VT: normal resting ECG, LBBB-type VT w/ inferior axis; idiopathic LV VT (respects 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 (eg, meds, lyes, see "ECG") or congenital (K/Na channelopathies; Tw abnl; TdP triggered by sympathetic stim [exercise, emotion, sudden loud noises]; Lancet 2008;372:750)

**Brugada syndrome** (Na channelopathy): pseudo-RBBB w/ STE in V1,3 (provoked w/ 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 VT
- **MMVT is regular, but initially it may be slightly irregular, mimicking AF w/ aberrancy; grossly irregularly irregular rhythm suggests AF w/ aberrancy**
- **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 typical for BBB (RBBB-type: absence of tall R’ [or presence of monophasic R]) in V1, r/S ratio <1 in V6; normal LBBB-type: onset to nadir >60–100 ms in V1, q wave in V6
  - **Concordance** (QRS in all precordial leads w/ same pattern/direction)

**Long-term management** (JACC 2006;48:1064)

- **Workup**: echo to LV size, 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**: prevention after documented VT/VF arrest (unless due to reversible cause)
  - 1st prevention if high-risk, eg, EF <30–35% (see "Heart Failure"); ARVD, Brugada, certain long QT syndromes, severe HCMP
- **Medications**: β-blockers (espec for LQTS), antiarrhythmics (eg, amiodarone) to suppress recurrent VT, triggering ICD firing, or if not ICD candidate, anti-tachycardic pacing
- If med a/w Tdp → QT >500 ± VPBs: d/c med, replete K, give Mg, pacing (JACC 2010;55:934)
- **Radiofrequency ablation** if isolated VT focus, or if recurrent VT triggering ICD firing; ablation before ICD implantation i discharge rate by 40% (Lancet 2010;375:31)
ATRIAL FIBRILLATION

Classification (JACC 2006;48:e149)
- Paroxysmal (self-terminating) vs. persistent (sustained >7 d) vs. permanent (typically >1 y and when cardioversion has failed or is foregone)
- Valvular (rheumatic MV disease, prosthetic valve, or valve repair) vs. nonvalvular
- Lone AF – age <60 y and w/o clinical or echo evidence of cardiac disease (including HTN)

Epidemiology and Etiologies (Annals 2008;149:ITC5-2)
- ~1% of population has recurrent AF (8% of elderly); mean age at presentation ~75 y
- Acute (up to 50% w/o identifiable cause)
  - Cardiac: CHF, myo/pericarditis, ischemia/MI, hypertensive crisis, cardiac surgery
  - Pulmonary: acute pulmonary disease or hypoxia (eg, COPD flare, pneumonia), PE
  - Metabolic: high catecholamine states (stress, infection, postop, pheo), thyrotoxicosis
  - Drugs: alcohol (“holiday heart”), cocaine, amphetamines, theophylline, caffeine
  - Neurogenic: subarachnoid hemorrhage, ischemic stroke
- Chronic: ↑ age, HTN, ischemia, valve dis. (MV, TV, AoV), CMP, hyperthyroidism, obesity

- Commonly originates from ectopic foci in atrial “sleeves” in the pulmonary veins
- Loss of atrial contraction → HF; LA stasis → thromboemboli; tachycardia → CMP

Evaluation
- H&P, ECG, CXR, echo (LA size, ? thrombus, valves, LV fxn, pericardium), K, Mg, FOBT
  before anticoag, TFTs, ? r/o ischemia (AF unlikely due to ischemia in absence of other sx)

Figure 1-5 Approach to acute AF

New or Recent-Onset AF → unstable → Urgent cardioversion
→ stable
  ↓

1. Rate Control
   (IB or CCB (see Table))

2. Anticoagulate
   IV UFH if admitting & cardioverting o/w oral anticoag

3. Cardiovert
   Cardioversion (electrical and/or pharmacologic)

AF <48 hrs & low risk of stroke
AF >48 hrs (or unknown) or high risk of stroke

Empiric oral anticoag x≥3 wks
TEE LA thromb. cardioversion → oral anticoag x≥4–12 wks

Rate Control for AF (Goal HR 60–80, 90–115 with exertion)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Acute (IV)</th>
<th>Maint. (PO)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>5–10 mg over 2'/ may repeat in 30'</td>
<td>120–360 mg/d in divided doses</td>
<td>↓ BP (Rx w/ Ca gluc) Watch for CHF</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg over 2' may repeat after 15' 5–15 mg/h infusion</td>
<td>120–360 mg/d in divided doses</td>
<td>Preferred if COPD Can ↓ dig levels</td>
</tr>
</tbody>
</table>

βB

| Metoprolol | 5 mg over 2' may repeat q5' × 3 | 25–100 mg bid or tid | ↓ BP (Rx w/ glucagon) Watch for CHF & bronchospasm Preferred if CAD |
| Propranolol | 1 mg q2' | 80–240 mg/d in divided doses |

Digoxin (takes hrs) | 0.25 mg q2h up to 1.5 mg | 0.125–0.375 mg qd (adj for Cr/Cr) |

Amiodarone | 150 mg over 10' → 0.5–1 mg/min |

IV βB, CCB, and digoxin contraindicated if evidence of WPW (e., pre-excitation or WCT) since may facilitate conduction down accessory pathway leading to VF; procaainamide 1st line Rx
Strategies for recurrent AF

- **Rate control**: goal HR typically 60–80 at rest (although no clear benefit vs. goal <110, NEJM 2010;362:1363) and 90–115 w/ exertion (see above table for options)
- AV node ablation + PPM as a last resort (NEJM 2001;344:1043; NEJM 2002;346:2062)
- **Rhythm control**: no clear survival benefit vs. rate ctrl (NEJM 2002;347:1825 & 2008;358:2667)
- **Anticoag** (if indicated) to prevent thromboemboli, whether rate or rhythm strategy

**Antithrombotic Therapy**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Conversion</th>
<th>Maintenance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>5–7 mg/kg IV over 30–60' to achieve 10-g load</td>
<td>200–400 mg qd (most effective drug)</td>
<td>QT, PFTs, LFTs, TFTs</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>n/a</td>
<td>400 mg bid</td>
<td>QT, contraind severe CHF, side effects c/w amio, efficacy but also CV mort</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1 mg IV over 10' may repeat × 1</td>
<td>n/a</td>
<td>Contraindic. if ÷ K or ÷ QT</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>0.5 mg PO bid</td>
<td>0.5 mg bid</td>
<td>QT, risk of TdP</td>
</tr>
<tr>
<td>Sotalol</td>
<td>n/a</td>
<td>90–160 mg bid</td>
<td>for ÷ HR, ÷ QT</td>
</tr>
<tr>
<td>IC Flecainide</td>
<td>300 mg PO × 1</td>
<td>100–150 mg bid</td>
<td>PreRx w/ AVN block</td>
</tr>
<tr>
<td>Propafenone</td>
<td>600 mg PO × 1</td>
<td>150–300 mg tid</td>
<td>Contraindic. if structural or ischemic heart disease</td>
</tr>
<tr>
<td>IA Procainamide</td>
<td>10–15 mg/kg IV over 1 h</td>
<td>1–2 g bid of slow release</td>
<td>BP, ÷ QT</td>
</tr>
</tbody>
</table>


- **Lone AF**: class IC drugs or sotalol, ÷ statins
- **CAD**: class III drugs
- **CHF**: doxifylline or amiodarone (NEJM 2007;356:935)

**Antiarrhythmic Drugs (AAD) for AF**

- **Cardioversion**: Consider pharm or DC cardioversion w/ 1st AF episode of if sx;
  if AF >48 h, 2–5% risk stroke w/ cardioversion (pharm. or electric)
  ÷ either TEE or r/o thrombus or therapeutic anticoagulation for ≥3 wks prior
  - Likelihood of success dependent on AF duration (better <7 d) and atrial size
- **Consider pre-Rx w/ antiarrhythmic drugs** (especially if 1st attempt fails)
- For pharmacologic cardioversion, class III and IC drugs have best proven efficacy
- Even if SR returns, atria mechanically stunned. Also, greatest likelihood of recurrent AF in first 3 mos after return to SR. ÷ must anticoagulate postcardioversion ≥4–12 wks.
  - “Pill-in-pocket”: if IC drugs have been safely tolerated in Pts w/o ischemic or structural heart disease, can take as outPt prn if recurrent sx AF (NEJM 2004;351:2384)

**Nonpharmacologic therapy**

- **Radiofrequency ablation** (circumferential pulm. vein isolation): ~80% success; consider if ÷ EF or AADs failed/contraindic (NEJM 2006;354:934, JAMA 2005;292:2634 & 2010;303:333)
- Surgical “maze” procedure (70–95% success rate) option if undergoing cardiac surgery
- **Left atrial appendage closure** if undergoing cardiac surgery ÷ risk of stroke; percutaneous closure may be comparable to warfarin and w/ ÷ risk ofICH (Lancet 2009;374:534)

**Anticoagulation**

(NEJM 2006;48:e149; Chest 2008;133:546)

- **Risk of stroke**: ~4.5% per year in nonvalvular AF; risk factors include:
  - CHADS₂: CHF (1 point), HTN (1), Age >75 y (1), DM (1), prior Stroke/TIA (2)
  - echo: EF ≥35%, dense spontaneous echo contrast in LAA, ↑ LA size, ÷ Ao athero
- **Risk of stroke**: ↑ in valvular AF. ÷ anticoagulate all
- **Rx options**: warfarin (INR 2–3) → 68% ↓ stroke (heparin → warfarin bridge if h/o stroke)
  - ASA (81–325 mg/d): better than placebo (21% ↓ stroke) but inferior to warfarin
  - clopi inferior to warfarin but ↓ stroke (Ì bleed) c/w ASA alone (NEJM 2009;360:2066)
  - dabigatran (oral direct thrombin inhib): 100 mg bid = efficacy & ÷ bleeding and 150 mg bid ↓ stroke and ÷ bleeding c/w warfarin (w/o need to √ INR, RE-LY, NEJM 2009;361:1139)
- Whom to Rx: valvular AF, prior stroke/TIA, or ≥2 risk factors → warfarin

1. **risk factor** → warfarin or ASA; 0 risk factors → ASA.
2. **if not good candidate for warfarin (÷ risk of bleeding)** → ASA + ÷ clopidogrel if require ASA + clopi + warfarin (eg, AF & s/p recent stenting) INR 2–2.5, ASA 75–81 mg/d
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)

Etiologies (NEJM 2002;347:878; JACC 2006;47:473; Eur Heart J 2009;30:2631)
• Neurocardiogenic (a.k.a. vasovagal, ~20%; NEJM 2003;350:1049): 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 related disorder: carotid sinus hypersensitivity

• Orthostatic hypotension (10%)
  hypovolemia, diuretics, deconditioning vasodilators (espec. if combined w/ chronotropes)
autonomic neuropathy (1º = Parkinson’s, Shy-Drager, Lewy body dementia, POTS; 2º = diabetes, EtOH, amyloidosis, renal failure) (NEJM 2008;358:615)

• Cardiovascular
  Arrhythmia (15%)
  Bradyarrrhythmias: SSS, high-grade AV block, chronotropes, PPM malfunction
  Tachyarrrhythmias: VT, SVT (syncope rare unless structural heart disease or WPW)
  Mechanical (5%)
  Endocardial: AS, MS, PS, prosthetic valve thrombosis, myxoma
  Myocardial: pump dysfxn from MI or outflow obstruction from HCM (but usually VT)
  Pericardial: tamponade
  Vascular: PE, PHT, aortic dissection, ruptured AAA, subclavian steal

• Neurologic (10%): seizure (technically not syncope), TIA/CVA, vertebrobasilar insufficiency, dissection of cerebral arteries, migraine, narcolepsy
• No cause identified in ~40% of cases
• Misc. causes of LOC (but not syncope): hypoglycemia, hypoxia, anemia, 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, HCM, PHT), positional ↓ (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, post-ictal, bowel or bladder incontinence) convulsive activity for < 10 sec may occur with transient cerebral hypoperfusion
• 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
  vasodilators: α-blockers, nitrates, ACEI/ARB, CCB, hydralazine, phenothiazines, antidep. diuretics; β-chronotropes (eg, β-blockers and CCB)
proarrhythmic or QT prolonging: class IA, IC, or III antarrhythmics, et al. (see “ECG”) psychoactive drugs: antipsychotics, TCA, barbiturates, benzodiazepines, EtOH

• Family history: CMP, SCD

• 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, S3), murmurs, LVH (S4, LV heave), PHT (RV heave, ↑ Pa) vascular exam: ∇ for asymmetric pulses, carotid bruits, carotid sinus massage neurologic exam: focal findings, evidence of tongue biting; fecal occult blood test
• ECG (afltnitively identifies cause of syncope in ~10%)
  sinus bradycardia, sinus pauses, AVB, BBB, SVT, VT ischemic changes (new or old); atrial or ventricular hypertrophy markers of arrhythmia: ectopy, ↑ QT, preexcitation (WPW), Brugada, e wave (ARVC)

Other diagnostic studies (consider ordering 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%); ax but not signif. arrhythmia (13%); sx but no arrhythmia (17%)
  Event recorder (activated by Pt to record rhythm strip): useful for infrequent events, but problematic if no prodrome; yield 20–50% over 30–60 d of monitoring
Loop recorders (continuously save rhythm strip and can be activated after an event): useful for infrequent events including w/o prodrome (Mayo Clin Proc 2008:83:1280).

Implantable loop recorders (inserted SC; can record up to 3 y): useful for very infrequent events; yield 90% after 1 y (JACC 2003:92:131)

- Echo: r/o structural heart disease (eg, CMP [incl HCMP & ARVD], valvular disease [incl AS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- ETT: esp. w/ exertional syncope; r/o ischemia- or catecholamine-induced arrhythmias
- Cardiac catheterization: consider if noninvasive tests suggest ischemia
- Electrophysiologic studies (EPS) consider if arrhythmia detected, if structural heart disease, or if CAD (esp. with low EF) 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 (provocative test for vasovagal syncope): r/o other causes first in 50% w/ recurrent unexplained syncope; Se 26–80%, Sp ≥ 90%; reprod. ≥ 80%
- Cardiac MRI: helpful to dx ARVC if suggestive ECG, echo (RV dysfxn), or FH of SCD
- Neurologic studies (cerebrovascular studies, CT, MRI, EEG): if H&P suggestive; low yield

Figure 1-6 Approach to syncope

High-risk features (usually warrant admission with telemetry & further testing)
- Age >60 y, h/o CAD, CMP, valvular disease, congenital heart disease, arrhythmias
- Syncope c/w cardiac cause (lack of prodrome, exertional, resultant trauma)
- Recurrent syncope
- Abnormal cardiac exam or ECG

Treatment
- Arrhythmic, cardiac mechanical, or neurologic syncope: treat underlying disorder
- Vasovagal syncope: use midodrine, fludrocortisone, disopyramide, SSRI
- 16 oz of H2O before at-risk situations (Circ 2003:108:2660)
- Orthostatic syncope: volume replete (eg, 500 mL PO q a.m.); if chronic → rise from supine to standing slowly, compressive stockings, midodrine, fludrocortisone, high Na diet

- 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).
Patient selection

- Goal
- Benefits

Treatment: abx and removal of system (warmth, erythema, tenderness) and/or pocket infection

Device infection

- Presents as pocket infection (warmth, erythema, tenderness) and/or sepsis w/ bacteremia
- Infection in ~1/2 of Pts w/ S. aureus bacteremia (even w/o s/s and w/ TTE/TEE)
- Treatment: abx and removal of system

Common Pacing Modes

<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VVI</td>
<td>Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradydysrhythmia.</td>
</tr>
<tr>
<td>Magnet</td>
<td>Pacing at fixed rate regardless of intrinsic activity. Use to α ability to capture when output inhibited by intrinsic rhythm. Use if Pt hemodynamically unstable due to inappropriate PPM inhibition or PPM-induced tachydysrhythmia.</td>
</tr>
</tbody>
</table>

Indications for Pacing (Circ 2008;117:2820)

- AV block
- Sinus node
- Acute MI
- Tachyarrhythmia
- Syncope
- CMP

Permanent Pacemaker (PPM) Complications

<table>
<thead>
<tr>
<th>Issue</th>
<th>Manifestation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to pace</td>
<td>Bradycardia</td>
<td>Battery depletion, lead fracture/dislodgment, ↑ pacing threshold due to local tissue rxn/injury, or myopotential sensing → inappropriate inhibition</td>
</tr>
<tr>
<td>Failure to sense</td>
<td>Inappropri. pacing</td>
<td>Lead dislodgment or sensing threshold too high</td>
</tr>
<tr>
<td>PM-mediated tachycardia</td>
<td>Tachycardia</td>
<td>Seen w/ DDD, V depol. → retrograde A activation → sensed by A lead → triggers V pacing → etc.</td>
</tr>
<tr>
<td>PM syndrome</td>
<td>Palpit, HF</td>
<td>Seen w/ VVI. Due to loss of AV synchrony.</td>
</tr>
</tbody>
</table>

Cardiac Resynch Therapy (CRT) / Biventricular (BiV) Pacing (JACC 2008;51:2085)

- 3-lead pacemaker (RA, RV, coronary sinus); R > S in V1 suggests appropriate LV capture
- Goal: enhance synch RV & LV fxn (↑ CO, ↓ remodeling, even if nl EF, NEJM 2009;361:2123)
- Pt selection: NYHA III/IV HF despite med Rx + LVEF < 35% or QRS > 120 ms; ↑ survival if QRS < 120 ms w/ echo dyssynchrony (NEJM 2007;357:2461); ↓ lesser benefit if chronic AF
- Benefits: ↑ HF sx, ↓ HF hosp., ↑ survival (NEJM 2004;350:2140 & 2005;352:1539); ↓ HF events compared w/ ICD alone in NYHA I/II & QRS > 150 ms (MADIT-CRT, NEJM 2009;361:1329)

Implantable Cardiac Defibrillator (ICD) (NEJM 2003;349:1836; JACC 2006;48:1064)

- RV lead capable of defibrillation & pacing ( ≤ antitachycardia pacing, ATP); ↓ RA lead
- Goal: terminate VT/VF w/ shock or burst of pacing, prevent sudden cardiac death (SCD)
- Patient selection (JACC 2008;51:2085)

2° prevention: survivors of VF arrest, unstable VT w/ reversible cause (NEJM 1997;337:1576); structural heart disease & spontaneous sustained VT (even if asx)
1° prevention: life expectancy > 1 y, LVEF < 30% or LVEF 30–35% & NYHA II–III or LVEF 35–40% & inducible VT/VF (waits ≥ 40 d if post-MI or ≥ 9 mos for non-ischemic CMP, NEJM 2009;361:1427); for HCM, ARVD, Brugada, sarcoid, LQTS, Chagas, or congenital heart, ICD if risk factors for SCD
- Benefits: ↓ mortality from SCD c/w antiarrhythmics or placebo
- ICD discharge: device to see if appropriate; r/o ischemia; 6 mos driving ban; if recurrent VT, ↓ drug Rx (eg, amio + βB, JAMA 2006;295:165) or VT ablation (NEJM 2007;357:2657). Nb, ablation at time of ICD ↓ risk of VT by 40% (Lancet 2010;375:31).

Device infection (Circ 2010;121:458)

- Presents as pocket infection (warmth, erythema, tenderness) and/or sepsis w/ bacteremia
- Infection in ~1/2 of Pts w/ S. aureus bacteremia (even w/o s/s and w/ TTE/TEE)
- Treatment: abx and removal of system


**Clinical Assessment**

<table>
<thead>
<tr>
<th>Active Cardiac Conditions</th>
<th>Clinical Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI w/in 30 d or current unstable or severe angina</td>
<td>h/o CAD</td>
</tr>
<tr>
<td>Decompensated HF</td>
<td>h/o HF</td>
</tr>
<tr>
<td>Significant arrhythmia (eg, high-grade AVB, Mobitz II, 3rd AVB, new or sx VT, SYT w/ HR &gt;100, sx brady)</td>
<td>h/o Cerebrovascular dis.</td>
</tr>
<tr>
<td>Severe AS or sx MS</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Severe HF</td>
<td>Renal insuffic. (Cr &gt;2 mg/dL)</td>
</tr>
</tbody>
</table>

**Surgery-Specific Risk**

<table>
<thead>
<tr>
<th>High (&gt;5% risk)</th>
<th>Intermediate (1–5%)</th>
<th>Low (&lt;1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic or other major vascular</td>
<td>Intrathoracic; intraperitoneal; prostate</td>
<td>Endoscopic</td>
</tr>
<tr>
<td>Peripheral vasc.</td>
<td>CEA; head &amp; neck</td>
<td>Breast: superficial</td>
</tr>
<tr>
<td></td>
<td>Orthopedic</td>
<td>Cataract: ambulatory</td>
</tr>
</tbody>
</table>

**Functional Capacity**

<table>
<thead>
<tr>
<th>1–4 METs</th>
<th>4–10 METs</th>
<th>&gt;10 METs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADLs</td>
<td>Climb a flight of stairs/hill</td>
<td>Strenuous sports</td>
</tr>
<tr>
<td>Walk indoors</td>
<td>Walk briskly; heavy housework</td>
<td></td>
</tr>
<tr>
<td>Walk 1–2 level blocks</td>
<td>Golf, doubles tennis</td>
<td></td>
</tr>
</tbody>
</table>

**Noninvasive Testing Result**

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia at &lt;4 METs manifested by ≥1 of:</td>
<td>Ischemia at 4–6 METs manifested by ≥1 of:</td>
<td>No ischemia or at &gt;7 METs w/</td>
</tr>
<tr>
<td>≥5 abnl leads or &gt;3 min after exert</td>
<td>≥4 abnl leads</td>
<td>ST ≥1 mm or</td>
</tr>
<tr>
<td>SBP ≥10 mmHg or typical angina</td>
<td>1–3 min after exert</td>
<td>1–2 abnl leads</td>
</tr>
</tbody>
</table>

**Preoperative evaluation**

Figure 1-7 ACC/AHA approach to preoperative cardiovascular evaluation for non–cardiac surgery

---

(Circ 2009;120:e169)
Pre-operative testing and therapy
- ECG if ≥1 risk factor and planned vascular surgery, or if known vascular disease and intermediate risk surgery. Prior to any vascular surgery.
- TTE if dyspnea of unknown origin or if HF w/ dyspnea and no TTE in past 12 mo
- Stress test if active cardiac issues (see above), or vascular surgery w/ ≥3 risk factors & it will Δ mgmt. Overall low PPV to predict periop CV events.
- Coronary revascularization should be based on standard indications (e.g., ACS, refractory sx, lg territory at risk). Has not been shown to Δ risk of death or postop MI when done prior to elective vasc. surgery based on perceived cardiac risk (NEJM 2004;351:2795) or documented extensive ischemia (AJC 2009;103:897), but systematic angiography Δ 2–5 y mortality in one vascular surgery trial (JACC 2009;54:989).
- Given need for dual antiplatelet Rx after stenting, wait 4 wk after BMS and ideally >12 mo after DES before discontinuing ADP receptor blockade; continue ASA
- If possible, wait >4–6 wk after MI (even if ETT or ETT & revascularized). If no revasc, wait 6 mo before elective surgery.
- Preop statins: ischemia & CV events in Pts undergoing vascular surg (NEJM 2009;361:980)

Perioperative β-blocker use
- Conflicting evidence regarding efficacy of βB for ↓ periop events. Some studies have shown ↓ cardiac death & MI (NEJM 1996;335:1713 & 1999;341:1789) whereas another ↓ MI but ↑ death & stroke and ↑ bradycardia/HoTN (Lancet 2008;371:1839).
- Consider periop βB if CAD, + stress test, or >1 cardiac risk factor, espec if vascular surgery
- Ideally initiate >1 wk prior to surgery and titrate during preop, intraop, and postop periods to achieve HR ~55–65 bpm and BP control. Avoid bradycardia and hypotension.

Postoperative monitoring
- Postop ECG if known CAD or high-risk surgery. Consider if >1 risk factor for CAD.
- Postop troponin only if new ECG Δs or chest pain suggestive of ACS
DYSPNEA

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway obstruction</td>
<td>Asthma, COPD, bronchiectasis (dilated, collapsible airways, impaired clearance of secretions, + hemoptysis; infxn #1 cause; Rx: mucolytics, bronchodilators, ± abx), CF (chronic resp infxn, bronchiectasis, infectivity, pancreatitis), tumor or foreign body</td>
</tr>
<tr>
<td>Parenchymal disease</td>
<td>Pulmonary edema: cardiogenic (LV systolic or diastolic dysfn) or noncardiogenic (ALI/ARDS) ILD</td>
</tr>
<tr>
<td>Vascular</td>
<td>Pulmonary edema: cardiogenic (LV systolic or diastolic dysfn) or noncardiogenic (ALI/ARDS) ILD</td>
</tr>
<tr>
<td>Bellowsis</td>
<td>Pleural disease: effusion, fibrosis</td>
</tr>
<tr>
<td>Stimulation of receptors</td>
<td>Chemoreceptors: hypoxemia, metabolic acidosis</td>
</tr>
<tr>
<td>Psychological</td>
<td>Anemia, methemoglobinemia, CO poisoning</td>
</tr>
<tr>
<td></td>
<td>Anxiety, panic attack, depression, somatization</td>
</tr>
</tbody>
</table>

Evaluation

- Cardiopulmonary exam, S02, CXR. (see Appendix & Radiology inserts), ECG predictors of CHF: h/o CHF, PND, S02, 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: PFTs, chest CT, TTE, cardiopulmonary testing
- BNP & NT-proBNP ↑ in CHF (but also ↑ in AF, RV strain from PE, COPD flare, PHT) BNP > 100 pg/mL: 90% Se, 76% Sp for CHF causing dyspnea (NEJM 2002;347:161)
  NT-proBNP: > 300 pg/mL → 99% Se, 60% Sp for CHF: (. use < 300 to rule out) to rule in use age-related cut points: > 450 pg/mL if < 50 y, > 900 if 50–75 y, > 1,800 if > 75 y → 90% Se, 84% Sp (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% ↓ FEV1 → asthma
- Lung volumes: evaluate for restrictive disease including NM causes
- Dl,CO: 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

Obstructive Pattern

- FEV1/FVC < 0.75
- TLC < 80% predicted
- Abnl Dl,CO w/ normal spirometry
- ↓ Dl,CO
- ↓ Pimax
- ↑ Pulm blood vol. (eg, obesity, mild CHF, L → R shunts)
- Asthma, PE, PHT, Vasculitis
- Early ILD
- Anemia

Restrictive Pattern

- ILD, CHF
- Pleural disease?
- NM disease
- ↓ Dl,CO
- normal spirometry
**ASTHMA**

**Definition and epidemiology**
- Chronic inflammatory disorder w/ airway hyperrespons. + var. airflow obstruction
- Affects ~5% population; ~85% of cases by age 40 y

**Clinical manifestations (NEJM 2001;344:350)**
- Classic triad = wheezing, cough, and dyspnea: others include chest tightness, sputum; symptoms typically chronic w/ 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, β2 via bronchospasm, MSO4 via histamine) emotional stress, cold air, exercise
- Exacerbations: important to note frequency, severity, duration, and required treatment (need for steroids, ED visits, hospitalizations, and intubations)

**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 suggests asthma. ≦80% personal best c/w poor control, ≦50% c/w severe exacerbation.
- Spirometry: ↓ FEV₁, ↓ FEV₁/FVC, coved flow-volume loop; lung volumes: ± ↑ RV & TLC bronchodilator response (↑ FEV₁ ≧12%) strongly suggestive of asthma methacholine challenge (↓ FEV₁ ≧20%) if PFTs nl: Se >90% (AJRCCM 2000:161:309)
- Sputum: eos >3% has 86% Se, 88% Sp; can also see Curschmann’s spirals (mucus casts of distal airways) and Charcot-Leyden crystals (eosinophil lyso phospholipase); Δ in sputum eos count may guide outpatient Rx (Lancet 2002;360:1715)
- 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- via GERD)
- COPD, bronchiectasis; ILD (including sarcoidosis); vasculitis; PE
- CHF

**“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
- Churg-Strauss = asthma + eosinophilia + granulomatous vasculitis

**“Reliever” medications (used prn to quickly relieve sx)**
- Short-acting inhaled β₂-agonists: albuterol Rx of choice; levoalbuterol (R-isomer) 2x potency, no outcome benefit, ? less tachycardia (J Allergy Clin Immunol 2008;122:544)
- Inhaled anticholinergics (ipratropium) improve β₂-agonist delivery → ↑ bronchodilation

**“Controller” meds (taken daily to keep control)** (NEJM 2009;360:1002)
- Inh corticosteroids: Rx of choice (JAMA 2001;285:2583), PRN? as good as daily for mild asthma (NEJM 2005;352:1519 & 2007;356:2040). PO steroids may be needed for severely uncontrolled asthma, but avoid if possible b/c systemic side effects.
- Nedocromil/cromolyn: limited use in adults. Useful in young Pts, exercise-induced bronchospasm; ineffective unless used before trigger or exercise exposure.
- Theophylline: useful in hard to control Pts, PO convenience, but high side effect profile
- Anti-IgE: allergic asthma (↑ IgE) uncontrolled on inh steroids (NEJM 2006;354:2689), not cost-effective for most cases of severe asthma (JACI 2007;120:1146)
Other

- Behavior modification: identify and avoid triggers
- Immunotherapy (e.g., desensitization): may be useful if significant allergic component
- TNF antagonists may be helpful in pts with refractory asthma (NEJM 2006;354:697)
- Anti-IL5 found to spare steroids in uncontrolled pts with sputum eos (NEJM 2009;360:985)
- Bronchial thermoplasty (exp'tal): radiofrequency destruction of airway smooth muscle may 
  no \( \Delta \) in FEVs, but \( \downarrow \) in sx and \# of exacerbations (NEJM 2007;356:1327)
- PPI: not found to improve asthma sx, even if asx GERD (NEJM 2009;360:1487)

Principles of treatment

- Education and avoidance of environmental triggers for all pts
- Use quick-relief rescue medication as needed for all pts
- Goal is to achieve complete control /H11005/
  daily sx /H11349/2/wk, \( \emptyset \) nocturnal sx or limitation of activity, reliever med \( \leq \)2/wk, nl PEF or FEV1; 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 \( \downarrow \) 15% \( \times \) 2 d or \( \downarrow \) 30%, quadrupling inh steroid dose \( \rightarrow \) need for PO steroids (AJRCCM 2009;180:598)

Asthma Stepwise Therapy

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting ( \beta_2 )-agonists prn</td>
<td>Select one</td>
<td>Select one</td>
<td>( \Delta ) low-dose ICS to med/high dose (w/LABA)</td>
<td>Oral steroids (lowest dose)</td>
</tr>
<tr>
<td>Low-dose ICS</td>
<td>Low-dose ICS + LABA</td>
<td>( \uparrow ) low-dose ICS to med/high dose (w/LABA)</td>
<td>Med/high-dose ICS</td>
<td></td>
</tr>
<tr>
<td>LTA</td>
<td>Med/high-dose ICS</td>
<td>Add LTA</td>
<td>Anti-IgE Rx</td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS + LTA</td>
<td>Add Theo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS + Theo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICS, inh corticosteroid; LABA, long-acting \( \beta_2 \)-agonist; LTA, leukotriene antag.; Theo, sustained-rel. theophylline

Boldfaced Rx preferred options. (Adapted from Global Initiative for Asthma [GINA] 2009)

Exacerbation

Direct evaluation

- History
  - Asthma Hx: baseline PEF, steroid requirement, ED visits, hospital admissions;
  - previous need for intubation a good predictor of risk of death (Thorax 1986;41:833)
  - Current exacerbation: duration, severity, potential precipitants, meds used
- Physical exam
  - Signs of severity: tachypnea, tachycardia, diaphoresis, cyanosis, fragmented speech, absent breath sounds, accessory muscle use, pulse paradox, abdominal paradox
  - Assess for barotrauma: asymmetric breath sounds, tracheal deviation, subcutaneous air \( \rightarrow \) pneumothorax, precordial (Hamman’s) crunch \rightarrow pneumomediatinum
- Diagnostic studies
  - ABG: not always considered essential because exam and \( S_O_2 \) provide equivalent info;
  - low \( P_CO_2 \) initially; nl or high \( P_CO_2 \) may signify tiring; may respond to bronchodilator
  - PEF: used to follow clinical course; CXR: not essential unless suspicion for PNA or PTX

Severity of Asthma Exacerbation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathless w/ . . .</td>
<td>Walking</td>
<td>Talking</td>
<td>At rest</td>
</tr>
<tr>
<td>Talking in . . .</td>
<td>Sentences</td>
<td>Phrases</td>
<td>Words</td>
</tr>
<tr>
<td>Mental status</td>
<td>( \uparrow ) Agitated</td>
<td>Agitated</td>
<td>Agitated</td>
</tr>
<tr>
<td>RR</td>
<td>( \uparrow )</td>
<td>( \uparrow )</td>
<td>( \geq 30 )</td>
</tr>
<tr>
<td>Accessory muscles</td>
<td>( \uparrow )</td>
<td>( \uparrow )</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Wheeze</td>
<td>Moderate, end-expir</td>
<td>Loud</td>
<td>Usually loud</td>
</tr>
<tr>
<td>HR</td>
<td>( &lt;100 )</td>
<td>100–120</td>
<td>( &gt;120 )</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Normal (( &lt;10 ))</td>
<td>10–25</td>
<td>( &gt;25 )</td>
</tr>
<tr>
<td>PEF</td>
<td>( &gt;80% )</td>
<td>60–80%</td>
<td>( &lt;60% )</td>
</tr>
<tr>
<td>( S_O_2 )</td>
<td>( &gt;95% )</td>
<td>91–95%</td>
<td>( &lt;90% )</td>
</tr>
<tr>
<td>( P_CO_2 )</td>
<td>Normal</td>
<td>( \geq 60 )</td>
<td>( &lt;60 )</td>
</tr>
<tr>
<td>( P_CO_2 )</td>
<td>( &lt;45 )</td>
<td>( &lt;45 )</td>
<td>( &gt;45 )</td>
</tr>
</tbody>
</table>

Presence of several parameters (not necessarily all) indicates classification (GINA 2009)

Resp arrest imminent: drowsy, abdominal paradox, wheezes inaudible (b/c air movement), bradycardia, loss of abdominal paradox (respiratory muscle fatigue).
### Acute Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Titrate to achieve $S_2O_2 &gt; 90%$</td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>MDI 4–8 puffs q20min or nebulizer 2.5–5 mg q20min continuous nebulizer if severe</td>
<td>First-line therapy</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>prednisone 60 mg PO or methylprednisolone 80 mg IV</td>
<td>IV not superior to PO (JAMA 1988;260:527)</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>MDI 4–8 puffs q30min or nebulizer 0.5 mg q30min × 3</td>
<td>↑ bronchodilation when combined w/ albuterol (Chest 2002;121:1977)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2 g IV over 20 min (Lancet 2003;361:2114)</td>
<td>↑ PEF &amp; FEV₁</td>
</tr>
</tbody>
</table>

---

**Figure 2-2: Initial assessment of asthma exacerbation**

- **Initial Assessment of Severity (as above)**
  - Oxygen to maintain $S_2O_2 > 90\%$
  - Inhaled $\beta_2$-agonists ± anticholinergic
  - Steroids PO or IV (if severe)
  - Magnesium IV (if severe)
  - Reassess after 1–2 h

- **Good response**
  - PEF > 70\%
  - $S_2O_2 > 90\%$
  - normal exam
  - response sustained 60' after Rx

- **Incomplete response**
  - PEF < 60\%
  - $S_2O_2$ not ↑
  - mild/mod signs or exam
  - RFs for near-fatal asthma

- **Poor response**
  - PEF < 30\%
  - $P_{2}O_2$ < 60 or $P_{CO}_{2}$ > 45
  - severe sx

- **Discharge home**
  - Inh $\beta_2$-agonists
  - Oral steroid taper
  - Close follow-up

- **Admit to hospital ward**
  - Inh $\beta_2$-agonists ± anticholinergic
  - Steroids PO/IV
  - Magnesium IV

- **Admit to ICU**
  - Inh $\beta_2$-agonists ± anticholinergic
  - Steroids IV ± $\beta_2$-agonist IV & theo IV ± intubation
  - Reassess periodically at intervals
    - Incomplete after 6–12 h or poor response

(Adapted from GINA 2009.) Risk factors for near-fatal asthma: h/o near-fatal asthma, ED visit or hosp for asthma in past 1 y, current or recent use of PO steroids, not using inh steroids, overdependent on rapid-acting $\beta_2$-agonists, psych issues, h/o noncompliance.

**Other treatments**

- Epinephrine (0.3–0.5 mL SC of 1:1000 dilution): no advantage over inhaled $\beta_2$-agonists
- Abx: not needed w/o evidence of bacterial infection. Evidence of improved sx & FEV₁ may be related to anti-inflammatory effect (NEJM 2006;354:1589; Chest 2009;136:498).

**ICU-level care**

- **High-dose steroids:** methylprednisolone 125 mg IV q6h (Archives 1983;143:1324)
- **Noninvasive ventilation:** likely improves obstruction (Chest 2003;123:1018), but controversial. Consider if mod distress, resp failure not imminent (Resp Care 2008;53:740).
- **Invasive ventilation:**
  - large ET tube, keep $P_{plat} < 30$ cm H₂O (predicts barotrauma better than PIP), maximize exp time, and use no PEEP to avoid hyperinflation (Resp Care 2008;53:740)
  - paralysis, inhalational anesthetics, bronchoalveolar lavage w/ mucolytic, heliox (need 60–80% helium), and ECMO have been used with success
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition and epidemiology (NEJM 2004;350:26)
- Progressive airflow limitation caused by airway and parenchymal inflammation

<table>
<thead>
<tr>
<th>Emphysema vs. Chronic Bronchitis</th>
<th>Emphysema</th>
<th>Chronic Bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Dilatation/ destruction of parenchyma (path definition)</td>
<td>Productive cough &gt; 3 mo/y × ≥ 2 y (clinical definition)</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Tissue destruction</td>
<td>Small airways affected</td>
</tr>
<tr>
<td></td>
<td>Matched V/Q defects</td>
<td>V/Q mismatch</td>
</tr>
<tr>
<td></td>
<td>Mild hypoxemia</td>
<td>Severe hypoxemia, hypercapnia</td>
</tr>
<tr>
<td><strong>Clinical manifestations</strong></td>
<td>Severe, constant dyspnea</td>
<td>Intermittent dyspnea</td>
</tr>
<tr>
<td></td>
<td>Mild cough</td>
<td>Copious sputum production</td>
</tr>
<tr>
<td><strong>Physical exam</strong></td>
<td>“Pink puffer”</td>
<td>“Blue bloater”</td>
</tr>
<tr>
<td></td>
<td>Tachypneic, noncyanotic, thin Diminished breath sounds</td>
<td>Cyanotic, obese, edematous Rhonchi &amp; wheezes</td>
</tr>
</tbody>
</table>

Pathogenesis (Lancet 2003;362:1053)
- Cigarette smoke (centrilobular emphysema, affects 15–20% of smokers)
- Recurrent airway infections
- α1-antitrypsin def.: early-onset panacinar emphysema, 1–3% of COPD cases. Suspect if age < 45, lower lungs affected, extrathoracic manifestations (liver disease [not if M2 subtype], FMD, pancreatitis). ✓ serum AAT level (nb, acute phase reactant).

Clinical manifestations
- Chronic cough, sputum production, dyspnea; later stages → freq exc., 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 2002;347:465)
- Physical exam: ↑ AP diameter of chest ("barrel-chest"), hyperresonance, ↓ diaphragmatic excursion, ↓ breath sounds, ↑ expiratory phase, rhonchi, wheezes during exacerbation: tachypnea, accessory muscle use, pulsum paradoxus, cyanosis

Diagnostic studies
- CXR (see Radiology inserts): hyperinflation, flattened diaphragms, ± interstitial markings and bullae
- PFTs: **Obstruction**: ↓↓ FEV₁, ↓ FVC, ↓ FEV₁/FVC, expir scooping of flow-volume loop Hyperinflation: ↑↑ RV, ↑↑ TLC, ↑↑ RV/TLC
- **Abnormal gas exchange**: ↓ Di, CO (in emphysema)
- **ABG**: ↓ P, O₂, ≥ 1 P, CO₂ (in chronic bronchitis, usually only if FEV₁ < 1.5 L) and ↓ pH
- **ECG**: PRWP, S1S2S3, R-sided strain, RVH, ↑ P waves in lead II (“P pulmonary”)

Chronic treatment (Annals 2007;147:633; NEJM 2010;362:1407)
- **Bronchodilators** (first-line therapy): anticholinergics, β₂-agonists, theophylline
- LA anticholinergic (tiotropium): ↓ exc., ↓ admit, ↓ resp failure (NEJM 2008;359:1543),
  - better than ipratropium (Cochrane 2005;CD002876) or LABA as mono RX (Chest 2004;125:249)
  - LABA: 15% ↓ in exacerbations, ↓ FEV₁ decline, trend toward ↓ mort. (NEJM 2007;356:775)
  - Tiotropium ↓ LABA ↓ inh steroid: ↑ FEV₁, ↓ COPD admits (Annals 2007;146:545)
- **Corticosteroids** (inhaled): ~20% ↓ in exacerbations if FEV₁ < 2.0 L (Chest 2009;136:1029)
  - may slow FEV₁ loss, but more so in combination with β₂-agonist (NEJM 2007;356:775)
  - ↑ in pneumonia (not seen w/ budesonide, Lancet 2009;374:712)
  - no Δ in mortality with inh steroids alone (NEJM 2007;356:775)
- **Mucolytics**: no Δ FEV₁, but ↑ ↓ exacerbation rate (Lancet 2008;371:2013)
- **Oxygen**: if P, O₂ ≤ 55 mm Hg or S, O₂ ≤89% (during rest, exercise, or sleep) to prevent cor pulmonary and ↓ mortality (Annals 1980;93:391 & Lancet 1981;1:681)
- **Prevention**: Flu/Pneumovax: smoking cessation (eg, varencliline, 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 (Chest 2007;131:45)
- **Experimental**
  - Lung volume reduction surgery: ↑ exer. capacity, ↓ mort. if FEV₁ >20%, upper-lobe, low exer. capacity (NEJM 2003;348:2059),
  - bronchoscopy (Chest 2006;129:513)
  - Bronchoscopic opening of extra-anatomical airway passages to ↑ exp collateral flow
  - Roflumilast (PDE-4 inhibitor): ↑ FEV₁ when added to standard RX (Lancet 2009;374:685695)
  - Nocturnal BiPAP: may improve survival, ↓ decrease QoL (Thorax 2009;64:561)
**Prognosis**

- **FEV₁ <60% predicted**: → 5-y mort ~10%; <40% → ~50%; <20% → ~90%
- **BODE 10-pt scale** (Lancet 2009;334:704); HR 1.62 for resp. mort, 1.34 mort for each 1-pt ↑
  - **BMI**: ≥21 (+1)
  - **Obstruction** (FEV₁): >50% (+1), 36–49 (+2), ≤35 (+3)
  - **Dyspnea** (MMRC scale): walking level (+1), after 100 yds (+2), with ADL (+3)
  - **Exs capacity** (6-min walk): 250–349 m (+1), 150–249 (+2), ≤149 (+3)

**COPD Staging and Recommended Therapies by GOLD Criteria**

<table>
<thead>
<tr>
<th>Stage</th>
<th>PFTs (of predicted)</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild</td>
<td>FEV₁ &lt;80%</td>
<td>Bronchodilator prn</td>
</tr>
<tr>
<td>II: Mod</td>
<td>FEV₁ 50–80%</td>
<td>Standing LA dilator (irotiopium &gt; β ag)</td>
</tr>
<tr>
<td>III: Severe</td>
<td>FEV₁ 30–50%</td>
<td>Rehabilitation</td>
</tr>
<tr>
<td>IV: Very Severe</td>
<td>FEV₁ &lt;30% or FEV₁ &lt;50% and chronic respiratory failure</td>
<td>Above + inhaled steroid if ↑ exacerbations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Above + O₂ if chronic resp failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experimental as indicated</td>
</tr>
</tbody>
</table>

(Adapted from Global Initiative for Chronic Obstructive Pulmonary Disease, 2009)

**Exacerbation**

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium</td>
<td>MDI 4–8 puffs q1–2h or Nebulizer 0.5 mg q1–2h</td>
<td>First-line therapy</td>
</tr>
<tr>
<td>Albuterol</td>
<td>MDI 4–8 puffs q1–2h or Nebulizer 2.5–5 mg q1–2h</td>
<td>Benefit if component of reversible bronchoconstriction</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>No consensus for optimal dose &amp; duration (Cochrane 2009:CD001288). Consider: Methylprednisolone 125 mg IV q8h × 72 h then: Prednisone 60 mg PO qd w/ 20 mg taper q3–4d (NEJM 1999;340:1941) or prednisone 40 mg x 10d or prednisone 30 mg qd × 2 wks if pH &gt;7.26 (Lancet 1999;354:456)</td>
<td>↓ treatment failure, ↓ hospital stay, ↑ FEV₁ but no mortality benefit, ↓ complications (Cochrane 2009:CD001288)</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>↑ F₂O₂ to achieve P₂O₂ =55–60 or S₂O₂ 90–93%</td>
<td>Watch for CO₂ retention (due to ↑ V/Q mismatch, loss of hypoxic resp. drive, Haldane effect) but must maintain oxygenation!</td>
</tr>
<tr>
<td>Noninvasive positive-pressure ventilation</td>
<td>Initiate early if mod/severe dyspnea, ↓ pH / ↑ P&lt;sub&gt;CO₂&lt;/sub&gt;, RR &gt;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; ERY 2005:25:348)</td>
<td></td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>Consider if P&lt;sub&gt;CO₂&lt;/sub&gt; &lt;55–60, ↑ ing P&lt;sub&gt;CO₂&lt;/sub&gt;, ↑ ing pH, ↑ RR, respiratory fatigue, Δ MS, or hemodynamic instability</td>
<td></td>
</tr>
<tr>
<td>Other measures</td>
<td>Mucolytics overall not supported by data (Chest 2001:119:1190) Monitor for cardiac arrhythmias</td>
<td></td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Infection/Inflammation</th>
<th>Bronchitis (most common cause of trivial hemoptysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bronchiectasis incl. CF (common cause of massive hemoptysis)</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis or aspergillosis (can be massive)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia or lung abscess</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Usually primary lung cancer, sometimes metastasis (can be massive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>PE (can be massive), pulmonary artery rupture (2” to instrumentation), CHF, mitral stenosis, trauma/foreign body, bronchovascular fistula</td>
</tr>
</tbody>
</table>

| Other                    | Vasculitis (Wegener’s, Goodpasture’s, Behçet’s; can be massive), AVM, anticoagulation (w/ underlying lung disease), coagulopathy, cocaine, idiopathic pulmonary hemosiderosis, catamenial (lung endometriosis) |

(Crit Care Med 2000;28:1642)

Diagnostic workup

- Localize bleeding site
- **Rule out GI or ENT source** by exam, history; may require endoscopy
- Pulmonary source: determine whether unilateral or bilateral, localized or diffuse, parenchymal or airway by CXR or chest CT, bronchoscopy if necessary
- 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: used for Dx & Rx (vascular occlusion balloons or selective embolization of bronchial circulation)
- Rigid bronchoscopy: allows more interventional options (electrocautery, laser) than flex.
- Surgical resection

SOLITARY PULMONARY NODULE

Principles

- Definition: single, <3 cm, surrounded by normal lung, no LAN or pleural effusion
- Often “incidentalomas,” but may represent early potentially curable localized malignancy

**Etiologies**

<table>
<thead>
<tr>
<th>Benign (70%)</th>
<th>Malignant (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granuloma (80%); TB, histo, coccidio</td>
<td>Bronchogenic carcinoma (75%): adeno &amp; large cell (peripheral)</td>
</tr>
<tr>
<td>Hamartoma (10%)</td>
<td>squamous &amp; small cell (central)</td>
</tr>
<tr>
<td>Bronchogenic cyst, AVM, pulm infarct</td>
<td>Metastatic (20%): breast, head &amp; neck, colon, testicular, renal, sarcoma, melanoma</td>
</tr>
<tr>
<td>Wegener’s, rheumatoid nodule</td>
<td>Carcinoid, primary sarcoma</td>
</tr>
<tr>
<td>Lipoma, fibroma, amyloidoma, pneumonitis</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of Cancer**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (cm)</td>
<td>&lt;1.5</td>
<td>1.5–2.2</td>
<td>≥2.3</td>
</tr>
<tr>
<td>Nodule shape</td>
<td>smooth</td>
<td>scalloped</td>
<td>spiculated</td>
</tr>
<tr>
<td>Age (y)</td>
<td>&lt;45</td>
<td>45–60</td>
<td>≥60</td>
</tr>
<tr>
<td>Smoking</td>
<td>never</td>
<td>current (&lt;1 ppd)</td>
<td>current (&gt;1 ppd)</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>none, quit ≥7 y</td>
<td>quit &lt;7 y ago</td>
<td>never quit</td>
</tr>
</tbody>
</table>

(NEJM 2003;348:2535)
Initial evaluation

- **History**: h/o cancer, smoking, age (≥30 y = 2% malignant, +15% ea. decade ≥30)

- **CT**: size/shape, Ca, LAN, effusions, bony destruction, c/w old studies
  - ∅ Ca → ↑ likelihood malignant; laminated → granuloma; “popcorn” → hamartoma

Diagnostic studies

- **PET**: detects metab. activity of tumors, 97% Se & 78% Sp for malig. (espec if ≥8 mm)
  - also useful for surgical staging b/c may detect unsuspected mets (Lancet 2001;2:659)
  - useful in deciding which lesions to bx vs. follow w/ serial CT (J Thor Oncol 2006;1:71)

- **Transthoracic needle biopsy**: if tech. feasible, 97% will obtain definitive tissue dx (AJR 2005;185:1294); if noninformative or malignant → resect

- **Video-assisted thorascopic surgery (VATS)**: for percutaneously inaccessible lesions; highly sensitive and allows resection; has replaced thoracotomy

- **Transbronchial bx**: most lesions too small to reliably sample w/o endobronchial U/S (Chest 2003;123:604); bronch w/ brushings low-yield unless invading bronchus

- **PPD, fungal serologies, ANCA**

Management

- **Low-risk**: serial CT (q3mo × 4, then q6mo × 2); shared decision w/ Pt regarding bx
- **Intermediate-risk**: PET, transthoracic needle bx or transbronchial bx depending on location, comorbidities and Pt preference; if noninformative → VATS
- **High-risk** (and surgical candidate): VATS → lobectomy if malignant

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**OBSTRUCTIVE SLEEP APNEA (OSA)**

Definition and pathophysiology

- Repetitive pharyngeal collapse during sleep causing apnea (≥10 s) or hypopnea (airflow reduction) ≥ desaturation, arousals from sleep → daytime sleepiness

- Apnea-hypopnea index (AHI) = avg # apneas and hypopneas per hr of sleep

- Sleep-induced loss of activity of pharyngeal dilator muscles → pharyngeal collapse → arousal → activation of sympathetic nervous system; phenotypes vary across OSA Pts

- Apnea → negative intrathoracic pressure → ↑ preload, ↑ afterload → HTN, CV sequelae

- Risk factors: obesity (present in 70%), male, age, alcohol, smoking, black race

Clinical manifestations (Lancet 2002;360:237)

- Snoring, witnessed apneas/gasping, daytime sleepiness

Cardiovascular

- HTN (JAMA 2000;283:1829; NEJM 2000;342:1378)
  - Associated with ↑ risk of stroke and death (NEJM 2005;353:2034) and possibly CAD and CHF (AJRCCM 2001;163:19)

Neurocognitive

- ↓ cognitive performance, ↓ QOL
  - ↑ MVA and work accidents (NEJM 1999;340:847; AJRCCM 2001;164:2031)

Diagnosis and treatment

- **Polysomnography** (sleep study); can do home-testing. If ∅, trial of CPAP.


- Oral appliances can prevent retroglossal collapse. Offer if refusing CPAP

- Avoid alcohol and sedatives

- Surgery (eg, uvulopalatopharyngoplasty, UPPP) of limited benefit (Chest 1997;111:265)
WORKUP OF ILD

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, medications, precipitating event
• Tempo (acute → infxn, CHF, hypersens pneumonitis, eos PNA, AIP, COP, drug-induced)
• Extrapulmonary s/s (skin Δs, arthralgias/arthritiis, clubbing, neuropathies, etc.)

Diagnostic studies (see Appendix & Radiology inserts)
• CXR and high-resolution chest CT: reticular, nodular, or ground glass pattern
  upper → coal, silicon, hypersens., sarcoid, TB, RA; lower → IPF; asbestos, scleroderma
  adenopathy → sarcoidosis, berylliosis, silicosis, malignancy, fungal infections
  pleural disease → collagen-vascular diseases, asbestosis, infections, XRT
• PFTs: restrictive pattern (i volumes), i DLCO, i PaO2 (especially w/ exercise); if also
  obstructive, consider sarcoid
• Serologies: → ACE, ANA, RF, ANCA, anti-GBM, HIV
• Bronchoalveolar lavage: dx infxn, hemorrhage, eosinophilic syndromes, PAP
• Biopsy (transbronch, CT-guided, VATS, open) if no clear precipitant and w/u unrevealing

ETIOLOGIES OF ILD

• Prevalence: African Americans, northern Europeans, and females; onset in 3rd–4th decade
• Pathophysiology: depression of cellular immune system peripherally, activation centrally

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Hilar LAN; fibrosis; pulm hypertension. Stages: I → bilat hilar LAN; II → LAN + ILD; III → ILD only; IV → diffuse fibrosis</td>
</tr>
</tbody>
</table>
| Cutaneous (25–33%) | Waxy skin plaques
|                  | Lupus pernio (violaceous indurated lesions on face)                           |
|                  | 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 (25–80%)  | Anterior → posterior uveitis; 1 lacrimal gland                                |
| Endo & renal (10%) | Nephrolithiasis, hypercalcemia (10%), hypercalciuria (40%)                    |
|                  | Due to vitamin D hydroxylation by M6                                          |
| Neuro (10% clin, 25% path) | CNVII 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                               |

• Løfgren’s syndrome: erythema nodosum + hilar adenopathy + arthritis (good prognosis)
• Diagnostic studies: LN bx → noncaseating granulomas + multinucleated giant cells
• 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 (eg, prednisone 20–40 mg/d) if sx or extrathoracic organ dysfxn (improves sx, but doesn’t ↓ long-term course); hydroxychloroquine for extensive skin disease; anti-TNF, MTX, AZA, mycophenolate, or cyclophosphamide for chronic/refractory disease
• Prognosis: ↓½ spontaneously remit w/in 10 y (60–80% of stage I, 50–60% stage II, 30% stage III), w/ relapses uncommon; ↓½ have progressive disease

Iatrogenic
• Amiodarone (~10%; dose & duration depend): chronic interstitial pneumonia → ARDS; bx → vacuolized M6 w/ lamellar inclusions on EM; Rx: d/c amio, give 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
Idiopathic interstitial pneumonias (IIPs) (AJRCCM 2005:172:248)

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

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

(2002;165:277; Archives 2001;161:158): UIP, usual interstitial PNA (IP); IF; idiopathic pulm fibrosis; NSIP, nonspecific IP; COP, cryoprotic organizing PNA; BOOP, bronchiolitis obliterans w/ organizing PNA; AIP, acute IP (Hamman-Rich syndrome); DS, desquamative IP; RB-ILD, resp bronchiolitis-assoc ILD.

- Rx for UIP/IPF: steroids + AZA; NAC 600 tid may slow ↓ lung fxn (NEJM 2005;353:2229)
- 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)

Environmental & occupational exposures (NEJM 2000;342:406)

- Pneumoconioses (inorganic dusts)
  - Coal work–r’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)
  - Pathophysiology: immunologic rxn; either acute (6 h after exposure) or chronic

Collagen vascular diseases (ERJ 2001;18:695; NEJM 2006;355:2655)

- 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

- Vascularitis (can p/w DAH)
  - Wegener’s granulomatosis (c- or ANCA) w/ necrotizing granulomas
  - Churg-Strauss syndrome (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%
- ?Idiopathic pulmonary hemosiderosis (IPH): a rare disease and dx of exclusion

Pulmonary infiltrates w/ eosinophilia (PIE) = eos on BAL ± perih. blood

- Allergic bronchopulmonary aspergillosis (ABPA): allergic reaction to Aspergillus
  - Criteria: asthma, pulm infiltrates (transient or fixed), skin rxn & serum precipitins to Aspergillus, ↑ IgE to Aspergillus & total (-1,000), ↑ eos, central bronchiectasis
  - Rx: steroids ± itraconazole for refractory cases (NEJM 2000;342:756)

- Löffler’s syndrome: parasites/drugs → transient pulm inflit + cough, fever, dyspnea, eos
- Acute eosinophilic pneumonia (AEP): acute hypoxic febrile illness; Rx: steroids
- Chronic eosinophilic pneumonia (CEP): “photonegative” of CHF, typically in women
- Other: Churg-Strauss syndrome; hypereos syndrome

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 & anti-GMCSF
- Langerhans cell granulomatosis (LCG): young ↓ smokers; apical cysts; PTX (25%)
- Lymphocytic interstitial pneumonia (LIP): polyclonal B-cell lung infiltration (? lymphoma) w/ retic. & ground glass opacities and septal/bronchovascular thickening; sx >1 y; Rx: steroids
PLEURAL EFFUSION

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

Transudates
- Congestive heart failure (40%): 80% bilateral, ± cardiomegaly on CXR; occasionally exudative (especially after aggressive diuresis or if chronic), 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 defect w/ passage of ascitic fluid often right-sided (25%) & 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).
  - 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 (especially 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
- Colagen vascular disease: RA (large), SLE (small), Wegener’s, Churg-Strauss
- Gastrointestinal diseases: pancreatitis, esophageal rupture, abdominal abscess
- Hemothorax (Hcteff/Hctblood >50%): trauma, PE, malignancy, coagulopathy, leaking aortic aneurysm, aortic dissection, pulmonary vascular malformation
- Chylothorax (triglycerides >110): thoracic duct damage due to trauma, malignancy, LAM
- Other: post-CABG: left-sided; initially bloody, clears after several wks
  - Dressler’s syndrome (pericarditis & pleuritis post-MI)
  - Uremia, post-radiation therapy
  - Asbestos exposure: benign; Dressler’s syndrome (pericarditis & pleuritis post-MI), uremia, post-radiation therapy
- Drug-induced (eg, nitrofurantoin, methysergide, bromocriptine, amiodarone): often right-sided (2/3) & massive (even w/o marked ascites)
- Mycoses: fungal, viral (usually small), parasitic (eg, amebiasis, echinococcosis, paragonimiasis)

Diagnostic studies
- Thoracentesis (NEJM 2006;355:16)
  - 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
  - parapneumonies 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)
- Transudate vs. exudate (Annals 1972;77:507)
  - Light’s criteria: exudate = TPeff/TPserum >0.5 or LDHuff/LDHserum >0.6 or LDHuff >1/2 ULN of LDHserum; 98% Se, 83% Sp; best Se of all methods (Chest 1995;107:1604); 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: serum-effusion alb gradient ≥1.2, Se 87%, Sp 92%; serum-effusion TP gradient ≥3.1, Se 84%, Sp 91%; cholest ≥45 mg/dL and LDHeff >200, 90% Se, 98% Sp (no serum required)
  - CHF effusions: TP may ↑ with diuresis or chronicity → “pseudoexudate”; use albumin gradient ≥1.2, cholest ≥60 mg/dL (Se 54%, Sp 92%), or clinical judgment to help 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 >1,500 pg/mL has 91% Se & 93% Sp for CHF (Km J Med 2004;116:417)

WBC & diff.: exudates tend to have 1 WBC vs. transudates but nonspecific neutrophils → parapneumonic, PE, pancreatitis

lymphocytes (~50%) → cancer, TB, rheumatologic
eos (~1%) → 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

amyrase: seen in pancreatic disease and esophageal rupture (salivary amyrase)
rheumatoid factor, CH50, ANA: limited utility in dx collagen vascular disease

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

lymphocytes (0%–20%)


Transudative: most commonly CHF or hepatic hydrothorax. / s/s CHF or cirrhosis,

Exudative: consider intrapleural injection of technetium-99m sulfur colloid

(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)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Appearance</th>
<th>WBC diff</th>
<th>RBC</th>
<th>pH</th>
<th>Glc</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>clear, straw</td>
<td>&lt;1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lymphs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bilateral, cardioangiely</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>clear, straw</td>
<td>&lt;1,000</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>lymphs</td>
<td></td>
<td></td>
<td></td>
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<td>right-sided</td>
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<tr>
<td>Uncomplicated parapneumonic</td>
<td>turbid</td>
<td>5–40,000</td>
<td>polys</td>
<td></td>
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</tr>
<tr>
<td>Complicated parapneumonic</td>
<td>turbid to purulent</td>
<td>5–40,000</td>
<td>polys</td>
<td></td>
<td></td>
<td>need drainage</td>
</tr>
<tr>
<td>Empyema</td>
<td>purulent</td>
<td>25–100,000</td>
<td>polys</td>
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<td></td>
<td>need drainage</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>serosang.</td>
<td>5–10,000</td>
<td>lymphs</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>lymphs</td>
<td></td>
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</tr>
<tr>
<td>Malignancy</td>
<td>turbid to bloody</td>
<td>1–100,000</td>
<td>lymphs</td>
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<tr>
<td>Pulmonary embolism</td>
<td>sometimes bloody</td>
<td>1–50,000</td>
<td>polys</td>
<td></td>
<td></td>
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<tr>
<td>Rheumatoid arthritis/SLE</td>
<td>turbid</td>
<td>1–20,000</td>
<td>variable</td>
<td></td>
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</tr>
<tr>
<td>Pancreatitis</td>
<td>serosang. to turbid</td>
<td>1–50,000</td>
<td>polys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal rupture</td>
<td>turbid to purulent</td>
<td>≤5,000</td>
<td>polys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥50,000</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Treatment

• Symptomatic effusion: therapeutic thoracentesis, treat underlying disease process

• Parapneumonic effusion (Chest 2000;118:1158)

uncomplicated → antibiotics for pneumonia

>½ hemothorax or complicated or empyema → tube thoracostomy

(a/w risk of organization and subsequent need for surgical decortication)
loculated → tube thoracostomy or VATS; intrapleural lytics w/o clear benefit

(although largest trial used lytics late and w/ small-bore chest tubes; NEJM 2005;352:865)

• Malignant effusion: serial thoracenteses vs. tube thoracostomy + pleurodesis (success rate ~80–90%) vs. indwelling pleural catheter for outPts (Cochrane database 2004;CD002916);
choice of specific pleurodesis agent (talc, bleo, doxy) controversial; systemic steroids and pH <7.2 a/w ↑ likelihood to fail pleurodesis

• TB effusions: effusion will often resolve spontaneously; however, treat Pt for active TB

• Hepatic hydrothorax

Rx: Δ pressure gradient (ie, Δ ascitic fluid volume, NIPPV)

avoid chest tube; 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
- Proximal deep venous thrombosis (DVT): thrombosis of popliteal, femoral, or iliac veins (nb, “superficial” femoral vein part of deep venous system)
- Pulmonary embolism (PE): thrombosis originating in venous system and embolizing to pulmonary arterial circulation; 1 case/1,000 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/H11021 6 h (NEJM 2001;345:779)
  - injury to endothelium: trauma, surgery, prior DVT, inflammation
  - thrombophilia: APC resistance, protein C or S deficiency, APS, prothrombin gene mutation, factor VIII, hyperhomocysteinemia, HIT, OCP, HRT, tamoxifen, raloxifene
- Malignancy (12% of “idiopathic” DVT/PE)
- History of thrombosis (greater risk of recurrent VTE than genetic thrombophilia)
- Statin therapy (NEJM 2009;360:1851)

Thromboprophylaxis (Chest 2008;133:3815)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Patient &amp; situation</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low VTE &lt;10%</td>
<td>Minor surgery in mobile Pt; fully mobile medical Pt</td>
<td>Early, aggressive ambulation</td>
</tr>
<tr>
<td>Moderate VTE 10–40%</td>
<td>Most surgery Pts; sick or bedrest medical Pts</td>
<td>UFH 5,000 USC bid or tid; LMWH, fonda if HIT ⊕; mechanical Ppx if high bleed risk</td>
</tr>
<tr>
<td>High VTE 40–80%</td>
<td>Ortho surgery, trauma, spinal cord injury</td>
<td>LMWH, fondaparinux, warfarin (INR 2–3); mechanical Ppx if high bleed risk</td>
</tr>
</tbody>
</table>

Rivaroxaban (oral anti-Xa: NEJM 2008;358:2765 & 2776) and dabigatran (oral anti-IIa) under study.

Clinical manifestations—DVT
- Calf pain, lower extremity swelling (>3 cm c/w unaffected side), venous distention, pain, erythema, warmth, tenderness, palpable cord, Homan’s sign (calf pain on dorsiflexion, seen in ~5% of Pts), phlegmasia cerulea dolens: stagnant blood edema, cyanosis, pain
- 50% of Pts with sx DVT have sx PE

Pretest Probability of DVT

<table>
<thead>
<tr>
<th>Major points</th>
<th>Minor points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>Trauma to symptomatic leg w/in 60 d</td>
</tr>
<tr>
<td>Paralysis, paresis, immobilization of foot</td>
<td>Pitting edema in symptomatic leg</td>
</tr>
<tr>
<td>Bed rest × &gt;3 d or major surg, w/in 4 wk</td>
<td>Dilated superficial veins (nonvaricose) in symptomatic leg only</td>
</tr>
<tr>
<td>Localized tenderness along veins</td>
<td>Hospitalization w/in previous 6 mo</td>
</tr>
<tr>
<td>Swelling of thigh and calf</td>
<td>Erythema</td>
</tr>
<tr>
<td>Swelling of calf &gt;3 cm c/w asx side</td>
<td></td>
</tr>
<tr>
<td>⊕FHx of DVT (=2 1° relatives)</td>
<td></td>
</tr>
</tbody>
</table>

High probability (~85% ⊕ DVT)
- ≥3 major + no alternative dx
- ≥2 major + ≥2 minor + no alternative dx
- Intermediate prob (~33% ⊕ DVT)
- neither high nor low probability

Low probability (~5% ⊕ DVT)
- 1 major + ≥2 minor + alternative dx
- 1 major + ≥1 minor + no alternative dx
- 0 major + ≥3 minor + alternative dx
- 0 major + ≥2 minor + no alternative dx

Diagnostic studies—DVT
- Compression U/S >95% Se & Sp for sx DVT (lower for asx DVT); survey whole leg rather than just proximal (JAMA 2010;303:438)
- D-dimer: <500 helps r/o DVT (see later for details); Venography: CT, MR, or angiography

Figure 2-1 Approach to suspected DVT
Clinical manifestations—PE
- Dyspnea (73%), pleuritic chest pain (66%), cough (37%), hemoptysis (13%)
- RR (>70%), crackles (51%), HR (30%), fever, cyanosis, pleural friction rub, loud P2
- Massive: syncope, HoTN, PEA; JVP, R-sided S3, Graham Steell (PR) murmur

“Modified Wells” Pretest Probability Scoring of PE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Point Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE as likely or more likely than alternate dx; clin. s/s of DVT</td>
<td>3 each</td>
</tr>
<tr>
<td>HR &gt;100 bpm; prior DVT or PE</td>
<td>1.5 each</td>
</tr>
<tr>
<td>Immobilization (bed rest ≥3 d) or surgery w/in 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis; malignancy</td>
<td>1 each</td>
</tr>
</tbody>
</table>

“Modified Wells” Pretest Probability Assessment (Use for V/Q)

<table>
<thead>
<tr>
<th>Score</th>
<th>Low probability</th>
<th>Intermediate probability</th>
<th>High probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

“Dichotomized Wells” Pretest Probability Assessment (Use for CTA)

<table>
<thead>
<tr>
<th>Score</th>
<th>PE “Unlikely”</th>
<th>PE “Likely”</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4</td>
<td></td>
<td></td>
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<tr>
<td>&lt;4</td>
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</tr>
</tbody>
</table>

Diagnostic studies—PE
- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, hemidiaphragm, Hampton hump, Westermark sign (vascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, S1QIIIIII & TWI V1–V4 (McGinn-White pattern, Chest 1991;115:537)
- 18% w/ room air FIO2 85–105 mm Hg, 6% w/ nl A-a gradient (CHEST 1991;100:598)
- D-dimer: high Se, poor Sp (25%); ELISA has 99% NPV and can be used to r/o PE in Pts w/ “unlikely” pretest prob. (JAMA 2006;295:172)
- Echocardiography: useful for risk stratification (RV dysfn), 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 or cannot be 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): Se ~90% & Sp ~95% w/ MDCT, CTV, good quality scans and experienced readers (NEJM 2005;353:2317); PPV & NPV >95% if imaging concordant w/ clinical suspicion, ≤80% if discordant (need to consider both); CT may also provide other dx
- Lower extremity compression U/S shows DVT in ~9%, sparing CTA, but when added to CTA, does not A outcomes (Lancet 2008;371:1343)
- Pulmonary angiography: gold standard (morbidity 5%, mortality <0.5%), infrequently performed
- MR angiography: Se 84% (segmental) to 100% (lobar) (Lancet 2002;359:1643)

Workup for Idiopathic VTE
- Thrombophilia workup: ✓ if FH, consider if age ≤50 y or on OCP/HRT. Send panel 2 wk after complete anticoagulation, as thrombus, heparin, and warfarin Δ results. Nb, does not change management after 1st idiopathic DVT if plan for long-term anticoagulation (JAMA 2005;293:2352; Blood 2008;112:4432; Am J Med 2008;121:458).
- Malignancy workup: 12% Pts w/ “idiopathic” DVT/PE will have malignancy; age-appropriate screening adequate; avoid extensive w/u (NEJM 1998;338:1169)
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 (Circ 2002;106:1263), ↑ BNP (Circ 2003;107:1576) a/w ↑ mortality
- Echocardiogram: RV dysfxn (controversial in absence of hypotension)

Treatment of VTE (Chest 2008;133:4545; NEJM 2008;359:2804)
- LE DVT: calf or proximal → anticoagulate (even if asx)
- UE DVT: anticoagulate (same guidelines as LE). If catheter-associated, need not remove if catheter fxnal and ongoing need for catheter
- Superficial venous thrombosis: anticoagulate (especially if extensive clot) as 10% experience thromboembolic event w/in 3 mo (Annals 2010;152:218)
- Early ambulation
- Chronic thromboembolic PHT after acute PE
  - Long-term anticoagulation
    - IV UFH: 80 U/kg bolus → 18 U/kg/h → titrate to goal PTT 1.5–2.3 × cntl (eg, 60–85 sec), or
    - LWMH (eg, enoxaparin 1 mg/kg SC bid or dalteparin 200 IU/kg SC qd)
      LWMH preferred over UFH except: renal failure (CrCl < 25%), obesity, hemodynamic instability, or bleed risk (Cochrane 2004;CD001100)
      No need to monitor anti-factor Xa unless concern re: dosing (eg, renal insuffi)
      Attractive option as outPt bridge to long-term oral anticoagulation
      Fondaparinux: 5–10 mg SC qd = UFH (NEJM 2003;349:1695), used in HIT + Pts
      Direct thrombin inhibitors (eg, argatroban, lepirudin) used in HIT + Pts
- Early ambulation
- Thrombolysis (eg, TPA 100 mg over 2 h)
  Use if PE a/w hemodynamic compromise ("massive PE")
  Consider if PE w/o hemodynamic compromise, but high-risk ("submassive PE," eg, marked dyspnea, severe hypoxemia, RV dysfxn on echo, RV enlargement on CTA) and low bleed risk. Risk of ICH ~ 3% and no proven mortality benefit (NEJM 2002;347:1143; Cochrane 2006;CD004437).
  Consider if extensive (eg, iliofemoral) acute DVT and catheter-directed Rx not available
- Catheter-directed therapy (fibrinolytic & thrombus fragmentation/aspiration)
  Consider if extensive (eg, iliofemoral) acute DVT
  Consider if PE w/ hemodynamic compromise or high-risk and not candidate for systemic fibrinolytic therapy or surgical thrombectomy
- 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: if anticoagulation contraindication, failure, or bleed, or ↑ ↓ CP reserve; temp. filter if risk time-limited; adding filter to anticoagulation → PE ↓ 1/2, DVT ↑ 1/2, no mort. diff. (NEJM 1999;388:499; Circ 2005;112:416)
- Long-term anticoagulation
  Warfarin (goal INR 2–3): start same day as heparin unless instability and ↓ need for lytic, catheter-based Rx, or surgery; overlap 2–5 d w/ heparin & until INR ≥2 × ≥24 h
  Superficial venous thrombosis: 4 wk
    1st prox DVT or PE 2+ reversible/time-limited risk factor or distal DVT: 3 mo
    1st unprovoked prox DVT or PE: ≥3 mo, then reassess; if low bleed risk → indefinite Rx
  2nd VTE event: indefinite warfarin (NEJM 1997;336:393 & 2003;348:1425)
  VTE a/w cancer: LMWH × 3–6 mo, then LMWH/warfarin indefinitely or until cancer cured (NEJM 2003;349:146); + head CT for brain mets if melanoma, renal cell, thyroid, chorioCA

Complications & Prognosis
- Postthrombotic syndrome (25%): pain, swelling; ↓ with compression stockings × 3 mo
- Recurrent VTE: 1%/y (after 1st VTE) to 5%/y (after recurrent VTE) after only 6 mo of Rx: 5%/y & > 10%/y, respectively
  predictors: abnl D-dimer 1 month after d/c anticoag (NEJM 2006;355:1780); U/S after 3 mo of anticoag (Annals 2002;137:955); thrombin generation >400 nM (JAMA 2006;296:397)
- Chronic thromboembolic PHT after acute PE ~ 3.8% (NEJM 2004;350:2257), consider thromboendarterectomy
- Mortality: ~ 10% for DVT and ~ 15% for PE after 6 mo (Circ 2003;107:1-4)
PULMONARY HYPERTENSION (PHT)

PA mean pressure >25 mm Hg at rest or >30 mm Hg with exertion

Pathobiology (NEJM 2004;35:1655)
- Smooth muscle & endothelial cell proliferation: ↑ VEGF, ET-1, 5-HT; ↓ PGIs, NO, VIP; mutations in bone morphogenetic protein receptor 2 (BMPR2; gene involved in prolif. & apoptosis) seen in ~50% familial and ~26% sporadic cases of PPH (NEJM 2001;345:319)
- Imbalance between vasoconstrictors and vasodilators
  - ↑ vasoconstrictors: thromboxane A2 (TXA2), serotonin (5-HT), endothelin-1 (ET-1)
  - ↓ vasodilators: prostacyclin (PGI2), nitric oxide (NO), vasoactive peptide (VIP)
- In situ thrombosis: ↑ TXA2, 5-HT, PAI-1; ↓ PGI2, NO, VIP; tissue plasminogen activator

<table>
<thead>
<tr>
<th>Etiologies of Pulmonary Hypertension (Revised WHO Classification)</th>
</tr>
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<tbody>
<tr>
<td><strong>Pulmonary arterial HTN (PAH)</strong></td>
</tr>
<tr>
<td>- Idiopathic (IPAH): mean age of onset 36 y (♂ older than ♀);</td>
</tr>
<tr>
<td>- Familial (FPAH)</td>
</tr>
<tr>
<td>- Associated conditions (APAH)</td>
</tr>
<tr>
<td>Connective tissue disorders: CREST, SLE, MCTD, RA, PM, SJogren</td>
</tr>
<tr>
<td>Congenital L→R shunts: ASD, VSD, PDA</td>
</tr>
<tr>
<td>Portopulmonary HTN (? 2° vasoactive substances not filtered in ESLD; hepatopulmonary syndrome)</td>
</tr>
<tr>
<td>HIV; drugs &amp; toxins: anorexic agents, rapeseed oil, L-tryptophan</td>
</tr>
<tr>
<td>Other: thyroid dis., glycogen storage dis., Gaucher disease, HHT, hemoglobinopathies, chronic myeloprolif d/o, splenectomy</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease: ↑ 2° chemo, BMT; orthopnea, CHF, pl eff, nl PCWP; art vasodil. worsen CHF (AJRCCM 2000;162:1964)</td>
</tr>
<tr>
<td>Pulmonary capillary hemangiomatosis</td>
</tr>
</tbody>
</table>

| Left heart disease                                             |
| Left atrial or ventricular (diastolic or systolic) dysfunction |
| Left-sided valvular heart disease (eg, MS/IMR)                |

| Lung diseases and/or chronic hypoxemia                        |
| COPD                                                          |
| Alveolar hypoventilation (eg, NM disease)                      |
|ILD                                                             |
| Chronic hypoxemia (eg, high altitude)                          |
| Sleep apnea                                                   |
| Developmental abnormalities                                   |

| Chronic thrombotic or embolic disease                         |
| Obstruction of proximal or distal pulmonary arteries          |
| Nonthrombotic emboli (tumor, foreign body, parasites)        |

| Miscellaneous                                                  |
| Sarcoïdosis, histiocytosis X, lymphangiomatosis, schistosomiasis |
| Compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis) |

(Circulation 2009;28:119:2250)

Clinical manifestations
- Dyspnea, exertional syncope (hypoxia, ↓ CO2, exertional chest pain (RV ischemia))
- Symptoms of R-sided CHF (eg, peripheral edema, RUL fullness, abdominal distention)

Physical exam
- PHT: prominent P2, R-sided S4, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- ↓ RV failure: ↑ JVP, hepatomegaly, peripheral edema

Diagnostic studies & workup (Circ 2009;119:2250)
- IPAH yearly incidence 1–2 per million, ↓ r/o 2° causes
- CXR and high-resolution chest CT: dilatation & pruning of pulmonary arteries, enlargement of RA and RV; r/o parenchymal lung disease
- ECG: RAD, RBBB, RAE (“P pulmonale”), RVH (Se 55%, Sp 70%)
- PFTs: ↓ DLCO, mild restrictive pattern: ↓ r/o obstructive and restrictive lung disease
- ABG & polysomnography: ↓ PaO2 and SaO2 (especially w/ exertion), ↓ P,CO2, ↑ A-a gradient: r/o hypoventilation and OSA
- TTE: ↑ RVSP (but over or under by ≥ 10 mm Hg in ½ of PHT Pts; AJRCCM 2009;179:615), flattened (“D”) septum, TR, PR; r/o LV dysfkn, MV disease, and congenital heart disease
- RHC: ↑ RA, RV, & PA pressures, nl PCWP (unless due to L-sided heart disease), ↑ transpulm gradient (PAP-PCWP >12–15, but can be nl if due to LV or valvular dis.), ↑ PVR, ↓ CO; r/o ↑ L-sided pressures shunt
- CTA (large/med vessel), V/Q scan (small vessel), ↓ pulmonary angiogram: r/o PE and chronic thromboembolic disease
- Vasculitis labs: ANA (commonly ↓ in PPH), RF, anti-Scl-70, anti-centromere, ESR
- LFTs & HIV: r/o portopulmonary and HIV-associated PAH
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

Treatment (NEJM 2004;351:1425; JIM 2005;258:199; Circ 2009;119:2250)
- Principles
  1) prevent and reverse vasoactive substance imbalance and vascular remodeling
  2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq. systemic DBP

(Circulation 2009:28:119:2250)
• Supportive
  Oxygen: maintain $S_O_2 > 90–92\%$ (reduces vasoconstriction)
  Diuretics: $\uparrow$ RV wall stress and relieve RHF sx; gentle b/c RV is preload dependent
  Digoxin: control AF, $\downarrow$ counteract neg. inotropic effects CCB
  Dobutamine and inhaled NO for decompensated PHT
  Anticoagulation: $\uparrow$ VTE risk of RHF, $\downarrow$ prevention of in situ microthrombi, $\downarrow$ mort. benefit
  (Circ 1984;70:580; Chest 2006;130:545)

• Vasodilators
  acute vasoreactivity test: use inhaled NO, adenosine, or prostacyclin to identify Pts likely to have a long-term response to oral CCB (vasoactive response defined as $\Delta$ PAP $> 10$ mm Hg to a level $< 40$ mm Hg with $\uparrow$ or stable CO); $\sim 10\%$ Pts are acute responders; no response $\rightarrow$ still candidates for other vasodilators (NEJM 2004;351:1425)

<table>
<thead>
<tr>
<th>Vasodilators</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral CCB</td>
<td><strong>Nifedipine, diltiazem</strong>&lt;br&gt;If $\uparrow$ acute vasoreactive response; $&lt; 1/2$ will be long-term responder&lt;br&gt;(NYHA III &amp; near-nil hemodynamics) &amp; have $\downarrow$ mortality. Side effects: HoTN, lower limb edema. (NEJM 1992;327:76; Circ 2005;111:3105)</td>
</tr>
<tr>
<td>IV Prostacyclin</td>
<td><strong>Epoprostenol, Flolan</strong>&lt;br&gt;Vasodilation, $\downarrow$ pit agg, $\downarrow$ smooth muscle proliferation; benefits $\uparrow$ w/ time ($\downarrow$ vascular remodeling). $\uparrow$ 6MWT, $\downarrow$ QoL, $\downarrow$ mortality. Side effects: HA, flushing, jaw/leg pain, abd cramps, nausea, diarrhea, cather infxn. (NEJM 1996;334:296 &amp; 1998:338:273; Annals 2000;132:425)</td>
</tr>
<tr>
<td>Prostacyclin analogues</td>
<td><strong>Illoprost (inhaled)</strong>&lt;br&gt;<strong>Treprostinil (IV or SC)</strong>&lt;br&gt;<strong>Beraprost (PO)</strong>&lt;br&gt;Same mechanism as prostacyclin IV, but easier to take, $\downarrow$ side effects, and $\downarrow$ risk of cather infxn. $\downarrow$ sx, $\uparrow$ 6MWT, trend to $\downarrow$ clinical events w/ illoprost but not treprostinil. Beraprost w/ sustained outcome improvement (n/a in U.S.). (NEJM 2002;347:322; AJRCCM 2002;165:800)</td>
</tr>
<tr>
<td>Endothelin receptor antagonists (ERAs)</td>
<td><strong>Bosentan, ambrisentan</strong>&lt;br&gt;$\downarrow$ Smooth muscle remodeling, $\uparrow$ vasodilation, $\downarrow$ fibrosis. $\downarrow$ sx, $\uparrow$ 6MWT, $\downarrow$ clinical events. Side effects: $\uparrow$ LFTs, headache, anemia, edema, teratogen. (NEJM 2002;346:896; JACC 2005;46:529; Circ 2008;117:3010)</td>
</tr>
<tr>
<td>PDE-5 Inhibitor</td>
<td><strong>Sildenafil, tadalafil</strong>&lt;br&gt;$\uparrow$ cGMP $\rightarrow$ $\downarrow$ NO $\rightarrow$ vasodilation, $\downarrow$ smooth muscle proliferation $\downarrow$ sx, $\uparrow$ 6MWT, $\downarrow$ D clinical outcomes. Low side effect profile: HA, vision $\Delta$‘s, sinus congestion. (NEJM 2009;361:1864)</td>
</tr>
</tbody>
</table>

• Treat underlying causes of 2nd PHT; can use vasodilators, although little evidence
• Refractory PHT
  balloon atrial septostomy: R $\rightarrow$ L shunt causes $\downarrow$ CO, $\downarrow$ S/O₂, net $\uparrow$ tissue O₂ delivery lung transplant (single or bilateral); heart-lung needed if Eisenmenger physiology

Figure 2-5 Treatment of PHT

<table>
<thead>
<tr>
<th>Acute vasoreactivity testing</th>
<th>$\uparrow$ &amp; lower risk</th>
<th>$\downarrow$ &amp; higher risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral CCB</td>
<td>sustained response?</td>
<td>no</td>
</tr>
<tr>
<td>CCB</td>
<td>Continue CCB</td>
<td></td>
</tr>
<tr>
<td>Investigational protocols</td>
<td>Atrial septostomy</td>
<td>Lung transplantation</td>
</tr>
<tr>
<td>Epoprostenol or treprostinil (IV)</td>
<td>Flolan</td>
<td>ERA or PDE-5 inhibit</td>
</tr>
<tr>
<td>Treprostinil (SC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>inadequate response</td>
<td>Treprostinil (IV)</td>
</tr>
</tbody>
</table>


**Management of ICU patient**
• Avoid overly aggressive volume resuscitation
• Caution with vasodilators if any L-sided dysfunction
• May benefit from inotropes/chronotropes
• Consider fibrinolysis if acute, refractory decompensation

**Prognosis**
• Median survival after dx $\sim 2.8$ 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 VO₂ $< 10.4$ mL/kg/min, $\uparrow$ RA or RV or RV dysexn, RA $> 20$ or CI $< 2.0$, $\uparrow$ BNP (Chest 2006;129:1313)
• Lung transplant: 1-y survival 66–75%; 5-y survival 45–55% (Chest 2004;126:63-S)
RESPIRATORY FAILURE

Hypoxemia → \( F_AO_2 = F_O_2 \times \left(760 - \frac{P_{CO_2}}{R}\right) \)

- **A-a gradient** = \( P_AO_2 - P_O_2 \): normal (on room air) = “4 + age/4” or “2.5 + (0.2 \times \text{age})” hypoxemia + normal A-a gradient → problem is excess \( P_{CO_2} \) (ie, hypoventilation)
- \( S_0_2 \): (mixed venous \( O_2 \) sat, nl 60–80%): measure \( O_2 \) consumption vs. delivery; low \( S_0_2 \) → ↓ \( O_2 \) delivery (ie, \( S_0_2 \) nl \( S_0_2 \) but ↓ \( CO \) or anemia) or excessive \( O_2 \) consump.
- **V/Q mismatch** and **shunt** represent spectrum w/ both coexisting in alveolar disease
  - 100% \( O_2 \) can overcome V/Q mismatch but not large shunt b/c sigmoidal \( Hg-O_2 \) curve

**Figure 2-6 Workup of acute hypoxemia**

### Chemical Causes of Cellular Hypoxia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Causes</th>
<th>Classic Features</th>
<th>( P_{O_2} )</th>
<th>Pulse Ox Sat</th>
<th>CO-Ox Sat</th>
<th>Treatment (+ 100% ( O_2 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon monoxide</td>
<td>Fires, portable heaters, auto exhaust</td>
<td>Cherry-red skin ( \text{COHb color} )</td>
<td>nl</td>
<td>nl</td>
<td>↓</td>
<td>Hyperbaric ( O_2 )</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Nitrites, sulfonamide, benzoic acid, dapsone</td>
<td>Chocolate brown blood</td>
<td>nl</td>
<td>mild ↓</td>
<td>↓</td>
<td>Methylene blue</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Nitroprusside, fires, industrial</td>
<td>Bitter almond odor; pink skin</td>
<td>nl</td>
<td>nl</td>
<td>nl</td>
<td>Hydroxy-cobelamin</td>
</tr>
</tbody>
</table>

CO binds to Hb more avidly than does \( O_2 \). Pulse ox misreads \( \text{COHb} \) as \( \text{HbO}_2 \) falsely nl sat.

