POCKET NOTEBOOK

POCKET MEDICINE

FOURTH EDITION

Edited by

Marc S. Sabatine

The Massachusetts General Hospital Handbook of Internal Medicine

Wolters Kluwer Health | Lippincott Williams & Wilkins

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Fourth Edition

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ASSOCIATE PROFESSOR OF MEDICINE

HARVARD MEDICAL SCHOOL

The Massachusetts General Hospital Handbook of Internal Medicine

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CONTENTS

NEPHROLOGY

Andrew L. Lundquist, Eugene P. Rhee, Hasan Bazari

HEMATOLOGY-ONCOLOGY

Andrew J. Aguirre, Franklin W. Huang, David B. Sykes, David T. Ting, Daniel J. DeAngelo, David P. Ryan

INFECTIOUS DISEASES

Roby P. Bhattacharyya, Rachel P. Simmons, Nesli Basgoz

ENDOCRINOLOGY

Alaka Ray, Geoffrey A. Walford, Michael Mannstadt

RHEUMATOLOGY

Gwen C. Crevensten, Katherine P. Liao, Robert P. Friday

NEUROLOGY

David Y. Hwang, Atul Maheshwari, Mikael L. Rinne, David M. Greer

APPENDIX

PHOTO INSERTS

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FOREWORD

To the 1st Edition

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

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

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

PREFACE

For Jenny, Matteo, and Natalie with love

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.

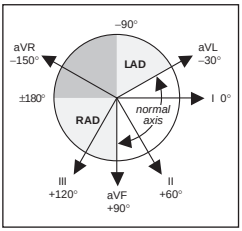
I hope that you find *Pocket Medicine* useful throughout the arduous but incredibly rewarding journey of practicing medicine.

Marc S. Sabatine, MD, MPH

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 V_1–V_6, ST ↑/↓, or T-wave Δs)

Figure 1-1 QRS axis

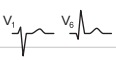
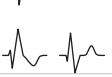
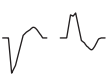


Left axis deviation (LAD)

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

Right axis deviation (RAD)

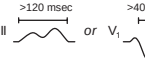
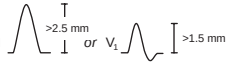
- **Definition**: axis beyond +90° (S > R in lead I)
- **Etiologies**: RVH, PE, COPD (usually not >+110°), septal defects, lateral MI, WPW
- **Left posterior fascicular block**: RAD (90–180°) *and* rS in I & aVL *and* qR in III & aVF *and* QRS <120 msec *and* no other cause of RAD

Bundle Branch Blocks (*Circ* 2009;119:e235)		
Normal		Initial depol. is left-to-right across septum (r in V_1 & q in V_6; nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB).
RBBB		1. QRS ≥120 msec (110–119 = incomplete) 2. rSR' in R precordial leads (V_1,V_2) 3. Wide S wave in I and V_6 4. ± ST↓ or TWI in R precordial leads
LBBB		1. QRS ≥120 msec (110–119 = incomplete) 2. Broad, slurred, monophasic R in I, aVL, V_5–V_6 (± RS in V_5–V_6 if cardiomegaly) 3. Absence of Q in I, V_5, and V_6 (may have narrow q in aVL) 4. Displacement of ST & Tw opposite major QRS deflection 5. ± PRWP, LAD, Qw's in inferior leads

Bifascicular block: RBBB + LAFB/LPFB

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)
- QT varies w/ HR → correct w/ Bazett formula: $QTc = QT/\sqrt{RR}$ (in sec), formula inaccurate at very high and low HR (nl QTc <450 msec ♂ and <460 msec ♀)
- Etiologies:
  - **Antiarrhythmics**: class Ia (procainamide, disopyramide), class III (amiodarone, sotalol)
  - **Psych drugs**: antipsychotics (phenothiazines, haloperidol, atypicals), Li, ? SSRI, TCA
  - **Antimicrobials**: macrolides, quinolones, voriconazole, pentamidine, atovaquone, chloroquine, amantadine, foscarnet, atazanavir, ? TMP-SMX
  - **Other**: antiemetics (droperidol, 5-HT_3 antagonists), alfuzosin, methadone, ranolazine
  - **Electrolyte disturbances**: hypoCa, ? hypoK, ? hypoMg
  - **Autonomic dysfxn**: ICH (deep TWI), stroke, carotid endarterectomy, neck dissection
  - **Congenital** (long QT syndrome): K, Na, Ca channelopathies (*Lancet* 2008;372:750)
  - **Misc**: CAD, CMP, bradycardia, high-grade AVB, hypothyroidism, hypothermia

ECG P wave Criteria	Left Atrial Abnormality (LAA)	Right Atrial Abnormality (RAA)
		
	>120 msec; >40 msec; II; *or* V_1; >1 mm	>2.5 mm; II; *or* V_1; >1.5 mm

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

- 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 V_1 or V_2 ≥30 mm *or* R in V_5 or V_6 ≥30 mm (3 points)

ST displacement opposite to QRS deflection: w/o dig (3 points); w/ dig (1 point)
LAA (3 points); LAD (2 points); QRS duration ≥90 msec (1 point)
Intrinsicoid deflection (QRS onset to peak of R) in V_5 or V_6 ≥50 msec (1 point)
Sokolow-Lyon: S in V_1 + R in V_5 or V_6 ≥35 mm
Cornell: R in aVL + S in V_3 >28 mm in men or >20 mm in women
Other: R in aVL ≥11 mm (or, if LAD/LAFB, ≥13 mm *and* S in III ≥15 mm)

Right ventricular hypertrophy (RVH) (*Circ* 2009;119:e251)

- Etiologies: cor pulmonale, congenital (tetralogy, TGA, PS, ASD, VSD), MS, TR
- Criteria (all tend to be insensitive, but highly specific, except in COPD)
  R > S in V_1 or R in V_1 ≥7 mm, S in V_5 or V_6 ≥7 mm, drop in R/S ratio across precordium
  RAD ≥+110° (LVH + RAD *or* prominent S in V_5 or V_6 → *biventricular* hypertrophy)

Ddx of dominant R wave in V_1 or V_2

- Ventricular enlargement: RVH (RAD, RAA, deep S waves in I, V_5, V_6); HCMP
- Myocardial injury: true posterior MI (often IMI); Duchenne muscular dystrophy
- Abnormal depolarization: RBBB (QRS >120 msec, rSR'); WPW (↓ PR, δ wave, ↑ QRS)
- Other: dextroversion; lead misplacement; normal variant

Poor R-wave progression (PRWP) (*Archives* 1982;142:1145)

- Definition: loss of anterior forces w/o frank Q waves (V_1–V_3); R wave in V_3 ≤3 mm
- Etiologies:
  old anteroseptal MI (usually R wave V_3 ≤1.5 mm, ± persistent ST ↑ or TWI V_2 & V_3)
  cardiomyopathy
  LVH (delayed RWP with prominent left precordial voltage)
  RVH/COPD (small R wave and prominent S wave in lead I)
  LBBB; WPW; clockwise rotation of the heart; lead misplacement

Pathologic Q waves

- Definition: ≥30 msec or >25% height of the R wave in that complex
- Small (septal) q waves in I, aVL, V_5 & V_6 are normal, as can be isolated Qw in III, aVR, V_1
- "Pseudoinfarct" pattern may be seen in LBBB, infiltrative disease, HCMP, COPD, PTX, WPW

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

- **Acute MI** (upward convexity ± TWI) 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 ↓; Tw usually upright)
- **HCMP**, **Takotsubo CMP**, **ventricular aneurysm**, cardiac contusion
- **Pulmonary embolism** (occ. STE V_1–V_3; typically associated TWI V_1–V_4, RAD, RBBB)
- **Repolarization abnormalities**
  LBBB (↑ QRS duration, STE discordant from QRS complex)
  dx of STEMI in setting of LBBB: ≥1 mm STE concordant w/ QRS (Se 73%, Sp 92%)
  or ≥5 mm discordant (Se 31%, Sp 92%) ("Sgarbossa criteria," *NEJM* 1996;334:481)
  LVH (↑ QRS amplitude); Brugada syndrome (rSR', downsloping STE V_1–V_2)
  Hyperkalemia (↑ QRS duration, tall Ts, no Ps)
- **Early repolarization**: most often seen in leads V_2–V_5 and in young adults
  J point ↑ 1–4 mm; notch in downstroke of R wave; upward concavity of ST; large Tw; ratio of STE / T wave amplitude <25%; pattern may disappear with exercise
  early repol in inf leads may be a/w ↑ risk of VF, but absolute risk low (*NEJM* 2009;361:2529)

ST depression (STD)

- **Myocardial ischemia** (± Tw abnl) or acute true posterior MI (V_1–V_3)
- Digitalis effect (downsloping ST ± Tw abnl, does *not* correlate w/ dig levels)
- Hypokalemia (± U wave)
- Repolarization abnl in a/w LBBB or LVH (usually in leads V_5, V_6, I, aVL)

T wave inversion (TWI; generally ≥1 mm; deep if ≥5 mm) (*Circ* 2009;119:e241)

- Ischemia or infarct; Wellens' sign (deep early precordial TWI) → proximal LCA lesion
- Myopericarditis; CMP (incl Takotsubo & ARVD); MVP; PE (especially if TWI V_1–V_4)
- Repolarization abnl in a/w LVH/RVH ("strain pattern"), BBB
- Post-tachycardia or post-pacing
- Electrolyte, digoxin, PaO_2, $PaCO_2$, pH, or core temperature disturbances
- Intracranial bleed ("cerebral T waves," usually w/ ↑ QT)
- Normal variant in children (V_1–V_4) and leads in which QRS complex predominantly ⊖; profound TWI in young athletes may predict future risk of CMP (*NEJM* 2008;358:152)

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

Cardiac Causes	
Disorder	**Typical Characteristics & Diagnostic Studies**
Unstable angina	Substernal 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 (*Annals EM* 2005;45:581). ± ECG Δs (ST ↓/↑,TWI).
MI	Same as angina but ↑ intensity & duration. ⊕ troponin or CK-MB.
Pericarditis & Myo-pericarditis	Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ± Pericardial friction rub. ECG Δs (diffuse STE & PR ↓). ± Pericardial effusion. If myocarditis, same as above + ↑Tn and ± s/s CHF and ↓ EF.
Aortic dissection	Abrupt onset severe tearing, knifelike pain (absence ⊖LR 0.3), ant or post mid-scapular. HTN or HoTN. ± Asymmetric (>20 mmHg) BP or pulse deficit (⊕LR 5.7), focal neuro deficit (⊕LR >6), AI, widened mediastinum on CXR (absence ⊖LR 0.3); false lumen on imaging. (*JAMA* 2002;287:2262)