Oxidizing drugs ↓ \( Hb \) (ferrous) to \( \text{MetHb} \) (ferric), which cannot carry \( O_2 \). Pulse ox misreads \( \text{MetHb} \) as \( \text{HbO}_2 \).

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

### Hypercapnia

\[ \mathrm{VCO}_2 = \frac{\mathrm{P}_{CO_2}}{R} \times \left(1 - \frac{\mathrm{V_O}}{\mathrm{V_T}}\right) \]

\[ \text{Hypercapnia} \rightarrow \frac{\text{P}_{CO_2}}{\text{VCO}_2} = k \times \frac{\text{V}_O}{\text{V}_T} \]

### “Won’t breathe”

**Respiratory Drive**

- ↓ \( \text{RR} \)
- ↓ \( \text{P}_{100} \)
- Voluntary hypervent, NL \( P_{max} \) & A-a gradient

**NM System**

- ↓ \( \text{P}_{max} \)
- \( \text{PE}_{max} \)

### “Can’t breathe”

**Lung/Airways**

- \( \text{Abnl PFTs} \)
- \( \text{Abnl PEx} \)

**CW/Pleura**

- \( \text{Abnl CXR/CT} \)

### Chemoreceptors

- Metab. alkalosis
- 1° neurologic
- Cerebral stroke tumor
- 1° alveolar hypvent
- 2° neurologic
- Sedatives
- CNS infection
- Hypothyroidism

### Neopathies

- Cervical spine
- Phrenic nerve
- GBs, ALS, polio
- NM

### Myopathies

- Diaphragm
- PM/DM
- \( P_{0_2} \)
- Musc dystrophies

### Lung parenchyma

- Emphysema
- ILD/fibrosis
- CHF, PNA

### Airways

- Asthma, COPD
- Bronchiectasis
- CF
- OSA

### Chest wall

- Obesity
- Kyphosis
- Scoliosis

### Pleura

- Fibrosis
- Effusion

\( \uparrow \text{VCO}_2 \) typically transient cause of \( \uparrow \text{P}_{CO_2} \) Ddc. exercise, fever, hypehyperthyroidism, ↑ work of breathing, ↑ carbs.
MECHANICAL VENTILATION

Indications
- Improve gas exchange
  - Oxygenation
  - Alveolar ventilation and/or reverse acute respiratory acidosis
- Relieve respiratory distress
  - Work of breathing (can account for up to 50% of total oxygen consumption)
  - Respiratory muscle fatigue
- Apnea, airway protection, pulmonary toilet

Choosing settings (NEJM 2001;344:1986)
1. Choose method (including potentially noninvasive ventilation, see later)
2. Pick ventilator mode, and (if appropriate) volume targeted or pressure targeted
3. Set or ✓ remaining variables (eg, F\textsubscript{O}_2, PEEP, I\!:E time, flow, airway pressures)

### Step 1: Pick Ventilator Mode

<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assist control (AC)</td>
<td>Vent delivers a minimum number of supported breaths Additional Pt-initiated breaths trigger fully-assisted vent breaths, i.e., vent-triggered breaths identical to Pt-triggered breaths. Tachypnea → ↑ respiratory alkalosis, breath-stacking, &amp; auto-PEEP. May be pressure targeted or volume targeted.</td>
</tr>
<tr>
<td>Synchronized intermittent mandatory vent (SIMV)</td>
<td>Vent delivers min. # supported breaths (synch. to Pt’s efforts) Additional Pt-initiated breaths → VT determined by Pt’s efforts. Vent-assisted breaths = spontaneous breaths. Must overcome resp. circuit during spont. breaths → ↑ fatigue. SIMV – AC in Pts who are not spontaneously breathing.</td>
</tr>
<tr>
<td>Pressure support vent (PSV)</td>
<td>Support Pt-initiated breaths w/ a set inspiratory pressure &amp; PEEP. A mode of partial vent support because no set rate.</td>
</tr>
<tr>
<td>Continuous positive airway pressure (CPAP)</td>
<td>Pt breathes spont. at his/her own rate while vent maintains constant positive airway pressure throughout respiratory cycle (7 cm H\textsubscript{2}O overcomes 7 Fr ET\textsubscript{T}).</td>
</tr>
<tr>
<td>T piece</td>
<td>No airway pressure, no rate set; patient breaths through ET\textsubscript{T}.</td>
</tr>
<tr>
<td>Other</td>
<td>High-frequency vent (AJRCCM 2002;166:801; CCM 2003;S-3;S-17), ECMO and ECCO\textsubscript{R} (Ann Surg 2004;240:595)</td>
</tr>
</tbody>
</table>

### Step 2: Choose Volume Targeted or Pressure Targeted

| Volume targeted | Vent delivers a set VT.
Airway pressures depend on airway resist. & lung/chest wall compliance

**Benefit:** Control over ventilation (ideal initial ventilator setting);
evidence-based benefit in ALI/ARDS; easy to measure mechanical respiratory properties (P\text{IP}, P\text{Plat}, airway resistance, compliance)

**Risk:** Patient at risk for ↑ pressures → barotrauma (and volutrauma if set volume too high!)
Volume control (VC) in AC or SIMV mode, vent delivers variable pressure (depending on real-time lung compliance) to achieve set VT. Volume support (VS) sample principle in spontaneous mode. |
| Pressure targeted | Vent delivers a fixed inspiratory pressure regardless of VT.
VT depends on airway resistance and lung/chest wall compliance

**Benefit:** May ↑ patient comfort (PSV) requiring less sedation

**Risk:** Pt at risk for ↓ volumes → inadequate VE. |
| Other | Proportional assist ventilation (PAV): vent delivers variable pressure (depending on real-time lung mech.) to achieve targeted % of work of breathing.
Airway pressure release ventilation (APRV): vent keeps lungs inflated at high pressure w/ intermittent release to allow for exhalation via passive recoil
Neurally adjusted ventilator assist (NAVA): vent support proportional to diaphragmatic electrical activity sensed using esophageal electrode |
| General principles | Institutional/practitioner preference and patient comfort usually dictate ventilator strategy; no strategy has proven superior

**Common reasons for Δ include:** dyssynchrony, poor gas exchange, Δ mech. resp properties, Δ goals of care (eg, sedation, weaning, lung protection)

**Alarms** can be set for ↑ volumes and ↑ airway pressures in pressure-targeted and volume-targeted strategies, respectively
**Step 3: Set or Remaining Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F_{O_2}</td>
<td>Fraction of inspired air that is oxygen</td>
</tr>
<tr>
<td>Positive end-expiratory pressure (PEEP)</td>
<td>Positive pressure applied during exhalation via resistor in exhalation port. Benefits: prevents alveoli collapse, ↓ intrapulmonary shunt, ↑ O_{2}. 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, &quot;breath stacking&quot;); if flow at end-expiration, there must be pressure − auto-PEEP. Will ↓ preload and may ↓ CO, especially if hypovolemic. Will ↓ work of breathing as must be overcome by Pt to trigger breaths; can prevent Pt from successfully triggering ventilator. Can be detected if end-expiratory flow &lt; 0 before next breath. Can measure by occluding expiratory port of vent at end-expiration. Can ↓ by: ↑ exp time, ↓ RR, ↓ V_t, Rx bronchospasms and secretions.</td>
</tr>
<tr>
<td>Inspiratory time</td>
<td>Normally I:E ratio is ~1:2; however, can alter I time (and consequently flow rate, see later); use in pressure-control mode.</td>
</tr>
<tr>
<td>Inspiratory flow rates</td>
<td>↑ flow rate → ↑ I time → ↑ E time → ↓: may improve ventilation in obstructive disease, but may affect resp rate and bronchodilation/constriction.</td>
</tr>
<tr>
<td>Peak inspiratory pressure (PIP)</td>
<td>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.</td>
</tr>
<tr>
<td>Plateau pressure (P_{plat})</td>
<td>Static measurement at the end of inspiration when there is no flow. Determined by resp system compliance (resist. not a factor since flow).</td>
</tr>
</tbody>
</table>

**Initial Settings**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Tidal volume</th>
<th>Respiratory rate</th>
<th>F_{O_2}</th>
<th>PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assist control volume-targeted</td>
<td>4–8 mL/kg IBW</td>
<td>12–14 breaths/min</td>
<td>1.0 (ie, 100%)</td>
<td>5 cm H_{2O}</td>
</tr>
</tbody>
</table>

*Goal for ARDS; ventilation at V_t > 8 mL/kg may be injurious in other types of ventilated pts as well.*

**Noninvasive Ventilation**

**Conditions**


**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_{CO_2} > 45 (& significantly worse than baseline), hypoxemia, P_{O_2}/F_{O_2} < 200.

**Contraindications** *(JAMA 2002:288:932)*

Claustrophobia, inability to fit mask, MS, vomiting, unable to protect airway, extrapulm organ failure, hemodyln instab, serv UGIB.

**Continuous positive airway pressure (CPAP)**

PEEP. No limit on O_{2} delivered (ie, can give hi-flow → F_{O_2} = 1.0). Used if primary problem hypoxemia (eg, CHF).

**NPPV/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}).

**Mask ventilation**

Tight-fitting mask connecting patient to a standard ventilator. Can receive PS ~ 20–30 cm H_{2O}, PEEP ~ 10 cm H_{2O}, F_{O_2} ~ 1.0. Used for short-term support (~24 h) for a reversible process.
Tailoring the ventilator settings

- To improve oxygenation: options include ↑ FiO₂, ↑ PEEP.
  First, ↑ FiO₂. If ↓ 0.6 and oxygenation remains suboptimal, then try ↑ PEEP.
  If ↑ Pplat/FiO₂ and Ppred stable, suggests recruitable lung (ie, atelectasis). Continue to ↑ PEEP until either can ↓ FIO₂ to < 0.6 or Pplat < 30 cm H₂O. If PEEP 20 & FiO₂ 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see ARDS).
  If ↑ PEEP → c or ↓ Pplat/FiO₂ or ↑ PcO₂ suggests additional lung not recruitable and instead overdistending lung → shunt & dead space; ↓ PEEP.
- To improve ventilation: ↑ VT or inspiratory pressure, ↑ RR (may need to ↓ I time). Nb, tolerate ↑ PcO₂ (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.

Weaning from the ventilator
- Weaning strategy: spontaneous breathing trial (SBT) for pts who meet screening criteria (qv) better than gradual weaning of PSV or SIMV (NEJM 1995;332:345). Daily awakening (d/c all sedation; pass if open eyes & w/o: agitation, RR < 35, SSO₂ < 88%, resp distress or arrhythmias) followed by SBT better than SBT alone (Lancet 2008;371:126).
- Identify pts who can breathe spontaneously (NEJM 1991;324:1445 & 1996;335:1864) screening criteria: sedation reversed, VS stable, minimal secretions, adequate cough, cause of respiratory failure or previously failed SBT reversed vent parameters: Pplat/FiO₂ > 200, PEEP ≤ 5, fVT < 105, V₆ < 12 L/min, VC > 10 mL/kg rapid shallow breathing index (fVT/V₆) > 105 predicts failure; NPV 0.95 (NEJM 1991;324:1444) SBT – CPAP or T piece x 30–120 min (ARCCM 1999;159:512) failure if: deteriorating ABGs, ↑ RR, ↑ or ↓ HR, ↑ or ↓ BP, diaphoresis, anxiety Tolerate SBT → extubation. Fail SBT → ? cause → work to correct → retry SBT qd

Complications
- Barotrauma and volutrauma (eg, PTX, pneumomediastinum)
  high PIPs usually safe unless ↑ Pplat (< 30 cm H₂O, but lower better) → alveolar damage
- Oxygen toxicity (theoretical): proportional to duration + degree of ↑ oxygen (FiO₂ > 0.6)
- Alterations in cardiac output (eg, PEEP can ↓ preload → hypotension)
- Ventilator-associated pneumonia (~ 1%/day, mortality rate ~ 30%)
- Laryngeal edema: for pts vent > 36 h; ? predicted by ᵃ 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)

Figure 2-7 Approach to acute ventilatory deterioration

(Adapted from Marino PL. The ICU Book, 3rd ed., Philadelphia: Lippincott Williams & Wilkins, 2007:467)
ACUTE RESPIRATORY DISTRESS SYNDROME

**Definition & Presentation** (NEJM 2000;342:1334; American-Euro Consensus Conf 1994)

- **Acute onset**: (<24 h)
- **Bilateral patchy airspace disease** (need not be diffuse)
- **Noncardiogenic pulmonary edema** (PCWP <18 or no clinical evidence of ↑ LAP)
- **Severe hypoxemia**: PaO₂/FiO₂ <200 → ARDS; PaO₂/FiO₂ <300 → ALI (acute lung injury)
- **Chest CT**: heterogeneous lung with densities greater in dependent areas
- **Lung bx**: classically shows diffuse alveolar damage (DAD); bx not required but often provides useful dx information (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**: V̇T/(Pplat – PEEP) <30 mL/cm H₂O

**Etiologies**

<table>
<thead>
<tr>
<th><strong>Direct Injury</strong></th>
<th><strong>Indirect Injury</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia (-40%)</td>
<td>Inhalation injury</td>
</tr>
<tr>
<td>Aspiration (-15%)</td>
<td>Lung contusion</td>
</tr>
<tr>
<td>Near drowning</td>
<td>DIC</td>
</tr>
<tr>
<td></td>
<td>Transfusion (TRALI)</td>
</tr>
</tbody>
</table>


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

**Mechanisms of VILI**

**Ventilator Strategies**

<table>
<thead>
<tr>
<th><strong>Barotrauma/volutrauma</strong></th>
<th><strong>V̇T ≤6 mL/kg</strong>, Pplat ≤30 cm H₂O, tolerate ↑ ṖCO₂ (but keep pH &gt;7.15), ↑ mortality (NEJM 2000;342:1301). Weight risk/benefit of sedation &amp; paralysis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biotrauma</strong> → SIRS</td>
<td>Low V̇T, open lung strategy w/ high PEEP</td>
</tr>
<tr>
<td><strong>Atelectrauma</strong></td>
<td>Titrated PEEP to prevent tidal alveolar collapse Variable benefit in different studies, Pt subgps. No benefit at given V̇T if titrated to ṖCO₂ alone (NEJM 2004;351:327; Jama 2008;299:637). If titrated to ṖCO₂ 28–30 cm H₂O → ↓ time on vent, better lung mechanics (JAMA 2008;299:646). ↑ mortality (JAMA 2010;303:865). If able to ↑ PEEP w/o ↑ Pplat, suggests “recruitability.” ↓ ↓:PEEP if → ↑ S₂O₂; target S₂O₂ ≥88%–90% &amp; Pplat ≤30</td>
</tr>
<tr>
<td><strong>Hyperoxia</strong>: ↑ injury; worsened V/Q matching</td>
<td>↑ PEEP rather than F₂O₂ (keep &lt;0.60) O₂-induced injury only theoretical in humans</td>
</tr>
</tbody>
</table>

See ARDSnet.org for ventilator protocol.

- **Fluid balance**: target CVP 4–6 cm H₂O (if nonoliguric & normotensive) → ↑ vent/ICU-free days, but no mortality difference (NEJM 2006;354:2564)
- **PA catheter for fluid management** → ↑ complications vs. CVP only (NEJM 2006;354:2213)
- **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); ↓ mort, ↑ vent/ICU-free days in 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)

**Experimental**

- **Inhaled nitric oxide**: no proven ↓ PAP, can ↑ ṖO₂/ḞO₂, no ↓ mort or vent-free days (BMJ 2007;334:779); inhaled prostacyclins similar physiologically, similar effect
- **Prone ventilation**: ↑ ṖO₂, but ↑ complications and no ↓ mortality (JAMA 2009;302:1977)
- **High-frequency oscillatory ventilation**: no mort benefit (AJRCCM 2002;166:801), can transiently ↑ ṖO₂ (Chest 2007:131:1907)
- **Lung recruitment**: apply CPAP 40–45 cm H₂O × 2 min to recruit lung and then ↑ PEEP to maintain; sicker Pts had ↑ recruitable lung (NEJM 2006;354:1775, 1839)
- **Esoph manometry**: adjust PEEP according to esoph pressure (~pleural pressure) to maintain positive transpulm pressure → ↑ ṖO₂/ḞO₂, ↑ compliance and possible outcome benefit (NEJM 2008;359:2095)

**Prognosis**

- **Mortality**: ~40% overall in clinical trials; 9–15% resp. causes, 85–91% extrapulm (MODS)
- **Survivors**: PFTs normal, ↓ DlCO; muscle wasting, weakness persists (NEJM 2003;348:683)
SEPSIS

Definitions

<table>
<thead>
<tr>
<th>Systemic Inflammatory Response Syndrome (SIRS)</th>
<th>2 or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Temp &gt;38 or &lt;36°C,</td>
<td></td>
</tr>
<tr>
<td>(2) HR &gt;90,</td>
<td></td>
</tr>
<tr>
<td>(3) RR &gt;20 or P_{CO}_2 &lt;32,</td>
<td></td>
</tr>
<tr>
<td>(4) WBC &gt;12,000 or &lt;4000 or &gt;10% bands</td>
<td></td>
</tr>
</tbody>
</table>

| Sepsis                                       | SIRS + suspected infection  |
| Severe Sepsis                                | Sepsis + organ dysfunction, hypoperfusion or hypotension |
| Septic Shock                                 | Sepsis-induced hypotension despite adequate fluid resuscitation, along with signs of hypoperfusion |

(Ches 1992;101;1644)

Fluids & Vasoactive Drugs

**Early goal-directed therapy** (“Rivers Protocol”, NEJM 2001;345:1368)
- Insert arterial & central venous lines (NEJM 2007;356:e21; PAC not needed) and √ MAP, CVP, & central venous (no need for mixed venous) O₂ sat
- Target MAP ≥ 65 mm Hg, CVP 8–12 mm Hg, & UOP ≥ 0.5 mL/kg/h using fluid (eg, 500 mL NS q30min) and vasopressors as needed
- Target S₂ O₂ ≥ 70% using PRBCs & inotropes (dobutamine, ↑ dose as needed q15min)
- When done w/in first 6 h for severe sepsis & septic shock, 42% ↓ mortality

- Normal saline as good as albumin for resuscitation (NEJM 2004;350:2247)
- Norepinephrine preferred to dopamine (i arrhythmias & trend ↓ mort.; NEJM 2010;362:779)
- Vasopressin added to low-dose norepinephrine not superior to high-dose norepinephrine (NEJM 2008;358:877); consider if HoTN refractory to catecholamine vasopressors

- Use PRBC w/ caution, may ↑ mortality/morbidity, ↑ risk of ARDS (Crit Care Med 2005;33:1191); ↓ goal Hb 7 unless active cardiac ischemia (NEJM 1999;340:409)
- After early resuscitation, if ALI/ARDS, target CVP 4–6 mm Hg as additional fluids may be harmful → ↑ ventilator/ICU days (NEJM 2006;354:2564; Chest 2008;133:252)
- Pulse pressure variation >13% with respiration → likely volume-responsive (Ches 2008;133:252); only validated in passive, intubated Pts

Antibiotics

- If possible, obtain 2 sets of BCx before starting abx
- Start empiric IV abx w/in 1 h of recognition of severe sepsis or septic shock
- Typically want broad gram-positive and gram-negative coverage, including MRSA and highly resistant gram-negative bacilli ± anaerobes

Steroids (NEJM 2003;348:727; JAMA 2009;301:2362)
- ACTH stimulation test helps predict mortality in sepsis, does not predict benefit from corticosteroid therapy (JAMA 2000;283:1038; NEJM 2008;358:111)
- Earlier study showed 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;288:882)
- No mortality benefit to early (<72 h) empiric corticosteroids in all Pts w/ septic shock, regardless of ACTH stim; faster resolution of shock, more superinfection (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)

Activated Protein C

- Remains controversial: 6% absolute ↓ mort., but ↓ bleeding (NEJM 2003:344:699); no mort. benefit if low risk of death (APACHE < 25 or single organ failure, NEJM 2005;353:1332)
- ↑ if APACHE > 25 or multi-organ failure w/o contraind. (Crit Care Med 2008:36:296)

Intensive Glycemic Control

- No evidence of improved outcomes in MICU population w/ intensive glycemic control
- Intensive glycemic control to goal 80–110 mg/dL in surgical ICU population → mortality benefit, greatest if >3-d ICU stay (NEJM 2001;345:1339)
- More recently, intensive glycemic control → either no Δ or ↑ increased mortality, and definite ↑ hypoglycemia (JAMA 2008;300:933; NEJM 2006;354:449; 2008;358:125; 2009;360:1283)
- Reasonable to keep glc < 150 mg/dL in severe sepsis, using validated protocol (Crit Care Med 2008;36:296)
ESOPHAGEAL AND GASTRIC DISORDERS

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)

- Mechanical Obstruction
  - difficulty w/ solids only
  - Ring, Web
  - Eos esophagitis
  - Peptic stricture

- Motility Disorder
  - difficulty w/ solids & liquids
  - intermittent sx
  - Achalasia
  - Scleroderma, Amyloid, DM

Achalasia

• Etiologies: idiopathic (most common), pseudoachalasia (due to GE jxn tumor), Chagas
• Sx: dysphagia (solid & liquid), chest pain (1/3 of Pts), regurgitation
• Dx: barium swallow
  - S dilated esophagus w/ distal “bird’s beak” narrowing; manometry
  - simultaneous, low amplitude contractions of esophageal body, incomplete relaxation of lower esophageal sphincter (∼LES hypertension); EGD → r/o pseudoachalasia (retroflex)
• Rx: Heller myotomy; balloon dilatation (2% eso perf); botulinum toxin (poor surg cand)

Other Esophageal Disorders

• Webs (upper or mid esoph; congenital, GVHD, Fe-defic anemia); Rings (lower; ? due to GERD); Zenker’s diverticulum (pharyngooesoph jxn); dx w/ barium swallow; Rx endo/surg
• Infx esophagitis: odynophagia > dysphagia; often immunosupp w/ Candida, HSV, CMV
• Pill esophagitis: odynophagia > dysphagia; NSAID, KCl, bisphosp., doxy & tetracycline
• Eos esophagitis: EGD w/ ringed, corrugated eso, stricture, >15 eos/hpf on bx; Rx steroids

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Pathophysiology

• Excessive transient relaxations of lower esophageal sphincter (LES) or incompetent LES
• Mucosal damage (esophagitis) due to prolonged contact w/ acid can evolve to stricture
• Risk factors: hiatal hernia, obesity, gastric hypersecretory states, delayed emptying
• Precipitants: supine position, fatty foods, caffeine, alcohol, cigarettes, CCB, pregnancy

Clinical manifestations

• Esophageal: heartburn, atypical chest pain, regurgitation, water brash, dysphagia
• Extrasophageal: cough (often poorly controlled), laryngitis, dental erosions

Diagnosis (Gastro 2008;135:1383)

• Based on hx and empiric trial of PPI (Se & Sp: 78% & 54%) (Annals 2004;140:518)
• EGD if failure to respond to BID PPI or alarm features: dysphagia, odynophagia, vomiting, wt loss, Fe-defic anemia, FOBT, palpable mass or adenopathy, age >55 y
• If dx uncertain & EGD nl → high res manometry w/ 24-h esophageal pH monitoring

Treatment (NEJM 2008:359:1700)

• Lifestyle: avoid precipitants, lose weight, avoid large & late meals, elevate head of bed
• Medical: PPI (up to BID) > H2RA, espec. if esophagitis (Coch 2007;2:003244), antacids
  - PPI achieve relief in 80–90%; side effects: diarrhea, H/A, ↑ risk of C. diff & hip fx
• Surgical: fundoplication if refractory sx on meds: success >90%, but >1/2 on meds after 10 y
Complications (NEJM 2009;361:2548)

- Barrett's esophagus: 10–15% ofPts w/ GERD, compared w/ 5–6% w/o GERD
- Esophageal adenocarcinoma: risk ~0.5%/y if Barrett's, ~1.6%/y if low-grade dysplasia, 6%/y if high-grade dysplasia
- Management: surveillance EGD w/ bx (or high-res imaging w/ narrow-band or OCT)
- Barrett's w/ no dysplasia: surveillance q 3 y; low-grade dysplasia: q 6 mos
  - High-grade: endoscopic mucosal resection to r/o cancer; then RFA or other ablative Rx

**ESOPHAGEAL DYSPEPSIA (“INDIGESTION”)**

**Definition**

- Upper abdominal sx: discomfort, pain, fullness, bloating, burning

**Etiologies**

- **Functional** (“nonulcer dyspepsia” or NUD ~60%): some combination of visceral afferent hypersensitivity & abnormal gastric motility (Rome III criteria in Gastro 2006;130:1377)
- **Organic** (~40%): GERD, PUD, rarely gastric cancer, other (meds, diabetic gastroparesis, lactose intolerance, biliary pain, chronic pancreatitis, mesenteric ischemia)
- **Alarm features** that suggest organic cause & warrant EGD: see list above under GERD

**Treatment of functional dyspepsia (NUD)** (Gastro 2005;129:1756)

- *H. pylori* eradication → empiric Rx if serology, NNT = 14 (Cochrane 2006(2) CD002096)
- PPI effective in some (? misdx GERD), other → prokinetics, TCA

**PEPTIC ULCER DISEASE (PUD)**

**Epidemiology & Etiologies** (Lancet 2009;374:1449)

- Lifetime prevalence ~10%, but incidence ↓ b/c ↓ incidence of *H. pylori* and potent acid suppression Rx. However, incidence of hospitalization for complications un↓d (in fact ↑ in elderly; likely 2° to NSAID use).
- *H. pylori* infection: 80% of duodenal ulcers (DU) and 60% of gastric ulcers (GU) ~50% of population colonized w/ *H. pylori*, but only 5–10% will develop PUD
- *ASA & NSAID*: 45% erosions, 15–30% GU, 0.1–4% UGIB
- Hypersecretory states (often mult. recurrent ulcers): gastrinoma (Zollinger-Ellison syndrome, also p/w diarrhea, <1% of PUD), carcinoid, mastocytosis
- Malignancy: 5–10% of GU
- Other: smoking, stress ulcers (if CNS process = “Cushing’s”; if burn = “Curling’s”), XRT, chemo, CMV or HSV (immunosupp), bisphosphonates; steroids alone not a risk factor, but may exacerbate NSAID-induced ulceration

**Clinical manifestations**

- *Epigastric abdominal pain*: relieved with food (DU) or worsened by food (GU)
- Complications: UGIB, perforation & penetrative, gastric outlet obstruction

**Diagnostic studies**

- **Test for *H. pylori***
  - Serology: Se ~80%, Sp >90%; not useful to confirm erad. as can stay + wks to y
  - Stool antigen: Se & Sp >90%; use to confirm erad.; high false + in acute GIB
  - EGD + rapid urease test (Se & Sp >95%) or histo: false + if on abx, bismuth, PPI
  - EGD req to def make dx; consider if fail empiric Rx or alarm features; bx GU to r/o malign; relook in 6–12 wks if apparently benign ulcer is lg or complicated or sx persist despite Rx

**Treatment** (NEJM 2010;362:1597)

- **If *H. pylori* +, eradicate**: 
  - Triple Rx: clarith 500 bid + amox 1 g bid + PPI bid × 10–14 d (but ↑ clarith resist rates)
  - Quadruple Rx: MNZ + TCN + bismuth + PPI (if *H. pylori* resist to clarith or amox allergy)
  - Sequential Rx (PPI + abx × 5 d → PPI + 2 different abx × 5 d): erad. rates >90% emerging as poss 1st-line Rx (Annals 2008;148:923)

- Besides PUD, test & Rx if: gastric MALT lymphoma, atrophic gastritis, FHX gastric ca
- **If *H. pylori* − gastric acid suppression w/ PPI**
- **Discontinue ASA and NSAIDs; add 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 (above) in ICU & coagulopathic, mech vent, h/o GIB, steroid use; Rx w/ PPI

**Prophylaxis if ASA/NSAID required** (JACC 2008;52:1502)

- 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 (i.e. PUD & UGIB but ↓ CV effects)** if low CV risk & not on ASA
- **Stress ulcer**: risk factors − ICU & coagulopathic, mech vent, h/o GIB, steroid use; Rx w/ PPI
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
- Signs: hematemesis – blood in vomitus (UGIB); hematochezia – bloody stools (LGIB or rapid UGIB); melena – black, tarry stools from digested blood (usually UGIB, but can be anywhere above and including the right colon)

Etiologies of upper GI bleed (UGIB)
- Peptic ulcer disease (50%): H. pylori, NSAIDs, gastric hypersecretory states
- Varices (10–30%): esophageal ⇒ gastric, 2’ to portal HTN. If isolated gastric ⇒ retching against closed glottis
- Gastritis/gastroptathy/duodenis (15%): NSAIDs, ASA, alcohol, stress, portal hypertensive
- Erosive esophagitis/ulcer (10%): GERD, XRT, infectious (CMV, HSV, or Candida if immunosuppressed), pill esophagitis (bisphosphonate, NSAIDs; ± odynophagia)
- Mallory-Weiss tear (10%): GE junction tear due to retching against closed glottis
- Vascular lesions (5%)
  - Dieulafoy’s lesion: superficial ectatic artery usually in cardia → sudden, massive UGIB
  - AVMs, angiectasias, hered. hemor: telangectasia: submucosal, anywhere in GI tract
  - Gastric antral vascular ectasia (GAVE): “watermelon stomach,” tortuous, dilated vessels; a/w cirrhosis, atrophic gastritis, CREST
  - Aorto-enteric fistula: AAA or aortic graft erodes into 3rd portion of duodenum; p/w “herald bleed”; if suspected, diagnose by endoscopy or CT
- Neoplastic disease: esophageal or gastric carcinoma, GIST
- Oropharyngeal bleeding and epistaxis → swallowed blood

Etiologies of lower GI bleed (LGIB)
- Diverticular hemorrhage (33%): 60% of diverticular bleeding localized to right colon
- Neoplastic disease (19%): usually occult bleeding, rarely severe
- Colitis (18%): infectious, ischemic, radiation, inflammatory bowel disease (UC >> CD)
- Angiodysplasia (8%): most commonly located in ascending colon and cecum
- Anorectal (4%): hemorrhoids, anal fissure, rectal ulcer
- Other: post-polypectomy, vasculitis

Clinical manifestations
- UGIB: LGIB, N/V, hematemesis, coffee-ground emesis, epigastric pain, vasovag, melena
- LGIB: UGIB: diarrhea, tenesmus, BRBPR, hematochezia (11% UGIB; Gastro 1988:95:1569)

Initial Management
- Assess severity: tachycardia suggests 10% volume loss, orthostatic hypotension 20% loss, shock ˃30% loss
- Resuscitation: placement of 2 large-bore (18-gauge or larger) intravenous lines
  - Volume replacement: NS or LR to achieve normal VS, UOP, & mental status
- Transfuse: blood bank sample for type & cross; use O-neg if emergent Transfuse 2–8 U and target Hct 25–30 depending on comorbidities
- Reverse coagulopathy: FFP & vit K to normalize PT; plts to keep count
- Triage: consider ICU if unstable VS or poor end organ perfusion
  - OutPt management if SBP ˃110, HR ˂100, Hb ˃13 (♂) or ˃12 (♀), BUN <18, melena, syncope, heart failure, liver disease (Lancet 2009;373:42)

Workup
- History: where (anatomic location) & why (etiopathology)
  - acute or chronic, prior GIB, # of episodes, other GI dx
  - hematemesis, vomiting prior to hematemesis (Mallory-Weiss), melena, hematochezia
  - abdominal pain, wt loss, anorexia, ∆ in stool caliber
  - ASA/NSAIDs, clopidogrel, anticoagulants, known coagulopathy
  - alcohol (gastritis, varices), cirrhosis, known liver disease, risk factors for liver disease
  - abdominal/rectal radiation, history of cancer, prior G or aortic surgery
- Physical exam: VS most important, orthostatic ∆s, JVP
  - localizable abd tenderness, peritoneal signs, masses, LAN, signs of prior surgery
  - signs of liver disease (hepatosplenomegaly, ascites, etc.)
  - rectal exam: masses, hemorrhoids, anal fissures, stool appearance, color, occult blood
  - pallor, jaundice, telangectasias (alcoholic liver disease or hered. hemor: telangectasia)
- Laboratory 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; pt, PT, PTT, BUN/Cr (ratio >36 in UGIB b/c GI resorption of blood → prerenal azotemia); LFTs...
Diagnostic studies

- **Nasogastric tube** can help for localization: fresh blood → active UGIB; coffee grounds → recent LGIB (can be confused w/ bile); nonbloody bile → ? lower source, but does not exclude active LGIB (~15% missed); occult blood testing of no value

- **UGIB: EGD** for dx and potential Rx, consider erythro 250 mg IV 30 min prior → empty stomach of blood → 1 Dx/Rx yield (Am J Gastro 2006;101:121)

- **LGIB: first r/o LGIB before attempting to localize presumed LGIB, then colonoscopy** (identifies cause in ~70%), consider rapid purge w/ PEG solution 4 L over 2 h

- Unstable or recurrent UGIB & LGIB:
  - **arteriography:** can localize if bleeding rates ≥0.5 mL/min and can Rx (coil, vaso, glue)
  - **tagged RBC scan:** can localize bleeding rates ≥0.1 mL/min for surg but unreliable emergent exploratory laparotomy (last resort)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PUD</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Pharmacologic</strong></td>
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<tr>
<td></td>
<td>octreotide 50 µg IVB → 50 µg/h infusion (84% success). Usually × 5 d, but most benefit w/in 24–48 h.</td>
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<tr>
<td></td>
<td>Abx: cirrhotics w/ any GIB should receive prophylaxis: Cfx IV vs. norfloxacin PO (Hep 2004;39:746 &amp; Gastro 2006;131:1049)</td>
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<tr>
<td></td>
<td><strong>Nonpharmacologic</strong></td>
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<tr>
<td></td>
<td>endoscopic band ligation (~90% success)</td>
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<tr>
<td></td>
<td>arteriography with coiling/glue occasionally for gastric varices</td>
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<tr>
<td></td>
<td>balloon tamponade (Sengstaken-Blakemore) if bleeding severe; mainly used as rescue procedure and bridge to TIPS</td>
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<tr>
<td></td>
<td>TIPS for esophageal variceal hemorrhage refractory to above, or for gastric varices; c/b encephalopathy, shunt occlusion surgery (portocaval/splenorenal shunts) rarely used now</td>
</tr>
<tr>
<td></td>
<td>If active bleeding or non-bleeding visible vessel (NBVV) on EGD</td>
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<td></td>
<td>PPI (eg, omeprazole 80 mg IVB → 8 mg/h) before EGD → ↓ need for endoscopic Rx and ↓ LOS continue IV dose × 72 h following EGD: ↓ rebled rate convert to PO after 72 h</td>
</tr>
<tr>
<td></td>
<td>↓ Octreotide if no access to EGD</td>
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<tr>
<td></td>
<td><strong>Endoscopic therapy</strong> (ET): epi inj + either bipolar cautery or hemoclip; reblooding risk: 43% (NBVV) to 85% (active bleed) w/o ET vs. 15–20% w/ ET vs. &lt;7% w/ ET + PPI (most w/in 48 h)</td>
</tr>
<tr>
<td></td>
<td>Clear liquids 6 h after ET if hemodynamically stable</td>
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<tr>
<td></td>
<td>Arteriography w/ vasopressin or embolization; surgery (last resort)</td>
</tr>
<tr>
<td></td>
<td>If adherent clot</td>
</tr>
<tr>
<td></td>
<td>PPI as above + endo removal of clot (if experienced ctr) to r/o NBVV; reblooding risk 22% w/o ET vs. 5% w/ ET</td>
</tr>
<tr>
<td></td>
<td>If flat, pigmented spot or clean base</td>
</tr>
<tr>
<td></td>
<td>No endo Rx indicated; rebled risk &lt;10%; oral PPI BID</td>
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<tr>
<td></td>
<td>Consider early hospital d/c (see criteria in NEJM 2008;359:928)</td>
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<tr>
<td></td>
<td>If Pt on ASA for CV disease and PUD GIB endoscopically controlled, resume ASA when CV risk &gt; reblooding risk, typically 7 d following index bleed (Annals 2010;152:101)</td>
</tr>
<tr>
<td><strong>Mallory-Weiss</strong></td>
<td>Usually stops spontaneously; endoscopic Rx if active</td>
</tr>
<tr>
<td><strong>Esophagitis</strong></td>
<td>PPI, H₂-receptor antagonists</td>
</tr>
<tr>
<td><strong>Gastritis</strong></td>
<td>PPI, H₂-receptor antagonists</td>
</tr>
<tr>
<td><strong>Diverticular disease</strong></td>
<td>Usually stops spontaneously (~75%)</td>
</tr>
<tr>
<td></td>
<td>Endoscopic Rx (eg, epinephrine injection, cautery, banding, or hemoclip), arterial vasopressin or embolization, surgery</td>
</tr>
<tr>
<td><strong>Angiodysplasia</strong></td>
<td>Usually stops spontaneously (~85%)</td>
</tr>
<tr>
<td></td>
<td>Endo Rx (cautery or argon plasma), arterio w/ vasopressin, surgery</td>
</tr>
</tbody>
</table>

### Obscure GIB (Gastro 2007;133:1694)

- **Definition:** continued bleeding (melena, hematochezia) despite EGD & colo; 5% of GIB

- **Etiologies:** Dieulafoy’s lesion, small bowel angiodysplasia or cancer, Crohn’s disease, aortoenteric fistula, Meckel’s diverticulum (2% of pop., remnant of vitelline duct w/ ectopic gastric mucosa), hemobilia

- **Diagnosis:** repeat EGD w/ push enteroscopy/colon—perform when bleeding is active
  - If perform video capsule to evaluate small intestine (Gastro 2009;137:1197)
  - If still consider 99mTc-pertechnetate scan (“Meckel’s scan”), double-balloon enteroscopy, tagged RBC scan, and arteriography
# DIARRHEA, CONSTIPATION AND ILEUS

## Acute Diarrhea (<4 wk)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Epidemiology &amp; Clinical Sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninflammatory</td>
<td>Predom. disruption small intestine absorp. &amp; secretion. Voluminous diarrhea. N/V. © fecal WBC &amp; FOB.</td>
</tr>
<tr>
<td>Preformed toxin</td>
<td>&quot;Food poisoning.&quot; &gt;24 h dur. S. aureus (meats &amp; dairy), B. cereus (fried rice), C. perfringens (rewarmed meats).</td>
</tr>
<tr>
<td>Viral</td>
<td>Rotavirus</td>
</tr>
<tr>
<td></td>
<td>Norovirus</td>
</tr>
<tr>
<td>Bacterial</td>
<td>E. coli (toxigenic)</td>
</tr>
<tr>
<td></td>
<td>Vibrio cholerae</td>
</tr>
<tr>
<td>Parasitic</td>
<td>Giardia (± malab for mos after Rx)</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidia</td>
</tr>
<tr>
<td></td>
<td>Cyclospora</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Predom. colonic invasion. Small vol diarrhea. LLQ cramps. tenesmus. fever, typically © fecal WBC or FOB.</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Campylobacter</td>
</tr>
<tr>
<td></td>
<td>Salmonella (nontyphoid)</td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
</tr>
<tr>
<td></td>
<td>E. coli (O157:H7 &amp; non-O157:H7)</td>
</tr>
<tr>
<td></td>
<td>C. difficile</td>
</tr>
<tr>
<td></td>
<td>Vibrio parahaem.</td>
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<tr>
<td></td>
<td>Salmonella typhi</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Parasitic</td>
<td>E. histolytica</td>
</tr>
<tr>
<td>Viral</td>
<td>CMV</td>
</tr>
</tbody>
</table>


- **Hx**: stool freq, bloody, abd pain, duration of sxs [-1 wk for viral & bacterial (except C. diff), >1 wk for parasitic], travel, food, recent abx
- **PEx**: vol depletion (VS, UOP, axillae, skin turgor, MS), fever, abd tenderness, ileus, rash
- **Further evaluation if warning signs**: fever, signific abd pain, blood or pus in stools, >6 stools/d, severe dehydration, immunosupp., elderly, duration >7 d, hosp-acquired
- **Etiology established in only ~3% of community-acquired diarrhea**
- **Laboratory**: fecal WBC (high false © & ✓ fecal calprotectin or lactoferrin), stool cx, BCx, lytes, C diff (if recent hosp or abx), stool O & P (if >10 d, travel to endemic area, exposure to unpurified H2O, community outbreak, daycare, HIV © or MSM) ± stool ELISAs (viruses, Crypto, Giardia), serologies (E. histolytica), special stool cx
- **Imaging/endoscopy**: CT/KUB if ≥ toxic megacolon; sig/colo if immunosupp or cx ©
- **Ddx**: infxn vs. preformed toxin vs. med-induced vs. initial presentation of chronic diarrhea

**Treatment**

- 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/ H2O or Gatorade, etc. If severe, LR IV.
- For traveler’s diarrhea, bismuth or rifaximin useful for prophylaxis & empiric Rx
• **Empiric abx for non-hospital-acquired inflammatory diarrhea reasonable: FQ × 5–7 d abx rec for Shigella, cholera, *C. diff*, *Giardia*, amebiasis, *Salmonella* if Pt >50 y or immunosupp. or hospitalized, † *Campylobacter* (if w/in 4 d of sx onset, Rx w/ azithro) avoid abx if suspect *E. coli* O157:H7 as may † risk of HUS

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**CLOSTRIDIUM DIFFICILE**

**Pathogenesis**
- Ingestion of *C. difficile* spores → colonization when colonic flora Δd by abx or chemo → release of toxin A/B → colonic mucosal necrosis & inflammation → pseudomembranes
- † toxic genic strain (NAP-1/027) † mort. & length of hosp. (esp. in elderly) (NEJM 2008;359:1932)
- † Additional risk factors: elderly, nursing home residents, IBD, ? PPI exposure

**Clinical manifestations (a spectrum of disease)**
- A sx colonization: <3% healthy adults; ~20% in hospitalized patients on antibiotics
- Acute watery diarrhea (occ bloody) ± mucus, often w/ lower abd pain, fever, ††† WBC
- Pseudomembranous colitis: above sx + pseudomembranes + bowel wall thickening
- Fulminant colitis (2–3%): toxic megacolon (colonic dilatation ≥ 6 cm on KUB, colonic atony, systemic toxicity) and/or bowel perforation

**Diagnosis**
- Stool ELISA: detects toxin A and/or B; fast (2–6 h); Se 90–95% if A
- Stool cytotoxin assay: gold standard, highly Se & Sp, but takes 24–48 h
- Consider flex sig if dx uncertain and/or evidence of no improvement w/ standard Rx

**Treatment** (Gastro 2009;136:1899)
- In everyone: start contact precautions, if possible d/c abx ASAP; stop antimotility agents
- Mild (<6 BM/d, temp <101°F, WBC <15 k, no peritoneal sx or SIRS, and age <65 y)
  - Rx: MNZ 500 mg PO tid × 10–14 d; IV equal efficacy, use if poor PO or ileus
- Moderate (6–12 BM/d, temp 101–103°F, WBC 15–25 k, visible LGIB, or age >65 y)
  - Rx: vanco 125–500 mg PO qid × 10–14 d; add MNZ 500 IV tid if not improved by 48 h
- Severe (>12 BM/d, temp >103°F, WBC >25k, † abd pain, sepsis, or no bowel sounds)
  - Rx: vanco PO + MNZ IV; PR vancomycin available if ileus, though avoid if evidence of toxic megacolon; † tigecycline (CID 2009;48:1732); Ab CT, urgent surgery consult re: colectomy; consider IVIG
- If Pt needs to stay on original abx, continue *C. diff* Rx for >7 d post-abx cessation
- Stool carriage may persist 3–6 wk post-treatment and should not trigger further Rx
- Recurrent infection: 15–30% risk after d/c of abx, most w/in 2 wk of stopping abx
  - 1st relapse: if mild; repeat 14-d course of MNZ or vanco
  - 2nd relapse: PO vanco taper for 6 wk
  - >2 relapses: vanco taper & adjunctive Rx such as *S. bovulardi*, probiotics, rifaximin, *nitazoxanide*, or *cholestyramine* (will bind vanco so cannot take concurrently)
  - Antitoxin A/B Ab to prevent recurrent infxn under study (NEJM 2010;362:197)

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**CHRONIC DIARRHEA** (≥4 WK; Gastro 2004;127:287)

**Medications** (cause † secretion, † motility, Δ flora, † cell death, or inflammation)
- PPI, cholchicine, abx, H2RA, SSRIs, ARBs, NSAIbs, chemo, caffeine

**Osmotic († osmotic gap, ‡ fecal fat, † diarrhea with fasting)**
- Lactose intolerance: seen in 75% nonwhites & in 25% whites; can be acquired after gastroenteritis, med illness, GI surgery. Clinical: bloating, flatulence, discomfort, diarrhea. Dx: hydrogen breath test or empiric lactose-free diet. Rx: lactose-free diet, use of lactaid milk and lactase enzyme tablets.
- Other: lactulose, laxatives, antacids, sorbitol, fructose

**Malabsorption († osmotic gap, † fecal fat, † diarrhea with fasting)**
- **Celiac disease** (NEJM 2007;357:1731)
  - Immune rxn in genetically predisposed Pts (~1% pop) to gliadin, a component of gluten (wheat protein) → small bowel inflammatory infiltrate → crypt hyperplasia, villus atrophy → impaired intestinal absorption
  - Other sls: Fe/folate defic anemia; osteoporosis; dermatitis herpetiformis (pruritic papulovesicular); † AST/ALT
Dx: IgA antitissue transglutaminase or anti-endomysial Ab has ≈ 90% Se & ≈ 98% Sp (JAMA 2010;303:1738). Small bowel bx and response to gluten-free diet definitive.

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

Complic: 5% refractory (sx despite strict dietary adherence), 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 cep

- Bacterial overgrowth: ↑ small intestinal bacteria from incompetent/absent ileocecal valve, s/p RYGB, scleroderma, diabetes, s/p vagotomy → fat & CHO malabsorption.
  - Dx: [14C]-xylose & H+ breath tests; Rx: cyclox abx (eg, MNZ, FQ, rifaximin)

- Pancreatic insufficiency: most commonly from chronic pancreatitis or pancreatic cancer
  - ↓ bile acids due to ↓ synthesis (cirrhosis) or cholestasis (PBC) → malabsorption
  - Other: s/p short bowel resection (short bowel syndrome), Crohn’s disease, chronic mesenteric ischemia, eosinophilic gastroenteritis, intestinal lymphoma, tropical sprue

Inflammatory (↑ fecal WBC or lactoferrin or calprotectin, ↑ FOB, fever, abd pain)

- Infections: particularly parasitic (incl above pathogens & Strongyloides), CMV, TB

- Inflammatory bowel disease
  - Radiation enteritis, ischemic colitis, neoplasia (colon cancer, lymphoma)

Secretory (normal osmotic gap, no ↑ diarrhea after NPO, nocturnal diarrhea freq described)

- Hormonal:VIP (VIPoma, Verner-Morrison), serotonin (carcinoid), thyroxine, calcitonin (medullary cancer of the thyroid), gastrin (Zollinger-Ellison), glucagon, substance P

- Laxative abuse
  - Neoplasm: carcinoma, lymphoma, villous adenoma
  - ↓ bile acids absorption (s/p ileal resection, Crohn’s) → colonic exposure & ↑ secretion
  - Lymphocytic colitis, collagenous colitis (often a/w meds, including NSAIDs)

Motility (normal osmotic gap)

- Irritable bowel syndrome (10–15% of adults; NEJM 2008;358:1692)
  - Due to altered intestinal motility/secretion in response to luminal or environmental stimuli w/ enhanced pain perception and dysregulation of the brain-gut axis
  - Rome III criteria: recurrent abd pain ≥ 3 d/mo over last 3 mo plus ≥ 2 of following: (i) improvement w/ defecation, (ii) onset w/ ↑ freq of stool, (iii) onset w/ ↓ in form of stool
  - Scleroderma; diabetic autonomic neuropathy; hyperthyroidism; amyloidosis; s/p vagotomy

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**Figure 3-2 Workup of chronic diarrhea**
CONSTIPATION & ADYNAMIC ILEUS

**Constipation** (NEJM 2003;349:1360)

- **Definition (Rome III):** ≥2 of the following during last 3 mo at least 25% of time: straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction, manual maneuvers to facilitate defecation, stool frequency <3 per wk

- **Etiology**
  - Functional: normal transit, slow transit, pelvic floor dysfunction, constipation-predom IBS
  - Meds: opioids, anticholinergics (TCAs & antipsychotics), Fe, CCB, diuretics, NSAIDs
  - Obstruction: cancer, stricture, rectocele, anal stenosis, extrinsic compression
  - Metabolic/endo: DM, hypothyroid, uremia, preg, panhypopit, porphyria, ↑ Ca, ↓ K, ↓ Mg
  - Neuro: Parkinson’s, Hirschsprung’s, amyloid, MS, spinal injury, autonomic neuropathy

- **Diagnosis:** H&P w/ DRE. Labs: consider CBC, electrolytes w/ Ca, TSH. Colonoscopy if alarm sx: wt loss, ↓ FOBT, fevers, FHx of IBD or colon cancer. Sigmoidoscopy if no alarm sx & ≥50 y/o.
  - For functional constipation: sitzmark study, anorectal manometry, defecography

- **Treatment:**
  - Bulk laxatives (fiber ≥20 g/d) → osmotic laxative → stimulant laxative
  - Bulk laxatives (psyllium, methylcellulose, 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)

**Adynamic ileus**

- **Definition:** loss of intestinal peristaltis in absence of mechanical obstruction

- **Precipitants:** intra-abd process (surgery, pancreatitis, peritonitis); severe medical illness (eg, PNA, sepsis); intestinal ischemia; meds (opiates, anticholinergics); electrolyte abnl

- **Clinical manifestations:** abd. discomfort, N/V, hiccups, abd. distention, ↓ or absent bowel sounds, no peritoneal signs (unless perforation); cecum ≥10–12 cm → ↑ rupture

- **Dx:** supine & upright KUB vs. CT→ gas-filled loops of small & large intestine. Must exclude mechanical obstruction (absence of gas in rectum).

- **Treatment:** NPO, mobilize (walk, roll), d/c drugs that ↓ intestinal motility, enemas; decompression (NGT, rectal tubes, colonoscope); erythromycin, neostigmine
DIVERTICULAR DISEASE

DIVERTICULOSIS

Definition and Pathobiology (Lancet 2004;363:631)
• Acquired herniations of colonic mucosa and submucosa through the colonic wall
• May be a consequence of low-fiber diet \(\uparrow\) stool transit time and \(\downarrow\) stool volume \(\uparrow\) intraluminal pressure \(\rightarrow\) herniation at site of relative muscle weakness where vasa recta penetrate to supply blood to colonic mucosa and submucosa

Epidemiology
• Prevalence higher \(\uparrow\) age (10% if <40 y; 50–66% if >80 y); “Westernized” societies
• Left side (90%, mostly sigmoid) \(\rightarrow\) right side of colon (except in Asia, where R>L)

Clinical manifestations
• Usually asx, but 5–15% develop diverticular hemorrhage and 10–25% diverticulitis
• Nuts/seeds/popcorn intake in asx diverticulosis does \(\not\) risk of 1st case of diverticulitis or diverticular bleeding (JAMA 2008;300:907)

DIVERTICULITIS

Pathophysiology (NEJM 2007;357:2057)
• Retention of undigested food and bacteria in diverticulum \(\rightarrow\) fecalith formation \(\rightarrow\) obstruction \(\rightarrow\) compromise of diverticulum’s blood supply, infection, perforation
• Uncomplicated: microperforation \(\rightarrow\) localized infection
• Complicated (25%): macroperforation \(\rightarrow\) abscess, peritonitis, fistula (65% w/ bladder), obstruction, stricture

Clinical manifestations
• LLQ abdominal pain, fever, nausea, vomiting, constipation
• PEx ranges from LLQ tenderness \(\pm\) 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 \(\uparrow\) risk of perforation; do 6 wks after to r/o neoplasm

Treatment (Am J Gastro 2008;103:1550)
• 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
• Severe: inPt Rx if cannot take POs, narcotics needed for pain, or complications
  NPO, IV fluids, NGT (if ileus)
  IV abx (GNR & anaerobic coverage): amp/gent/MNZ or piperacillin-tazobactam
• Abscesses >4 cm should be drained percutaneously or surgically
• Surgery: if progression despite med Rx, undrainable abscess, free perforation, or recurrent disease (\(=\)2 severe episodes)
• Colonic stricture: late complication of diverticulitis; Rx w/ endoscopic dilation vs. resection

Prevention
• Low-fiber diet immediately after acute episode; high-fiber diet when \(>\)6 wks w/o sx
• Consider mesalamine \(\pm\) rifaximin if multiple episodes
• Risk of recurrence 10–30% w/in 10 y of 1st episode; more likely 2nd episode complicated

DIVERTICULAR HEMORRHAGE (also see “Gastrointestinal Bleeding”)

Pathophysiology
• Intimal thickening and medial thinning of vasa recta as it courses over dome of diverticulum \(\rightarrow\) weakening of vascular wall \(\rightarrow\) arterial rupture
• Diverticula more common in left colon; but bleeding diverticula more often in right colon

Clinical manifestations
• Painless hematochezia/BRBPR, but can have abdominal cramping
• Usually stops spontaneously (~75%) but resolution may occur over hrs–days; \(\sim\)20% recur

Diagnostic studies
• Colonoscopy: rapid prep w/ Go-Lytely via NGT (4–6 L over 2–4 h)
• Arteriography \(\pm\) tagged RBC scan if severe bleeding

Treatment
• Colonoscopy: epinephrine injection \(\pm\) electrocautery (NEJM 2000;342:78), hemoclip, banding
• Arteriography: intra-arterial vasopressin infusion or embolization
• Surgery: if above modalities fail & bleeding is persistent & hemodynamically significant
INFLAMMATORY BOWEL DISEASE

Definition
- Ulcerative colitis (UC): idiopathic inflammation of the colonic mucosa
- Crohn's disease (CD): idiopathic transmural inflammation of the GI tract, skip areas
- Indeterminate colitis: in 5–10% of chronic colitis, cannot distinguish UC vs. CD even w/ bx

- 1.4 million people in US, prev 1:1000 UC and 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 + disruption of intestinal barrier (epithelial or ↓ immune) ± Δ in gut microbiome → acute inflam w/o immune downregulation or tolerance → chronic inflam

Ulcerative Colitis (Lancet 2007;369:1641)
Clinical manifestations
- Grossly bloody diarrhea, lower abdominal cramps, urgency, tenesmus
- Severe colitis (15%): progresses rapidly over 1–2 wks w/ ↓ Hct, ↑ ESR, fever, hypotension, >6 bloody BMs per day, distended abdomen w/ absent bowel sounds
- Extracolonic (≥25%): erythema nodosum, pyoderma gangrenosum, aphthous ulcers, uveitis, episcleritis, thromboembolic events (esp during a flare; Lancet 2010;375:657), AIHA, sroenitis arthritis, chronic hepatitis, cirrhosis, PSC (↑ risk of cholangiocarcinoma)

Diagnosis
- Colonoscopy: involves rectum (95%) & extends proximally and contiguously within colon
- Classify by location: proctitis (25–55%), left-sided colitis (ie, sigmoid 50–70%), and pancolitis (20%)
- Appearance: granular, friable mucosa w/ diffuse ulceration; pseudopolyps
- Microscopy: superficial chronic inflammation; crypt abscess and architectural distortion

Complications
- Toxic megacolon (5%): colon dilatation (∼6 cm on KUB), colonic atony, systemic toxicity, & ↑ risk of perfor. Rx w/ IV steroids & broad-spectrum abx; surgery if fail to improve w/in 48–72 h
- Stricture (5%): occurs in rectosigmoid after repeated episodes of inflammation

Prognosis
- 50% of Pts in remission at any given time; intermittent exacerbations in 90%; contniual 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

Crohn's Disease (Lancet 2007;369:1641)
Clinical manifestations
- Smoldering disease w/ abd pain, fevers, malaise, wt loss
- Mucus-containing, non-grossly bloody diarrhea; n/v, bloating, obstipation
- ↓ albumin, ↑ ESR/CRP, ↓ Hct (due to Fe, B12, folate deficiency; chronic inflammation)
- Extracolonic as in UC

Diagnosis
- EGD/Colonoscopy + small bowel imaging (eg, video capsule endoscopy or CT enterography); CD can affect any portion of GI tract w/ skip lesions
- Classify by location: small bowel (47%), ileocolonic (21%), colonic (28%); upper tract rare
- Appearance: nonfriable mucosa, cobblestoning, aphthous ulcers, deep & long fissures
- Microscopy: transmural inflammation w/ mononuclear cell infiltrate, noncaseating granulomas (seen in <25% of mucosal biopsies), fibrosis, ulcers, fissures

Complications
- Perianal disease: fissures, fistulas, perirectal abscesses (up to 30% of Pts)
- Stricture: small bowel, postprandial abd pain; can lead to complete SBO
- Fistulas: perianal, enteroenteric, rectovaginal, enterovesicular, enterovesicouterine
- 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
- High variable: 1 y following dx, 55–65% in remission, 10–30% have flared, 15–25% have low activity, and 13–20% have chronic active course
- At 20 y, majority will have required some surgery; overall life expectancy is slightly ↓

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MANAGEMENT (Lancet 2007;369:1641 & Gastro 2007;133:1670)

**Initial Evaluation**
- H&P (✓ for intestinal & extraintestinal manifestations) and endoscopy as above
- Laboratory: ESR, CRP, CBC, LFTs, Fe, B12, folate, Vit D. Anti-Saccharomyces cerevisiae Abs (ASCA) for CD & p-ANCA for UC have low Se, higher Sp; : not dx.
- Exclude other etiologies: infectious/ischemic colitis, med adverse effect, intestinal lymphoma/carcinoma, colon cancer, IBS, vasculitis, Behcet’s, sprue, bacterial overgrowth
- Rule out infection before treating with immunosuppressants and biologics

**Goals of Treatment**
- Avoid NSAIDs (both UC and CD)
- Induce remission of acute flare
- Convention has been step-up Rx (least toxic)

**Laboratory**
- Colon cancer
- Anti-TNF
- Complications of therapy

**Cancer screening** (Gastro 2010;138:738)
- Colon cancer: risk in UC – 2% at 10 y, ~8% at 20 y, ~18% at 30 y. Similar for colonic CD, except 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 with random biops after dx to eval for dysplasia, q1–3y thereafter based on risk factors. If high-grade dysplasia or dysplasia assoc. lesion/mass → colectomy. Chemoprophylaxis: 5-ASA & ursodeoxycholic acid (if PSC) beneficial.
INTESTINAL ISCHEMIA

**Acute Mesenteric Ischemia (25%)**

**Etiologies**
- SMA embolism (50%): from LA (AF), LV (EF), or valves; SMA most prone to embolism
- Nonocclusive mesenteric ischemia (25%): transient intestinal hypoperfusion due to ↓ CO, atherosclerosis, sepsis, drugs that ↓ gut perfusion (pressors, cocaine, dig, diuretic)
- SMA thrombosis (10%): usually at site of atherosclerosis, often at origin of artery
- Venous thrombosis (10%): hypercoagulable 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**
- Occlusive: sudden abd pain out of proportion to abdominal tenderness on exam at least initially (2–4 h) until severe ischemia → frank infarction w/ peritoneal signs
- Nonocclusive: abd distension & pain, though up to 25% may be pain-free, V/N; often in setting of CHF → h/o chronic mesenteric ischemia sx
- Hematochezia due to mucosal sloughing (right colon supplied by SMA)
- "Intestinal angina": postprandial abd pain, early satiety, & ↓ wt from gastric vascular "steal"; may occur wks to mos before onset of acute pain in pts w/ chronic mesenteric ischemia

**Physical exam**
- May be unremarkable, or may only show abdominal distention; FOBT ~75% of Pts
- Bowel infarction suggested by peritoneal signs (diffuse tenderness, rebound, guarding)

**Diagnostic studies**
- Dx relies on high level of suspicion; rapid dx essential to avoid infarction (occurs w/in h)
- Laboratory: often nl; 75% cWBC; camylase & LDH; 50% acidosis w/ lactate (late)
- KUB: nl early before infarct; “thumbprinting,” ileus, pneumatosis in later stages
- CT angiogram (arterial phase imaging): non-invasive test of choice; can detect thrombi in mesenteric vessels, colonic dilatation, bowel wall thickening, pneumatosis/portal venous gas; venous phase imaging for dx of mesenteric vein thrombosis
- Angiography: gold standard; potentially therapeutic; indicated if suspect occlusion

**Treatment**
- Fluid resuscitation, optimize hemodynamics (minimize pressors); broad-spectrum abx
- Emergent surgery for prompt resection of necrotic bowel if evidence of peritonitis
- Anticoagulation for arterial & venous thrombosis and embolic disease
- Papaverine (vasodilator) catheter-directed infusion into SMA, typically in nonocclusive ischemia when spasm is considered the primary cause of the ischemia
- SMA embolism: consider fibrinolytics; if no quick improvement surgical embolectomy if possible, o/w aortomesenteric bypass
- SMA thrombosis: percutaneous or surgical revascularization (J Vasc Surg 2009;50:341)
- Nonocclusive: correct underlying cause (especially cardiac)
- Consider angioplasty/stent vs. surg revasc in cases of chronic mesenteric ischemia if: ≥2 vessels or occl SMA, supportive clinical hx, & other etiologies for abd pain excluded

**Prognosis**
- Mortality 20 co >70% if bowel infarcted; dx prior to infarction strongest predictor of survival

**Ischemic Colitis (75%)**

**Definition and pathophysiology**
- Non-occlusive 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 & recto-sigmoid) most susceptible, 25% involve R side

**Clinical manifestations, diagnosis, and treatment**
- Disease spectrum: reversible colopathy (35%), transient colitis (15%), chronic ulcerating colitis (20%), stricture (10%), gangrene (15%), fulminant colitis (<5%)
- Usually p/w cramping LLQ pain w/ FOBT or overtly bloody stool; fever and peritoneal signs should raise clinical suspicion for infarction
- Dx: r/o infectious colitis; consider flexible sig/colonoscopy if sx persist and no alternative etiology identified (only if peritonitis not present, o/w avoid overtreatment of colon)
- Treatment: bowel rest, IV fluids, broad-spectrum abx, serial abd exams; surgery for infarction, fulminant colitis, hemorrhage, failure of medical Rx, recurrent sepsis, stricture
- Resolution w/in 48 h w/ conservative measures occurs in >50% of cases
Pathogenesis
- Acinar injury via direct or indirect toxicity → release or impaired secretion (ie, duct obstruction) of enzymes → autodigestion → fat necrosis
- Profound acute inflammatory response

Etiologies
- Gallstones (40%): > , usually small stones (<5 mm) are culprit, also microcholangitis
- Alcohol (30%): > , usually chronic, w/ acute flares
- Drugs (occur via hypersensitivity, toxic metab, or direct toxicity): furosemide, thiazides, sulfa, DDI, asparaginase, estrogen, 6-MP/PAZA, ACEI, dapsone, 5-ASA, valproic acid
- Obstructive: panc/ampullary tumors, mets (breast, lung), annular pancreas, divisum w/ concurrent minor papilla stenosis, and ascaris
- Metabolic: hypertriglyceridemia (TG need to be >1000 and usually ~4500; seen w/ type I and type V familial hypertriglyceridemia), hypercalcemia
- Infections: coxsackie, mumps, EBV, CMV, HAV, HBV, mycoplasma, TB, candida/toxo/crypto
- Autoimmune: can p/w chronic disease or panc mass; ↑ IgG4, ↑ ANA, duct abnl
- Ischemia: vasculitis, cholesterol emboli, hypovolemic shock, cardiopulmonary bypass
- Post ERCP: ~5% w/ clinical, overt pancreatitis; 35–70% w/ axx ↑ amylase
- Post trauma: blunt abd trauma, pancreatic/biliary surgery
- Familial: autosomal dominant w/ variable penetrance (PRSS1, CFTR, SPINK1 genes)
- Scorpion sting (in Trinidad): mechanism believed to be hyperstimulation of pancreas

Clinical manifestations
- Epigastric abdominal pain
- Physical exam
  - Abdominal tenderness and guarding, ↓ bowel sounds (adynamic ileus)
  - Palpable abdominal mass; jaundice if biliary obstruction
  - Signs of retroperitoneal hemorrhage (Cullen’s – periumbilical; Grey Turner’s – flank) rare
  - Fever, tachycardia, hypotension ± shock
- Diagnostic studies (Gastro 2007;132:2022)
  - Laboratory
    - ↑ amylase: levels >3 × ULN suggestive of pancreatitis; level ≠ severity
    - ↑ lipase: more specific than amylase
  - Imaging studies
    - KUB/CXR: can see “sentinel loop” air in small bowel in LUQ, atelectasis, effusion
  - Abd CT: not required for dx, but test of choice to make dx. Helps exclude other dx, stage severity, r/o complications. CT w/ IV contrast on day 3 of presentation in severe cases to evaluate for pancreatic necrosis (avoid on presentation to defer if concomitant ARF).
  - Abd US: typically not useful to visualize pancreas (obscured by bowel gas), but helpful to investigate biliary etiology, ie, gallstones and BD dilatation; can see pseudocyst MRI/IRCP: can detect necrosis; also used to assess for stones & ductal disruption
  - Endoscopic US (EUS): limited role acutely; useful for occult biliary disease (microlithiasis)

Treatment (Lancet 2008;371:143)
- Supportive therapy: in mild cases, bowel rest is usually sufficient
- Fluid resuscitation (may need up to 10 L/d if hemodynamically severe pancreatitis)
- Analgesia: IV meperidine, morphine (theoretical risk of sphincter of Oddi spasm, but has not been shown to adversely affect outcome), hydromorphone
- Prophylactic systemic abx (eg, imipenem) to ↓ mortality & prevent conversion of sterile necrosis to infected necrosis remains controversial (Am J Surg 2009;197:806 & Gastro 2007;132:2022); reserve for severe pancreatitis w/ >30% necrosis by CT, & no more than 14 d
- Surgery: infected necrosis (qv) nearly always requires debridement. Improved outcomes by delaying (if possible) surgery ≥2 wks to allow organization of necrosis. Cholecystectomy if gallstones (w/in 48 h if mild, o/w w/in 14 d; Surg 2009;145:260; Ann Surg 2010;251:615)
- ERCP + sphincterotomy: in acute setting, reserved for severe cholangitis/sepsis and T bili >5 (ie, presumptive obstructive BD stone). Otherwise, early ERCP does not reduce risk of local or systemic pancreatitis complications (Ann Surg 2007;245:10).

Complications
- Systemic: shock, ARDS, renal failure, GI hemorrhage, DIC
- Metabolic: hypocalcemia, hyperglycemia, hypertriglyceridemia
- Acute fluid collection (30–50%): seen early, no capsule, no Rx required
- Pseudocyst (10–20%): fluid collection, persists for 4–6 wks, encapsulated
- Sterile pancreatic necrosis (20%): area of nonviable pancreatic tissue
- Infection (5% of all cases, 30% of severe): usually 2e enteric GNR infected pancreatic necrosis: fever & ↑ WBC not specific; ↓ FNA in deteriorating Pt w/ necrosis (small risk of seeding sterile necrosis); if gram stain/cx ➔ abx + evacuation (percutaneously, followed by surgical debridement after 4 wks; NEJM 2010;362:1491)
- Pancreatic abscess: circumscribed collection of pus (usually w/o pancreatic tissue) treat w/ abx + drainage (CT-guided if possible), usually seen ≈4 wks into course
- Ascites or pleural effusion: occurs due to disrupted pancreatic duct; consider early ERCP w/ stent across duct; can also occur from draining pseudocyst

Prognosis
- Severe pancreatitis (20%) – organ failure or local complications (necrosis, pseudocyst)
- Scoring systems: HAPS, BISAP, APACHE II, Ranson’s criteria, CT Severity Index
  - HAPS: no abd tenderness or rebound on exam plus nl Hct and Cr on admission predicts non-severe course w/ 98% accuracy (Clin Gas Hep 2009;6:702)
  - BISAP: 5-point scoring system on admission (BUN ➔ 25, GCS ➔ 15, SIRS, age ➔ 60, and pleural effusion) identifiesPts at risk for ↑d mortality (Am J Gastro 2009;104:966)
  - APACHE II (www.mdcalc.com/apache-II-score-for-icu-mortality): severe if score ➔8

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<th>Ranson’s Criteria</th>
<th>At diagnosis</th>
<th>At 48 hours</th>
<th>Prognosis</th>
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<td>age ➔55</td>
<td>Hct ➔10%</td>
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<td>WBC ➔16,000/mm³</td>
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<td>3–4</td>
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<td>base deficit ➔4 mEq/L</td>
<td>5–6</td>
<td>40%</td>
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<td>Ca ➔8 mEq/L</td>
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<td>&gt;99%</td>
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<td>fluid sequestration ➔6 L</td>
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(Ann J Gastro 1982;77:633)

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<th>Necrosis Points</th>
<th>Total Index</th>
<th>Mortality</th>
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<td>&lt;33%</td>
<td>0–3</td>
<td>3%</td>
</tr>
<tr>
<td>B</td>
<td>Enlarged pancreas but w/o inflammation</td>
<td>1</td>
<td>33–50%</td>
<td>4–6</td>
<td>6%</td>
</tr>
<tr>
<td>C</td>
<td>Pancreatic or peripancreatic inflammation</td>
<td>2</td>
<td>&gt;50%</td>
<td>7–10</td>
<td>17%</td>
</tr>
<tr>
<td>D</td>
<td>Single peripancreatic fluid collection</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>≥2 Peripancreatic fluid collections or gas in pancreas/retroperitoneum</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Radiology 1990;174: 331)

Chronic pancreatitis
- 70–80% due to alcohol, also consider autoimmune pancreatitis
- Often, but not always, recurrent acute attacks → inflammatory infiltrate → fibrosis → exocrine then endocrine insufficiency
- Sxs include epigastric pain, N/V; over time will be painless and p/w steatorrhea and wt loss
- Amylase/lipase ↑ early, but may be nl later. e fat, i’d stool elastase & chymotrypsin, Ca²⁺ in pancreas on KUB/CT
- ERCP/MRCP/EUS high Se for dx: stricture, dil ducts, honeycombing of parenchyma
- Treatment is low-fat diet and enzyme replacement
ABNORMAL LIVER TESTS

Tests of hepatocellular injury or cholestasis
- **Aminotransferases** (AST, ALT): intracellular enzymes released following necrosis/inflammation.
  - ALT more specific for liver than AST (heart, skeletal muscle, kidney, brain, RBC/WBC).
  - ALT > AST → viral hepatitis or fatty liver/nonalcoholic steatohepatitis (pericirrhotic).
  -ALT-AST > 2.1 → alcoholic hepatitis, cirrhosis, NAFLD; nonhepatic source.
  - ALT/AST > 15 × ULN → etiologies of acute liver failure (LDH → ischemia/toxic).
- **Alkaline phosphatase** (Aph): enzyme bound in hepatic canicular membrane.
  - Besides liver, also found in bone, intestines, kidney, and placenta.
  - Confirms liver origin with: c5’NT, cGGT, or APH heat fractionation.
  - Levels seen with biliary obstruction or intrahepatic cholestasis (eg, hepatic infiltration).

Tests of hepatic function
- **Albumin**: marker for liver protein synthesis, slowly in liver failure (t 1/2 = 20 d).
- **Prothrombin time (PT)**: depends on synthesis of coag factors by the liver (except FVIII);
  - b/c t 1/2 of some of these factors (eg, V, VII) is short, PT can occur w/in hrs of liver dysfxn.
- **Bilirubin**: product of heme metabolism carried by albumin to liver where it must be
  - taken up for conjugation (to make soluble) and then excreted into bile.

Patterns of liver injury
- **Hepatocellular**: ↑ aminotransferases, ± ↑ bilirubin or Aph.
  - ALT & AST (>1000): severe viral hepatitis, acetaminophen, ischemia, Wilson’s, AIH.
- **Cholestasis**: ↑ Aph and bilirubin, ± ↑ aminotransferases.
- **Isolated hyperbilirubinemia**: ↑ bilirubin (direct or indirect), n Aph and aminotransferases.
- **Infiltrative**: ↑ Aph, ± ↑ bilirubin or aminotransferases.
  - Jaundice is a clinical sign seen when bilirubin > 2.5 mg/dL (especially in sclera or under tongue).
  - If hyperbilirubinemia conjugated → ↑ urine bilirubin.

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

Hepatocellular injury
(predom ↑ AST & ALT, ± ↑ bili and Aph)

- **Viral hepatitis**: HAV, HBV, HCV, HDV, HEV, CMV, EBV, HSV, VZV.
- **Autoimmune**: alcohol, acetaminophen, meds, toxins.
- **Toxins**: NAFLD, Vascular, Hereditary.
- **AutoAbs**: ANA, ASMA, ALKM.
- **Drug & toxins**: Budd-Chiari, CHF.
- **Hyperlipidemia**: Wilson’s, celiac sprue.

- Acute workup: toxins (EtOH, acetaminophen) & vascular abnl (U/S w/ Doppler).
- Chronic workup: HBV sAg, HCV Ab, Fe,TIBC, glc, HbA1c,TG; ANA, ASMA, ALKM; anti-tissue transglutaminase; ceruloplasmin & α1-AT; TSH; vascular abnl (U/S w/ Doppler).

Figure 3-4 Approach to abnormal liver tests with cholestatic pattern
Abnormal liver tests in asymptomatic patients (Gastro 2002;123:1364)

- Careful review of history (meds, ETX/other drug use, exposures, risk factors for liver disease) and physical exam. Evaluate for any clues to etiology 1st (eg, d/c med and repeat LFTs).
- Confirm hepatic source: if primarily compensation (✓ GGT) or ASTALT (✓ CK, aldolase, TFT)
- Hepatocellular Evaluate for most common causes: hepatitis A/B/C, hemochromatosis; screen for evidence of chronic liver disease (platelets, PT/INR, albumin)
  - If evaluation → lifestyle modification (wt loss, DM control) + repeat test 6 mo
  - If evidence of chronic liver disease or persistent lab abnl, screen for less common causes: AIH, Wilson's, celiac, <at; ✓ U/S & consider liver bx
  - If still → liver bx if ALT or ASTULN for 6 mo; o/w observe
- Cholestatic ✓ RUQ U/S, AMA
  - if biliary dilatation or obstruction → MRCP
  - if AMA and U/S, or AMA and U/S w/ abnl parenchyma → liver bx
  - if AMA & U/S <:A <1.5 × ULN → consider bx; A <1.5 × ULN → observe
- Isolated hyperbilirubinemia: ✓ conjugated vs. unconjugated
  - conjugated → perform abdominal U/S → MRCP if dilatation or obstruction; if n't ultrasound ✓ AMA and consider MRCP or liver bx
  - unconjugated → ✓ Hct, retic count, smear, LDH, haptoglobin

Common medications that cause abnormal liver tests

<table>
<thead>
<tr>
<th>Hepatocellular</th>
<th>Cholestatic</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Methotrexate</td>
<td>Amoxiclav</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>NSAID</td>
<td>Anabolic</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Omeprazole</td>
<td>Steroids</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Panretine</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Pyrazinamide</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Rifampin</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Risperidone</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>HAART</td>
<td>Sertraline</td>
<td>Erythromycins</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Statins</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Tetracyclines</td>
<td>Amoxiclav</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Trazodone</td>
<td>Irbesartan</td>
</tr>
<tr>
<td>Losartan</td>
<td>Valproic Acid</td>
<td>Mirtazapine</td>
</tr>
</tbody>
</table>

Does not include herbal supplements or toxins (NEJM 2006;354:731)
HEPATITIS

VIRAL

Hepatitis A (ssRNA; accounts for 30–45% of acute viral hepatitis)
- Transmission: fecal-oral route; contaminated food, water, shellfish; day-care ctr outbreaks
- Incubation: 2–6 wks; no chronic carrier state
- Sx: ↓ appetite, malaise, fever, N/V, RUQ pain, ↑ jaundice; rarely fulminant
- Diagnosis: acute hepatitis = ⊕ IgM anti-HAV; past exposure = ⊕ IgG anti-HAV (⊕ IgM)
- Treatment for acute HAV supportive. Prevention: vaccinate children & Pts w/ chronic HBV, HCV, or other chronic liver disease (2 doses at 0, 6–12 mos)
- Postexposure ppx: age 1–40 y = vaccine; age <1 or >40 y or immunosupp → Ig

Hepatitis B (dsDNA; accounts for ~45% of acute viral hepatitis; Lancet 2009;373:582)
- Transmission: blood, sexual, perinatal
- Incubation: 6 wks–6 mos (mean 12–14 wks)
- Acute infxn: 70% subclinical, 30% jaundice, <1% fulminant hepatitis (up to 60% mortality)
- Chronic infxn: <5% (adult-acquired; higher if immunosupp), >90% (perinatally acquired); ~40% chronic carriers → cirrhosis; ↑ risk of cirrhosis if HCV, HDV, or HIV coinfection
- Risk of hepatocellular carcinoma: 25–40%; highest risk w/ perinatal transmission & ‘d HBV DNA; risk of HCC w/ or w/o concurrent cirrhosis. Screen w/ AFP & US vs MRI q6mo.
- Extrahepatic syndromes: PAN (1.1%), MPGN, arthritis, dermatitis, PMR
- Serologic and virologic tests
  - HBsAg: appears before sx; used to screen blood donors; persists >6 mo – chronic HBV
  - HBeAg: evidence of viral replication and infectivity
    - IgM anti-HBc: first Ab to appear; indicates acute infection
    - “window period” – HBsAg become ⊕, anti-HBs not yet ⊕, anti-HBc only clue to infection
  - 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 vac)
  - HBV DNA: presence in serum correlates w/ active viral replication in liver

Figure 3-7 Serologic course of acute HBV infection with resolution

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HBsAg</th>
<th>anti-HBs</th>
<th>anti-HBc</th>
<th>HBeAg</th>
<th>anti-HBe</th>
<th>HBV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕M</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
</tr>
<tr>
<td>Window period</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕M</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
</tr>
<tr>
<td>Recovery</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕G</td>
<td>⊕</td>
<td>±</td>
<td>⊕</td>
</tr>
<tr>
<td>Immunization</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕G</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
</tr>
<tr>
<td>HBeAg</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕G</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
</tr>
</tbody>
</table>

*Precore mutant: HBeAg not generated, but anti-HBe can develop due to cross-reactivity w/ HbcAg; a/w high serum HBV DNA levels

• Treatment for acute HBV: supportive; hospitalize for Δ MS or ↑ INR (liver transplant ctr)
• Treatment for chronic HBV: if (1) HBeAg + w/ DNA >20,000 IU/mL & elevated ALT; (2) HBeAg + w/ DNA >2,000 IU/mL & elevated ALT or liver bx demonstrates stage ≥2 fibrosis (NEJM 2008;359:1486 & Hep 2009;50:661)
• PEG IFN-α-2a: best rate of HBeAg seroconversion at 1 y (27%), low tolerability limits use
• 1st line is entecavir or tenofovir: well-tolerated & low resistance, HBeAg seroconversion at 1 yr is 21%; seroconversion at 3 y for entecavir is 39%; lamivudine 15–30% resis at 1 y; telbivudine ↑ CK & neuropathy; adefovir (add to lamivudine-resistant pts) nephrotoxic & resistance occurs, too
• Goal: if HBeAg + → HBeAg −, anti-HBe +; if HBeAg + or + seroconversion → indefinite
• If undergo liver transplant: HBIG + nucleoside analog effective in preventing reinfection
• HIV/HBV coinfection: Rx w/ 2 drugs active against both HBV & HIV (NEJM 2007;356:1445)
• If inactive carrier scheduled to receive immunosuppression/chemotherapy → Rx
• Prevention: vaccinate high-risk Pts (3 doses 0.1 & 6 mos)
• Postexposure (risk infxn <30%) ppx: HBIG → vaccine (if unvac. or known nonresponder)

Hepatitis C (RNA; accounts for 10–30% of acute viral hepatitis; Lancet 2008;372:321)
• Transmission: blood >> sexual; ~20% w/o clear precipitant
• Incubation: 1–5 mos; mean 6–7 wks
• Natural hx
  acute infection: 80% subclinical; 10–20% symptomatic hepatitis w/ jaundice; fulminant hepatitis very rare; spontaneous clearance in up to 30% chronic: up to 80% → chronic hepatitis, 20–30% of whom develop cirrhosis (after ~20 y)
• Risk of cirrhosis in men, with hepatocellular carcinoma in 2–5% of cirrhosis/y
• Extrahepatic syndromes: cryoglobulinemia, porphyria cutanea tarda (blistering rash in sun-exposed areas), MPGN, MGUS, IFP, NHL, and DM
• Serologic and virologic tests
  anti-HCV (ELISA): + in 6 wks, does not → recovery or immunity; can be + after recovery HCV RNA + w/in 2 wks, marker of active infection
  HCV RIBA: used to confirm + anti-HCV ELISA in Pts w/ undetectable HCV RNA
  HCV genotype (1–4): guides duration & predicts response to Rx (genotype 2,3 > 1,4)
• Diagnosis: acute hepatitis → + HCV RNA, → anti-HCV resolved hepatitis → + HCV RNA, + anti-HCV chronic hepatitis → + HCV RNA, + anti-HCV
• Treatment indications (Hep 2009;49:1335)
  Acute: if no spont clearance at 8–12 wks, consider PEG-IFN-α-2a/b × 12–24 wks
  Chronic RNA +, plus bx w/ either chronic hepatitis & fibrosis stage >1 or compensated liver disease (in genotype 2 or 3, may proceed to Rx w/o bx b/c high response rate)
• Genotypes 1 or 4: Rx 48 wks. If early vir resp (EVR) not achieved by wk 12 (ie, RNA ↓ <2 log) stop Rx, as EVR best predictor of lack of SVR. If partial EVR (RNA ↓ ≥2 log at 12 wks & undetectable at 24 wks), consider prolonging Rx to 72 wks. Overall SVR rate 50–60%.
• Genotypes 2 or 3: Rx 24 wks; SVR rate ~80%
• Predictors of response: RNA <400k IU/mL, rapid vir resp (≥ RNA at wk 4), cirrhosis, age <40 y, wt <75 kg, white/Hispanic, ≥ HIV, SNPs in IL28B
  (Nat Gen 2009;41:1100; Gastro 2010;138:2307)
• Risks of Rx: flu-like sx, psych sx (if depressed can give SSRI), thyroid dysfunction, marrow suppression (can give EPO & GCSF), hemolysis (ribavirin), sexual dysfunction
• Contraind.: decompensated cirrhosis, preg, severe psych illness, active substance abuse, severe cardiac/pulm disease, uncontrolled DM, seizure d/o, autoimmune disease
• 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 mos

Hepatitis D (RNA)
• Transmission: blood or sexual; endemic in Africa & E. Europe
• Natural hx:
  hepatic: in HBV ↑ severity of infxn and ↑ progression to cirrhosis; clear w/ HBV
  Extrahepatic: cryoglobulinemia, porphyria cutanea tarda (blistering rash in sun-exposed areas), MPGN, MGUS, IPF, NHL, and DM
  HBeAg +, plus bx w/ either chronic hepatitis & fibrosis stage 1 or 2 fibrosis (NEJM 2007;356:445)
  NEJM 2008;372:445)
• Risk of cirrhosis in men, EtOH, HIV; HCC in 2–5% of cirrhotics/y
• Pathogenesis: requires HBV to cause either simultaneous or superimposed infection
• Transmission: blood
• Genotypes 1 or 4: Rx 48 wks. If early vir resp (EVR) not achieved by wk 12 (ie, RNA ↓ <2 log) stop Rx, as EVR best predictor of lack of SVR. If partial EVR (RNA ↓ ≥2 log at 12 wks & undetectable at 24 wks), consider prolonging Rx to 72 wks. Overall SVR rate 50–60%.
• Genotypes 2 or 3: Rx 24 wks; SVR rate ~80%
• Predictors of response: RNA <400k IU/mL, rapid vir resp (≥ RNA at wk 4), cirrhosis, age <40 y, wt <75 kg, white/Hispanic, ≥ HIV, SNPs in IL28B
  (Nat Gen 2009;41:1100; Gastro 2010;138:2307)
• Risks of Rx: flu-like sx, psych sx (if depressed can give SSRI), thyroid dysfunction, marrow suppression (can give EPO & GCSF), hemolysis (ribavirin), sexual dysfunction
• Contraind.: decompensated cirrhosis, preg, severe psych illness, active substance abuse, severe cardiac/pulm disease, uncontrolled DM, seizure d/o, autoimmune disease
• 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 mos

Hepatitis E (RNA)
• Transmission: fecal-oral; travelers to Pakistan, India, SE Asia, Africa, and Mexico
• Natural hx:
  acute hepatitis w/ ↑ mortality (10–20%) if pregnant; rare chronic in transplant Pts
• Diagnosis: IgM anti-HEV (through CDC)

Other viruses (CMV, EBV, HSV, VZV)
Autoimmune Hepatitis (AIH)

Classification (NEJM 2006;354:54)
- Type 1: anti–smooth muscle Ab (ASMA), ANA; anti–soluble liver antigen (anti-SLA) a/w more severe disease and relapsing disease
- Type 2: anti–liver/kidney microsome type 1 (anti-LKM1); children (age 2–14 y);
- Meditarranean
- Overlap syndrome: autoimmune hepatitis + PBC or PSC

Diagnosis and Treatment
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs,
- Liver transplant for ESLD; recurs in Mediterranean

Acetaminophen hepatotoxicity
- Dx: scoring system combining serologies,
- Clinical: 80% asx, ALT/H9004
- Lille model predicts nonresponse to corticosteroids & mortality, powered by
- Sxs: can range from asx hepatomegaly to decompensation w/ ascites, encephalopathy,

Other Causes of Hepatitis or Hepatotoxicity

Alcoholic hepatitis (NEJM 2009;360:2758)
- Sxs: can range from asx hepatomegaly to decompensation w/ asites, encephalopathy, and death; AST & ALT usually <300–500 w/ AST:ALT >2:1, in part b/c concomitant
- Rx: if discriminant fnx (< 4.6 [PT-control] + Tβ in mg/dL) >32 or encephalopathy
- methylprednisolone 32 mg/d
- pentoxifylline 400 mg tid
- 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.

Ischemic hepatitis
- "Shock liver" w/ AST & ALT >1000 + ↑ LDH; delayed ↑ Tβili
- Often requires ↑ venous pressure = ↑ portal/arterial pressure + hypoxia
- Typically seen in hypotension, sepsis, CHF

Nonalcoholic fatty liver disease (NAFLD) (Gastro 2008;134:1682)
- Fatty infiltration of the liver and absence of EtOH or other cause of liver disease.
- Nonalcoholic steatohepatitis (NASH) = NAFLD + inflammation ± fibrosis on liver bx
- (hyperinsulinemia, obesity, ↑ TGs), HAART, tamoxifen, amiodarone, TPN, rapid wt loss.
- Clinical: 80% asx, ALT >AST; NAFLD can progress to cirrhosis in 1–3% of Pts w/ NAFLD and up to 25% of Pts w/ NASH
- Dx: U/S, MRI, CT suggest fatty infiltration but liver bx only way to dx NASH vs. NAFLD
- Rx: wt loss, glycemic/lipid control; both pioglitazone and vitamin E ↓ steatosis & inflammation, but not fibrosis (NEJM 2010;362:1675)
ACUTE LIVER FAILURE

Definition
- Acute hepatic disease + coagulopathy + encephalopathy; w/o known pre-existing liver dis.
- Fulminant – develops w/in 8 ws; subfulminant – develops between 8 ws and 6 mos

Etiology (Hep 2008;47:1401)
- Viral
  - HAV, HBV, HCV (rare), HDV + HBV, HEV (especially if pregnant)
  - HSV (immunosupp. Pt.), EBV, CMV, adenovirus, paramyxovirus, parvovirus B19
- Drugs/Toxins
  - Drugs: acetaminophen (most common cause: >40% of all cases), phenytoin, INH, rifampin, sulfonamides, tetracycline, telithromycin, amidadone, PTU, valproate
  - Toxins: fluorinated hydrocarbons, CCl₄, Amanita phalloides
- Vascular: ischemic hepatitis, Budd-Chiari syndrome, hepatic, malignant infiltration
- Autoimmune hepatitis (usually initial presentation)
- Misc.: Wilson’s, acute fatty liver of pregnancy (HELLP, Reye’s), idiopathic (~20%)

Clinical manifestations
- Initial presentation usually nonspecific, w/ nausea, vomiting, malaise, followed by jaundice
- Neurologic
  - Encephalopathy: stage I – ∆MS; stage II – lethargy, confusion; stage III – stupor; stage IV – coma
  - Asterixis in stage I/II/III encephalopathy; hyperreflexia, clonus, rigidity in stage III/IV
- Cerebral edema
  - → ↑ ICP, ↑ CPP → cerebral hypoxia, uncal herniation, Cushing’s reflex (hypertension + bradycardia), pupillary dilatation, decerebrate posturing, apnea
- Cardiovascular: hypotension with low SVR
- Pulmonary: respiratory alkalosis, impaired peripheral O₂ uptake, pulm edema, ARDS
- Gastrointestinal: GIB (↓ clotting factors, ↓ plt, DIC), pancreatitis (↑ due to ischemia)
- Renal: ATN, hepatorenal syndrome, hyponatremia, hypokalemia, hypophosphatemia
- Hematology: coagulopathy (due to ↓ synthesis of clotting factors = DIC)
- Infection (~90% ofPts): especially 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
- Viral serologies (HBV DNA, HCV RNA)
- Autoimmune hepatitis serologies, ceruloplasmin & urine copper
- Toxicology screen (acetaminophen levels q1-2h until peak determined)
- Imaging studies (RUQ U/S or abd CT, Doppler studies of portal and hepatic veins)
- Liver biopsy (unless precluded by coagulopathy = in which case consider transjugular)

- ICU care at liver transplant ctr for hemodynamic & ventilatory support; CVVH for ARF
- IV N-acetylcysteine (same dose as for acetaminophen): all Pts w/ hepatic failure and grade 1–2 enceph: ↑ cerebral blood flow and ↑ transplant-free survival (Gastro 2009;137:856)
- Cerebral edema: CT Se only ~60%, ↓ consider ICP monitoring if stage III/IV enceph; head of bed > 30° and hypertonic saline for goal Na 145–155 mEq/L; other potential measures: hyperventilation, mannitol, barbiturates, ↓ induction of hypothermia, IV indomethacin
- Encephalopathy: intubate for grade III or IV; ↑ lactulose, but no efficacy data
- Coagulopathy: vit K; FFP/plts/cryo if active bleeding; ↑ recombl. factor Vlla; PPI prophylaxis
- Infection: low threshold for abx (broad spectrum, eg, vancomycin & 3rd-gen ceph.), albeit no proven mortality benefit to empiric abx
- Treatment of specific causes: nucleosides for HBV; corticosteroids for autoimmune hepatitis; chelation Rx for Wilson’s; IV acyclovir for HSV; gastric lavage and charcoal ↓ penicillin and silymarin for Amanita phalloides; delivery of child for pregnancy-related; TIPS and anticoagulation for Budd-Chiari
- Liver transplantation if poor prognosis w/ grade II or III encephalopathy (see below)
- Extracorporeal liver assist devices (cell-based vs. non) under study as bridge to transplant

Prognosis
- Non-acetaminophen ALF mortality ~80%, acetaminophen-induced ALF mortality ~30%
- Predictors of poor outcome
  - Acetaminophen-induced: pH < 7.3 after fluids or INR > 6.5, GFR > 1.4, or grade III/IV enceph.
  - Non-acetaminophen-induced: INR > 6.5 or 3 of the following: non-A/B viral hep; non-acetaminophen drug toxicity; time from jaundice to enceph. > 7 d; age < 10 or > 40 y; INR > 3.5; T bili > 17.4
  - ~25–30% of Pts w/ ALF undergo liver transplantation w/ 5-y survival rate of 70%
CIRRHOSIS

Definition (Lancet 2008;371:838)
- Definition: fibrosis and nodular regeneration resulting from hepatocellular injury
- Decompensated: jaundice, variceal bleed, encephalopathy, ascites; worse prognosis

Etiologies
- Alcohol (~60–70%): Laennec’s cirrhosis; micronodular
- Viral hepatitis (~20%): chronic HBV, HCV, HDV infection
- Autoimmune hepatitis: female, ↑ IgG, ∩ ANA, anti-smooth muscle Ab
- Metabolic diseases (~5%): hemochromatosis, Wilson’s disease, α1-antitrypsin deficiency
- Biliary tract diseases (~5%): primary biliary cirrhosis, secondary biliary cirrhosis (calcus, neoplasm, stricture, biliary atresia), primary sclerosing cholangitis
- Vascular diseases: Budd-Chiari syndrome, R-sided CHF, constrictive pericarditis
- Nonalcoholic fatty liver disease (NAFLD, 10–15%) cause of most “cryptogenic cirrhosis”

Clinical manifestations
- Subclinical or may p/w liver dysfunction (jaundice, coagulopathy, encephalopathy) and/or
  - Clinical manifestations
    - Signs of liver failure: jaundice (↑ bilirubin), ascites
    - Due to portal HTN (defined as hepatic venous pressure gradient [HVPG] >5 mmHg)
    - Ascites: develop in 60% w/in 10 y
      - Nonalcoholic fatty liver disease (NAFLD, 10–15%)
      - Viral hepatitis
      - Autoimmune hepatitis
      - Biliary tract diseases (calcus, neoplasm, stricture, biliary atresia), primary sclerosing cholangitis
      - Vascular diseases: Budd-Chiari syndrome, R-sided CHF, constrictive pericarditis
      - Nonalcoholic fatty liver disease (NAFLD, 10–15%) cause of most “cryptogenic cirrhosis”

Physical exam
- Liver: initially enlarged, palpable (L lobe predom), firm; eventually shrunken and nodular
- Signs of liver failure: jaundice (bilirubin >2), spider angiomata & palmar erythema († eastradiol), 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
- ↑ bilirubin, ↑ PT (poor correlation w/ bleeding; factor VIII nl as not synthesized by liver), ↓ alb, ± ↑ aminotransferases (AST > ALT if late) and ↑ Ads (variable), ↓ Na, ↑ gamma glob
- Anemia (marrow suppression, hypersplenism, Fe and/or folate deficiencies), neutropenia (hypersplenism), thrombocytopenia (hypersplenism), ↓ Tpo production by liver; EtOH tox

Workup
- Abdominal U/S w/ Doppler: liver size (↑ L & caudate lobe), r/o HCC, ascites, cirrhosis
- Assess fibrosis: biomarkers ( FibroSURE = panel of 6 markers, ↓ score predictive of fibrosis, esp in Hep C); US/MR elastography
- Determine etiology: hepatitis serologies (HBsAg, anti-HBs, anti-HCV), autoimmune hepatitis studies (IgG, ANA, anti-smooth muscle Ab), Fe and Cu studies, c-A1-AT, AMA
- ± Liver bx: percutaneous or transjugular (consider if ascites or coagulopathy) used to dx etiology and presence of cirrhosis

Ascites (see “Ascites” for details on dx eval)
- 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 (Hepatology 2009;29:2087)
- Treatment (Am J Gastro 2009;104:1802): ↓ Na intake (1–2 g/d) in all free H2O restriction only if Na <125
  - Diuretics: goal 1 L/d; urine Na/K >1 implies effective aldo block
  - Spironolactone (100 mg PO qd) ± furosemide (40 mg PO qd); ↑ doses in proportion to diuretic action (common cause of refractory ascites)
  - Refractory ascites: ↑ ascites despite med/diet compliance; ~20% mortality at 3 mo

Large-volume paracentesis (LVP) remove 4–6 L per session until dry or ↓ sx
- albumin replacement: ↓ chemical abnl; no Δ mortality (Gastro 1988;94:1493)
- Beware LVP if SBP as ↑ risk of ARF → consider dx tap to r/o SBP first

Transjugular intrahepatic portosystemic shunt (TIPS)
- ↓ ascites in 75%, ↑ CrCl, ↓ transplant-free survival (NEJM 2000;342:1701)
- ↑ encephalopathy (↑ TIPS contraindic. if ↑ mild at baseline), no Δ quality of life (Gastro 2003;124:634); by 1 y ~40% occlude (metal stent); new coated stent ↓ (~20%) occlusion and ↓ mortality (Gastro 2004;126:469)
- LVP 1st line Rx b/c TIPS complications (metal stent), but TIPS ↓ mort (Gastro 2007;133:825)
- Hepatic hydrothorax: 2º diaphragmatic defect; often unilateral, R > L, ± ascites
  - Treatment: ↑ chest tube due to ↑ complications; Rx same as ascites
- Spontaneous bacterial empyema can occur (even w/o SBP) → consider dx thoracentesis; Rx same as for SBP (see later)
Cirrhosis

3.22

Spontaneous bacterial peritonitis (SBP; see “Ascites” for details on dx)

• Develops in ~20% of cirrhotics; risk factors – AFTP < 1 g/dL, h/o prior SBP, current GI bleed

• Can p/w encephalopathy, abd pain, fever; but only (25%) sx; ∴ consider paracentesis in all hospitalized cirrhotics w/ ascites

• Micro: 70% GNR (E. coli, Klebs), 30% GPC (Enterococcus, S. pneumoniae), nosocomial (fungi, Pseud)

• Rx: cefotaxime 2 gm IV q8h (or ampiclox) × 5 d; if O enceph/ARF can use ofloxacin PO IV albumin 1.5 g/kg at time of dx and 1 g/kg on day 3; survival (NEJM 1999;341:403)

• If not improving consider repeat paracentesis at 48 h; ~25% ↓ PMN count – Rx success ~20% mortality during hospitalization

Gastroesophageal varices ± UGIB (see also “GI”: NEJM 2010;362:822)

• At risk if HVPGE > 12 mmHg; screen all cirrhotics at time of dx

• 1° prevention of UGIB: consider if mod-large varices or “red wale” marks or Child-Pugh B/C

• Precipitants:

  • “Cirrhotic” cardiomyopathy
  • Micro: 70% GNR (Infxns:
    • Other complications
  • Pathobiology unknown, though kidney is pathologically normal; ? vascular
  • Hepatorenal syndrome

• 2° prevention: for all Pts after 1st bleed b/c ~50% rebleed & ~30% mortality

Portosystemic (hepatic) encephalopathy (PSE)

• Pathogenesis: failure of liver to detoxify NH₃ + other substances that cause cerebral edema and/or act as false neurotransmitters (GABA-like)

• Precipitants: ↑ dietary protein, constipation, GIB, med noncompliance, infection, azotemia, ↓K, ↓ volume/water, hypoxia, HCC, portosystemic shunt, meds, portal vein thrombosis

• Stages: (1) confusion; (2) drowsiness; (3) stupor; (4) coma

• Dx: asterixis can be seen; NH₃ poor Se for dx & monitoring Rx; remains a clinical dx

• Acute treatment: identify/correct precipitants, restrict dietary protein acutely (60–80 g/d), lactulose (acidification of colon: NH₃ uptake), or rifaximin 400 mg tid (↑ gut bacteria → ↓ NH₃ prod); rifaximin and lactulose similar efficacy (J Hep 2003;38:51)

• 2° prevention: lactulose + rifaximin 550 bid (Gastro 2009;137:885 NEJM 2010;362:1071)

Hepatorenal syndrome (NEJM 2009;361:1279)

• Pathobiology unknown, though kidney is pathologically normal; ? vascular

• Definition: progressive azotemia (Cr > 1.5 or > 1.5 × baseline) despite volume challenge (1 g/kg/d of albumin × 2 d), and exclusion of other causes (drugs, ATN, obstruction); (nb, often overestimate renal fxn in cirhottics b/c ↓ muscle mass; ↓ less creatine), ↑ Cr renal tubular secretion, and ↓ conversion of creatine → creatinine

Type I: Cr > 2.5 or 1.5 × baseline 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 but < type I

Both a/w ascites (usually h/o refractory ascites), oliguria, U₆ < 10 mLg/dL and ↓ Na

• Precipitants: GIB, overdiuresis, infection, paracentesis, drugs (aminoglycosides, NSAIDs)

• Rx: octreotide (200 mcg SC tid) + midodrine (12.5 mg PO tid) + albumin (Hep 1999;29:1690); albumin + tretipressin (Gastro 2008;134:1352 & 1360); ↑ TIPS; definitive Rx = liver transplant

Other complications

• Hepatopulmonary syndrome (NEJM 2008;358:2378)

  • Definition/etiology: abnl pulm gas exchange (A-a gradient > 15 or P₅O₂ < 80)

  • Intrapulm vascular shunting w/o intrinsic pulm disease; ? due to ↑ pulmonary NO S/S: platypnea-orthodeoxia, clubbing, cyanosis

  • Dx w/ contrast echo showing pulm A-V shunt (opac. in LA 3–6 cycles after RA)

  • Rx: O₂ potential embolization if large vessel on CT, liver transplant only definitive Rx

• Portopulmonary hypertension: ↑ PAP; unclear pathogenesis though some response to prostacyclin or to endothelin antagonists; poor prognosis

• “Cirrhotic” cardiomyopathy: ↓ inotropic & chronotropic response, ↓ systolic and diastolic fxn, prolonged QT, hyperkinetic circulation; ↑ troponin, BNP (Gut 2008;57:268)

• Infxsns: Kupffer cell (hepatic md) dysfxn, ↓ opsonic activity; vaccinate for HAV & HBV, influenza yearly, pneumonia

• Hepatocellular carcinoma: incidence ~3.5% (↑ risk if HBV or hemochromatosis)

  • Sx: liver size, ascites, encephalopathy, wt loss; screen all cirrhotics w/ U/S ≥ AFP q6–12 mo → ↓ mortality (Clin Gastro Hep 2005;3:508), though CT/MRI more sensitive

• Diabetes (15–30%): due to altered glic & insulin metabolism
Prognosis

<table>
<thead>
<tr>
<th>Modified Child-Turcotte-Pugh Scoring System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Points scored</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Ascents</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
</tr>
<tr>
<td>PT (sec &gt; control) or INR</td>
</tr>
<tr>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

**Classification**

- A: Total points 5–6
- B: 7–9
- C: 10–15

1-y survival 100% 80% 45%


Liver transplantation

- Evaluate when Child class B and MELD ≥10
- Indications: recurrent or severe encephalopathy, refractory ascites, SBP, recurrent variceal bleeding, hepatorenal or hepatopulmonary syndrome, hepatocellular carcinoma (if no single lesion is ≤5 cm or ≥3 lesions with largest ≤3 cm), fulminant hepatic failure
- Contraindic. advanced HIV, active substance abuse (EtOH w/in 6 mo), sepsis, severe comorbidity (cardiopulm in particular), extrahepatic malignancy, persistent noncompliance
- Survival: 1-y survival up to 90%, 5-y survival up to 80%; autoimmune hepatitis, hep B/C and some forms of Budd-Chiari may recur posttransplant

Other Etiologies of Cirrhosis

  - Recessive disorders of iron sensing (hepcidin) and transport (transferrin)
  - Iron overload: nonhereditary. Ineffec. erythropoiesis ≠ transfusions
  - HFE mutations (85% of cases), typically C282Y homozygotes (0.5% of N. European Caucasians), rarely C282Y/H63D compound heterozygotes: H/FY mut. → juvenile onset. C282Y homozygotes: 28% of C develop sx (88% lab abnl), and 1% of C develop sx (due to menses ↓ Fe load → later presentation). C282Y/H63D: only 1.5% manifest dis.
  - Sax fatigue & arthralgias. In advanced disease (rare): bronze skin (melanin + iron), hypogonadism (espec. in juvenile onset), DM, arthropathy (MCP), CHF, infxs (Vibrio, Listeria, Yersinia), cirrhosis (↑ risk if EtOH/hatty liver disease; 15% risk of HCC). Disease also a/w ALS & porphyria.
  - Dx: iron sat ≥50% (Hb/TIBC × 100%; most Se & Sp), ↑ ferritin (acute phase reactant, so poor Sp; often nl in young Pts); MRI (shows “black liver” and can ↓ iron stores). If ↑ iron saturation → ↑ HFE gene mutation (C282Y/C282Y or C282Y/H63D are C). Liver bx to assess damage if HFE c and ferritin >1000 ng/ml, ↑ LFTs, or ↑ liver size.
  - Treatment: phlebotomy (500 mL – 1 unit) qwk until Fe sat <50% and ferritin <50, then prn; PPI (i intestinal iron transport); deferoxamine if phleb. contraind.; genetic counseling


- Recessive disorder of copper transport (mutation in ATP7B) → copper overload: primarily affects liver, but also other tissues (brain, eye)
- Epidemiology: 1 in 40,000, usually manifests before age 30 y; almost always before 40 y
- Extrahepatic s/s: neuro ψ disease, parkinsonism and movement disorder (hepatolenticular disease), Kayser-Fleischer rings (C in 99% w/ neuro ψ but in <50% w/ hepatic disease), hemolytic anemia, renal disease
- Dx: ↑ 24-h urine Cu, ↑ serum ceruloplasmin (Se 90%), penicillamine challenge w/ ↑ urine Cu excretion. In acute liver failure, Ads/bili <4 + AST/ALT >2 better Se & Sp than urine Cu or ceruloplasmin (Hepatology 2008;6:1167). Gold standard – liver bx w/ hepatic Cu content.
- Treatment: chelation therapy w/ penicillamine + pyridoxine; 2nd line trientine (↓ toxicity w/ similar efficacy). Zinc: ↓ intestinal Cu transport and can help delay disease; best used if axs or in conjunction w/ chelation (must give 4–5 h apart from chelators).
α1-antitrypsin deficiency (α1-AT) (NEJM 2009;360:2749)
• Abnl α1-AT → polymerization in liver (cirrhosis) & uninhibited protease activity in lung (emphysema). Affects 1/3000 of European ancestry; 1% of all COPDers (onset before 40 y)
• Extrahepatic disease: emphysema, necrotizing panniculitis, ANCA vasculitis (Wegener)
• Dx: absence of α1-AT globulin on SPEP, PAS inclusion bodies on liver bx 
gold standard – protein phenotyping of protease inhibitor (Pi); ZZ, null/null, or null/Z → clinical sx; null/null makes no α1-AT, ⇒ only COPD and not liver dz (no polymerization)
• Treatment: standard Rx for cirrhosis/chronic liver dis.; α1-AT replacement for emphysema

Primary biliary cirrhosis (PBC) (NEJM 2005;353:1261; Hepatology 2009;50:291)
• Autoimmune destruction of intrahepatic bile ducts; may be triggered by certain infections or toxins; a/w X monosomy, variants in IL12 & IL12 receptor genes (NEJM 2009;360:2544)
• Epidemiology: middle-aged women; a/w Sjögren’s, Raynaud’s, scleroderma, celiac dis.
• Sx: fatigue, pruritus, jaundice, steatorrhea, xanthelasma, autonomic and cognitive dysfxn
• Ddx: biliary stricture/cancer, PSC, autoimmune hepatitis (overlap syndrome), sarcoid, meds, idiopathic adult ductopenia, eosinophilic cholangitis, AIDS cholangiopathy, ischemic damage. Imaging of biliary tree (MRCP, CT, ERCP) + serology can help.
• Dx: ↑ Ab, ↑ bil, ↑ chol, anti-mitochondrial Ab (AMA) in 95%. If ↑ AMA, liver bx not needed due to high Se & Sp. 0.5% gen pop AMA & normal LFTs → 10% develop PBC at 6 y. If AMA ± liver bx (Pts often ± ANA, anti–smooth muscle; same prognosis as ± AMA).
• Rx: ursodeoxycholic acid (13–15 mg/kg/d) regardless of stage, ~25% complete response ↑ survival & ↓ histologic change and complications (eg, varices) (Gastro 2005:128:297)
? colchicine, methotrexate, budesonide if refractory
Pruritus: cholestyramine (give 2–4 h after UDCA); if refractory sx: naltrexone, sertraline
Fat-soluble vitamins; screen/Rx osteoporosis (risk indepedent of vit D deficiency)
Liver transplant: ~20% recur but no impact on long-term survival

Primary sclerosing cholangitis (PSC) (Liver Transpl 2008;14:735)
• Idiopathic cholestasis w/ fibrosis, stricturing, and dilatation of intrahepatic and extrahepatic bile ducts; a/w HLA types, autoantibodies but poor response to immunomodulator Rx suggesting nonautoimmune pathogenesis
• Epidemiology: young men (age 20–50 y), 70% a/w ulcerative colitis (rarely Crohn’s disease)
• Clinical manifestations: fatigue, pruritus, jaundice, fevers, RUQ pain, cholangiocarcinoma
• Ddx: same as PBC, may also have overlap w/ autoimmune hepatitis and similar presentation to IgG4 autoimmune cholangitis (steroid responsive) (Gastro 2008;134:706)
• Dx: ↑ bilirubin, ↑ Ab, p-ANCA in 70% but nonspecific MRCP → multifocal beaded bile duct strictures, but may miss dx if confined to small intrahepatic ducts (~2% “small duct PSC”: better prognosis, ? different disease)
ERCP w/ liver bx gold standard: “onion-skin” fibrosis around bile ducts
• Treatment: supportive care, fat-soluble vitamins; no meds have improved survival
Ursodeoxycholic acid may ↓ colon CA risk in Pts w/ UC and improve LFTs in Pts w/o UC
Dominant stricture: endoscopic dilation, short-term stenting, or surgical resection
Cholangiocarcinoma (20%): ? annual surveillance w RUQ U/S and CA 19-9; ? PET
Liver transplantation: ~30% recurrence, though if UC, colectomy may ↓ recurrence
HEPATIC VASCULAR DISEASE

Portal vein thrombosis (PVT) (Al Phar Ther 2009;30:881)
- Definition: thrombosis, constriction, or invasion of portal vein → portal HTN → varices.
- Etiologies: cirrhosis, neoplasm (pancreas, HCC), abdominal infxn → pylephlebitis (infected thrombosis of PVT), hypercoag state (incl MPS), pancreatitis, IBD, surgery, trauma
- Clinical manifestations
  - **Acute PVT**: can p/w pain; often asx and dx as incidental finding on U/S or CT
  - **Chronic PVT**: asx/incidental finding; may p/w s/s of portal HTN, variceal bleeding, splenomegaly, mild encephalopathy; ascites rare unless cirrhosis
- Etiologies: cirrhosis, neoplasm (pancreas, HCC), abdominal infxn → pylephlebitis (infected thrombosis of PVT), hypercoag state (incl MPS), pancreatitis, IBD, surgery, trauma
- Diagnostic studies: LFTs usually normal; U/S w/ Doppler, MRA, CT (I/H11001), angiography; “portal cavernoma” network of hepatopedal collaterals in chronic PVT—can rarely cause biliary obstruction and cholesatic LFT → portal cholangiopathy (may require surgery)
- Treatment: eval for underlying cause (cirrhosis, MDS, hypercoag); if cirrhotic, Rx less clear
  - **Acute**: anticoagulation 6 mo unless irreversible etiology (not cirrhosis), then indefinite
  - **Chronic**: anticoagulation if hypercoag. state (not cirrhosis); unclear if benefit if refractory bleed consider TIPS, shunt. Isolated gastric varices 2° splenic vein thrombosis: splenectomy is curative.

Budd-Chiari syndrome (NEJM 2004;350:578)
- Occlusion of hepatic veins or IVC → sinusoidal congestion and portal HTN
- Etiologies: 50% due to myeloproliferative disorder a/w JAK2 mutations (esp P. vera), hypercoag. state, tumor invasion (HCC, renal, adrenal), IVC webs, trauma, ¼ idiopathic
- Symptoms: hepatomegaly, RUQ pain, ascites, dilated venous collaterals
- Dx: ≤ ↑ aminotransferases & A/G; Doppler U/S of hepatic veins (85% Se & Sp); CT (l’); MRI/MRA → vein occlusion or ↑ caudate lobe (separate venous drainage); “spider-web” pattern on hepatic venography; liver bx showing congestion (r/o right-sided CHF)
- Treatment: anticoagulation (heparin), thrombolysis if acute clot; TIPS preferred over surgical shunt; angioplasty w/ metallic stent if web or small clot; liver transplant

Sinusoidal obstruction syndrome (SOS) (Mayo 2003;78:589)
- Occlusion of hepatic venules and sinusoids (formerly veno-occlusive disease)
- Etiologies: HSCT, chemio (esp cyclopho), 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: ursodeoxycholic acid for high risk HSCT pop; use of low-dose heparin

Figure 3-8

ASCITES

Pathophysiology

- “Underfill” theory: portal hypertension → transudation of fluid into peritoneum → ↓ plasma volume → renal Na retention
- “Overflow” theory: hepatorenal reflex → Na retention
- Peripheral vasodilation theory (favored): portal hypertension → systemic vasodilation (↑ due to release of NO) → ↓ effective arterial volume → renal Na retention
- Other: ↓ serum oncotic pressure from hypoalbuminemia; ↑ hepatic lymph production

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Portal hypertension related SAAG ≥1.1</th>
<th>Nonportal hypertension related SAAG &lt;1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusoidal</td>
<td>cirrhosis (81%), including SBP acute hepatitis extensive malignancy (HCC or mets)</td>
<td>Peritonitis: TB, ruptured viscus (↑ amy) Peritoneal carcinomatosis Pancreatitis Vasculitis Hypoaalbuminemic states: nephrotic syndrome, protein-losing enteropathy Meigs’ syndrome (ovarian tumor) Bowel obstruction/infarction Postoperative lymphatic leak</td>
</tr>
<tr>
<td>Postsinusoidal</td>
<td>right-sided CHF incl. constriction &amp; TR Budd-Chiari syndrome, SOS</td>
<td></td>
</tr>
<tr>
<td>Presinusoidal</td>
<td>(g/w varices &gt; ascites) portal or splenic vein thrombosis, schistosomiasis</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms

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


- Physical exam: flank dullness (NPV ~90%, >1500 mL needed), shifting dullness (Se ~83%)
- Radiologic: U/S detects >100 mL; MRI/CT scan (also help with Ddx)
- Serum-ascites albumin gradient (SAAG): ~95% acc for portal HTN (Am J Gastro 1992:117:215) ≥1.1 g/dL → portal hypertension related; <1.1 g/dL → non–portal hypertension related if portal HTN + another cause (see in ~5% of cases) SAAG still ≥1.1 if known cirrhosis and SAAG <1.1 but no other readily identifiable cause, likely just cirrhosis (Am J Gastro 2009:104:1401)
- 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)
- Rule out infection: cell count w/ diff + gram stain/cx define bacterial peritonitis (see later); bedside inoculation of cx bottles ↑ yield to 90% (Gastro 1988:95:1351) fungal cx if prolonged hosp.; abx use; AFB cx + adenosine deaminase to r/o TB
- Other tests: amylase (pancreatitis, gut perforation); triglycerides (chylous ascites); cytology (peritoneal carcinomatosis, ~95% Se w/ 3 samples); LDH, glc, CEA, Ab (perforation)

Treatment

- If 2” to portal HTN (see “Cirrhosis” for details): ↓ Na intake + diuretics (spironolactone + lasix); if refractory → large-volume paracentesis or TIPS
- If non–portal HTN related: depends on underlying cause (TB, malignancy, etc.)

Bacterial peritonitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Ascites cell count/mm³</th>
<th>Ascites culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile</td>
<td>&lt;250 polys</td>
<td>☒</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis (SBP)</td>
<td>≥250 polys</td>
<td>(1 organism)</td>
</tr>
<tr>
<td>Culture-positive neutrocytic ascites (CNNA)</td>
<td>≥250 polys</td>
<td>☒</td>
</tr>
<tr>
<td>Nonneutrocytic bacteraemia (NNBA)</td>
<td>&lt;250 polys</td>
<td>(1 organism)</td>
</tr>
<tr>
<td>Secondary</td>
<td>≥250 polys</td>
<td>(polymerase)</td>
</tr>
<tr>
<td>Peritoneal dialysis-associated</td>
<td>≥100, poly predomin.</td>
<td>☒</td>
</tr>
</tbody>
</table>

- SBP/CNNA: seen in cirrhosis (qv) b/c ascites have ↓ opsonins; rare in other causes
- NNBA: often resolves w/o Rx; follow closely → Rx only if sx or persistently culture ☒
- Secondary intraabdominal abscess or perforation so often polymicrobial ascitic fluid TP >1 g/dL, glc ~50 mg/dL, LDH >225 U, CEA >5, Ab >240 Rx: 3rd-gen. ceph + metronidazole; urgent abdominal imaging + ex lap
- Peritoneal dialysis-associated: cloudy fluid, abd pain, fever, nausea pathogens: 70% GFC, 30% GNR; Rx: vanc + gent (IV load, then administer in PD)
BILIARY TRACT DISEASE

CHOLELITHIASIS (GALLSTONES)

Epidemiology & Pathogenesis ([J Hep 2008;48:S124])
- >10% adults in the U.S. have gallstones
- Bile = bile salts, phospholipids, cholesterol; ↑ cholesterol saturation in bile + accelerated nucleation → gallstones
- Risk factors: female; 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;302:201)

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 bilirubin (chronic hemolysis, cirrhosis) and calcium
  - Brown: stasis & infection in bile ducts → bacteria deconjugate bilirubin → precipitates w/ calcium; seen w/ duodenal diverticula, biliary strictures, parasites

Clinical manifestations
- May be asx; biliary colic in ~2%/y; once sx, rate of complications ~2%/y
- Biliary colic = episodic RUQ or epigastric abd pain that begins abruptly, is continuous, resolves slowly, and lasts for 30 min to 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
- Cholecystectomy (CCY), usually laparoscopic, if symptomatic
- CCY in asx Pts w/ selective mucosal GB calcification (~7% risk of ca) (Surgery 2001;129:699), GB polyps >10 mm, Native American, stones >3 cm
- Ursodeoxycholic acid (rare) for cholesterol stones w/ uncomplicated biliary pain or if poor surgical candidate; also reduces risk of gallstone formation with rapid weight loss

Complications
- Cholecystitis: 20% of sx biliary pain → cholecystitis w/in 2 y
- Choledocholithiasis → cholangitis or gallstone pancreatitis
- Mirizzi’s syndrome: common hepatic duct compression by cystic duct stone → jaundice, biliary obstruction
- Cholecystoenteric 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 examination: 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, Ab, ALT/AST, and amylase; AST/ALT >500 U/L, bili >4 mg/dL, or amylase >1,000 U/L → choledocholithiasis

Diagnostic studies
- RUQ U/S: high Se & Sp for stones, but need specific signs of cholecystitis: GB wall thickening >5 mm, pericholecystic fluid, and a sonographic Murphy’s sign
**HIDA scan**: most Se test (80–90%) for acute cholecystitis. IV inj of HIDA, which is 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 pipracillin-tazobactam
- **Early CCY (usually w/in 72 h)**. Delaying surgery 2–3 mos ↓ operative time w/o Δ rate of complications or conversion to open procedure *(Am J Surg 2008;194:40).*
- **Cholecystostomy and percutaneous drainage** if too sick for surgery
- 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

---

**CHOLEDOCHOLITHIASIS**

**Definition**
- Gallstone lodged in bile duct (BD)

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

**Clinical manifestations**
- Asymptomatic (50%)
- RUQ/epigastric pain due to obstruction of bile flow → ↑ BD pressure, jaundice, pruritis, nausea

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

**Treatment**
- ERCP & papillotomy w/ stone extraction
- CCY typically w/in 6 wks unless contraindication (~15% Pts will develop indication for CCY if left unRx’d)

**Complications**
- Cholangitis, cholecystitis, pancreatitis, stricture

---

**CHOLANGITIS**

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

**Clinical manifestations**
- Charcot’s triad: RUQ pain, jaundice, fever/chills; present in ~70% of Pts
- Reynold’s pentad: Charcot’s triad + shock and Δ MS; present in ~15% of Pts

**Diagnostic studies**
- RUQ U/S
- Labs: ↑ WBC, bilirubin, Aδ, amylase; Ω 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 PaCO₂ to counteract 1° metabolic process
  - Renal: excretion/retention of H⁺ or HCO₃⁻ to counteract 1° respiratory process
- Compensatory respiratory compensation occurs in min; renal compensation takes hrs to days
- Compensation never fully corrects pH; if pH normal, consider mixed disorder

Consequences of Severe Acid-Base Disturbances

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Acidemia (pH &lt; 7.20)</th>
<th>Alkalemia (pH &gt; 7.60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ contractility, arteriolar vasodilation</td>
<td>↓ arteriolar vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>↓ MAP &amp; CO₂ response to catecholamines</td>
<td>↓ coronary blood flow</td>
</tr>
<tr>
<td></td>
<td>↑ risk of arrhythmias</td>
<td>↑ risk of arrhythmias</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperventilation, ↓ resp muscle strength</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Metabolic</td>
<td>↑ K</td>
<td>↓ K, ICa, Mg, PO₄</td>
</tr>
<tr>
<td>Neurologic</td>
<td>∆ MS</td>
<td>∆ MS, seizures</td>
</tr>
</tbody>
</table>

NEJM 1998;338:26 & 107

Workup
- Determine primary disorder: ✓ pH, PaCO₂, HCO₃
- Determine if degree of compensation is appropriate

Primary Disorders

<table>
<thead>
<tr>
<th>Primary disorder</th>
<th>Problem</th>
<th>pH</th>
<th>HCO₃</th>
<th>PaCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>gain of H⁺ or loss of HCO₃</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>gain of HCO₃ or loss of H⁺</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>hyperventilation</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>hyperventilation</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Compensation for Acid/Base Disorders

<table>
<thead>
<tr>
<th>Primary disorder</th>
<th>Expected compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>↓ PaCO₂ = 1.25 × ΔHCO₃ or PaCO₂ = (1.5 × HCO₃) + 8 ± 2 (also, PaCO₂ = last two digits of pH)</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑ PaCO₂ = 0.75 × ΔHCO₃</td>
</tr>
<tr>
<td>Acute respiratory acidosis</td>
<td>↑ HCO₃ = 0.1 × ΔPaCO₂ (also, pH = 0.008 × ΔPaCO₂)</td>
</tr>
<tr>
<td>Chronic respiratory acidosis</td>
<td>↑ HCO₃ = 0.4 × ΔPaCO₂ (also, pH = 0.003 × ΔPaCO₂)</td>
</tr>
<tr>
<td>Acute respiratory alkalosis</td>
<td>↓ HCO₃ = 0.2 × ΔPaCO₂ (also, pH = 0.008 × ΔPaCO₂)</td>
</tr>
<tr>
<td>Chronic respiratory alkalosis</td>
<td>↓ HCO₃ = 0.4 × ΔPaCO₂</td>
</tr>
</tbody>
</table>

Mixed disorders (more than one primary disorder at the same time)
- If compensation less or greater than predicted, may be 2 disorders:
  - PaCO₂ too low → concomitant 1° resp. alk.
  - PaCO₂ too high → concomitant 1° resp. acid.
  - HCO₃ too low → concomitant 1° met. acid.
  - HCO₃ too high → concomitant 1° met. alk.
- Normal pH but...
  - ↓ PaCO₂ + ↓ HCO₃ → resp. acid. + met. alk.
  - ↓ PaCO₂ + ↓ HCO₃ → resp. alk. + met. acid.
  - normal PaCO₂ & HCO₃, but ↑ AG → AG met. acid. + met. alk.
  - normal PaCO₂, HCO₃, & AG → no disturbance or non-AG met. acid. + met. alk.
- Cannot have resp. acid. (hyperventilation) and resp. alk. (hyperventilation) simultaneously
Metabolic Acidosis

**Initial workup**
- √ anion gap (AG) = Na – (Cl + HCO₃) – 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 → ↑ xalb or ↑ unmeasured cations (Ca, Mg, K, Li, bromine, immunoglobulin)
- If ↑ AG, ∆ delta-delta (∆AG → ∆AG/ΔHCO₃) to assess if there is an additional metabolic acid-base disturbance; ∆AG = (calculated AG – expected AG), ∆HCO₃ = (24 – HCO₃)
  - ∆AG < 1 → AG metabolic acidosis and simultaneous non-AG acidosis
  - ∆AG > 2 → AG metabolic acidosis and simultaneous metabolic alkalosis

**Etiologies of AG Metabolic Acidosis**

<table>
<thead>
<tr>
<th>Ketoadicidosis</th>
<th>Diabetes mellitus, alcoholism, starvation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>Type A: impairment in tissue oxygenation, eg, circulatory or respiratory failure, sepsis, ischemic bowel, carbon monoxide, cyanide</td>
</tr>
<tr>
<td>Type B: no impairment in tissue oxygenation, eg, malignancy, alcoholism, meds (metformin, NRTIs, salicylates, propylene glycol)</td>
<td></td>
</tr>
<tr>
<td>α-lactic acidosis: short bowel syndrome → precip by glc ingest → metab by colonic bacteria to α-lactate; not detected by standard lactate assay</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>Accumulation of organic anions such as phosphates, sulfates, urate, etc.</td>
</tr>
<tr>
<td>Ingestions</td>
<td>Methanol (windshield fluid, antifreeze, solvents, fuel): metab to formic acid</td>
</tr>
<tr>
<td>Ethylene glycol (antifreeze): metab to glycolic and oxalid acids</td>
<td></td>
</tr>
<tr>
<td>Propylene glycol (pharmaceutical solvent, eg, IV diazepam &amp; lorazepam; antifreeze): lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Salicylates: metabolic acidosis (from lactate, ketones) + respiratory alkalosis due to stimulation of CNS respiratory center</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen: glutathione depletion → 1 endogenous organic acid 5-oxoproline in susceptible host (malnourished, female, renal failure)</td>
<td></td>
</tr>
</tbody>
</table>
Workup for AG metabolic acidosis
• ✓ for ketonuria (dipstick acetoacetate) or plasma β-hydroxybutyrate (βOHB)
  nb, urine acetoacetate often not present in early ketoadidosis 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 osmole - calculated osmole (can + [EtOH/4.6] if have EtOH level and want to test if other ingestions)
  • OG >10 → suggests ingestion (see below)

<table>
<thead>
<tr>
<th>Ingestions</th>
<th>AG</th>
<th>OG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Salicylates</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Ethanol</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Methanol</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>→</td>
<td>→</td>
</tr>
</tbody>
</table>

Etiologies of Non-AG Metabolic Acidosis
GI losses of HCO3
RTAs
Early renal failure
Ingestions
Dilutional
Post-hypocapnia
Ureteral diversion

Workup for non-AG metabolic acidosis
• Evaluate history for causes (see above)
• ✓ urine anion gap (UAG) = (UNa + UK) - UCl
  UAG = unmeasured anions - unmeasured cations; as NH4⁺ is primary unmeasured cation, UAG is indirect assay for renal NH4⁺ excretion (NEJM 1988;318:594)
• ☐ UAG → ↑ renal NH4⁺ excretion → appropriate renal response to acidemia
  Ddx: GI causes, type II RTA, ingestions or dilutional
• ☑ UAG → failure of kidneys to secrete NH4⁺
  Ddx: type I or IV RTA, early renal failure
  nb, plasma K usually ↓ in type I and ↑ in type IV
• UAG evaluation assumes Pt not volume deplete (UNa >25) & w/o AG met. acid. → ☑ UAG

Renal tubular acidoses (RTAs)
• Proximal (Type II): ↓ proximal reabsorption of HCO3
  1° (Fanconi’s syndrome → ↓ proximal reabsorption of HCO3, PO4, glc, amino acids), paraprotein (multiple myeloma, amyloidosis), mds (acetazolamide, heavy metals, ifosfamide), renal transplant, ↓ Vit D, NRTIs
• Distal (Type I): defective distal H⁺ secretion
  1°, autoimmune (Sjögren’s, RA), nephrocalcinosis, mds (ampho, Li, ifosfamide); normally a/w ↓ K; if with ↑ K → sickle cell, obstruction, SLE, renal transplant
• Hypoald (Type IV): ↑ K → ↓ NH4 synthesis/delivery → ↓ urine acid carrying capacity
  ↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV normal renin, ↓ aldosterone synthesis: 1° adrenal disorders, ACEI, ARBs, heparin
  ↓ response to aldosterone
  mds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors tuberculosis; sicle cell, SLE, amyloid, diabetes
Renal Tubular Acidosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Type</th>
<th>Acidosis</th>
<th>UAG</th>
<th>U pH</th>
<th>FeHCO₃</th>
<th>Serum K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>II</td>
<td>moderate</td>
<td>±</td>
<td>&lt;5.3</td>
<td>&gt;15%</td>
<td>↓</td>
</tr>
<tr>
<td>Distal</td>
<td>I</td>
<td>severe</td>
<td>+</td>
<td>&gt;5.3</td>
<td>&lt;3%</td>
<td>↓</td>
</tr>
<tr>
<td>Hypoaldo</td>
<td>IV</td>
<td>mild</td>
<td>+</td>
<td>&lt;5.3</td>
<td>&lt;3%</td>
<td>↑</td>
</tr>
</tbody>
</table>

*Urine pH will rise above 5.3 in the setting of HCO₃ load

FeHCO₃ should be checked after an HCO₃ load

*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) *(NEJM 1998;338:26)*

- DKA: insulin & IVF; AKA: dextrose, IVF, replete K, Mg, PO₄ as needed
- Lactic acidosis: treat underlying condition, avoid vasoconstrictors
- Renal failure: hemodialysis
- Methanol & ethylene glycol: early fomepizole, vit. B₆ (ethylene glycol), folate (methanol), hemodialysis (especially if late presentation) *(NEJM 2009;360:22)*
- Alkali therapy: NaHCO₃ (eg, 3 50-mmol amp in 1 L D₅W) to get serum HCO₃ > 8 and pH > 7.2 (estimate mmol of HCO₃ needed as 8-[HCO₃]serum × wt × 0.5) side effects: volume overload, hypernatremia, i. ICa, ↑ P₃CO₂ (and ↓ possibly intracellular acidosis), overshoot; no proven benefit in lactic acidosis *(Annals 1990;112:492)*

---

### Metabolic Alkalosis

**Pathophysiology**

- Saline-responsive etiologies require initiating event and maintenance factors, whereas saline-resistant etiologies develop from various causes
  - **Initiating event**
    - Loss of H⁺ from GI tract or kidneys
    - Exogenous alkali
  - Contracture alkalosis: diuresis → excretion of HCO₃-poor fluid → extracellular fluid “contracts” around fixed amount of HCO₃ → ↑ HCO₃ concentration
  - Posthypercapnia: respiratory acidosis → renal compensation with HCO₃ retention; rapid correction of respiratory disorder (eg, with intubation) → transient excess HCO₃
  - Maintenance factors
    - Volume depletion → ↑ proximal reabsorption of NaHCO₃ and ↑ aldosterone (see next)
    - Hyperaldosteronism (either 1° or 2°) → distal Na reabsorption in exchange for K⁺ and H⁺ excretion (and consequent HCO₃ 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 $\text{H}^+$: 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 $U_{Cl^-}$
  - $U_{Cl^-} < 20 \text{ mEq/L} \rightarrow$ saline-responsive
  - $U_{Cl^-} > 20 \text{ mEq/L} \rightarrow$ saline-resistant (unless currently receiving diuretics)
  - $U_{Na^+}$ unreliable determinant of volume status as alkalemia → $\uparrow$ HCO$_3^-$ excretion → $\uparrow$ Na excretion; negatively charged HCO$_3^-$ “drags” Na$^+$ along
  - If $U_{Cl^-} > 20$ and volume replete, ✓ blood pressure

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 d/c: PPI
- Hyperaldosteronism: treat underlying condition

Respiratory Acidosis

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

Respiratory Alkalosis

Etiologies (NEJM 2002;347:43)
- Hypoxia → hyperventilation: pneumonia, pulm. edema, PE, restrictive lung disease
- Primary hyperventilation
  - CNS disorders, pain, anxiety
  - drugs: salicylates, progesterone, methylxanthines
  - pregnancy, sepsis, hepatic failure
SODIUM AND WATER HOMEOSTASIS

Overview

General
- Disorders of serum sodium are generally due to \( \Delta s \) in total body water, not sodium
- Hyper- or hypoosmolality \( \rightarrow \) rapid water shifts \( \rightarrow \Delta s \) in brain cell volume \( \rightarrow \Delta \text{MS, seizures} \)

Key hormones
- Antidiuretic hormone (ADH): primary hormone that regulates sodium concentration
  - stimuli for secretion: hyperosmolality, \( \downarrow \) effective arterial volume (EAV)
  - action: insertion of aquaporin-2 channels in collecting ducts \( \rightarrow \) passive water reabsorption
  - urine osmolality is an indirect functional assay of the ADH-renal axis
    - \( U_{\text{osm}} \) range: 60 mOsm/L (no ADH) to 1200 mOsm/L (maximal ADH)
- Aldosterone: primary hormone that regulates total body sodium (and \( \therefore \) 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
- Excess of water relative to sodium: almost always due to \( \uparrow \) ADH
  - \( \uparrow \) ADH may be appropriate (eg, hypovolemia or hypervolemia with \( \downarrow \) EAV)
  - \( \uparrow \) ADH may be inappropriate (SIADH)
- Rarely, \( \downarrow \) ADH (appropriately suppressed), but kidneys unable to maintain nl [Na\(_{\text{serum}}\)]
  - primary polydipsia: ingestion of massive quantities (usually \( \geq 12 \text{ L/d} \) of free H\(_2\)O
    - overloads diluting ability of kidney (normal solute load \( \sim 750 \text{ mOsm/d, min } U_{\text{osm}} = 60 \text{ mOsm/L} \rightarrow \) excrete in \( \sim 12 \text{ L} \); if H\(_2\)O ingestion exceeds this, H\(_2\)O retention)
    - "tea & toast" and "beer potomania"; \( \downarrow \) daily solute load, \( \uparrow \) free H\(_2\)O \( \rightarrow \) insufficient solute to excrete H\(_2\)O intake (eg, if only 250 mOsm/d, minimum \( U_{\text{osm}} = 60 \text{ mOsm/L} \rightarrow \) excrete in \( \sim 4 \text{ L} \); if H\(_2\)O ingestion exceeds this, H\(_2\)O retention)

Workup (NEJM 2000;342:1581)
- Measure plasma osmolality
  - Hypotonic hyponatremia most common scenario; true excess of free H\(_2\)O relative to Na
  - Hypertonic hyponatremia: excess of another effective osmole (eg, glc, mannitol) that draws H\(_2\)O intravascularly; each 100 mg/dL \( \uparrow \) glc \( \uparrow 2.4 \text{ mEq/L} \) \( [\text{Na}] \)
  - Isotonic hyponatremia: rare lab artifact from hyperlipidemia or hyperproteinemia
- For hypotonic hyponatremia, \( \sqrt{\text{volume status}} \) (vital signs, orthostatics, JVP, skin turgor, mucus membranes, peripheral edema, BUN, Cr, uric acid)
- \( U_{\text{osm}} \) diagnostically useful in limited circumstances, because almost always \( \geq 300 \text{ mOsm/L} \)
  - exceptions: \( U_{\text{osm}} < 100 \text{ mOsm/L} \rightarrow \) SIADH; must determine if \( \uparrow \) ADH appropriate or inappropriate
  - however, \( U_{\text{osm}} \) important when deciding on treatment (see below)
- If euvolemic and \( \downarrow U_{\text{osm}} \), evaluate for glucocorticoid insufficiency and hypothyroidism

Figure 4-4 Approach to hyponatremia
Hypovolemic hypotonic hyponatremia (ie, ↓ total body Na, ↓ TBW)

- **Renal losses** ($U_{\text{Na}} > 20$ mEq/L, $FE_{\text{Na}} > 1\%$): diuretics (espec. thiazides, as loop diuretics ↓ tonicity of medullary interstitium and impair urine concentrating ability), salt-wasting nephropathy, cerebral salt wasting, mineralocorticoid deficiency

- **Extrarenal losses** ($U_{\text{Na}} < 10$ mEq/L, $FE_{\text{Na}} < 1\%$): GI losses (eg, diarrhea), third-spacing (eg, pancreatitis), inadequate intake, insensible losses

**Euvolemic hypotonic hyponatremia** (ie, ¬nl total body Na, ↑ TBW)

- **SIADH** (eu- or mild hypervolemia, inappro $U_{\text{osm}}$ normal $U_{\text{Na}}$, ↓ BUN & UA) malignancy: lung, brain, GI, GU, lymphoma, leukemia, thyromma, mesothelioma pulmonary: pneumonia, asthma, COPD, PTX, ↓ pressure ventilation intracranial: trauma, stroke, hemorrhage, infxn, hydrocephalus drugs: antipsychotics, antidepressants, chemotherapy, vasopressin, dDAVP, MDMA miscellaneous: pain, nausea, postoperative state

- **Endocrinopathies**: ↑ ADH activity seen in glucocorticoid deficiency (co-secretion of ADH & CRH) and hypothyroidism (↓ CO & ↓ GFR)

- **Psychogenic polydipsia** ($U_{\text{osm}} < 100$, ↓ uric acid): usually requires intake > 12 L/d

- **Low solute** (“tea & toast”; “beer potomania”)

- **Reset osmostat**: chronic malnutrition (↓ intracellular osmole) or pregnancy (hormonal effects) → ADH physiology reset to regulate a lower $[\text{Na}]_{\text{serum}}$

**Hypervolemic hypotonic hyponatremia** (ie, ↑ total body Na, ↑↑ TBW)

- **CHF** (↓ CO → ↓ EAV; $U_{\text{Na}} < 10$ mEq/L, $FE_{\text{Na}} < 1\%$)

- **Cirrhosis** (splanchnic arterial vasodilation and ascites → ↓ EAV; $U_{\text{Na}} < 10$ mEq/L, $FE_{\text{Na}} < 1\%$)

- **Nephrotic syndrome** (hypoalbuminemia → edema → ↓ EAV; $U_{\text{Na}} < 10$ mEq/L, $FE_{\text{Na}} < 1\%$)

- **Advanced renal failure** (diminished ability to excrete free H$_2$O; $U_{\text{Na}} > 20$ mEq/L)

**Treatment**

- **Goals of treatment**

  Asymptomatic hyponatremia: correct $[\text{Na}]_{\text{serum}}$ at rate of ± 0.5 mEq/L/h

  Symptomatic hyponatremia: initial rapid correction of Na (2 mEq/L/h for the first 2–3 h) until sx resolve

  Rate of ↑ Na should not exceed 10–12 mEq/L/d to avoid osmotic demyelination syndrome (spastic quadriplegia, dysarthria, dysphagia), espec if hypoNa chronic

- **Effect of IV fluids**

  initial $\Delta[\text{Na}]_{\text{serum}}$ per L infusate = $\frac{[\text{Na}]_{\text{infusate}} - [\text{Na}]_{\text{serum}}}{TBW + 1}$ TBW = wt (kg) × 0.6 (♂) or 0.5 (♀); if elderly use 0.5 (♂) or 0.45 (♀)

  eg, 1 L hypertonic saline (513 mEq Na) given to 70-kg man w/ $[\text{Na}] = 110$ mEq/L will ↑ $[\text{Na}]_{\text{serum}}$ by 9.4 mEq

  however, above assumes entire infusate retained without any output of Na or H$_2$O

  if Pt is euvoletic, as in SIADH, then infused Na will be excreted

  eg, 1 L NS (154 mEq of Na or 308 mOsm of solute in 1 L free H$_2$O) given to Pt with SIADH with $U_{\text{osm}} = 616$ → 308 mOsm solute excreted in 0.5 L H$_2$O → net gain 0.5 L H$_2$O → ↓ $[\text{Na}]_{\text{serum}}$

  ↓ normal saline can worsen hyponatremia 2° SIADH if $U_{\text{osm}} >$ infusate$_{\text{osm}}$

- **Hypovolemic hyponatremia**: volume repletion with normal saline once volume replete → stimulus for ADH removed → kidneys will excrete free H$_2$O → serum Na will correct rapidly

- **SIADH** (NEJM 2007;356:2064): free water restrict → treat underlying cause

  - hypertonic saline (↓ loop diuretics) if sx or Na fails to ↑ w/ free H$_2$O restriction

  - $1$ L hypertonic saline will raise $[\text{Na}]_{\text{serum}}$ by ~10 mEq (see above)

  - $50$ mL/h will ↑ $[\text{Na}]$ by ~0.5 mEq/L/h; 100–200 mL/h will ↑ $[\text{Na}]$ by ~1–2 mEq/L/h

  formula only provides estimate: → recheck serum Na frequently

  salt tabs: particularly if chronic and no CHF

- **Aquareisis** (IV V1a & V2 vasopressin receptor antag) or tolvaptan (oral V2 antag): used for symptomatic SIADH resistant to above Rx

  aquareisis: tolvaptan (NEJM 2006;355:2099), consider in symptomatic hyponatremia resistant to above Rx, monitor for overcorrection
HYPERNATREMIA

Pathophysiology (NEJM 2000;342:1493)

- Deficit of water relative to sodium; by definition, all hypernatremic Pts are hypertonic
- Usually loss of hypotonic fluid; occasionally infusion of hypertonic fluid
- And impaired access to free water (eg, intubation, Δ M5, elderly): hypernatremia is a powerful thirst stimulus, ∴ usually only develops in Pts w/o access to H2O

Workup

- Uosm, UNa; volume status (vital signs, orthostatics, JVP, skin turgor, BUN, Cr)
  - Uosm > 700–800 → extrarenal loss or Na overload; to differentiate
  - UNa to differentiate Uosm > 700–800 → renal loss; differentiate DI vs. diuresis based on Uosm and clinical hx

Figure 4-5 Approach to hypernatremia

Extrarenal H2O loss (Uosm > 700–800)
- GI H2O loss: vomiting, NGT drainage, osmotic diarrhea, fistula
- Insensible loss: fever, exercise, ventilation

Renal H2O loss (Uosm < 700–800)
- Diuresis: osmotic (glc, mannitol, urea), loop diuretics
- Diabetes insipidus: ADH deficiency (central) or resistance (nephrogenic)
  - Central: hypothalamic or posterior pituitary disease (congenital, trauma/surgery, tumors, infiltrative); also idiopathic, hypoxic encephalopathy, anorexia, EtOH
  - Nephrogenic (Annals 2006;144:186)
    - congenital (ADH receptor V2 mutation, aquaporin-2 mutation)
    - drugs: Li, 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 (Uosm > 700–800)
- Na overload: hypertonic saline (eg, resuscitation w/ NaHCO3), mineralocorticoid excess
- Seizures, exercise: ↑ intracellular osmolytes → H2O shifts → transient ↑ [Na]serum

Treatment

- Restore access to H2O or supply daily requirement of H2O (≥ 1 L/d)
- Replace free H2O deficit (also replace concurrent volume deficit if appropriate):
  - Free H2O deficit (L) = \(\frac{[Na]_{serum} - 140}{140} \times TBW\)
  - shortcut: for typical 70-kg man, free H2O deficit (L) = \(\frac{[Na]_{serum} - 140}{3}\)
  - Δ [Na]serum per L infusate = \(\frac{[Na]_{serum} - [Na]_{infusate}}{TBW + 1}\)
    - eg, 1 L D5W given to 70-kg man w/ [Na]~160 mEq/L will ↓ [Na]serum by 3.7 mEq
    - 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 H2O will ↓ [Na] by ~0.5 mEq/L/h
    - ½ NS (77 mEq/L) or ⅔ NS (38 mEq/L) provides both volume & free H2O (500 or 750 mL of free H2O per L, respectively); can give free H2O via NGT/OGT
- Formulas provide only estimates; ∴ recheck serum Na frequently
- DI and osmotic diuresis: see “Polyuria” section below
- Na overload: D5W + loop 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 $U_{\text{osm}}$
- 24-h osmole excretion rate = 24-h UOP (actual or estimate) $\times U_{\text{osm}}$
  - $>1000 \text{ mOsm/d} \rightarrow$ osmotic diuresis
  - $<800 \text{ mOsm/d} \rightarrow$ water diuresis

**Osmotic diuresis**
- Etiologies
  - Glucose (uncontrolled diabetes mellitus)
  - Mannitol
  - Urea: recovering ARF, $\uparrow$ protein feeds, hypercatabolism (burns, steroids), GI bleed
  - NaCl administration
  - Propylene glycol

**Water diuresis**
- Etiologies: diabetes insipidus (DI) ($N_{\text{serum}} > 140$) or $1^\circ$ polydipsia ($N_{\text{serum}} < 140$)
  - see “Hypernatremia” above for list of causes of central and nephrogenic DI
- Workup of DI: $U_{\text{osm}} < 300$ (complete) or 300–600 (partial)
  - **water deprivation test** (start in a.m., $N_{\text{serum}}, P_{\text{osm}}, U_{\text{osm}}, \text{UOP} \ q1–2h$)
    - Deprive until $P_{\text{osm}} > 295$, then $U_{\text{osm}}$.
    - If $U_{\text{osm}} < 300$, then administer vasopressin (5 U SC) or dDAVP (10 $\mu$g intranasal), then check $U_{\text{osm}}$ in 1–2 hrs:
      - $U_{\text{osm}} \downarrow$ by $>50\%$ – central DI
      - $U_{\text{osm}}$ unchanged – nephrogenic DI
    - $\checkmark$ ADH level before and after water deprivation to evaluate proper response

**Treatment**
- $1^\circ$ polydipsia: treat psychiatric illness, check meds, restrict access to free H$_2$O
- Osmotic diuresis: address underlying cause, replace free H$_2$O 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 $\rightarrow \downarrow$ delivery of filtrate to dysfxnal diluting segment of kidney)
  - pregnancy-induced DI: due to vasopressinase from placenta, $..$ Rx w/ dDAVP

![Figure 4-6 Approach to polyuria](image-url)
Overview (Annals 2009;150:619)

- Renal: potassium excretion regulated at distal nephron (collecting tubule)
  - distal Na delivery & urine flow: Na absorption → lumen electronegative → K secretion
  - Aldosterone: increases Na absorption, K secretion
- Transcellular shifts: most common cause of acute change in serum potassium
  - Acid-base disturbance: K⁺/H⁺ exchange across cell membranes
  - Insulin: stimulates Na-K ATPase → hypokalemia (mitigates postprandial ↑ K)
  - Catecholamines: stimulate Na-K ATPase → hyperkalemia; reversed by β-blockers
  - Digoxin: blocks Na-K ATPase → hyperkalemia
  - Massive necrosis (eg, tumor lysis, rhabdomyolysis, ischemic bowel) → release of intracellular K
- Hypo- or hyperkalemic periodic paralysis: rare disorders due to channel mutations

Transcellular shifts

- Alkalemia, insulin, catecholamines, hypokalemic periodic paralysis, acute ↑ in hematopoesis (megaloblastic anemia Rx w/ B₁₂, AML crisis), hypothermia

GI potassium losses (Uₖ < 25 mEq/d or < 15 mEq/L or TTKG < 3)

- GI losses plus metabolic acidosis: diarrhea, laxative abuse, villous adenoma
- Vomiting & NGT drainage usually manifest as renal losses due to 2° hyperald. & met. alk.

Renal potassium losses (Uₖ > 30 mEq/d or > 15 mEq/L or TTKG > 7)

- Hypotensive or normotensive acidosis: DKA, RTA (type I) and some distal RTAs (type II)
- 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 depletion: ? ↑ distal K secretion (JASN 2007;18:2649)

Hypertensive: mineralocorticoid excess

- 1° hyperaldosteronism (eg, Conn’s syndrome)
- 2° hyperaldosteronism (eg, renovascular disease, renin-secreting tumor)
- Non-aldosterone mineralocorticoid (eg, Cushing’s, Liddle’s, exogenous mineralocort., licorice)

Clinical manifestations

- Nausea, vomiting, ileus, weakness, muscle cramps, rhabdomyolysis, polyuria
- ECG: U waves, ↑ QT interval, ventricular ectopy (PVCs, VT, VF)

Workup (NEJM 1998;339:451)

- Rule-out transcellular shifts
- Check Uₖ and transtubular potassium gradient (TTKG) = (Uₖ/Pₖ) / (U₉₀₀/P₉₀₀)
  - Uₖ < 25 mEq/d or < 15 mEq/L or TTKG < 3 → renal loss
  - Uₖ > 25 mEq/d or > 15 mEq/L or TTKG > 7 → extrarenal loss
- If renal losses, check blood acid-base status, Uₙ₄ (Uₙ₄ 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 Mg as necessary

HYPERKALEMIA

Transcellular shifts
- Acidemia, insulin defic. (DM), β-blockers, dig intox., massive cellular necrosis (tumor lysis, rhabdo, ischem. bowel, hemolysis), hyperkalemic periodic paralysis, succinylcholine

Decreased GFR
- Any cause of oligouric 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
- Hyperaldosteronism: same as etiologies of hypoaldo RTA (type IV)
  - ↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV
  - normal renin, ↓aldo synthesis: ↑ renal K excretion limited by ↑ distal Na delivery and urine flow
  - meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors

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:
  - Consider ↓ distal Na delivery and urine flow
  - transtubular K gradient (TTKG) = (Uosm/Posm)/(UK/Pk), <7 c/w hypoaldo

<table>
<thead>
<tr>
<th>Treatment of Hyperkalemia</th>
<th>Dose</th>
<th>Onset</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium gluconate</td>
<td>1–2 amps IV</td>
<td>&lt;3 min</td>
<td>transient effect (30–60 min) stabilizes cell membrane</td>
</tr>
<tr>
<td>Calcium chloride¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>reg. insulin 10 U IV + 1–2 amps D50W</td>
<td>15–30 min</td>
<td>transient effect (30–60 min) drives K into cells</td>
</tr>
<tr>
<td>Bicarbonate (esp. if acidic)</td>
<td>1–3 amps IV</td>
<td>15–30 min</td>
<td>transient effect (60 min) drives K into cells in exchange for H</td>
</tr>
<tr>
<td>β2 agonists</td>
<td>albuterol 10–20 mg inh. or 0.5 mg IV</td>
<td>30–90 min</td>
<td>transient effect (~2 h) drives K into cells</td>
</tr>
<tr>
<td>Kayexalate²</td>
<td>30–90 g PO/PR</td>
<td>1–2 h</td>
<td>↓ total body K (over ~6 h) exchanges Na for K in gut</td>
</tr>
<tr>
<td>Diuretics</td>
<td>furosemide ≈40 mg IV</td>
<td>30 min</td>
<td>↓ total body K</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td></td>
<td></td>
<td>↓ total body K</td>
</tr>
</tbody>
</table>

¹calcium chloride contains more calcium and is typically reserved for use in codes (↑ risk of tissue necrosis)
²increased risk of intestinal necrosis with postoperative ileus

- Rate of onset important to note when establishing a treatment plan
- Calcium helps prevent cardiac complications; should be initial Rx, esp. if ECG Δs
- Insulin, bicarbonate (esp. if acidic), and β2 agonists should follow to ↓ plasma K
- Treatments that eliminate total body K essential as other Rx will wear off with time; kayexalate ± diuretics may be effective in many cases, but emergent hemodialysis should be considered in life-threatening situations
**Acute Kidney Injury (AKI)**

**Definition** *(Crit Care 2007;11:R31)*
- AKI: an abrupt (<48 h) ↑ Cr ≥ 0.3 mg/dL, ↑ Cr ≥ 50%, or UOP < 0.5 mL/kg/hr for >6 h

**Workup** *(JAMA 2003:289:747)*
- H&P: recent procedures & meds; 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\textsubscript{Na}) = (U\textsubscript{Na}/P\textsubscript{Na})/(U\textsubscript{Cr}/P\textsubscript{Cr})
- In setting of diuretics, FE\textsubscript{Na} = (U\textsubscript{Na}/P\textsubscript{Na})/(U\textsubscript{Cr}/P\textsubscript{Cr}) < 1% → prerenal, contrast, or glomerulonephritis: 2% → ATN
- Renal bx: may be necessary if cause remains unclear
- Serologies (if indicated): see “Glomerular Disease”
- 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 wks post exposure in Pts w/ moderate to severe CKD *(JACC 2009;53:1621)*

**Etiologies and Diagnosis of Acute Kidney Injury** *(Lancet 2005;365:417)*

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>U/A, Sediment, Indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute tubular necrosis (ATN)</td>
<td>Bland</td>
</tr>
<tr>
<td>Ischemia: progression of prerenal disease</td>
<td>Transparent hyaline casts</td>
</tr>
<tr>
<td>Toxins</td>
<td>Pigmented granular muddy brown casts in ~75%</td>
</tr>
<tr>
<td>Drugs: AG, amphetamine, cisplatin</td>
<td>(≠ in CIAKI)</td>
</tr>
<tr>
<td>Pigments: HB, myoglobin</td>
<td>± RBCs &amp; protein from tubular damage</td>
</tr>
<tr>
<td>Proteins: Ig light chains</td>
<td>FE\textsubscript{Na} &gt; 2% (except pigment &amp; CIAKI)</td>
</tr>
<tr>
<td>Crystals: UA, ACV, MTX, indinavir, oral NaPO4</td>
<td>U\textsubscript{Urea} &lt; 350</td>
</tr>
<tr>
<td>Contrast-induced AKI (CIAKI): ↓ RBF + toxin</td>
<td></td>
</tr>
</tbody>
</table>

| Acute interstitial nephritis (AIN) | WBCs, WBC casts, ± RBCs |
| Allergic: β-lactams, sulfa drugs, NSAIDs, PPIs | uric acid in abx |
| Infection: pyelonephritis, legionella | lymphs in NSAIDs |
| Infiltrative: sarcoid, lymphoma, leukemia | |
| Autoimmune: Sjogren’s, TINU syndrome, IgG4, SLE | |

| Glomerulonephritis (see “Glomerular Disease”) | Dysmorphic RBCs & RBC casts |

| Small vessel: cholesterol emboli, thrombotic microangiopathy (HUS/ITP, DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis) | ± RBCs |
| Glomerulonephritis | uric acid in chol emboli |

| Post | |
| Bladder neck: BPH, prostate cancer, neurogenic bladder, anticholinergic meds | Bland |
| Ureteral (bladderal): malig, LAM, retroperitoneal fibrosis, nephrothiasis | ± RBCs if nephrothiasis |

**Contrast-induced acute kidney injury (CIAKI)**
- Risk factors: CKD, DM, CHF, age, hypertension, ↑ contrast volume *(JACC 2004:44:1393)*
- Clinical: Cr ↑ 25% or 0.5 mg/dL w/in 48 h, peaks in 3–5 d, resolves in 7–10 d

**Prehydration/posthydration** *(NEJM 1994:331:1416)* unless contraindicated to IVf (eg, CHF)
- N-acetylcysteine 1,200 mg PO bid on day prior to and day of contrast *(NEJM 2006:354:2777)*
- Hydration is the key *(Annals 2009;5:28)*
- min 2% of in-hospital AKI

**Hold ACEI/ARB, NSAIDs, diuretics**

**Minimize contrast volume and consider iso-osmolar contrast** *(JACC 2006:48:692)*
- Hemofiltration (before & for 24 h after) if Cr > 2.0 *(NEJM 2003:349:1333)*
- Gadolinium: can cause AKI in stage IV CKD *(Neph Dial Trans 2006:21:697)*, no effective ppx
Dietary restrictions
- Metabolic acidosis
  - Etiologies: DM (45%), HTN/RAS (27%), glomerular
  - If obstruction is diagnosed and relieved, watch for:
    - Hypotonic diuresis (2\textdegree\ buildup of BUN, tubular damage); Rx w/ IVF (eg, 1/2 NS)
    - Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly
  - Indications for urgent dialysis (when condition refractory to conventional therapy)
    - Acid-base disturbance: acidemia
    - Electrolyte disorder: generally hyperkalemia; occasionally hypercalcemia, tumor lysis
    - Intoxication: methanol, ethylene glycol, lithium, salicylates
    - Overload of volume (CHF)
    - Uremia: pericarditis, encephalopathy, bleeding
  - No benefit to dopamine (Annals 2005;142:510), diuretics (JAMA 2002;288:2547), or mannitol

**Treatment**

- Treat underlying disorder (see relevant sections); ? steroids if AIN (Ki 2008;73:940)
- Avoid nephrotoxic insults; review dosing of renally cleared drugs
- Optimize hemodynamics (both MAP & CO); may take 1–2 wks to recover from ATN
- Watch for and correct volume overload, electrolyte (↑ K, ↑ PO₄), & acid/base status
- If obstruction is diagnosed and relieved, watch for:
  - Hypotonic diuresis (2\textdegree\ buildup of BUN, tubular damage); Rx w/ IVF (eg, 1/2 NS)
  - Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly
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**CHRONIC KIDNEY DISEASE (CKD)**

**Definition and Etiologies** (Annals 2009;150:TC2-1 & Lancet 2010;375:1296)
- ≥3 mos of reduced GFR (< 60) and/or kidney damage (path, markers, imaging)
- Prevalence 13% in U.S.; Cr poor estimate of GFR; use prediction equation, eg, MDRD equation: www.kidney.org/professionals/KDOQI/gfr_calculator.cfm
  - nb, equation may underestimate GFR in Pts w/ normal renal fxn
- 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)
- Rates of all-cause mortality and CV events increase with each stage of CKD and are significantly higher than the rate of progression to kidney failure (NEJM 2004;351:1296)

<table>
<thead>
<tr>
<th>Stages of CKD</th>
<th>GFR mL/min/1.73 m²</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (nl or ↑ GFR)</td>
<td>&gt;90</td>
<td>Dx/Rx of underlying condition &amp; comorbidities, slow progression; cardiovascular risk reduction</td>
</tr>
<tr>
<td>2 (mild)</td>
<td>60–89</td>
<td>Estimate progression</td>
</tr>
<tr>
<td>3 (moderate)</td>
<td>30–59</td>
<td>Evaluate and treat complications</td>
</tr>
<tr>
<td>4 (severe)</td>
<td>15–29</td>
<td>Prepare for renal replacement therapy (RRT)</td>
</tr>
<tr>
<td>5 (kidney failure)</td>
<td>&lt;15 or dialysis</td>
<td>Dialysis if uremic</td>
</tr>
</tbody>
</table>

**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, i memory & attention), seizures, neuropathy, impaired sleep, restless leg syndrome
- Cardiovascular: Pericarditis, accelerated atherosclerosis, hypertension, hyperlipidemia, volume overload, CHF, cardiomyopathy (especially LVH)
- Hematologic: Anemia, bleeding (due to platelet dysfunction)
- Metabolic: ↑ K, ↑ PO₄, acidosis, ↓ Ca, Z⁺ hyperparathyroidism, osteodystrophy

**Treatment** (Annals 2009;150:TC2-1, NEJM 2010;342:57)
- General: nephrology referral when GFR <30 and access planning (avoid subclavian lines; preserve an arm for access by avoiding blood draws, BP measurements, IVs)
- Dietary restrictions: Na (if HTN), K (if oliguric or hyperkalemic), PO₄, ↑ moderate protein restriction, strict glc control in DM
  - For outPts, Cr & K in 1–2 wks, d/c if Cr ↑ 30% or K >5.4 (after dietary Δ & loop diuretic).
  - ACEI may be effective & safe in advanced nondiabetic CKD (Cr 3–5) (NEJM 2006;354:131).
- Metabolic acidosis: sodium bicarbonate or sodium citrate if HCO₃⁻ <22 (JASN 2009;20:2075)
- Anemia: goal Hb 11–12 g/dL, ↑ death, HTN, stroke, & thromb w/ ↑ Hb (NEJM 2006;355:2085); no survival benefit w/ Hb >9 via epo if diabetic nephropathy (NEJM 2009;361:2019) epoetin (start 80–120 U/kg SC, divided 3 × wk) or darbepoetin (0.45 mcg/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
• **Hyperparathyroidism:** ↑ PO₄, ↓ Ca, ↓ calcitriol → ↑ PTH → renal osteodystrophy

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target PTH (pg/mL)</td>
<td>35–70</td>
<td>70–110</td>
<td>150–300</td>
</tr>
</tbody>
</table>

phosphorus binders (take with meals!) (NEJM 2010;362:1312)

- if ↑ PO₄ and ↓ Ca → calcium acetate (PhosLo) or calcium carbonate
- if refractory ↑ PO₄ or in setting of ↑ Ca → sevelamer (Renagel), lanthanum (Fosrenol)
- if severe ↑ PO₄ → aluminum hydroxide (Amphojel), short-term use only calcitriol or paricalcitol if Ca-PO₄ product <55 (! survival in HD pts, NEJM 2003;349:446)
- cinacalcet (parathyroid calcium-sensing receptor agonist) if PTH remains elevated despite phosphorus binders ± vit D analogue (NEJM 2004;350:1516)

- **Consider 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
- **Mechanism:** inhibit Na-K-2Cl transporter in thick ascending limb (ThAL)

  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 ~2x 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

  - ↑ diuresis w/ contin. infusion (bolus → titrate drip) vs. bolus alone (Annals 1991;115:360)

- **Dosing** 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)
- **Mechanism:** inhibit Na-K cotransporter in the distal convoluted tube (DCT) 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
- **Mechanism:** ↓ Na reabsorption 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.