Pulmonary Causes	
Disorder	**Typical Characteristics & Diagnostic Studies**
Pneumonia	Pleuritic; dyspnea, fever, cough, sputum. ↑ RR, crackles. CXR infiltrate.
Pleuritis	Sharp, pleuritic pain. ± Pleuritic friction rub.
PTX	Sudden onset, sharp pleuritic pain. Hyperresonance, ↓ BS. PTX on CXR.
PE	Sudden onset pleuritic pain. ↑ RR & HR, ↓ S_aO_2, ECG Δs (RAD, RBBB, TWI V_1–V_4, occ STE V_1–V_3). ⊕ CTA.
PHT	Exertional pressure, dyspnea. ↓ S_aO_2, loud P_2, right-sided S_3 and/or S_4.

GI Causes	
Disorder	**Typical Characteristics & Diagnostic Studies**
Esophageal reflux	Substernal burning, acid taste in mouth, water brash. ↑ by meals, recumbency; ↓ by antacids. EGD, manometry, pH monitoring.
Esoph spasm	Intense substernal pain. ↑ by swallowing, ↓ by NTG/CCB. Manometry.
Mallory-Weiss	Precipitated by vomiting. EGD.
Boerhaave syndrome	Precipitated by vomiting. Severe pain, ↑ w/ swallowing. Palpable SC emphysema; mediastinal air on chest CT.
PUD	Epigastric pain, relieved by antacids. ± GIB. EGD, ± *H. pylori* test.
Biliary dis.	RUQ pain, nausea/vomiting. ↑ by fatty foods. RUQ U/S, LFTs.
Pancreatitis	Epigastric/back discomfort. ↑ amylase & lipase; abd CT.

Musculoskeletal and Miscellaneous Causes	
Disorder	**Typical Characteristics & Diagnostic Studies**
Chostochondritis	Localized sharp pain. ↑ w/ movement. Reproduced by palpation.
Herpes zoster	Intense unilateral pain. Dermatomal rash & sensory findings.
Anxiety	"Tightness"

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 (V_7–V_9) 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 (I/T): most Se & Sp marker; level >99th %ile in approp. 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

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

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

- **Indications**: dx CAD, evaluate if known CAD & Δ 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 bradycardia and bronchospasm). *Chronotropes/inotropes* (~physiologic): dobutamine (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 **SPECT** (eg, ^{99m}Tc-sestamibi), **PET** (rubidium-82; usually w/ pharm test), **echo**, **MRI**

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 (HR_{peak} – $HR_{1\ min\ later}$; nl >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 ⊕: breast → ant "defect" and diaphragm → inf "defect"
  false ⊖ may be seen if balanced (eg, 3VD) ischemia (global ↓ perfusion w/o regional Δs)
  ECG-gating allows assessment of LV systolic function

High-risk test results (PPV ~50% for LM or 3VD, ∴ 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: ↓ BP, exercise <4 METS, angina during exercise, Duke score ≤ –11; EF <35%
- Radionuclide: ≥1 lg 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;369:2324; *Circ* 2010;121:2509)

- Image quality best at slower & regular HR (give βB 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)
- ? 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 text to r/o CAD in sx Pt (CACS <100 → 3% probability of signif CAD; but high scores have poor specificity)

Indications for coronary angiography in stable CAD or asx 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 >6 h
- ✓ CBC, PT, & Cr; give IVF (± bicarb, acetylcysteine; see "CIAKI"); blood bank sample
- ASA 325 mg; consider clopidogrel preRx (300–600 mg ≥2–6 h before) vs. prasugrel at time of PCI (if ACS)

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

- CABG: ↓ mortality c/w med Rx (albeit pre statins & ACEI/ARB) in Pts w/ 3VD, LM, or 2VD w/ critical prox LAD, and espec. if ↓ EF (but viable myocardium); ↓ repeat revasc and trend toward ↓ D/MI but ↑ stroke c/w PCI in LM/3VD (*NEJM* 2009;360:961); CABG vs. PCI being studied in DM (FREEDOM trial)
- PCI: ↓ angina c/w med Rx; does *not* ↓ D/MI (COURAGE, *NEJM* 2007;356:1503); prompt revasc (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 revasc deemed necessary, PCI if limited # of discrete lesions, nl EF, no DM, poor operative candidate; CABG if extensive or diffuse disease, ↓ EF, DM, or valvular disease
- Fractional flow reserve [ratio of maximal flow (induced by IV or IC adenosine) distal vs. proximal to a stenosis]: PCI only if <0.8 → ↓ # stents & ↓ D/MI/revasc (*NEJM* 2009;360:213)