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Loop diuretic PO: ✓ response at 3 h, redose at 2× prior dose if needed</td>
</tr>
<tr>
<td>2</td>
<td>Add thiazide diuretic PO (potentiates response to loop diuretic)</td>
</tr>
<tr>
<td>3</td>
<td>Loop diuretic IV: bolus bid-qid ± thiazide (may start here if inPt)</td>
</tr>
<tr>
<td></td>
<td>↑ dose needed w/ ↑ Cr; initial effective IV lasix dose = 30 × Cr</td>
</tr>
<tr>
<td></td>
<td>(ie, if Cr = 4 → 120 mg IV lasix)</td>
</tr>
<tr>
<td>4</td>
<td>Loop diuretic infusion: bolus + continuous IV infusion ± thiazide</td>
</tr>
<tr>
<td>5</td>
<td>RRT: consider ultrafiltration, CVVH, or HD</td>
</tr>
</tbody>
</table>

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

### 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
- **Thiazide:** ↓ Na, ↓ K, ↓ Mg, ↑ Ca, hyperlipidemia, pancreatitis
- **K-sparing:** ↑ K (especially w/ ACEI), metabolic acidosis
Dialysis

General
• Substitutes for renal solute and fluid removal
• Acute: CVVH vs. HD (Chest 2007;132:1379); Chronic: PD vs. HD

Hemodialysis (HD) (NEJM 1998;338:1428; 339:1054)
• Physiology: blood flows along one side of semipermeable membrane, dialysate along other
  Fluid removal (ie, Na + H2O) 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 PO4)
• Typical orders: duration, volume removal goals, K and Ca in dialysate bath, anticoagulation
• Complications: hypotension, arrhythmia, access complications, disequilibrium syndrome

Vascular Access

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV Fistula</td>
<td>Highest patency</td>
<td>Long maturation time (2–6 mo)</td>
</tr>
<tr>
<td></td>
<td>Lowest risk of bacteremia</td>
<td>Primary nonfunction (20%)</td>
</tr>
<tr>
<td>AV Graft</td>
<td>Easier to create than AVF</td>
<td>Poor 1° patency, often requiring</td>
</tr>
<tr>
<td></td>
<td>Maturation time (2–3 wks)</td>
<td>thrombectomy or angioplasty</td>
</tr>
<tr>
<td>Catheter</td>
<td>Immediate use</td>
<td>Highest risk of bacteremia</td>
</tr>
<tr>
<td></td>
<td>Use as bridge to AVF/AVG</td>
<td>↓ blood flow → ↓ HD efficiency</td>
</tr>
</tbody>
</table>

Continuous Veno-Venous Hemofiltration (CVVH) (NEJM 1997;336:1303)
• Physiology: based on hemofiltration rather than dialysis. Blood under pressure passes down one side of a highly permeable membrane allowing water and solutes to pass across the membrane via TMP gradient (convective clearance). Filtrate is discarded. Replacement fluid is infused (solute concentrations similar to plasma, except no K, urea, Cr, PO4). Fluid balance precisely controlled by adjusting amounts of filtrate and replacement fluid.
• Access: double-lumen central venous catheter
• Typical orders: volume removal goals, replacement fluid buffer: HCO3 (requires heparin to prevent machine from clotting) vs. citrate (hepatically metabolized to HCO3; provides anticoagulation w/ in machine via Ca chelation; ∴ need Ca infusion to maintain serum Ca)
• Complications: hypotension, ↓ PO4, access complications; ↓ ICa (citrate toxicity in Pts with hepatic dysfunction → look for ↓ ICa but normal/↑ serum Ca and AG metabolic 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)

• Physiology: peritoneum acts as membrane. Fluid balance controlled by choosing dialysate glucose concentration (higher concentrations pull more fluid into peritoneum); longer dwell times pull less fluid as glucose equilibrates across peritoneum
• Access: permanent catheter inserted in OR
• Typical orders for CAPD (continuous ambulatory peritoneal dialysis): PD fluid – 1.5%, 2.5%, or 4.25% dextrose buffer (lactate), Na+, K+, Ca2+, Mg2+ infuse 10 min, dwell 30 min–5.5 h, drain 20 min
• Can use overnight cycler device that infuses & drains more rapidly, while Pt sleeps. Called automated or continuous cycling peritoneal dialysis (APD, CCPD).
• Complications:
  Peritonitis (abdominal pain, tenderness, cloudy drainage)
  diagnosis: 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 [glc]
  ↓ albumin; right-sided pleural effusion
GLOMERULAR DISEASE

GLOMERULONEPHRITIS (GN)

• 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/ renal failure, HTN, edema; spectrum of progression tempo:
  acute GN – over days; rapidly progressive GN (RPGN) – wks; chronic GN – mos; can simply have ax hematuria

| ANCA + Vasculitis (pauci-immune or minimal staining) – 40–45% of total |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Disease                    | Gran Renal Pulm Asthma | ANCA Type* | ANCA + |
| Wegener’s granulomatosis    | + 80% 90% (ENT) 0% | c-ANCA (anti-PR3) | 90% |
| Microscopic polyangitis     | 90% 50% 0%       | p-ANCA (anti-MPO) | 70% |
| Churg-Strauss syndrome      | + 45% 70%       | p-ANCA (anti-MPO) | 50% |

*Predominant ANCA type; either p- or c-ANCA can be seen in all three diseases. (NEJM 1997;337:1512)

| 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 |
| Poststreptococcal GN        | SLE |
(PSGN, usually 10–14 d, ASLO, C3) |
| Membranoproliferative GN    | Cryoglobulinemia |
(MPGN, C3) |
| Fibrillary glomerulonephritis | Endocarditis |
(normal C3) |
| IgA nephropathy             | Henoch-Schönlein purpura |
(normal C3) |

| Workup (Archives 2001;161:25) |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| • AGN/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 microangiopathy: ↓ Hct & Plts, schistocytes on smear, ↑ LDH |
|  cholesterol emboli (Lancet 2010;375:1650): purple toes, livedo, ↓ C3/C4, eos, prior cath |
|  AIN: rash, new drug exposure, urine WBCs (incl eos) ≤ WBC casts |
|  myeloma: anemia, hypercalcemia, lytic bone lesions, SPEP/UPEP |
| • Renal biopsy with immunofluorescence (IF) ± electron microscopy (EM) |

Figure 4-8 Approach to glomerulonephritis

ANCA + Vasculitis (pauci-immune)
ANCA + anti-GBM
anti-GBM + complement

Glomerulonephritis

ANCA @ Granuloma

Wegener’s Lupus

Microscopic Polyangitis

Churg-Strauss

Anti-GBM Disease (linear IF)

Anti-GBM

lungs

Goodpasture’s Lupus

Anti-GBM

lungs

Immune Complex Disease (granular IF)

clinical history

lungs

PSPN, MPGN

SLE, IE

Cryoglobulinemia

Fibrillary GN

lgA/HSP
Treatment
- ANCA \( \oplus \) or anti-GBM: steroids ASAP + cyclophos; ± plasmapheresis (JASN 2007;18:2180)
- SLE nephritis: IV cyclophosphamide + steroids \( \rightarrow \) azathioprine or MMF (JAMA 2005;293:3053); induction with MMF (no cyclophosphamide) may be as effective (NEJM 2005;353:2219)
- Other IC disease: ± steroids ± alkylation agents; treat underlying systemic disease

**ASYMPTOMATIC GLOMERULAR HEMATURIA**

**Definition and Etiologies**
- Hematuria \( \pm \) proteinuria of glomerular origin w/o renal insufficiency or systemic disease (nonglomerular hematuria more common; see “Hematuria”)
- Dx: any cause of GN, especially IgA; also consider Alport’s (X-linked, deafness, renal failure) and thin basement membrane nephropathy (autosomal dominant, benign course)

**IgA Nephropathy** (NEJM 2002;347:738 & JASN 2005;16:2088)
- Most common cause of GN; male predominance w/ peak incidence 20–30s
- Wide range of clinical presentations: ax hematuria (30–40%), gross hematuria \( \sim 1–3 \) d after URI (30–40%), chronic GN (10%), nephrotic syndrome (5%), RPGN (\( \sim 5 \% \))
- Though clinical presentation can be highly suggestive, definitive dx only w/ bx
- Prognosis: 25–30% will reach ESRD w/in 20–25 y of presentation

**Nephrotic Syndrome**

**Definition**
- Proteinuria > 3.5 g/d, albumin < 3.5 mg/dL, edema, \( \uparrow \) cholesterol

**Primary glomerular diseases (grouped by pathology)**
- Focal segmental glomerulosclerosis (40%)
  - idiopathic, HIV (collapsing variant), panidronate, heroin, congenital, hyperfiltration due to prior nephron loss, obesity, vesicoureteral reflux
- Membranous nephropathy (30%)
  - idiopathic (phospholipase A\(_2\) receptor Abs; NEJM 2009;361:11), infxn (espec. HBV, also HCV, sphyillis), autoimmune (espec. SLE), carcinomas, drugs (NSAIDs, penicillamine)
- Minimal change disease (20%, more common in children)
  - idiopathic, NSAIDs, Hodkin’s disease & other lymphoproliferative disorders
- Membranoproliferative GN (5%, mixed nephrotic/nephritic features)
  - Type I: infection (especially HCV \( \pm \) cryos; IE, HBV, other chronic infxn), immune complex disease (SLE, cryos, Sjögren’s), lymphoproliferative disorders, idiopathic
  - Type II: very rare; autoAb blocks inactivation of C3 convertase \( \rightarrow \) C3 nephritic factor
- Fibrillar-immunotactoid glomerulopathy (1%)
- Mesangial proliferative GN (likely atypical forms of MCD or FSGS, 5%)

**Systemic diseases**
- Diabetes mellitus: nodular glomerulosclerosis (Kimmelstiel-Wilson lesion); large kidneys hyperfiltration → microalbuminuria → dipstick \( \oplus \) → 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 w/o concurrent nephritis; ± oval fat bodies (“Maltese crosses,” NEJM 2007;357:806)
- Measure proteinuria: 24-h urine collection or urine prot/Cr ratio (not accurate in AKI)
- r/o secondary causes: \( \uparrow \) Hb\(_{A2}\) + retinopathy → presumpt. dx of diabetic nephropathy;
  - ANA, anti-dsDNA, C3, C4, SPEP/UPEP, fat pad bx, cryocrit, HBV, HCV, HIV, RPR, phospholipase A\(_2\) receptor Ab
- Renal biopsy

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

**Urine Dipstick**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Significance and uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific Gravity</td>
<td>estimate $U_{osm}$; each 0.001 above 1 – 30 osm (SG 1.010 → $U_{osm}$ 1 – 300)</td>
</tr>
<tr>
<td>pH</td>
<td>range: 4.5–8.5; useful in evaluation of stones and RTAs, infection</td>
</tr>
<tr>
<td>Protein</td>
<td>detects albumin (marker for glomerular dysfxn); see “Proteinuria”</td>
</tr>
<tr>
<td>RBC</td>
<td>see “Hematuria”; also with myoglobinuria (rhabdomyolysis)</td>
</tr>
<tr>
<td>WBC</td>
<td>suggests inflammation (UTI, interstitial nephritis, GN)</td>
</tr>
<tr>
<td>Ketones</td>
<td>detects acetone (i.e., ketoacidosis), but not β-hydroxybutyrate</td>
</tr>
<tr>
<td>Nitrite</td>
<td>suggests presence of Enterobacteriaceae</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>↑ in biliary or hepatic disease</td>
</tr>
<tr>
<td>Glucose</td>
<td>↑ in hyperglycemia (&gt;180 mg/dL), pregnancy, Fanconi’s syndrome</td>
</tr>
</tbody>
</table>

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

**Method:** centripetal fresh sample × 3–5 min at 1500–3000 RPM; pour off supernatant in one motion; resuspend pellet by agitating base of tube; pour suspension onto slide, place 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**

- Proteins molded in lumen of renal tubule → entrapped cellular elements
- See Urinalysis Photo Inserts
- 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**

- 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

**PROTEINURIA**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular (can be &gt; 3 g/d)</td>
<td>Disruption of filtration barrier → lose albumin</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Tubulointerstitial (usually &lt; 1–2 g/d)</td>
<td>↓ reabsorption of freely filtered proteins → lose globulins</td>
<td>ATN, AIN</td>
</tr>
<tr>
<td>Overflow</td>
<td>↑ production of freely filtered proteins</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Isolated</td>
<td>By def’n: axx, normal renal fxn, sed, &amp; imaging, no h/o renal disease</td>
<td>Functional (fever, exercise, CHF)</td>
</tr>
</tbody>
</table>

- **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
- **Spot urine:** protein (mg/dL)/creatinine (mg/dL) = g/d of proteinuria (NEJM 1983:309:1543)
- Orthostatic proteinuria: typically in adolescents; >90% of young with isolated proteinuria have orthostatic proteinuria; typically resolves spontaneously
HEMATURIA

Etiologies of Hematuria

Extrarenal (far more common)

- Infection: cystitis, urethritis, prostatitis
- Neoplasm: transitional cell, prostate
- Blunt trauma
- Foley trauma
- Vascular: renal infarcts, renal vein thromb., sickle cell disease and trait
- BPH

Intrarenal

- Nephrolithiasis or crystalluria
- Trauma / exercise
- Glomerular disease (IgA, thin BM > others)
- PKD (NEJM 2008;359:1477)

• Wide, overlapping ages for various etiologies, but general guide for common causes:
  - <20 y: GN, UTI, congenital; 20–60 y: UTI, nephrolithiasis, cancer
  - >60 y: prostatitis, cancer, UTI


- Urine dipstick: 
  - if 3 RBCs; 
  - dipstick and sediment
- Urine sediment: dysmorphic RBCs or RBC casts
- If no evidence of glomerulonephritis:
  - r/o UTI
- Urine cytology (Se 70%, Sp 95%; ✓ am void 3 to 6 to yield)
- Renal imaging: helical CT (r/o nephrolithiasis and neoplasia of upper tract), cystoscopy (r/o bladder neoplasia, esp. >50 y), ? U/S (r/o obstruction or parenchymal disease)

Nephrolithiasis

Types of stones and risk factors (Lancet 2006;367:333 & Annals 2009;151:ITC2)

- Calcium (Ca oxalate Ca phosphate): 70–90% of kidney stones
  - Urine characteristics: ↑ Ca, ↑ oxalate, ↑ urate, ↑ pH, ↓ citrate, ↓ volume
  - Hypercalcemia: ↑ hyperparathyroidism, type 1 RTA, sarcoid
  - Hyperoxaluria: ↑ animal protein, ↑ sucrose, ↑ Na, ↓ K, ↓ fluid, ↑ fruits/vegetables
- Uric acid: 5–10% of kidney stones, radiolucent on plain film
  - Urine characteristics: ↑ uric acid (eg, gout), ↑ pH (eg, from chronic diarrhea)
- Magnesium ammonium phosphate ("struvite" or "triple phosphate")
  - Chronic UTI w urea-splitting organisms (eg, Proteus, Klebs) → ↑ urine NH₃ and 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; urological distal urine may be normal

Workup

- Noncontrast helical CT scan (ureteral dilation w/o stone suggests recent passage)
- Strain urine for stone to analyze: U/A & UCx, electrolytes, BUN/Cr, Ca, PO₄, PTH, UA
- 24-h urine for Ca, PO₄, UA, oxalate, citrate, Na, Cr

Acute treatment (NEJM 2004;350:684)

- Analgesia (narcotics NSAIDs; combination superior, Ann Emerg Med 2006;48:173), aggressive PO/IV hydration, antibiotics if UTI
- Consider CCB or alpha blocker to promote ureteral relaxation (Lancet 2006;368:1171)
- Indications for immediate urologic evaluation and/or hospitalization: obstruction (especially solitary or transplant kidney), urosepsis, intractable pain or vomiting, AKI
- Urologic Rx: lithotripsy, cystoscopic stent, percutaneous nephrostomy, stone removal

Chronic treatment

- 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
- Cystine: urine alkalinization (K-citrate), D-penicillamine, tiopronin, captopril
Thalassemias

- **Iron deficiency** (NEJM 1999;341:1986 & Hematology ASH Educ Prog 2003;40)
  - ↓ 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—including cancer, menstrual, etc.), ↓ supply (malnutrition; ↓ absorp. due to celiac sprue, Crohn’s, ↓ gastric pH, subtotal gastrectomy), ↑ demand (preg., epi). Rare Fe-refractory genetic disorder due to hepcidin dysregulation (Nat Genet 2008;40:569).
  - Diagnosis: ↓ Fe, ↑ TIBC, ↓ ferritin (espec. <15), ↑ transferrin sat (Fe/TIBC; espec. <15%), ↓ soluble transferrin receptor; ↑ plt; unless hx c/w different etiology, initiate workup for GIb: incl. H. pylori serology, ↑ celiac sprue labs (anti-TTG, antigliadin, antiendomysial Ab)
  - Treatment (Fe supplementation): oral Fe tid (~6 wk to correct anemia; ~6 mo to replete Fe stores); in cases of excessive/persistent GI losses or for dialysis or cancer
  - Pts prior to EPO Rx, IV iron (Fe-sucrose, -gluconate, -dextrose) should be considered
  - Rare Fe-refractory (silent carrier; 2 genes)

**Thalassemia syndromes**

- **α-thalassemia**: deletions in α-globin gene complex on chr. 16 (nl 4 α genes)
  - 3 α → α-thal-2 trait – silent carrier; 2 α → α-thal-1 trait or α-thal minor – mild anemia
  - 1 α → HbH (βα) disease – severe anemia, hemolysis, and splenomegaly
  - 0 α genes → Hb Barts (γγ) → intrauterine hypoxia and hydrops fetalis

- **β-thalassemia**: mutations in β-globin gene on chr. 11 → absent or ↓ gene product
  - 1 mutated β gene → thal minor (or trait) – mild anemia (no transfusions)
  - 2 mutated β genes → thal intermedia (occasional transfusions) or thal major (~ Cooley’s anemia; transfusion-dependent) depending on severity of mutations
• Special clinical manifestations (in severe cases): chipmunk facies, pathologic fractures, hepatosplenomegaly (due to extramedullary hematopoiesis), high-output CHF, bilirubin gallstones, iron overload syndromes (from chronic transfusions)
• Diagnosis: MCV / H11021 < 100, normal Fe, MCV/RBC count / H11021 > 13, ± ↑ retics, basophilic stippling; Hb electrophoresis: ↑ HbA2 (α2δ2) in β-thal, normal pattern in α-thal trait
• Treatment: folate; transfusions + deferoxamine, deferasirox (oral iron chelator); splenectomy if ≥ 50% ↑ in transfusions; consider allogeneic HSCT in children w/ severe β-thal major

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: review social, work, & TB hx; can be microcytic, normocytic, or macrocytic; variable pop of hypochromic RBCs; cFe, nl TIBC, cferritin, 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; high-dose pyridoxine for some hereditary cases

Figure 5-2
Approach to microcytic anemias

Microcytic Anemia

↓ Fe, ↑ TIBC
Fe/TIBC < 18%
MCV/RBC > 13
↓ marrow Fe
Iron deficiency anemia

Thalassemia
Anemia of chronic inflammation
Sideroblastic anemia

↑ Fe, nl TIBC
↑ ferritin
basophilic stippling
ring sideroblasts in BM

↑ Fe, ↓ TIBC
MCV/RBC < 13
basophilic stippling
± ↑ retics
± abnl Hb electro.

↓ Fe, ↓ TIBC
MCV/RBC > 13
basophilic stippling
iron deficiency anemia

Normocytic Anemias

Anemia of chronic inflammation
• ↓ 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 with erythropoietin (? if Epo < 500 mU/mL); for cancer- or chemo-related ACI, use epo if Hb ≥ 10 g/dL. Iron if ferritin < 100 or Fe/TIBC < 20%

Anemias of chronic disorders
• Anemia of chronic inflammation (see above)
• Anemia of chronic kidney disease: ↓ epo; may see burr cells; treat w/ epo (see “Chronic Kidney Disease”)
• Endocrine deficiencies: hypometabolism and ↓ O2 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
• Diagnostic studies: lack of erythroid precursors on BM bx, other lines normal
• Treatment: thymectomy if thymus enlarged; IVlg if parvovirus infection; immunosuppression if CLL or idiopathic; supportive care with PRBC transfusions; ↑ erythropoietin receptor agonist if due to antierythropoietin Ab (NEJM 2009;361:1848)
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 B₁₂ deficiency
- ✓ folate and vitamin B₁₂, ↑ 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), ↑ requirement (chronic hemolytic anemia, pregnancy, malignancy, dialysis)
- Diagnosis: folate; RBC folate, homocysteine but nl methylmalonic acid (unlike B₁₂ defic.)
- Treatment: folate 1–5 mg PO qd for 1–4 mo or until complete hematologic recovery; critical to r/o B₁₂ deficiency first (see below)

Vitamin B₁₂ deficiency
- B₁₂ 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: B₁₂; homocysteine and methylmalonic acid; anti-IF Ab; Schilling test; gastrin in PA
- Treatment: 1 mg B₁₂ IM qd/H₁₁003 7 d/H₁₁003 4–8 wk/H₁₁003 1 mo for life; neurologic abnormalities are reversible if treated w/in 6 mo; folate can reverse hematologic abnormalities of B₁₂ deficiency but not neurologic changes (and can lead to “steal” of B₁₂ stores → worsening of neuro complications)
- Oral supplementation (2 mg qd) appears feasible as well (Blood 1998;92:1191) even w/o IF

Nonmegaloblastic macrocytic anemias
- Liver disease: often macrocytic, may see target cells
- Alcoholism: BM suppression & macrocytosis independent of folate/B₁₂ defic. or cirrhosis
- Reticulocytosis
- Other causes: hypothyroidism; MDS; meds that impair DNA synthesis (zidovudine, 5-FU, hydroxyurea, Ara-C); hereditary orotic aciduria; Lesch-Nyhan synd.

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 (Lancet 2005:365:1647)
- Epidemiology: 2–5 cases/10⁶/y; biphasic (major peak in adolescents, 2nd peak in elderly)
- Diagnosis: pancytopenia w/ ↓ retics, BM bx w/ cytogenetics showing hypocellularity
- Etiologies: idiopathic (1⁄2–3⁄5 of cases)
- stem cell destruction: radiation, chemotherapy, chemicals (eg, benzene) idiosyncratic med rxn (eg, chloramphenicol, NSAIDs, sulfu drugs, gold, carbamazepine, antithyroid)
- viruses (HHV-6, HIV, EBV, parvovirus B19); also posthepatitis (non A, B, or C) immune disorders (SLE, GVHD post H SCT, 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); telomerase (hTERT) mutation (NEJM 2005:352:1413)
Treatment and prognosis

allogeneic HSCT: for young Pts S/H/11011 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; 15–20% 10-y incidence of clonal disorders (mostly MDS, AML, PNH)

supportive care: transfusions, antibiotics, possible utility of G-CSF and epo

Myelodysplastic syndromes (MDS) (q)

Paroxysmal nocturnal hemoglobinuria (PNH)

• Acquired clonal stem cell disorder – inactivating somatic mutation of PIG-A gene → inability to form GPI-anchor for CD55 & CD59 (inhb 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: peripheral blood flow cytometry (i CD55 & CD59); urine hemosiderosis

• Treatment: supportive care (iron, folate, transfusions)
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)

Myelophthisic anemia (see “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

<table>
<thead>
<tr>
<th>Location</th>
<th>Mechanism</th>
<th>Examples</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic</td>
<td>Enzyme deficiency</td>
<td>G6PD deficiency</td>
<td>Hereditary</td>
</tr>
<tr>
<td></td>
<td>Hemoglobinopathies</td>
<td>Sickle cell anemia, thalassemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Membrane abnormalities</td>
<td>Hereditary spherocytosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PNH</td>
<td></td>
</tr>
<tr>
<td>Extrinsic</td>
<td>Immune-mediated</td>
<td>Autoimmune; drug-induced, tx rxn</td>
<td>Acquired</td>
</tr>
<tr>
<td></td>
<td>Traumatic</td>
<td>MAHA; prostheses (valves, TIPS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Direct infections, toxins</td>
<td>Malaria, babesiosis; snake &amp; spider venoms; Wilson's; hypotonic infusions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Entrapment</td>
<td>Hypersplenism</td>
<td></td>
</tr>
</tbody>
</table>

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 males of African or Mediterranean descent (malaria-endemic areas)

• Hemolysis precipitated by drugs (sulfonamides, dapsone, primaquine, doxorubicin, methylene blue), infection, DKA, or foods (fava beans in children)

• 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)


• Recessive β-globin mutation → structurally abnl hemoglobin (HbS);

• ~8% of African Americans are heterozygotes ("sickle trait"; usually w/o sx)

• ~1 in 400 are homozygotes (sickle cell disease)

• Deoxygenated HbS polymerizes → RBC sickles and ↓ RBC deformability → hemolysis and microvascular occlusion

• 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
• Diagnosis: sickle-shaped RBCs and Howell-Jolly bodies on smear; Hb electrophoresis
• Treatment: treat underlying disease; urgent plasma exchange for TIA or stroke, severe acute chest syndrome, and preop (goal Hb 10 g/dL)

**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 in 5,000 births); ✓ FHx (75% ofPts)
• Anemia, jaundice, splenomegaly, pigmented gallstones
• Diagnosis: spherocytes on smear; ✓ osmotic fragility test (~80% Se), ↓ eosin-5-maleimide (EMA) binding (92% Se; 99% Sp)
• Treatment: folic acid qd; pneumococcal, meningococcal, H. flu & HBV vaccination; pain crises treated with hydration, oxygen, and analgesia: simple or exchange transfusion for TIA or stroke, severe acute chest syndrome, and preop (goal Hb 10 g/dL)

**Autoimmune hemolytic anemia (AIHA)**
• Acquired, antibody-mediated RBC destruction
• **Warm AIHA:** IgG Abs opsonize RBCs at body temp → removal by spleen
  Etiologies: idiopathic, lymphoproliferative disorders (CLL, NHL), autoimmune diseases (SLE), drugs (see below)
• **Cold AIHA:** IgM Ab bind to RBCs at temp <37°C → complement fixation
  → intravascular hemolysis and acrocyanosis on exposure to cold
  Etiologies: idiopathic, lymphoproliferative (eg, Waldenström’s) disorders (monoclonal), Mycoplasma pneumoniae infection and infectious mononucleosis (polyclonal)
• Diagnosis: spherocytes on smear; ✓ Coombs’; ✓ cold agglutinin titer; splenomegaly
• Treatment: treat underlying disease; **warm AIHA:** corticosteroids → splenectomy, IVlg, cytotoxic agents, rituximab; **cold AIHA:** cold avoidance, steroids often 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
other: TCAs, phenothiazines, NSAIDs, sulfonylureas, MTX, 5-FU
• Diagnosis: Coombs’ usually negative. ↑ LDH
• Treatment: discontinue offending agent

**Microangiopathic hemolytic anemia (MAHA)**
• Intraarteriolar fibrin damages RBCs → acquired intravascular hemolysis
• Etiologies: hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), malignancy, malignant HTN, eclampsia/HELLP, mec. cardiac valves, infected vascular prostheses
• Diagnosis: schistocytes ± thrombocytopenia ± abnormalities associated with specific disorders, eg, ↑ PT in DIC, ↑ Cr in HUS, ↑ LFTs in HELLP
• Treatment: treat underlying abnormality; urgent plasma exchange for TTP

**Hypersplenism**
• Splenomegaly → stasis and trapping in the spleen → macrophagic attack and remodeling of RBC surface → spherocytosis → hemolysis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE* system hyperplasia</td>
<td>Hemolytic anemia, sickle cell disease, thalassemia major</td>
</tr>
<tr>
<td>Immune hyperplasia</td>
<td>Infection (HIV, EBV, CMV, TB, malaria, kala azar, Mycobacterium avium complex), autoimmune disorders (SLE, RA with Felt’s syndrome), sarcoidosis, serum sickness</td>
</tr>
<tr>
<td>Congestion</td>
<td>Cirrhosis, CHF, portal/splenic vein thrombosis, schistosomiasis</td>
</tr>
<tr>
<td>Infiltration (nonmalignant)</td>
<td>Lysosomal storage disorders (Gaucher’s, Niemann-Pick), glycogen storage diseases, histiocytosis X, splenic cysts</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>MPN (CML, PMF, PV, ET), CMML, acute leukemia, lymphoma (NHL, HL, hairy cell leukemia. CLL, PLL, Waldenstrom’s), TLGL leukemia, multiple myeloma, amyloid</td>
</tr>
</tbody>
</table>

**Causes of Splenomegaly**

- **boldface** – causes of massive splenomegaly; *Reticuloendothelial
**DISORDERS OF HEMOSTASIS**

### Clinical Characteristics of Bleeding Disorders

<table>
<thead>
<tr>
<th>Feature</th>
<th>Platelet/Vascular Defect</th>
<th>Coagulation Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Skin, mucous membranes</td>
<td>Deep in soft tissues (muscles, joints)</td>
</tr>
<tr>
<td>Lesions</td>
<td>Petechiae, ecchymoses</td>
<td>Hemarthroses, hematomas</td>
</tr>
<tr>
<td>Bleeding</td>
<td>After minor cuts: yes</td>
<td>After minor cuts: unusual</td>
</tr>
<tr>
<td></td>
<td>After surgery: immediate, mild</td>
<td>After surgery: delayed, severe</td>
</tr>
</tbody>
</table>

### 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 function
- **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

---

**Figure 5-3 Coagulation Cascade**

Coagulation factors shown by number. APC, activated protein C; AT, antithrombin; PrC, protein C; PrS, protein S; TF, tissue factor; TFPI, tissue factor pathway inhibitor. (NEJM 2008;359:938)

**Figure 5-4 Approach to abnormal hemostasis**

Abnormal Hemostasis

**PLATELET DISORDER**

- mucocutaneous bleeding
- ↓ platelet count
- thrombocytopenia
  - congenital (eg, vWD)
  - acquired (eg, aplastic anemia)
  - Hx, CBC, smear, BMBx

**COAGULOPATHY**

- soft tissue bleeding
- normal platelet count
- ↓ platelet function
  - congenital (eg, vWD)
  - acquired (eg, medics, uremia)
  - Hx, personal & family Hx

- congenital (eg, hemophilia, vWD)
- acquired (eg, meds, liver disease, vitamin K defici., DIC)

- splenic sequestration
- ↓ production (eg, aplastic anemia)
- ↑ destruction (eg, ITP, DIC, TTP)
PLATELET DISORDERS

THROMBOCYTOPENIA (Plt count <150,000/µL)

<table>
<thead>
<tr>
<th>Platelet count (cells/µL)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>– 100,000</td>
<td>No 1 risk</td>
</tr>
<tr>
<td>50,000–100,000</td>
<td>Risk with major trauma; can proceed with general surgery</td>
</tr>
<tr>
<td>20,000–50,000</td>
<td>Risk with minor trauma or surgery</td>
</tr>
<tr>
<td>– 20,000</td>
<td>Risk of spontaneous bleeding (less so with ITP)</td>
</tr>
<tr>
<td>– 10,000</td>
<td>Risk of severe, life-threatening bleeding</td>
</tr>
</tbody>
</table>

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: infections (HIV, herpes viruses, HCV), collagen vascular diseases (SLE), antiphospholipid syndrome, lymphoproliferative disorders (CLL, lymphoma), drugs (many, including heparin, abciximab, quinidine, sulfonamides, vancomycin), alloimmune (posttransfusion)
  non–immune-mediated: MAHA (DIC, HUS, TTP), ticlopidine/clopidogrel, vasculitis, preeclampsia/HELLP syndrome, cardiopulmonary bypass, CVVH, IABP, cavernous hemangioma

• Abnormal distribution or pooling: splenic sequestration, dilutional, hypothermia

• Unknown: ehrlichiosis, babesiosis, RMSF

Diagnostic evaluation

• H&P: meds, infxns, underlying conditions, splenomegaly, lymph nodes, bleeding
• CBC with differential: isolated thrombocytopenia vs. multilineage involvement
• Peripheral smear
  ↓ production → look for large plts, schistocytes (see Peripheral Smear inserts)
  ↓ production rarely limited to platelets → look for blasts, hypersegmented PMNs, leukoerythroblastic Δs
  rule out pseudothrombocytopenia due to platelet clumping (✓ platelet count in non–EDTA-containing tube, eg, citrate-containing yellow top tube)

Figure 5-5 Approach to thrombocytopenia

- Additional laboratory evaluations as indicated
  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 platelet destruction (secondary ITP a/w disease or 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**: c megakaryocytes; perform in adults ≥ 60 y to r/o myelodysplasia
  - Rule out other etiologies: viral serologies (HIV, HCV, HBV, EBV), H. pylori Ab, ANA, pregnancy test, APLA, 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 and splenectomy mainstay of initial Rx, but TPO-receptor agonists (eg, romiplostim and eltrombopag) likely to play increasing role

<table>
<thead>
<tr>
<th>Treatment of Primary ITP in Adults</th>
<th>Approach</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td><strong>Steroids</strong>: prednisone 0.5–2 mg/kg/d PO tapered -4 wk vs. dexamethasone 40 mg PO × 4 d</td>
<td>70–90% initial response -20% sustained remission ↓ Mø FcR &amp; ↓ anti-plt Ab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-Rh(D) Ig 75 μg/kg/d IV</td>
<td>For Rh(D) + Ps w/ spleen Ab-coated RBCs overwhelm Mø FcR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVIg (1 g/kg/d IV × 2–3 d) consider if need rapid ↑ in plt</td>
<td>Up to 80% initial response Blocks Mø FcR, ↓ anti-plt Ab</td>
<td></td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td>Splenectomy</td>
<td>Persistent disease → 6 mo -65% long-term remission</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rituximab (anti-CD20) + dexamethasone</td>
<td>anti-B-cell Ab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Romiplostim or eltrombopag</td>
<td>TPO-R agonists → ↑ plt prod</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azathioprine, cyclophosphamide</td>
<td>Immunosuppressants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Danazol, vincristine</td>
<td>↓ plt clearance</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>Aminocaproic acid</td>
<td>Inhibits plasmin activation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone 1 g/d IV × 3 d</td>
<td>See above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVIg</td>
<td>See above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelet transfusion</td>
<td>Given w/ IVIg or anti-Rh(D)</td>
<td></td>
</tr>
<tr>
<td><strong>Refractory</strong></td>
<td>Romiplostim or eltrombopag</td>
<td>See above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autologous HSCT</td>
<td>Limited data, investigational</td>
<td></td>
</tr>
</tbody>
</table>

**Overview of Heparin-Induced Thrombocytopenias**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Direct effect of heparin (nonimmune)</td>
<td>Immune (Ab)-mediated IgG against plt factor 4—heparin complex</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>10–20%</td>
<td>1–3% with UFH, 0–0.8% LMWH</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>After 1–4 d of heparin therapy</td>
<td>After 4–10 d; but can occur in &lt;24 h if prior exposure w/in 100 d (persistent Ab). Postop highest risk. Can occur after heparin d/c</td>
</tr>
<tr>
<td><strong>Platelet nadir</strong></td>
<td>&gt; 100,000/μL</td>
<td>~ 60,000/μL, ↓ &gt; 50%</td>
</tr>
<tr>
<td><strong>Sequelae</strong></td>
<td>None</td>
<td>Thrombotic events (HITT) in 30–50% Rare hemorrhagic complications</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Can continue heparin and observe</td>
<td>Discontinue heparin Alternative anticoagulation</td>
</tr>
</tbody>
</table>

**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 plt and tissue factor released by endothelial cells damaged by HIT Abs → prothrombotic state**

**Diagnosis: need to meet clinical and pathologic criteria (⊕ HIT Ab alone = HIT)**

<table>
<thead>
<tr>
<th>Clinical:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>plt &lt; 100,000 or ↓ 50% from baseline; or venous (DVT, PE) or arterial (limb ischemia, CVA, MI) thrombosis (4:1 ratio); or heparin-induced skin lesions (may also manifest ↑ heparin resistance)</td>
<td><strong>Pathologic:</strong> ⊕ HIT Ab using PF4-heparin ELISA (~ 90% Se, re if high suspicion), may confirm w/ fnal plt aggregation (serotonin-release) assay (~90% Sp)</td>
<td></td>
</tr>
</tbody>
</table>
• Treatment of type II (NEJM 2006;355:809; Chest 2008;133:3405)
  Discontinue heparin (including flushes, LMWH prophylaxis, heparin-impregnated lines)
  Avoid plt transfusions if not actively bleeding (anecdotally linked w/ thrombotic events)
  Nonheparin anticoag. (argatroban, lepirudin, bivalirudin) regardless if thrombosis; initiate
  warfarin when plt > 150,000, overlap ≈5 days (/ chromogenic Xa to titrate)
  ○ thrombosis (HITT): anticogulate for ≥3–6 mo
  ○ thrombosis (isolated HIT): screen for LE DVT; no consensus on duration of subsequent
  anticoag. (at least until plt count recovers, more often ~2–3 mo if no clot)
  • Heparin use if h/o HIT: if PF4 Ab ⊙ (typically > 100 d after dx) → re-exposure to UFH
    reasonable (eg, for surgery); HIT recurrence low (NEJM 2001;344:1286; Chest 2008;133:3405)
  
  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 – thrombocytopenia + MAHA ± Δ MS ± renal failure ± fever
  • Pathophysiology: mechanism in most HUS cases is distinct from TTP (NEJM 1998;339:1578)
  HUS: Shiga toxin binds & activates renal endothelial cells & plt → intrarenal thrombi
  TTP: ADAMTS13 protease activity → 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: usually in adults; idiopathic, drugs (CsA, gemcitabine, mitomycin C, ticlopidine, clopidogrel, quinine),
    HIV, pregnancy, H SCT, autoimmune disease, familial
  • Diagnosis: unexplained thrombocytopenia (typically <20 k) + 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
  • Treatment: urgent plasma exchange → glucocorticoids in all adults w/ suspected
    TTP-HUS; FFP if delay to plasma exchange
    platelet transfusions contraindicated → ↑ microvascular thrombosis (NEJM 2006;354:1927)
  
  Disseminated intravascular coagulation (DIC): see “Disorders of Coagulation”

---

**Mechanisms and Etiologies of Platelet Function Abnormalities**

<table>
<thead>
<tr>
<th>Function</th>
<th>Inherited</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesion</td>
<td>Bernard-Soulier; vWD</td>
<td>Uremia; acquired vWD</td>
</tr>
<tr>
<td>Aggregation</td>
<td>Afibrinogenemia; Glanzmann’s throbasthenia</td>
<td>Ticlopidine, clopidogrel, GP IIb/IIIa</td>
</tr>
<tr>
<td>Granule release</td>
<td>Chediak-Higashi syndrome; Hermansky-Pudlak syndrome</td>
<td>Drugs (ASA, NSAIDs); liver disease; MPN; cardiopulmonary bypass</td>
</tr>
</tbody>
</table>

**Tests of platelet function**

- Bleeding time: global screen of platelet function; not reliable and rarely used
- Platelet aggregation tests: measure aggregation in response to agonists (eg, ADP)

**von Willebrand’s disease (vWDD)** (NEJM 2004;351:683)

- von Willebrand’s factor (vWF) function → platelet glue & plasma carrier of factor VIII
- vWD is the most common inherited bleeding disorder.
  - Type 1 (autosomal dominant; 85% of cases): partial quantitative deficiency in vWF
  - Type 2 (autosomal dominant; 15% of cases): qualitative deficiency of vWF
  - Type 3 (autosomal recessive; rare): near complete deficiency of vWF
- Acquired vWD: associated with many disorders (malignancy, autoimmune, hypothyroidism, drugs) and caused by different mechanisms (anti-vWF Abs, ↑ clearance, ↓ synthesis)
- Diagnosis: ↓ vWF:Ag, ↓ vWF activity (measured by ristocetin cofactor assay), ↓ factor VIII, ↓ PT, ↓ platelets; confirm with vWF multimer analysis
- Clinical condition, factor VIII levels and ristocetin cofactor assay useful to guide Rx decision
- Treatment: desmopressin (dDAVP, IV/IN) → endothelial cell release of vWF; variable efficacy depending on type; ○ response before use w/ subseq. bleeding or procedures; vWF replacement: cryoprecipitate, factor VIII concentrates rich in vWF; recomb. vWF

**Uremia Bleeding**

- Uremia → platelet dysfunction including ↓ aggregation, impaired adhesiveness
- Treatment: dDAVP, cryoprecipitate, correct anemia (improves plt aggregation and adhesion by increasing plt interactions with endothelium), consider holding anti-plt agents
COAGULOPATHIES

Screening Test Abnormalities in Inherited and Acquired Coagulopathies

<table>
<thead>
<tr>
<th>PT</th>
<th>PTT</th>
<th>Factors</th>
<th>Inherited</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>←</td>
<td>↑</td>
<td>VIII or IX</td>
<td>Hemophilia, vWD</td>
<td>Antiphospholipid Ab; factor inhib.</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>I, II, V, or X</td>
<td>Fbg, FII, or FV defic.</td>
<td>DIC; liver dis.; factor inhib.</td>
</tr>
</tbody>
</table>

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: ↓ factor 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 fibrinogen)

Hemophiliias (NEJM 2001:344:1773)
- X-linked 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
- Treatment: purified/recomb. factor VIII or IX concentrate, desmopressin (mild disease), aminocaproic acid; recomb. factor VIIIa if factor inhib., cryo (only has factor VIII)

Coagulation factor inhibitors
- Etiologies: hemophilia (treated with factor replacement); postpartum; lymphoproliferative disorders and other malignancies; autoimmune diseases; most commonly anti-factor VIII
- Diagnosis: ↑ PTT (does not normalize w/mixing study); Bethesda assay quantitates titer
- Treatment: high titer → recomb. factor VIIIa, porcine factor concentrates, activated prothrombin complex; others → high-purity human factor, plasmapheresis, immuno-suppression w/ steroids, cyclophosphamide, and/or rituximab (Curr Opin Hematol 2008:15:451)

Disseminated intravascular coagulation (DIC) (NEJM 1999:341:586)
- 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 replete factors and platelets → thrombosis
- Diagnosis: ↑ PT, ↑ PTT, ↓ fibrinogen (may be nl b/c acute phase), ↓ FDP/D-dimer, ↓ plts, ↓ schisto, ↓ LDH, ↓ haptoc; chronic DIC: ↓ FDP/D-dimer, variable plts, other labs nl
- Treatment: treat underlying process; support with FFP, cryoprecipitate (goal fibrinogen >100 mg/dl), and platelets; consider activated protein C in severe sepsis

Vitamin K deficiency
- Etiologies: malnutrition, ↓ absorption (antibiotic suppression of vitamin K-producing intestinal flora or malabsorption), liver disease (i.e. stores), warfarin

Properties and Antidotes for Anticoagulants & Fibrinolytics

<table>
<thead>
<tr>
<th>Anticoag.</th>
<th>t1/2</th>
<th>Labs</th>
<th>Rx for O/D w/ serious bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>60–90’ RES</td>
<td>↑ PTT</td>
<td>Protamine IV 1 mg/100 U UFH (max 50 mg). For infusions, dose to reverse 2× UFH given per h</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>25’, K</td>
<td>↑ PTT</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>80’, K</td>
<td>↑ PTT</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Argatroban</td>
<td>45’, L</td>
<td>↑ PTT</td>
<td>? Dialysis</td>
</tr>
<tr>
<td>Enoxaparin, Dalteparin</td>
<td>2–7’, K (anti-Xa)</td>
<td>?</td>
<td>Protamine (reversal incomplete)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>24’, K (anti-Xa)</td>
<td>?</td>
<td>Dialysis</td>
</tr>
</tbody>
</table>
| Warfarin  | 36’, L  | ↑ PT | No bleeding; if INR 6–10 give vit. K 2.5 mg PO (superior to SC, = IV at 24 h) or ↓ Rx; if INR >10 give 5 mg (Archives 2003;163:2469; Annals 2009;150:293)
Bleeding: vit. K 10 mg IV + FFP 2–4 units IV q 6–8 |
| Fibrinolytic | 20–90’, LK | ↓ fbg | Cryoprecipitate, FFP, ↓ aminocaproic acid |

*Initial step should be immediate d/c of anticoag. K, kidney; L, liver; RES, reticuloendothelial system.
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

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence</th>
<th>VTE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>3–7%</td>
<td>4.3x</td>
<td>Activated protein C (APC) resist.</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>2%</td>
<td>2.8x</td>
<td>G20210A → ↑ prothrombin level</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5–10%</td>
<td>2.5x</td>
<td>Inherited or acquired</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.02–0.05%</td>
<td>11</td>
<td>Warfarin-induced skin necrosis risk</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>0.01–1%</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>0.04%</td>
<td>17.5</td>
<td>May be relatively heparin-resistant</td>
</tr>
</tbody>
</table>

Prevalence is in Caucasians. (NEJM 2001;344:1222; Hematology ASH Educ Prog 2007;127)

### Vascular Beds Affected by Inherited and Acquired Hypercoagulable States

#### Venous

- Factor V Leiden
- Prothrombin mutation
- Protein C, S, or AT III

#### Arterial

- Stasis: immobilization, surgery, CHF
- Malignancy: OCPs, HRT, tamoxifen, pregnancy
- Necrotic syndrome

#### Acquired

- Dysfibrinogenemia
- Platelet defects: myeloproliferative disorders, HIT, PNH
- Hyperviscosity: polycythemia vera, Waldenström's macroglobulinemia, sickle cell, acute leukemia
- Vessel wall defects: vasculitis, trauma, foreign bodies

#### Others: antiphospholipid syndrome, IBD

### Diagnostic evaluation

- APC resistance screen; prothrombin PCR test; functional assays for protein C and S, ATIII; homocysteine level; factor VIII levels; anticardiolipin and lupus anticoagulant Ab. Also consider necrotic syndrome, PNH (especially if mesenteric thrombus).
- Consider JAK2 mutation screen if suspect myeloproliferative disorder, especially if Budd-Chiari.
- 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 (ço) in 12% with “idiopathic” DVT (Annals 1996;125:785)

### Treatment

- Asx w/ inherited risk factor: consider prophylactic anticoag, if develops acquired risk factor
- Thrombosis w/ inherited risk factor: see “Venous Thromboembolism”

#### Antiphospholipid syndrome (APS) (NEJM 2002;346:752)

- 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 β2-glycoprotein-I (β2-GP-I) Ab on ≥2 occasions at least 12 wk apart
- Clinical manifestations: DVT, PE, CVA, recurrent fetal loss, thrombocytopenia, hemolytic anemia, livedo reticularis; "catastrophic APS" – widespread acute thrombotic microangiopathy with multiorgan visceral damage → high mortality

#### 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
- β2-GP-I: Ab against β2-glycoprotein-I, IgG or IgM
- False © VDRL: non-treponemal test for syphilis in which cardiolipin is part of Ag complex
- Clinical significance of different Abs in pathogenesis uncertain

#### 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 (life long for most Pts)

- Intensity of anticoagulation controversial (Arthritis Rheum 2007;57:1487)
- INR 3–4 for an initial arterial thrombosis or for recurrent venous thrombosis on warfarin
- Consider ASA prophylaxis for high-risk asx Pt (eg, SLE)
## 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

### 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 (ALL, CLL, others), lymphoma

### Monocytosis (>500/μL)

- **Infection**: Usually TB, SBE, Listeria, Brucella, rickettsias, fungi, parasites
- **Inflammation**: IBD, sarcoidosis, collagen vascular diseases
- **Neoplasm**: Hodgkin’s disease, leukemias, MPD, carcinomas

### Eosinophilia (>500/μL)

- **Infection**: Usually parasitic (helminths)
  - *Allergic*: Drugs; asthma, hay fever, eczema; ABPA
- **Collagen vascular disease**: RA, Churg-Strauss syndrome, eosinophilic fascitis, PAN
- **Endocrine**: Adrenal insufficiency
- **Neoplasm**: Hodgkin’s lymphoma, CML, mycosis fungoides, carcinomas, mastocytosis
- **Atheroembolic disease**: Cholesterol emboli syndrome
- **Hyphereosinophilic syndrome**: Multiorgan system involvement including heart and CNS, associated with FIP1L1-PDGFRα fusion (NEJM 2003;348:1201) D816kit-positive systemic mastocytosis (Lancet 2003;362:535)

### Basophilia (>150/μL)

- **Neoplasm**: MPD, Hodgkin’s disease
- **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
- **Immunologic**: Toxoplasmosis
- **Collagen vascular disease**: Drug hypersensitivity (eg, phenytoin), serum sickness, histiocytosis X, Castleman’s and Kawasaki disease
- **Neoplasm**: Lymphoma, leukemia, amyloidosis, metastatic carcinoma
- **Other**: Sarcomatosis; lipid storage diseases
- **Factors that favor biopsy**: Age (<40 y), size (<2 cm), location (supraclavicular is always abnormal), duration (<1 m).
  - *Consistency* (hard vs. rubbery vs. soft) & tenderness are not reliable.
# TRANSFUSION THERAPY

## Blood Products and Indications

<table>
<thead>
<tr>
<th>Blood Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed red blood cells (PRBCs)</td>
<td>For acute blood loss or to ↑ O₂-carrying capacity if end organ ischemia. In critical illness, Hb goal 7–9 g/dL adequate; consider 10–12 g/dL if coronary ischemia (NEJM 1999;340:409 &amp; 2001;345:1230). 1 U PRBC → Hb by ~1 g/dL. Large-volume transfusion PRBC → ↓ Ca, ↑ K, ↓ plt, ↓ coags (may need concurrent transfusion plt &amp; FFP).</td>
</tr>
<tr>
<td>Platelets (plt)</td>
<td>Pts &lt;10,000/µL or &lt;20,000/µL with infection or ↑ bleeding risk or &lt;30,000/µL with active bleeding or preprocedure. 6 U pooled donor plt → 1 single donor plt spheresis unit (reduces alloimmunization) → ↑ plt count by ~30–60,000/µL. Contraindicated in TTP/HUS, HELLP, HIT. Refractory: ↓ &lt;5000/µL 30–60 min posttransfusion. Suggests alloimmunization → trial ABO-matched plt. If still refractory, panel reactive Abs (PRA) to assess utility HLA-matched plt.</td>
</tr>
<tr>
<td>Fresh frozen plasma (FFP)</td>
<td>Contains all coagulation factors. For bleeding due to deficiency of multiple coagulation factors (eg, DIC, TTP/HUS, liver disease, warfarin excess, dilution) or PT &gt;17 sec preprocedure.</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Enriched for fibrinogen, vWF, VIII, and XIII. For bleeding in vWD, factor XIII deficiency or fibrinogen &lt;100 mg/dL.</td>
</tr>
<tr>
<td>Irradiated</td>
<td>Prevents donor T-cell proliferation. Use if risk of transfusion-assoc GVHD (HSCT, heme malig, congenital immunodef).</td>
</tr>
<tr>
<td>CMV-negative</td>
<td>From CMV-negative donors. For CMV-seronegative pregnant women, transplant candidates/recipients, SCID, AIDS Pts.</td>
</tr>
<tr>
<td>Leukoreduced</td>
<td>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.</td>
</tr>
<tr>
<td>Intravenous immune globulin (IVIg)</td>
<td>Polyvalent IgG from &gt;1000 donors. For postexposure prophylaxis (eg, HAV), certain autoimmune disorders (eg, ITP, Guillain-Barré, MG ? CIDP), congenital or acquired hypogammaglobulinemia (CVID, CLL).</td>
</tr>
<tr>
<td>Plasmapheresis and cytapheresis</td>
<td>Removes lg molec wt subst. (eg, cryoglobulinemia, Goodpasture’s, Guillain-Barré, hyperviscosity syndrome, TTP) or cells (eg, leukemia w/ hyperleukocytosis, sx thrombocytosis, sickle cell) from plasma.</td>
</tr>
</tbody>
</table>

## Transfusion Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk (per unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile</td>
<td>1:100</td>
</tr>
<tr>
<td>Allergic</td>
<td>1:100</td>
</tr>
<tr>
<td>Delayed hemolytic</td>
<td>1:1000</td>
</tr>
<tr>
<td>Acute hemolytic</td>
<td>&lt;1:250,000</td>
</tr>
<tr>
<td>Fatal hemolytic</td>
<td>&lt;1:100,000</td>
</tr>
<tr>
<td>TRALI</td>
<td>1:5000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk (per unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>common</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1:220,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1:1,600,000</td>
</tr>
<tr>
<td>HIV</td>
<td>1:1,800,000</td>
</tr>
<tr>
<td>Bacteria (PRBCs)</td>
<td>1:500,000</td>
</tr>
<tr>
<td>Bacteria (platelets)</td>
<td>1:12,000</td>
</tr>
</tbody>
</table>

**Transfusion reactions**

- For all reactions (except minor allergic): **stop transfusion**; send remaining blood product and fresh blood sample to blood bank
- **Acute hemolytic** fever, hypertension, flank pain, renal failure <24 h after transfusion
  - Due to ABO incompatibility → preformed Abs against donor RBCs
  - Treatment: vigorous IVF, maintain UOP with 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
  - Treatment: usually no specific therapy required; dx is important for future transfusion
- **Febrile nonhemolytic** fever and rigors 0–6 h after transfusion
  - Due to Abs against donor WBCs and cytokines released from cells in blood product
  - Treatment: acetaminophen ± meperidine; rule out infection and hemolysis
- **Allergic** urticaria; rarely, anaphylaxis: bronchospasm, laryngeal edema, hypotension
  - Reaction to transfused proteins; anaphylaxis seen in IgA-deficient Pts w/ anti-IgA Abs
  - Treatment: urticaria → diphenhydramine; anaphylaxis → epinephrine ± glucocorticoids
- **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 2009;114:937)
• Myeloid neoplasms are classified into 5 categories based on bone marrow morphology, clinical characteristics and genetics (WHO 2008 system)

WHO 2008 Myeloid Neoplasm Categories
Acute myeloid leukemia Dysplastic clonal myeloid stem cell (SC) disorder w/ ≥20% blasts in the bone marrow or peripheral blood
Myelodysplastic syndromes Dysplastic clonal myeloid SC disorder → cytopenias; <20% blasts, but risk of leukemic transformation
Myeloproliferative neoplasms Clonal expansion of nondysplastic multipotent myeloid SC
MDS/MPN Features of both MDS & MPN (eg, CML, atypical CML)
Myeloid/lymphoid malign. a/w PDGFR or FGFR 1 Δ

Myelodysplastic syndromes (MDS) overview (NEJM 2009;361:1872)
• Acquired clonal stem cell disorder → ineffective hematopoiesis → cytopenias, dysmorphic blood cells and precursors, variable risk of leukemic transformation
• Epidemiology: <100 cases/10^4/y; median age ~65 y; male predominance (1.8x)
• Idiopathic or < 2% to chemo w/ alkylating agents, topo II inhib., 1 risk w/ radiation, benzene Clinical manifestations: anemia (85%), neutropenia (50%), thrombocytopenia (25%)
• Diagnostic: dysplasia (usually multilineage) in peripheral smear (ovalomacrocyes, pseudo-Pelger-Huët anomaly) and bone marrow (>10% dysplasia with blasts ≤ RS)
• Cytogenetic abnormalities: several are characteristic of MDS and have prognostic significance [eg, del(5q), monosomy 7, del(7q), trisomy 8, del(20q)]
• Prior to dx MDS: exclude AML (>20% blasts) and CMML (monocyte count >1 x 10^9/L); r/o 2° BM Δs due to defic. of B12, folate, copper; viral infections (eg, HIV); chemotherapy; alcohol abuse; lead or arsenic toxicity

WHO 2008 Classification Systems for MDS

WHO 2008 Classification Systems for MDS

Classification Bone Marrow Features
Refractory cytophenias with unilineage dysplasia (RCUD): including refractory anemia, refractory neutropenia, or refractory thrombocytopenia ≥10% dysplastic cells in one myeloid lineage ≤5% blasts; ≤15% RS
Refractory anemia with ring sideroblasts (RARS) ≤5% blasts, ≤15% RS
Refractory cytophenias with multilineage dysplasia (RCMD) ≥10% dysplasia ≥2 lines ≤5% blasts, w/o or w/o RS
MDS with isolated del(5q) ≤5% blasts, del(5q)
Refractory anemia with excess blasts – 1 (RAEB-1) 5–9% blasts, no Auer rods 10–19% blasts, ± Auer rods
Refractory anemia with excess blasts – 2 (RAEB-2) 5–9% blasts, no Auer rods 10–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U) ≤10% dysplasia + ≤5% blasts + cytogen. abnl.

FAB classification no longer used clinically. RAEB-T reclassified as AML with multilineage dysplasia and CMML as MDS/MPN. Presence of cytogenetic anomalies, such as t(15;17), t(8;21), inv16, t(16;16) or MLL rearrangement, warrant classification as AML, regardless of BM blast count. RS, ring sideroblasts.
• Treatment: intensity based on risk category (see below), age, performance status (PS)
  Poor PS, any risk → supportive care – transfusions, G-CSF, epo, abx if needed
  Low/intermediate risk → Epo (esp if Epo level <500); lenalidomide (esp for 5q- syndrome; NEJM 2003;352:549); DNA demethylating agents (azacitidine or decitabine)
  Intermediate/high risk → DNA demethylating agents, combination chemotherapies (akin to AML therapy) or allogeneic HSCT (HLA-matched sibling donor preferred)
• Hypoplastic MDS (rare) → can consider immunosuppression (CsA, ATG, prednisone)
• Prognosis: IPSS correlates with survival and progression to AML

International Prognostic Scoring System (IPSS) Score

Risk group Total score Median survival
Low 0 5.7 y
Int-1 0.5–1 3.5 y
Int-2 1.5–2 1.2 y
High ≥2.5 0.4 y

(Blood 1997;89:2079) LDH may add further prognostic value to traditional IPSS score (Leukemia 2005;19:2223)
MYELOPROLIFERATIVE NEOPLASMS (MPN)

• Results from clonal expansion of multipotent hematopoietic stem cell
• A type of myeloid neoplasm (see MDS for classification)
• Different from MDS in that the cells are not dysplastic (ie, normally developed)
• 8 categories of MPN: polycythemia vera (PV); essential thrombocythemia (ET); primary myelofibrosis (PM); chronic myelogenous leukemia (CML); BCR-ABL1–/H17053 chronic neutrophilic leukemia; chronic eosinophilic leukemia, not otherwise specified; mastocytosis; myeloproliferative neoplasms, unclassifiable
• Gain of fxn mutations in JAK2 (Janus kinase) present in most cases of MPN (PV/H11011 100%, ET/H11011 50%, PMF/H11011 50%; NEJM 2005;352:1779) and BCR-ABL fusion in all cases of CML; KIT mutations in virtually all mastocytosis; MPL and TET2 mutations w/ lower frequency; genetic lesions are useful as a clonal marker and dx tool

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 (Gaissböck’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 thrombi); ↑ risk of DVT, MI, stroke.
  • bleeding (abnormal platelet function): easy bruising, epistaxis, GI bleeding
• Signs: plethora, splenomegaly, hypertension, engorged retinal veins

Diagnostic evaluation
• Hb >18.5 g/dL (men), >16.5 g/dL (women)
• √ Epo to rule out secondary causes of erythrocytosis; if Epo ↓, PV likely
• JAK2 V617F mutation screen on peripheral blood is positive in ~95% of PV and JAK2 exon 12 mutations are present in the remainder of Pts
• ↑ WBC, platelets, basophils; ↑ uric acid, leukocyte alkaline phosphatase, vitamin B12
• Peripheral smear → no morphologic abnormalities
• BM bx → hypercellular, megakaryocytic hyperplasia, ↓ iron, absence of Ph chromosome

Treatment
• Phlebotomy (espec if sx) to moderate degree of Fe defic. → Hct <45% (♂) or <42% (♀)
• Low-dose ASA in all Pts (NEJM 2004;350:114)
• Hydroxyurea if high risk of thrombosis (age ≥60, prior thrombosis) or sx thrombocytosis (plt >1.5 × 10³/µL)
• Supportive: allopurinol (gout), H2-blockers/antihistamines (pruritus)

Prognosis
• Median survival if treated is 9–12 y
• Risk of transformation into acute leukemia (2% for untreated Pts, higher if previous chemo)
• Post-PV myelofibrosis (spent phase) occurs in 15% of cases, usually after 10 y

ESSENTIAL THROMBOCYTEMIA (ET)
Definition
• ↑ in platelets (>450,000/µL) ± ↑ RBC and granulocytes

Etiologies of thrombocytosis
• 1° = ET or other MPN, myelodysplastic syndromes (Sq-syndrome)
• 2° = reactive thrombocytosis: inflammation (RA, IBD, vasculitis), infection, acute bleeding, iron deficiency, postsplenectomy, neoplasms (particularly Hodgkin’s disease)
• Of Pts w/ plt >10³¹/µL, <1 in 6 will have ET
Clinical manifestations (see “Polycythemia Vera”)
- Thrombosis with erythromelalgia (risk of thrombosis highest in Pts with WBC ≥ 8700), bleeding, pruritus; mild splenomegaly; migraine, TIA

Diagnostic evaluation
- Peripheral smear: large hypogranular platelets
- BM bx: megakaryocytic hyperplasia; absence of Philadelphia chromosome and lack of collagen fibrosis; normal iron stores
- JAK2 V617F present in ~50% of ET
- Does not meet WHO criteria for diagnosis of CML, PV, PMF or MDS

<table>
<thead>
<tr>
<th>Treatment of ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Features</td>
</tr>
<tr>
<td>Low Age &lt; 60 and no h/o thrombosis and plt &lt; 1.5 x 10^9/L and no CV risk factors</td>
</tr>
<tr>
<td>Int. Neither low nor high</td>
</tr>
<tr>
<td>High Age ≥ 60 or platelets or plt ≥ 1.5 x 10^9/L</td>
</tr>
</tbody>
</table>

Prognosis
- Overall survival similar to control population with low rate of transformation into PV, PMF or acute leukemia; low-risk Pts (see above) do not need treatment

Primary Myelofibrosis (PMF)

Definition
- Clonal myeloproliferation with reactive marrow fibrosis & extramedullary hematopoiesis
- Formerly known as agnogenic myeloid metaplasia with myelofibrosis

Etiologies of myelophthisis (marrow replacement)
- 1°: primary myelofibrosis; post-PV/ET myelofibrosis
- 2°: hematologic (eg, leukemia, MDS) or metastatic malignancies (eg, breast, prostate) collagen vascular disorders (eg, SLE) toxins (eg, benzene, radiation) granulomas from infection (eg, TB, fungal) or sarcoid deposition diseases (eg, Gaucher’s disease)

Clinical manifestations (NEJM 2000;342:1255)
- 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)
- 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 present in ~50% of PMF; MPL mutations in ~11% of JAK2-negative pts
- Does not meet WHO criteria for CML (absence of BCR-ABL translocation), PV, MDS

Treatment
- 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 for blood counts refractory to transfusion or painful splenomegaly
- Hydroxyurea for significant leukocytosis or thrombocytosis

Complications and prognosis
- Median survival ~5 y; transformation into AML occurs at a rate of ~8%/y
- Worse prognosis with Hb < 10 g/dL or with either WBC > 30,000/μL or WBC < 4000/μL

Chronic Myelogenous Leukemia
(see “Leukemia”)
LEUKEMIA

ACUTE LEUKEMIA

Definition
- Clonal proliferation of hematopoietic progenitor with ↓ ability to differentiate into mature elements → ↑ blasts in bone marrow and periphery → ↓ RBCs, platelets, and neutrophils

Epidemiology and risk factors
- Acute myelogenous leukemia (AML): ~12,000 cases/y; median age 65 y; ~>80% of adult acute leukemia cases
- Acute lymphocytic leukemia (ALL): ~4000 cases/y; median age 10 y; bimodal with 2nd peak in elderly
- Risk factors: radiation, chemo (alkylating agents, topo II inhib), benzene, smoking
- Acquired hematopoietic diseases: MDS, MPN (especially 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 (when blast count ~>50,000/µL): occluded microcirculation → local hypoxemia and hemorrhage → headache, blurred vision, TIA/CVA, dyspnea, hypoxia; look for hyperviscosity retinopathy (vascular engorgement, exudates, hemorrhage)
  - DIC (especially with APL)
  - Leukemic infiltration of skin, gingiva (especially with monocytic subtypes)
  - Chloroma: extramedullary tumor of leukemic cells, virtually any location
- More common in ALL:
  - Bone pain, lymphadenopathy, hepatosplenomegaly (also seen in monocytic AML)
  - CNS involvement (~15%): cranial neuropathies, nausea and vomiting, headache anterior mediastinal mass (especially in T-cell); tumor lysis syndrome (qv)

Diagnostic evaluation
- Peripheral smear: anemia, thrombocytopenia, variable WBC (50% p/w C WBC, 50% p/w normal or T WBC) + circulating blasts (seen in ~>95%; ⊀ Auer Rods in AML)
- Bone marrow: hypercellular with ≥20% blasts; cytogenetics, flow cytometry
- Presence of certain cytogenetic anomalies, ie, 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, ↑ PO4, ↓ Ca
- Coagulation studies to r/o DIC: PT, PTT, fibrinogen, D-dimer
- LP (w/ co-admin of intrathecal chemotherapy to avoid seeding CSF w/ circulating blasts) for ALL Pts (CNS is sanctuary site) and for AML w/ CNS sx
- TTE if prior cardiac history or before use of anthracyclines
- HLA typing of Pt, siblings, and parents for potential allogeneic HSCT candidates

Acute Myelogenous Leukemia (AML)

Classification (FAB no longer used clinically; Blood 2009:114:937)
- 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: CD13 & CD33 are myeloid antigens; ⊀ CD41 associated with M7
cytogenetics: important for prognosis, see below.

WHO 2008 Classification of AML (Blood 2009:114:937)

<table>
<thead>
<tr>
<th>4 Major Subtypes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>With recurrent genetic abnormalities</td>
<td>t(8;21); inv(16); t(15;17); 11q23 anomalies</td>
</tr>
<tr>
<td>With myelodysplasia-related change</td>
<td>W/ or w/o antecedent MDS or MPN</td>
</tr>
<tr>
<td>Therapy-related</td>
<td>Eg, alkylating agents or topoisoamerase inhibitors</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>W/ min differentiation; w/ maturation; W/ maturation; myelomonocytic; monoblastic/monocytic; erythroid; megakaryoblastic</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Favorable Prognosis</th>
<th>Unfavorable Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td>t(15;17) in APL; t(8;21); inv(16); t(16;16)</td>
</tr>
<tr>
<td>Gene mutations</td>
<td>NPM1; CEBPA</td>
</tr>
</tbody>
</table>

Gene mutations
- NPM1
- FLT3 ITD
- MLL partial tandem dup
- BAALC
Treatment (Blood 2009;113:1875 & 2010;115:453)
- Induction chemo followed by consolidation Rx
- Induction chemo: “3 + 7” – ida/daunorubicin × 3 d + cytarabine × 7 d; daunorubicin high-dose (90 mg/m²) superior to standard dose (45 mg/m²) (NEJM 2009;361:1235 & 1249)
- For complete remission (CR) – normal peripheral counts, <5% BM blasts
- CR = cure – must always f/u induction with consolidation Rx
- If CR: consolidation Rx based on risk stratification (age, genetics, PS): chemo or allogeneic HSCT or autologous HSCT (JAMA 2009;301:1349)
- If CR: reinduction with similar chemotherapy (2-5) or alternative regimen
- If relapse after CR: salvage chemotherapy followed by allogeneic or autologous HSCT
- Supportive care: hydration + allopurinol or rasburicase for tumor lysis prophylaxis; transfusions ± G-CSF; antibiotics for fever and neutropenia; antifungals for prolonged fever & neutropaenia; hydroxyurea ± leukophoresis for leukostasis

Prognosis
- CR achieved in 70–80% of Pts <60 y and in 40–50% for Pts >60 y
- Overall survival depends on prognostic factors: ranges from ~50% for Pts <60 y w/o poor prognostic factors to ~10% for Pts >60 y w/ poor prognostic factors
- Poor prognostic factors: age >60, unfavorable cytogenetics (see above), poor performance score, antecedent MDS/MPN, therapy-related AML
- Gene expression profiling may be useful (NEJM 2004;330:1605, 1617; JCO 2005;23:6296)

Acute Promyelocytic Leukemia (APL) (Blood 2009;113:1875)
- Rare disease w/ only 600–800 cases/y in US, but biologically and clinically distinct
- Atypical promyelocytes (large, granular cells; creased nuclei) in blood and bone marrow
- Defined by translocation of retinoic acid receptor: t(15;17): PML-RARα (>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 is critical as soon as APL suspected
- Induction chemo typically anthracycline + ATRA + cytarabine → CR in ~90% of Pts
- Consolidation Rx (eg, ATO → anthracycline + ATRA) followed by prolonged maintenance Rx (eg, ATRA + 6MP + MTX); ATO highly active in induction and consolidation and is promising as 1st-line Rx or for treatment of refractory disease
- Overall best prognosis of all AMLs w/ >80% cure rate; WBC >10,000/μL is adverse prognostic factor (Blood 2000;96:1247)

Acute Lymphoblastic Leukemia (ALL)
- 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 (JCO 2005;23:6306): t(9;22) – Philadelphia chrom (Ph) ~25% of adults w/ ALL
- Immunohistochemistry: 3 major phenotypes (Burkitt’s usually treated differently)

<table>
<thead>
<tr>
<th>WHO Type</th>
<th>Adult Freq</th>
<th>Immunophenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor B-cell</td>
<td>75%</td>
<td>TdT, CD19; variable CD10, CD20</td>
</tr>
<tr>
<td>Precursor T-cell</td>
<td>20%</td>
<td>TdT, CD1-cell Ag (CD2, 3, 5, 7); CD10, mature T-cell Ag (CD4, 8)</td>
</tr>
<tr>
<td>Burkitt’s Lymphoma</td>
<td>5%</td>
<td>TdT, surface Ig</td>
</tr>
</tbody>
</table>

*Burkitt’s lymphoma may present as an acute leukemia, with circulating tumor cells (see “Lymphoma”)

Treatment (NEJM 2006;354:166)
- Induction chemo: multiple acceptable regimens including combination of anthracycline, vincristine, steroids, cyclophosphamide, ± asparaginase
- CNS prophylaxis: intrathecal MTX/cytarabine ± cranial irradiation or systemic MTX
- Postremission therapy options: consolidation/intensification chemo (~7 mos) followed by maintenance chemo (~2–3 y) high-dose chemo w/ allo HSCT considered for all Pts in CR1 w/ available donor
- If relapse → salvage chemo followed by allogeneic HSCT if able
- Ph + t(9;22) → add imatinib or dasatinib & consider for allogeneic HSCT
- MLL-AF4 t(4;11) → consider for allogeneic HSCT
Prognosis
• CR achieved in >80% of adults
• Cure achieved in 50-70% if good prog. factors vs. in 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
• Gene expression patterns may be useful in predicting chemo resistance (NEJM 2004;351:533)

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 of CML
• “Atypical CML” (BCR-ABL ) considered a separate disease and reclassified as MDS/MPN (see “Myelodysplastic Syndromes”)

Epidemiology and risk factors
• ~4300 new cases/y in U.S.; median age ~50 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 and worsening symptoms → fever, weight loss, progressive 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 (often >100,000/µL), left-shifted with all stages of myeloid maturation: anemia, thrombocytopenia, basophilia
• Bone marrow: hypercellular, ↑myeloid to erythroid ratio, ↑leuk alkaline phosphatase
• Chronic: <10% blasts (peripheral or BM)
• Accelerated: 10–20% blasts, >20% basos, plts <100K, ↑spleen size, karyotypic prog.
• Blastic: >20% blasts (2/3 myeloid, 1/3 lymphoid), may see extramedullary leukemia

Treatment (NEJM 2006;355:2408; Lancet 2007;370:342; NEJM 2007;357:258)
• Tyrosine kinase inhibitors: 1st line Rx chronic phase; continued indef in responders
• Imatinib active in chronic, accelerated, blastic phases (but less as disease advances)
• Imatinib resistance is associated with BCR-ABL mutation or amplification of dasatinib and nilotinib are more potent BCR-ABL inhibitors and yield higher response rates than imatinib as initial therapy (NEJM 2010;362:2251 & 2260); both are effective against most imatinib resistance mutations except T315I (NEJM 2006;354:2531 & 2542)
• Side effects include nausea, diarrhea, muscle cramps, cytophenias, ↓PO4, rarely CHF; dasatinib also a/w pericardial & pleural effusions, nilotinib w/ ↑bili & lipase
• Allogeneic HSCT: consider for pts w/ available donor who present in accelerated or blastic phase; reasonable option for pts with relapsed/refractory disease to imatinib (especially pts w/ BCR-ABL T315I mutation)

Goals of Imatinib Therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Goal time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>WBC &lt;10K, Pt. &lt;450, &lt;5% myelocytes &amp; metamyelocytes, &lt;20% basos, no immature cells in blood, no extramedullary involvement</td>
<td>3 mo</td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>Absence of the Ph chromosome in metaphase cells</td>
<td>12 mo</td>
</tr>
<tr>
<td>Molecular</td>
<td>3-log reduction by quantitative PCR</td>
<td>12–18 mo</td>
</tr>
</tbody>
</table>

Prognosis
• Natural hx (untreated) of chronic phase CML is prog to blast phase and death w/in 4–6 y
• Chronic phase CML Rx’d w/ imatinib: 89% 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, percentage of blasts...
CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Definition (NEJM 2005;352:804; Br J Haematol 2007;139:672)
- Monoclonal accumulation of functionally incompetent mature B-lymphocytes
- CLL & small lymphocytic lymphoma (SLL) now classified as same disease

Epidemiology and risk factors
- ~10,000 new cases/y; median age at dx is 65 y; most common adult leukemia
- 1 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) or thrombocytopenia (ITP)
- Hypogammaglobulinemia / neutropenia; susceptibility to infections
- Bone marrow failure
- Monoclonal gammopathy in ~5%
- Aggressive transformation: ~5% develop Richter’s syndrome – transformation into high-grade lymphoma (usually DLBCL) and sudden clinical deterioration

Diagnostic evaluation (see “Lymphoma” for general approach)
- Peripheral smear: lymphocytosis (~5000/μL, mature-appearing small cells)
- “smudge” cells from damage to abnl lymphs from shear stress of making blood smear
- Flow cytometry: clonality with dim surface Ig (sIg); CD5, CD23, CD20, CD38, ZAP70 a/w unmutated Ig variable heavy chain region & worse prognosis
- Bone marrow: normo- or hypercellular; infiltrated w/ small B-cell lymphocytes (~30%)
- Lymph nodes: infiltrated w/ small lymphocytic or diffuse small cleaved cells – SLL
- Cytogenetics: ~11q22-23 & 17p- unfavorable; trisomy 12 neutral; 13q14 favorable

CLL Staging
<table>
<thead>
<tr>
<th>Rai System</th>
<th>Median survival</th>
<th>Binet System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Lymphocytosis only</td>
<td>&gt;10 y</td>
</tr>
<tr>
<td>I</td>
<td>lymphadenopathy</td>
<td>7 y</td>
</tr>
<tr>
<td>II</td>
<td>hepatosplenomegaly</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>anemia (not AIHA)</td>
<td>1–2 y</td>
</tr>
<tr>
<td>IV</td>
<td>thrombocytopenia (not ITP)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment
- Treatment is 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 for treatment
  - purine analogs: fludarabine (“F”), pentostatin (“P”)
  - alkylating agents: cyclophosphamide (“C”), CVP, CHOP; chlorambucil for elderly
  - monoclonal Ab against CD20 (rituximab, “R”) or CD52 (alemtuzumab)
- Role of autologous and allogeneic HSCT being studied
- Localized SLL can be treated with involved-field radiation therapy alone, rather than chemo
- Supportive care: PCP, HZV, VZV prophylaxis; CMV monitoring for Pts receiving CD52; AIHA/ITP → steroids; recurrent infections → IVIg; bulky disease with compressive symptoms → XRT; splenomegaly with refractory cytopenias → splenectomy

Prognostic Factors & Median Survival in CLL
<table>
<thead>
<tr>
<th>Factor</th>
<th>Years</th>
<th>Factor</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td></td>
<td>CD38 expression</td>
<td></td>
</tr>
<tr>
<td>17p-</td>
<td>2.5</td>
<td>Low (~20–30%)</td>
<td>8</td>
</tr>
<tr>
<td>11q-</td>
<td>6.6</td>
<td>High (~20–30%)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Trisomy 12 or Normal</td>
<td>9</td>
<td>Zap-70 expression</td>
<td></td>
</tr>
<tr>
<td>13q-</td>
<td>11</td>
<td>Low (~20–30%)</td>
<td>24.3</td>
</tr>
<tr>
<td>IgVH gene status</td>
<td></td>
<td>High (~20–30%)</td>
<td>9.3</td>
</tr>
<tr>
<td>Mutated (~2%)</td>
<td>&gt;24</td>
<td>β2-microglobulin: higher levels correlate with disease stage, tumor burden and a poorer prognosis.</td>
<td></td>
</tr>
<tr>
<td>Unmutated (~2%)</td>
<td>&lt;8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LYMPHOMA

Definition
• Malignant disorder of lymphoid cells that reside predominantly in lymphoid tissues
• **Hodgkin lymphoma** (HL) is distinguished from **non-Hodgkin’s lymphoma** (NHL) by the presence of **Reed-Sternberg** (RS) cells

Clinical manifestations
• Lymphadenopathy (nontender)
  - **HL**: superficial (usually cervical/supraclavicular) and mediastinal lymphadenopathy;
  - **NHL**: diffuse nodal and extranodal disease with noncontiguous spread;
  - Symptoms reflect involved sites (abdominal fullness, bone pain)
• Constitutional (“B”) symptoms: fever (>38°), sweats, weight loss (>10% over 6 mos)
  - **HL**: periodic, recurrent “Pel-Ebstein” fever; 10–15% have pruritus
  - **NHL**: “B” symptoms less common than in HL

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, need surrounding architecture) with immunophenotyping and cytogenetics; BM bx (except in HL clinical stage IA/IIA with favorable features); LP if CNS involvement is clinically suspected
• Lab tests: CBC, BUN/Cr, LFTs, ESR, LDH, UA, Ca, alb; must 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: chest/abd/pelvic CT (but don’t reliably detect spleen/liver involvement)
  - also need PET scans
  - head CT/MRI if neurological symptoms; bone scan if bony pain or if A/E elevated

### Ann Arbor Staging System with Cotswolds Modifications

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single lymph node (LN) region</td>
</tr>
<tr>
<td>II</td>
<td>≥2 LN regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>LN regions on both sides of the diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Disseminated involvement of one or more extralymphatic organs</td>
</tr>
</tbody>
</table>

Modifiers:
- **A**: no symptoms
- **B**: fever, night sweats or weight loss
- **X**: bulky disease
- **H**: hepatic
- **S**: splenic

**HODGKIN LYMPHOMA (HL)**

Epidemiology and risk factors
• ~8,500 cases/y; bimodal distribution (15–35 & >50 y); ↑ male; ↑ role for EBV

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- by flow cytometry.