PCI

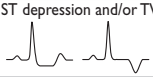
- **Balloon angioplasty (POBA)**: effective, but c/b dissection & elastic recoil & neointimal hyperplasia → restenosis; now reserved for small lesions & ? some SVG lesions
- **Bare metal stents (BMS)**: ↓ elastic recoil → 33–50% ↓ restenosis & repeat revasc (to ~10% by 12 mos) c/w POBA; requires ASA lifelong & clopidogrel × ≥4 wks
- **Drug-eluting stents (DES)**: ↓ neointimal hyperplasia → ~75% ↓ restenosis, ~50% ↓ repeat revasc (to <5% by 1 y), no ↑ D/MI c/w BMS (*NEJM* 2008;359:1330); 2nd gen. everolimus DES promising (*NEJM* 2010;362:1728); require ASA lifelong & clopidogrel × ≥1 y (*Circ* 2007;115:813)
- **Anticoagulant**: UFH (short-acting, rapidly reversible, but need to ✓ PTT/ACT), LMWH (no need for monitoring, but $t_{1/2}$ 8–12 h), bivalirudin (↓ bleeding, but ±↑ MI; *NEJM* 2009;359:688)

Post-PCI complications

- Postprocedure ✓ vascular access site, distal pulses, ECG, CBC, Cr, CK-MB
- **Bleeding**
  hematoma/overt bleeding: manual compression, reverse/stop anticoag
  retroperitoneal bleed: may present with ↓ Hct ± back pain; ↑ HR & ↓ BP late; Dx: abd/pelvic CT (I^-); Rx: reverse/stop anticoag, IVF/PRBC as required
  if bleeding uncontrolled, consult performing interventionalist or surgery
- **Vascular damage**
  pseudoaneurysm: triad of pain, expansile 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× ULN 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

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

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

- Nonatherosclerotic coronary artery disease
  - Spasm: Prinzmetal's variant, cocaine-induced (6% of 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 O_2 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: S_4, new MR murmur 2° papillary muscle dysfxn, paradoxical S_2
- Signs of heart failure: ↑ JVP, crackles in lung fields, ⊕ S_3, 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
  - ✓ ECG w/in 10 min of presentation, with any Δ in sx, and at 6–12 h; c/w baseline
  - dx of STEMI in setting of LBBB: ≥1 mm STE concordant w/ QRS (Se 73%, Sp 92%) or ≥5 mm discordant (Se 31%, Sp 92%) in any lead (*NEJM* 1996;334:481)

Localization of MI		
Anatomic Area	**ECG Leads w/ STE**	**Coronary Artery**
Septal	V_1–V_2	Proximal LAD
Anterior	V_3–V_4	LAD
Apical	V_5–V_6	Distal LAD, LCx, or RCA
Lateral	I, aVL	LCx
Inferior	II, III, aVF	RCA (~85%), LCx (~15%)
RV	V_1–V_2 & V_4R (most Se)	Proximal RCA
Posterior	ST *depression* V_1–V_3	RCA or LCx

If ECG non-dx and suspicion high, consider addt'l lateral (posterior) leads (V_7–V_9) to further assess LCx territory. Check right-sided precordial leads in patients with IMI to help detect RV involvement (STE in V_4R most Se). STE in III > STE in II and lack of STE in I or aVL suggest RCA rather than LCx culprit in IMI.

- **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**: ∅ signif stenosis 98% NPV; ⊕ 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 βB as unopposed α-stimulation can worsen spasm

Likelihood of ACS			
Feature	**High** (any of below)	**Intermediate** (no high features, any of below)	**Low** (no high/inter. features, may have below)
History	chest or L arm pain like prior angina h/o CAD (incl MI)	chest or L arm pain age >70 y male, diabetes	atypical sx (eg, pleuritic, sharp, or positional pain)
Exam	HoTN, diaphoresis, CHF, transient MR	PAD or CVD	pain reproduced on palp.
ECG	new STD (≥1 mm) TWI in mult leads	old Qw, STD (0.5–0.9 mm), TWI (>1 mm)	TWF/TWI (<1 mm) in leads w/ dominant R wave
Biomarkers	⊕ Tn or CK-MB	Normal	Normal

(Adapted from ACC/AHA 2007 Guideline Update for UA/NSTEMI, *Circ* 2007;116:e148)

Approach to triage

- If hx and initial ECG & biomarkers non-dx, repeat ECG & biomarkers 12 h later
- If remain nl and low likelihood of ACS, search for alternative causes of chest pain
- If remain nl & Pt pain-free, have r/o MI, *but* if suspicion for ACS based on hx, then still need to r/o UA w/ stress test to assess for inducible ischemia (or CTA to r/o CAD);
  if low risk (age ≤70; Ø prior CAD, CVD, PAD; Ø rest angina) can do as outPt w/in 72 h (0% mortality, <0.5% MI, *Ann Emerg Med* 2006;47:427);
  if not low risk, admit and evaluate for ischemia (stress test or cath)
- If ECG or biomarker abnl or high likelihood of ACS, then admit and Rx as per below

UA/NSTEMI (NSTE ACS)

Anti-Ischemic and Other Treatment	
Nitrates (SL, PO, topical, or IV)	↓ anginal sx, no ↓ in mortality
β-blockers: PO; IV if ongoing pain, HTN or ↑ HR (w/o s/s CHF) eg, metoprolol 5 mg IV q5 min × 3 then 25–50 mg PO q6h titrate to HR 50–60	13% ↓ in progression to MI (*JAMA* 1988;260:2259) *Contraindicated* if HR <50, SBP <90, moderate or severe CHF, 2°/3° AVB, severe bronchospasm
CCB (nondihydropyridines)	If cannot tolerate βB b/c bronchospasm
ACEI or **ARB**	Especially if CHF or EF <0.40 and if SBP >100
Morphine	Consider if persistent sx or pulmonary edema Should not be used to mask persistent CP
Oxygen	Use if necessary to keep S_aO_2 >90%