### WHO Histologic Classification of Classical HL

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphocyte rich</strong></td>
<td>5% Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis</td>
</tr>
<tr>
<td><strong>Nodular sclerosis</strong></td>
<td>60–80% Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I/II at dx</td>
</tr>
<tr>
<td><strong>Mixed cellularity</strong></td>
<td>15–30% Pleomorphic; older age; male predominance; &gt;50% stage III/IV at presentation; intermediate prognosis</td>
</tr>
<tr>
<td><strong>Lymphocyte depletion</strong></td>
<td>&lt;1% Diffuse fibrosis and large numbers of RS cells; older, male patients; disseminated at dx; seen in HIV; worst prognosis</td>
</tr>
</tbody>
</table>

- **Nonclassical** (5%): nodular lymphocyte predominant (NLP); involves peripheral LN 80% present in stage 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 + Stage III-IV treated with combination chemo (see below)
Treatment

- **Stage I-II classical HL**: consider ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + RT (or ABVD × 6 cycles alone in select cases)
- **Stage III-IV**: ABVD × 6 cycles or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in high-risk advanced Pts
- Refractory/relapsed disease: salvage chemo, high-dose chemo + auto HSCT, allo HSCT
- Late effects: ↑ risk for second malignancies including lung cancer (XRT and chemo), breast cancer (XRT), acute leukemia/MDS, NHL; cardiac disease (XRT and anthracycline); pulmonary toxicity (bleomycin); hypothyroidism (XRT)

### International Prognostic Score (IPS)

<table>
<thead>
<tr>
<th>Negative Prognostic Indicators</th>
<th>Total # of Indicators</th>
<th>5-y PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &lt; 4 g/dL</td>
<td>0</td>
<td>84%</td>
</tr>
<tr>
<td>Hb &lt; 10.5 g/dL</td>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>Age &gt; 45 y</td>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>4</td>
<td>51%</td>
</tr>
<tr>
<td>WBC ≥ 15k/µL</td>
<td>5</td>
<td>42%</td>
</tr>
</tbody>
</table>

Lymphocytes < 600/µL or <8% of differential

(NEJM 1998;339:1506)

### Non-Hodgkin’s Lymphoma (NHL)

#### Epidemiology and risk factors

- ~66,000 new cases/y; median age at diagnosis ~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’s 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

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>Associated genetic abnl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature B Cell</td>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
<td>IGH-BCL2</td>
</tr>
<tr>
<td></td>
<td>Follicular lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLL/small lymphocytic lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mantle cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marginal zone lymphoma (nodal, extranodal [MALT], splenic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkitt’s lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hairy cell leukemia (p/w fatigue, l monos, massive splenomegaly; ☀ TRAP)</td>
<td></td>
</tr>
<tr>
<td>Mature T Cell &amp; NK Cell</td>
<td>Periferal T cell lymphoma</td>
<td>Some ALK1 ☉</td>
</tr>
<tr>
<td></td>
<td>Mycosis fungoides (cutaneous lymphoma) / Sézary syndrome (+ LAN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic large cell lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angioimmunoblastic T cell lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

(Blood 2007;110:695; NEJM 2010; 362:1417)

#### Treatment

- Treatment and prognosis determined by histopathologic classification rather than stage
- **Indolent**: goal is sx management (bulky dis., cytopenias, “B” sx); not curable w/o allo HSCT
  - Options include radiation for localized disease, rituximab ± chemo (CVP, fludarabine, bendamustine), single-agent chemo (chlorambucil, cyclophosphamide, fludarabine). Newer rituximab radioimmunotherapy (RIT) conjugates include 131I tositumomab and Y90 ibritumomab tiuxetan.
  - Rituximab maintenance ↑ survival in relapsed disease (JNCI 2009;101:248); growing role for rituximab maintenance in indolent and aggressive disease (trials pending)
- **Aggressive** (DLBCL, 30–40% of NHL): goal is cure (JCO 2005;23:6387)
  - CHOP-R (cyclophosphamide, doxorubicin — hydroxydaunorubicin, vincristine — Oncovorin, prednisone, rituximab) (NEJM 2002;346:235 & 2008;359:13);
  - 5-y progression-free survival — 54%; overall survival — 58% (JCO 2005;23:4117)
  - 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 site + ↑ LDH may also warrant
Refractory/relapsed disease: salvage chemo; high-dose chemo + auto-HSCT (*NEJM* 1995;333:1540); allo-HSCT if beyond 2nd relapse

**Highly Aggressive**
Burkitt’s: intensive short-course chemotherapy (*Blood* 2004;104:3009)
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)
All Pts receive CNS prophylaxis and tumor lysis syndrome prophylaxis
Lymphoblastic lymphoma (B- or T-cell): treated like ALL (see “Acute Leukemia”)

**Prognosis**
• Indolent: ↓ response to chemotherapy, but long median survival

<table>
<thead>
<tr>
<th>Follicular Lymphoma International Prognostic Index (FLIPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors: age &gt;60, stage III/IV, Hb &lt;12 g/dL, &gt;4 nodal areas, LDH &gt;nl</td>
</tr>
<tr>
<td># Factors</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>0–1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>≥3</td>
</tr>
</tbody>
</table>

(*Blood* 2004;104:1258)

<table>
<thead>
<tr>
<th>International Prognostic Index (IPI) for Aggressive NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors: age &gt;60, stage III/IV, ≥2 extranodal sites, performance status ≥2, LDH &gt;nl</td>
</tr>
<tr>
<td># Factors</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>0–1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4–5</td>
</tr>
</tbody>
</table>

Revised IPI Prognosis in Patients Rx’d with CHOP-R

<table>
<thead>
<tr>
<th>Factors</th>
<th>% at dx</th>
<th>4-y Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10%</td>
<td>94%</td>
</tr>
<tr>
<td>1–2</td>
<td>45%</td>
<td>79%</td>
</tr>
<tr>
<td>3–5</td>
<td>45%</td>
<td>55%</td>
</tr>
</tbody>
</table>


**HIV-associated NHL** (*Blood* 2006;107:13; www.nccn.org)
• HIV ⊘ imparts 60–100× relative risk
• NHL is an AIDS-defining malignancy along with Kaposi’s, cervical CA, anal CA
• Concurrent HAART & chemotherapy likely provides survival benefit
• DLBCL & immunoblastic lymphoma (67%): CD4 < 100, EBV-associated
  Treat as immunocompetent (CHOP-R), but avoid rituximab if CD4 < 100
• Burkitt’s and Burkitt’s-like (20%): can occur with CD4 >200
  Treat as immunocompetent, though prognosis is significantly worse
• Primary CNS lymphoma (16%): CD4 >50, EBV-associated (also seen in Pts w/o HIV)
  Treat with high-dose methotrexate + steroids ± RT
• Primary effusion lymphoma (5%): HHV8 driven; also can be seen in other immuno-supp. Pts such as s/p solid organ transplant or w/ chronic HBV. Treat with standard CHOP (often CD20-), but poor prognosis.
PLASMA CELL DYSCRASIAS

Multiple Myeloma (MM)

Definition and epidemiology
- Malignant neoplasm of plasma cells producing a monoclonal Ig – "M protein"
- ~20,580 new cases and ~10,580 deaths/y in U.S. (2009); median age at diagnosis 66 y
- African American:Caucasian ratio ~2:1

Clinical manifestations
- Anemia (normocytic) due to bone marrow involvement and autoimmune Ab
- Bone pain and hypercalcemia due to osteoclast activity → lytic lesions, pathologic fx
- Recurrent infections due to relative hypogammaglobulinemia as clonal plasma cells suppress nl immunoglobulin
- Renal disease: multiple mechanisms include toxic effect of filtered light chains → renal failure (cast nephropathy) or type II RTA; amyloidosis or light chain deposition disease → nephrotic syndrome; hypercalcemia, urate nephropathy, type I cryoglobulinemia
- 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
- Amyloidosis (see "Amyloidosis")

Diagnostic and staging evaluation
(NCCN Version 3.2010)
- Sx MM criteria
  - M protein in serum (usually >3 g/dL) or urine, marrow plasmacytosis (usually 90%) or presence of a plasmacytoma, and myeloma-related organ or tissue impairment (ROTI)
  - 2-microglobulin all of the following:
    - Hb <10 g/dL; Ca >11.5 g/dL; Cr >2 mg/dL; or Hb <10
- Variants
  - Smoldering MM: M protein >3 g/dL and/or plasmacytosis >10%, but asx & no ROTI
  - Risk of progression related to level of plasmacytosis and M protein (NEJM 2007;160:2582)
  - Solitary bone plasmacytoma: lytic lesion w/o M protein, plasmacytosis, or other ROTI
  - Extramedullary plasmacytoma: usually upper respiratory tract
  - Plasma cell leukemia: plasma cell count >2000/μL
  - Amyloidosis (see "Amyloidosis")
  - Nonsecretory MM: no M protein, but marrow plasmacytosis & ROTI
  - Dx of M component: MM, MGUS (see below), CLL, lymphoma, cirrhosis, sarcoidosis, RA
  - Peripheral smear: rouleaux (see Peripheral Smear 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 the ~20% of 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-free light chain assay: important test for dx and to follow treatment response
- 2-microglobulin and LDH levels reflect tumor burden
- Bone marrow bx: better prognosis → hyperdiploidy; worse prognosis → del. of chromosome 17p13 (~10% of Pts) & certain translocations
- 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>ISS Criteria</th>
<th>Durie-Salmon Criteria</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>β2-microglobulin &gt;3.5 mg/L and albumin &gt;3.5 g/dL</td>
<td>all of the following: Hb &gt;10 g/dL; Ca ≥12 mg/dL; 0–1 lytic bone lesions; IgG &lt;5 g/dL or IgA &lt;3 g/dL or urine light chain &lt;4 g/24 h</td>
<td>61 mo</td>
</tr>
<tr>
<td>II</td>
<td>fulfilling criteria for neither I nor III</td>
<td></td>
<td>55 mo</td>
</tr>
<tr>
<td>III</td>
<td>β2-microglobulin &gt;5.5 mg/L</td>
<td>any of the following: Hb &gt;8.5 g/dL; Ca &gt;12 mg/dL; &gt;5 lytic bone lesions; IgG &gt;7 g/dL or IgA &gt;5 g/dL or urine light chain &gt;12 g/24 h</td>
<td>30 mo for IIIA; 15 mo for IIIB</td>
</tr>
</tbody>
</table>

Subclassification by serum Cr:
A: <2 mg/dL; B =2 mg/dL
**WALDENSTRÖM’S MACROGLOBULINEMIA (WM)**

- B-cell neoplasm (lymphoplasmacytic lymphoma) that secretes monoclonal IgM
- 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 on funduscopy), HA, dizziness, MS
e    - cardiopulmonary: congestive heart failure, pulmonary infiltrates
type I cryoglobulinemia → Raynaud’s phenomenon
  - platelet dysf (→ 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 + immuno fixation with IgM > 3 g/dL; 24-h urine for UPEP (only 20% have UPEP)
- Bone marrow biopsy: ↑ plasmacytoid lymphocytes; β2-microglobulin for prognostic eval
- **Relative serum viscosity**: defined as ratio of viscosity of serum to H2O (nl ratio 1.8) hyperviscosity syndrome when relative serum viscosity > 5–6

**Treatment** (NCCN Version 3.2010)
- **Hyperviscosity: plasmapheresis**
- Symptoms (eg, progressive anemia): systemic chemotherapy w/ chlorambucil, fludarabine, cladribine, rituximab, bortezomib or combination therapy
- Thalidomide and H SCT are investigational modalities
HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplantation of donor pluripotent cells that can reconstitute all recipient blood lineages

<table>
<thead>
<tr>
<th>Feature</th>
<th>Allogeneic (Allo)</th>
<th>Autologous (Auto)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor-recipient relationship</td>
<td>Immunologically distinct</td>
<td>Donor is also recipient</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Graft-versus-tumor effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk of graft contam. w/ tumor</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Relapse risk (leukemia)</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Transplant-related mortality</td>
<td>Higher</td>
<td>Lower</td>
</tr>
</tbody>
</table>

- **Types of Allo HSCT**: based on donor/recipient matching of major HLA antigens on Chr. 6 (3 principal genes for serotyping: HLA-A, -B, & -DR; each w/ 2 alleles : 6 major Ag)
  Matched related (sibling matched at 6/6 major Ag): lowest risk of GVHD; preferred donor
  Mismatched related (eg, 1/6 Ag mismatch) or haploidentical (mismatch at 3/6 Ag): easiest to find, but ↑ risk of GVHD; need to deplete T cells first
  Matched unrelated: ↑ risk of GVHD; adv. molecular matching of 8 HLA alleles to ↓ risk
- **Graft-versus-host disease (GVHD)**: undesirable side effect of allo HSCT
  allo T cells view host cells as foreign; ↓ risk of GVHD; tolerant mismatch
- **Graft-versus-tumor (GVT)**: desirable consequence of allo HSCT
  allo T cells attack host tumor cells

**Indications** *(NEJM 2006;354:1813)*

- **Malignant disease**: Auto HSCT allows higher doses of chemo by rescuing hematopoietic system (used for lymphoma, multiple myeloma, testicular cancer)
  Allo HSCT produces graft-versus-tumor (GVT) effect, in addition to hematopoietic rescue (used for AML, ALL, CML, 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 (traditional): chemotherapy and/or total body irradiation. Goal is eradication of underlying disease for which transplant is being performed.
  nonmyeloablative ("mini"): reduced-intensity conditioning regimens → ↓ toxicity to allow Pts w/ comorbidities or ↑ age to tolerate HSCT. Goal to proceed w/ transplant when in disease remission, harnessing GVT effect while tolerating GVHD.
- **Sources of stem cells**: bone marrow (BM): original source of HSCT but now less common than PBSC
  peripheral blood stem cells (PBSC): easier collection, most commonly used source
  umbilical cord blood (UCB): less stringent HLA-matching requirements, though fewer available cells from single donor (↓: 2 donors typically combined), slower engraftment
- **Engraftment**: absolute neutrophil count (ANC) recovers to 500/µL w/in ~2 wk w/ PBSC, ~3 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/ IV steroids.

**Complications**

- Either direct chemoradiotoxicites associated with preparative regimen or consequences of interaction between donor and recipient immune systems

**Timing and Mechanism of Noninfectious Complications of HSCT**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Regimen-related</th>
<th>Immune-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 d</td>
<td>Pancytopenia</td>
<td>Acute GVHD</td>
</tr>
<tr>
<td></td>
<td>Mucositis, rash, alopecia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting, diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic cystitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Veno-occlusive disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td>30–90 d</td>
<td>Growth failure</td>
<td>Chronic GVHD</td>
</tr>
<tr>
<td></td>
<td>Hypogonadism/infertility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avascular necrosis of bone</td>
<td></td>
</tr>
<tr>
<td>&gt;90 d</td>
<td>2nd malignancy</td>
<td>Secondary graft failure</td>
</tr>
</tbody>
</table>

LWBK634-c5[01-38].qxd  7/6/10  6:14PM  Page 26 Aptara Inc
• Sinusoidal obstruction syndrome (SOS; incidence ~10%, mortality ~30%)
  Previously known as veno-occlusive disease (VOD)
  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; defibrotide

• Idiopathic interstitial pneumonitis (IIP, up to 70% mortality; Curr Opin Oncol 2008;20:227)
  Mech: alveolar injury due to direct toxicity → fever, hypoxia, diffuse pulmonary infiltrates
  Diffuse alveolar hemorrhage (DAH): subset of IIP
  Diagnosis: bronchoscopy to exclude infection; ↑ bloody lavage fluid seen with DAH

• Acute GVHD (within 3 mos of transplant; Lancet 2009;373:1550)
  Clinical grade 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 → none; grade II-IV → associated with ↓ survival and ↓ treated with
  immunosuppressants (corticosteroids, CsA, tacrolimus, rapamycin, rituximab, MMF)

• Chronic GVHD (developing or persisting beyond 3 mos posttransplant)
  Clinical: malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, bile duct
  degeneration and cholestasis. More common w/ PBSC than BM.
  Treatment: immunosuppressants as above; photopheresis

• Graft failure
  Primary — persistent neutropenia without evidence of engraftment
  Secondary — delayed pancytopenia after initial engraftment; either immune mediated due
  to attack by immunocompetent host cells in the allogenic setting (termed graft
  rejection) or non–immune mediated (eg, CMV infection)

• Infectious complications
  due to regimen-induced pancytopenia and immunosuppression
  auto HSCT recipients do not require immunosuppression and remain at ↑ risk only
  during the pre-engraftment and immediate postengraftment phases
  both primary infections and reactivation events occur (eg, CMV, HSV, VZV)

---

**Infectious Complications Following Allogeneic HSCT**

<table>
<thead>
<tr>
<th>Time after transplant and associated risk factors</th>
<th>Days 0–30</th>
<th>Days 30–90</th>
<th>&gt;90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class of pathogen and associated prophylaxis</td>
<td>Days 0–30</td>
<td>Days 30–90</td>
<td>&gt;90 days</td>
</tr>
<tr>
<td>Viral</td>
<td>Mucositis</td>
<td>Organ dysfunction</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>acyclovir to d 365 (HSV/VZV); valganciclovir or ganciclovir if CMV ♦ (monitor until d 100 or until no longer immunesupp.)</td>
<td>HSV ♦</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial antibiotics (eg, fluoroquinolone) while neutopenic</td>
<td>Gram ⊗ cocci (coagulase-negative staph., S. aureus, S. viridans)</td>
<td>GNRs (Enterobacteriaceae, Pseudomonas, Legionella, S. maltophilia)</td>
<td>Encapsulated bacteria</td>
</tr>
<tr>
<td>Fungal</td>
<td>fluconazole or posaconazole (NEJM 2007;356:335) to d 75 for Candida</td>
<td>Candida spp</td>
<td></td>
</tr>
<tr>
<td>Aspergillus spp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasitic</td>
<td>TMP-SMX to d 180 (or off immunosuppression) for PCP</td>
<td>T. gondii</td>
<td>T. gondii</td>
</tr>
<tr>
<td>P. carinii</td>
<td>S. stercoralis</td>
<td>P. carinii</td>
<td></td>
</tr>
</tbody>
</table>

*Primarily among persons who are seropositive before transplant*
LUNG CANCER

Pathology and genetics (NEJM 2008;359:1367)

- **Non–small cell lung cancer (NSCLC, ~85%)**
  - Adenocarcinoma: typically peripheral; tumor cells can have mutations in KRAS, EGFR, p53, LKB1, and EML4-ALK fusion protein.
  - Squamous cell: typically central; tumor cells can have mutations in p53, MET, LKB1, and/or amplifications in EGFR, MET, & PIK3CA.
  - Large cell: typically peripheral.
  - Bronchioalveolar carcinoma: track along airways, can be multifocal.
- **Small cell lung cancer (SCLC, ~15%)**: typically central; mutations in p53 & MET.

Epidemiology and risk factors

- Most common cause of cancer-related death for both men and women in U.S.
- **Cigarette smoking**: 85% of lung cancers occur in smokers; risk total pack-yrs, ↓ risk after quitting/reducing, but not to baseline (JAMA 2005;294:1505).
- Squamous & small cell almost exclusively in smokers.
- Adenocarcinoma most common type in nonsmokers.
- Bronchioalveolar carcinoma associated with females, nonsmokers, EGFR mutations.
- Asbestos: when combined with smoking, synergistic in risk of lung cancer.
- Radon: risk to general population unclear.

Clinical manifestations

- ~ 10% are ax symmetric and are detected incidentally by imaging.
- **Endobronchial growth** of 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, XRT after tissue dx, SVC stent for severe sx, fibrinolytic anticoag if thrombus.
- Extrathoracic metastases: brain, bone, liver, adrenal, skin.
- **Paraneoplastic syndromes**:
  - Endocrine: ACTH (SCLC) → Cushing’s syndrome; ADH (SCLC) → SIADH.
  - Skeletal: digital clubbing (non–small cell), hypertrophic pulmonary osteoarthropathy (adenocarcinoma) → symmetric polyarthritis and proliferative periostitis of long bones.
  - Neurologic (usually small cell): Eaton-Lambert, periph. neuropathy, cerebellar degen.
  - Cutaneous: acanthosis nigricans, dermatomyositis.
  - Hematologic: hypercoagulable state (adenocarcinoma), DIC, marantic endocarditis.

Screening (NEJM 2005;352:2714)

- No proven survival benefit to screening CXR or sputum cytology, even in high-risk Pts.
- Survival benefit of screening chest CT in observational studies controversial (NEJM 2006;355:1763; JAMA 2007;297:953); await RCTs.

Diagnostic and staging evaluation (AJCC Cancer Staging Manual, 7th ed, 2010)

- Imaging: CXR, chest CT (include liver and adrenal glands).
- Tissue:
  - Bronchoscopy (for central lesions) or CT-guided needle bx (for peripheral lesions or accessible sites of suspected metastasis).
  - Mediastinoscopy (lymph node bx), VATS (eval. of pleura peripheral lesions).
  - Thoracentesis (cell block for cytology).
- Staging:
  - Intrathoracic: mediastinoscopy or VATS; thoracentesis if pleural effusion.
  - Extrathoracic:
    - PET scan or integrated PET-CT more Se than CT alone for detecting mediastinal and distant mets as well as bone mets (NEJM 2000;343:254; 2003;348:2500; 2009;361:32).
    - Brain MRI for all Pts and bone scan for those w/ localizing sx or lab abnormalities.
    - BM bx for SCLC if peripheral smear abnl.
- PFTs with 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

<table>
<thead>
<tr>
<th>T/M stage</th>
<th>Definition</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T ≤ 2 cm (T1a) or T &gt; 2–3 cm (T1b)</td>
<td>IA</td>
<td>IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>T ≤ 5 cm (T2a) or T 5–7 cm (T2b)</td>
<td>IB/IIA</td>
<td>IIA/B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>T &gt; 7 cm or invasion of chest wall, diaphragm, mediastinum, pleura, pericardium</td>
<td>IIB</td>
<td>IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body; separate tumor nodule ipsilateral lobe</td>
<td>IIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Nodules contralateral lobe; pleural nodules or malignant effusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NSCLC treatment (NCCN Clinical Practice Guidelines in Oncology, www.nccn.org)

- **Stages I & II:** surgical resection + adjuvant chemo for stage IB-II (NEJM 2004;350:351 & 2005;352:2589); gene expression data identify early NSCLC w/ ↑ risk of recurrence that may benefit from more aggressive chemo (NEJM 2006;355:570).
- **Stage III:** chemoradiation is main treatment modality. IIIA viewed as potentially resectable (Lancet 2009;374:379) and IIB as unresectable neoadjuvant chemoradiation may convert unresectable → resectable.
- **Stage IV:** chemotherapy + survival c/w best supportive care standard is a platinum-based doublet (eg, carboplatin + paclitaxel).

### Biologic therapy (for stage IIIb/IV)

- anti-VEGF mAb (bevacizumab) added to chemo → ↑ median survival by 2 mo; ↑ risk of bleeding. Do not use if brain mets or squamous cell (hemoptysis) (NEJM 2006;355:2542).
- EGFR inhibitor (gefitinib, erlotinib, cetuximab) ↑ survival as 1st line Rx and if progress after chemo (NEJM 2005;353:123;2009;361:947 & 2010;362:2380; Lancet 2009;373:1525); target to pts w/ EGFR mutations (more common in Asians, females, nonsmokers, bronchioalveolar histology).
- ALK inhibitors in clinical trials for EML4-ALK+ NSCLC.

### NSCLC Simplified Staging Schema, Treatment, and 5-y Survival

<table>
<thead>
<tr>
<th>Stage % at dx</th>
<th>Definition</th>
<th>Treatment</th>
<th>5-y (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Isolated lesion</td>
<td>Surgery + chemo</td>
<td>&gt;60</td>
</tr>
<tr>
<td>II</td>
<td>Hilar node spread</td>
<td>Surgery ± radiation ± chemo</td>
<td>40–50</td>
</tr>
<tr>
<td>IIIA</td>
<td>Mediastinal spread but resectable</td>
<td>Chemoradiation ± surgery ± resection</td>
<td>25–30</td>
</tr>
<tr>
<td>IIIB</td>
<td>Unresectable</td>
<td>Chemoradiation ± biologic ± surgery (selected cases)</td>
<td>10–20</td>
</tr>
<tr>
<td>IV</td>
<td>Metastatic</td>
<td>Chemo ± biologic and/or supportive care Palliative radiation</td>
<td>1</td>
</tr>
</tbody>
</table>

### NSCLC prognosis

- EGFR mutations are associated with an improved prognosis in NSCLC (Lancet 2008;372:1809).

### SCLC Treatment (NCCN Clinical Practice Guidelines in Oncology, www.nccn.org)

- SCLC usually disseminated at presentation, but can be very responsive to chemoradiation.
- Chemotherapy (platinum + etoposide) is primary treatment modality.
- Thoracic radiation added to chemoradiation improves survival in limited stage disease.
- Prophylactic cranial irradiation (PCI) improves survival for limited stage disease in complete remission (NEJM 1999;341:476).

### SCLC Staging Schema and Treatment

<table>
<thead>
<tr>
<th>Stage % at dx</th>
<th>Definition</th>
<th>Treatment</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>Confined to ipsilateral hemithorax w/in one radiation port</td>
<td>Radiation ± chemotherapy ± PCI</td>
<td>1–2 y</td>
</tr>
<tr>
<td>Extensive</td>
<td>Beyond one radiation port</td>
<td>Chemotherapy ± PCI</td>
<td>~1 y</td>
</tr>
</tbody>
</table>
Epidemiology and genetics

- Most common cancer in U.S. women; 2nd leading cause of cancer death in women
- Age: incidence rates ↑ with age, with decrease in slope at age of menopause
- Genetics (NEJM 2007;357:154 & 2008;359:2143): 15–20% have \( \bigcirc \) FHx. Risk depends on # of affected 1° relatives and their age at dx. ~45% of familial cases a/w known germline mut.
- BRCA1/2: 35–85% lifetime risk of breast cancer & ↑ risk of ovarian cancer; ↑ ↑ colon & prostate cancer; prog not worse than in non-carriers w/ breast cancer (NEJM 2007;357:115); BRCA2: a/w ↑ male breast cancer & pancreatic cancer; rare mutations in CHEK2 or TP53 a/w ↑ risk in familial breast cancer (JAMA 2006;295:1379)
- 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;346:2125)
- Benign breast conditions: ↑ ↑ risk w/ atypia (atypical ductal or lobular hyperplasia) & proliferative (ductal hyperplasia, papilloma, radial scar, or sclerosing adenosis) features; no ↑ ↑ risk w/ cysts, fibroadenoma, or columnar changes (NEJM 2005;352:229)
- ↑ ↑ risk with h/o ionizing radiation to chest for treatment of Hodgkin’s lymphoma

Clinical manifestations

- Breast mass (hard, irregular, fixed, nontender), nipple discharge (higher risk if unilateral, Clinical manifestations
- Suspicious mammogram
  - Benign breast conditions: ↑ ↑ risk w/ atypia (atypical ductal or lobular hyperplasia) & proliferative (ductal hyperplasia, papilloma, radial scar, or sclerosing adenosis) features; no ↑ ↑ risk w/ cysts, fibroadenoma, or columnar changes (NEJM 2005;352:229)
  - ↑ ↑ risk with h/o ionizing radiation to chest for treatment of Hodgkin’s lymphoma

Screening

- Self breast exam (SBE): no proven mortality benefit (NCI 2002;94:1445); not recommended
- Clinical breast exam (CBE): benefit independent of mammography not established
- Mammography: ~20–30% ↓ in breast cancer mortality (smaller absolute benefit in women <50 y) (Lancet 2001;358:1340 & 2002;359:909; Annals 2002;137:347; Lancet 2006;368:2053); 75% of all abnl finding benign; suspicious: clustered microcalc., spiculated, enlarging, adding U/S ↑ Se, but ↓ PPV (JAMA 2008;299:1351)
- ACS/NCI recommend annual mammo + CBE beginning at age 40; USPSTF recommends begin at 50 and biennially (Annals 2009;151:716), controversial (NEJM 2009;361:2499)
- ↑ ↑ risk: screen earlier w/ CBE and mammo (age 25 in BRCA1/2 carrier, 5–10 y before earliest FHx case, 8–10 y after thoracic XRT, upon dx of ↑ ↑ risk benign disease)
- MRI: superior to mammography in high-risk Pts; consider annually if ~20% lifetime risk (eg, \( \bigcirc \) FHx, BRCA 1 or 2, prior chest XRT) (NEJM 2004;351:427; Lancet 2005;365:1769 & 2007;370:485)
- 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 → mammography (detect other lesions) and either fine-needle aspir. or core-needle bx
  - Clearly cancerous on exam or indeter. read/atypia on needle bx → excisional bx
- Suspicious mammogram with normal exam: stereotactically-guided bx
  - MRI: detects contralateral cancer in 3% of women w/ recently dx breast cancer & negative contralateral mammogram (but PPV only 21%) (NEJM 2007;356:1293); whether to use routinely remains unclear

Staging

- Anatomic: tumor size, chest wall invasion, axillary LN mets (strongest prognostic factor)
- Histopathologic: type (little prognostic relevance) & grade; lymphatic/vascular invasion
  - 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: determine estrogen, progesterone receptor (ER/PR) and HER2/neu status for all invasive breast cancers
- Recurrence score and risk with Oncotype DX 21-gene assay in ER \( \varnothing \), node \( \varnothing \) Pts (NEJM 2004;351:2817; 2006;355:560)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Description</th>
<th>5-y surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor ≤ 2 cm</td>
<td>Operable locoregional</td>
<td>90%</td>
</tr>
<tr>
<td>IIA</td>
<td>Tumor &gt; 2 cm or mobile axillary nodes</td>
<td>Operable locoregional</td>
<td>80%</td>
</tr>
<tr>
<td>IIB</td>
<td>Tumor &gt; 5 cm</td>
<td>Locally advanced</td>
<td>65%</td>
</tr>
<tr>
<td>IIIA</td>
<td>Internal mammary or fixed axillary nodes</td>
<td>Locally advanced</td>
<td>50%</td>
</tr>
<tr>
<td>IIIB</td>
<td>Direct extension to chest wall or skin</td>
<td>Inoperable</td>
<td>45%</td>
</tr>
<tr>
<td>IIIC</td>
<td>Infracavicular or supraclavicular nodes</td>
<td>Locoregional</td>
<td>40%</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
<td>Metastatic</td>
<td>15%</td>
</tr>
</tbody>
</table>

**Simplified Staging System for Breast Cancer**

**Treatment**

- **Local control: surgery and radiation therapy (RT)**
  - Breast-conserving = lumpectomy + breast RT + axillary node dissection (ALND) is equivalent to mastectomy + ALND (NEJM 2002;347:1227; 1233); contraindications: multicentric disease, diffuse microcalcifications, prior RT, pregnancy, tumor > 5 cm, Sentinel lymph node bx prior to ALND preferred if w/o palpable axillary LNs. Radiation therapy (RT):mastectomy for ≤ 4 LN, tumor > 5 cm or surgical margins → locoregional recurrence and survival (Lancet 2005;366:2087).

- **Systemic therapy:** for stage I-III except tumors ≤ 1 cm (complex risk assessment needed).
  - Usually used after anthracycline regimens or concurrently w/ taxane regimens. Lapatinib (tyrosine kinase inhib. of HER2 & EGFR): if mets, delays progression if failed trastuzumab (NEJM 2006:355:2733).
  - Hormonal (in ER/PR+ or unknown status)
    - Tamoxifen: 41% ↓ recurrence and 34% ↓ breast cancer mortality in postmenopausal Pts (Lancet 2003;365:1687).
  - 2nd-line: ovarian ablation with LHRH agonists (goserelin) or oophorectomy if premenopausal, pure antiestrogens (fulvestrant) if postmenopausal; ovarian ablation + AI or tamoxifen for premenopausal women is under study.
  - PARP1 (poly[adenosine diphosphate [ADP]–ribose] polymerase 1) inhib. against BRCA1 or BRCA2 defective breast cancers (NEJM 2009;361:189).

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

<table>
<thead>
<tr>
<th>LCIS</th>
<th>Mastectomy or lumpectomy + RT; ALND not indicated; ± chemoprevention (NEJM 2004:350:1430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-y surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surgery + RT + Adjuvant chemo if ↑ risk: tumor &gt; 1 cm or + LN or ER/PR+ (Lancet 1998;352:930) + Hormonal therapy if ER/PR+ (or unknown status) + Trastuzumab if HER2+ and tumor ≥ 1 cm or + LN</td>
<td>↓ recurrence in HER2+ cancers (NEJM 2009:374:2055)</td>
</tr>
<tr>
<td>II</td>
<td>Neoadjuvant chemo → surgery + RT ± adjuvant chemotherapy + Hormonal therapy for ER/PR+ (or unknown status) tumors + Trastuzumab if HER2+</td>
<td>↓ locoregional recurrence and survival (NEJM 2005:366:2087)</td>
</tr>
<tr>
<td>III</td>
<td>ER/PR+ ○ hormonal therapy ± chemotherapy</td>
<td>↓ recurrence in HER2+ cancers (NEJM 2009:374:2055)</td>
</tr>
<tr>
<td>IV</td>
<td>ER/PR+ ○ HER2+ ○ chemotherapy</td>
<td>↓ locoregional recurrence and survival (NEJM 2005:366:2087)</td>
</tr>
</tbody>
</table>

**Prevention**

- **Selective estrogen receptor modulators (SERMs)**
  - Tamoxifen: ↓ risk contralat breast CA as adjuvant Rx; approved for 1° prevent. if ↑ risk: invasive breast CA, but ↑ DVT & uterine CA; ↑ in mortality (Lancet 2002;360:817).

- **BRCA1/2 carriers:** intensified surveillance as described above. Prophylactic bilateral mastectomy → ~ 90% ↓ risk & bilateral salpingo-oophorectomy ↓ risk of ovarian and breast cancer.
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%
- More common with ↑ age (rare if <45 y), in African Americans, and if ◀ FHx

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 2009;360:1351)
- Mortality benefit from screening has not been established, with one recent trial showing a 20% ↓ mortality, but another no benefit (NEJM 2009;360:1310 & 1320)

Digital rectal exam (DRE): size, consistency, lesions
- PSA: 4 ng/mL cutpoint 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)
- Per American Cancer Soc., offer PSA + DRE screening to men age ≥50 (=45 if high risk) with life expectancy ≥10 y; USPSTF has no rec. for PSA if <75 y, rec. against if ≥75 y

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 two 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Nodes, Mets</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1a – non-palp., not visible on imaging</td>
<td>N0, M0, Gleason 2–4</td>
<td>Active surveillance (consider if life expect. &lt;10 y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radiation (external or brachy; NEJM 2006;355:1583)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radical prostatectomy (= radiation and/or hormonal Rx if high-risk features found at surgery). Min. invasive RP a/w ↓ hospital stay, but ↑ risk of salvage Rx (JCO 2008;26:2278).</td>
</tr>
<tr>
<td>II</td>
<td>T1/T2 – w/ in prostate</td>
<td>N0, M0</td>
<td>Radiation + androgen deprivation (see below) (Lancet 2009;373:301)</td>
</tr>
<tr>
<td>III</td>
<td>T3 – extends thru capsule</td>
<td>N0, M0</td>
<td>Radiation (for M0 disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Androgen deprivation (NEJM 2009;360:2516)</td>
</tr>
<tr>
<td></td>
<td>T4 – invades adjacent structures</td>
<td>N0, M0</td>
<td>GnRH analogues (leuproide, goserelin)</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1, M0</td>
<td>antiandrogens (flutamide, bicalutamide)</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N, M1*</td>
<td>2nd-line: androgen synthesis inhibitor (ketoconazole, aminoglutethimide), antiandrogen withdrawal (see below)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemo (docetaxel + prednisone) if refractory</td>
</tr>
</tbody>
</table>

*Bisphosphonates (alendronate, zolendronate) & palliative radiation for bone mets

Prognosis
- PSA level, Gleason grade, and age are predictors of metastatic disease
- In surgically treated Pt’s, 5-y relapse-free survival >90% if disease confined to organ, ~75% if extension through capsule, and ~40% if seminal vesicle invasion
- Compared to active surveillance surgery ↓ prostate cancer mortality & overall mortality in Pt’s <75 y (NEJM 2005;352:1977); comparisons of surgery and radiation are underway
- 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 ~24–30 mos; all progress to androgen independence (in 15–20% discontinuation of anti-androgens results in paradoxical ↓ in PSA)
- Long-term consequences of anti-androgen therapy include osteoporosis

Prevention
- Finasteride and dutasteride ↓ total prostate cancers detected by bx, but ↑ number of high Gleason grade tumors (NEJM 2003;349:215 & 2010;362:1192)
COLORECTAL CANCER (CRC)

Epidemiology and risk factors

• 4th most common cancer in U.S men and women; 2nd leading cause of cancer death overall
• Rare before age 40, w/ 90% of cases occurring after age 50. ~70% are sporadic.
• Family History: up to 25% ofPts 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 of APC tumor suppressor → 1000s of polyps at young age → ~100% lifetime risk; ↑ risk of thyroid, stomach, SI cancers

Hereditary nonpolyposis colorectal cancer (HNPCC): mutations in DNA mismatch repair genes → ↑ tumor progression → ~80% lifetime risk; predom. right-sided tumors; ↑ risk of endometrial, ovarian, stomach, small bowel cancers.

Amsterdam criteria: ≥3 family members w/ HNPCC-related cancer, one of which dx before age 50, affecting 2 successive generations.

• Other factors a/w ↑ risk of CRC: diet rich in animal fat, ↑ smoking, ↑ diabetes/obesity
• ↓ risk of adenomas w/ ASA & NSAIDs, incl. COX-2
• Colonoscopy alone, but with only 8% needing colonoscopy (2453).

Inflammatory bowel disease: ↑ risk with ↑ extent and duration of disease

• Other factors a/w ↑ risk of CRC: diet rich in animal fat, ↑ smoking, ↑ diabetes/obesity

Pathology and Genetics

• Adenoma → carcinoma sequence: reflects accumulation of multiple genetic mutations

Familial adenomatous polyposis (FAP)

• Genetic profile in sporadic CRC: APC (–80%), KRAS (–50%), TP53 (50–70%), DCC or SMAD4, chromosomal instability (majority) or mismatch repair deficiency (10–15%)

• Upfront genotyping at dx may guide Rx (eg, KRAS, see below)

Clinical manifestations

• Distal colon: Δ bowel habits, obstruction, colicky abdominal pain, hematochezia
• Proximal colon: iron defic. anemia, dull vague ab 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

• 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 & early screening (eg, age 20–25), then q1–2y.

• Colonoscopy: test of choice as examines entire colon; 90% Se for lesions >1 cm. Flex sig less Se but better than no endoscopy (1992;361:653). If polyp found, re ↑ in 3–5 y.
• Fecal occult blood test (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.
• Fecal DNA: ↑ Se, – Sp c/w FOBT, but less Se than colonoscopy (NEJM 2004;351:2704)
• CT colonography (CTC): c/w colonoscopy; 90% Se for lesions ≥1 cm but considerably less for smaller lesions (NEJM 2008;359:1207). Strategy of CTC followed by colonoscopy for lesions ≥6 mm diagnoses similar # of advanced neoplasms as colonoscopy alone, but with only 8% needing colonoscopy (NEJM 2007;357:1403).

Staging

• TNM staging: Size/depth of primary (T), locoregional nodes (N), distant metastases (M).

Colorectal Cancer (CRC) 5-33

• 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
<table>
<thead>
<tr>
<th>TNM</th>
<th>Dukes</th>
<th>Path. Criteria</th>
<th>5-y surv.</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Into submucosa or muscularis</td>
<td>94–97%</td>
<td>Surgery alone (resection and analysis of ≥ 12 LN)</td>
</tr>
<tr>
<td>IIA</td>
<td>B</td>
<td>Into serosa</td>
<td>83%</td>
<td>Surgery: no established role for adjuvant chemo for colon cancer&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIB</td>
<td>B</td>
<td>Into peritoneum</td>
<td>74%</td>
<td>Preop XRT or 5FU/XRT added for rectal cancer followed by postop chemo (FOLFOX)</td>
</tr>
<tr>
<td>IIC</td>
<td>B</td>
<td>Direct invasion</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>C</td>
<td>≤ 6 LN or local invasion</td>
<td>86%</td>
<td>Surgery + chemotherapy&lt;sup&gt;a&lt;/sup&gt; 5-FU + leucovorin + oxaliplatin = FOLFOX (NEJM 2004;350:2343)</td>
</tr>
<tr>
<td>IIIB</td>
<td>C</td>
<td>Varying degrees of LN or local invasion</td>
<td>51–77%</td>
<td>Preop XRT or chemorad added for rectal cancer (NEJM 2006;355:1114)</td>
</tr>
<tr>
<td>IIIC</td>
<td>C</td>
<td>Local invasion</td>
<td>15–47%</td>
<td>Chemotherapy (NEJM 2005;352:476): FOLFOX, FOLFIRI or CapeOX ± bevacizumab or cetuximab (benefit limited to Pts w/o KRAS mutation) ± surgical resection isolated mets (a/w ~ 30% 5-y survival) Consider resection of primary tumor if perf, obstruction, or bleeding</td>
</tr>
<tr>
<td>IV</td>
<td>D</td>
<td>Distant metastases</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Consider adjuvant chemo for high-risk stage II (obstruction, perforation, adherence to adjacent structures, inadequate nodal sampling, lymphovascular invasion, poorly differentiated). Bevacizumab is an anti-VEGFA mAb (NEJM 2004;350:2333); cetuximab is an anti-EGFR mAb (NEJM 2004;351:337).
**PANCREATIC TUMORS**

**Pathology and genetics** *(Ann Rev Pathol 2008;3:157; Genes Dev 2006;20:1218)*
- Histologic types: adenocarcinoma (~85%), acinar cell carcinoma, endocrine tumors, cystic neoplasms (eg, IPMN, see below), rare 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 adenocarc.: KRAS (~90%), p16 (80–95%), p53 (50–75%), SMAD4 (~55%)

**Epidemiology and risk factors** *(Lancet 2004;363:1049)*
- Pancreatic adenocarcinoma is 4th leading cause of death in U.S. men and women
- 80% of pancreatic adenocarcinomas occur inPts 60–80 y
- Acquired risk factors:
  - Smoking (RR ~1.5), 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 (PRSS1)
    - Familial cancer syndromes and gene mutations with ↑ risk: familial atypical multiple mole melanoma (CDKN2A/p16), familial breast and ovarian cancer (BRCA2), Peutz-Jeghers syndrome (LKB1), ataxia-telangiectasia (ATM), hereditary colorectal cancer (HNPCC and FAP)

**Clinical manifestations**
- Painless jaundice (w/ pancreatic head mass), pain (radiating to back), weight loss
- New-onset atypical diabetes mellitus; unexplained malabsorption; unexplained pancreatitis
- Migratory thrombophlebitis (Trousseau’s sign)
- Exam: abdominal mass; nontender, palpable gallbladder (Courvoisier’s sign, but more often seen with biliary tract cancers); hepatomegaly; ascites; left supraclavicular (Virchow’s) node & palpable rectal shelf (both nonspecific signs of carcinomatosis)
- Laboratory tests may show ↑ bilirubin, ↑ α_fetoprotein, anemia

**Diagnostic and staging evaluation**
- Pancreatic protocol CT scan *(Iw/ arterial & venous phase imaging)*
- 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 metastasis
- Tumor markers: ↑ CA 19-9 (nb, falsely ↑ in liver failure); may be useful to follow dis. postop

<table>
<thead>
<tr>
<th>Clinical (Radiologic) Staging &amp; Prognosis of Pancreatic Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage, % at dx</strong></td>
</tr>
<tr>
<td>Resectable, 15–20%</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Locally advanced (unresect.), 40%</td>
</tr>
<tr>
<td>Metastatic, 40%</td>
</tr>
</tbody>
</table>

**Treatment of pancreatic adenocarcinoma** *(NEJM 2010;362:1605)*
- Resectable: surgery ± adjuvant (neo)adjuvant or postoperative) therapy
  - pancreaticoduodenectomy – Whipple procedure – resection of pancreatic head, duodenum, CBD and gallbladder ± partial gastrectomy
- 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; The 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 size, location, dysplasia.
**Fever and Neutropenia (FN)**

**Definition**
- Fever: single oral temp $\geq 38.3^\circ$C ($101^\circ$F) or $\geq 38^\circ$C ($100.4^\circ$F) for $\geq 1$ h
- Neutropenia: ANC $\leq 500$ cells/$\mu$L or $< 1,000$ cells/$\mu$L with predicted nadir $< 500$ cells/$\mu$L

**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 (especially *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**
- Levofoxacin (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
  - *S. stercoralis* stool (*C. difficile*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s
  - CNS, sinus, chest, or abdomen/pelvis imaging
- Caveats: neutropenia $\rightarrow$ 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 $\leq 60$ y, no symptoms, no major comorbidities, cancer in remission, solid tumor, no h/o fungal infection or recent antifungal Rx
- Exam: temp $< 39^\circ$C, no tachypnea, no hypotension, no Δ MS, no dehydration
- Studies: ANC $> 100$ cells/$\mu$L, anticipated duration of neutropenia $< 10$ d, normal CXR

**Initial antibiotic therapy** (*Clin Infect Dis* 2002;34:730)
- Empirc regimens should include a drug with antipseudomonal activity
- PO abx may be used in low-risk Pts: 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 added in select cases (hypotension, indwelling catheter, severe mucositis, MRSA colonization, h/o quinolone prophylaxis), discontinue when cultures $\times 48$ h

**Modification to initial antibiotic regimen**
- Low-risk Pts who become afebrile w/in 3–5 d can be switched to PO antibiotics
- Empirc antibiotics changed for fever $3–5$ d or progressive disease (eg, add vancomycin)
- Antifungal therapy is added for neutropenic fever $> 5$ d

**Duration of therapy**
- Known source: complete standard course (eg, 14 d for bacteremia)
- Unknown source: continue antibiotics until afebrile and ANC $> 500$ cells/$\mu$L
- Less clear when to d/c abx when Pt is afebrile but prolonged neutropenia

**Role of hematopoietic growth factors** (*JCO* 2005;23:198 & 2006;24:3187)
- 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). CSF ↓ 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**
- Metastases located in vertebral body extend and cause epidural spinal cord compression
Prostate, breast, and lung cancer are the most common causes, followed by renal cell carcinoma, NHL, and myeloma.

Site of involvement: thoracic (70%), lumbar (20%), cervical (10%).

Signs and symptoms: pain (96%), precedes neuro deficits, 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 because duration & severity of neurologic dysfunction before Rx are best predictors of neurologic outcome.
- Urgent whole-spine MRI is study of choice. Consider CT myelogram if unable to get MRI.

Treatment
- Dexamethasone (10 mg IV → 4 mg IV or PO q6h) initiate immediately while awaiting imaging if back pain / neurologic deficits.
- Emergent XRT or surgical decompression if confirmed compression / neuro deficits.
- Surgery prior to XRT alone for neuro recovery in solid tumors.
- If pathologic fracture causing compression → surgery; if not surgical candidate → XRT.

Tumor Lysis Syndrome

Clinical manifestations
- 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, ↓ PO4, ↓ 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 XRT.
- Rasburicase (recombinant urate oxidase) 0.15 mg/kg or 6 mg fixed dose (except in obese Pts) & aggressive hydration prior to beginning chemotherapy or XRT.

Treatment
- Avoid IV contrast and NSAIDs.
- Allopurinol + aggressive IV hydration ± diuretics to ↑ UOP.
- Consider alkalization of urine w/ isotonic NaHCO₃ to ↑ UA solubility & ↓ risk of urate nephropathy (controversial: may cause metabolic alkalosis or Ca₃(PO₄)₂ precipitation).
- Rasburicase (0.15–0.2 mg/kg/d × 3–7 d) for severe ↑ UA, esp in aggressive malig; UA level must be drawn on ice to quench ex vivo enzyme activity.
- Treat hyperkalemia, hyperphosphatemia, and symptomatic hypocalcemia.
- Hemodialysis may be necessary; early renal consultation for Pts w/ renal insufficiency or ARF.

Cancer of Unknown Primary Site

Evaluation of Cancer of Unknown Primary

<table>
<thead>
<tr>
<th>Path</th>
<th>Possible Sources</th>
<th>Markers</th>
<th>Imaging</th>
<th>Additional Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno.</td>
<td>Colon, upper GI, panc.</td>
<td>CEA, CA19-9, AFP, CA-15-3, CA125, PSA</td>
<td>Endoscopy/EUS, Abdom/Pelvic CT, Mammography, Pelvic U/S, Chest CT</td>
<td>CDX1, CK7/20, ER/PR, GCDFP, CA-125, PSAP, TTF1, CK7</td>
</tr>
<tr>
<td>Squam.</td>
<td>Head &amp; Neck, Esophageal, Cervix, Anus</td>
<td>None</td>
<td>Chest CT, Laryngoscopy, Endoscopy</td>
<td>TTF1, CK7</td>
</tr>
<tr>
<td>Poorly Differ.</td>
<td>Germ cell Lymphoma, Thyroid, GIST, Sarcoma, Neuroendocrine</td>
<td>hCG, AFP, LDH, Thyroglobulin</td>
<td>Testicular U/S, PET, Thyroid U/S, Abdom/Pelvic CT</td>
<td>PLAP, isochrom 12p, LCA, flow, cytogenetics, Thyroglobulin, c-KIT, desmin, vimentin, NSE, chromogranin, Consider EM for all</td>
</tr>
</tbody>
</table>

Additional studies for each possible source listed in same row.

- Bony mets: breast, lung, thyroid, kidney, prostate.
**Clinical manifestations**

- “Typical”: acute onset of fever, cough w/ purulent sputum, dyspnea, consolidation on CXR
- “Atypical” (originally described as culture 🎓): tends to p/w insidious onset of dry cough, extrapulmonary sx (N/V, diarrhea, headache, myalgias, sore throat), patchy interstitial pattern on CXR, and 🆕 transaminases & ↓ Na w/ Legionella
- S/s & imaging do not reliably distinguish between “typical” (S. pneumoniae, H. flu) and “atypical” (Mycoplasma, Chlamydia, Legionella, viral)

**Diagnostic studies**

- **Sputum Gram stain**: utility debated. Is it a good sample (ie, sputum or spit)? → should be <10 squamous cells/lpf. Is it a purulent sample? → should be >25 PMNs/lpf
- **Sputum bacterial culture**: should be transported to lab w/in 1–2 h of collection.
  - In select situations, consider respiratory viral testing (DEA or PCR), rarely viral cx.
- **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 labs:** S. O₂, PaO₂, CBC w/ diff, lymphs, BUN/Cr, glc, LFTs; arterial pH (if severe)
- **Other microbiologic studies (paired serologies available for most atypicals):**
  - **Mycoplasma**: PCR of throat or sputum/BAL before first dose abx
  - **Legionella**: urine Ag (detects L. pneumophila L1 serotype, 60–70% of clinical disease)
  - **S. pneumoniae urinary Ag** (50–80%, Sp >90%)
  - **MTb**: induced sputum for AFB stain and mycobact. cx (empiric respiratory isolation while pending); avoid quinolones if considering TB; request rapid DNA probe if stain 🆕
  - **Bronchoscopy**: consider if Pt immunosuppr., critically ill, failing to respond, or has chronic pneumonia. Also in suspected TB if no adequate sputum and in suspected PCP if induced sputum unavailable or 🆕 but clinical suspicion high.
  - **Reasons for failure to improve on initial Rx:**
    - Insufficient time: may take >72 h to see clinical improvement
    - Insufficient drug levels: eg, vanco trough <15–20 μg/mL (needed for lung penetration)
    - Resistant organisms (or superinfxn): eg, MRSA, Pseudomonas; consider bronchoscopy
    - Wrong dx: fungal/viral, chemical pneumonia, PE, CHF, ARDS, DAH, ILD; consider CT
    - Parapneumonic effusion/empyema: esp. seen w/ Strep pneumonia, Grp A strep; if CXR neg, consider CT (cx tap ≠ chest tube if effusion present; particularly if loculated)
    - Metastatic infection (endocarditis, meningitis, arthritis), abscess

**Prognosis** (also see PORT score, next page)

- Pneumonia and influenza are the 8th leading cause of death in the U.S.
- For low-risk Pts, can discharge immediately after switching to PO abx (CID 2007:44:527)
- CXR resolves in most by 6 wks; consider flu to r/o underlying malignancy or other dx
- Newer metrics proposed to replace Pneumonia Severity Index (PSI, aka PORT score; simpler parameters, similar performance characteristics, but not as well validated
- **Curb-65** (Thorax 2003:58:377): Confusion, Uremia, RR 30, BP 90/60, age >65
- **Smart-Cop** (CID 2008:47:375): SBP <90, Multilobar infiltrates, Alb < 3.5 g/dL, RR ≥30, Tachycardia (HR >125 bpm), Confusion, O₂ sat <90%, pH <7.35 (arterial)
PORT Score, Prognosis, and Recommended Triage

<table>
<thead>
<tr>
<th>Class</th>
<th>Score</th>
<th>Mortality</th>
<th>Suggested Triage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Age &lt;50, no comorbidities</td>
<td>&lt;1%</td>
<td>Outpatient</td>
</tr>
<tr>
<td>II</td>
<td>≤70</td>
<td>&lt;1%</td>
<td>Outpatient</td>
</tr>
<tr>
<td>III</td>
<td>71–90</td>
<td>2.8%</td>
<td>Brief inpatient</td>
</tr>
<tr>
<td>IV</td>
<td>91–130</td>
<td>8.2%</td>
<td>Inpatient</td>
</tr>
<tr>
<td>V</td>
<td>&gt;130</td>
<td>29.2%</td>
<td>ICU</td>
</tr>
</tbody>
</table>

Variables

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, O2 < 60 or S, O2 < 90 (≥ 10), pleural effusion (≥ 10) |

When possible, organism-directed therapy, guided by in vitro susceptibilities or local patterns of drug resistance should be used. For ventilator-associated pneumonia, 8 – 15 d of Rx, except for Pseudomonas and other non-fermenting GNR (JAMA 2003;290:2588; AJRCCM 2005;171:388; CID 2007;44:527) Prevention

• Pneumococcal polysaccharide vaccine: persons ≥65 y of age or high-risk medical illness
• VAP precautions: HOB ≥30°, chlorhexidine rinse; aspiration precautions in high-risk Pts

Viral Respiratory Infections

Microbiology and Epidemiology

• Typical pathogens: short, mild – rhinovirus, coronavirus; longer, more severe or complicated – influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus
• Seasonal flu: 365,000 hosp., 51,000 deaths per y in U.S.; most ≥65 y (NEJM 2008;359:2579)
• Pandemic 2009 H1N1: more severe disease in younger Pts (JAMA 2009;302:1996)

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 (flu, paraflu, RSV, adenov) 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 types)

Treatment

• Seasonal influenza: M2 inh. (amantadine, rimantadine) effective only against some type A; neuraminidase inh. (oseltamivir, zanamivir) effective vs. A & B, but resistance emerging
• Pandemic H1N1 influenza: nearly 100% sensitive to oseltamivir, consider IV peramivir for critically ill Pts unable to take PO (currently emergency use in U.S.); resistant to amantidine
• Oseltamivir dosed 75 mg PO bid × 5 d, effective only if started w/in 48 h of sx, but used anytime in immunosupp. & considered in all Pts w/ or predisposed to severe influenza
• Consider inhaled ribavirin for RSV in immunosupp. (eg, BMT, lung tx); limited adult data

Prevention

• Inactivated influenza vaccine: available for seasonal and select pandemic flu, incl. H1N1 rec if ≥50 y, at risk for complic., HCW, caretakers of high-risk Pts; for all if surplus
• 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 prior Rx or nonalbicans; C. parapsilosis more likely to be echinocandin resistant)
- **Risk factors:** neutropenia, immunosupp., broad-spectrum abx, intravascular catheters (esp. if TPN), IVDU, abd surgery, DM, renal failure
- **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 (#4 cause of nosocomial bloodstream infxn): r/o retinal involvement (req ↑ Rx); endocarditis rare but serious (esp. w/ nonalbicans & prostatic valve)
  - Hepatosplenic: intestinal seeding of portal & venous circulation; seen in acute leukemias
  - Hematogenous dissemination → lung, brain, meninges, etc

<table>
<thead>
<tr>
<th>Empiric Treatment</th>
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</thead>
<tbody>
<tr>
<td>Mucocutaneous</td>
</tr>
<tr>
<td>Candiduria</td>
</tr>
<tr>
<td>Candidemia w/o neutropenia</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Remove intravascular catheters (CID 2009:48:503)</td>
</tr>
</tbody>
</table>

Histoplasmosis

- **Epidemiology:** hyperendemic in central & SE U.S. (esp. in areas w/ bird & bat droppings), present in river banks elsewhere including northeast
- **Clinical manifestations**
  - Acute pulmonary: often subclinical, but may see mild to severe ≥ cavitary
  - Chronic pulmonary: ↑ productive cough, wt loss, night sweats, infiltrates, cavitation
  - Disseminated (immunosupp.): fever, wt loss, HSM, LAN, oral ulcers, skin lesion
- **Treatment:** itraconazole; amphotericin ≥ steroids if severe or disseminated (CID 2007:45:807)

Coccidioidomycosis

- **Epidemiology:** SW U.S. (San Joaquin or “Valley” fever)
- **Clinical manifestations**
  - Acute pulmonary: often subclinical; chest pain, cough, fever, arthralgias
  - Chronic pulmonary: cough, hemoptysis, fever, night sweats, wt loss
  - Chronic disseminated (in immunosupp., pregnant, & DM): fever, malaise, diffuse pulmonary process, bone, skin, & meningeal involvement
- **Treatment** for disseminated or high-risk 1° pulmonary: fluconazole or itraconazole, or amphotericin if severe (CID 2005:41:1217)

Blastomycosis

- **Epidemiology:** south central, SE, and midwest U.S.
- **Clinical manifestations**
  - Acute pulmonary: often asx, acute PNA, chronic pneumonia; extrapulmonary: verrucous & ulcerated skin lesions, bone & GU involvement, CNS
- **Treatment:** itraconazole; amp B if severe or immunosupp. (CID 2008:46:1801)


- **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:** seen in COPD, mild immunosupp.; subacute sputum, fever, wt loss; CT: infiltrate ≥ nodule ≥ thick pleura; lung bx → invasion; Rx – voriconazole > amp B
- **Invasive/disseminated:** seen if immunosupp. (neutropenia, s/p transplant, steroid Rx, AIDS esp. w/ steroids or neutropenia); s/PNA w/ chest pain & hemoptysis; CT: nodules, halo sign, air crescent sign; lung bx if dx inconclusive; Rx – voriconazole > amp B

Zygomycetes (eg, Mucor, Rhizopus)

- **Epidemiology:** diabetes mellitus (70%), heme malignancy, s/p transplant, chronic steroids, deferoxamine or iron overload
- **Clinical manifestations:** rhinoencephalitis – orbital/forehead pain (more extensive than orbital cellulitis), ≥ fever (may appear nontoxic at first), exophthalmos, decreased EOM, may involve CNs (V > VII); nasal turbinates ≥ black eschar; Dx: careful ENT exam + bx
- **Treatment:** Serial debridements, amp. Very high mortality even if treated.
**Cryptococcus** (CID 2010:50:291)

- Epidemiology: immunosupp. (esp. AIDS) most susceptible, but may occur in healthy host
- Clinical manifestations
  - CNS (meningitis) – HA, fever, meningismus, high ICP, ± stupor; Dx: LP w/ CSF CrAg, India ink stain, fungal cx (cell counts vary); serum CrAg > 1.8 highly Se/Sp in AIDS.
  - Other forms: pulmonary, urinary, cutaneous, CNS cryptococcoma. With any evidence of cryptococcal disease, exonerate CNS infxn w/ LP.
- Treatment:
  - CNS disease (or non-CNS disease in immunosupp. Pts):
    - HIV: Induction: ampho (Ampho B 0.7–1.0 mg/kg/d, liposomal ampho B 3–4 mg/kg/d or ABLC 5 mg/kg/d and if bone marrow allows, flucytosine 100 mg/kg/d in 4 divided doses) ×2 wk; Consolidation: fluconazole 800 mg/d ×8 wk; Maintenance: ≥12 mo antifungal Rx and until immune recovery on ARVs.
  - Transplant:
    - Induction: liposomal ampho B and flucytosine ×2 wk; Consolidation: fluconazole 400 mg/d ×8 wk; Maintenance: fluconazole 6–12 mo if able to reduce immunosuppressive Rx, o/w longer.
  - Treat high ICP w/ repeat large-volume LPs or temp. lumbar drain; few require VP shunt.
- Non-CNS disease in healthy Pts: fluconazole vs. observation, based on clinical setting.

**Fungal diagnostics**

- Culture: Candida grows well in blood/urine cx, others (eg, Crypto, Histo) grow better in fungal isolator BCx.Cx insensitive for Coccidioides.
- Antigen detection:
  - Histo urine/serum Ag: Se of urine Ag 90% (serum Ag 80%) for disseminated disease; Sp limited by cross-reactivity with other fungal infxn.
  - 1,3-β-D-glucan: Se for many fungal infxn (Candida, Aspergillus, Histo, Coccidio, Fusarium, Pneumocystis, Sporothric; but not Crypto, Blasto, Mucor, Rhizopus); not Sp.
  - Galactomannan (GM): more specific for Aspergillus, but Se ~50%.
  - Crypto Ag (serum, CSF): serum Ag 90% Se & Sp in invasive infxn, lower for pulm only.
- Histopathologic exam (nb, no grinding of tissue if Zygomycetes suspected).

**INFECTIONS IN SUSCEPTIBLE HOSTS**

**Overview**

- Many immunophenotypes, meds, or systemic diseases may predispose to infection.
- The following is not an exhaustive list, but a delineation of common or classic etiologies.
- Many immunophenotypes, meds, or systemic diseases may predispose to infection.
- Many Pts will fit into more than one category (eg, DM, ESRD, extremes of age).

<table>
<thead>
<tr>
<th>Predisposition</th>
<th>Classic infectious etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral immune dysfunction (eg, CVID, myeloma)</td>
<td>Encapsulated bacteria: <em>S. pneumoniae, H. flu, N. meningitidis</em> Other bacteria: <em>E. coli</em> and other GNRs</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Splenectomy: <em>S. pneumoniae, H. flu, N. meningitidis</em> (vaccine against these 3, ideally prior to splenectomy); Campylobacter, Babesia Liver (esp. cirrhosis): Vibrio spp., encapsulated bacteria ESRD: impaired granulocyte fxn and CMI as above. Iron overload (or deferoxamine Rx): <em>Yersinia, Mucor</em></td>
</tr>
<tr>
<td>Biologics (eg, TNF inhibitors, anti-B-cell Rx)</td>
<td>Bacteria: sepsis, TB, other mycobacteria Fungi: Pneumocystis, Histo, Coccidio, other endemic fungi Viruses: JC virus (PML), EBV, HSV, VZV, HBV Parasites: Strongyloides reactivation</td>
</tr>
</tbody>
</table>
**URINARY TRACT INFECTIONS (UTI)**

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

**Microbiology**
- **Uncomplicated UTI**: *E. coli* (80%), *Proteus*, *Klebsiella*, *S. saprophyticus* (CID 2004;39:75)
- **Complicated UTI**: *E. coli* (30%), enterococci (20%), *Pseudomonas* (20%), *S. epidermidis* (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, Δ in urine color/odor, suprapubic pain; fever generally absent
- **Urethritis**: may be identical to cystitis except urethral discharge may be present
- **Prostatitis**
  - **chronic**: similar to cystitis except symptoms of obstruction (hesitancy, weak stream)
  - **acute**: perineal pain, fever, tenderness on prostate exam
- **Pyelonephritis**: fever, shaking chills, flank or back pain, nausea, vomiting, diarrhea
- **Renal abscess** (intrarenal or perinephric): identical to pyelonephritis except persistent fever despite appropriate antibiotics

**Diagnostic studies**
- **Urinalysis**: pyuria + bacteriuria ± hematuria ± nitrites
- **Urine Cx** (from clean-catch midstream or straight-cath specimen)
  - significant bacterial counts: ≥10^5 CFU/mL in axw women, ≥10^3 CFU/mL in men, ≥10^2 CFU/mL in sx or catheterizedPts (hydration may falsely dilute counts)
  - pyuria & UCx → sterile pyuria → urethritis, nephritis, renal tuberculosis, foreign body
- **Pregnant women & those undergoing urologic surgery**: screen for axs bacteriuria
- **Blood cultures**: in febrile and possibly complicated UTIs
- **DNA detection/cx for C. trachomatis/N. gonorrhoeae** in high-risk Pts or sterile pyuria
- **1st-void and midstream urine specimens, prostatic expressage, and post–prostatic massage urine specimens** in cases of suspected prostatitis
- **Abdominal CT to r/o abscess in Pts with pyelo who fail to defervesce after 72 h**
- **Urologic workup** (renal U/S w/ PVR, abd CT, voiding cystography) if recurrent UTIs in men

**Treatment of UTIs**

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Empiric treatment guidelines*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystitis</strong></td>
<td>FQ or TMP-SMX PO × 3 d (uncomp.) or × 10–14 d (complicated)</td>
</tr>
<tr>
<td></td>
<td>Asx bacteriuria in pregnancy or prior to urologic surgery → abx × 3 d</td>
</tr>
<tr>
<td><strong>Catheterized Pts</strong></td>
<td>Abx as above and remove or exchange catheter</td>
</tr>
<tr>
<td><strong>Urethritis</strong></td>
<td>Treat for both Neisseria and Chlamydia</td>
</tr>
<tr>
<td></td>
<td>Neisseria: ceftaxime 125 mg IM × 1</td>
</tr>
<tr>
<td></td>
<td>Chlamydia: doxy 100 mg PO bid × 7 d or azithromycin 1 g PO × 1</td>
</tr>
<tr>
<td><strong>Prostatitis</strong></td>
<td>FQ or TMP-SMX PO × 14–28 d (acute) or 6–12 wks (chronic)</td>
</tr>
<tr>
<td><strong>Pyelonephritis</strong></td>
<td>Outpatient: FQ or oral cephal. PO × 14 d</td>
</tr>
<tr>
<td></td>
<td>Inpatient: ceftriaxone IV or FQ PO or aminoglycoside or ampicillin/sulbactam × 14 d</td>
</tr>
<tr>
<td></td>
<td>(Δ IV → PO when Pt improved clinically and afebrile × 24–48 h and then complete 14-d course)</td>
</tr>
<tr>
<td><strong>Renal abscess</strong></td>
<td>Drainage + antibiotics as for pyelonephritis</td>
</tr>
</tbody>
</table>

*When possible, use organism-directed therapy, guided by in vitro susceptibilities, Pt’s past microbiology data and recent antibiotic exposure, or local patterns of drug resistance.*
SOFT TISSUE AND BONE INFECTIONS

CELLULITIS
Infection of superficial and deep dermis and subcutaneous fat

Microbiology (NEJM 2004;350:904; CID 2005;41:1-1373)
- Primarily Strep and Staph, including MRSA; may include GNRs in diabetics/immunosupp.
  Up to 75% of purulent skin/soft tissue infxns, depending on location (rapidly increasing)
  Clinically indistinguishable from MSSA, though may be more aggressive/abscess-forming
  High-risk groups: athletic teams, military, prison, MSM, communities w/ MRSA infxns
  Often TMP-SMX sensitive; variably clindamycin sensitive (may falsely appear sus-
 ceptible on lab testing, requires confirmation w/ D-test; NEJM 2007;357:380)
- Special cases: cat bite P. multocida; dog bite P. multocida, C. canimorsus; penetrating
  injury S Pseudomonas; gardening S Sporothrix; salt water S V. vulnificus (classically
  from raw oysters), Erysipelothrix; fresh water S Aeromonas

Clinical manifestations
- Erythema, edema, warmth, pain (rubor, tumor, calor, dolor)
- Lymphangitis (proximal red streaking) and regional lymphadenopathy
- P multocida rapid onset; C. canimorsus sepsis w/ symmetric, peripheral gangrene
  in splenectomized and other immunosupp. Pts; V. vulnificus hemorrhagic bullae &
  sepsis (especially in cirrhotics); Sporothrix ulcerating nodules
- Toxic shock syndrome can be seen w/ Staph or Strep infxn. Fever, HA, vomiting,
  myalgias, pharyngitis, diarrhea, diffuse rash w/ desquamation. Hypotension, shock.
  BCx may be ...

Diagnosis
- Largely clinical diagnosis; BCx low yield (Se <5% in simple cellulitis) but useful if ...
- Aspirate of bulla or pus from furuncle or pustule may provide dx

Treatment
- Abx: PCNase-resist PCN or 1st-gen. ceph.; if MRSA risk: inPt vanco; outPt S TMP-
  SMX + agent for strep (eg, PCN, amox, clinda) or doxy (active against MRSA
- Limb elevation (erythema may worsen after starting abx b/c bacterial killing → inflamm.)
- Worse outcomes if vasc. insuff., edema, immunosupp., resistant orgs., or deeper infxn

OTHER CUTANEOUS INFECTIONS

Definitions
- Impetigo: superficial purulent lesions, usually on face/extrem, bullae, gold crust
- Erysipelas: raised erythematous lesion with clear demarcation from normal skin
- Folliculitis: superficial inflammation of hair follicles, limited to epidermis
- Furunculosis: infxn of follicle extending to dermis (mult. coalescent furuncles → carbuncle)

Microbiology and treatment (CID 2005;41:1373)
- Impetigo: Strep or Staph; Rx = topical mupirocin or other top. antibacterial usually sufficient
- Erysipelas: mainly Grp A Strep; Rx = PCN unless Staph suspected
- Folliculitis/furunculosis: S. aureus, Pseud. (“hot tub folliculitis”); Rx = warm compress
  ± I&D; abx controversial, give if assoc. cellulitis, lyphangitis, systemic sx, immunosupp.

“DIABETIC FOOT”
Infected neuropathic foot ulcer

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
  monomicrobial or polymicrobial with aerobes + anaerobes
  aerobes = staphylococci, streptococci, enterococci, and GNR (including Pseudomonas)
  anaerobes = anaerobic streptococci, Bacteroides, Clostridium (rare)

Clinical manifestations
- Ulcer with surrounding erythema and warmth ± purulent drainage
- Tenderness may be absent due to neuropathy
- ± Crepitus (indicating gas and ± mixed infection w/ GNR & anaerobes or Clostridium)
- ± Underlying osteomyelitis
- ± Systemic toxicity (fever, chills, leukocytosis, hyperglycemia)
- #1 cause of DM-related hosp. days; #1 proximal cause of non-traumatic amputations in U.S.
Diagnostic studies

• Superficial swabs from ulcers not helpful (only yield superficial colonizing organisms)
• Wound cx (eg, curettage at base of ulcer after débridement) has † Se
• Blood cx should be obtained in all Pts, ⊠ in 10–15%

• Osteomyelitis should always be ruled out (see below for specific imaging tests)

Treatment

• Bedrest, elevation, non–weight-bearing status, wound care, antibiotics

<table>
<thead>
<tr>
<th>Severity of infection</th>
<th>Empiric antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>PCNase-resistant PCN or 1st-gen. ceph. (TMP-SMX if MRSA suspected)</td>
</tr>
<tr>
<td>Chronic non-limb &amp; non-life-threatening</td>
<td>(FQ + clindamycin) or ampicillin-sublactam or ticarcillin-clavulanate or (ceftriaxone + clinda) or ertapenem; add vanco or TMP-SMX or doxycycline if suspect MRSA</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Vanco + one of the following: imipenem or (piperacillin/tazobactam) or (aztreonam + metronidazole)</td>
</tr>
</tbody>
</table>

Surgery: early, aggressive, and repeated surgical débridement; revascularization or amputation may be necessary

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 (used by some to describe involvement of male or female perineum)

Epidemiology

• ↑ risk in diabetes, PVD, alcohol abuse, IVDU, immunosuppression, cirrhosis
• Can also affect healthy individuals

Microbiology

• Group I (often after abd/perineal surgery or trauma): polymicrobial (anaerobe + facultative anaerobe + GNR); often with DM, PVD and other comorbidities.
• Group II (usually extrem): Strep pyogenes + Staph; often healthy w/o obvious portal of entry; up to ½ have toxic shock syndrome (TSS). CA-MRSA can rarely cause monomicrobial necrotizing fasciitis.

Clinical manifestations

• Most common sites: extremities, abdominal wall, and perineum, but can occur anywhere
• Cellulitic skin △s with poorly defined margins + rapid spread + systemic toxicity
• Pain out of proportion to apparent cellulitis; skin hyperesthetic and later anesthetic
• Bullae (serous → hemorrhagic); darkening of skin to bluish-gray → cutaneous gangrene ± crepitus or radiographically visible gas

Diagnostic signs

• Need high degree of clinical suspicion because of nonspecific physical exam
• Aspiration of necrotic center; blood cultures; Gram stain; CK for tissue necrosis
• Imaging studies: MRI → best tissue contrast; plain radiographs → soft tissue gas; CT → extent of infection, soft tissue gas
• Clinical diagnosis enough to initiate urgent surgical exploration
• Microbiologic diagnosis from Gram stain and culture of surgical specimens

Treatment

• Definitive treatment is surgical débridement of necrotic tissue and fasciotomy
• Type I: breadth of GNR coverage determined by host, prev hosp, prev Rx and initial Gram stain; eg, carbapenem or (3rd-gen ceph + amp + [clinda or metronidazole])
• Type II: PCN + clindamycin. If community-acquired MRSA a consideration, + vanco. If TSS, add high dose IVIG.
• Hyperbaric oxygen: adjunct, but should not delay definitive surgical treatment

Prognosis

• Generally fatal if untreated; reported mortality 20–50%

Clostridial Myonecrosis (Gas Gangrene)

Definition

• Life-threatening, fulminant clostridial infection of skeletal muscle
• Usually muscle trauma (penetrating wound or crush injury) + wound contamination w/ clostridial spores
• 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
- Acute onset with sense of heaviness or pain, often at site of trauma or surgery, that rapidly worsens with 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 of discharge: Ig, Gram bacilli w/ blunt ends, 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
- Hyperbaric oxygen

OSTEOMYELITIS

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

Microbiology (NEJM 1997;336:999)

- 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
  - vasc. insuffic. (eg, diabetic foot): polymicrobial (aerobic + anaerobic GPC & GNR)

Clinical manifestations

- Surrounding soft-tissue compromise ± fistula to superficial skin
- Fever, malaise, and night sweats (more common in hematogenous than contiguous)
- Vertebral osteomyelitis (seen in Pts over 50 y): unremitting, focal back pain, usually fever (NEJM 2010;362:1022)

Diagnostic studies (JAMA 2008;299:806)

- Identification of the causative organism is key
- Culture data from tissue (surgical sampling/needle bx), not swabs of ulcers/fistulae
- 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 wks
  - MRI: can detect very early changes (overall Se 90%, Sp 82%; Archives 2007;167:125)
  - CT: can demonstrate periosteal reaction and cortical and medullary destruction
  - CT & MRI very Se but not completely Sp; false – if contiguous focus w/ periosteal reaction, Charcot changes
  - radionuclide imaging: very Se but non-Sp (false – if soft-tissue inflammation)

Treatment

- Antibiotics (based on cx data) × 4–6 wks
- 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, early signs of cord compression, spinal instability, epidural abscess), or infected prosthesis

EPIDURAL ABSCESS

Etiology

- Hematogenous spread (2/3): skin infection, soft tissue (dental abscess), or endocarditis
- Direct extension (1/3): vertebral osteomyelitis, sacral decubitus ulcer, spinal anesthesia or surgery, lumbar puncture
- Risk factors: diabetes, renal failure, alcoholism, IVDU, immunosuppression
- S. aureus most common pathogen

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 or early s/s of cord compression (w/ vertebral osteo and epidural abscess, may see paraplegia 48–72 h after first signs)
**INFECTIONS OF THE NERVOUS SYSTEM**

### Acute Bacterial Meningitis

**Definition**
- Bacterial infection of the subarachnoid space

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em> (30–60%)</td>
<td>Look for distant infection (eg, Osler’s triad = meningitis, pneumonia, endocarditis). Drug-resistant <em>S. pneumoniae</em> (DRSP): ~40% PCN-resistant (even <em>intermed</em> resist problematic for Rx) ~&lt;10% 3rd-gen. ceph.-resistant Vaccine reduces rate of invasive disease</td>
</tr>
<tr>
<td><em>N. meningitidis</em> (10–35%)</td>
<td>Primarily in children and young adults; may be associated with petechiae or purpura. Deficiencies in terminal complement predispose to recurrent meningococcemia &amp; rarely, meningitis. Vaccine rec for all adolescents, college freshmen living in dorm, military recruits, s/p splenectomy, or CS–9 deficiency.</td>
</tr>
<tr>
<td><em>H. influenzae</em> (~5%)</td>
<td>↓ Incidence in children because of <em>H. influenzae</em> type b vaccine. Look for predisposing factors in adults (eg, CSF leak, recent neurosurgical procedure, trauma, mastoiditis).</td>
</tr>
<tr>
<td><em>L. monocytogenes</em> (5–10%)</td>
<td>Seen in elderly, alcoholics, or patients with malignancy, immunosuppression, or iron overload. Outbreaks associated with contaminated milk, cheese, coleslaw, raw vegetables. Despite name, often associated with poly-predominant pleocytosis.</td>
</tr>
<tr>
<td>GNRs (1–10%)</td>
<td>Usually nosocomial or postprocedure or in elderly or immunosuppressed</td>
</tr>
<tr>
<td>Staphylococci (5%)</td>
<td>Seen with indwelling CSF shunt (<em>S. epidermidis</em>) or following neurosurgery or head trauma (<em>S. aureus</em>)</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>Suspect parameningeal focus or CSF leak</td>
</tr>
</tbody>
</table>

**Clinical manifestations** *(NEJM 2006;354:44)*
- **Fever** (77%)
- **Headache** (87%), stiff neck (83%), and 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.

**Recurrent meningitis**
- Bacterial: consider CSF leak, dermal sinus, or other congenital/acquired anatomic defects
- Viral: HSV-2 (causes majority of Mollaret’s meningitis)
- Aseptic (see below): leak from cyst/tumor/lesion with dermoid/epidermoid elements, autoimmune (eg, SLE, Behçet’s), medications

**Physical exam**
- **Nuchal rigidity** (Se 30%), **Kernig’s sign** (Pt supine, hip flexed at 90°, knee flexed at 90°; ᵃ if passive extension of knee results in resistance), **Brudzinski’s sign** (Pt supine and limbs supine; ᵃ if passive neck flexion → involuntary hip and/or knee flexion)
- nb, Kernig’s and Brudzinski’s signs ᵃ in only ~5% of Pts *(CID 2002;33:46)*
- ± Focal neuro findings (~30%; hemiparesis, aphasia, visual field cuts, CN palsies)
- ± Funduscopic findings: papilledema, absent venous pulsations
- ± Rash: maculopapular, petechial, or purpuric

**Diagnostic studies**
- **Blood cultures before abx**
- **WBC count**: >10,000 in 83% of bacterial meningitis
- Consider **head CT** to r/o mass effect before LP if presence of 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 60–90% Se; cx 70–85% Se if LP done prior to abx; repeat LP only if no clinical response after 48 h of appropriate abx, or CSF shunt present
- **Rule of 2s**: CSF WBC >2k, glc <20, & TP >200 has >98% Sp for bacterial meningitis
Typical CSF Findings in Meningitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Appearance</th>
<th>Pressure (cm H2O)</th>
<th>WBC/mm³</th>
<th>Predom type</th>
<th>Glc (mg/dL)</th>
<th>TP (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear</td>
<td>9–18</td>
<td>0–5 lymphs</td>
<td></td>
<td>50–75</td>
<td>15–40</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Cloudy</td>
<td>18–30</td>
<td>100–10,000 polys</td>
<td></td>
<td>&lt;4.5</td>
<td>100–1000</td>
</tr>
<tr>
<td>TB</td>
<td>Cloudy</td>
<td>18–30</td>
<td>&lt;500 lymphs</td>
<td></td>
<td>&lt;4.5</td>
<td>40–200</td>
</tr>
<tr>
<td>Fungal</td>
<td>Cloudy</td>
<td>18–30</td>
<td>&lt;300 lymphs</td>
<td></td>
<td>&lt;4.5</td>
<td>50–100</td>
</tr>
<tr>
<td>Aseptic</td>
<td>Clear</td>
<td>9–18</td>
<td>&lt;300 polys → lymphs</td>
<td></td>
<td>50–100</td>
<td>50–100</td>
</tr>
</tbody>
</table>

- Additional CSF studies depending on clinical suspicion: acid-fast smear and cx, India ink prep, cryptococcal Ag, fungal cx, VDRL, PCR (eg, of HSV, VZV, enteroviral), cytology

**Treatment of Meningitis**

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Empiric treatment guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal adult</td>
<td>Ceftriaxone 2 g IV q12h + Vancomycin 15–20 mg/kg IV q12h (nb, Cftx in case PCN-resistant S. pneumonia; Vanco, which has poorer CSF penetration, in case Cftx-resistant S. Pneumo)</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>Ampicillin + ceftazidime 2 g IV q8h + vancomycin + acyclovir</td>
</tr>
<tr>
<td>CSF shunts, recent neurosurgery, or head trauma</td>
<td>Vancomycin + ceftazidime 2 g IV q8h (NEJM 2010;362:146)</td>
</tr>
</tbody>
</table>

Empiric antibiotics should be started as soon as possible. If concerned about ↑ ICP, obtain BCx → start empiric abx → obtain head CT → LP (if not contraindicated); yield of CSF fluid unlikely to be changed if obtained w/in 4 h of initiation of abx.

**Corticosteroids:** Dexamethasone 10 mg IV q6h × 4 d → ↑ neuro disability & mort. by ~50% w/ S. pneumonia & 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).

**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/ meningococcal meningitis

Precautions: droplet precautions until N. meningitidis is ruled out

When possible, organism-directed Rx, guided by suscept. or local patterns of drug resistance should be used.

**Prognosis**

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

**Aseptic Meningitis**

**Definition**

- Negative bacterial microbiologic data, CSF pleocytosis with appropriate blood and CSF cultures (aseptic meningitis can be neutrophilic, though less common)
- Aseptic – 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
- **Parameningeal focus of infection** (eg, brain abscess, epidural abscess, septic thrombophlebitis of dural venous sinuses, or subdural empyema)
- **TB. fungal, spirochetal** (Lyme, syphilis, leptospirosis), rickettsial, Coxiella, Ehrlichia
- Partially treated bacterial meningitis
- **Medications:** TMP/SMX, NSAIDs, IV Ig and antilymphocyte globulins, penicillin, isoniazid
- **Systemic illness:** SLE, sarcoidosis, Behçet’s, Sjögren’s syndrome, rheumatoid arthritis
- **Neoplasms:** 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
- MTb = antmycobacterial Rx + dexamethasone (NEJM 2004;351:1741)
- Fungal: amphotericin B or lipid formulation, = 5-fluorouracil
VIRAL ENCEPHALITIS

Definition
• Viral infection of the brain parenchyma with evidence of neurologic dysfunction

Etiologies
• 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, West Nile, St. Louis, Japanese, Powassan
  W Nile (NEJM 2005;353:287): mosquito vector; bird reservoir; fever, HA, flaccid paralysis, rash
• 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: bacterial endocarditis, brain abscess, toxoplasmosis, TB, toxins, vasculitis, hematologic malignancies, subdural hematoma, encephalomyelitis (eg, ADEM), paraneoplastic syndromes, seizure, mitochondrial disorders

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

Diagnostic studies (etiologic dx made in only about 25% of cases)
• Lumbar puncture: lymphocytic pleocytosis; PCR for HSV (95% Se & Sp at 2–3 d), VZV, CMV, EBV, HIV, JC, adenovirus, W Nile (~60% Se); W Nile CSF IgM 80% Se
• MRI (CT if MRI unavailable); W Nile w/ thalamic hyperintensity
• EEG (to r/o seizure; findings in encephalitis are non-specific)
• Dilated retinal exam
• Serologies; vaccine history, ELISA or DFA of nasal or resp swabs for respiratory viruses

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

BELL’S PALSY

Definition & Etiology
• Acute, idiopathic, unilateral facial nerve palsy (peripheral CN VII)
• Postulated to be due to reactivation of HSV-1 in cranial nerve VII

Clinical manifestations
• Unilateral facial muscle weakness, hyperacusis, decreased taste/lacrimation/salivation

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

Treatment (NEJM 2007;357:1598 & JAMA 2009;302:985)
• ~80% recover spontaneously by 9 mos (much lower rate in diabetics)
• 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 diabetics, immunosuppressed)
• No conclusive data to support the use of acyclovir or valacyclovir, though often given

ZOSTER

Definition & Etiology
• Zoster – herpes zoster – shingles: acute, unilateral, 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 w/ delay of antiviral Rx

Diagnosis
• Physical appearance of rash; most sensitive is DFA from scraping of unroofed vesicle, Tzanck does not distinguish HSV or VZV, culture insensitive for VZV (unlike HSV)

Treatment
• Rx if can initiate w/in 72 h of skin lesions in normal host or at any time dx in immunosupp.
• Valacyclovir or famciclovir × ~7 d in normal host; acyclovir 10 mg/kg IV q8h if disseminated or high-risk Pt (medically ill, immunosupp., V1 zoster w/ any ophthalmic s/s, etc).
• Prevention: vaccine approved for Pts ≥60 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): infection of normal valves with a virulent organism (eg, S. aureus, group A or other beta-hemolytic strep, Strep pneumo)
- Subacute (SBE): indolent infection of abnl valves w/ less virulent organism (eg, S. viridans)

Predisposing conditions
- Abnormal valve
  - high-risk: prior endocarditis, rheumatic valvarular disease, AoV disease (incl. bicuspid), complex cyanotic lesions, prosthesis (annual risk 0.3–1%)
  - medium-risk: MV disease (including MVP w/ MR or leaflet thickening), HCMP
- Abnormal risk of bacteremia: IVDU, indwelling venous catheters, poor dentition, hemodialysis, DM, intracardiac devices (eg, pacemaker, ICD)

Modified Duke Criteria

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sustained bacteremia by an organism known to cause endocarditis (or 1 BCx or serology for Coxiella)*</td>
<td>• Predisposing condition (see above)</td>
</tr>
<tr>
<td>• Endocardial involvement document by either echocardiogram (vegetation, abscess, prosthetic dehiscence) or new valvular regurgitation</td>
<td>• Fever</td>
</tr>
<tr>
<td>• Vascular phenomena: septic arterial endocardial involvement document by or pulmonary emboli, mycotic aneurysms, ICH, Janeway lesions</td>
<td>• Immune phenomena: RF, GN, Osler’s nodes, Roth spots</td>
</tr>
<tr>
<td>• Immune phenomena: arthritis, glomerulonephritis, new valvular regurgitation</td>
<td>• blood cx not meeting major criteria</td>
</tr>
</tbody>
</table>

Definitive (ie, highly probable): 2 major or 1 major + 3 minor or 5 minor criteria
Possible: 1 major + 1 minor or 3 minor criteria

Microbiology of Endocarditis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Native valve endocarditis (NVE)</th>
<th>Prosthetic valve endocarditis (PVE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early (&lt;60 d post)</td>
<td>Late (≥60 d post)</td>
</tr>
<tr>
<td>S. viridans et al.</td>
<td>36%</td>
<td>13%</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>S. aureus</td>
<td>28%</td>
<td>68%</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>9%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>GNR</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Other</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Culture</td>
<td>11%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Culture ♂ = nutritionally-deficient streptococci, HACEK (Haemophilus parainfluenzae & aphrophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella), Bartonella, Coxiella, Chlamydia, Legionella, Brucella

Clinical manifestations
- Persistent bacteremia: fever (80–90%), chills, 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), stroke, pulmonary emboli (if right-sided), mycotic aneurysm, MI (coronary artery embolism)
- Immune complex phenomena: arthritis, glomerulonephritis, RF, ESR

Physical exam
- HEENT: Roth spots (retinal hemorrhage + pale center), petechiae (conjunctivae, palate)
- Cardiac: murmur (85%), new valvular regurgitation (40–85%) ± thrill (fenestrated valve or ruptured chordae), muffled prosthetic valve sounds. Frequent exams for Δ murmurs.
- 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

- **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 AB; anemia in 90% SBE; ESR, RF, BUN/Cr, UA & 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 clinical suspicion, (ii) high-risk Pt (prosthetic valve, prior IE, CHD), (iii) TTE nondx, (iv) TTE ⊗ but endocarditis strongly suspected, or (v) suspect progressive or invasive infection (eg, persistent bacteremia or fever, new conduction abnl, intracardiac shunt, etc.) (Circ 2005;111:394)

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transthoracic (TTE)</td>
<td>NVE 50–65%</td>
</tr>
<tr>
<td></td>
<td>PVE 36–69%</td>
</tr>
<tr>
<td></td>
<td>Abscess 28–36%</td>
</tr>
<tr>
<td>Transesophageal (TEE)</td>
<td>NVE &gt;90%</td>
</tr>
<tr>
<td></td>
<td>PVE -90%</td>
</tr>
<tr>
<td></td>
<td>Abscess 80–87%</td>
</tr>
</tbody>
</table>


- **Culture ⊗ endocarditis**: may be due to abx prior to BCx. Detailed hx: animal exposure, travel, unpasteurized dairy, etc. Seek ID eval (Med 2005;84:162; NEJM 2007;356:715).

### Treatment

- **Obtain culture data first**
  - ABE → abx should be started promptly after culture data obtained
  - SBE → if Pt hemodynamically stable, abx may be delayed to properly obtain adequate BCx data, especially in the case of prior abx Rx
- **Suggested empiric therapy** (Circ 2005;111:394)
  - native valve ABE: vanco ∪ gent
  - native valve SBE: ceftaxime (or amp if † enterococcus; eg, older z or ob/gyn) + gent
  - PVE: early (<60 d): vanco + cefepime + gent; intermediate (60–365 d): vanco + gent; late (>1 y): vanco + ceftaxime + gent
  - native or prosthetic valve, culture ⊗ depends on host & epi, seek ID consultation
- **Adjust abx regimen and duration based on valve (NVE vs. PVE), organism, & sensitivities**
- Repeat BCx qd until Pt defervesces and BCx ⊗; usually 2–3 d
- Fever may persist up to 1 wk after appropriate abx therapy instituted or in setting of metastatic sites of infection
- Systemic anticoagulation relatively contraindicated given risk of hemorrhagic transformation of cerebral embolic strokes (however, in absence of cerebral emboli, can continue anticoagulation for pre-existing indication)
- **Monitor for complications of endocarditis** (CHF, conduction block, new emboli, etc.) and complications of abx therapy (interstitial nephritis, renal failure, neutropenia, etc.)
- **Duration of Rx**: usually 4–6 wks. With NVE & sx <3 mos → 4 wks of abx; sx >3 mos → 6 wks. Uncomplicated right-sided NVE → 2 wks may be comparable, 2–3 wks of aminoglycoside † = 4 wks for native valve enterococcus (CID 2002;34:159).

### Indications for surgery

- **Try for as many days of abx as possible, in hopes of i incidence of recurrent infection in prosthesis, as well as to improve structural integrity of tissue that will receive prosthesis**
- **Severe valvular dysfunction → refractory CHF**: emergent if refractory cardiogenic shock (ie, despite ICU-level Rx); urgent (w/in days) if persistent refractory HF; elective (w/in wks) if asx severe AL or MR or PVE w/ dehiscence
- **Uncontrolled infxn** (urgent surgery w/in days indicated): periannular abscess (10–40% NVE, 60–100% PVE), fistula, worsening conduction, ↑ veg. size, or persistent sepsis (eg, ⊗ BCx † or fever) after ~1 wk of appropriate IV abx and no drainable metastatic focus or other identifiable cause); also consider for S. aureus, fungal or multiresistant organisms
- **Systemic embolism** (20–50%): L-sided w/ despite approb. abx, either recurrent emboli, >10 mm veg. & prior embolic event, or >15 mm veg.; risk of embolism 4.8/1000 Pt days in 1st wk, 1.7/1000 Pt days thereafter; cerebral emboli no longer considered contraindicated to surgery unless hemorrhage (then ideally wait 1 mo) or severe stroke
- **PVE**, especially with valve dysfunction or dehiscence or S. aureus or GNR infection

### Prognosis

- **NVE**: non-IVDU S. aureus → 30–45% mortality; IVDU S. aureus (typically right-sided) → 10–15% mortality; SBE → 10–15% mortality
- **PVE**: 23% mortality
- Aortic valve worse prognosis than mitral valve
**Endocarditis Prophylaxis**

### Cardiac conditions

| Organism | Prophylaxis
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valve; previous NVE; congenital heart disease (CHD)</td>
<td>Unrepaired or incompletely repaired cyanotic CHD (palliative shunts or conduits), 1st 6 mos after completely repaired CHD using prosthetic material; cardiac transplant recipients w/ valvulopathy. (Prophylaxis no longer rec. in acquired valvular dysfunction, bicuspid AoV, MVP with leaflet thickening or regurgitation, HCMP)</td>
</tr>
</tbody>
</table>

### Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental</td>
<td>Endocarditis associated with manipulation of gingival tissue or periapical region of teeth (eg, extractions, periodontal procedures, implant, root canal, cleanings)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Incision or biopsy of respiratory mucosa (Prophylaxis no longer rec. for GI or GU procedures)</td>
</tr>
</tbody>
</table>

### Regimens

<table>
<thead>
<tr>
<th>Route</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin 2 g 30–60 min before</td>
</tr>
<tr>
<td>Oral</td>
<td>Unable to take PO: amp 2 g IM/IV or cefazolin or cftx 1 g IM/IV</td>
</tr>
<tr>
<td>Oral</td>
<td>PCN-allergic clindamycin 600 mg PO/IM/IV</td>
</tr>
</tbody>
</table>

*Pts should meet both indications (conditions and procedure) to qualify for prophylaxis. (Circ 2007;116:1736)*

---

**BACTEREMIA**

### Etiologies

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

### Microbiology

- 1° infxn/indwelling catheters (CID 2004;39:309): coagulase-neg staphylococci, S. epidermidis and others 31%. Staphylococcus aureus 20%, enterococci 9%, Candida species 9%, E. coli 6%, Klebsiella species 5%
- 2° infxn: dependent on source

### Risk factors for true bacteremia (JAMA 1992;267:1962)

- Pt: fever, shaking chills, IVDU, major comorbidities, immunosupp, indwelling catheter
- Organism: higher risk: S. aureus, β-hemolytic strep, enterococci. GNR, S. pneumoniae, Neisseria lower risk: 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)
- Confirmatory cultures: draw prior to first abx dose in stable Pts if possible
- Factors favoring endocarditis: bacteremia that is high-grade w/o identifiable source, persisting after line removal or drainage of focal source, in hosts at risk for endocarditis, or w/ organisms known to cause IE (Duke criteria); emboli

### Treatment

- 1° infxn: antibiotics based on Gram stain/culture results; tailor abx to sensitivities
- Empirc therapy for GPC: vanco to cover coag-neg staph and MRSA while awaiting sensit.

### Short-Term Central Venous Catheter-Related Blood Stream Infections* (CID 2009;49:1)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Risk of endocarditis in bacteremia</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>~25% (JACC 1993:30:1072)</td>
<td>D/c catheter, TEE to r/o endocarditis; if echo and not immunosupp and no intravasc prosthesis, Rx x 2 wks from first BCx. If no echo obtained, Rx x 4–6 wks. <strong>Preferred abx</strong>: MSSA → nafcilin or oxacillin; MRSA → vancomycin</td>
</tr>
<tr>
<td>Coag-neg staphylococci</td>
<td>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 x 10–14 d and consider antibiotic lock Rx (instill high-concentration abx into catheter lumen for hrs to days)</td>
<td>If catheter d/c, Rx x 5–7 d</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>D/c catheter &amp; Rx x 7–14 d</td>
<td><strong>Coag-neg staphylococci</strong></td>
</tr>
<tr>
<td>GNR</td>
<td>D/c catheter &amp; Rx x 7–14 d Abs based on suscept.</td>
<td><strong>Fungi</strong></td>
</tr>
<tr>
<td>Fungi</td>
<td>D/c catheter &amp; Rx x 14 d from first BCx</td>
<td></td>
</tr>
</tbody>
</table>

*Complicated infections w/ suppurative thrombophlebitis, osteomyelitis, or endocarditis require longer treatment

- 2° infxn: assess for primary source of infection and treat underlying infection. Control essential when possible for cure and preventing recurrent infection.
- Persistently **BCx**: d/c indwelling catheters, consider metastatic infxn, infected thrombosis or infected prosthetic material (joint, vascular graft, pacemaker, 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, though slower than CDC goals
- **Pt is more likely to develop TB disease if:**
  - High-prevalence populations (more likely to be exposed to & infected w/ bacillus): immigrant from high-prevalence area, homeless 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 (more likely to progress from infxn → active disease): HIV + or other immunosupp, chronic renal failure, DM, organ Tx, IVDU, EtOH, malnourished, malignancy, gastrectomy, on biologics (eg, TNF inhibitors, rituximab)

Microbiology and natural history
- Transmission of *Mycobacterium tuberculosis* via small-particle aerosols (ie, droplet nuclei)
- 90% of infected normal hosts will never develop clinically evident disease, 10% will
- Localized disease: healing & calcification or progressive 1st TB (at site of infection)
- Hematogenous spread: latent infection or reactivation TB or progressive disseminated TB
- Two-thirds of clinically evident disease in U.S. due to reactivation

Screening for prior 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 S-TU (0.1 mL) intradermally. Strength PPD intradermally
  - Whom to screen: high-prevalence and high-risk populations (HIV +Pts)
  - How to interpret PPD: determine max diameter of induration by palpation

<table>
<thead>
<tr>
<th>Size of reaction</th>
<th>Persons considered to have + test</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 mm</td>
<td>HIV + or immunosupp (eg, prednisone 15 mg/d × &gt;1 mo) Close contacts with Pt w/ active TB; CXR w/ apical fibrosis c/w TB</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>All other high-risk or high-prevalence populations Recent conversion (+ in induration by &gt;10 mm in last 2 yr)</td>
</tr>
<tr>
<td>&gt;15 mm</td>
<td>Everyone else</td>
</tr>
<tr>
<td>False ☞</td>
<td>Faulty application, anergy (including from active TB), acute TB (2–10 wk to convert), acute non-TB infections, malignancy</td>
</tr>
<tr>
<td>False ☞</td>
<td>Improper reading, cross-reaction with nontuberculous mycobacteria (NTM), BCG vaccination (although usually &lt;10 mm by adulthood)</td>
</tr>
<tr>
<td>Booster effect</td>
<td>↑ induration due to immunologic boost by prior skin test in previously sensitized individual (by TB or NTM, or BCG). Test goes from ☞ → ☞ but does not represent true conversion due to recent infection. 2nd test is Pt’s true baseline. Can be 1 y after initial test.</td>
</tr>
</tbody>
</table>

**NEJM 2002;347:1860**

- **IFN-γ release assays (IGRA):** (Ag-stimulated IFN-γ release from Pt’s T-cells): may be used for screening where you would use PPD; may have ↑ Sp, esp in BCG Rx’d Pts (Annals 2009;149:177). Relies on host immune fxn, so Se still limited in immunosupp. Lack of gold standard for latent TB infxn compromises Se/Sp estimates (J Clin Epi 2010;63:257). One-step test, but more expensive than PPD.

Clinical manifestations
- **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 dis.:** apical infiltrate ± volume loss ± cavitation
- **Miliary TB:** acute or insidious; due to widespread hematogenous dissemination; usually in immunosupp, DM, EtOH, elderly or malnourished. **Constitutional sx** (fever, night sweats, weight loss) usually prominent. Pulm disease w/ small 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-infected & other immunosupp Pts at ↑ risk for infxn, progressive 1st infxn, and reactivation. Risk of progression from infxn to disease ~8–10%/yr. Can occur at any CD4 count, but more likely to disseminate at lower CD4 counts. Reinfction (including w/ drug-resistant strains) is clinically significant, particularly in hyperendemic areas.
- **Multi-drug resistant (MDR)** TB: resistant to isoniazid (INH) and rifampin (RIF)
- Extensively drug resistant (XDR) TB: resistant to INH, RIF, quinolone, & 2nd-line injectables

- Size of reaction Persons considered to have + test
- >5 mm HIV + or immunosupp (eg, prednisone 15 mg/d × >1 mo) Close contacts with 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 yr)
- >15 mm Everyone else
- False ☞ Faulty application, anergy (including from active TB), acute TB (2–10 wk to convert), acute non-TB infections, malignancy
- False ☞ Improper reading, cross-reaction with nontuberculous mycobacteria (NTM), BCG vaccination (although usually <10 mm by adulthood)
- Booster effect ↑ induration due to immunologic boost by prior skin test in previously sensitized individual (by TB or NTM, or BCG). Test goes from ☞ → ☞ but does not represent true conversion due to recent infection. 2nd test is Pt’s true baseline. Can be 1 y after initial test.

(NEJM 2002;347:1860)
**Diagnostic studies for active TB** *(high index of suspicion is key!)*

- **Acid-fast smear** (rapid dx) and **culture** *(↓ Se and allows susceptibility testing) of sputum, bronchoscopy alveolar lavage, pleura, or other clinical specimens; avoid **FQ** if considering dx of TB, as they can compromise dx yield
- **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 and HIV + strongly assoc. with non-apical disease, regardless of timing *(JAMA 2005;293:2740)*

- **Adenosine deaminase (ADA)**: useful in extrapulmonary sites, best validated for ascites

**Preventive therapy** *(JAMA 2005;293:2776; Annals 2009;150:ITC6-1)*

- Appropriate prophylaxis reduces incidence of subsequent disease by 65–75%
- Treat Pts who are ↑ based on screening guidelines listed above, or any exposed HIV + 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 *(NEJM 2010;362:707)*

### Scenario | Regimen
--- | ---
Likely INH-sensitive | INH 300 mg PO qd + pyridoxine 25 mg PO qd × 6–9 mo
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)

- **Monitor for hepatitis**: if aminotransferases ↑ x normal (risk ↓ w/ age; Chest 2005:128:116) or symptomatic -> d/c current anti-TB meds and reevaluate

**Treatment of active tuberculosis** *(JAMA 2005;293:2776; Annals 2009;150:ITC6-1)*

- Isolate Pt
- Use multiple drugs to which organism susceptible (see below); consult ID specialist before empiric Rx for possible MDR-TB (suspect if prior TB Rx, from or travel to area w/ high rates of MDR-TB, exposure to person w/ likely MDR-TB, poor Rx adherence, ↓ HIV)
- 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
- Screen for HIV in all Pts in whom initiating anti-TB Rx; if indicated, should initiate HIV Rx concurrently *(NEJM 2010;362:697)*
- Paradoxical worsening of sx can occur after starting Rx. More common w/ extrapulmonary TB (eg, tuberculosis, 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 immunosuppressants, etc). Must r/o treatment failure (repeat Cx, imaging, etc).

**Antituberculous Medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>300 mg PO qd</td>
<td>Hepatitis, periph neuropathy (risk ↓ by concomitant vt B6), lupus-like synd.</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>600 mg PO qd</td>
<td>Orange discoloration of urine/tears, GI upset, hepatitis, hypersensitivity, fever</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>25 mg/kg PO qd</td>
<td>Hepatitis, hyperuricemia, arthritis</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td>15–25 mg/kg PO qd</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Streptomycin (SM)</td>
<td>15 mg/kg IM qd</td>
<td>Ototoxicity, nephrotoxicity</td>
</tr>
<tr>
<td>Amikacin (AMK)</td>
<td>15 mg/kg IM qd</td>
<td>Ototoxicity, nephrotoxicity</td>
</tr>
<tr>
<td>Quinolone (moxifloxacin)</td>
<td>400 mg PO qd</td>
<td>GI upset</td>
</tr>
</tbody>
</table>

Risk of hepatitis ↓ w/ pre-existing liver disease. Consult ID specialist if moderate to severe liver disease, and consider withholding or replacing PZA or INH.

**Antituberculous Regimens**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td>INH + Rif + PZA + (EMB) until suscept. known</td>
</tr>
<tr>
<td>≥4% INH-resistant in community (includes most of U.S.)</td>
<td>If sensitive to INH &amp; Rif → INH + Rif + PZA × 2 mos, then ↓ INH + Rif × 4 mos</td>
</tr>
<tr>
<td><strong>Extrapulmonary TB</strong></td>
<td>Consult ID specialist</td>
</tr>
<tr>
<td><strong>TB in HIV + patient</strong></td>
<td>Consult ID specialist</td>
</tr>
</tbody>
</table>

*Individualize duration based on host, disease form, and rate of clinical/microbiologic improvement.*
HIV/AIDS

Definition
- AIDS: HIV + CD4 count <200/mm³ or opportunistic infection (OI) or malignancy

Epidemiology
- ~1 million Americans infected w/ HIV; 6th leading cause of death in 25–44 y-old age group
- ~33.4 million individuals infected worldwide
- Routes: sexual (risk is 0.3% for male-to-male, 0.2% for male-to-female, 0.1% for female-to-male transmission), IVDA, transfusions, needle sticks (0.3%), vertical (15–40% w/o ARV)
- Postexposure (risk infxn ~0.3%) ppx: 2 NRTIs (+ PI or NNRTI if high-risk) × 4 wks

Acute retroviral syndrome (ARS)
- Occurs in ~40–90% of Pts ~2–6 wks after infxn; ± ELISA, viral load (2 wks after infxn)
- Mononucleosis-like syndrome (incid mucocut. & neuro manifestations c/w EBV or CMV)

Diagnostic studies
- ELISA for HIV-1 Ab: 1–12 wks after acute infection; >99% Se; 99% Sp; confirmatory after ELISA
- Western blot: 2 bands from diff regions of HIV genome; >99% Se; confirmatory after ELISA
- Rapid preliminary tests: 4 Ab tests; use saliva, plasma, blood, or serum; 99% Se & 96–99% Sp (Annals 2008;149:133); PPV in low prev populations as low as 50%
- PCR (viral load): detects HIV-1 RNA in plasma; assay range is 48–10 million copies/mL ~2% false, but usually low # copies; in contrast, should be very high (~750 k) in 1° infxn
- When testing, obtain informed consent for ELISA, Western, and PCR
- HIV screening is recommended for all Pts in all health care settings (MMWR Sept 22, 2006)
- CD4 count: not a dx test per se, as may be HIV ± and have a normal CD4 count or may have a low CD4 count and not be HIV ±; many other illnesses impact CD4 count

Initial approach to HIV ± Pt
- Document HIV infection (if adequate documentation is not available, repeat dx studies)
- H&P (mucocutaneous, neurocognitive issues, OIs, malignancies, STDs); review all ARVs and other meds
- Lab evaluation: CD4 count, viral load, HIV genotype, CBC w/ diff., Cr, lytes, LFTs, fasting glc and lipids; PPD or IGRA, syphilis serology; toxoplasmosis & CMV IgG; HAV, HBV, HCV serologies; Chlamydia & gonorrhea screening; baseline CXR; Pap smear in

Antiretrovirals (ARVs)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td></td>
</tr>
<tr>
<td>abacavir (ABC; Ziagen)</td>
<td>Class: GI intol. common (less w/ 3TC,ABC,TDF) lipoatrophy (less w/ 3TC,ABC,TDF)</td>
</tr>
<tr>
<td>didanosine (ddI;Videx)</td>
<td>lactic acidosis (less w/ 3TC,ABC,TDF) ABC:hypersensitivity (3%), HLA-B*5701</td>
</tr>
<tr>
<td>emtricitabine (FTC; Emtriva)</td>
<td>AZT: BM suppression (esp macrocytic anemia) ddi &amp; d4T: peripheral neuropathy &amp; pancreatitis</td>
</tr>
<tr>
<td>lamivudine (3TC; Epivir)</td>
<td>ddi &amp; ABC: MI (Lancet 2003;371:1417) TDF: acute or chronic renal insufficiency</td>
</tr>
<tr>
<td>stavudine (d4T; Zerit)</td>
<td></td>
</tr>
<tr>
<td>tenofovir (TDF;Viread)</td>
<td></td>
</tr>
<tr>
<td>zidovudine (AZT; Retrovir)</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
</tr>
<tr>
<td>delavirdine (DLV; Rescriptor)</td>
<td>Class: rash, hepatitis, mixed CYP450 inducer/inhib ETR: rare hypersensitivity NVP: rash and hypersensitivity [risk factors are female, CD4 &gt;250, pregnancy (~ avoids)]</td>
</tr>
<tr>
<td>efavirenz (EFV; Sustiva)</td>
<td></td>
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<tr>
<td>etravirine (ETR; Intellece)</td>
<td></td>
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<tr>
<td>nevirapine (NVP;Viramune)</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td></td>
</tr>
<tr>
<td>amprenavir (APV;Agenerase)</td>
<td>Class: GI intolerance inhibit CYP450 (~ caution w/ simva &amp; lovastatin) type II DM hepatotoxicity</td>
</tr>
<tr>
<td>atazanavir (ATV; Reyzat)</td>
<td></td>
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<tr>
<td>darunavir (DRV; Prezista)</td>
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<tr>
<td>fosamprenavir (FPV;Lexiva)</td>
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<tr>
<td>indinavir (IDV; Crivixan)</td>
<td></td>
</tr>
<tr>
<td>lopinavir/riton. (LPV/r; Kaletra)</td>
<td></td>
</tr>
<tr>
<td>nelﬁnavir (NFV;Viracept)</td>
<td></td>
</tr>
<tr>
<td>ritonavir (RTV; Norvir)</td>
<td></td>
</tr>
<tr>
<td>saquinavir (SQV; Invirape)</td>
<td></td>
</tr>
<tr>
<td>tipranavir (TPV;Aptivus)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
</tr>
<tr>
<td>enfuvirtide (T20; Fuzeon)</td>
<td>injection site reaction</td>
</tr>
<tr>
<td>maraviroc (MVC; Selzentry)</td>
<td>dizziness, hepatotoxicity</td>
</tr>
<tr>
<td>raltegravir (RAL; Isentress)</td>
<td>GI intol, CPK elevation</td>
</tr>
</tbody>
</table>

NRTI, nucleoside/tide reverse transcriptase inhibitor; NNRTI, nonnucleoside RTI; PI, protease inhibitor; FI, fusion inhibitor; EI, entry inhibitor (CCR5 antagonists); II, integrase inhibitor
• ARVs should be given in consultation with HIV specialist as recommendations continue to be in flux, and drug resistance and adverse reactions can be complicated to manage.

• Indications for initiation of ARVs (DHHS guidelines Dec 1, 2009; http://aidsinfo.nih.gov) AIDS-defining illness or CD4 <350/mm³ (also gen rec. at 350–500/mm³; NEJM 2009;360:1815) or pregnancy, HIV-assoc. nephropathy, HBV co-infection requiring Rx, or HIV-assoc. sx (systemic, neurocognitive, mucocutaneous, etc.)

• Genotypic resistance testing recommended for all pts in U.S. starting ARV.


• Maraviroc (E) under study in naïve & Rx’d pts, CCR5 tropism assay (NEJM 2008;359:1429).

• Viral load should ↓ 1 log copies/mL 2–8 wks after starting and be undetectable by 12–24 wks.

• Initiation of ARVs may transiently worsen existing OIs for several wks bl/c immune response (immune reconstitution inflammatory syndrome or IRIS).

• If Rx needs to be interrupted, stop all ARVs to minimize development 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).

### Complications of HIV/AIDS

#### Fever

  - infxn (82–90%): MAC, TB, CMV, early PCP, histoplasmosis, cryptococcosis, coccidioidomycosis, toxoplasmosis, endocarditis
  - noninfectious: lymphoma, drug reaction

- Workup: guided by CD4 count, s/s, epi, & exposures CBC, chem, LFTs, Bx, CXR, UA, mycobact. & fungal cx, meds, chest & abd CT CD4 <100–200 → serum cryptococcal Ag, LP, urinary Histo Ag, CMV PCR or antigenemia pulmonary s/s → CXR; ABG; spumt for bacterial cx, PCP, AFB; bronchoscopy diarrhea → stool for fecal leuks, culture, O&P, AFB; endoscopy abnormal LFTs → abd CT, liver bx cytopenias → BM bx (include aspirate for culture)
Cutaneous
- Seborrheic dermatitis; eosinophilic folliculitis; HSV & VZV infections; prurigo nodularis; scabies; cutaneous candidiasis; eczema; psoriasis; cutaneous drug eruptions
- Dermatophyte infections: proximal subungual onychomycosis (onychomycosis starting at nail bed) virtually 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
- Warts (HPV infection)
- ↑ rates of MRSA skin & soft tissue infections

Ophthalmologic
- CMV retinitis (CD4 count usually <50); Rx: ganciclovir, valganciclovir, ganciclovir ocular insert, foscarnet, or cidofovir (also HZV,VZV)

Oral
- Aphthous ulcers
- Thrush (oral candidiasis): typically associated with burning or pain. Types: exudative (curdlike patches that reveal raw surface when scraped off), erythematous (erythema without exudates), atrophic
- Oral hairy leukoplakia: painless proliferation of papillae. Caused by EBV but not precancerous; adherent white coating usually on lateral tongue.
- Kaposi’s sarcoma

Cardiac
- Dilated CMP; PHT; PI → ↑ risk of MI (NEJM 2007;356:1723; JID 2010;201:318)

Pulmonary

<table>
<thead>
<tr>
<th>Radiographic pattern</th>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Early P. jiroveci (PCP)</td>
</tr>
<tr>
<td>Diffuse interstitial infiltrates</td>
<td>P. jiroveci, TB, viral or disseminated fungal PNA</td>
</tr>
<tr>
<td>Focal consolidation or masses</td>
<td>Bacterial or fungal PNA, TB, Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Cavitary lesions</td>
<td>TB, aspergillosis, and other fungal PNA</td>
</tr>
<tr>
<td></td>
<td>Bacterial PNA (including MRSA, Nocardia, and Rhodococcus)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>TB, bacterial or fungal PNA</td>
</tr>
<tr>
<td></td>
<td>Kaposi’s sarcoma, lymphoma</td>
</tr>
</tbody>
</table>

- *Pneumocystis jiroveci (PCP) pneumonia (CD4 <200)*
  constitutional sx, fever, night sweats, dyspnea on exertion, nonproductive cough
  CXR w/ interstitial pattern, ↑ PO2, ↑ A-a, ↑ LDH, + PCI sputum stain, + beta-glucan
  Rx if F/P >70: TMP-SMX 15–20 mg of TMP/kg, divided tid, avg dose = DS 2 tabs PO tid or [TMP 5 mg/kg PO tid + dapsone 100 mg PO qd] or [clindamycin + primaquine] or atovaquone
  Rx if F/P2 <70 or A-a gradient >35: prednisone (40 mg PO bid, then ↑ after 5 d; start before TMP/SMX; NEJM 1990;323:1444); TMP-SMX 15–20 mg of TMP/kg IV divided q8h or [clindamycin + primaquine] or pentamidine or [trimetrexate + leucovorin]

Gastrointestinal
- *Esophagitis:* Candida, CMV, HSV, aphthous ulcers, pill-induced
  upper endoscopy if no thrush or unresponsive to empiric antifungal therapy
- *Enterocolitis*
  bacterial (usually acute): Salmonella, Shigella, Campylobacter, Yersinia, C. difficile
  protozoal (usually chronic): Giardia, Entamoeba, Cryptosporidium, Isospora, Microsporidium, Cyclospora
  viral (CMV, adenovirus); fungal (histoplasmosis); MAC; AIDS enteropathy
- *GI bleeding:* CMV, Kaposi’s sarcoma, lymphoma, histo
- *Proctitis:* HSV, CMV, Chlamydia (lymphogranuloma venereum), N. gonorrhoeae

Hepatobiliary
- *Hepatitis:* HBV, HCV, CMV, MAC, drug-induced
- *AIDS cholangiopathy:* often in a/w CMV or Cryptosporidium or Microsporidium

Renal
- *HIV-associated* nephropathy (collapsing FSGS); nephrotoxic drugs
Hematologic
- Anemia: ACD, BM infiltration by infxn or tumor, drug toxicity, hemolysis
- Leukopenia
- Thrombocytopenia: bone marrow involvement, ITP
- Globulin

Oncologic
- Non-Hodgkin’s lymphoma: ↑ frequency regardless of CD4 count, but incidence ↑ as CD4 count ↓
- CNS lymphoma: CD4 count <50, EBV-associated
- Kaposis’s sarcoma (HIV+): can occur at any CD4 count, but incidence ↑ as CD4 count ↓ usually occurs in MSM
- Globulin

Endocrine/metabolic
- Hypogonadism
- Adrenal insufficiency (CMV, MAC, or HIV-associated)
- Wasting syndrome
- Lipodystrophy and metabolic syndrome: central obesity, lipoatrophy of extremities, dyslipidemia, hyperglycemia (insulin resistance)
- Lactic acidosis: N/V, abdominal pain; ? mitochondrial toxicity of AZT, d4T, ddI, and, less commonly, other NRTI

Neurologic
- Meningitis: Cryptococcus (p/w HA, MS, CN palsy ± other classic meningal s/s; dx w/ CSF; serum CRAg 90% Se; Rx w/ fluconazole; if opening pressure high, repeat LP qd), bacterial (incl. Listeria), viral (HSV, CMV, HIV seroconversion), tuberculosis, lymphomatous, histoplasmosis, coccidioidomycosis
- Neurosyphilis: meningitis, cranial nerve palsies, dementia
- Space-occupying lesions: may present as headache, focal deficits, or Δ MS

AIDS dementia complex: memory loss, gait disorder, spasticity
- Myelopathy: infection (CMV, HSV), cord compression (epidural abscess, lymphoma), vacuolar (HIV)
- Peripheral neuropathy: meds, HIV, CMV, demyelinating

Disseminated Mycobacterium avium complex (DMAC)
- Clinical manifestations: fever, night sweats, wt loss, hepatosplenomegaly, diarrhea, pancytopenia. May see enteritis and mesenteric lymphadenitis with CD4 <100–150, bacteremia usually when CD4 ≤50
- Treatment: clarithromycin + ethambutol ± rifabutin

Cytomegalovirus (CMV)
- Usually reactivation
- Clinical manifestations: retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis
- Treatment: valganciclovir, ganciclovir, foscarnet, or cidofovir

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Imaging Appearance</th>
<th>Diagnostic studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>enhancing lesions, typically in basal ganglia (can be multiple)</td>
<td>+ Toxoplasma serology (Se = 85%)</td>
</tr>
<tr>
<td>CNS lymphoma</td>
<td>enhancing ring lesion (single 60% of the time)</td>
<td>+ CSF PCR for EBV</td>
</tr>
<tr>
<td>Progressive multifocal leukencephalopathy (PML)</td>
<td>Multiple nonenhancing lesions in white matter</td>
<td>+ CSF PCR for JC virus</td>
</tr>
<tr>
<td>Other: bacterial abscess, nocardiosis, cryptococcoma, tuberculoma, CMV, HIV</td>
<td>Variable</td>
<td>Biopsy</td>
</tr>
</tbody>
</table>

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TICK-BORNE DISEASES

### Distinguishing Features of Tick-Borne Illnesses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rash</th>
<th>↓ WBC</th>
<th>Anemia</th>
<th>↓ Plts</th>
<th>↑ LFTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyme</td>
<td>Erythema migrans</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RMSF</td>
<td>Petechiae, palms/soles</td>
<td>—</td>
<td>—</td>
<td>+++  (late)</td>
<td>+</td>
</tr>
<tr>
<td>Ehrlichia</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Babesia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+++ (hemolytic)</td>
<td>—</td>
</tr>
</tbody>
</table>

### Lyme Disease

**Microbiology**
- Infection with *spirochete* *Borrelia burgdorferi* (consider coinfection w/ *Ehrlichia, Babesia*).
- Transmitted by ticks (*Ixodes, deer tick*); animal hosts include deer and mice.
- Infection usually requires *tick attachment >36–48 h*.

**Epidemiology**
- Most common vector-borne illness in U.S.; peak incidence in summer (May–Aug).
- Majority of cases in NY, NJ, CT, RI, WI, PA, MA, ME, NH, MI, MD, DE, northern CA.
- Humans contact ticks usually in fields with low brush near wooded areas.

**Clinical Manifestations**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (early localized)</td>
<td>Due to local effects of spirochete. General: flu-like illness. Derm (~80%): <em>erythema migrans</em> (EM) — erythematous patches w/ central clearing, size 6–38 cm; lymphocytomas; regional LN.</td>
</tr>
<tr>
<td>Stage 2 (early dissem.)</td>
<td>Due to spirochetaemia and immune response. General: fatigue, malaise, LAN, HA; fever uncommon. Derm: <em>multiple</em> (~100) <em>annular lesions</em> = EM. Rheum (~10%): <em>migratory arthralgias</em> (knee &amp; hip) &amp; myalgias. Neurologic (<del>15%): cranial neuropathies (esp. CN VII), aseptic meningitis, mononeuritis multiplex (</del> pain), transverse myelitis. Cardiac (~8%): heart block, myopericarditis.</td>
</tr>
<tr>
<td>Stage 3 (late persistent)</td>
<td>Due to chronic infection or autoimmune response. Derm: <em>acrodermatitis chronica atrophicans, panniculitis</em>. Rheum (~60%): joint pain, recurrent mono- or oligoarthritides of large joints (classically knee), synovitis. Neurologic: subacute encephalomyelitis, polyneuropathy, dementia.</td>
</tr>
</tbody>
</table>

**Diagnostic studies**
- In general, a clinical diagnosis, but rigorous dx requires confirmatory testing (per IDSA).
- Serology (in right clinical setting): screen w/ ELISA, but false positive due to other spirochetal diseases, SLE, RA, EBV, HIV, etc.; false negative due to early abx therapy or w/in 6 wks of infxn confirm positive ELISA results w/ Western blot (IgGaCSF/IgGaSerum)/(albCSF/albSerum) >1.
- CSF if suspected neuro disease: intrathecal Ab if (IgGaCSF/IgGaSerum)/(albCSF/albSerum) >1.

**Treatment**
- Prophylaxis (best prevention is tick avoidance): protective clothing, tick check q24h, DEET. Chemoprophylaxis w/ doxycycline 200 mg PO qd 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.
- No contraindicated to doxy (eg, preg, allergy, age >8 y).
- If all the above met, NNT still 40–150 to prevent 1 case of Lyme (NEJM 2001;345:79).
- Antibiotics: if clin. manifestations and positive serology (IgG & IgM) tick bite if nonendemic area local or early dissem. w/o neuro or cardiac involvement: *doxycycline* 100 mg PO bid × 2 wks (range: 10–21 d); alternative (eg, pregnancy, doxy allergy): amox 500 mg PO tid or cefuroxime 500 mg PO bid × 14–21 d; neuro (other than isolated CN VII palsy), cardiac, chronic arthritis: *ceftriaxone* 2 g IV daily × 2–4 wks; alternative (eg, severe β-lactam allergy): doxy 100–200 mg PO bid × 2–4 wks.
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias.
ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

Microbiology & Epidemiology
- Infection with *Rickettsia rickettsii* (Gram negative obligate intracellular bacterium)
- Transmitted by *Dermacentor variabilis, Dermacentor andersoni*
- Coastal mid-Atl, New Engl, midwest, northwest, southeast, Canada, Mexico, Central & South America
- Peak incidence spring and early summer

Clinical manifestations (typically within 1 week of tick exposure)
- 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 progress to vasculitis, hypoperfusion/shock, end-organ damage
- Up to 75% mortality if untreated, 5–10% even with Rx (esp. if delayed) (NEJM 2005;353:551)

Diagnosis
- Usually a clinical diagnosis; requires early clinical suspicion given risks of delayed Rx
- During acute illness can dx by examining skin bx for rickettsiae (Se 70%)
- 7–10 d after onset of sx, serology (indirect fluorescent antibody test) turns positive

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

EHRLICHIOSIS/ANAPLASMOSIS

Microbiology
- Infection with Gram negative obligate intracellular bacterium
- Human monocytic ehrlichiosis (*Ehrlichiosis chaffeensis*) (HME)
- Human granulocytic anaplasmosis (*Anaplasma phagocytophilum*) (HGA)

Epidemiology
- Majority of HGA cases found in RI, MN, CT, NY, MD
- Majority of cases of HME found in SE, southcentral, and mid-Atlantic regions of U.S.
- Peak incidence spring and early summer

Clinical manifestations (typically within 3 wks of tick exposure)
- Fever, myalgias, malaise, HA, occasional cough, dyspnea; onset often acute
- Laboratory: leukopenia, thrombocytopenia, renal failure, ↑ aminotransferases, LDH, A↓

Diagnosis
- Start Rx based on clinical suspicion; however, definitive dx requires confirmation
- Acute illness: intraleukocytic morulae on peripheral blood smear (rare); PCR; later: serology

Treatment
- Doxycycline 100 mg PO bid (often × 10 d); should defervesce in <48 h, else reconsider dx

BABESIOSIS

Microbiology & Epidemiology
- Infection with parasite *Babesia microti* (U.S.), *Babesia divergens* (Europe)
- Transmitted by *Ixodes*
- Europe & U.S. (more commonly coastal areas & islands off of MA, NY, RI, CT)
- Peak incidence spring and summer

Clinical manifestations
- 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 include asplenia, ↓ cellular immunity, ↑ age, pregnancy

Diagnosis
- Clinical syndrome + blood smear with intraerythrocytic parasites; PCR; serology (late)

Treatment
- [Atovaquone + azithromycin] (1st line) or [clindamycin + quinine] (for more severe cases)
- Exchange transfusion if parasitemia >10%, severe hemolysis, or SIRS

TULAREMIA

Microbiology
- Infection with *Francisella tularensis* via contact w/ animal tissue, tick/insect bite, or aerosol

Clinical manifestations (typically within 2–10 d of infxn)
- Acute onset of fever, HA, nausea; ulcer w/ black eschar at site of entry; LAN; PNA

Diagnosis & Treatment
- Hazardous to cx. Serology + by 2nd week.
- Streptomycin or gentamicin × 7–14 d
FEVER OF UNKNOWN ORIGIN (FUO)

Definition
- Fever >101°F or >38.3°C on more than one occasion
- Duration ≥3 wks
- No diagnosis despite 1 wk of intensive evaluation

Etiologies
- Differential extensive, but following are some common causes in immunocompetent hosts
  - More likely to be subtle manifestation of common disease than an uncommon disease
  - In Pts with HIV: >75% infectious, rarely due to HIV itself
  - Up to 30% of cases undiagnosed, most spontaneously defervesce

### Category Etiologies of Classic FUO

#### Infection ~30%
- **Tuberculosis**: disseminated or extrapulmonary disease can have normal CXR, PPD, sputum AFB; biopsy (lung, liver, bone marrow) for granulomas has 80–90% yield in miliary disease
- **Intra-abdominal abscess**: hepatic, splenic, subphrenic, pancreatic, perinephric, pelvic, prostatic abscess or prostatitis, appendicitis
- **Endocarditis**: consider HACEK orgs, Bartonella, Legionella, Coxiella
- **Osteomyelitis**: dental abscess, sinusitis, paraspinal abscess
- **CMV, EBV, Lyme, malaria, Babesia, ameba, fungus, typhoid**

#### Connective tissue disease ~30%
- **Giant cell arteritis**: headache, scalp pain, jaw claudication, visual disturbances, myalgias, arthralgias, † ESR
- **Adult-onset Still's disease** (juvenile RA): fevers w/ evanescent truncal rash, pharyngitis, very high ferritin
- **Polyarteritis nodosa, other vasculitides**: RA, SLE, PMR, psoriatic arthritis, reactive arthritis

#### Neoplasm ~20%
- **Lymphoma**: LAN, HSM, † Hct or plt, † LDH; leukemia, myelodyplasia
- **Renal cell carcinoma**: microscopic hematuria, † Hct
- **Hepatocellular, pancreatic, and colon cancers, sarcomas**: Atrial myxomas: obstruction, embolism, constitutional symptoms

#### Miscellaneous ~20%
- Drugs, factitious
- DVT, PE, hematoma
- Thyroiditis or thyroid storm, adrenal insufficiency, pheochromocytoma
- Granulomatous hepatitis (many causes), sarcoidosis
- Familial Mediterranean fever (mutation in pyrin in myeloid cells; episodic fever, peritonitis, pleuritis; † WBC & ESR during attacks); other defects in innate immunity

(Archives 2003;163:545; Medicine 2007;86:26)

### Workup
- History: thorough hx, ROS, PMHx and PSHx, fever curve (consider holding antipyretics), infectious contacts, travel, pets, occupation, meds, TB hx
- Careful physical exam w/ attention to skin/mucous memb., LAN, murmurs, HSM, arthritis
- Laboratory evaluation
  - CBC with diff, lyses, BUN, Cr, LFTs, ESR, CRP, ANA, RF, cryoglobulin, LDH, CK, SPEP
  - BCx × 3 sets (off abx; hold for HACEK, RMSF, Q fever, Brucella), UA, UCx, PPD or IGRA, HIV Ab, PCR, heterophile Ab (specific EBV serologies if neg), CMV antigenemia, Hep serologies if LFTs abnl
- Discontinue unnecessary meds (only 20% w/ med-induced FUO have eos or rash), reassess 1–3 wks after meds d/c'd
- Imaging studies: CXR, chest & abd CT (oral & IV contrast), ? tagged WBC or gallium scan, ? FDG PET, ? echo, † lower extremity Doppler US
- Pursue abnormalities raised by above w/u (eg, bx, MRI, etc., for dx, not screening)
- Duke’s criteria for endocarditis (qv) have good Se & Sp in Pts with FUO
- Consider temporal artery bx if † ESR and age >60, particularly if other s/s
- ? Bone marrow aspirate & bx (esp if signs of marrow infiltration) or liver bx (espec. if † Abds); even w/o localizing s/s, yield may be up to 24% (path and culture) (Archives 2009;169:189-201)
- More likely to make a dx if: continuous fever; duration <180 d, † ESR/CRP/LDH, leukopenia, thrombocytosis, abnl chest CT, or abnl FDG-PET

### Treatment
- Empiric antibiotics are not indicated (unless Pt neutropenic)
- Empiric glucocorticoids not indicated unless strong suspicion for specific rheumatologic dx
- 5–15% of FUO resolve on their own (wks to mos) w/o dx
HYPOPITUITARY SYNDROMES

Panhypopituitarism

- Etiologies
  Primary: surgery, radiation, 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
  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 dysfunction, loss of axillary & pubic hair; wt loss, amenorrhea
  Mass effect: headache, visual field defects, cranial nerve palsies, galactorrhea
  Apoplexy (pituitary hemorrhage or infarction, usually w/ underlying pituitary adenoma): sudden headache, N/V, visual field defects, 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
- Adrenal insufficiency similar to 1° (see “Adrenal Disorders”) except:
  no salt cravings or hypokalemia (b/c aldosterone preserved)
  no hyperpigmentation (b/c ACTH/MSH is not ↑)

↓ TSH
- Central hypothyroidism similar to 1° (see “Thyroid Disorders”) except absence of goiter
  Dx with free T₄ 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

↓ FSH & LH
- Clinical manifestations: ↓ libido, impotence, oligomenorrhea or amenorrhea, infertility
  Physical examination: ↓ testicular size; loss of axillary, pubic, and body hair
  Dx with: ↓ a.m. testosterone or estradiol 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
- Clinical manifestations: severe polyuria, mild hypernatremia (severe if ↓ access to H₂O)
- Diagnostic studies: see “Disorders of Sodium 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)
- Workup: MRI, hormone levels, visual field testing, consider MEN1 (see below) if <10 mm, mass effect, no hormonal effects, can f/up q 3–6 mos

Hyperprolactinemia (NEJM 2010;362:1219)

- 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, but elevated in many situations, ∴ r/o pregnancy or exogenous estrogens, hypothyroidism, dopamine agonists (psych meds, antiemetics), renal failure (T clearance), cirrhosis, stress, ↓ carb diet. MRI to evaluate for tumor, visual field testing if MRI shows compression of optic chiasm.

Treatment

- If asx (no HA or hypogonadal sx) and microadenoma (<10 mm), follow with MRI
- If sx or macroadenoma (≥10 mm) options include:
  - medical with dopamine agonist such as bromocriptine (70–100% success rate) or cabergoline (better tolerated); side effects include N/V, orthostasis, nasal congestion
  - surgical: transsphenoidal surgery (main indications: failed medical Rx, GH co-secretion, 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)

- Physiology: stimulates secretion of insulin-like growth factor 1 (IGF-1)
- Clinical manifestations: ↑ soft tissue, arthralgias, jaw enlargement, headache, carpal tunnel syndrome, macroglisia, 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; pituitary MRI to evaluate for tumor oral glc tolerance test → GH not suppressed to <1 (<0.3 if newer assay) ng/mL by 2 h
- Treatment: surgery, octreotide (long- and short-acting preparations), dopamine agonists (if PRL co-secretion), pegvisomant (GH receptor antagonist), radiation
- Prognosis: w/o Rx there is 2–3/1000 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”

DISORDERS OF MULTIPLE ENDOCRINE SYSTEMS

Multiple Endocrine Neoplasia (MEN) Syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (MENIN inact.)</td>
<td>Parathyroid hyperplasia/adenomas → hypercalcemia (~100% penetrance) Pancreatic islet cell neoplasia (gastrin, VIP, insulin, glucagon) Pituitary adenomas (fxn or non-fxn)</td>
</tr>
<tr>
<td>2A (RET proto-oncogene)</td>
<td>Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Parathyroid hyperplasia → hypercalcemia (15–20%)</td>
</tr>
<tr>
<td>2B (RET proto-oncogene)</td>
<td>Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Mucosal and gastrointestinal neuromas</td>
</tr>
</tbody>
</table>

Polyglandular Autoimmune (PGA) Syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (children)</td>
<td>Mucocutaneous candidiasis, hyperparathyroidism, adrenal insufficiency</td>
</tr>
<tr>
<td>II (adults)</td>
<td>Adrenal insufficiency, autoimmune thyroid disease, diabetes mellitus type 1</td>
</tr>
</tbody>
</table>
## Diagnostic Studies in Thyroid Disorders

<table>
<thead>
<tr>
<th>Test</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Most sensitive test to detect 1° hypothyroidism and hyperthyroidism. May be inappropriately normal in central etiologies. ‘Id by dopamine, steroids, severe illness.</td>
</tr>
<tr>
<td>T₃ and T₄ immunoassays</td>
<td>Measure total serum concentrations (↓ influenced by TBG).</td>
</tr>
<tr>
<td>Free T₄ immunoassay (FT₄)</td>
<td>Free T₄, not influenced by TBG, increasingly popular.</td>
</tr>
<tr>
<td>Thyroxine-binding globulin (TBG)</td>
<td>↑ TBG (↓ T₄): estrogens, OCP, pregnancy, hepatitis, opioids, hereditary. ↓ TBG (↑ T₄): androgens, glucocorticoids, nephritic syndrome, cirrhosis, acromegaly, nicotinic acid, hereditary.</td>
</tr>
<tr>
<td>Reverse T₃</td>
<td>Inactive, ‘Id in sick euthyroid syndrome.</td>
</tr>
<tr>
<td>Thyroid antibodies</td>
<td>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.</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>↑ in goiter, hyperthyroidism and thyroiditis. ↓ in factitious ingestion of thyroid hormone. Tumor marker for thyroid cancer only after total thyroidectomy and radioiodine therapy.</td>
</tr>
<tr>
<td>Radioactive iodine uptake (RAIU) scan</td>
<td>Useful to differentiate causes of hyperthyroidism. ↑ uptake homogeneous – Graves’ disease. heterogeneous – multinodular goiter. ↑ focus of uptake w/ suppression of rest of gland – hot nodule. no uptake – subacutet pain or silent thyroiditis, exogenous thyroid hormone, struma ovarii, recent iodine load, or antithyroid drugs.</td>
</tr>
</tbody>
</table>

### Figure 7-1 Approach to thyroid disorders

![Figure 7-1 Approach to thyroid disorders](LWBK634-c07[01-16].qxd 7/6/10 3:43 PM Page 3 Aptara Inc)
HYPOTHYROIDISM

Etiologies
• Primary (>90% of cases of hypothyroidism; ↓ free $T_4$, ↑ TSH)
  Goitrous: Hashimoto's thyroiditis, recovery after thyroiditis, iodine defic., Li, amiodarone
  Nongoitrous: surgical destruction, s/p radioactive iodine or XRT, amiodarone
• Central (↓ free $T_4$, low/nl or slightly high TSH): hypothalamic or pituitary failure (TSH levels ↓ or
  “normal,” can be slightly ↑ although functionally inactive due to abnormal glycosylation)

Hashimoto’s thyroiditis
• Autoimmune destruction with patchy lymphocytic infiltration
• Associated with other autoimmune disease and may be part of PGA syndrome type II
• $\ominus$ antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) Abs in >90%

Clinical manifestations
• Early: weakness, fatigue, arthralgias, myalgias, headache, depression, cold intolerance, weight gain, constipation, 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 coma
• Hypothermia, hypotension, hypoventilation, $\ominus$ MS

Diagnostic studies
• $\ominus$ FT$_4$, $\ominus$ TSH in primary hypothyroidism; $\ominus$ antithyroid Ab in Hashimoto’s thyroiditis
• May see hyponatremia, hypoglycemia, anemia, ↑ LDL, $\ominus$ HDL, and ↑ CK
• Screening recommended for pregnant women

Treatment of overt hypothyroidism
• Levothyroxine (1.5–1.7 $\mu$g/kg/d), re $\vee$ TSH q5–6wks and titrate until euthyroid; sx can take mos to resolve; lower starting dose (0.3–0.5 $\mu$g/kg/d) if at risk for ischemic heart disease; advise Pt to keep same formulation of levothyroxine; ↑ dose typically needed if: pregnancy (~30% ↑ by wk 8), initiation of estrogen replacement, poor GI absorption (concomitant Fe or Ca suppl., PPI, sucralfate, celiac disease, IBD)
• Myxedema coma: load 5–8 $\mu$g/kg T$_4$ IV, then 50–100 $\mu$g IV qd; b/c peripheral conversion impaired, may also give 5–10 $\mu$g T$_3$ IV q8h if unstable w/ bradycardia and/or hypothermia (T$_3$ more arrhythmogenic); must give empiric adrenal replacement therapy first as $\ominus$ adrenal reserves in myxedema coma

Subclinical hypothyroidism (NEJM 2001:345:260)
• Mild $\ominus$ TSH and normal free $T_4$ with only subtle or no sx
• 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

HYPERTHYROIDISM

• Graves’ disease (60–80% of thyrotoxicosis)
• Thyroiditis: thyrotoxic phase of subacute (granulomatous) thyroiditis or painless (lymphocytic) thyroiditis
• 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 ovari (3% of ovarian dermoid tumors and teratomas), hCG-secreting tumors (eg, choriocarcinoma), large deposits of metastatic follicular thyroid cancer

Graves’ disease (NEJM 2008:358:2594)
• Female: male ratio is 5–10:1, most Pts between 40 and 60 y at dx
• $\ominus$ thyroid antibodies: TSI or TBII (↑ in 80%), anti-TPO, antithyroglobulin; ANA
• Clinical manifestations in addition to those of hyperthyroidism (see below): goiter: diffuse, nontender, w/ thyroid bruit
  Ophthalmopathy (NEJM 2009:360:994): 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
Clinical manifestations of hyperthyroidism

- Restlessness, sweating, tremor, moist warm skin, fine hair, tachycardia, AF, weight loss, ↑ frequency of stools, menstrual irregularities, hyperreflexia, hypermetabolism, and ↓ lid lag (due 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
- TFTs and FT3; ↑ TSH (except in TSH-secreting tumors)
- RAIU scan is very useful study to differentiate causes (see table on page 7-3)
- Rarely need to √ for autoantibodies except in pregnancy (to assess risk of fetal Graves’)
- May see hypercalciuria ± hypercalcemia, ↑ A6, anemia

Treatment
- β-blockers: control tachycardia (propranolol also ↓ T4 → T3 conversion)
- Graves’ disease: either antithyroid drugs or radioactive iodine (NEJM 2005;352:905)
  - 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). For both, need to √ LFTs, WBC, TSH at baseline and in follow-up.
  - radioactive iodine (RAI): preRx selected Pt’s w/ cardiovascular disease or elderly w/ antithyroid drugs to prevent ↑ thyrotoxicosis, stop 3 d before to allow RAI uptake; >75% of treated Pt’s become hypothyroid
- Surgery: less commonly chosen for Graves’, usually for Pt’s w/ obstructive goiter or ophthalmopathy
  - Toxic adenoma or toxic multinodular goiter: RAI or surgery (methimazole preRx for surgery, in selected patients before RAI)
  - Thyroid storm: β-blocker, PTU, lioselective acid or iodide (for Wolff-Chaikoff effect) >1 h after PTU, → steroids (↓ T4 → T3)
  - Ophthalmopathy: can worsen after RAI, prevented by prophylactic Rx w/ prednisone in high-risk patients; can be Rx’d w/ radiation and/or surgical decompression of the orbits

Subclinical hyperthyroidism (NEJM 2001;345:512)
- Mild ↓ TSH and normal free T4, with only subtle or no sx
- ~15% will develop overt hyperthyroidism in 2 y; ↑ risk of AF & osteoporosis
- Rx controversial: consider if TSH <0.1 mU/L and ↑ risk for CV disease or osteopenic

Thyroiditis (NEJM 2003;348:2646)
- Acute: bacterial infection (very rare in U.S. except postpartum)
- Subacute: transient thyrotoxicosis → transient hypothyroidism → normal thyroid fxn
  - painful (viral, granulomatous, or de Quervain’s); fever, ESR; Rx = NSAIDs, ASA, steroids
  - silent (postpartum, autoimmune, or lymphocytic): painless, TPO Abs; if postpartum, can recur with subsequent pregnancies
- Other: amiodarone, palpation thyroiditis, after radiation
- Chronic: Hashimoto’s (hypothyroidism), Riedel’s (idiopathic fibrosis)

Nonthyroidal Illness (Sick euthyroid Syndrome)
- TFT abnormalities in Pt’s w/ severe nonthyroidal illness (… in acute illness, √ TFTs only if ↑ concern for thyroid disease); may have acquired transient central hypothyroidism
- If thyroid dysfunction suspected in critically ill Pt, TFTs alone not reliable; must measure total T4, FT4, & T3
- Mild illness: ↓ T4 → T3 conversion, ↓ T4, ↓ T3; in severe illness: ↓ TBG & albumin, ↑ rT3 ⇒ ↓ T3, ↑ degradation of T4, central ↓ TSH ⇒ ↓ FT4, ↓ T4, ↓ FT3, ↓ TSH
- Recovery phase: ↑ TSH followed by recovery of T4 and then T3
- Replacement thyroxine not helpful or recommended for critically ill Pt’s w/ ↓ T3 and T4 unless other sx/s of hypothyroidism

Amiodarone and Thyroid Disease

Risk of thyroid dysfunction is 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 T4 & T3
  2. Inhibits T4 → T3 conversion
  3. Direct/immune-mediated thyroid destruction
• Normal individuals: \( T_4 \) then escape Wolff-Chaikoff effect and have \( T_3 \), \( T_4 \), \( TSH \); then \( TSH \) normalizes (after 1–3 mos).
• Susceptible individuals (eg, subclinical Hashimoto’s, \( \sim \) anti-TPO) do not escape effects.
• Treatment: thyroxine to normalize \( TSH \); may need larger than usual dose.

**Thyroid Nodules**

- **Prevalence**: 5–10% (50–60% if screen with U/S), ~5% malignant.
- **Features associated with risk of malignancy**: age <20 or >70 y, male sex, h/o neck XRT, hard and immobile mass, cold nodule on RAIU, large size, worrisome U/S findings (hypoechoic, solid, irregular borders, microcalcifications, central blood flow), cervical LAN.
- **Features associated with benign dx**: FHx of autoimmune thyroid disease or goiter, presence of hypothyroidism or hyperthyroidism, nodule tenderness.
- **Screening U/S** recommended for those with FHx of MEN2 or medullary thyroid cancer, personal h/o neck XRT, palpable nodules, or multinodular goiter.
- **FNA** for nodules >10 mm (~8 mm if irregular borders), microcalcifications, or central vasculature; FNA any nodules in Pts with h/o neck XRT or FHx of MEN2 or MTC.

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

- **Type 1** – underlyng multinodular goiter or autonomous thyroid tissue. Pathophysiology: Jod-Basedow effect (iodine load \( \rightarrow \) synthesis of \( T_4 \) and \( T_3 \) in autonomous tissue). Diagnostic studies: \( \uparrow \) thyroid blood flow on Doppler U/S; treatment: methimazole.
- **Type 2** – destructive thyroiditis. Pathophysiology: \( \uparrow \) release of preformed \( T_4 \) & \( T_3 \) \( \rightarrow \) hyperthyroidism \( \rightarrow \) recovery. Diagnostic studies: \( \uparrow \) flow on Doppler U/S; treatment: steroids.
- **Type 1 vs. 2** often difficult to distinguish and Rx for both initiated (JCEM 2001;86:3).
ADRENAL DISORDERS

Cushing’s Syndrome (Hypercortisolism)

Definitions
• Cushing’s syndrome – cortisol excess
• Cushing’s disease – Cushing’s syndrome 2 to pituitary ACTH hypersecretion

Etiologies of hypercortisolism
• Most common cause is iatrogenic Cushing’s syndrome caused by exogenous glucocorticoids
• Cushing’s disease (60–70%): 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, pheochromocytoma

Clinical manifestations
• Nonspecific: glucose intolerance or DM, HTN, obesity, oligomenorrhea, osteoporosis
• More specific: central obesity w/ extremity wasting, dorsocervical fat pads, rounded facies
• Most specific: spontaneous bruising, proximal myopathy, wide striae, hypokalemia
• Other: depression, insomnia, psychosis, impaired cognition, facial plethora, acne, hirsutism, hyperpigmentation

Figure 7-3 Approach to suspected Cushing’s syndrome

Suspect Cushing’s Syndrome Clinically

3 Options for Screening for Hypercortisolism:
24-h UFC or Overnight 1 mg DST or 11 pm Salivary Cortisol

- and low clinical suspicion
- or but high clinical suspicion
- but in Pt w/ acute illness, EtOH, depression

Not Cushing’s

✓ (or repeat) 24-h UFC

re ✓ after resolution of illness or ✓ combined

48-h LD DST + CRH

Differentiate level of defect by checking serum ACTH

? Pseudo-Cushing’s

ACTH-dependent

normal or high

48-h or O/N high-dose DST
(or CRH test)

Will not suppress (or (○) stim)

Will suppress (or (○) stim)

undifferentiated

ACTH-independent

adrenal CT or MRI

ACTH-dependent

normal or high

48-h or O/N high-dose DST
(or CRH test)

Will not suppress (or (○) stim)

Will suppress (or (○) stim)

differentiated

Cushing’s disease

Adrenal tumor

ACTH-independent

Ectopic ACTH

CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; UFC, urinary free cortisol

Overnight 1 mg DST – give 1 mg at 11 pm, ✓ 8 am serum cortisol (suppression if < 1.8 μg/dL); 1–2% false + (primarily used to evaluate subclinical Cushing’s in adrenal “incidentalomas”) (JCEM 2008;93:1526)

11 pm 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 (suppression 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 pm; ✓ 9 am 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) (Endo & Metab Clin North Am 2005;34:385)
Treatment of Cushing’s syndrome
- Surgical resection of pituitary adenoma, adrenal tumor, or ectopic ACTH-secreting tumor
- If transsphenoidal surgery (TSS) not successful
  - Pituitary XRT, medical adrenalectomy w/ mitotane, or bilateral surgical adrenalectomy; ketoconazole (metyrapone) to ↓ cortisol
- Glucocorticoid replacement therapy × 6–36 mos after TSS (lifelong glucocorticoid + mineralocorticoid replacement if medical or surgical adrenalectomy)

Hyperaldosteronism

Etiologies
- **Primary** (adrenal disorders, renin independent increase in aldosterone)
  - Adrenal hyperplasia (70%), adenoma (**Conn’s syndrome**, 25%), carcinoma (5%)
  - glucocorticoid-removable 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)

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
- 5–10% of Pts w/ HTN; ∴ screen if HTN/hypokalemia, adrenal mass, or refractory HTN
- Screening: aldosterone (~15–20 ng/dL) and plasma aldosterone:renin ratio (~20 if 1°)
  - obtain 8 a.m. paired values (off spironolactone & eplerenone for 6 wks); 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 ald on sodium load)
  - oral salt load (+ KCl) × 3 d, 24-h urine (~12 μg/d while Na >200 mEq/d) or 2L NS over 4 h, measure ald on end of infusion (~12 if ald >5 ng/dL)

Figure 7-4 Approach to suspected hyperaldosteronism

(Adapted from Trends in Endocrine Metabolism 1999;5:97)
Treatment
• Adenoma or carcinoma → surgery
• Hyperplasia → spironolactone or eplerenone; GRA → glucocorticoids ± spironolactone

ADRENAL INSUFFICIENCY

Etiologies
• Primary – adrenocortical disease – Addison’s disease
  autoimmune: isolated or in assoc w/ PGA syndromes (see table on page 7-2)
  infection: TB, CMV, histoplasmosis
  vascular: hemorrhage (usually in setting of sepsis), thrombosis, and trauma
  metastatic disease: (90% of adrenals must be destroyed to cause insufficiency)
  deposition diseases: hemochromatosis, amyloidosis, sarcoidosis
  drugs: ketoconazole, 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 wks of “suppressive doses”; dose effect variable; ≤10 mg prednisone daily chronically can be suppressive)
  megestrol (a progestin with some glucocorticoid activity)

Clinical manifestations (NEJM 1996;335:1206)
• 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), hyperpigmentation (seen in creases, mucous membranes, pressure areas, nipples), hyperkalemia
• Secondary only: other manifestations of hypopituitarism (see “Pituitary Disorders”)

Diagnostic studies
• Early a.m. serum cortisol: <3 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 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 secondary b/c adrenals still able to respond; early a.m. cortisol can be used rather than post-stim value in these cases)
• Low-dose (1 μg) cort stim: ? more Se than high-dose test (controversial)
• Other tests to evaluate HPA axis (w/ guidance by endocrinologist): insulin-induced hypoglycemia (measure serum cortisol response); metyrapone (blocks cortisol synthesis and therefore stimulates ACTH, measure plasma 11-deoxycortisol and urinary 17-hydroxy cortisol steroid 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)
• Perform ACTH stim ASAP in hypotensive Pt suspected to have absolute adrenal insuffic.
• Initiate corticosteroids early: use dexamethasone 2–4 mg IV q6h + fludrocortisone 50 μg daily prior to ACTH stim; change to hydrocortisone 50–100 mg IV q6–8h once test completed.
• Rx of relative adrenal insufficiency controversial (see “Sepsis”).

Treatment
• Acute insufficiency: volume resuscitation w/ normal saline + hydrocortisone IV as above
• Chronic insufficiency
  Hydrocortisone: 20–30 mg PO qd (½ a.m., ½ early p.m.) or prednisone ~5 mg PO qam
  Fludrocortisone (not needed in 2° adrenal insufficiency): 0.05–0.1 mg PO qam
  back-up dexamethasone 4 mg IM prefilled syringe given to Pt for emergency situations
**PHEOCHROMOCYTOMA**

**Clinical manifestations (five Ps)**

- **Pressure** (hypertension, paroxysmal in 50%, severe and resistant to therapy)
- **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

- Emotional stress does not trigger paroxysms, but abdominal manipulation can trigger catecholamine release; some reports of IV contrast causing paroxysms
- Associated with MEN 2A/2B, Von Hippel Lindau, neurofibromatosis type 1, familial paraganglioma (mutations in succinate dehydrogenase gene, B, C and D)

**Diagnostic studies**

- 24-h urinary fractionated metanephrines & catechols: 90% Se, 98% Sp (JCEM 2003;88:553).
- Screening test of choice if low-risk (as false + with severe illness, renal failure, OSA, labetalol due to assay interference, TCAs, medications containing sympathomimetics)
- Plasma free metanephrines: 99% Se, 89% Sp (JAMA 2002;287:1427). Screening test of choice if high-risk, but ↑ rate of false + in low-preval. population.
- Adrenal CT or MRI; consider MIBG scintigraphy if CT/MRI, PET can be used to localize nonadrenal mass, but usually easy to find
- Consider genetic testing in appropriate circumstances (bilateral, young Pt, FHx, extra-adrenal)

**Treatment**

- α-blockade first (usually phenoxybenzamine) ± β-blockade (often propranolol) → surgery

---

**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
- Nonadrenal mass: renal, pancreatic, gastric, artifact

**Workup** (NEJM 2007;356:601)

- 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 and catecholamines or plasma free metanephrines.
- Rule out metastatic cancer and infection by history or CT-guided biopsy if suspicious (in Pts w/ h/o cancer, ~50% of adrenal incidentalomas are malignant)
- CT and MRI characteristics may suggest adenoma vs. carcinoma
  - Benign features: size <4 cm; smooth margins, homogeneous 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 >4 cm or ↑ size on repeat scan; irregular margins, heterogeneous, dense, or vascular appearance; h/o malignancy or young age (incidentaloma less common). Such incidentalomas warrant FNA biopsy, repeat scan in 3 mos, or resection.
CALCIUM DISORDERS

Laboratory Findings in Calcium Disorders

<table>
<thead>
<tr>
<th>Ca</th>
<th>PTH</th>
<th>Disease</th>
<th>PO4</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td></td>
<td>Hyperparathyroidism (1° and 3°)</td>
<td></td>
</tr>
<tr>
<td>↑ ✧</td>
<td></td>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td>↑</td>
<td>✧</td>
<td>Vitamin D excess</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✧</td>
<td>Milk-alkali syndrome, thiazides</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone turnover</td>
<td></td>
</tr>
<tr>
<td>↓</td>
<td>✧</td>
<td>Pseudohypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✧</td>
<td>Vitamin D deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic renal failure (2° hyperpara)</td>
<td></td>
</tr>
<tr>
<td>var.</td>
<td></td>
<td>Acute calcium sequestration</td>
<td>var.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperparathyroidism</td>
<td></td>
</tr>
</tbody>
</table>

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 \times [4 - albumin (gm/dL)])
- Alkalosis will cause more Ca to be bound to albumin (Ca may be normal but ⊠ ICa)
- Best to measure ionized Ca directly

Hypercalcemia

Etiologies of Hypercalcemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism (HPT)</td>
<td>1°: adenoma (85%), hyperplasia (15–20%; spont. vs. MEN 1/2A), carcinoma (&lt;1%) 3°: after long-standing 2° hyperparathyroidism (as in renal failure) → autonomous nodule develops, requires surgery Lithium → ↑ PTH</td>
</tr>
<tr>
<td>Familial hypocalciuric hypercalcemia (FHH)</td>
<td>Inact. mut. in Ca-sensing receptor in parathyroid and kidney → ↑ Ca set point; ± ↑ PTH (and less ↑ than in 1° hyperpara.) Acquired form due to autoAb vs. Ca-sensing receptor (rare) FE&lt;sub&gt;24&lt;/sub&gt; [(24h U&lt;sub&gt;Ca&lt;/sub&gt;/serum Ca) / (24h U&lt;sub&gt;Cr&lt;/sub&gt;/serum Cr)] &lt; 0.01</td>
</tr>
<tr>
<td>Malignancy</td>
<td>PTH-related peptide (PTHrP) → humoral ↑ Ca of malignancy (e.g., squamous cell cancers, renal, breast, bladder) Cytokines &amp; ↑ 1,25(OH)&lt;sub&gt;2&lt;/sub&gt;D&lt;sub&gt;3&lt;/sub&gt; (eg, hematologic malignancies) Local osteolysis (eg, breast cancer, myeloma)</td>
</tr>
<tr>
<td>Vitamin D excess</td>
<td>Granulomas (sarcoïd, TB, histo, Wegener’s) → ↑ 1-DOH → ↑ 1,25(OH)&lt;sub&gt;2&lt;/sub&gt;D&lt;sub&gt;3&lt;/sub&gt; Vitamin D intoxication.</td>
</tr>
<tr>
<td>✧ Bone turnover</td>
<td>Hyperthyroidism, immobilization + Paget’s disease, vitamin A</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Thiazides; Ca-based antacids or massive dairy consumption (milk-alkali syndrome); adrenal insufficiency</td>
</tr>
</tbody>
</table>

Among inPts w/ hypercalcemia: 45% have cancer, 25% 1° HPT, 10% CKD → 3° HPT

Clinical manifestations (“bones, stones, abdominal groans, and psychic moans”)
- Hypercalcemic crisis (usually when Ca >13–15): polyuria, dehydration, mental status Δs. 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.
- Calciphylaxis (calcific uremic arteriopathy): calcification of media of small- to med-sized blood vessels of dermis & SC fat → ischemia and skin necrosis (NEJM 2007;356:1049). Associated w/ uremia, ↑ PTH, ↑ Ca, ↑ PO<sub>4</sub>, and ↑ (Ca × PO<sub>4</sub>) product. Dx by biopsy. Rx: aggressive wound care, keep Ca & PO<sub>4</sub> nl (goal <55), avoid vitamin D & Ca suppl. IV Na thiosulfate & parathyroidectomy controvers. Overall portends a poor prognosis
Diagnostic studies
- Hyperparathyroidism and malignancy account for 90% of cases of hypercalcemia
  - Hyperparathyroidism more likely if sx or chronic hypercalcemia
  - Malignancy more likely if acute or sx; malignancy usually overt or becomes so in mos
- Ca, alb, ICa, PTH (may be inappropriately normal in 1° hyperparathyroidism & FHH), PO4:
  - Based on results consider checking PTHrP, 25-(OH)D, 1,25-(OH)2D, A, UCa, SPEP, UPEP, ACE, CXR/CT, mammogram

Acute Treatment of Hypercalcemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Onset</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline (4–6 L/d)</td>
<td>h</td>
<td>during Rx</td>
<td>Natriuresis → ↑ renal Ca excretion</td>
</tr>
<tr>
<td>± Furosemide</td>
<td>h</td>
<td>during Rx</td>
<td>Use only if volume overloaded.</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>1–2 d</td>
<td>var.</td>
<td>Inhibit osteoclasts, useful in malignancy; caution in renal failure; risk of jaw osteonecrosis</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>h</td>
<td>2–3 d</td>
<td>Quickly develop tachyphylaxis</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>days</td>
<td>days</td>
<td>? Useful in some malign, granulomatous disorders &amp; vitamin D intox.</td>
</tr>
</tbody>
</table>

(Acute Treatment of Hypercalcemia) (NEJM 2005;352:373)

Treatment of asymptomatic 1° HPT (JCEM 2009;94:335)
- Surgery if: age <50 y; serum Ca >1 mg/dL >ULN; CrCl <60 mL/min, DEXA T score <-2.5
- If not yet candidate for surgery: ✓ serum Ca & Cr annually and BMD q1–2y
  - No data yet to support use of bisphosphonates, estrogen, SERMs, or calcimimetic

Hypocalcemia

Etiologies of Hypocalcemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoparathyroidism (NEJM 2008;359:391)</td>
<td>Sporadic; familial (PGA 1, activating Ca-sensing receptor mutations; see 7-2); iatrogenic (s/p thyroid, cancer surgery, neck irradiation); Wilson’s, hemochromatosis; hypoMg (↓ secretion and effect); activating Ca-sensing receptor autoAb</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Ia and Ib: PTH end organ resistance (↓ serum PTH) Ia: skeletal abnormalities, short stature, &amp; retardation Pseudopseudohypoparathyroidism = la syndrome but nl Ca &amp; PTH</td>
</tr>
<tr>
<td>Vitamin D deficiency or resistance</td>
<td>Nutritional/sunlight deprivation; GI disease/fat malabs.; drugs (anticonvulsants, rifampin, ketoconazole, 5-FU/leucovorin); genetic (1α-hydroxylase, VDR mutations)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>↓ 1,25-(OH)2D production, ↑ PO4 from ↓ clearance</td>
</tr>
<tr>
<td>Accelerated net bone formation</td>
<td>Postparathyroidectomy, Rx of severe vit D deficiency or Paget’s disease (NEJM 2006;355:593), osteoblastic metastases</td>
</tr>
<tr>
<td>Calcium sequestration</td>
<td>Pancreatitis, citrate excess (after blood transfusions), acute ↑ PO4 (ARF, rhabdomyolysis, tumor lysis), bisphosphonates</td>
</tr>
</tbody>
</table>

Clinical manifestations
- Neuromuscular irritability: perioral paresthesias, cramps, Chvostek’s (tapping facial nerve → contraction of facial muscles), Trousseau’s (inflation of BP cuff → carpal spasm), laryngospasm; irritability, depression, psychosis, ↓ ICP, seizures, ↓ QT
- Rickets and/or osteomalacia: chronic ↓ vit D → ↓ Ca, ↓ PO4 → ↓ 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)2D) & osteitis fibrosa cystica (due to ↓ PTH)

Diagnostic studies
- Ca, alb, ICa, PTH, 25-(OH)D, 1,25-(OH)2D (if renal failure or rickets), Cr, Mg, PO4, A, UCa

Treatment (also treat concomitant vitamin D deficiency)
- Symptomatic: intravenous Ca gluconate (1–2 g IV over 20 mins) + calcitriol (most effective in acute hypocalcemia, but takes hrs to work) + Mg (50–100 mEq/d)
- Asymptomatic and/or chronic oral Ca (1–3 g/d) & vitamin D (eg, ergocalciferol 50,000 IU PO q wk × 8–10 wks). In chronic hypopara., calcitriol is needed, consider also thiazide
- Chronic renal failure: phosphate binder(s), oral Ca, calcitriol or analog (calcimimetic may be needed later to prevent hypercalcemia)
DIABETES MELLITUS

**Definition** (Diabetes Care 2003;26:333 & 2009:32:1327)

- Fasting glc ≥126 mg/dL × 2; random glc ≥200 mg/dL × 2 or × 1 if severe hyperglycemia and acute metabolic decompensation; or 75 g OGTT w/ 2-h glc ≥200 mg/dL (routine OGTT not recommended)
- Blood glc higher than normal, but not frank DM ("prediabetics," ~40% U.S. population)
- Impaired fasting glc (IFG): 100–125 mg/dL
- Impaired glc tolerance (IGT): 140–199 mg/dL 2 h after 75 g OGTT
- Preventing progression to DM: diet & exercise (58% ↓), metformin (31% ↓), TZD (60% ↓)
- ↑ HbA1C (no accepted criterion yet, ≥6.5% recommended by int’l expert cmte)

**Categories**

- **Type 1**: islet destruction; absolute insulin deficiency; ketosis in absence of insulin prevalence 0.4%; usual onset in childhood but can occur throughout adulthood; ↑ risk ifFHx, HLA associations; anti-GAD, anti-islet cell & anti-insulin autoantibodies
- **Type 2**: insulin resistance + relative insulin deficiency prevalence 8%; onset generally later in life; ↑ risk ifFHx; no HLA associations
- **Type 2 DM p/w DKA** ("ketosis-prone type 2 diabetes"): most often seen in nonwhite,↑ anti-GAD Ab, eventually may not require insulin (Endo Rev 2008:29:292)
- **Mature-Onset Diabetes of the Young (MODY)**: autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (NEJM 2001:345:971)
- **Secondary causes of diabetes**: exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF, resection), endocrinopathies (Cushing’s disease, acromegaly), gestational, drugs (protease inhibitors, atypical antipsychotics)

**Clinical manifestations**

- Polyuria, polydipsia, polyphagia with unexplained weight loss; can also be asymptomatic

### Diabetes Treatment Options

**Diet**

- Type 1: carb counting; Type 2: wt reduction diet + exercise

**Metformin**

- ↓ hepatic gluconeogenesis, ↓ HbA1C ~1.5%
- Wt neutral, N/V & diarrhea, rare lactic acidosis
- Contraind. in renal (eg, Cr >1.5) or liver failure
- Consider first-line Rx w/ lifestyle mod. for all T2D w/ HbA1C ≥7%

**Sulfonylureas (SU)**

- ↑ insulin secretion, ↓ HbA1C ~1.5%. Hypoglycemia, wt gain.

**Thiazolidinediones (TZD)**

- (PPARγ agonists)
  - ↑ insulin sens. in adipose & muscle, ↓ HbA1C ~1%
  - Wt gain, hepatotoxicity, fluid retention & CHF, bone fractures
  - but not w/ pioglitazone (JAMA 2007:298:1180)
  - Contraind. in liver disease and NYHA III–IV, monitor LFTs

**Glinides**

- ↑ insulin secretion, ↓ HbA1C ~1.5%
- Hypoglycemia (but less than w/ SU), wt gain

**Exenatide**

- ↑ gluc-depend insulin secretion (GLP-1 agonist), ↓ HbA1C ~0.5%
- Wt loss, N/V & diarrhea (30–45%), pancreatitis (rare)

**α-glucosidase inhibitor**

- ↓ intestinal CHO absorption, ↓ HbA1C 0.5–0.8%. GI distress (gas).

**Pramlintide**

- Delays gastric emptying & ↓ glucagon, ↓ HbA1C 0.5%
- To be used as adjunctive Rx w/ insulin in T1D or T2D

**DPP-4 inhibitor**

- Blocks degrad. of GLP-1 & GIP → ↑ insulin, ↓ HbA1C ~0.5%

**Insulin**

- Hypoglycemia, wt gain

(Additional T1D options:
- insulin pump, pancreatic or islet cell transplant)

- Generally combine intermed./long-acting (NPH or glargine) and short/rapid-acting (regular or lispro) insulin for all T1D.
- In T2D, consider starting if mono oral Rx not adequate (espec if HbA1C high) and definitely start if combo oral Rx not adequate.

### Insulin Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Side effects/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro, aspart</td>
<td>5–15 min</td>
<td>60–90 min</td>
<td>2–4 h</td>
<td>Give immediately before meal</td>
</tr>
<tr>
<td>Regular</td>
<td>30–60 min</td>
<td>2–4 h</td>
<td>5–8 h</td>
<td>Give ~30 min before meal</td>
</tr>
<tr>
<td>NPH</td>
<td>1–2 h</td>
<td>4–8 h</td>
<td>12–18 h</td>
<td>Can cause protamine Ab prod</td>
</tr>
<tr>
<td>Glargine</td>
<td>2 h</td>
<td>No peak</td>
<td>20–24 h</td>
<td>Once daily (AM or PM)</td>
</tr>
</tbody>
</table>

(NEJM 2005:352:174)
Complications

- Retinopathy: non-proliferative ("dot & blot" and retinal hemorrhages, cotton-wool/protein exudates); proliferative: neovascularization, vitreous hemorrhage, retinal detachment, blindness; treatment: photocoagulation, surgery
- Nephropathy: microalbuminuria → proteinuria → nephrotic syndrome → renal failure due to 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 (NEJM 1993;329:1456 & 35.1941; Lancet 1997;349:1787) or ARBs (NEJM 2001;345:851, 861), low-protein diet, dialysis, or transplant
- Neuropathy: symmetric peripheral: symmetric distal sensory loss, paresthesias, motor loss; autonomic: gastroparesis, constipation, neurogenic bladder, erectile dysfunction, 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 2009;32:193 & S1-513)

- Microalbuminuria screening yearly with spot microalbumin/Cr ratio, goal <30 mg/g
- BP <130/80; LDL <100, TG <150, HDL >40; benefit of statins even w/o overt CAD (Lancet 2003;361:2005 & 2004;364:685); ASA if age >50 (6) or other cardiac risk factors (Circ 2010;121:2694)
- Dilated retinal exam yearly; comprehensive foot exam qy (Diabetes Care 2009;32:51, 513)

Management of hyperglycemia in inpatients

- Identify reversible causes/exacerbaters (dextrose IVF, glucocorticoids, postop, ↑ carb diet)
- Dx studies: BG fingersticks (fasting, qAC, qHS; or Q6h if NPO), HbA1C
- Treatment goals: avoid hypoglycemia, extreme hyperglycemia (<180 mg/dL)
- Modification of outPt treatment regimen: in T1D, do not stop basal insulin (can cause DKA). In T2D-stopping oral DM meds generally preferred to avoid hypoglycemia or med interaction (except if short stay, excellent outPt cns, no plan for IV contrast, nl diet)
- InP insulin: can use outPt regimen as guide; if insulin naive: 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 cns or strong reason for Δ. Arrange early insulin and glucometer teaching, prompt outP follow-up.

Diabetic Ketoacidosis (DKA)

Precipitants (the Is)

- Insulin defic. (ie, failure to take enough insulin): Iatrogenesis (glucocorticoids)
- Infection (pneumonia, UTI) or Inflammation (pancreatitis, cholecystitis)
- Ischemia or Infarction (myocardial, cerebral, gut): Intoxication (alcohol, drugs)

Pathophysiology

- Occurs in T1D (and in ketosis-prone T2D); ↑ gluconogen, ↓ insulin
euglycemia due to: ↑ gluconegenesis, ↑ glycolgenolysis, ↓ 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 2003;26:S109)

- Polyuria, polydipsia, & dehydration → ↑ HR, HoTN, dry mucous membranes, ↓ skin turgor
- Nausea, vomiting, 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 (HCO3 equivalents) and fluid resuscitation with chloride
- Ketosis: ↑ urine and serum ketones (acetoacetate measured by nitroprusside, but predominant ketone is β-OHB-buturate; urine ketones may be ↑ in fasting normal Pts)
  - serum glc, ↑ BUN & Cr (dehydration ± artifact due to ketones interfering w/ some assays)
  - Pseudohyponatremia: 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

<table>
<thead>
<tr>
<th>VS</th>
<th>UOP</th>
<th>pH</th>
<th>HCO₃⁻</th>
<th>AG</th>
<th>Ketones</th>
<th>Glc</th>
<th>K</th>
<th>PO₄</th>
<th>IVF</th>
<th>Insulin</th>
</tr>
</thead>
</table>

Note: Main ketone produced is β-OH-butyrate (βOHB), but ketone measured by nitroprusside is acetocetate (Ac-Ac). As DKA is treated, βOHB → Ac-Ac, ∴ AG can decrease while measured ketones can increase.