(Adapted from ACC/AHA 2007 Guideline Update for UA/NSTEMI, *Circ* 2007;116:e148)

Antiplatelet Therapy	
Aspirin 162–325 mg × 1 (1st dose crushed/chewed) then 75–325 mg/d	50–70% ↓ D/MI (*NEJM* 1988;319:1105) If ASA allergy, use clopidogrel instead (and desensitize to ASA)
Clopidogrel (ADP receptor blocker) 300 mg × 1 → 75 mg/d (requires ~6 h to steady-state) 600 mg × 1 → 150 mg/d × 7d may ↓ D/MI/stroke by 15% in PCI Pts (CURRENT/OASIS-7, ESC 2009)	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 ↓ fxn *CYP2C19* allele → ↓ plt inhib & ↑ ischemic events (*NEJM* 2009;360:354)
Prasugrel (ADP receptor blocker) 60 mg × 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;359:2001). Particularly efficacious in DM (*Circ* 2008;118:1626). Avoid if >75 y; contraindic. if h/o TIA/CVA.
Ticagrelor (ADP receptor blocker) 180 mg × 1 → 90 mg bid reversible (~nl plt fxn after 72 h) *under review at FDA*	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 IIb/IIIa 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)

(Adapted from ACC/AHA 2007 Guideline Update for UA/NSTEMI, *Circ* 2007;116:e148)

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. ~10% ↓ D/MI (*JAMA* 2004;292:89). Benefit greatest if conservative strategy. Can perform PCI on enoxaparin.
Bivalirudin (direct thrombin inhibitor) 0.75mg/kg IVB at time of PCI → 1.75 mg/kg/h	Use instead of heparin for Pts w/ HIT. With invasive strategy, bival alone noninferior to heparin + GPI (non-signif 8% ↑ D/MI/UR) w/ 47% ↓ bleeding (*NEJM* 2006;355:2203).
Fondaparinux (Xa inhibitor) 2.5 mg SC qd	C/w enox, 17% ↓ mortality & 38% ↓ bleeding by 30 d (*NEJM* 2006;354:1464). However, ↑ risk of cath thromb.; ∴ must supplement w/ UFH if PCI.

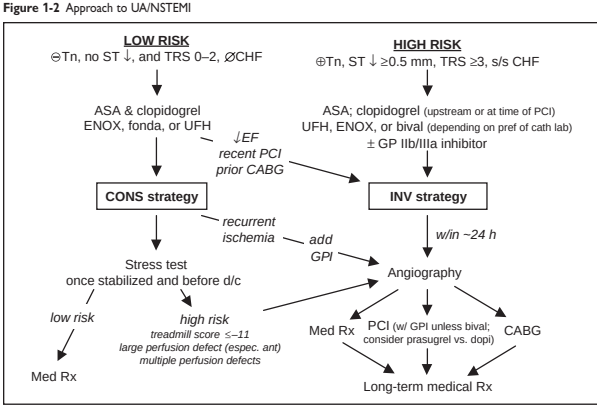
Coronary angiography (*Circ* 2007;116:e148 & 2009;120:2271)

- **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, STΔ, TRS ≥3, CHF, ↓ EF, recent PCI <6 mos, sustained VT, prior CABG, hemodynamic instability
  32% ↓ rehosp for ACS, nonsignif 16% ↓ MI, no Δ in mortality c/w cons. (*JAMA* 2008;300:71)
  ↑ peri-PCI MI counterbalanced by ↓↓ in spont. MI
  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;360:2165);
  ∴ reasonable to cath high-risk Pts (GRACE score >140) w/ 12–24 of admission

TIMI Risk Score for UA/NSTEMI (*JAMA* 2000;284:825)

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

Figure 1-2 Approach to UA/NSTEMI



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

Adapted from ACC/AHA 2004 STEMI Guidelines (*Circ* 2004;110:e82)

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 contraindic., ↑ risk of ICH in elderly (>75 y) makes PCI more attractive

Contraindications to Fibrinolysis

Absolute Contraindications	*Relative Contraindications*
• Any prior ICH	• Hx of severe HTN or SBP >180 or DBP >110 on presentation (? absolute contra. if low-risk MI)
• Intracranial neoplasm, aneurysm, AVM	• Ischemic stroke >3 mos prior
• Nonhemorrhagic stroke or closed head trauma w/in 3 mo	• Prolonged CPR (>10 min)
• Active internal bleeding or known bleeding diathesis	• Trauma or major surgery w/in 3 wk
• Suspected aortic dissection	• Recent internal bleed (w/in 2–4 wk); active PUD
	• Noncompressible vascular punctures
	• Prior SK exposure (if considering SK)
	• Pregnancy
	• Current use of anticoagulants

Nonprimary PCI

- Facilitated PCI: upstream lytic, GPI, or GPI + ½ dose lytic before PCI of no benefit
- Rescue PCI if shock, unstable, failed reperfusion or persistent sx (*NEJM* 2005;353:2758)
- Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/Revasc (*Lancet* 2004;364:1045) and w/in 6 h ↓ reMI, recurrent ischemia & CHF c/w w/in 2 wk (*NEJM* 2009;360:2705);
  ∴ *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)*
- *Late* PCI (median day 8) of occluded infarct-related artery: no benefit (*NEJM* 2006;355:2395)

Antiplatelet Therapy

Aspirin 162–325 mg (crushed/chewed)	23% ↓ in death (*Lancet* 1988;ii:349)
ADP receptor blocker Clopidogrel: 600 mg pre-PCI, 300 mg if lysis (not if >75 y) → 75 mg/d Prasugrel & ticagrelor as above	*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 *PCI:* prasugrel and ticagrelor ↓ CV events c/w clopi
GP IIb/IIIa inhibitors abciximab, eptifibatide, tirofiban	*Lysis:* no indication (*Lancet* 2001;357:1905) *Peri-PCI:* 60% ↓ D/MI/UR (*NEJM* 2001;344:1895)

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

Anticoagulant Therapy	
UFH 60 U/kg IVB (max 4000 U) 12 U/kg/h (max 1000 U/h)	No demonstrated mortality benefit ↑ patency with fibrin-specific lytics Titrate to aPTT 1.5–2x cntl (~50–70 sec)
Enoxaparin 30 mg IVB × 1 → 1 mg/kg SC bid (>75 y: no bolus, 0.75 mg/kg SC bid) (CrCl < 30 mL/min: 1 mg/kg SC qd)	*Lysis*: 17% ↓ D/MI w/ ENOX × 7 d vs. UFH × 2 d (*NEJM* 2006;354;1477) *PCI*: acceptable alternative to UFH (age & CrCl adjustments untested in 1° PCI)
Bivalirudin 0.75 mg/kg IVB → 1.75 mg/kg/hr IV	*PCI*: ↓ death & ↓ bleeding but ↑ acute stent thrombosis c/w heparin + GPI (*NEJM* 2008;358:2218)
Fondaparinux 2.5 mg SC QD	*Lysis:* superior to placebo & to UFH, with less bleeding (*JAMA* 2006;295;1519) *PCI*: risk of cath thromb.; should not be used

Immediate Adjunctive Therapy	
β-blockers eg, metoprolol 25 mg PO q6h titrate to HR 55–60 IV only if HTN & no s/s CHF	~20% ↓ arrhythmic death or reMI, 30% ↑ cardiogenic shock, & no Δ overall mortality when given to Pts incl. those w/ mod CHF (*Lancet* 2005;366:1622) *Contraindic.* if HR <60 or >110, SBP <120, mod/severe CHF, late present., 2°/3° AVB, severe bronchospasm
Nitrates SL or IV	? ~5% ↓ mortality (*Lancet* 1994;343:1115;1995;345:669) Use for relief of sx, control of BP, or Rx of CHF *Contraindic.* in hypovolemia, sx RV infarcts, sildenafil
Oxygen	Use if necessary to keep S_aO_2 >90%.
Morphine	Relieves pain, ↓ anxiety, venodilation → ↓ preload
ACE inhibitors eg, captopril 6.25 mg tid, titrate up as tolerated	~10% ↓ mortality (*Lancet* 1994:343:1115 & 1995;345:669) Greatest benefit in ant. MI, EF <40%, or prior MI *Contraindicated* in severe hypotension or renal failure
ARBs	Appear ≈ ACEI (VALIANT, *NEJM* 2003;349:20)
Insulin	Treat hyperglycemia >180 mg/dL while avoiding hypoglycemia, no clear benefit for intensive control

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 O_2 demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O_2 demand
  can use IV NTG or nitroprusside (risk of coronary steal) → short-acting ACEI
- Inotropes if CHF despite diuresis & ↓ afterload; use dopamine, dobutamine, or milrinone
- **Cardiogenic shock** (~7%) = MAP <60 mmHg, CI <2 L/min/m^2, PCWP >18 mmHg
  inotropes, IABP, percutaneous VAD to keep CI > 2; pressors (eg, norepinephrine) to keep MAP >60; if not done already, coronary revascularization ASAP (*NEJM* 1999;341:625)

MI complications (*Circ* 1990;81:401; *Annals* 1995;123:509)

- **Heart block** (~20%, occurs because RCA typically supplies AV node)
  40% on present., 20% w/in 24 h, rest by 72 h; high-grade AVB can develop abruptly
  Rx: atropine, epi, aminophylline (100 mg/min × 2.5 min), temp wire
- **Precordial ST** ↓ (15–30%): anterior ischemia *vs.* true posterior STEMI *vs.* reciprocal Δs
- **RV infarct** (30–50%, but only ½ of those clinically significant)
  hypotension; ↑ JVP, ⊕ Kussmaul's; 1 mm STE in V_4R; RA/PCWP ≥0.8; prox RCA occl.
  Rx: optimize preload (RA goal 10–14, *BHJ* 1990;63:98); ↑ contractility (dobutamine); maintain AV synchrony (pacing as necessary); reperfusion (*NEJM* 1998;338:933); mechanical support (IABP or RVAD); pulmonary vasodilators (eg, inhaled NO)

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

- **Free wall rupture**: ↑ risk w/ fibrinolysis, size of MI, age; p/w PEA or hypoTN, pericardial sx, tamponade; Rx: volume resusc., ? pericardiocentesis, inotropes, **surgery**
- **VSD**: large MI in elderly; AMI → apical VSD, IMI → basal septum; 90% w/ harsh murmur ± thrill (*NEJM* 2002;347:1426); Rx: diuretics, vasodil., inotropes, IABP, **surgery**, perc. closure
- **Papillary muscle rupture**: 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; ↑ βB 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)