Treatment of DKA

<table>
<thead>
<tr>
<th>Rule out possible precipitants</th>
<th>Infection, intra-abdominal process, MI, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive hydration</td>
<td>NS 10–14 mL/kg/h, tailor to dehydration &amp; CV status</td>
</tr>
<tr>
<td>Insulin</td>
<td>10 U IV push followed by 0.1 U/kg/h Continue insulin drip until AG normal If glc &lt;250 and AG still high → add dextrose to IVF and continue insulin to metabolize ketones AG normal → SC insulin (overlap IV &amp; SC 2–3 h)</td>
</tr>
</tbody>
</table>

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 HCO₃⁻ replete if pH <7 or if cardiac instability PO₄ replete if <1

Hyperosmolar Hyperglycemic State

Definition, Precipitants, Pathophysiology (Diabetes Care 2003;26:S33)

- 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 2006;29[12]:2739)

- 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 1/2 NS, average fluid loss up to 8–10 L
- Insulin (eg, 10 U IV followed by 0.05–0.1 U/kg/h)

Hypoglycemia

Etiologies in diabetics

- Excess insulin, oral hypoglycemics, missed meals, renal failure (↓ insulin & SU clearance)
- β-blockers can mask 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
- ↑ IGF-II: non–islet tumor
- Postprandial, esp. postgastrectomy or gastric bypass: excessive response to glc load
- Low glc w/o sx can be normal

Clinical manifestations (glucose <55 mg/dL)

- CNS: headache, visual δs, Δ MS, weakness, seizure, LOC (neuroglycopenic sx)
- Autonomic: diaphoresis, palpitations, tremor (adrenergic sx)

Evaluation in nondiabetics (J Clin Endocrinol Metab 2009;94:709)

- If clinically ill: take measures to avoid recurrent hypoglycemia; ✓ BUN, Cr, LFTs, TFTs; 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 D₅₀ (50% dextrose)
- If no IV, can give glucagon 0.5–1 mg IM or SC (side effect: N/V)
LIPID DISORDERS

Measurements

- Lipoproteins – lipids (cholesterol esters & triglycerides) + phospholipids + proteins
  include: chylomicrons, VLDL, IDL, LDL, HDL, Lp(a)
- Measure after 12-h fast; LDL is calculated – TC - HDL - (TG/5) (if TG > 400, order direct LDL measurement as calc. LDL inaccurate). Lipid levels stable up to 24 h after ACS and other acute illnesses, then ↓ and may take 6 wks to return to nl.
- Metabolic syndrome (≥ 3 of following): waist ≥ 40” (♀) or ≥ 35” (♂); TG ≥ 150; HDL < 40 mg/dL (♀) or < 50 mg/dL (♂); BP ≥ 130/85 mm Hg; fasting glc ≥ 100 mg/dL (Circ 2009;120:1640)

Secondary Dyslipidemias

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinopathies</td>
<td>Type 2 diabetes (↑ TG, ↓ HDL)</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism (↑ LDL, ↓ TG)</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism (↓ LDL)</td>
</tr>
<tr>
<td></td>
<td>Cushing’s syndrome &amp; exogenous steroids (↑ TG)</td>
</tr>
<tr>
<td>Renal diseases</td>
<td>Renal failure (↑ TG)</td>
</tr>
<tr>
<td></td>
<td>nephrotic syndrome (↑ LDL)</td>
</tr>
<tr>
<td>Hepatic diseases</td>
<td>Cholestatics, PBC (↑ LDL); liver failure (↑ LDL); acute hepatitis (↑ TG)</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Obesity (↑ TG, ↓ HDL); sedentary lifestyle (↓ HDL); alcohol (↑ TG, ↑ HDL); tobacco (↓ HDL)</td>
</tr>
<tr>
<td>Medications</td>
<td>Thiazides (↑ LDL); β-blockers (↑ TG, ↓ HDL); protease inhibitors (↑ TG)</td>
</tr>
</tbody>
</table>

Primary dyslipidemias

- Familial hypercholesterolemia (FH, 1:500): defective LDL receptor; ↓ chol, nl TG; ↑ CAD
- Familial defective apoB100 (FDB, 1:1000): similar to FH
- Familial combined hyperlipidemia (FCH, 1:200): polygenic; ↓ chol, ↑ TG, ↓ HDL; ↑ CAD
- Familial dysbetalipoproteinemia (FDBL, 1:10,000): apoE ε2/ε2 + DM, obesity, renal disease, etc.; ↑ chol and TG; tuberoeruptive and palmar striated xanthomas; ↑ CAD
- Familial hypertriglyceridemia (FHTG, 1:500): ↑ TG, ↓ chol, ↓ HDL, pancreatitis

Physical examination findings

- Tendon xanthomas: seen on Achilles, elbows, and hands; imply LDL > 300 mg/dL
- Eruptive xanthomas: pimplelike lesions on extensor surfaces; imply TG > 1000 mg/dL
- Xanthelasmas: yellowish streaks on eyelids seen in various dyslipidemias
- Corneal arcus: common in older adults, imply hyperlipidemia in young Pts

Treatment

- Every 1 mmol (39 mg/dL) ↓ LDL → 21% ↓ major vascular events (CV death, MI, stroke, revasc) in individuals w/ & w/o CAD (Lancet 2005;366:1267); in healthy individuals w/ LDL < 130 mg/dL & hs-CRP > 2, rosuvastatin → 47% ↓ CVD/MI/stroke (NEJM 2008;359:2195)
- Fewer clinical data, but TG < 400 and HDL > 40 are additional reasonable targets

NCEP Guidelines

<table>
<thead>
<tr>
<th>Clinical risk</th>
<th>LDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High: ≥ 2 RFs &amp; 10-yr risk &gt; 20%</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>Mod high: ≥ 2 RFs &amp; 10-yr risk 10–20%</td>
<td>&lt;130 mg/dL (optional &lt;100 mg/dL)</td>
</tr>
<tr>
<td>Mod: ≥ 2 RFs &amp; 10-yr risk &lt;10%</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Lower: 0–1 RFs</td>
<td>&lt;160 mg/dL</td>
</tr>
</tbody>
</table>

RFS: male ≥ 45 y or female ≥ 55 y, smoking, HTN, FHS, HDL < 40. If HDL < 60, subtract 1 RF. Framingham 10-y CHD risk score at www.nhlbi.nih.gov/guidelines/cholesterol. (JAMA 2001;385:2486; Circulation 2004;110:227)

Drug Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>↓ LDL</th>
<th>↑ HDL</th>
<th>↑ TG</th>
<th>Side effects/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>20–60%</td>
<td>5–10%</td>
<td>10–25%</td>
<td>↑ aminotransferases in 0.5–3%; √ LFTs before, at 8–12 wks, and then q6mos; risk dose-depend. Myalgias &lt; 10% (not always ↑ CK), myositis 0.5%, rhabdo &lt; 0.1%, risk dose-depend. Doubling of dose ~ 6% further ↓ LDL.</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>15–20%</td>
<td>—</td>
<td>—</td>
<td>Well tolerated; typically w/ statin</td>
</tr>
<tr>
<td>Fibrates</td>
<td>5–15%</td>
<td>5–15%</td>
<td>35–50%</td>
<td>Myopathy risk ↑ w/ statin. Dyspepsia, gallstones</td>
</tr>
<tr>
<td>Niacin</td>
<td>10–25%</td>
<td>−30%</td>
<td>40%</td>
<td>Flushing (Rx w/ ASA), pruritis, ↑ glc, gout, nausea, severe hepatitis (rare)</td>
</tr>
<tr>
<td>Resins</td>
<td>20%</td>
<td>3–5%</td>
<td>—</td>
<td>↑ Bloating, binds other meds</td>
</tr>
<tr>
<td>Ω-3 FA</td>
<td>5%</td>
<td>3%</td>
<td>25–30%</td>
<td>Dyspepsia, diarrhea</td>
</tr>
</tbody>
</table>
**ARTHRITIS—OVERVIEW**

**Approach to patient with joint pain**
- **Hx:** distinguish joint vs. soft tissue pain, inflammatory vs. noninflammatory pain
  - Features suggestive of inflammatory pain: swelling in specific joint (w/o h/o trauma), persistence over days to weeks, morning stiffness, improvement of pain and stiffness w/ motion & exercise, improvement w/ NSAIDs or steroids
- **Physical exam (see later):** localize complaint and determine if there are objective signs of inflammation (arthritis, bursitis, tendinitis) or noninflammatory pain
  - Arthralgia, myofascial pain
- Osteoarthritis can p/w bony enlargement or crepitus, w/ or w/o noninflammatory effusion

<table>
<thead>
<tr>
<th>Key Physical Exam Findings in Joint Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joint</strong></td>
</tr>
<tr>
<td><strong>Inspection</strong></td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td><strong>Palpation</strong></td>
</tr>
<tr>
<td>Warmth</td>
</tr>
<tr>
<td>Tenderness</td>
</tr>
<tr>
<td><strong>ROM</strong></td>
</tr>
<tr>
<td>ROM</td>
</tr>
<tr>
<td>Pain w/ active or passive ROM</td>
</tr>
</tbody>
</table>

*Range of motion (ROM) of joint or joint associated with bursa or tendon

**Approach to arthritis**

**Figure 8-1 Approach to arthritis**

<table>
<thead>
<tr>
<th>Etiologies of Arthritis by Joint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shoulder</strong></td>
</tr>
<tr>
<td><strong>Elbow</strong></td>
</tr>
<tr>
<td><strong>Wrist</strong></td>
</tr>
<tr>
<td><strong>1st CMC</strong></td>
</tr>
<tr>
<td><strong>MCP</strong></td>
</tr>
<tr>
<td><strong>PIP</strong></td>
</tr>
<tr>
<td><strong>DIP</strong></td>
</tr>
<tr>
<td><strong>Hip</strong></td>
</tr>
<tr>
<td><strong>Knee/ankle</strong></td>
</tr>
<tr>
<td><strong>Toes</strong></td>
</tr>
</tbody>
</table>
### Comparison of Major Arthritides

<table>
<thead>
<tr>
<th>Feature</th>
<th>OA</th>
<th>RA</th>
<th>Gout</th>
<th>Spondyloarthritides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>gradual</td>
<td>gradual</td>
<td>acute</td>
<td>variable</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td>degeneration</td>
<td>pannus</td>
<td>microtophi</td>
<td>enthesitis</td>
</tr>
<tr>
<td># of joints</td>
<td>poly</td>
<td>mono to poly</td>
<td>poly or poly</td>
<td>large</td>
</tr>
<tr>
<td>Type of joints</td>
<td>small or large</td>
<td>small</td>
<td>small or large</td>
<td>large</td>
</tr>
<tr>
<td>Locations typically involved</td>
<td>hips, knees, spine</td>
<td>MCP, PIP wrists feet, ankles</td>
<td>MTP feet, ankles knees</td>
<td>sacroiliac spine large peripheral</td>
</tr>
<tr>
<td>Special articular findings</td>
<td>Bouchard’s nodes Heberden’s nodes</td>
<td>ulnar dev. swan neck boutonnière</td>
<td>urate crystals</td>
<td>en bloc spine enthesopathy (eg, Achilles)</td>
</tr>
<tr>
<td>Bone changes</td>
<td>osteophytes</td>
<td>osteopenia erosions</td>
<td>erosions</td>
<td>erosions ankylosis</td>
</tr>
<tr>
<td>Extra-articular features</td>
<td>SC nodules pulmonary cardiac splenomegaly</td>
<td>tophi olic. bursitis renal stones</td>
<td>uveitis conjunctivitis aortic insuff. psoriasis IBD</td>
<td></td>
</tr>
<tr>
<td>Lab data</td>
<td>normal</td>
<td></td>
<td>RF, anti-CCP</td>
<td>↑ UA</td>
</tr>
</tbody>
</table>

### Analysis of Joint Fluid

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Noninflammatory</th>
<th>Inflammatory</th>
<th>Septic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>clear</td>
<td>clear, yellow</td>
<td>clear to opaque yellow-white</td>
<td>opaque</td>
</tr>
<tr>
<td>WBC/mm³</td>
<td>&lt;200</td>
<td>&lt;2000</td>
<td>&gt;2000</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Polys</td>
<td>&lt;25%</td>
<td>&lt;25%</td>
<td>≥50%</td>
<td>≥75%</td>
</tr>
<tr>
<td>Culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditions</td>
<td>OA, internal derangement</td>
<td>RA, crystal CTD spondyloarth.</td>
<td></td>
<td>infection</td>
</tr>
</tbody>
</table>
RHEUMATOID ARTHRITIS (RA)

Definition and epidemiology
• Chronic, symmetric, debilitating, and destructive polyarthritis caused by inflammatory, proliferative synovial tissue (pannus) formation in affected joints
• Genetic factors: ↑ incidence in Pts w/ shared epitope on class II MHC DRB1 and DR4
• Environmental factors: smoking, silica dust exposure
• ↑ risk w/ shared epitope & smoke b/c gene–environment interaction (Ann Rheum Dis 2010;69:70)
• Prevalence – 1% of adults; female: male = 3:1; onset 35–50 y; worldwide

Clinical manifestations (Lancet 2001;358:903)
• Pain, swelling, and impaired function of joints (typically PIPs, MCPs, wrists, knees, ankles, MTPs, and cervical spine) with morning stiffness for ≥ 1 h
• Polyarticular in 75% (60% small joints, 30% large joints, 10% both), monoarticular in 25% (knee, shoulder, wrist)
• Joint immobilization, muscle shortening, bone & cartilage destruction, 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
• Rheumatoid nodules (20–30%; usually in sero- Pts): SC nodules on extensor surfaces along tendon sheaths and in bursae; also occur in lung, heart, and sclera
• Constitutional symptoms: fever, weight loss, malaise
• Ocular: scleritis, episcleritis, keratoconjunctivitis sicca (associated Sjögren’s)
• Pulmonary (20% of the time precedes joint manifestations)
  ILD: COP fibrosis, nodules, Caplan’s syndrome (pneumoconiosis + rheumatoid nodules)
  pleural disease: pleuritis, pleural effusions (classically low glucose)
  pulmonary hypertension
  airway disease: obstruction (cricoarytenoid arthritis), bronchiolitis, bronchiectasis
• Cardiac: pericarditis (effusion in 1/3 of sero- Pts), myocarditis, nodules can cause valvar and/or conduction disease. Associated with ↑ risk of cardiovascular death compared with that of general population (Rheum 2009;48:1309).
• Heme: anemia of chronic inflammation, leukemia, lymphoma
• Vascular: small nail fold infarcts, palpable purpura, leukocytoclastic vasculitis
• Renal: glomerulonephritis (membranous, mesangial, MPGN); nephrotic syndrome due to AA amyloidosis; Rx-induced, including NSAIDs (AIN, membranous GN), gold, MTX
• Longstanding seropositive, erosive RA:
  Felty’s syndrome (1%); neutropenia, RF, RF or ACPA, splenomegaly; ↑ risk of NHL
  large granular lymphocyte syndrome: neutropenia, lymphocytosis blood/marrow
• Remember that rheumatoid joints can become superinfected

Laboratory and radiologic studies
• RF (IgM anti-IgG Ab) in 85% of Pts; nonspecific as also seen in other rheumatic diseases (SLE, Sjögren’s), chronic inflammation (SBE, hepatitis, TB), type II cryoglobulinemia, 5% of healthy population
• ACPA (anti–citrullinated peptide Ab) or anti-CCP (Ab to cyclic citrullinated peptide): similar Se (~ 80%), more Sp (~ 90%) than RF particularly for early RA (Arth Rheum 2009;61:1472)
• ↑ ESR and CRP, RF or ACPA in ~ 15%; ↑ globulin during periods of active disease; anemia
• Radiographs of hands and wrists: periarticular osteopenia, bone erosions, and deformities

ACR/EULAR Classification Criteria (Arth Rheum 2010; in press)
• Use for Pts with ≥ 1 joint with synovitis not better explained by another disease
• Summed score of ≥ 6 c/w RA

<table>
<thead>
<tr>
<th>Joint involvement</th>
<th>Score</th>
<th>Acute phase reactants</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 med-large</td>
<td>0</td>
<td>Normal ESR &amp; CRP</td>
<td>0</td>
</tr>
<tr>
<td>2–10 med-large</td>
<td>1</td>
<td>Abnormal ESR or CRP</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small</td>
<td>2</td>
<td>Duration of sx</td>
<td>Score</td>
</tr>
<tr>
<td>4–10 small</td>
<td>3</td>
<td>≥ 6 wk</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10 (= 1 small)</td>
<td>5</td>
<td>≥ 6 wk</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF &amp; ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low- RF or ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High RF or ACPA</td>
<td>3</td>
</tr>
</tbody>
</table>

Choose highest number from each category and add for total score. Small joints exclude 1st MTP & 1st CMC; med-large joints = elbows, shoulders, hips, knees, ankles. Low- serology < 3× ULN.
Management (Lancet 2009;373:659)

- Early dx and Rx w/ frequent follow-up and escalation of Rx as needed → ↓ disease activity and radiographic progression, ↑ physical fnx and quality of life
- Initial therapy: none selective NSAIDs (? ↑ CV adverse events) or COX-2 inhibitors (? CV adverse events w/ some); sx control as indicated; glucocorticoids (joint injection or low-dose oral); acutely ↓ inflammation; physical and occupational therapy
- Start Disease-Modifying Anti-Rheumatic Drug (DMARD) w/in 3 mo if established disease and ongoing inflammation (Annals 2007;146:406); all take ≥1 mo to have an effect

<table>
<thead>
<tr>
<th>DMARDs</th>
<th>Class</th>
<th>Drug</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antimetab</td>
<td>Methotrexate (MTX)</td>
<td>Gl distress, myelosuppression, hepatotoxicity. Supplement MTX w/ folate.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leflunomide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azathioprine (AZA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biologic</td>
<td>Anti-TNF: etanercept, infliximab, adalimumab, certolizumab, golimumab</td>
<td>TB, zoster, &amp; other infxs. =&gt; screen for TB prior to starting Rx.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-1RA: anakinra</td>
<td>↑ CHF &amp; demyelinating CNS disease for anti-TNF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTLA4-lg abatacept</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-6R Ab: tocilizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Hydroxychloroquine (HCQ)</td>
<td>Retinopathy, maculopapular rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gold</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minocycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclosporine</td>
<td>Nephrotox, HTN, gum hyperplasia</td>
</tr>
</tbody>
</table>


  - monotherapy with MTX (a/w lower mortality; Lancet 2007;359:1173), sulfasalazine, leflunomide, or hydroxychloroquine, or
  - combination of DMARD + glucocorticoid or anti-TNF (Arch Rheum 2005;52:3360 & 3371)
    - eg, MTX + anti-TNF ↑ remission rate vs. MTX alone (Lancet 2008;372:375)
  - escalation Rx → add medication (usually biologic) or change DMARD, eg, if suboptimal response to MTX, addition of anti-TNF superior to SAS & HCQ
  - biologics: never use 2 biologics concurrently in the same Pt

RELAPSING POLYCHONDritis

Definition & Epidemiology

- Inflammatory destruction of cartilaginous structures
  - Defined by chondritis in 2 of the following sites: auricular, nasal, or laryngotracheal; or chondritis in 1 of these sites + 2 other manifestations (below) (Annals 1986;104:74)
  - 40% of cases a/w immunologic disorder (eg, RA, SLE, vasc., Sjögren’s), cancer, or MDS
  - Mean age at diagnosis is 47 y, men – women

Clinical manifestations (Curr Opin Rheumatol 2004;16:56)

- Subacute onset of red, painful, and swollen cartilage; ultimately atrophic & deformed
- Relapsing-remitting pattern
- Frequency of involved cartilage: external ear (89%), migratory asymmetric nonerosive arthropathy (72%), episcleritis/scleritis (59%), laryngotracheal sx (55%), inner ear (28%), nasal cartilage, saddle deformity (25%), skin (25%), laryngotracheal stricture (23%), kidney (22%), heart valves (12%), AI > MR 
- Dx: Infxn (eg, Pseudomonal external otitis), Wegener’s, IBD chondritis, trauma

Diagnosis

- 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

Evaluation and Treatment

- Screen for pulm (PFTs, CXR/CT, ± bronch) and cardiac (ECG, TTE) involvement
- Therapy guided by disease activity and severity: steroids first line; NSAIDs, dapsone for sx control of arthralgias and mild disease; MTX or AZA for steroid-sparing; cyclophosphamide for organ-threatening disease
Gout

Definition & Pathobiology (Lancet 2010;375:318)
- Monosodium urate (MSU) crystal deposition in joints and other tissues
- Activate cryopyrin inflammasome → IL-1β → inflammation (Nature 2006;440:237)

Epidemiology
- More common in men than in women (9:1); peak incidence 5th decade
- Most common cause of inflammatory arthritis in men over 30 y
- Rare in premenopausal women (estrogens promote renal urate excretion)
- Risk factors: ↑ serum uric acid (UA) related to metabolic syndrome; HTN; chronic kidney disease; ↑ intake of meat, seafood, and EtOH (Lancet 2004;363:1277; NEJM 2004;350:1093)

Etiologies
- Uric acid (UA) is end product of purine catabolism and is renally excreted

<table>
<thead>
<tr>
<th>Primary hyperuricemia</th>
<th>UA Overproduction</th>
<th>UA Underexcretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Rare inherited enzyme (HGPRT, PRPP) defic.</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Common genetic variants (Lancet 2008;372:1953)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary hyperuricemia</th>
<th>UA Overproduction</th>
<th>UA Underexcretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ meat, seafood, EtOH intake</td>
<td>Myelo- &amp; lymphoproliferative dis.</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Chronic hemolytic anemia</td>
<td>Cytotoxic drugs, psoriasis</td>
<td>↑ renal function</td>
</tr>
<tr>
<td>Severe muscle exertion</td>
<td>Chronic hemolytic anemia</td>
<td>Drugs: diuretics, PZA, EMB, salicylates, CsA</td>
</tr>
<tr>
<td>Renal: uric acid stones; urate nephropathy (interstitial deposits)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic hyperuricemia: serum UA &gt;6.8 mg/dL w/o disease manifestations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical manifestations
- Acute arthritis: sudden onset (freq. nocturnal) of painful monoarticular arthritis
  - location: MTP of great toe (“podagra”), feet, ankles, knees; occasionally polyarticular overlying skin is warm, tense, dusky red; Pt may be febrile
  - precipitants: rapid Δ UA; ↑ dietary purine; surgery; infection; diuretics, dehydration
  - frequent in hospitalized Pts
  - recovery: subsides in 3–10 d; intercritical period – remission of joint pain between attacks
- Tophi: deposits of urate crystals in SC tissue & joints; commonly in joints of fingers, wrists, knees; also on pinna, Achilles tendon, and pressure areas, eg, ulnar aspect of forearm
- Bursitis: olecranon, patellar (must be differentiated from intra-articular effusion)
- Chronic tophaceous gout: deforming arthritis from tophus formation → pain, joint erosion
- Renal: uric acid stones; urate nephropathy (interstitial deposits)
- Asymptomatic hyperuricemia: serum UA >6.8 mg/dL w/o disease manifestations

Diagnostic studies
- ↑ UA does not make dx: 25% of measurements nl during acute attack, though >7.5 mg/dL in 95% at some time during an attack; ↑ WBC count & ESR
- Arthrocentesis: take care not to tap through an infected area thus introducing infections into joint space
  - polarized microscopy → needle-shaped, negatively birefringent crystals (yellow parallel to axis marked on polarizer), intracellular or extracellular (less specific)
  - WBC 20,000–100,000/mm³, >50% polys
  - infection can coexist with acute attacks, :: always check Gram stain and culture
- Radiographs: early → show soft tissue swelling; useful to exclude chondrocalcinosis or septic changes late → bony erosions with overhanging edge, soft tissue calcifications within tophi

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>↓ inflammation</td>
<td>Gastritis; ↓ dose in renal insufficiency</td>
</tr>
<tr>
<td>Colchicine (PO or IV)</td>
<td>inhibits polymerization of microtubules预防 chemotaxis and phagocytosis</td>
<td>Nausea, vomiting, and diarrhea</td>
</tr>
<tr>
<td>Corticosteroids (PO, IA, or IV) or Corticotropin (SC, IM, or IV)</td>
<td>↓ inflammation</td>
<td>For initial Rx, efficacy = NSAIDs; Rule out joint infection first</td>
</tr>
</tbody>
</table>

(NEJM 2003;349:1647; Lancet 2008;371:1854)
Chronic treatment

- Turate production by intake of meat and seafood (note: high-purine vegetables a/w risk); intake of low-fat dairy products; alcohol (esp. beer); wt control
- Avoid dehydration and hyperuricemia-promoting drugs (eg, thiazide and loop diuretics)
- Prophylaxis if frequent attacks and when starting antihyperuricemic therapy: daily low-dose colchicine (~50% risk of acute flare; J Rheum 2004;31:2429) or NSAIDs (less evidence of effectiveness; Ann Rheum Dis 2006:65:1132)
- Antihyperuricemic therapy for tophi, frequent attacks, nephrolithiasis; goal UA <6 mg/dL however, do not start w/o prophylaxis and until 2–4 wk after acute attack as in serum UA concentration can precipitate an attack
- Allopurinol (xanthine oxidase inhibitor); side effects: hypersensitivity, rash, diarrhea, dyspepsia, headache, renal failure, BM suppression, and hepatitis; monitor CBC & LFTs; dose adjustment necessary in Pts concurrently taking AZA
- Febuxostat (nonpurine xanthine oxidase inhibitor): consider if allopurinol intolerance/failure or CKD; side effects: liver abnl, rash, arthralgias, nausea; monitor LFTs (Arth Rheum 2008;59:1540); dose adjustment also necessary for AZA
- Probenecid (uricosuric) for underexcreters (urine UA <600 mg/24 h)

Calcium Pyrophosphate Dihydrate (CPPD) Deposition Disease

Definition

- Deposition of CPPD crystals w/in tendons, ligaments, articular capsules, synovium, cartilage
- Acute inflammation due to CPPD crystals in a joint is termed pseudogout
- Chondrocalcinosis: calcification of cartilage visible on radiographs, resulting from CPPD deposition in articular cartilage, fibrocartilage, or menisci

Epidemiology

- More common in elderly: 20% over age 60 y have knee chondrocalcinosis in autopsy studies

Etiologies

- Most cases idiopathic, but consider search for underlying cause, especially in the young
- Metabolic: the 3 Hs: hemochromatosis, hypothyroidism, hyperparathyroidism
- Diabetes, hypomagnesemia, alkaline phosphatase deficiency, familial hypocalciuric hypercalcemia, gout, Gitelman’s syndrome, X-linked hypophosphatemic rickets
- Joint trauma (incl. previous surgery); joint injections with hyaluronate can precipitate attacks
- Familial chondrocalcinosis (autosomal dominant disorder)

Pathogenesis

- Synovial & joint fluid levels of inorganic pyrophosphate produced by articular chondrocytes from ATP hydrolysis in response to various insults or inherited defects favors CPPD crystallogenesis and deposition in the cartilage matrix
- Crystals activate cryopyrin inflammasome → IL-1β → inflammation (Nature 2006;440:237)

Clinical manifestations

- Pseudogout: acute mono- or asymmetric oligoarticular arthritis, indistinguishable from gout except through synovial fluid exam for crystals
- "Pseudo-RA": chronic polyarticular arthritis with morning stiffness; RF
- Premature OA: destruction of articular cartilage and bony overgrowths → degen. of joints

Diagnostic studies

- Arthrocentesis: take care not to tap through an infected area thus introducing infxn into joint space
- Polarized microscopy → rhomboid-shaped, weakly positively birefringent crystals (yellow perpendicular and blue parallel to axis marked on polarizer)
- Infection can coexist with acute attacks, always check Gram stain and culture
- Screen for associated metabolic diseases when dx a new case: Ca, Mg, TSH, Fe, glc, UA
- Radiographs: though not a prerequisite for the diagnosis of CPPD disease, chondrocalcinosis appears as punctate and linear densities in articular cartilage, menisci, triangular fibrocartilage of the wrist, small joints of fingers, and symphysis pubis

Treatment

- Acute therapy for pseudogout: same as for gout, though colchicine not as effective
- Chronic therapy: treat predisposing disease
- Low-dose daily colchicine may be effective prophylaxis in some Pts
### General

**Definition** ([Annals 2002;136:896])
- A spectrum of systemic inflammatory arthritides with predilection for the spine, entheses, sacroiliac, and peripheral joints; affects 0.5–2% of population
- 5 subtypes: ankylosing spondylitis, reactive, psoriatic, IBD-associated, and undifferentiated (does not meet criteria for other subtypes, wide clinical spectrum)
- Notable for absence of rheumatoid factor or autoantibodies; ++ ESR
- Synovial fluid of affected joints shows an inflammatory, non-septic picture

**Pathogenesis** ([Semin Arthritis Rheum 2008;38:83])
- **c** prevalence of HLA-B27: ++ in 50–90% of pts, but common in general pop. (6–8%)
- HLA-B27 accounts for ~30% of attributable genetic risk, but not used for dx
- Other gene associations: IL23R (26% of attributable risk) and ARTS 1 (9%)
- Environmental factors likely critical for disease, esp. reactive arthritis (eg, infection)

### Ankylosing Spondylitis

**Epidemiology**
- Onset in teens or mid-20s; onset after age 40 y very unusual; male:female ratio 3:1; HLA-B27 ++ in 90%

**Clinical manifestations**
- Gradual onset of chronic, intermittent bouts of lower back pain and stiffness
- **Morning stiffness** that improves with hot shower and exercise
- Progressive limitation of motion in cervical, thoracic, and/or lumbar spine over time
- Severity of lumbar flexion deformity assessed by modified **Wright-Schober test** (-4 cm ↑ in distance between a point at lumbosacral jn and another point 10 cm above, when going from standing to maximum forward flexion)
- Ts spine mobility (extension) and kyphosis severity measured by occiput-to-wall distance
- **Enthesitis**: inflammation at site of tendon/ligament insertion into bone, eg, Achilles tendinitis, plantar fasciitis, rigidity of spine (bamboo spine by x-ray)
- **Arthritis in peripheral joints can occur**, eg, hips, shoulders, knees
- Acute anterior **uveitis** (25–40% at some time during disease): presents with unilateral blurred vision, lacrimation, and photophobia
- Cardiovascular disease (5%): ascending aortitis, AI, conduction system abnormalities
- Neurologic complications: spinal fractures, C1/2 subluxation, or cauda equina syndrome

**Imaging studies**
- Radiographs of spine to assess progression of disease: Sacroiliac joint disease with erosions and sclerosis
- Calcification of spinal ligaments with bridging syndesmophytes ("bamboo spine")
- Squaring and generalized demineralization of vertebral bodies, "shiny corners"
- MRI spine to assess inflammation in sacroiliac joint, esp. early in disease course

**Treatment** ([Lancet 2007;369:1379; Curr Opin Rheumatol 2009;21:324])
- Supportive: physical therapy, NSAIDs, steroid injection
- Anti-TNF shown to improve symptoms and function ([Ann Rheum Dis 2006;65:423])
- MTX: somewhat effective for peripheral arthritis, but little or no effect on spinal sx; SAS may provide benefit in pts w/o peripheral arthritis ([Ann Rheum Dis 2006;65:1147])

### Reactive Arthritis

**Epidemiology**
- Ages 20–40 y; male:female ratio 5:1; more common in Caucasians

**Pathogenesis**
- Immune-mediated aseptic synovitis in a genetically susceptible host post-GU or GI infxn
- Bacteria associated with disease
  - **GU**: Chlamydia and Ureaplasma urealyticum
  - **GI**: Shigella, Salmonella, Yersinia, Campylobacter, C. difficile

**Clinical presentation**
- Originally described as a triad of seronegative arthritis, nongonococcal urethritis, and noninfectious conjunctivitis (Reiter’s syndrome)
- **Arthritis**: 10–30 d post-inciting infection → mild constitutional sx, low back pain, asymmetric, mono- or oligoarticular arthritis of primarily large joints (knees, ankles, feet), enthesopathy, and sacroilitis. Can develop sausage digits (dactylitis) of extremities.
**Urethritis/cervicitis:** usually *Chlamydia* infection preceding arthritis, but also can see sterile urethritis in postgastroenteric reactive arthritis

**Conjunctivitis:** noninfectious, unilateral or bilateral and ± uveitis, iritis, and keratitis

Cutaneous manifestations (may go unnoticed by Pt)
- **circinate balanitis:** shallow, painless ulcers of glans penis and urethral meatus
- **keratoderma blenorrhagica:** hyperkeratotic skin lesions on soles of feet, scrotum, palms, trunk, scalp

Gastrointestinal manifestations (may go unnoticed by Pt)
- GI: diarrhea and abdominal pain either w/ or w/o infectious agent
- CV: AI from inflammation and scarring of aorta and valve; conduction defects

Radiographs
- Early: soft tissue swelling and effusions around affected joints
- Late: asymmetric proliferation of bone at site of inflammation

**Asymmetric sacroiliitis** in 70%

Diagnostic studies
- PCR of urine or genital swab for *Chlamydia*, stool cultures, *C. difficile* toxin, etc., but studies do not rule out

Treatment and prognosis
- NSAIDs, steroid injection for mono- or oligoarthritis, SAS if inflammation persists
- Antibiotics if evidence of active or antecedent infection, as cx may be
- Arthritis may persist for months to years, and recurrences are common

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**Psoriatic Arthritis**

Epidemiology
- Seen in 20–30% of Pt's w/ psoriasis (and not necessarily those with severe skin disease)
- Arthritis may precede onset of skin disease, even by years; ± nail changes
- 20–40% of Pt's with psoriatic arthritis have spinal or sacroiliac involvement
- Men and women are affected equally and most Pt's in 30s and 40s

Clinical manifestations
- Several clinical patterns of arthritis:
  - **monoarticular/oligoarticular** (eg, large joint, DIP joint, dactylitic digit): most common initial manifestation
  - **polyarthritis** (small joints of the hands and feet, wrists, ankles, knees, elbows): indistinguishable from RA, but often asymmetric
  - **arthritis mutilans:** severe destructive arthritis with bone resorption, esp. hands
  - **axial disease:** similar to ankylosing spondylitis ± peripheral arthritis
  - **Enthesopathies, tendinitis**
  - **Fingernails:** pitting, transverse depressions, onycholysis, subungal hyperkeratosis
  - **Eye inflammation** (30%): conjunctivitis, iritis, episcleritis, and keratoconjunctivitis sicca
  - **Psoriatic skin lesions**

Radiographs
- "Pencil-in-cup" deformity seen at DIP joints, erosive changes
- Spinal involvement, sacroiliitis

Treatment
- Symptom control: NSAIDs; intra-articular glucocorticoid injections
- Anti-TNF (etanercept, infliximab, adalimumab) ↓ progression of disease
- Sulfasalazine: only DMARD shown to improve sx, but not progression of disease
- Other: MTX, leflunomide, CsA, Aza, PUVA, antimalarials, gold

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**Enteropathic (IBD-Associated)**

Epidemiology
- Seen in 20% of Pt's w/ IBD; more frequently seen in Crohn's than UC

Clinical manifestations
- Peripheral, migratory, asymmetric, nondeforming oligoarthritis: abrupt onset, large joints, course parallels GI disease
- Spondylitis: associated more strongly with HLA-B27, course does not parallel GI disease
- Sacroiliitis
- Erythema nodosum, pyoderma gangrenosum (~ neutrophilic dermatosis → painful ulcers w/ violaceous border; Ddx incl. idiopathic, IBD, RA, myelogenous leukemia), anterior uveitis

Treatment
- 5-ASA compounds, etc., for underlying IBD (see IBD)
INFECTIONOUS ARTHRITIS & BURSITIS

DIAGNOSIS AND EMPIRIC TREATMENT OF INFECTIOUS ARTHRITIS

Diagnosis
- Arthrocentesis should be performed as soon as suspected
- Take care not to tap through an infected area thus introducing infxn into joint space
- Send fluid for cell count, gram stain, bacterial culture, crystals
- **WBC >50,000 with poly predominance** suspicion for bacterial infection (crystals do not rule out septic arthritis)

Initial therapy
- Prompt empiric antibiotics guided by gram stain
- If gram stain negative, empiric Rx w/ cefazolin (eg, low risk of MRSA and gonorrhea) or vancomycin (IVDU, MRSA risk factors); add cefepime if elderly, immunosupp.
- Modify antibiotics based on culture results and clinical course

<table>
<thead>
<tr>
<th>Common microbes</th>
<th>Population</th>
<th>Initial antibiotic regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>Normal joints</td>
<td>Nafcillin or Vancomycin if suspect MRSA (eg, hospitalized Pt)</td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>Prosthetic joints</td>
<td>Nafcillin or Vancomycin if suspect MRSA (eg, hospitalized Pt)</td>
</tr>
<tr>
<td>Streptococci</td>
<td>Healthy adults</td>
<td>Penicillin G or ampicillin</td>
</tr>
<tr>
<td>Rods: <em>E. coli</em>, <em>Pseudomonas</em>, <em>Serratia</em></td>
<td>IVDU, GI infection</td>
<td>Cefepime or piperacillin/tazobactam + antipseudomonal aminoglycoside if suspect IVDU</td>
</tr>
</tbody>
</table>

**BACTERIAL (NGONOCOCCAL) ARTHRITIS**

Epidemiology and risk factors
- Immunocompromised host (eg, diabetics, HIV, elderly, SLE)
- 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 (*Lancet* 2010;375:846)
- Acute onset of monoarticular arthritis (~80%) with pain, swelling, and warmth
- Location: **knee** (most common), hip, wrist, shoulder, ankle. In IVDA, tends to involve other areas, eg, sacroiliac joint, symphysis pubis, sternoclavicular and manubrial joints
- **Constitutional symptoms**: fevers, chills, sweats, 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
- Synovial fluid: **WBC usually ~50,000** (but can be as low as ~1,000), ~90% polys
- Gram stain @ ~75% of Staph, ~50% of GNR; culture @ in ~90% of cases
- Leukocytosis with neutrophilic predominance ± bandemia
- Blood cultures @ in ~50% of cases
- Conventional radiographs usually normal until after ~2 wk of infection when bony erosions, joint space narrowing, osteomyelitis, periostitis can be seen
- CT and MRI useful especially for suspected hip infection or epidural abscess

Definitive treatment (for nonprosthetic joints)
- **Antibiotics** (as earlier)
- **Surgical drainage/lavage** indicated in many joints, especially for larger joints
- **Prognosis**: 10–50% mortality depending on virulence of organism, time to Rx, host
**DISSEMINATED GONOCOCCAL INFECTION (DGI)**

**Epidemiology**
- Most frequent type of infectious arthritis in sexually active young adults
- Caused by *Neisseria gonorrhoea*
- Normal host as well as Pts w/ deficiencies of terminal components of complement
- Female: male ratio ~ 4:1; incidence during menses, pregnancy, and postpartum period. ↑ incidence in homosexual males. Rare after age 40 y.

**Clinical manifestations**
- Preceded by mucosal infection (eg, endocervix, urethra, or pharynx) that is often asx
- Usually presents as two distinct syndromes:
  - **Joint localized**: purulent arthritis (40%) usually of knees, wrists, hands, or ankles
  - **Bacteremia**: triad of polyarthritis, tenosynovitis, skin lesions
    - prodrome: fever, malaise, migratory polyarthralgias (wrist, knees, ankles, elbows)
  - 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, myocarditis, osteomyelitis

**Additional diagnostic studies**
- **Leukocytosis** with increased neutrophils; ↑ ESR
- **Synovial fluid**: WBC >50,000 (but can be <10,000), poly predominant
  - Gram stain in ~25% of cases
  - Culture in up to 50% of cases if culture anaerobically on Thayer-Martin media
  - PCR for gonococcal DNA can improve Se (not widely available or standardized)
- **Blood culture**: more likely in tenosynovitis; rarely in joint localized disease
- **Gram stain and culture of skin lesions occasionally**
- Cervical, urethral, pharyngeal, rectal cultures on Thayer-Martin media indicated; check for *Chlamydia*

**Treatment**
- **Ceftriaxone or cefotaxime** × 7 d w/ empiric doxycycline for possible concurrent *Chlamydia* (fluoroquinolones no longer recommended due to resistance)
- Joint aspiration or arthroscopy/lavage may be required for Pts with purulent arthritis

**OLECRANON AND PREPATELLAR BURSITIS**

**Epidemiology and risk factors** *(Infect Dis North Am 2005;19:991)*
- ~150 bursae in the body; two most commonly infected are olecranon and prepatellar
- Most commonly 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 >20,000 with 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: cefazolin or oxacillin, vancomycin if concern for MRSA, broaden spectrum based on other risk factors
- PO antibiotics acceptable for mild presentation
- Modify antibiotics based on gram stain, culture results, and clinical course
- Duration of therapy is 1–4 wk
- **Serial aspirations** every 1–3 d until sterile or no reaccumulation of fluid
- Surgical intervention if unable to drain bursa through aspiration, evidence of foreign body or necrosis, recurrent or refractory bursitis with concern for infection of adjacent structures
**CONNECTIVE TISSUE DISEASES**

<table>
<thead>
<tr>
<th>Disease</th>
<th>% Autoantibodies in Patients with Rheumatic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>ANA &amp; Pattern: D, S, N</td>
</tr>
<tr>
<td>RA</td>
<td>ANA &amp; Pattern: D</td>
</tr>
<tr>
<td>Sjögren's</td>
<td>ANA &amp; Pattern: D, S</td>
</tr>
<tr>
<td>Diffuse SSc</td>
<td>ANA &amp; Pattern: N, S, D</td>
</tr>
<tr>
<td>Limited SSc</td>
<td>ANA &amp; Pattern: S, N, D</td>
</tr>
<tr>
<td>PM-DM</td>
<td>ANA &amp; Pattern: D</td>
</tr>
<tr>
<td>MCTD</td>
<td>ANA &amp; Pattern: D</td>
</tr>
</tbody>
</table>

(D = diffuse or homogeneous, S = speckled, N = nucleolar; Primer on the Rheumatic Diseases, 12th ed., 2001)

- Autoantibody testing is directed by clinical findings, as autoantibodies themselves do not define a particular connective tissue disease
- Overlap syndromes encompassing more than one connective tissue disorder may be reflected serologically by the presence of multiple autoantibodies

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**SYSTEMIC SCLEROSIS AND SCLERODERMA DISORDERS**

**Definition and epidemiology**
- 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. Subgroups: SSc w/ limited cutaneous disease (hands, arms, face): CREST syndrome, pulm HTN; renal and cardiac manifestations rare
  - SSc w/ diffuse cutaneous disease (incl. proximal extremities & trunk): rapidly progressing disorder affecting skin, one or more internal organs
  - SSc sine scleroderma (visceral disease without skin involvement, rare)
- Peak onset of SSc between ages 30–50; more common in women than men
- 1–2/100,000 annual incidence of systemic disease in the U.S.
- Pathogenesis: immune damage to endothelial cells and reactive O2 species production → persistent oxidative stress → perivascular inflammation → fibroblast activation and fibrosis. Cytokines, growth factors, and autoantibodies (against PDGF receptor, endothelial cells, and fibroblasts) all contribute (NEJM 2009;360:1989).

**Classification criteria** (1 major or 2 minor; 97% Se, 98% Sp; Arth Rheum 1980;23:581)
- Major: skin findings extend proximal to MCP or MTP joints
- Minor: sclerodactyly (skin findings limited to the fingers)
- Digital pitting scars from loss of substance on the finger pad
- Basilar pulmonary fibrosis
- Other causes of thickened skin: diabetes (scleredema ≠ scleroderma), hypothyroidism, nephrogenic systemic fibrosis, eosinophilic fasciitis, amyloidosis, GVHD, drug or toxin

**Diagnostic studies**
- Autoantibodies
  - Anti-Scl-70 (anti-topoisomerase 1): 40% of diffuse, 15% of limited
  - Anti-centromere: 60–80% of limited, <5% of diffuse
  - ANA (>90%), RF (30%)
- If renal involvement → ↑ BUN and Cr, proteinuria
- If pulmonary involvement → interstitial pattern on CXR/chest CT, restriction and/or ↓ DLCO on PFTs; PHT revealed by echocardiography
- Skin bx not routine, but helpful to assess other possible causes for skin thickening
Clinical Manifestations of Systemic Sclerosis

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>Tightening and thickening of extremities, face, trunk (bx not req for dx)</td>
</tr>
<tr>
<td></td>
<td>“Puffy” hands, carpal tunnel syndrome, sclerodactyly</td>
</tr>
<tr>
<td></td>
<td>Nailfold capillary dilatation &amp; dropout</td>
</tr>
<tr>
<td></td>
<td>Immobile, pinched, “mouselike” facies and “purse-string” mouth</td>
</tr>
<tr>
<td></td>
<td>Telangiecstasias</td>
</tr>
<tr>
<td><strong>Arteries</strong></td>
<td>Raynaud’s phenomenon (80%); digital or visceral ischemia</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Sclerderma renal crisis – sudden onset severe HTN, RPGN, MAHA</td>
</tr>
<tr>
<td></td>
<td>Crescentic GN (rare) with p-ANCA (J Rheum 2006;33:1886)</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>GERD and erosive esophagitis</td>
</tr>
<tr>
<td></td>
<td>Esophageal dysmotility → dysphagia, odynophagia, aspiration</td>
</tr>
<tr>
<td></td>
<td>Gastric dysmotility → early satiety and gastric outlet obstruction</td>
</tr>
<tr>
<td></td>
<td>Small intestinal dysmotility → bloating, diarrhea, malabsorption</td>
</tr>
<tr>
<td><strong>Musculoskel</strong></td>
<td>Polyarthralgias &amp; joint stiffness; muscle weakness, tendon friction rubs</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>Myocardial fibrosis, pericarditis; conduction abnormalities</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Pulmonary fibrosis (typically develops w/in 4 y); pulmonary arterial hypertension (typically develops after many yrs). #1 cause of mortality.</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Amenorrhea and infertility common; thyroid fibrosis ± hypothyroidism</td>
</tr>
</tbody>
</table>

Systemic Sclerosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Limited</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td>Fatigue, weight loss</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Thckening on distal extremities and face only</td>
<td>Thickening on extremities (incl. digits), face, and trunk</td>
</tr>
<tr>
<td><strong>Nails</strong></td>
<td>Capillary dropout ± dilatation</td>
<td>Capillary dropout &amp; dilatation</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>PAH &gt; fibrosis</td>
<td>Fibrosis → PAH</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>GERD, hypomotility, PBC</td>
<td>GERD, hypomotility</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Renovascular HTN</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>Restrictive cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>CREST syndrome = Calcium, Raynaud’s Esophageal dysmotility Sclerodactyly, Telangiecstasias</td>
<td></td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td>Anticentromere (70%)</td>
<td>Anti-Scl 70 (40%)</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Survival &gt;70% at 10 y</td>
<td>Survival 40–60% at 10 y</td>
</tr>
</tbody>
</table>

**Treatment** (organ-based approach)

- **Pulmonary**
  - fibrosis: cyclophosphamide (NEJM 2006;354:2653), steroids
  - PAH: pulmonary vasodilators (see “Pulmonary Hypertension”)
- **Renal**: monitor BP monthly, intervene early to avoid HTN crisis; dipstick for protein
- **ACE inhibitors** (not ARB) for HTN crisis (poor prognosis w/ 50% mortality)
- **GI**: PPI and/or H2-blockers for GERD; antibiotics for malabsorption
- **Cardiac**: NSAIDs or steroids for pericarditis
- **Arthritis**: acetaminophen, NSAIDs, PT
- **Myositis**: MTX, AZA, steroids
- **Skin**: PUVA for morphea. For pruritis: emollients, topical or oral steroids (use w/ caution, can precip HTN renal crisis, Arthritis Rheum 1998;41:1613). Immunosuppressives offer only minimal to modest benefit for skin fibrosis.

**Inflammatory Myopathies**

**Definition and epidemiology** (Lancet 2003;362:971)

- **Polymyositis (PM)**: T cell-mediated muscle injury → skeletal muscle inflam. & weakness
- **Dermatomyositis (DM)**: immune complex deposition in blood vessels with complement activation → skeletal muscle inflam. & weakness + skin manifestations
- **Inclusion body myositis (IBM)**: T cell-mediated muscle injury, vacuole formation with amyloid deposition → skeletal muscle inflam. & weakness
- **10% of PM and 15% of DM associated with malignancy (NEJM 1992; 326:363)**
- **PM/DM**: onset typically 40s and 50s; more common in women than men
- **IBM**: onset after age 50; men > women; often misdiagnosed as polymyositis
Clinical manifestations

- **Muscle weakness**: gradual, progressive, often painless, symmetric, and **proximal**; typically difficulty climbing stairs, arising from chairs, brushing hair; ± tenderness of affected areas; **asymmetry and distal weakness more common in IBM than PM/DM**
- **Dermatologic**
  - **erythematous rash** on sun-exposed skin: neck & shoulders (shawl sign), face, chest
  - **heliotrope rash** (purplish discoloration) over upper eyelids ± periorbital edema
  - **Gottron’s papules** (**pathognomonic**): violaceous often scaly areas symmetrically over dorsum of PIP and MCP joints, elbows, patellae, medial malleoli
  - subungal erythema, dilation and dropout of nailbed capillaries, cuticular telangiectases, “mechanic’s hands” (skin cracks on digits)
- **Polyarthralgias or polyarthritis**
- **Vasculitis** of skin, muscle, GI tract and eyes; Raynaud’s (30%, usu. DM and overlap CTD)
- **Visceral involvement**
  - **pulmonary**: acute alveolitis, chronic ILD, weakness of respiratory muscles
  - **cardiac** (33%): myocarditis, pericarditis, arrhythmias; HF uncommon; ↑ CK-MB & Tn (J Rheumatol 2009;36:2711)
  - **GI**: dysphagia, aspiration
- **Ddx**: drug-induced myopathy (statins, cocaine, steroids, colchicine); infxn (HIV, EBV, CMV); metabolic (hypothyroid, hypo K, hypo Ca); neuromuscular disease (eg, myasthenia gravis); glycogen storage disease; mitochondrial myopathy; muscular dystrophy

Diagnostic studies

- ↑ CK, aldolase, SGOT, and LDH; ± ESR & CRP
- Autoantibodies: ○ ANA (~75%), ○ RF (33%)
- ○ anti-Jo-1 (25%), a/w nonerosive polyarthritis, Raynaud’s, ILD, mechanic’s hands
- ○ anti-Mi-2 (5-10%), more common with DM, may have better prognosis
- ○ anti-SRP (signal recognition peptide), seen in PM, indicates more aggressive disease
- **EMG**: ↑ spontaneous activity, ↓ amplitude, polyphasic potentials with contraction
- **Muscle biopsy**: all with muscle fiber necrosis, degeneration & regeneration
- DM/PM/IBM as above

Treatment (PM and DM, no effective treatment for IBM)

- **High-dose steroids**, add MTX or AZA if tapering fails at 2–3 mo
- **For resistant disease**: IVIg (DM ± PM), MMF, rituximab, CsA, tacrolimus, cyclophosphamide (esp. if ILD or vasculitis)
- **IVIg** for life-threatening esophageal or respiratory muscle involvement
- ✓ for occult malignancy; monitor respiratory muscle strength with spirometry

### Myositides, Myopathies, and Myalgias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Weakness</th>
<th>Pain</th>
<th>↑ CK</th>
<th>↑ ESR</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM/PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>as above</td>
</tr>
<tr>
<td>IBM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>as above</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mild necrosis inflammation atrophy</td>
</tr>
<tr>
<td>Steroid-induced</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>atrophy</td>
</tr>
<tr>
<td>PMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>normal</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>(limited by pain)</td>
<td>(tender points)</td>
<td></td>
<td></td>
<td>normal</td>
</tr>
</tbody>
</table>

**Sjögren’s Syndrome**

Definition and epidemiology

- Chronic dysfunction of **exocrine glands** due to lymphoplasmacytic infiltration
- Can be primary or secondary (a/w RA, scleroderma, SLE, PM, hypothyroidism, HIV)
- More prevalent in women than in men; typically presents between 40 and 60 y of age

Clinical manifestations

- **Dry eyes** (keratoconjunctivitis sicca): ↓ tear production; burning, scratchy sensation
- **Dry mouth** (xerostomia): difficulty speaking/swallowing; dental caries; xerotrichia; thrush
- **Parotid gland enlargement** or intermittent swelling (bilateral)
Other manifestations: chronic arthritis; interstitial nephritis (40%), type I RTA (20%); vasculitis (25%); vaginal dryness/dyspareunia; pleuritis; pancreatitis

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 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
- Biopsy (minor salivary, labial, lacrimal, or parotid gland): lymphoplasmacytic infiltration

Classification criteria (4 of 6 has 94% Se & 94% Sp; Arthritis Rheum 1993;36:340)
1. Dry eyes 5. Objective ↓ in salivary gland function
2. Dry mouth 6. Ab to Ro/SS-A or La/SS-B
3. Schirmer test or Rose-Bengal staining 4. Inflammatory foci on minor salivary gland bx

Treatment
- Ocular: artificial tears, cyclosporine eyedrops
- Oral: sugarfree gum, lemondrops, saliva substitute, hydration, cholinergic Rx
- Systemic: NSAIDs, steroids, DMARDs; treat underlying disease (secondary Sjögren’s)

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

Definition
- MCTD pts have features of SLE, systemic sclerosis, and/or polymyositis, often evolving a dominant phenotype of SLE or systemic sclerosis

Clinical manifestations
- Raynaud’s phenomenon typical presenting symptom
  - Hand edema: “puffy hands,” sclerodactyly, RA-like arthritis without erosions
  - Pulmonary involvement (85%) with pulmonary hypertension, fibrosis
  - GI dysmotility (70%)
  - Low risk for renal HTN crisis or glomerulonephritis; if either, reconsider diagnosis of MCTD

Diagnostic studies
- ANA (95–99%), RF (50%)
- Anti-U1-RNP present by definition in MCTD, but not specific (seen in up to 50% SLE Pts)

Treatment
- As per specific rheumatic diseases detailed above

RAYNAUD’S PHENOMENON

Clinical manifestations (NEJM 2002;347:1001)
- Episodic, reversible digital ischemia, in response to cold or stress, classically: blanching (ischemia) → cyanosis (venule dilatation) → rubor (resolution with reactive hyperemia); color change usually well demarcated; affects fingers, toes, ears, nose
- Associated sx include cold, numbness, & paresthesias
- Primary = Raynaud’s disease (50%; excluded all secondary causes)
  - Onset age 20–40 y, female:male 5:1
  - Clinical: mild, symmetric episodic attacks; no evidence of peripheral vascular disease, no tissue injury, normal nailfold capillary examination, ANA, normal ESR
- Secondary = Raynaud’s phenomenon (50%)
  - Typically, Pts >35 y of age
  - Collagen vascular disease: SSC, SLE, RA, PM-DM, MCTD, Sjögren’s (abnl nailfold exam)
  - Arterial disease: peripheral atherosclerosis, thromboangiitis obliterans (abnormal pulses)
  - Hematologic: cryoglobulinemia, Waldenström’s, antiphospholipid syndrome
  - Trauma (vibration or repetitive motion injury) & drugs (ergot alkaloids)

Treatment
- All: avoid cold, maintain warmth of digits & body; avoid cigarettes, drugs, and trauma
- Mild to moderate: long-acting CCB, β-blockers, topical nitrates, low-dose ASA
- Moderate to severe: sildenafil, bosentan (esp. w/ PHT); consider digital sympathectomy
- Digit-threatening: IV prostaglandins, digital sympathectomy
- Others: ARBs, fish oil (primary RP only; Am J Med 1989;86:158)
### Systemic Lupus Erythematosus (SLE)

**Multisystem inflammatory autoimmune disease with a broad spectrum of clinical manifestations in association with antinuclear antibody (ANA) production**

#### Epidemiology
- Prevalence 15–50/100,000; predominantly affects women 2nd to 4th decade
- Female:male ratio – 8:1; African American:Caucasian ratio – 4:1
- Complex genetics; some HLA assoc.; rare c1q & c2 defic.

#### Classification Criteria and Other Clinical Manifestations of SLE

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Am. Coll. Rheum. Criteria</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional (84%)</td>
<td>Fever, malaise, anorexia, weight loss</td>
<td></td>
</tr>
</tbody>
</table>

**Cutaneous**
- (81%)
  1. **Malar rash** (spares nasolabial folds)
  2. **Discoir rash** (erythematous papules w/ keratosis & plugging)
  3. **Photosensitivity** (rash, fever, NV)
  4. **Oral/nasopharyngeal ulcers**
  5. **Nonerosive arthritis:** episodic, oligoarticular, symmetrical, migratory

**Musculoskeletal**
- (85–95%)
  6. **Serositis:** pleuritis (37%) or pneumonitis, IPF, shrinking (33%) or pericardial effusion

**Cardiopulmonary**
- (33%)
  7. **Proteinuria** (>500 mg/dL or ≥3+ on dipstick) or **urinary cellular casts**

**Renal**
- (77%)
  8. **Seizures or psychosis** without other cause

**Neurologic**
- (54%)
  9. **Hemolytic anemia** (DAT κ or leukopenia (<4000/mm³), or lymphopenia (<1500/mm³), or thrombocytopenia (<100,000/mm³)

**Gastrointestinal**
- (~30%)
  10. Serositis (peritonitis, ascites)

**Hematologic**
- (58%)
  11. **Serologies**

**Other**

**Serologies**
- 10. **ANA**
- 11. **anti-ds-DNA, anti-Sm, or antiphospholipid Abs**

#### Workup
- Detailed history and exam to assess for signs and symptoms of disease
- Autoantibodies: ANA, if ⊕ → ✓
- Antiphospholipid syndrome (VTE w/ ⊕ ACL Abs or ⊕ LAC)
- ESR, ↑ CRP, anti-FF or anti-RNP, RF, anti-CCP
- CBC, Coombs’ test, PTT, APLA (anticardiolipin or lupus anticoagulant ⊕ in 20–40%), C3, C4

---

If ≥4 of 11 criteria met, Se & Sp for SLE ≥95%. However, Pt may have SLE but not have 4 criteria at a given point in time. (*Lancet* 2007;369:587)
### Autoantibodies in SLE

<table>
<thead>
<tr>
<th>AutoAb</th>
<th>Frequency (approx)</th>
<th>Clinical Associations</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>95–99% if active disease 90% if in remission Homogeneous or speckled</td>
<td>Any or all of the broad spectrum of clinical manifestations Sensitive but not specific</td>
<td>May appear yrs before overt disease</td>
</tr>
<tr>
<td>Ro</td>
<td>15–35% anti-Ro in ANA</td>
<td>Sjögren’s/SLE overlap</td>
<td></td>
</tr>
<tr>
<td>La</td>
<td></td>
<td>Neonatal lupus Photosensitivity</td>
<td></td>
</tr>
<tr>
<td>ds-DNA</td>
<td>70%; very specific for SLE Titors parallel disease activity, especially renal disease</td>
<td>Lupus nephritis Vasculitis</td>
<td>Appears mos before or at diagnosis</td>
</tr>
<tr>
<td>Sm</td>
<td>30%; very specific for SLE</td>
<td>Lupus nephritis</td>
<td></td>
</tr>
<tr>
<td>U1-RNP</td>
<td>40% MCTD; Raynaud’s T end not to have nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>histone</td>
<td>SLE 80%, c/w 90% in DLE</td>
<td>Mild arthritis and serositis</td>
<td>At diagnosis</td>
</tr>
</tbody>
</table>

(NEJM 2003:349:1526)

### Treatment of SLE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Arthralgias/arthritis, myalgias, mild serositis</td>
<td>Gastritis, UGIB, Renal failure</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Mild disease complicated by serositis, arthritis, skin Δs</td>
<td>Retinal damage Stevens-Johnson synd. Myopathy</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Low doses for mild disease High doses for major manifestations including renal, hematologic, CNS</td>
<td>Adrenal suppression, osteopenia, avascular necrosis of bone, myopathy</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Severe nephritis, vasculitis or CNS disease (induction ± maintenance)</td>
<td>Myelosuppression Myeloproliferative disorders Immunosuppression/infxn Hemorrhagic cystitis, bladder cancer Infertility; teratogen</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td>Mild nephritis (2nd line) Steroid-sparing agent</td>
<td>Myelosuppression Hepatotoxicity Lymphoproliferative disorders</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>Skin and joint disease Serositis</td>
<td>Myelosuppression Hepatotoxicity Pneumonitis ± fibrosis Alopecia, stomatitis</td>
</tr>
<tr>
<td>Cyclosporine (CsA)</td>
<td>Renal disease</td>
<td>Hyperplastic gums, HTN Hirsutism Renal impairment, anemia</td>
</tr>
<tr>
<td>Rituximab</td>
<td>? Refractory ITP or AIHA</td>
<td>B-cell depletion; PML (?)</td>
</tr>
<tr>
<td>Belimumumab</td>
<td>Refractory SLE: compassionate use only (Arth Rheum 2010:62:201)</td>
<td>B-cell depletion</td>
</tr>
</tbody>
</table>

### Prognosis
- 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 2003:82:239)

### Drug-induced lupus (DLE)
- Drugs: procainamide, hydralazine, penicillamine, minocycline, INH, methyldopa, quinidine, chlorpromazine, diltiazem, anti-TNF
- Clinical: generally milder disease with predominantly arthritis and serositis
- Laboratory: anti-histone (95%); anti-ds-DNA & anti-Sm; normal complement levels
- Course: usually reversible w/in 4–6 wk after stopping medication
VASCULITIS

LARGE-VESSEL VASCULITIS

Takayasu's arteritis ("pulseless disease")
- Systemic granulomatous vasculitis involving Ao and branches; most often subclavian and innominate arteries (~90%), as well as carotid, renal, pulmonary (~50%)
- Most common in Asia and in young women of reproductive age
- Clinical manifestations
  - Phase I: inflammatory period with fever, arthralgias, weight loss
  - Phase II: vessel pain and tenderness, and unequal pulses in extremities, bruits, limb claudication, renovascular hypertension (~50%), neurogenic syncope. Ao aneurysm and AI may accompany aortic involvement.
  - Phase III: burnt out, fibrotic period
- Dx studies:
  - ↑ ESR (75%), CRP; arteriography → occlusion, stenosis, irregularity and aneurysms; carotid Doppler studies; MRA; pathology → focal panarteritis, cellular infiltrate with granulomas and giant cells. MRI useful for monitoring.
- Classification criteria (3 of 5 is 93.5% Se & 91% Sp; Arth Rheum 1990;33:1129)
  1. age < 50 y at dis. onset
  2. temporal artery bx: 3–5 cm, bilat. ↑ yield (Arth Rheum 2009;66:790); look for vasculitis, granul.
  3. if suspect Ao involvement: MRI/MRA or CT-PET to identify stenoses, aneurysms; carotid Doppler studies; pathology → occlusion, stenosis, irregularity and aneurysms; carotid Doppler studies; MRA; pathology → focal panarteritis, cellular infiltrate with granulomas and giant cells. MRI useful for monitoring.
- Treatment: steroids, MTX, antiplatelet Rx, surgical/endovascular revasc

Giant cell arteritis (GCA) (NEJM 2003;349:160)
- Vasculitis affecting cranial branches of aortic arch, especially temporal artery
- 90% of Pts > 60 y, rare < 50 y; female: male ratio ~ 2:1
- Clinical manifestations (JAMA 2002;287:92)
  - constitutional sx: low-grade fevers, fatigue, weight loss, myalgias, anorexia
  - headache, tender temporal arteries and scalp and absent temporal artery pulsation
  - ophthalmic artery (20%)
  - temporal arteritis, but can cause aortitis as well
  - Dx studies: ↑ ESR (75%), CRP; arteriography → occlusion, stenosis, irregularity and aneurysms; carotid Doppler studies; MRA; pathology → focal panarteritis, cellular infiltrate with granulomas and giant cells. MRI useful for monitoring.
  - Classification criteria (3 of 5 is 93.5% Se & 91.2% Sp; Arth Rheum 1990;33:1122)
    1. age < 50 y
    2. new headache
    3. biopsy → vasculitis & granulomas
- Treatment: steroids (if vision threatened do not await path results before starting Rx); 40–60 mg/d for GCA; 10–20 mg/d for PMR; follow clinical status and ESR ≥ CRP

MEDIUM-VESSEL VASCULITIS

Polyarteritis nodosa ("classic" PAN) (JAMA 2002;288:1632)
- Acute or chronic systemic necrotizing vasculitis, typically of renal and other visceral arteries, without granuloma formation
- More common in men; average age of onset ~ 50 y; strongly associated with HBV
  - constitutional sx: weight loss, fevers, fatigue
  - musculoskeletal (64%): myalgias, arthralgias, arthritis
  - renal involvement (60%) with active urinary sediment, hypertension, renal failure
  - nervous system (51%): peripheral neuropathies, mononeuritis multiplex, stroke (44%); abd pain, GI infarction, cholecystitis; GU (25%): ovarian or testicular pain, urogenital lesions (43%); livedo reticularis, purpura, nodules, Raynaud’s cardiac, (36%); coronary arteritis, cardiomyopathy, pericarditis
  - if lung involvement, suspect other vasculitis
• Dx studies: ↑ ESR & CRP, ↑ WBC, rare eosinophilia, HBsAg (in ~30%), ↓ C’, ANCA
  angiogram (mesenteric or renal vessels) → microaneurysms and focal vessel narrowing
  CTA may be adequate to make the dx; MRA is not as sensitive as angi or CTA
  biopsy (sural nerve, skin or affected organ) → vasculitis of small and medium vessel
  arteries with fibrinoid necrosis without granulomas
• Classification criteria (3 of 10 criteria is 82% Se & 87% Sp; Arth Rheum 1990;33:1088)
  1. weight loss ≥4 kg
  2. livedo reticularis
  3. testicular pain/tenderness
  4. myalgias, weakness, leg tenderness
  5. mononeuropathy or polyneuropathy
  6. diastolic BP >90 mmHg
  7. elevated BUN >40 mg/dL or Cr >1.5 mg/dL
  8. Hepatitis B virus
  9. Arteriographic abnormality (aneurysms, occlusion of visceral arteries)
  10. Biopsy → vasculitis of small or medium-sized vessel
• Treatment: steroids, cyclophosphamide; antiviral therapy for HBV-related PAN

### ANCA-ASSOCIATED SMALL-VESSSEL VASCULITIS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gran.</th>
<th>Renal</th>
<th>Pulm.</th>
<th>Asthma</th>
<th>ANCA Type*</th>
<th>ANCA ⊕</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis</td>
<td>⊕</td>
<td>80%</td>
<td>90%</td>
<td>—</td>
<td>c-ANCA (anti-PR3)</td>
<td>90%</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>—</td>
<td>90%</td>
<td>50%</td>
<td>—</td>
<td>p-ANCA (anti-MPO)</td>
<td>70%</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>⊕</td>
<td>45%</td>
<td>70%</td>
<td>⊕</td>
<td>p-ANCA (anti-MPO)</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Predominant ANCA type; either p- or c-ANCA can be seen in all three diseases. (NEJM 1997;337:1512)

**Differential diagnosis of ANCA**
- **c-ANCA (anti-PR3):** Wegener’s granulomatosis, Churg-Strauss, microscopic polyangiitis
- **p-ANCA (anti-MPO):** microscopic polyangiitis, Churg-Strauss, Wegener’s
- **atypical ANCA patterns:** drug-induced vasculitis, nonvasculitic rheumatic diseases, ulcerative colitis, primary sclerosing cholangitis, endocarditis, cystic fibrosis

**Wegener’s granulomatosis**
- Necrotizing granulomatous inflammatory disease with systemic vasculitis, particularly
  involving the upper and lower respiratory tract, and kidney
- Can occur at any age, but ↑ incidence in young and middle-aged adults
- Clinical manifestations
  - pulmonary (90%)
    - upper: sinusitis, otitis (rare in adults), rhinitis, nasal mucosal ulceration, saddle-nose deformity
    - lower: pleurisy, pulmonary infiltrate, nodules, hemorrhage, hemoptysis
  - renal (80%): hematuria, RPGN (pauci-immune)
  - ocular (50%): episcleritis, uveitis, & proptosis from orbital granulomas, corneal ulcer neurologic: cranial and peripheral neuropathies, mononeuritis multiplex
  - hematologic: ↑ incidence DVT/PE (20–30%) when disease active (Annals 2005;142:620)
- Dx studies: 90% ⊕ ANCA (80–95% c-ANCA, remainder p-ANCA)
  - CXR or CT → nodules, infiltrates, cavities; sinus CT → sinusitis
  - ↑ BUN & Cr, proteinuria, hematuria; sediment w/ RBC casts, dysmorphic RBCs
  - biopsy → necrotizing granulomatous inflammation of arterioles, capillaries, veins
- Classification criteria (2 of 4 criteria is 88% Se & 92% Sp; Arth Rheum 1990;33:1101)
  1. nasal or oral inflammation: oral ulcers, purulent or bloody nasal discharge
  2. CXR showing nodules, fixed infiltrates, or cavities
  3. microscopic hematuria or urinary red cell casts
  4. granulomatous inflammation on biopsy
- Treatment (NEJM 2003;349:36; Annals 2009;150:670)
  - Induction: cyclophosphamide PO (2 mg/kg/d × 3–6 mo or pulse 15 mg/kg/d q2–3 wk)
  - & prednisone (1–2 mg/kg/d taper over 6–18 mo)
  - RPGN: consider adding plasma exchange to regimen (J Am Soc Nephrol 2007;18:2180)
**Maintenance:** MTX or AZA for ≥2 y for mild disease. MTX/prednisone may be adequate for induction. Disease relapses: match aggressive disease with aggressive Rx as needed.

↑ ANCA w/o clinical evidence of flare should not prompt Δ Rx (Annals 2007;147:611)

TMP-SMX may prevent upper airway disease relapse incited by respiratory infections.

**Microscopic polyangiitis (MPA)**
- Necrotizing small-vessel vasculitis → glomerulonephritis, pulmonary capillary alveolitis, & dermal leukocytoclastic venulitis
- Not associated with HBV (unlike classic PAN)
- Clinical manifestations: similar to Wegener’s but renal > respiratory involvement; constitutional and neuro sx as per Wegener’s, lower rate of relapse
- Dx studies: 70% ↑ ANCA (almost all p-ANCA), biopsy → necrotizing, pauci-immune inflammation of arterioles, capillaries, & venules; urine sediment and CXR findings similar to those seen in Wegener’s.
- Treatment: as for Wegener’s → cyclophosphamide; high-dose corticosteroids; AZA for maintenance; plasmapheresis.

**Churg-Strauss syndrome**
- Eosinophil-rich granulomatous inflammation involving lung, peripheral nerves, heart, kidneys, and skin
- Rare condition that can present at any age, but typically 30–40 y; a/w HLA-DRB4
- Clinical manifestations:
  - asthma and allergic rhinitis (new asthma in an adult raises suspicion)
  - eosinophilic infiltrative disease or eosinophilic pneumonia
  - systemic small-vessel vasculitis with granulomas
  - neuropathy (incl. mononeuritis multiplex), glomerulonephritis
- Cardiac involvement: coronary arteritis, myocarditis, CHF, valvular insufficiency (Medicine 2009;88:236)
- Dx studies: 50% ↑ ANCA (c-ANCA or p-ANCA), eosinophilia (5–10 k/L, 80%), biopsy → microgranulomas, fibrinoid necrosis, and thrombosis of small arteries and veins with eosinophilic infiltrates; CXR may show shifting pulmonary infiltrates.
- Classification criteria (4 of 6 criteria is 85% Se & 99.7% Sp; Arth Rheum 1990;33:1094)
  1. asthma
  2. eosinophilia > 10%
  3. mono- or polyneuropathy
  4. extravascular eosinophils on biopsy
- Treatment: high-dose corticosteroids (+ cyclophosphamide or other DMARDs if nec.)

**Immune Complex–Associated Small-Vessel Vasculitis**

**Henoch-Schönlein purpura (HSP)**
- Systemic vasculitis characterized by palpable purpura, arthralgia, abd pain, hematuria
- Epidemiology: male > female, children > adults, onset in winter > summer
- Begins after upper respiratory tract infection (esp. Strep) or drug exposure; IgA-mediated
- Clinical manifestations: palpable purpura on extensor surfaces & buttocks; nondeforming polyarthralgias especially involving hips, knees, and ankles; colicky abdominal pain + GB or intussusception; nephritis ranging from microscopic hematuria and proteinuria to ESRD; many have fever.
- Diagnostic studies: normal plt count; skin bx → leukocytoclastic vasculitis with IgA and C3 deposition in vessel wall; renal bx → mesangial IgA deposition.
- Criteria for classification (2 of 4 is 87% Se and 88% Sp; Arth Rheum 1990;33:1114)
  1. palpable purpura
  2. age = 20 y at disease onset
  3. bowel angina
  4. biopsy showing granulocytes in the walls of arterioles or venules
- Treatment: supportive; steroids ± DMARDs for renal or severe disease.

**Cryoglobulinemic vasculitis:** see “Cryoglobulinemia”

**Connective tissue disease–associated vasculitis**
- Vasculitis associated with 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
- Diagnostic studies: skin & sural nerve bx, angiography, EMG; ↓ C’ in SLE; RF in RA
- Treatment: steroids, cyclophosphamide, MTX (other DMARDs).
Cutaneous leukocytoclastic angiitis
- Heterogeneous group of clinical syndromes due to immune complex deposition in capillaries, venules, and arterioles; includes hypersensitivity vasculitis
- Overall the most common type of vasculitis
- Etiologies
  - drugs: penicillin, aspirin, amphetamines, thiazides, chemicals, immunizations
  - infections: strep throat, bacterial endocarditis, TB, hepatitis, staphylococcal infections
  - tumor antigens
  - foreign proteins (serum sickness)
- Clinical manifestations: abrupt onset of palpable purpura, cutaneous ulceration, and transient arthralgias after exposure to the offending agent, variably accompanied by fever, arthralgias, and other organ involvement; peripheral neuropathy
- Dx studies: ↑ ESR, ↓ complement levels, eosinophilia; skin biopsy → leukocytoclastic vasculitis with neutrophils, nuclear fragments 2⁻ to karyorrhexis, Ig + complement deposition on direct immunofluorescence perivascular hemorrhage and fibrinoid deposits distinguished from HSP by absence of IgA deposition in skin, and from cryoglobulinemic vasculitis by absence of cryoglobulins
- Classification criteria (3 of 5 criteria is 71% Se & 84% Sp; Arh Rheum 1990;33:1108)
  1. age >16 y
  2. medication taken at disease onset
  3. palpable purpura
  4. maculopapular rash
  5. biopsy showing granulocytes in a perivascular or extravascular location
- Treatment: withdrawal of offending agent ± rapid prednisone taper

Behcet’s syndrome
- Multisystem vasculitis that may involve small-, medium- and large-sized vessels, characterized by recurrent oral and genital ulcers with variable manifestations affecting the skin, eye, CNS, and musculoskeletal system
- Associated with HLA B51, highest prevalence on the old Silk Road (Turkey) and other Asian countries
- Classification criteria (#1 + ≥2 others is 91% Se & 96% Sp; Lancet 1990;335:1078)
  1. recurrent oral aphthous ulceration (at least 3 times in one year)
  2. recurrent genital ulceration
  3. eye lesions: uveitis (with hypopyon), scleritis, retinal vasculitis, optic neuritis
  4. skin lesions: pustules, papules, folliculitis, erythema nodosum
  5. pathergy test (prick forearm with sterile needle → pustule)
- Other clinical manifestations
  - arthritis: mild, symmetric, chronic and nondestructive, involving knees and ankles
  - neurologic: focal deficits, pleocytosis, inflammatory infiltrates w/o vasculitis
  - vascular: superficial or deep vein thrombosis (25%); arterial stenosis, occlusion, and aneurysm can also occur
- Evaluation: ulcer bx, cerebral angio (rarely necessary); slitlamp exam and funduscopy
  - mucocutaneous
    - mild: colchicine, topical steroids, dapsone
    - severe: oral steroids, AZA, thalidomide (males), MTX, CsA, anti-TNF
  - arthritis: NSAIDs, colchicine, steroids, AZA, anti-TNF, IFN-α2a
  - ocular: steroids, AZA, infliximab, IFN-α2a, CsA, cyclophosphamide, chlorambucil
  - vascular: large artery (esp pulmonary), high-dose steroids + cyclophosphamide then AZA maintenance; for venous thrombosis, control inflammation ± anticoagulation
  - CNS
    - parenchymal: steroids, MTX, AZA, infliximab, adalimumab, cyclophosphamide, chlorambucil
    - dural sinus thrombosis: steroids and anticoagulation
  - AZA early helps prevent ocular disease and ulcerations, and improves prognosis
Definition & Types

- Proteins that precipitate on exposure to the cold, characterized by their composition

<table>
<thead>
<tr>
<th>Types of Cryoglobulinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>Proportion of cases</td>
</tr>
<tr>
<td>Cryoglobulin</td>
</tr>
<tr>
<td>Common etiologies</td>
</tr>
<tr>
<td>Primary manifestations</td>
</tr>
</tbody>
</table>

Etiologies

- Infections (type II & III): viral (HCV, HBV, HAV, EBV, CMV, HIV), bacterial (endocarditis, Lyme, syphilis), fungal (coccidiomycosis), and parasitic (malaria, schistosomiasis)
- Hematologic diseases (type I): MM, NHL, HL, CLL, CML, TTP, myelodyssplasia
- Autoimmune syndromes (type III predominant, also type II): SLE, Sjögren’s syndrome, PAN, RA, sarcoid, IBD
- Essential (idiopathic)
- Renal transplant recipients

Pathophysiology

- Chronic immune stimulation and/or lymphoproliferation → immune complex (IC) formation
- Defective/insufficient IC clearance → IC deposition with complement activation
- Promotes: platelet aggregation → small vessel thromboses, inflammation → vasculitis

Clinical manifestations (systemic sx usually due to type II > III)

- General: weakness, low-grade fever
- Dermatologic (can also be seen in type I): lower extremity purpura, livedo reticularis, leg ulcers, Raynaud’s phenomenon, leukocytoclastic vasculitis
- Rheumatologic: symmetric, migratory arthralgias of small or medium joints
- Renal (50%): glomerulonephritis (proteinuria, hematuria, ARF, hypertension, edema)
- Hematologic: anemia, thrombocytopenia
- GI: abdominal pain, hepatosplenomegaly, abnormal LFTs
- Neurologic: peripheral neuropathy and mononeuritis multiplex

Diagnostic studies

- Cryoglobulins – proteins that precipitate from serum or plasma when cooled; cryocrit is quantitation of cryoprotein, does not nec. correlate w/ disease activity
- Must distinguish from cryofibrinogenemia – proteins that precipitate from plasma only (eg, fibrin, fibrinogen). Separate disorder that can be seen in CTD, infection, malignancy. Usually axs or may promote thrombosis.
- ★ rheumatoid factor (RF)
- False elevations in WBC or plt count on automated CBC, due to cryoprecipitation
- ★ C4 levels, variable C3 levels, ↑ ESR
- Must keep blood warmed to 37°C at all times en route to lab; early cooling causes false ★ cryoglobulin, loss of RF and ↓ complement
- In HCV-associated type 2 cryoglobulinemia: ★ HCV RNA, ★ anti-HCV Ab
- Biopsy of affected tissue (skin, kidney)

Treatment

- Treat underlying disorder:
  - chemotherapy and/or radiation for lymphoproliferative disorders
  - antiviral therapy and/or rituximab for HCV (Arth Rheum 2009;60:2531)
  - DMARDs for rheumatic disease
  - NSAIDs for control of mild symptoms for Pts with normal renal function
  - Prednisone + other immunosuppressants (eg, cyclophosphamide) for major organ involvement
- Plasmapheresis in severe disease
AMYLOIDOSIS

Accumulation of insoluble fibrillar proteins that form β-pleated sheets

Classification of Amyloidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Precursor</th>
<th>Causative diseases</th>
<th>Organ systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (Primary)</td>
<td>Ig light chain (monoclonal)</td>
<td>MM Light chain disease (∝ &gt; κ) MGUS, WM</td>
<td>Renal, cardiac, GI, neuro, cutaneous, hepatic, pulmonary, musculoskeletal, heme</td>
</tr>
<tr>
<td>AA (Secondary)</td>
<td>Serum amyloid (SAA)</td>
<td>Inflam: RA, IBD, FMF Chronic infxn: osteo, TB Neoplasms: renal, HD</td>
<td>Renal, GI, hepatic, neuro, cutaneous</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Transthyretin, et al.</td>
<td>Mutant proteins</td>
<td>Neurologic, cardiac</td>
</tr>
<tr>
<td>Senile</td>
<td>TTR, ANP</td>
<td>Normal proteins; 2° aging</td>
<td>Cardiac, aorta, GI</td>
</tr>
<tr>
<td>Aβ-M</td>
<td>β2-microglobulin</td>
<td>Dialysis-associated β2m (normally renally excreted)</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Organ-specific</td>
<td>β-amyloid protein</td>
<td>Peptide hormones</td>
<td>Localized production and processing</td>
</tr>
</tbody>
</table>

(Adapted from NEJM 1997;337:898; 2003;349:583; 2007;356:236)

Clinical Manifestations of Amyloidosis

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestations</th>
<th>Amyloid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Proteinuria or nephrotic syndrome</td>
<td>AL, AA</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Cardiomyopathy (restrictive &amp; dilated) ↓ QRS amplitude, conduction abnormalities, AF Orthostatic hypotension</td>
<td>AL, hereditary, senile, organ-specific</td>
</tr>
<tr>
<td>GI</td>
<td>Diarrhea, malabsorption, protein loss Ulceration, hemorrhage, obstruction</td>
<td>all systemic</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Peripheral neuropathy with painful paresthesias</td>
<td>hereditary, AL, organ-specific, Aβ-M</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Macroglial → dysphoria and dysphagia</td>
<td>Organ-selective</td>
</tr>
<tr>
<td>Hepatic &amp; Splenic</td>
<td>Hepatomegaly, usually without dysfunction Splenomegaly, usually without leukopenia or anemia</td>
<td>all systemic</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Deposition with rare hormonal insufficiency</td>
<td>organ-specific</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgias and arthritis</td>
<td>AL, Aβ-M</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Airway obstruction</td>
<td>AL, AA</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Factor X deficiency</td>
<td>AL</td>
</tr>
</tbody>
</table>

Diagnostic studies
- If suspect AL → ✓ SIEP (not SPEP or UPEP) & free light chains, ± BM bx
- If suspect renal involvement ✓ U/A (proteinuria)
- If suspect cardiac involvement ✓ ECG (i voltage, conduction abnl), echo (biventricular thickening with “granular sparkling” appearance; ↑ wall w/o ↑ volt 75% Se, 95% Sp), MRI
- Serum amyloid P scintigraphy (NEJM 1990;323:508)
- Biopsy (abdominal SC fat pad, rectal, or affected tissue [eg, heart]) → apple-green birefringence on Congo red stain
- Genetic testing for hereditary forms

Treatment
- AL: melphalan + dex, ± autologous SCT if limited organ involvement (NEJM 2007;357:1083)
- AA: Rx underlying disease; colchicine for FMF (NEJM 2007;356:23); eprodisate promising for renal disease (NEJM 2007;356:2349)
- For hereditary amyloidoses in which amyloid precursor protein is produced by the liver (eg, TTR), liver transplantation may prevent further deposition
- If cardiac involvement: diuretics; avoid digoxin & CCB; may not tolerate vasodilators
- Heart, kidney, and liver transplantation may be considered in those with advanced disease

Prognosis
- AL amyloid: median survival ~ 12–18 mo; if cardiac involvement, median survival ~ 6 mo
- AA amyloid: median survival ~ 11 y (NEJM 2007;356:2361)
CHANGE IN MENTAL STATUS

Definitions (nb. description of state better than imprecise use of terms)

- **Confusion** (encephalopathy): unable to maintain coherent thought process
- **Delirium**: waxing & waning confusional state w/ additional sympathetic signs
- **Drowsiness**: level of consciousness, but rapid arousal to verbal or noxious stimuli
- **Stupor**: impaired arousal to noxious stimuli, but some preserved purposeful movements
- **Coma**: sleeplike state of unresponsiveness, with no purposeful response to stimuli

### Etiologies

<table>
<thead>
<tr>
<th>Primary Neurologic (usually with focal signs)</th>
<th>Systemic (especially in elderly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Cardiac: severe CHF, HTN encephalopathy</td>
</tr>
<tr>
<td>Seizure (postictal, status, nonconvulsive)</td>
<td>Pulmonary: ↓ P,O₂, ↑ P,CO₂</td>
</tr>
<tr>
<td>Infection: meningocoelephalitis, abscess</td>
<td>Gl: liver failure, constipation, Wilson's</td>
</tr>
<tr>
<td>Epidural/subdural hematoma</td>
<td>Renal: uremia, hyponatremia and hypernatremia</td>
</tr>
<tr>
<td>Concussion</td>
<td>Endocrine: ↓ glc, DKA, HHNS, ↑ Ca, hypothyroidism or hyperthyroidism, Addisonian crisis</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>ID: pneumonia, UTI, sepsis</td>
</tr>
<tr>
<td>Complicated migraine</td>
<td>Hypothermia and hyperthermia</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>Medications (espec. opiates &amp; sedatives)</td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>Alcohol &amp; toxins</td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td></td>
</tr>
<tr>
<td>TTP</td>
<td></td>
</tr>
</tbody>
</table>

### Initial evaluation

- **History** (typically from others): previous or recent illnesses, including underlying dementia or psychiatric disorders; head trauma; meds, drug or alcohol use
- **General physical examination**: evaluate for asterixis, signs of trauma, stigmata of liver disease, embolic phenomena, signs of drug use, nuchal rigidity (may be present in meningitis or subarachnoid hemorrhage, but do not test if question of trauma/cervical spine fracture)
- **Neurologic examination** (if possible, off sedatives/paralytics)
  - Observation for response to stimuli, papilledema, spontaneous movements
  - Pupil size & reactivity: pinpoint → opiates; midposition & fixed → midbrain lesion; fixed & dilated → severe anoxic encephalopathy, herniation
  - Intact oculocephalophic (“doll’s eyes,” eyes move opposite head movement) or oculovestibular (“cold calorics,” eyes move slowly toward lavaged ear and then quick horizontal nystagmus away) imply brainstem intact
  - Other cranial nerves: eye position at rest, response to visual threat, corneal reflex, facial grimace to nasal tickle, cough/gag (with ET tube manipulation if necessary)
  - Look for s/s of ↑ ICP: HA, vomiting, HTN, ↑ HR, papilledema, unilateral dilated pupil
  - Motor response in the extremities to noxious stimuli, noting purposeful vs. posturing: decerebrate → arms extended; decorticate → arms flexed; both with legs extended
  - Deep tendon reflexes, Babinski response

### Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye opening</th>
<th>Best verbal response</th>
<th>Best motor response</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Follows commands</td>
<td>Localizes pain</td>
<td>6</td>
</tr>
<tr>
<td>To voice</td>
<td>Inappropriate words</td>
<td>Withdraws from pain</td>
<td>4</td>
</tr>
<tr>
<td>To painful stimuli</td>
<td>Unintelligible sounds</td>
<td>Decorticate posturing</td>
<td>3</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

*Sum points from each of the 3 categories to calculate the score*

### Initial treatment

- Control airway, monitor vital signs, IV access
- Immobilization of C-spine if concern for cervical trauma
- Thiamine (100 mg IV) *prior to dextrose* to prevent exacerb. of Wernicke's encephalopathy
- Dextrose (50 g IV push)
- Naloxone 0.01 mg/kg if opiates suspected; flumazenil 0.2 mg IV if benzos suspected
- If concern for ↑ ICP and herniation: ↑ head of bed; osmotherapy with mannitol; hyperventilation; dexamethasone; consider emergent surgical decompression
Diagnostic studies
• Head CT; radiographs to r/o C-spine fracture; CXR to r/o PNA (in elderly)
• Laboratory: electrolytes, BUN, Cr, ABG, LFTs, CBC, PT, PTT, NH₃, tox screen, TSH, U/A
• Lumbar puncture to r/o meningitis
• EEG to r/o nonconvulsive seizures

Anoxic Brain Injury

Prevalence
• Pts w/ at least 5 min of cerebral hypoxia at risk
• 1.5 million cardiac arrests per year in U.S.; 30% survive, but only 10–20% return to independence

Initial evaluation
• Neuro exam: focus on coma exam → cranial nerves, motor response to pain
• Imaging; usually not informative w/in first day after arrest, but should be done prior to initiating hypothermia if patient found down or witnessed to hit head

<table>
<thead>
<tr>
<th>Coma Exam Checklist</th>
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<tbody>
<tr>
<td>Cranial nerves</td>
</tr>
<tr>
<td>Motor</td>
</tr>
<tr>
<td>Sensory</td>
</tr>
<tr>
<td>Reflexes</td>
</tr>
</tbody>
</table>

Induced hypothermia (NEJM 2002;346:549, 559)
• Indications: comatose w/in 6 h following cardiac arrest (not isolated resp. arrest).
  Fully studied only in VT/VF, but acceptable to perform after asystole or PEA arrest.
• Contraindications: active bleeding, including cerebral; known sepsis; recent surgery or trauma (relative); CV instability; clear improvement in neurologic exam (purposeful movements, vocalizations)
• Method: target temperature 32–34°C × 24 h (from time of initiation of cooling)
  cold saline infusions; ice packs to the head, neck, and torso; cooling blankets may use cooling vest or endovascular catheter if available
• Complications
  cardiac dysrhythmias (bradycardia most common): if significant dysrhythmia or hemodynamic instability, d/c cooling and actively rewarm patient (this is only circumstance in which active rewarming should be performed; o/w rewarm no faster than 0.5°C per h)
  coagulopathy: Pts can receive fibrinolytics, GP IIb/IIIa inhibitors, etc., and still undergo cooling.
  infection: surveillance blood cultures during cooling
  hyperglycemia
  hypokalemia during cooling, hyperkalemia w/ rewarming; keep K 4–5 mEq/L

Ongoing evaluation
• Neuro exam: daily focus on coma exam, cranial nerves, GCS score. Pt needs to be off sedation for 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 day 1–3
• Imaging: noncontrast CT 24 h after arrest; if unrevealing, MRI around day 3–5
• EEG: should be performed in any Pt w/ seizures or myoclonus (to r/o status epilepticus); should be considered in all unresponsive Pts (to r/o nonconvulsive seizures)
• Somatosensory evoked potentials (SSEP): helpful for prediction of poor outcome if absent cortical responses bilaterally; should not be performed earlier than 48 h after arrest (72 h if cooled)

Prognosis (Neuro 2006;67:203; NEJM 2009;361:605)
• Uniformly poor prognosis can be predicted at 72 h only in Pts who have absent pupillary and corneal reflexes, and no motor response to pain; also with absent SSEPs at 48 h
• Otherwise, requires multifactorial approach, considering neuro exam, age and comorbid diseases, and ancillary data (serum NSE, neuroimaging, EEG, SSEP)
• When in doubt, err on the side of giving more time (especially in younger Pts and induced hypothermia Pts)
Definitions (NEJM 2003;349:1257)

• **Seizure** – abnormal, paroxysmal, excessive discharge of CNS neurons; occurs in 5–10% of the population; clinical manifestations can range from dramatic to subtle

• **Epilepsy** – recurrent seizures due to an underlying cause; 0.5–1.0% of population

• **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
  - **Myoclonic** (infantile spasms & juvenile myoclonic epilepsy): sudden, brief contraction

• **Partial or focal seizures** (involves discrete areas, implies a focal, structural lesion)
  - **Simple:** without impairment of consciousness; may be motor, sensory, or autonomic
  - **Complex:** with impairment of consciousness → automatisms
  - **Partial with secondary generalization:** starts focal, becomes diffuse

**Ddx**

- **Syncope**
  - **Feature** | **Seizure** | **Syncope**
  - Aura | Unusual behavior/automatisms | Diaphoresis, nausea, tunnel vision
  - Convulsions | Variable duration | Usually <10 sec
  - Post-ictal state | Yes | No
  - Other clues | Tongue biting, incontinence | Skin pallor, clamminess

• **Nonepileptic seizure** (NES, aka “psychogenic”): may see side-to-side head turning, asymmetric large-amplitude limb movements, diffuse twitching w/o LOC, and crying or talking during event

• Other: metabolic disorders (eg, alcoholic blackouts, hypoglycemia); migraines; TIA; narcolepsy; nonepileptic myoclonus; tics; asterixis

**Etiologies**

- Alcohol withdrawal, illicit drugs, meds (eg, β-lactams, bupropion, tramadol, metronidazole, meperidine, CsA, antidep., clozapine can lower seizure threshold)
- Brain tumor or penetrating trauma
- Cerebrovascular disease, including subdural hematomas, hypertensive encephalopathy
- Degenerative disorders of the CNS (eg, Alzheimer’s)
- Electrolyte (hyponatremia) & other metabolic (eg, uremia, liver failure, hypoglycemia)

**Clinical manifestations**

- **Aura** (sec to mins): premonition consisting of abnormal smells/tastes, unusual behavior, oral or appendicular 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).
- **Status epilepticus**: continuous tonic-clonic seizure ≥30 min, or repeated seizures such that there is no resolution of postictal periods. Complications include neuronal death, rhabdomyolysis, and lactic acidosis.
- **Nonconvulsive status epilepticus** alteration of awareness (ranging from confusion to coma) w/o motor manifestations. Dx with EEG.

**Clinical evaluation**

- Seizure: patient usually w/o recollection, must talk to witnesses unusual behavior before seizure (ie, an aura) type & pattern of abnl movements, incl. head turning & eye deviation (gaze preference usually away from seizure focus) loss of responsiveness
- HPI: recent illnesses/fevers, head trauma, sleep deprivation, medication compliance
- PMH: prior seizures or FHx, prior meningitis/encephalitis, prior stroke or head trauma
- Medications, 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**

- Laboratory: full electrolytes, BUN, Cr, glc, LFTs, tox screen, medication levels
- EEG: if frequent, can capture repetitive rhythmic activity (nb, generalized seizures will always have abnl EEG; partial may not); eval for interictal epileptiform activity
(eg, spikes or sharp waves), but seen in up to 2% of normal population; sleep deprivation ↑ dx yield of EEG; video monitoring may help w/ nonepileptic seizures
• MRI to r/o structural abnormalities; ↑ Se w/ fine coronal cuts of frontal & temporal lobes
• LP (after r/o space-occupying lesion): if suspect meningitis (eg, fever, ↑ WBC, nuchal rigidity) or encephalitis and in all HIV Pts

**Treatment** *(Lancet 2006;367:1087 & 2007;369:1000, 1016; NEJM 2008;359:166)*

• Treat any underlying causes, including CNS infections, intoxication, or withdrawal, etc.
• Antiepileptic drug (AED) therapy is usually reserved for Pts w/ underlying structural abnormality or an idiopathic seizure plus (i) status epilepticus on presentation, (ii) focal neurologic exam, (iii) postictal Todd’s paralysis, or (iv) abnormal EEG
• For Pts w/ infrequent seizures, early (vs. delayed) intervention w/ AED ↑ time to seizure recurrence, but has no effect on long-term seizure-free status *(Lancet 2005;365:2007)*
• AED choice dependent on type of seizure, side effects, cost, 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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Avg daily dose</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>300–400 mg</td>
<td>Gum hyperplasia</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>600–1800 mg</td>
<td>Aplastic anemia, ↑ WBC, rash, hepatotoxicity, ↓ Na</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>750–2000 mg</td>
<td>Hepatotoxicity, ↑ NH₃, ↑ wt, hair loss</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>60–180 mg</td>
<td>Rash</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>750–1250 mg</td>
<td>Rash, bone marrow suppression</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900–2400 mg</td>
<td>GI upset, wt gain</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>200–400 mg</td>
<td>Rash (Stevens-Johnson syndrome)</td>
</tr>
<tr>
<td>Leviteracitam</td>
<td>1500–3000 mg</td>
<td>GI upset (rare)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>1200–2400 mg</td>
<td>Hyponatremia, rash</td>
</tr>
<tr>
<td>Topiramate</td>
<td>100–400 mg</td>
<td>i. wt, hypohidrosis, kidney stones, glaucoma</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>200–400 mg</td>
<td>i. wt, hypohidrosis, kidney stones</td>
</tr>
</tbody>
</table>

**Status epilepticus** *(consult neurology)*

• Place Pt in semiprone position to ↓ risk of aspiration
• Oral airway or, if prolonged, endotracheal intubation
• IV access, start normal saline infusion
• STAT labs including glc, Na, Ca, serum & urine toxicology screen, anticonvulsant levels
• Thiamine (100 mg IV) prior to dextrose to prevent exacerb. of Wernicke’s encephalopathy
• Dextrose (50 g IV push)

### Treatment of Status Epilepticus *(Proceed to next step if seizures continue)*

<table>
<thead>
<tr>
<th>Step</th>
<th>Antiepileptic</th>
<th>Dosing regimen</th>
<th>Typical adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lorazepam or Diazepam</td>
<td>0.1 mg/kg at 2 mg/min</td>
<td>Successive 2–4 mg IV pushes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 mg/kg at 5 mg/min</td>
<td>Successive 5–10 mg IV pushes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lorazepam marginally slower onset of action (3 vs. 2 min) but at least as efficacious (success 65%) &amp; longer duration of effect (12–24 h vs. 15–30 min)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Phenytoin or Fosphenytoin</td>
<td>20 mg/kg at 50 mg/min</td>
<td>1.0–1.5 g IV over 20 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg PE/kg at 150 mg/min + 5–10 mg/kg if still seizing</td>
<td>1.0–1.5 g PE IV over 5–10 min + 500 mg IV if still seizing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent steps typically mandate intubation, EEG monitoring, and ICU admission</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Phenobarbital</td>
<td>20 mg/kg at 50–75 mg/min + 5–10 mg/kg if still seizing</td>
<td>1.0–1.5 g IV over 30 min + 500 g IV if still seizing</td>
</tr>
<tr>
<td>4</td>
<td>General anesthesia with midazolam, pentobarbital, or propofol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALCOHOL WITHDRAWAL

Pathophysiology
• Alcohol is 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
• Need to consider other dx: CNS infxn, CNS bleed, drug O/D, acute liver failure, GIB

Clinical Institute Withdrawal Assessment scale for alcohol (CIWA-Ar)
• Assign points for each of the 10 criteria; add points to calculate score

<table>
<thead>
<tr>
<th>Points</th>
<th>Anxiety</th>
<th>Agitation</th>
<th>Tremor</th>
<th>HA</th>
<th>Orientation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Oriented</td>
</tr>
<tr>
<td>1</td>
<td>Somewhat</td>
<td>Not visible, but felt at fingertips</td>
<td>Very mild</td>
<td>Cannot do serial additions</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Disorient. by ≥ 2 d</td>
<td>Mod severe</td>
<td>Disoriented to person or place</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Guarded</td>
<td>Restless</td>
<td>Moderate w/ hands extended</td>
<td>Mod severe</td>
<td>Disoriented to person or place</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Oriented</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Oriented</td>
</tr>
<tr>
<td>7</td>
<td>Panic</td>
<td>Pacing or thrashing</td>
<td>Severe</td>
<td>Extremely severe</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>N/V</th>
<th>Sweats</th>
<th>Auditory halluc.</th>
<th>Visual</th>
<th>Tactile disturb</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Moist palms</td>
<td>Very mild</td>
<td>Very mild photosens.</td>
<td>Very mild paresthesias</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Mild paresthesias</td>
<td>Mild photosens.</td>
<td>Mild paresthesias</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Mod photosens.</td>
<td>Mod paresthesias</td>
<td>Mod paresthesias</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Intermittent w/ dry heaves</td>
<td>Beads</td>
<td>Mod severe</td>
<td>Mod severe visual halluc.</td>
<td>Mod severe visual hallucinations</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Very severe</td>
<td>Very severe</td>
<td>Very severe</td>
<td>Very severe</td>
<td>Very severe</td>
</tr>
<tr>
<td>7</td>
<td>Constant</td>
<td>Drenching</td>
<td>Continuous</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

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 q10–15 min (or lorazepam 2–4 mg IV q15–20 min) until appropriate sedation achieved, then titrate to CIWA-Ar scale, evaluating q1h until score <8 × 8h, then q2h × 8h, and if stable then q4h (JAMA 1994;272:519)
  • If refractory to BDZ, prn, consider BDZ gtt, phenobarbital or propofol (& intubation)
  • Do not give haloperidol (↓ seizure threshold) or βB / central α2-agonists (mask sx)
  • Mechanical restraints as needed until chemical sedation achieved
  • Volume resuscitation as needed; thiamine then gtc to prevent Wernicke’s encephalopathy (ataxia, ophthalmoplegia, short-term memory loss); replete K, Mg, PO4
• 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 × 24h, then 25–50 mg q6h × 2d
STROKE

Ischemic (~70%)

Etiologies

- Embolic (~75%): artery → artery, cardioembolic, paradoxical (NEJM 2007;357:2262), cryptogenic
- Thrombotic (~25%): lacunar (arteriolar, seen in HTN & DM) or large vessel
- Other: dissection, vasculitis, vasospasm, hyperviscosity, watershed

Clinical Manifestations

<table>
<thead>
<tr>
<th>Artery/Ophthalmic</th>
<th>Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA/Ophthalmic</td>
<td>Amaurosis fugax (transient monocular blindness)</td>
</tr>
<tr>
<td>ACA</td>
<td>Hemiplegia (leg &gt; arm) Confusion, abulia, urinary incontinence, primitive reflexes</td>
</tr>
<tr>
<td>MCA</td>
<td>Hemiplegia (arm &amp; face &gt; leg); hemianesthesia; homonymous hemianopia Aphasia if dom. hemisphere: sup. div. → expressive; inf. → receptive Apraxia and neglect if nondominant hemisphere Drowsiness &amp; stupor seen later (due to brain swelling)</td>
</tr>
<tr>
<td>PCA</td>
<td>Thalamic syndromes with contralateral hemisensory disturbance, aphasia Macular-sparing homonymous hemianopia</td>
</tr>
<tr>
<td>Vertebral</td>
<td>Wallenberg syndrome → numbness of ipsilateral face and contralateral limbs, diplopia, dysarthria, ipsilateral Horner’s</td>
</tr>
<tr>
<td>Basilar</td>
<td>Pinpoint pupils, long tract signs (quadriplegia and sensory loss), cranial nerve abnormalities, cerebellar dysfunction</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>Vertigo, nausea/vomiting, diplopia, nystagmus, ipsilateral limb ataxia</td>
</tr>
<tr>
<td>Lacunar</td>
<td>Pure hemiplegia, pure hemianesthesia, ataxic hemiparesis, or dysarthria + clumsy hand</td>
</tr>
</tbody>
</table>

Transit ischemia attacks (TIAs) are sudden neurologic deficits caused by cerebral ischemia w/o evidence of infarction on imaging; sx typically resolve w/in 24 h (usually w/in 1 h); a harbinger of stroke.

Ddx: seizure, migraine, syncope, hypoglycemia, anxiety

Physical examination

- General including rhythm, murmurs, carotid & subclavian bruits, signs of peripheral emboli
- Neurologic including NIH stroke scale (NIHSS)

Diagnostic studies

- Laboratory: electrolytes, Cr, glc, CBC, PT, PTT, LFTs, ESR, tox screen, BCx (if suspicion for endocarditis); once stable, lipids, HbA1c, TSH, homocysteine, Lp(a), hypercoag w/u (if ≥65 y or in those w/ cryptogenic strokes; ideally drawn before anticoagulation initiated)
- ECG
- Urgent CT is usually the initial imaging study because of its rapidity and availability first, noncontrast CT to r/o hemorrhage (Se for ischemic sx is ~20% w/in 12 h) then, CT angi/perfusion to evaluate cerebrovascular patency and areas of reversible ischemia (if intra-arterial catheter-based interventions are being considered)
- MRI offers superior imaging but may not identify acute hemorrhage (although data suggest may be equivalent; JAMA 2004;292:1823) and may be falsely negative for small brainstem strokes w/in 1st 3 h; should be delayed if Pt is unstable or will delay therapy
- Carotid Doppler U/S, transcranial Doppler (TCD)
- Holter monitoring to assess for paroxysmal AF
- Echocardiography w/ bubble study to r/o PFO or atrial septal aneurysm (confer risk of stroke; NEJM 2001;345:1740), cardiac thrombus, valvular vegetations

Treatment of TIA (NEJM 2002;347:1687)

- Immediate evaluation and treatment as clinically indicated (Lancet 2007;370:1432)
- Consider heparin IV if: known or presumptive cardioembolic TIAs or if bridging to mechanical intervention (CEA, stenting) for large vessel atherothrombotic dis.
- Antiplaquelet therapy with ASA, clopidogrel, or ASA + dipyridamole
- Carotid revascularization if sx ≥70% ipsilateral stenosis (see later)

Risk of progression of TIA to stroke (Lancet 2007;369:283)

- ABCD<sup>2</sup>: Age ≥60 y (+1); BP ≥140/90 (+1); Clin. features: unilateral weakness (+2), speech impairment w/o weakness (+1); Duration ≥60 (+2) or 10–59 min (+1); Diabetes (+1)
- Risk of stroke at 2 d: low risk (0–3) ~ 1.0%; moderate (4–5) ~ 4.1%; high (6–7) ~ 8.1%
- Risk of progression higher for TIAs due to large artery/lacunar dis. (vs. cardioembolic)
Treatment of ischemic stroke (NEJM 2008;359:1317; Lancet 2010;375:169S)

- Thrombolysis (IV): 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, large deficit, OI hemorrhage, and OI contraindication to lysis. For Pts Rx’d w/in 3 h, 12% absolute ↑ in excellent functional outcome, 5.8% absolute ↑ ICH, trend toward 4% absolute ↓ mortality (NEJM 1999;333:1381)
- Intra-arterial therapy with thrombolysis (JAMA 1999;282:2003) or catheter-based techniques promising (66% rate of recanalization) but still experimental; currently reserved for occlusion of a major vessel (ICA, MCA, basilar)
- Anticoag w/ UFH of no proven benefit w/ ↑ risk of hemorrhagic transformation consider infusion w/o bolus if Pt not thrombolysed and having progressive sx long-term warfarin if embolic stroke; no role in nonembolic stroke (NEJM 2001;345:1444)

Antiplatelet therapy

- ASA ↓ death & recurrent stroke (Stroke 2000;31:1240) and is superior to warfarin alone (NEJM 2005;352:1305)
- Dipyridamole + ASA superior to ASA alone (Lancet 2006;367:1665)
- Clopidogrel + ASA not more effective than ASA alone and ↓ bleeding (Lancet 2004;364:331)
- Dipyridamole + ASA = clopidogrel alone in risk of recurrent stroke, and ↓ bleeding w/ clopidogrel, but study limited by preponderance of small- vessel subtype (NEJM 2008;359:1238)
- BP should not be lowered acutely unless severe (SBP >200) or evidence of MI or CHF if considering thrombolysis, then lower to <180/110 with nitrates or labetalol
- DVT prophylaxis: enoxaparin more efficacious than UFH (Lancet 2007;369:1347)
- Cerebral edema peaks at 3–4 d postsstroke → ↑ ICP requiring elevated head of bed >30°; intubation & hyperventilation to PaCO2 ~30 (transient benefit); osmotherapy with mannitol IV 1 gm/kg → 0.25 g/kg q6h; ± hypertonic saline surgical decompression
- Statin → ↓ in recurrent stroke & ↓ MACE (Lancet 2002;360:7; NEJM 2006;355:549)

Carotid revascularization

- Carotid endarterectomy (if institutional morbidity & mortality ≤6%) indicated for: sx stenosis ≥70% (! 50–69% if male, age ≥75 y, or recent sx) → 65% ↓ stroke (NEJM 1991;325:445; Lancet 2004;363:915)
- Asx stenosis ≥70% & <75 y → ~50% ↓ stroke (Lancet 2004;363:1491)

Patent foramen ovale (PFO) (NEJM 2005;353:2361)

- Present in ~27% of population; may be a/w stroke, but yearly risk 0.1% in healthy pop.
- Features a/w ↑ risk of stroke: ≥4 mm separation, R → L shunting at rest, ↑ septal mobility
- If PFO & stroke/TIA: no evidence to favor warfarin over ASA (Circ 2002;105:2625); consider anticoagulation if Pt is at high risk or has DVT/PE; closure trials ongoing

Hemorrhagic (~30%)

Etiologies

- Intracerebral (~90%): HTN (brainstem/cerebellum, basal ganglia), AVM, amyloid angiopathy (lobar), anticoagulation/thrombolysis, venous thrombosis, tumors
- Subarachnoid (SAH, ~10%; Lancet 2007;369:306): ruptured aneurysm, trauma

Clinical manifestations

- Impairment in level of consciousness, vomiting ↑ headache, may cause progressive focal neurologic deficit depending on site of hemorrhage, nuchal rigidity if SAH present

Diagnostic studies

- CT or ↑ MRI (JAMA 2004;292:1823)
- Angiography (CT or conventional) to determine the source of bleeding (aneurysm, AVM)
- LP to ↑ for xanthochromia if no evidence of hemorrhage on CT and suspicious for SAH

Treatment

- Reverse any coagulopathies
- Platelets: keep >100k; unclear if transfusions necessary for patients on ASA
- Recombinant activated factor VII is currently investigational, but may ↓ hematoma expansion and mortality at the expense of ↑ risk of adverse thromboembolic events (NEJM 2005;352:777)
- Strict BP control w/ goal SBP <140, unless risk for hypoperfusion b/c critical carotid sten.
- ICH: surgical decompression for large hemorrhage with clinical deterioration
- SAH: nimodipine to ↓ risk of vasospasm, phenytoin for seizure prophylaxis, endovascular (Lancet 2005;366:783) or surgical correction of aneurysm/AVM to prevent rebleeding
- Cerebral venous thrombosis: paradoxically, requires anticoagulation with IV heparin
WEAKNESS & NEUROMUSCULAR DYSFUNCTION

<table>
<thead>
<tr>
<th>Feature</th>
<th>Upper Motor Neuron</th>
<th>Lower Motor Neuron</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution of weakness</td>
<td>Regional</td>
<td>Distal, segmental</td>
<td>Proximal, symmetric</td>
</tr>
<tr>
<td>Atrophy</td>
<td>None</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>None</td>
<td>Common</td>
<td>None</td>
</tr>
<tr>
<td>Tone</td>
<td>↑</td>
<td>↓</td>
<td>Normal or ↓</td>
</tr>
<tr>
<td>Reflexes (DTRs)</td>
<td>+ + + +</td>
<td>0/ +</td>
<td>+ / +</td>
</tr>
<tr>
<td>Babinski</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

PERIPHERAL NEUROPATHIES

Etiologies
- **Mononeuropathy** (one nerve): entrapment, compression, trauma, DM, Lyme
- **Mononeuropathy multiplex** (axonal loss of multiple, separate, noncontiguous nerves): vasculitides, sarcoid, DM, Lyme, Sjögren, hereditary neuropathy with pressure palsies
- **Polyneuropathy** (multiple symmetric nerves, generally length dependent)
  - **Demyelinating**
    - acute: acute inflammatory demyelinating polyneuropathy (AIDP) – Guillain-Barré
    - subacute: meds (paclitaxel), paraneoplastic
    - chronic: DM, CIDP, hypothyroidism, toxins, paraproteinemia, hereditary
  - **Axonal**
    - acute: porphyria, vasculitis, uremia
    - subacute: meds (cisplatin, paclitaxel, vincristine, INH, ddI), EtOH, sepsis, paraneo.
    - chronic: DM, uremia, lead, arsenic, Lyme, HIV, paraproteinemia, B12 defic

Clinical manifestations
- Weakness, fasciculations, numbness, dysesthesias (burning/tingling)
- Autonomic dysfn (orthostasis, bowel/bladder retention/incontinence, impotence)
- Depressed or absent DTRs (may be normal in small fiber neuropathy)

Diagnostic studies
- Distal symmetric polyneuropathy: start w/ glc or HbA1c, B12, SPEP + SIEP
- Electrolytes, BUN/Cr, CBC, TSH, LFTs, ANA, ESR, HIV, Cu, Lyme titers, genetic testing, and heavy metal screening as indicated by clinical history and exam
- EMG & NCS (often no change in first 10–14 d or in small fiber neuropathy)
- Autonomic testing / skin bx (polyneuropathy), nerve bx (mononeuropathy multiplex)
- MRI if possible radiculopathy or plexopathy

GUILLAIN-BARRÉ Syndrome (GBS)

Definition and epidemiology
- Acute inflammatory demyelinating polyneuropathy (AIDP)
- Incidence 1–2 per 100,000; most common acute / subacute paralysis
- Precipitants: viral illness (EBV, CMV, HSV, HIV), URI (Mycoplasma), gastroenteritis (Campylobacter), Lyme, surgery, older immunizations

Clinical manifestations
- Ascending paralysis over hours to days
- Hypoactive then absent reflexes
- Sensory dysesthesias and numbness often first symptoms, back pain also common
- Respiratory failure requiring ventilatory assistance occurs in 30%;
  - autonomic instability and arrhythmias occur in 50%
- Fisher variant: ophthalmoplegia, ataxia, areflexia; associated with anti-GQ1b antibodies

Diagnostic studies (results may be normal in first several days)
- LP: albuminocytologic dissociation – ↑ protein w/o pleocytosis (~20 lymphs)
- EMG & NCS: ↓ nerve conduction velocity and conduction block
- FVC & NIF: to assess for risk of respiratory failure (cannot rely on P aO2 or SaO2)

Treatment
- Plasma exchange (Neuro 1985;35:1096) or IVIg (NEJM 1992;326:1123)
  - no additional benefit with both (Lancet 1997;349:225)
- 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; axonal variant (~5%) with incomplete recovery; 3–5% mortality
MYASTHENIA GRAVIS

Definition and epidemiology
• Autoimmune disorder with Ab directed against acetylcholine receptor (AChR) in NMJ
• Prevalence: 1 in 7,500; affects all ages, peak incidence 20s–30s (women), 60s–70s (men)

Clinical manifestations
• Fluctuating weakness w/ fatigability (worse w/ repetitive use, relieved by rest)
• Cranial muscles involved early → ocular (ptosis, diplopia) in 50%; bulbar (difficulty chewing, dysarthria, dysphagia) in 15%. Often later progresses to generalized weakness.
• Limb weakness proximal > distal; DTRs preserved; minimal / no atrophy
• Exacerbations triggered by stressors such as URI, surgery, pregnancy or postpartum, meds (eg, aminoglycosides, procainamide, phenytoin); prednisone can worsen acutely
• Myasthenic crisis → exacerbation → need for respiratory assistance
• Cholinergic crisis → weakness due to overtreatment with anticholinesterase medications; may have excessive salivation, abdominal cramping; and diarrhea; rare at normal doses

Diagnostic studies
• Bedside: ptosis after >30 seconds of sustained upgaze, improved with ice pack over eyes
• 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 account for most AChR Ab cases
• CT or MRI of thorax to evaluate thymus (65% hyperplasia, 10% thymoma)

Treatment
• Anticholinesterase medications (eg, pyridostigmine)
• Thymectomy if thymoma; may lead to improvement in up to 85% Pts w/o thymoma
• Immunosuppression: prednisone ± azathioprine, cyclophosphamide
• Myasthenic crisis: treat precipitant consider d/c anticholinesterase if suspect cholinergic crisis aggressive immunosuppression with glucocorticoids (but watch for initial worsening) IVIg, plasmapheresis
• 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 (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)
• May develop either pseudohypertrophy (dystrophies) or mild muscle atrophy

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-amplitude, polyphasic units with early recruitment, ± fibrillation potentials
• Muscle biopsy, molecular genetic testing (where indicated)
Primary headache syndromes
• Tension: associated with muscle contraction in neck or lower head; treat with NSAIDs
• Migraine: see later
• Cluster: periodic, paroxysmal, brief, sharp, orbital headache that may awaken from sleep
  ± lacrimation, rhinorrhea, conjunctival injection, or unilateral Horner’s syndrome.
  Acute treatments: oxygen, triptans; chronic prophylaxis: calcium-channel blocker.

Secondary causes of headaches
• Vascular: stroke, intracerebral hemorrhage, SAH, subdural hematoma, AVM, unruptured
  aneurysm, arterial hypertension, venous thrombosis
• Infection: meningitis, encephalitis, abscess
• Brain tumor
• Pseudotumor cerebri (idiopathic intracranial hypertension)
• CSF disorder: ↑ (hydrocephalus) or ↓ (s/p LP)
• Trigeminal neuralgia
• Extracranial: sinusitis, TMJ syndrome, temporal arteritis
• Medication (analgesic) overuse

Clinical evaluation (JAMA 2006;296:1274)
• History: quality, severity, location, duration, time of onset, precipitants/relieving factors
• Associated symptoms (visual Δs, nausea, vomiting, photophobia)
• Focal neurologic symptoms
• Head or neck trauma, constitutional symptoms
• Medications, substance abuse
• General and neurologic examination
• Warning signs that should prompt neuroimaging:
  worst ever, worsening over days, wakes from sleep vomiting, aggravated by exertion or Valsalva
  age >50 y, fever, abnl neurologic exam, aura, cluster-type headache, unilateral

MIGRAINE

Epidemiology
• Affects 15% of women and 6% of men; onset usually by 30 y

Clinical manifestations (Lancet 2004;363:381; JAMA 2006;296:1274)
• Unilateral or bilateral, retro-orbital, throbbing or pulsatile headache; lasts 4–72 h
• Often accompanied by nausea, vomiting, photophobia
• “POUNDing”: Pulsatile; duration 4–72 h; Ours; Unilateral; Nausea & vomiting; Disabling
  LR 3.5 if 3 criteria are met, LR 24 if 4 criteria are met
• Classic (18%) – visual aura (scotomata with jagged or colored edge) precedes
  headache
• Common (64%) – headache without aura
• Complicated – accompanied by stereotypical neurologic deficit that may last hrs
• Precipitants: stress, hunger, foods (cheese, chocolate) and food additives (MSG),
  fatigue, alcohol, menstruation, exercise

Treatment (NEJM 2002;346:257)
• Eliminate precipitants
• Prophylaxis: TCA, βB, CCB, valproic acid, topiramate (JAMA 2004;291:965)
• Abortive therapy
  ASA, acetaminophen, caffeine, high-dose NSAIDs
  metoclopramide IV, prochlorperazine IM or IV
  5-HT1 agonists (“triptans”); contraind. if complicated migraine, CAD, prior stroke
  combo of triptan + NSAID more efficacious than either alone (JAMA 2007;297:1443)
  ergotamine, dihydroergotamine; use with caution in Pts with CAD
BACK AND SPINAL CORD DISEASE

Ddx of back pain

- **Musculoskeletal**: musculoligamentous “strain” (experienced by up to 80% of population at some time), OA, RA, spondylolisthesis, vertebral compression fx, inflammatory spondyloarthritides (ankylosing spondylitis, reactive, psoriatic)
- **Spinal cord** (myelopathy) / nerve root (radiculopathy):
  - Degenerative/traumatic: disc herniation, spondylolisthesis, fracture
  - Neoplastic: lung, breast, prostate, multiple myeloma, lymphoma
  - Infectious (also see ID section): osteomyelitis, epidural abscess, zoster, Lyme, CMV, HIV
- **Referred pain from visceral disease**: (quality of pain can be important to distinguish)
  - 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, neurologic symptoms, infection, malignancy
- **General physical examination**: local tenderness, ROM, signs of infection or malignancy, signs of radiculopathy (experienced as sharp/lancinating pain radiating into limb):
  - Spurling sign (radicular pain w/ downward force to extended & ipsilaterally rotated head) straight leg raise (radicular pain at 30–70°): ipsilateral: 95% Se, 40% Sp; crossed (contralateral leg raised): 25% Se, 90% Sp
- **Neurologic examination**: full motor (including sphincter tone), sensory (including perineal region), and reflexes including anal (S4) and cremasteric (L2)
- **Laboratory** (depending on suspicion): CBC, ESR, Ca, PO4, A, 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
- Bilateral prominent Babinski responses ± ankle clonus

**Evaluation and treatment**

- Empiric spine immobilization (collar, board) for all trauma patients
- STAT MRI (at and above clinical spinal level, pre- and postgadolinium) or CT myelogram
- Emergency neurosurgical and/or neurology consultation
- Urgent radiation therapy ± surgery for compression if due to metastatic disease
- High-dose steroids depending on cause:
  - Tumor: dexamethasone 10–100 mg IV x 1 then 4–24 mg every 6 hr
  - Trauma: controversial (may have slight benefit but ↑ risk of infection, poor healing)
    - methylprednisolone 30 mg/kg IV over 15 min then 45 min later: 5.4 mg/kg/h × 23 h

<table>
<thead>
<tr>
<th>Features</th>
<th>Conus Medullaris</th>
<th>Cauda Equina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization</td>
<td>Cord (UMN) &gt; nerve roots (LMN) Bilateral</td>
<td>Nerve roots (LMN) Unilateral</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild, back &gt; radicular</td>
<td>Severe, radicular &gt; back</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>Symmetric perianal</td>
<td>Asymmetric saddle/leg</td>
</tr>
<tr>
<td>Motor dysfxn</td>
<td>Mild symmetric weakness</td>
<td>Marked asymmetric weakness</td>
</tr>
<tr>
<td>Reflexes</td>
<td>↓ ankle but knee preserved</td>
<td>↓ ankle, ↓ knee</td>
</tr>
<tr>
<td></td>
<td>May have ↓ reflexes, Babinski</td>
<td>Babinski absent</td>
</tr>
<tr>
<td>Bowel-Bladder -Sexual dysfxn</td>
<td>Early retention, incontinence, ↓ anal tone, &amp; impotence</td>
<td>sx’s less frequent / occur late</td>
</tr>
</tbody>
</table>

**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
### Disc Herniation: Cervical and Lumbar Radiculopathy

<table>
<thead>
<tr>
<th>Disc</th>
<th>Root</th>
<th>Pain / Paresthesias</th>
<th>Sensory loss</th>
<th>Motor loss</th>
<th>Reflex Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4–C5</td>
<td>C5</td>
<td>Neck, shoulder, upper arm</td>
<td>Shoulder</td>
<td>Deltoid, biceps, infraspinatus</td>
<td>Biceps</td>
</tr>
<tr>
<td>C5–C6</td>
<td>C6</td>
<td>Neck, shoulder, lat. arm, radial forearm, thumb &amp; index finger</td>
<td>Lat. arm, radial forearm, thumb &amp; index finger</td>
<td>Biceps, brachioradialis</td>
<td>Biceps, brachioradialis, supinator</td>
</tr>
<tr>
<td>C6–C7</td>
<td>C7</td>
<td>Neck, lat. arm, ring &amp; index fingers</td>
<td>Radial forearm, index &amp; middle fingers</td>
<td>Triceps, extensor carpi ulnaris</td>
<td>Triceps, supinator</td>
</tr>
<tr>
<td>C7–T1</td>
<td>C8</td>
<td>Ulnar forearm and hand</td>
<td>Ulnar half of ring finger, little finger</td>
<td>Intrinsic hand muscles, wrist extensors, flexor dig profundus</td>
<td>Finger flexion</td>
</tr>
<tr>
<td>L3–L4</td>
<td>L4</td>
<td>Anterior thigh, inner shin</td>
<td>Anteromedial thigh and shin, inner foot</td>
<td>Quadriceps</td>
<td>Patella</td>
</tr>
<tr>
<td>L4–L5</td>
<td>L5</td>
<td>Lat. thigh and calf, dorsum of foot, great toe</td>
<td>Lat. calf and great toe</td>
<td>Extensor hallucis longus, foot dorsiflexion, invers. &amp; evers.</td>
<td>None</td>
</tr>
<tr>
<td>L5–S1</td>
<td>S1</td>
<td>Back of thigh, lateral posterior calf, lat. foot</td>
<td>Posterolat. calf, lat. and sole of foot, smaller toes</td>
<td>Gastrocnemius, foot eversion</td>
<td>Achilles</td>
</tr>
</tbody>
</table>

(Nb, lumbar disc protrusion tends to compress the nerve root that exits one vertebral level below the protrusion.)

### Neurogenic vs. Vascular Claudication

<table>
<thead>
<tr>
<th>Features</th>
<th>Neurogenic Claudication</th>
<th>Vascular Claudication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Lumbar spinal stenosis (with nerve root compression)</td>
<td>Peripheral artery disease (with limb ischemia)</td>
</tr>
<tr>
<td>Pain</td>
<td>Radicular back / buttock pain</td>
<td>Cramping leg pain</td>
</tr>
<tr>
<td></td>
<td>Maximal anterior thighs</td>
<td>Most common in calves</td>
</tr>
<tr>
<td></td>
<td>Radiating down legs</td>
<td>Radiating up legs</td>
</tr>
<tr>
<td>Worse with</td>
<td>Walking &amp; standing</td>
<td>Walking</td>
</tr>
<tr>
<td></td>
<td>Hypextension / lying prone</td>
<td>Biking</td>
</tr>
<tr>
<td>Better with</td>
<td>Bending forward, sitting</td>
<td>Rest (standing or sitting)</td>
</tr>
<tr>
<td>Other Sx</td>
<td>Numbness / paresthesias</td>
<td>Pale, cool extremity</td>
</tr>
<tr>
<td>Exam</td>
<td>≥ Focal weakness, ↓ reflexes</td>
<td>Diminished/absent pulses</td>
</tr>
<tr>
<td></td>
<td>↓ Lumbar extension</td>
<td>(dorsalis pedis / posterior tibialis)</td>
</tr>
<tr>
<td></td>
<td>Preserved pulses</td>
<td>Pallor</td>
</tr>
<tr>
<td>Diagnostic studies</td>
<td>MRI lumbar spine</td>
<td>Arterial Doppler studies</td>
</tr>
<tr>
<td></td>
<td>CT myelogram (if no MRI)</td>
<td>Ankle-brachial index (ABI) &lt; 0.90</td>
</tr>
<tr>
<td></td>
<td>EMG/NCS</td>
<td>Arteriography</td>
</tr>
<tr>
<td>Treatment</td>
<td>PT (flexion exercise), NSAIDs, steroid injections (ESI)</td>
<td>Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization</td>
</tr>
<tr>
<td></td>
<td>Surgery (if other Rx fails)</td>
<td></td>
</tr>
</tbody>
</table>

(Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient. NEJM 2007;356:2245 & 2008;358:818.)

### Treatment of nerve root compression

- **Conservative:** avoid bending/lifting; NSAIDs
- **Spinal epidural steroid injections (ESI):** limited short-term relief of refractory radicular pain
- **Surgery:** cord compression or cauda equina syndrome; progressive motor dysfunction; bowel / bladder dysfunction; failure to respond to conservative Rx (NEJM 2007;356:2245)
**ACLS ALGORITHMS**

**Figure 10-1 ACLS VF/pulseless VT, asystole & PEA algorithms**

**Pulseless Arrest**

---

**Primary ABCD Survey**

- **Airway**: open airway (head tilt-chin lift or jaw thrust)
- **Breathing**: positive pressure ventilation (give 2 breaths)
- **Circulation**: chest compressions (1½–2 inches, ~100/min; 30:2 comp-vent ratio)
- **Defibrillation**: rhythm ASAP

---

**VF or VT**

- **Defib** × 1
  - (200 J biphasic or 360 J monophasic)
  - CPR × 5 cycles (= 2 mins)

---

**ASYSTOLE or PEA**

- **Defib** × 1
  - (before or after shock)

---

**SECONDARY ABCD SURVEY**

- **Airway**: remove obstructions; insert airway; ? advanced airway
- **Breathing**: placement of airway (clinical & CO₂ detector); O₂
  - 1 breath q6–8 sec (8–10 breaths per min) w/o stopping CPR
- **Circulation**: IV access
- **Differential dx**: consider causes (H’s & T’s, see below)

- **Vasopressor** q3–5 min
  - (before or after shock)
  - Epinephrine or Vasopressin

- **Defib** × 1
  - (before or after shock)
  - Antiarrhythmic
  - Amiodarone, Lidocaine, or Mg

---

**MEDICATIONS**

- **Epinephrine**: 1 mg IV (10 mL of 1:10,000 solution) or 2 mg ETT q3–5 min
- **Vasopressin**: 40 U IV to replace 1st or 2nd epi dose
- **Amiodarone**: 300 mg IVP ± 150 mg IVP in 3–5 min
- **Lidocaine**: 1.0–1.5 mg/kg IVP (~100 mg)
  - then 0.5–0.75 mg/kg (~50 mg) q5–10 min, max 3 mg/kg
- **Atropine**: 1 mg IV q3–5 min × 3
- **Magnesium**: 1–2 g IV for TdP

---

**Treatment of reversible causes of PEA & asystole**

- **Hypovolemia**: volume infusion
- **Hypoxia**: oxygenate
- **Hydrogen ions (acidsosis)**: NaHCO₃
- **Hypokalemia**: KCl
- **Hyperkalemia**: Ca, NaHCO₃, insulin/gluc
- **Hyperglycemia**: glucose
- **Hypothermia**: warming
- **Toxins/Tablets**: med-specific
- **Tamponade**: pericardiocentesis
- **Thrombosis (PTX)**: needle decompression
- **Thrombosis (PE)**: lysis, thrombectomy
- **Trauma (hypovol, ↑ ICP)**: per ATLS

---

(Aadapted from ACLS 2005 Guidelines, Circ 2005;112(Suppl I):IV-58)
**Figure 10-2 ACLS tachycardia algorithm**

**Tachycardia**

- unstable = hypotension or other s/s shock, s MS, chest pain

- IV Access, O₂, 12-lead ECG, focused H & P for reversible causes

- QRS <120 msec

- QRS ≥120 msec

**NARROW COMPLEX**

- regular

- irregular

- vagal maneuvers

- adenosine

- convert

- does not convert

- Likely AVNRT or AVRT

- Rx recurrence w/ adenosine or long-acting AV nodal agent such as diltiazem or metoprolol

**WIDE COMPLEX**

- regular

- irregular

- AF, AFL, or MAT

- Control rate w/ diltiazem or metoprolol

- AF w/ aber.

- Control rate w/ diltiazem or metoprolol

- VT or ? WCT

- amiodarone

- procainamide

- lidocaine

- & prepare for synch cardioversion

- SVT w/ aber.

- adenosine

- Possible AFL, ATAC, NPJT

- Control rate w/ diltiazem or metoprolol

- AMF + WPW

- amiodarone, procainamide, or ibutilide avoid adenosine, digoxin, CCB & βB

- PMVT (nl QT)

- treat ischemia

- amiodarone

- or lidocaine

- & prepare for defibrillation

- Torsades (↑ QT) correct abnl lytes & other precip.

- Mg 2 g IV

- overdrive pacing or isoproterenol

- ? lidocaine

**CARDIOVERSION**

Ancillary equipment

- O₂, sat monitor

- suction device

- IV line

- intubation equipment

Premedicate

- call anesthesia service

- midazolam 1–5 mg

- fentanyl 100–300 μg

- titrate to effect

Synchronized cardioversion

- 100, 200, 300, 360 J or biphasic equivalent

**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 min later if needed, 5–15 mg/h

- **ibutilide**: 1 mg over 10 min, repeat × 1 if needed

- **lidocaine**: 1–1.5 mg/kg IVP, repeat in 5–10 min

- **metoprolol**: 5 mg IV q5min × 3

- **procainamide**: 17 mg/kg at 50 mg/min (avoid if EF ↓)

- **verapamil**: 2.5–5 mg IV over 2 min, 5–10 mg 15–30 min later if needed

(Adapted from ACLS 2005 Guidelines, Circ 2005;112(Suppl I):IV-67)
**Figure 10-3** ACLS bradycardia algorithms

**Bradycardia** (HR < 60 & inadequate for clinical condition)
- ABCs, IV Access, O₂, 12-lead ECG, focused H&P for reversible causes
  - Unstable?
    - No
      - observe
    - Yes
      - prep for transcutaneous pacing
      - use w/o delay for Type II 2° AVB or 3° AVB
      - atropine 0.5 mg IV q3–5min, max 3 mg
      - transcutaneous pacing
      - dopamine 2–10 μg/kg/min or epinephrine 2–10 μg/min while awaiting pacer or if pacer ineffective
      - transvenous pacing

(Adapted from ACLS 2005 Guidelines, Circ 2005;112(Suppl I):IV–67)

**Figure 10-4** ACLS pulmonary edema, hypotension, or shock algorithm

**Acute Pulmonary Edema, Hypotension, or Shock**
- ABCs, IV Access, O₂, 12-lead ECG, focused H&P, CXR
- What is the nature of the problem?
  - Volume problem
  - Pump problem
  - Rate problem

**Volume problem**
- Fluids and/or blood
  - Consider vasopressors
  - What is BP? (after empiric 250–500 cc NS bolus unless in CHF)

**Pump problem**
- Go to tachycardia or bradycardia algorithm

**Rate problem**
- SBP < 70
  - Cardiogenic shock
    - Norepinephrine 1–30 μg/min
    - Dopamine 5–20 μg/kg/min

- SBP 70–100
  - Cardiogenic shock
    - Dopamine 2–20 μg/kg/min
    - Norepinephrine if dopamine > 20 μg/kg/min

- SBP 70–100
  - No shock
    - Dobutamine 2–20 μg/kg/min

- SBP > 100
  - CHF
    - Nitroglycerin 10–1000 μg/min
    - Nitroprusside 0.1–5 μg/kg/min

If in pulmonary edema, consider:
- Furosemide 0.5–1 mg/kg IV
- Morphine 2–4 mg IV
- Oxygen/noninvasive vent./intub., further interventions based on etiology

(Adapted from ACLS 2005 Guidelines)
## ICU Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dose per kg</th>
<th>average per kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pressors, Inotropes, and Chronotropes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>$\alpha_1$</td>
<td>10–300 µg/min</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>$\alpha_1 &gt; \beta_1$</td>
<td>1–40 µg/min</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>$\nu_1$</td>
<td>0.01–0.1 UI/min (usually &lt;0.04)</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>$\alpha_1, \beta_1, \beta_2$</td>
<td>2–20 µg/min</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>$\beta_1, \beta_2$</td>
<td>0.1–10 µg/min</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>$\beta$, $\beta_D$</td>
<td>0.5–2 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–10 µg/kg/min</td>
<td>50–200 µg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;10 µg/kg/min</td>
<td>200–500 µg/min</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>$\beta_1 &gt; \beta_2$</td>
<td>2–20 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–100 µg/kg/min</td>
<td>50–1000 µg/min</td>
</tr>
<tr>
<td>Milrinone</td>
<td>PDE</td>
<td>50 µg/kg over 10 min then 0.375–0.75 µg/kg/min</td>
<td>3–4 mg over 10 min then 20–50 µg/min</td>
</tr>
<tr>
<td>Inamrinone</td>
<td>PDE</td>
<td>0.75 mg/kg over 3 min then 5–15 µg/kg/min</td>
<td>40–50 mg over 3 min then 250–900 µg/min</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
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</tr>
<tr>
<td>Nitroglycerin</td>
<td>NO</td>
<td>10–1000 µg/min</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>NO</td>
<td>0.1–10 µg/kg/min</td>
<td>5–800 µg/min</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>BNP</td>
<td>2 µg/kg IVB then 0.01 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>$\alpha_1, \beta_1$, and $\beta_2$ blocker</td>
<td>20 mg over 2 min then 20–80 mg q10min or 10–120 mg/h</td>
<td></td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>D</td>
<td>0.1–1.6 µg/kg/min</td>
<td>10–120 µg/min</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>vasodilator</td>
<td>2–20 ng/kg/min</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>vasodilator</td>
<td>5–20 mg q20–30min</td>
<td></td>
</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>K et al. (Class III)</td>
<td>150 mg over 10 min, then 1 mg/min x 6h, then 0.5 mg/min x 18h</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Na channel (Class IB)</td>
<td>1–1.5 mg/kg then 1–4 mg/min</td>
<td>100 mg then 1–4 mg/min</td>
</tr>
<tr>
<td>Procaainamide</td>
<td>Na channel (Class IA)</td>
<td>17 mg/kg over 60 min then 1–4 mg/min</td>
<td>1 g over 60 min then 1–4 mg/min</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>K channel (Class III)</td>
<td>1 mg over 10 min, may repeat x 1</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>$\beta$ blocker</td>
<td>0.5–1 mg q5min then 1–10 mg/h</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>$\beta_1 &gt; \beta_2$ blocker</td>
<td>500 µg/kg then 25–300 µg/kg/min</td>
<td>20–40 mg over 1 min then 2–20 mg/min</td>
</tr>
<tr>
<td>Verapamil</td>
<td>CCB</td>
<td>2.5–5 mg over 1–2 min repeat 5–10 mg in 15–30 min prn 5–20 mg/h</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>CCB</td>
<td>0.25 mg/kg over 2 min reload 0.35 mg/kg x 1 prn then 5–15 mg/h</td>
<td>20 mg over 2 min reload 25 mg x 1 prn then 5–15 mg/h</td>
</tr>
<tr>
<td>Adenosine</td>
<td>purinergic</td>
<td>6 mg rapid push if no response: 12 mg → 12–18 mg</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Sedation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>opioid</td>
<td>1–unlimited mg/h</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>opioid</td>
<td>50–100 µg then 50–unlimited µg/h</td>
<td></td>
</tr>
<tr>
<td>Thiopental</td>
<td>barbiturate</td>
<td>3–5 mg/kg over 2 min, 200–400 mg over 2 min</td>
<td></td>
</tr>
<tr>
<td>Etomidate</td>
<td>anesthetic</td>
<td>0.2–0.5 mg/kg/h, 100–300 mg</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>anesthetic</td>
<td>1–3 mg/kg then 100–200 mg/h, 3–5 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>BDZ</td>
<td>1–5 mg q1–2h then q6h prn</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>BDZ</td>
<td>0.5–2 mg q5min prn or 0.5–4 mg then 1–10 mg/h</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>anesthetic</td>
<td>1–2 mg/kg, 60–150 mg</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>antipsychotic</td>
<td>2–5 mg q20–30min</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>opioid antag.</td>
<td>0.4–2 mg q2–3min to total of 10 mg</td>
<td></td>
</tr>
<tr>
<td>Flumazenil</td>
<td>BDZ antag.</td>
<td>0.2 mg over 30 sec then 0.3 mg over 30 sec if still lethargic, may repeat 0.5 mg over 30 sec to total of 3 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Paralysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>depolar. paralytic</td>
<td>0.6–1.1 mg/kg then 70–100 mg/h</td>
<td></td>
</tr>
<tr>
<td>Tubocurare</td>
<td>nACh</td>
<td>0.08 mg/kg then 2–4 mg q30–90’</td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>nACh</td>
<td>0.08 mg/kg then 0.05–0.1 mg/kg/h then 5–10 mg over 1–3 min</td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>nACh</td>
<td>0.08 mg/kg then 5–10 mg then 2–8 mg/h</td>
<td></td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>nACh</td>
<td>5–10 µg/kg/min</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminophylline</td>
<td>PDE</td>
<td>5.5 mg/kg over 20 min then 0.5–1 mg/kg/h, 250–500 mg then 10–80 mg/h</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td>10 U then 0.1 U/kg/h</td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td></td>
<td>5–10 mg then 1–5 mg/h</td>
<td></td>
</tr>
<tr>
<td>Octreotide</td>
<td>somatostatin analog</td>
<td>50 µg then 50 µg/h</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>antiepileptic</td>
<td>20 mg/kg at 50 mg/min then 1–1.5 g over 20–30 min</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>antiepileptic</td>
<td>20 mg/kg at 150 mg/min then 1–1.5 g over 10 min</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>barbiturate</td>
<td>20 mg/kg at 50–75 mg/min then 1–1.5 g over 20 min</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>osmole</td>
<td>1.5–2 g/kg over 30–60 min repeat q6–12h to keep osm 310–320</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Generation</th>
<th>Properties</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>Some GPC, GPR, GNC, most anaerobes (except Bacteroides)</td>
<td>Group A streptococci, Enterococci, Listeria, Pasteurella, Actinomyces, Syphilis</td>
</tr>
<tr>
<td>Anti-Staph</td>
<td>Active vs. PCNase-producing Staph, Little activity vs. Gram</td>
<td>Staphylococci (except MRSA), Streptococci</td>
</tr>
<tr>
<td>Amino</td>
<td>Penetrate porin channel of Gram, Not stable against PCNases</td>
<td>E. coli, Proteus, H. influenzae, Salmonella, Shigella, Enterococci, Listeria</td>
</tr>
<tr>
<td>Extended</td>
<td>Penetrate porin channel of Gram, More resistant to PCNases</td>
<td>Most GNR incl. Enterobacter, Pseudomonas, Serratia</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>Resistant to most β-lactamases</td>
<td>Most Gram + and - bacteria including anaerobes, but not MRSA or VRE</td>
</tr>
<tr>
<td>Monobactams</td>
<td>Active vs. Gram but not Gram</td>
<td>Gram ++ bacterial infxn in Pt w/ PCN or Ceph allergy</td>
</tr>
<tr>
<td>β-lact. Inhib.</td>
<td>Inhibit plasma-mediated β-lactamases</td>
<td>Adds Staph, B. fragilis and some GNR (H. influenzae, M. catarrhalis, some Klebsiella); intrinsic activity against Acinetobacter (sulbactam only)</td>
</tr>
</tbody>
</table>

### Cephalosporins

Resistant to most β-lactamases. No activity vs. MRSA or enterococci.

<table>
<thead>
<tr>
<th>Gen.</th>
<th>Spectrum</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Most GPC (incl. Staph &amp; Strep, not MRSA) Some GNR (incl. E. coli, Proteus, Klebsiella)</td>
<td>Used for surgical ppx &amp; skin infxn</td>
</tr>
<tr>
<td>Second</td>
<td>↓ activity vs. GPC, ↑ vs. GNR. 2 subgroups: Respiratory: H. influenzae &amp; M. catarrhalis GI/GU: ↑ activity vs. B. fragilis</td>
<td>PNA/COPD flare, Abdominal infxn</td>
</tr>
<tr>
<td>Third</td>
<td>Broad activity vs. GNR &amp; some anaerobes Cefazidine active vs. Pseudomonas</td>
<td>PNA, sepsis, meningitis</td>
</tr>
<tr>
<td>Fourth</td>
<td>↑ resistance to β-lactamases (incl. of Staph and Enterobacter)</td>
<td>Similar to 3rd gen. MonoRx for nonlocalizing febrile neutropenia</td>
</tr>
</tbody>
</table>

### Other Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Spectrum</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Gram ++ bacteria incl. MRSA, PCNase-producing pneumococci and enterococci (except VRE)</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>GPC incl. MRSA &amp; VRE (check susceptibility for VRE)</td>
<td></td>
</tr>
<tr>
<td>Daptomycin/</td>
<td>GPC incl. MRSA &amp; VRE (check susceptibility for VRE)</td>
<td></td>
</tr>
<tr>
<td>Quinupristin/</td>
<td>GPC incl. MRSA &amp; VRE (check susceptibility for VRE)</td>
<td></td>
</tr>
<tr>
<td>Dalofpristin/</td>
<td>GPC incl. MRSA &amp; VRE (check susceptibility for VRE)</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>Enteric GNR &amp; atypicals. 3rd &amp; 4th gen. ↑ activity vs. Gram</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>GNR. Synergy w/ cell-wall active abx (β-lactam, vanco) vs. GPC. ↓ activity in low pH (eg, abscess). No activity vs. anaerobes.</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td>GPC, some respiratory Gram++, atypicals</td>
<td></td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>Some enteric GNR, PCP, Nocardia, Toxoplasma, most community-acquired MRSA</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Most Gram ++ (except enterococci) &amp; anaerobes (incl. B. fragilis)</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Almost all anaerobic Gram++, most anaerobic Gram++</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Rickettsia, Ehrlichia, Chlamydia, Mycoplasma, Nocardia, Lyme</td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Many GPC incl. MRSA &amp; VRE, some GNR incl. ESBL but not Pseudomonas or Proteus. Approved for abdominal or skin/soft tissue infections. Check susceptibility if organism isolated.</td>
<td></td>
</tr>
</tbody>
</table>
**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/m²
- **Stroke volume (SV)**: \( \frac{CO}{HR} \) 60–120 mL/contraction
- **Stroke volume index (SVI)**: \( \frac{CI}{HR} \) 40–50 mL/contraction/m²
- **Systemic vascular resistance (SVR)**: \( \frac{MAP - mean \ RA}{CO} \times 80 \) 800–1200 dynes \( \cdot \) sec/cm²
- **Pulmonary vascular resistance (PVR)**: \( \frac{mean \ PA - mean \ PCWP}{CO} \times 80 \) 120–250 dynes \( \cdot \) sec/cm²

“Rule of 6s” for PAC: RA ≤ 6, RV ≤ 30/6, PA ≤ 30/12, WP ≤ 12. 1 mmHg = 1.36 cm water or blood.

**Fick cardiac output**

Oxygen consumption (L/min) = \( CO \times \text{AV oxygen difference} \)

CO – oxygen consumption / AV oxygen difference

Oxygen consumption must be measured (can estimate w/ 125 mL/min/m², but inaccurate)

AV oxygen difference = Hb (g/dL) \( \times \) 13.6 (mL O₂/g of Hb) \( \times \) (S₁O₂ – S₂O₂)

S₁O₂ is measured in any arterial sample (usually 93–98%)

S₂O₂ (mixed venous O₂) is measured in RA, RV, or PA (assuming no shunt) (normal ~75%)

\[ \therefore \text{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{Hb (g/dL) \times 13.6 \times (S₁O₂ - S₂O₂)} \]

**Shunts**

- **Qp** = Oxygen consumption
  Pulm. vein O₂ sat – Pulm. artery O₂ sat (if no R → L shunt, PV O₂ sat – SvO₂)

- **Qs** = Oxygen consumption
  SvO₂ - mixed venous O₂ sat

- **Qp** = Oxygen consumption
  S₁O₂ – MV O₂ sat

- **Qs** = Oxygen consumption
  PV O₂ sat – PA O₂ sat

**Valve equations**

- **Simplified Bernoulli equation**: Pressure gradient (ΔP) = \( 4 \times v^2 \) (where \( v \) – peak flow velocity)

- **Continuity eq., (conservation of flow)**: \( A₁ \times V₁ = A₂ \times V₂ \) (where 1 & 2 different points)

- **or AVA (unknown)** = \( A_{AVA} \times \frac{\sqrt{V_{LVO}}}{V_{AVA}} \) (all of which can be measured on echo)

- **Gorlin equation**: Valve area = \( \frac{CO \times (DEP \ or \ SEP) \times HR}{44.3 \times \text{constant} \times \sqrt{\Delta P}} \) (constant = 1 for AS, 0.85 for MS)

- **Hakki equation**: Valve area = \( \frac{CO}{\sqrt{\Delta P}} \)
Chest Imaging (CXR & CT) Patterns

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Pathophysiology</th>
<th>Ddx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>Radiopaque material in air space &amp; interstitium</td>
<td>Acute: water (pulm edema), pus (PNA), blood</td>
</tr>
<tr>
<td></td>
<td>„air bronchograms“</td>
<td>Chronic: neoplasm (BAC, lymphoma), aspiration, inflammatory (BOOP, esophinophilic PNA), PAP, granuloma (TB/fungal, alveolar sarcoma)</td>
</tr>
<tr>
<td>Ground glass</td>
<td>Interstitial thickening or partial filling of alveoli (but vessels visible)</td>
<td>Acute: pulm edema, infxn (PCP, viral, resolving bact. PNA)</td>
</tr>
<tr>
<td>(CT easier than CXR)</td>
<td></td>
<td>Chronic: ILD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>w/o fibrosis: acute hypersens., DIP/GB, PAP w/ fibrosis: IPF</td>
</tr>
<tr>
<td>Septal lines</td>
<td>Radiopaque material in septae</td>
<td>Cardiogenic pulm edema, interstitial PNA</td>
</tr>
<tr>
<td>Kerley A &amp; B</td>
<td></td>
<td>viral, mycoplasma, lymphangitic tumor</td>
</tr>
<tr>
<td>Reticular</td>
<td>Lace-like net (ILD)</td>
<td></td>
</tr>
<tr>
<td>Nodules</td>
<td>Tumor</td>
<td>Cavitary: Primary or metastatic cancer</td>
</tr>
<tr>
<td></td>
<td>Granulomas Abscess</td>
<td>TB (react. or miliary), fungus, Wegener’s, RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>septic emboli, PNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Noncavitary: any of above + sarcoid, hypersens. pneum., HIV, Kapoš’s  sarcoma</td>
</tr>
<tr>
<td>Wedge opac.</td>
<td>Peripheral infarct</td>
<td>PE, cocaine, angioinv. aspergillus, Wegener’s</td>
</tr>
<tr>
<td>Tree-in-bud (best on CT)</td>
<td>Inflammation of small airways</td>
<td>Bronchopneumonia, endobronchial TB/MAI, viral PNA, aspiration, ABPA, CF, asthma, BOOP</td>
</tr>
<tr>
<td>Hilar fullness</td>
<td>↑ LN or pulm arteries</td>
<td>Neoplasm (lung, mets, lymphoma)</td>
</tr>
<tr>
<td>Upper lobe</td>
<td>n/a</td>
<td>Infxn (AIDS): Granuloma (sarcoid/TB/fungal) Pulmonary hypertension</td>
</tr>
<tr>
<td>Lower lobe</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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: \( P_{A}O_2 = \) \[ F_{I}O_2 \times (760 - 47) \] \( - \) \( \frac{P_{CO_2}}{R} \) (where \( R = 0.8 \))
\( P_{A}O_2 = 150 - \frac{P_{CO_2}}{0.8} \) (on room air)

A-a gradient – \( P_AO_2 - P_{A}O_2 \) [normal A-a gradient = 4 + (age/4)]

Minute ventilation (V_i) – tidal volume (V_T) \( \times \) respiratory rate (RR) (normal 4–6 L/min)

Tidal volume (V_T) – alveolar space (V_A) + dead space (V_D)

Fraction of tidal volume that is dead space \( \left( \frac{V_D}{V_T} \right) = \frac{P_{CO_2} - P_{expiredCO_2}}{P_{A}CO_2} \)

\( P_{CO_2} = k \times \frac{CO_2 \text{ Production}}{\text{alveolar ventilation}} = k \times \frac{V_{CO_2}}{RR \times V_T \times \left( 1 - \frac{V_D}{V_T} \right)} \)
**GASTROENTEROLOGY**

Figure 10-5 Acetaminophen toxicity nomogram

(Adapted Archives 1981;141:382 & Guidelines for Management of Acute Acetaminophen Overdose. McNeil, 1999.)

**NEPHROLOGY**

Anion gap (AG) = Na – (Cl + HCO₃⁻) (normal = [alb] × 2.5; typically 12 ± 2 mEq)

Delta-delta (ΔΔ) = [Δ AG (ie, calc. AG - expected) / Δ HCO₃⁻ (ie, 24 - measured HCO₃⁻)]

Urine anion gap (UAG) = (UNa + UK) – UCl

Calculated osmolytes = (2 × Na) + \( \frac{\text{glc}}{18} \) + \( \frac{\text{BUN}}{2.8} \) + \( \frac{\text{EtOH}}{4.6} \)

Osmal gap (OG) = measured osmolytes – calculated osmolytes (normal < 10)

Estimated creatinine clearance = \( \frac{140 - \text{age (yrs)} \times \text{wt (kg)}}{72} \) × (× 0.85 in women)

Fractional excretion of Na (FENa, %) = \( \frac{\text{UNa (mEq/L)}}{\text{PNa (mEq/L)}} \times 100\% \) \( \times \) \( \frac{\text{UCr (mg/dL)}}{\text{PCr (mg/dL)}} \times 100 \) (mL/dl)

Corrected Na in hyperglycemia

estimate in all Pts: corrected Na = measured Na + \( \frac{2.4 \times \text{(measured glc} - 100)}{100} \)

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 H₂O deficit = TBW × \( \frac{\text{Na}_{\text{serum}} - 140}{140} \) = \( \frac{\text{Na}_{\text{serum}} - 140}{3} \) (in 70 kg Pt)

Trans-tubular potassium gradient (TTKG) = \( \frac{\text{UNa}}{\text{PNa}} \times \text{UNa}_{\text{Osm}} \)

\( \frac{\text{PK}}{\text{PNa}_{\text{Osm}}} \)
**Hematology**

### Peripheral Smear Findings (also see Photo Inserts)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Abnormalities and diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>normocytic vs. microcytic vs. macrocytic → see below</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td>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 (event, 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 stomatocytes → central pallor appears as curved slit → liver disease, EtOH target cells → liver disease, hemoglobinopathies, splenectomy tear drop cells → dacrocytes → myelofibrosis, myelophthisic anemia, megaloblastic anemia, thalassemia</td>
</tr>
<tr>
<td><strong>Intra-RBC findings</strong></td>
<td>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 hemato poiesis</td>
</tr>
<tr>
<td><strong>WBC findings</strong></td>
<td>blasts → leukemia, lymphoma; Auer rods → acute myelogenous leukemia hypersegmented (&gt;3 lobes) PMNs: megaloblastic anemia (B12/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)</td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
<td>clumping → artifact, repeat plt count number → periph blood plt count approximately 10,000 plt for every one plt seen at hpf (100×) size → MPV (mean platelet volume) enlarged in ITP</td>
</tr>
</tbody>
</table>

(NEJM 2005;353:498)

---

### Heparin for Thromboembolism

<table>
<thead>
<tr>
<th>PTT</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>bolus 5000 U, ↑ rate 300 U/h</td>
</tr>
<tr>
<td>40–49</td>
<td>bolus 3000 U, ↑ rate 200 U/h</td>
</tr>
<tr>
<td>50–59</td>
<td>↑ rate 150 U/h</td>
</tr>
<tr>
<td>60–85</td>
<td>no Δ</td>
</tr>
<tr>
<td>86–95</td>
<td>↓ rate 100 U/h</td>
</tr>
<tr>
<td>96–120</td>
<td>hold 30 min, ↓ rate 100 U/h</td>
</tr>
<tr>
<td>&gt;120</td>
<td>hold 60 min, ↓ rate 150 U/h</td>
</tr>
</tbody>
</table>

(Modified from Chest 2008;133:1415)

### Heparin for ACS

<table>
<thead>
<tr>
<th>PTT</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>bolus 3000 U, ↑ rate 100 U/h</td>
</tr>
<tr>
<td>40–49</td>
<td>↑ rate 100 U/h</td>
</tr>
<tr>
<td>50–75</td>
<td>no Δ</td>
</tr>
<tr>
<td>76–85</td>
<td>↓ rate 100 U/h</td>
</tr>
<tr>
<td>86–100</td>
<td>hold 30 min, ↓ rate 100 U/h</td>
</tr>
<tr>
<td>&gt;100</td>
<td>hold 60 min, ↓ rate 200 U/h</td>
</tr>
</tbody>
</table>


- ✓ PTT q6h after every change (half-life of heparin is ~90 min)
- ✓ PTT qd or bid once PTT is therapeutic
- ✓ CBC qd (to ensure Hct and plt counts are stable)

### Warfarin Loading Nomogram

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>1.5–1.9</td>
</tr>
<tr>
<td>1–3</td>
<td>5 mg (7.5 mg if &gt; 80 kg)</td>
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<tr>
<td>4–5</td>
<td>10 mg</td>
</tr>
<tr>
<td>6</td>
<td>Dose based on requirements over preceding 5 days</td>
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(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 (e.g., 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); therefore, warfarin can elevate PT before achieving a true antithrombotic state
  2. Protein C also has half-life less than that of factor II; therefore, 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 at least 2 d and 4–5 d of warfarin (roughly corresponds to 2 half-lives of factor II or a reduction to ~25%)

### OTHER

**Ideal body weight (IBW)** = [50 kg (men) or 45.5 kg (women)] + 2.3 kg/inch over 5 ft

**Body surface area (BSA, m²)** = \[ \frac{\sqrt{\text{height (cm) \times weight (kg)}}}{3600} \]

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<th>absent</th>
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<td>c</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>(false)</td>
<td>(true)</td>
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- **Prevalence** = \[ \frac{a + b}{a + b + c + d} \]
- **Sensitivity** = \[ \frac{a}{a + c} \]
- **Specificity** = \[ \frac{d}{b + d} \]
- **Predictive value** = \[ \frac{a}{a + b} \]
- **Predictive value** = \[ \frac{d}{c + d} \]
- **Accuracy** = \[ \frac{a + d}{a + b + c + d} \]
- **Likelihood ratio** = \[ \frac{Se}{1 - Sp} \]
- **Likelihood ratio** = \[ \frac{Sp}{1 - Se} \]
- **Odds** = \[ \frac{\text{probability}}{1 - \text{probability}} \]
- **Probability** = \[ \frac{\text{odds}}{\text{odds} + 1} \]
- **Posttest odds** = pretest odds \times LR
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<td>6-MP</td>
<td>6-mercaptopurine</td>
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<td>AAD</td>
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<td>antibody</td>
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<td>anticolcholipin antibody</td>
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<td>Abbreviation</td>
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<td>functional residual capacity</td>
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<td>incision &amp; drainage</td>
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<td>intensive care unit</td>
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<td>IGF</td>
<td>insulin-like growth factor</td>
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<td>interferon-γ release assay</td>
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<td>LABA</td>
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<td>left bundle branch block</td>
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<td>lower extremity</td>
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<td>lower gastrointestinal bleed</td>
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<td>LH</td>
<td>luteinizing hormone</td>
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<td>LLQ</td>
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<td>LMMWH</td>
<td>low-molecular-weight heparin</td>
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<td>LN</td>
<td>lymph node</td>
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<td>loss of consciousness</td>
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<td>LOS</td>
<td>length of stay</td>
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<td>LP</td>
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<td>Ipf</td>
<td>low power field</td>
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<td>LR</td>
<td>lactated Ringer's</td>
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<td>LQTS</td>
<td>long QT syndrome</td>
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<td>LUSB</td>
<td>left upper sternal border</td>
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LV  left ventricle
LVAD  LV assist device
LVADP  LV end-diastolic pressure
LVEDV  LV end-diastolic volume
LVH  left ventricular hypertrophy
LVOT  left ventricular outflow tract
LVSD  LV systolic dimension
MAC  mitral annular calcification
MAHA  Mycobacterium avium complex
MAHA  microangiopathic hemolytic anemia
MAO  monoamine oxidase
MAP  mean arterial pressure
MAT  multifocal atrial tachycardia
MC  minimal change disease
MCP  mitral valve prolapse
MDA  mean corpuscular volume
MDMA  3,4-methylenedioxyamphetamine (Ecstasy)
MDS  myelodysplastic syndrome
MDT  metatirial phalangeal (joint)
MCTD  mixed connective tissue disease
MCV  mean corpuscular volume
ME  metered dose inhaler
MEN  multiple endocrine neoplasia
MG  myasthenia gravis
MGUS  monoclonal gammopathy of uncertain significance
MI  myocardial infarction
MIO  myointimal hyperplasia
MIN  minute
MIN  minimal
MM  multiple myeloma
MMEFR  maximal mid-expiratory flow rate
MMF  mycopenolate mofetil
MN  membranous nephropathy
MNZ  metronidazole
MODS  multiple organ dysfunction syndrome
MOG  myotonic myopathy
MPN  myeloproliferative neoplasm
MPGN  membranoproliferative glomerulonephritis
MR  magnetic resonance
MRA  magnetic resonance angiography
MRCP  magnetic resonance cholangiopancreatoctigraphy
MRI  magnetic resonance imaging
MRSA  methicillin-resistant S. aureus
MTb  Mycobacterium tuberculosis
MTA  methotrexate
MTV  mitral valve
MV  mitral valve
MVP  mitral valve prolapse
MVR  mitral valve replacement
M  macrogloss
N/V  nausea and/or vomiting
NAC  N-acetylcysteine
NAFLD  non-alcoholic fatty liver disease
NASH  non-alcoholic steatohepatitis
NG  nasogastric
NGT  nasogastric tube
NHL  Non-Hodgkin lymphoma
NIF  negative inspiratory force
NJ  nasojunal
n  normal
NM  neuromuscular
NMJ  neuromuscular junction
NNRTI  non-nucleoside reverse transcriptase inhibitor
NNT  number needed to treat
NNT  nitric oxide
NPJ  nonparoxysmal junctional tachycardia
NPO  nothing by mouth
NPV  negative predictive value
NS  normal saline
NSAID  nonsteroidal anti-inflammatory drug
NSCLC  non-small cell lung cancer
NYHA  New York Heart Association
NPPV  noninvasive positive pressure ventilation
NRTI  nucleoside reverse transcriptase inhibitor
NSF  nephrogenic systemic fibrosis
NTG  nitroglycerin
NU  nephrogenic systemic fibrosis
NVE  native valve endocarditis
O/D  overdose
OA  osteoarthritis
OCP  oral contraceptive pill
OG  osmotic gap
OGT  orogastric tube
OGTT  oral glucose tolerance test
OI  opportunistic infection
OM  obliterative collateral coronary artery
OSA  obstructive sleep apnea
OTC  over-the-counter
P/w  present(s) with
PA  pulmonary artery
PAC  pulmonary artery catheter
PAD  peripheral arterial disease
PAN  polyarteritis nodosa
PASP  pulmonary artery systolic pressure
PCE  percutaneous aortic valvuloplasty
pc  problem
PBC  primary biliary cirrhosis
PC  pulmonary capillary wedge pressure
PD  Parkinson's disease
PDA  patent ductus arteriosus
PER  perieral retinal artery
PCO2  positive end-expiratory pressure
PET  positron emission tomography
PEX  physical examination
PG  inflammatory bowel disease
PFO  patent foramen ovale
PFT  pulmonary function test
PGA  polyglutamyl anticollagen syndrome
PHT  pulmonary hypertension
PIS  protease inhibitor
<table>
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<td>PIF</td>
<td>prolactin inhibitory factor</td>
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<td>peak inspiratory pressure proximal interphalangeal (joint)</td>
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<td>PM</td>
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<td>rheumatic heart disease</td>
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<tr>
<td>RI</td>
<td>reticulocyte index</td>
</tr>
<tr>
<td>RIBA</td>
<td>recombinant immunoblot assay</td>
</tr>
<tr>
<td>RMSF</td>
<td>Rocky Mountain spotted fever review of systems</td>
</tr>
<tr>
<td>ROS</td>
<td>rapidly progressive glomerulonephritis</td>
</tr>
<tr>
<td>RSPG</td>
<td></td>
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<tr>
<td>Rv</td>
<td>right ventricle</td>
</tr>
<tr>
<td>RVAD</td>
<td>RV assist device</td>
</tr>
<tr>
<td>RVH</td>
<td>right ventricular hypertrophy</td>
</tr>
<tr>
<td>RVOT</td>
<td>RV outflow tract</td>
</tr>
<tr>
<td>RVSP</td>
<td>RV systolic pressure</td>
</tr>
<tr>
<td>Rx</td>
<td>therapy</td>
</tr>
<tr>
<td>s/e</td>
<td>side effect</td>
</tr>
<tr>
<td>s/p</td>
<td>status post</td>
</tr>
<tr>
<td>s/s</td>
<td>signs and symptoms</td>
</tr>
<tr>
<td>SA</td>
<td>sinoatrial</td>
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<tr>
<td>SAAG</td>
<td>serum-ascites albumin gradient</td>
</tr>
<tr>
<td>SAH</td>
<td>subarachnoid hemorrhage</td>
</tr>
<tr>
<td>SAS</td>
<td>sulfasalazine</td>
</tr>
<tr>
<td>SBE</td>
<td>subacute bacterial endocarditis</td>
</tr>
<tr>
<td>SBP</td>
<td>spontaneous bacterial peritonitis</td>
</tr>
<tr>
<td>SBT</td>
<td>spontaneous breathing trial</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SCD</td>
<td>sudden cardiac death</td>
</tr>
<tr>
<td>SCID</td>
<td>severe combined immunodeficiency</td>
</tr>
<tr>
<td>SCLC</td>
<td>small cell lung cancer</td>
</tr>
<tr>
<td>Se</td>
<td>sensitivity</td>
</tr>
<tr>
<td>sec</td>
<td>second</td>
</tr>
<tr>
<td>SERM</td>
<td>selective estrogen receptor modulator</td>
</tr>
<tr>
<td>sev.</td>
<td>severe</td>
</tr>
<tr>
<td>SIADH</td>
<td>syndrome of inappropriate antidiuretic hormone</td>
</tr>
<tr>
<td>SIEOP</td>
<td>serum immuonoelectrophoresis</td>
</tr>
<tr>
<td>SIMV</td>
<td>synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>SME</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SLE</td>
<td>superior mesenteric artery</td>
</tr>
<tr>
<td>SMV</td>
<td>superior mesenteric vein</td>
</tr>
</tbody>
</table>
ABBREV

SOS sinusoidal obstructive syndrome
Sp specificity
SPEP serum protein electrophoresis
SR sinus rhythm
SSCY Salmonella, Shigella, Campylobacter, Yersinia
SSRI selective serotonin reuptake inhibitor
SSS sick sinus syndrome
ST sinus tachycardia
STD sexually transmitted disease
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-RU T3 resin uptake
TAA thoracic aortic aneurysm
TB tuberculosis
TBC thyroid binding globulin
TRA tricuspid regurgitation
TRALI transfusion-related acute lung injury
TSH thyroid stimulating hormone
TSI thyroid-stimulating immunoglobulin
TSS toxic shock syndrome
TTKGP thrombotic thrombocytopenic purpura
TV tricuspid valve
Tw T wave
TWF T-wave flattening
TWI T-wave inversion
Tx transplant
TZD thiazolidinediones
U/A urinalysis
U/S ultrasound
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 respiratory tract infection
UTI urinary tract infection
V/Q ventilation-perfusion
VAD ventricular assist device
VAP ventilator-associated pneumonia
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
VSD ventricular septal defect
VT tidal volume
VT ventricular tachycardia
VT venous thromboembolus
vWD von Willebrand's disease
VWF von Willebrand's factor
VZV varicella zoster virus
w/ with
w/o without
w/u workup
WBC white blood cell (count)
WCT wide-complex tachycardia
WHO World Health Organization
wk week
WM Waldenström's macroglobulinemia
WMA wall motion abnormality
WPW Wolff-Parkinson-White syndrome
XRT radiation therapy
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1 **Normal PA CXR.** The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicated the location of the superior vena cava. The left cardiac and great vessels border what might be considered as four skiing moguls. From cephalad to caudal, 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.)


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.)

10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow) (PA). (Radiology 101, 3rd ed, 2009.)


12 Pneumothorax. (Radiology 101, 3rd ed, 2009.)
13 Normal chest CT at level of pulmonary arteries (parenchymal windows).

(Radiology 101, 3rd ed, 2009.)
14 Bilateral PE (mediastinal windows). (Radiology 101, 3rd ed, 2009.)


17 Normal abdomen CT at level of liver & spleen. (Radiology 101, 3rd ed, 2009.)
18 Normal abdomen CT at level of pancreas. (Radiology 101, 3rd ed, 2009.)
Echocardiography

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

### LEFT CORONARY ARTERY
- 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

### RIGHT CORONARY ARTERY
- 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.

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**Leukemias**

1 AML with Auer rod.

2 ALL.
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 **Granular cast.** (College of Am. Pathologist, with permission.)


3 **RBC cast.** (*Dis. of Kidney & Urinary Tract*, 8th ed, 2006.)