Other Post-MI Complications

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

Prognosis

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

Killip Class

Class	Definition	Mort.
I	no CHF	6%
II	⊕ S_3 and/or basilar rales	17%
III	pulmonary edema	30–40%
IV	cardiogenic shock	60–80%

(*Am J Cardiol* 1967;20:457)

Forrester Class Mortality

		PCWP (mmHg)	
		<18	>18
CI	>2.2	3%	9%
	≤2.2	23%	51%

(*NEJM* 1976;295:1356)

Predischarge Checklist 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 ∴ plt 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 IIa inhibitors post-ACS under study (*Lancet* 2009;374:29)

ICD (*NEJM* 2008;359:2245)

- If sust. 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/d) & low fat (<7% saturated) diet; LDL goal <70 mg/dL; ? fish oil (*BMJ* 2008;337:a2931)
- 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/m^2
- Influenza vaccination (*Circ* 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 (*JACC* 1998;32:840 & *Circ* 2009;119:e391)

- **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_vO_2 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

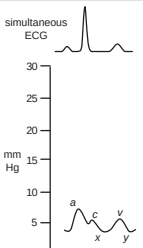
Intracardiac pressures

- 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 cmH_2O to mmHg by × ¾).
- 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 over time measured at thermistor (in PA) is integrated ≈ 1/CO. Inaccurate if ↓ CO, sev TR, or shunt.
- **Fick method**: O_2 consumption (L/min) = CO (L/min) × arteriovenous O_2 difference.
  CO derived by dividing O_2 consumption by observed AV O_2 difference [10 × 1.34 ml O_2/g Hb × Hb g/dl × ($S_aO_2 - S_vO_2$)].
  Can estimate O_2 consumption using wt-based formula, but best to measure (espec if ↑ metabolism, eg, sepsis).
  If S_vO_2 >80%, consider wedged (ie, pulm vein) sat, L→R shunt, impaired O_2 utilization (severe sepsis, cyanide, carbon monoxide), ↑↑ O_2 delivery.

PA Catheter Waveforms

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

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

Hemodynamic Profiles of Various Forms of Shock

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

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

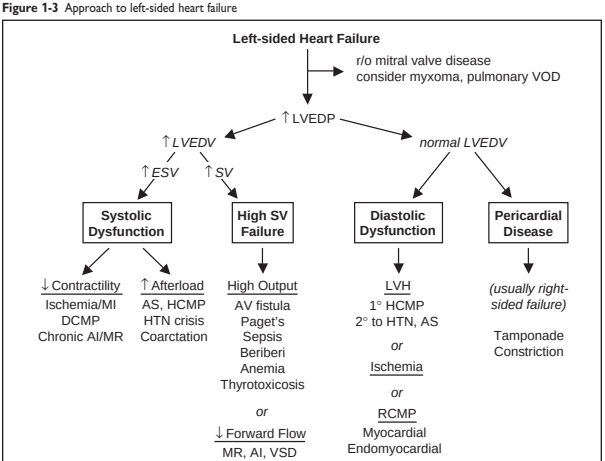
Tailored therapy in cardiogenic shock *(Circ 2009;119:e391)*

- **Goals**: optimize both MAP and CO while ↓ risk of pulmonary edema
  MAP = CO × SVR; CO = HR × SV (which depends on preload, afterload, and contractility)
  pulmonary edema when PCWP >20–25 (higher levels may be tolerated in chronic HF)
- **Optimize preload** = LVEDV ≈ LVEDP ≈ 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.)] and ∴ ∝ MAP and ∝ SVR = (MAP – CVP / CO); goals: **MAP >60**, **SVR 800–1200**
  MAP >60 & SVR ↑: vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or wean pressors
  MAP <60 & SVR ↑ (& ∴ CO ↓): temporize w/ pressors until can ↑ CO (see below)
  MAP <60 & SVR low/nl (& ∴ inappropriate vasoplegia): vasopressors (eg, norepinephrine [α, β], dopamine [D, α, β], phenylephrine [α], or vasopressin [V_1] if refractory)
- **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

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 >8 and 55% Se & 83% Sp for PCWP >15 (*AJC* 1990;66:1002)
  Valsalva square wave (↑ SBP thru strain) (*JAMA* 1996;275:630)
  S_3 (in Pts w/ HF → ~40% ↑ risk of HF hosp. or pump failure death; *NEJM* 2001;1345:574)
  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), S_4 (diast. dysfxn), murmur (valvular dis., ↑ MV annulus, displaced papillary muscles)

Evaluation for the presence of heart failure

- CXR (see Radiology insert): pulm edema, pleural effusions ± cardiomegaly, cephalization, Kerley B-lines
- 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 MV 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, HCMP, or RCMP (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** (βB, CCB, NSAIDs, TZDs) or **toxins** (EtOH, anthracyclines)
- Arrhythmias; acute valvular dysfxn (eg, endocarditis), espec. mitral or aortic regurgitation
- COPD or PE → ↑ right-sided afterload
- Anemia, systemic infection, thyroid disease

Treatment of acute decompensated heart failure
- Assess degree of congestion & adequacy of perfusion
- For **congestion**: **"LMNOP"**
  - **L**asix w/ monitoring of UOP; high-dose (IVB 2.5× PO dose) vs. low-dose (IVB 1× PO dose) → ↑ UOP but transient ↑ in renal dysfxn; ∅ clear diff between cont vs. intermittent (DOSE,ACC 2010)
  - **M**orphine (↓ sx, venodilator, ↓ afterload)
  - **N**itrates (venodilator)
  - **O**xygen ± noninvasive ventilation (see "Mechanical Ventilation")
  - **P**osition (sitting up & legs dangling over side of bed → ↓ preload)
- For **low perfusion**, see below

Low perfusion?	Congestion? No	Congestion? Yes
No	**Warm & Dry**	**Warm & Wet**
	OutPt Rx	*Diuresis ± vasodilator*
Yes	**Cold & Dry**	**Cold & Wet**
	± Inotropes (CCU)	*Tailored Rx (CCU)*

Treatment of advanced heart failure (*Circ* 2009;119:e391)
- Tailored Rx w/ PAC (qv); goals of MAP >60, CI >2.2 (MVO_2 >60%), SVR <800, PCWP <18
- **IV vasodilators**: NTG, nitroprusside (risk of coronary steal in Pts w/ CAD; prolonged use → cyanide/thiocyanate toxicity); nesiritide (rBNP) ↓ 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 vasodil. → ↑ GFR & natriuresis; vasoconstrict. at ≥5 μg/kg/min
  - milrinone: prominent systemic & pulmonary vasodilation; ↓ dose by 50% in renal failure
- **Ultrafiltration**: >1 L fluid loss at 48 h and ~50% ↓ in rehosp. (*JACC* 2007;49:675)
- **Mechanical circulatory support**
  - intraaortic balloon pump (IABP): deflates in diastole & inflates in systole to ↓ impedence to LV ejection of blood & ↑ coronary perfusion
  - ventricular assist device (LVAD ± RVAD): as bridge to recovery (*NEJM* 2006;355:1873) or transplant (some temporary types can be placed percutaneously = PVAD), or as destination therapy (45–50% ↓ mort. vs. med Rx; *NEJM* 2001;345:1435 & 2009;361:2241)
- Cardiac transplantation: 15–20% mort. in 1st y, median survival 10 y

Recommended Chronic Therapy by CHF Stage (*Circ* 2009;119: e391)

Stage (Not NYHA Class)		Pt Characteristics	Therapy
A	High risk for HF ⊖ Structural heart dis. Asx	HTN, DM, CAD Cardiotoxin 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 & βB if MI/CAD or ↓ EF
C	⊕ Structural heart dis. ⊕ Symptoms of HF (prior or current)	Overt HF	All measures for stage A ACEI, βB, diuretics, Na restrict Consider aldactone, ICD, CRT Consider nitrate/hydral, 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;301:383)
- Implantable PA pressure sensor may ↓ risk of hosp (CHAMPION, HF Congress 2010)

Treatment of Chronic Heart Failure with Reduced Ejection Fraction	
Diet, exercise	Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
ACEI	↓ mortality: 40% in NYHA IV, 16% in NYHA II/III, 20% in asx, post-MI, EF ≤40% (*NEJM* 1987;316:1429; 1991;325:293; 1992;327:669) 20% ↓ reMI; 20–30% ↓ rehosp for HF (↑ amt of benefit w/ ↓ EF) 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
ATII receptor blockers (ARBs)	*Consider as alternative if cannot tolerate ACEI (eg, b/c cough)* Noninferior to ACEI (VALIANT, *NEJM* 2003;349:1893) Good alternative if ACEI intol (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
Hydralazine + nitrates	*Consider if cannot tolerate ACEI/ARB or in blacks w/ Class III/IV* 25% ↓ mort. (*NEJM* 1986;314:1547); infer. to ACEI (*NEJM* 1991;325:303) 40% ↓ mort. in blacks on standard Rx (A-HEFT, *NEJM* 2004;351:2049)
β-blocker (data for carvedilol, metoprolol, bisoprolol)	*EF will transiently ↓, then ↑. Contraindic. in decompensated HF.* 35% ↓ mort. & 40% ↓ rehosp. in NYHA II–IV (*JAMA* 2002;287:883) Carvedilol superior to low-dose metoprolol (*Lancet* 2003;362:7)
Aldosterone antagonists	*Consider if HF severe or post-MI, adeq. renal fxn; watch for ↑ K* 30% ↓ mort. in NYHA III/IV & EF ≤35% (RALES, *NEJM* 1999;341:709) 15% ↓ mort. in HF post-MI, EF ≤40% (EPHESUS, *NEJM* 2003;348:1309)
Cardiac resynchronization therapy (CRT)	*Consider if EF ≤35%, QRS ≥120 ms, and symptomatic* 36% ↓ mort. & ↑ EF in NYHA III–IV (CARE-HF, *NEJM* 2005;352:1539) ↓ HF if EF<30% & NYHA I/II, espec if QRS ≥150 ms, no Δ in mortality (*NEJM 2009;361:1329*) No single measure of dyssynchrony on echo improves Pt selection for CRT (*Circ* 2008;117:2608)
ICD	*Use for 1° prevention if sx & EF ≤35% or for 2° prevention* ↓ mort. in Pts w/ MI & 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)
Diuretics	Loop ± thiazides diuretics (sx relief; no mortality benefit)
Digoxin	23% ↓ HF hosp., no Δ mortality (*NEJM* 1997:336:525) ? ↑ mort. in women, ? related to ↑ levels (*NEJM* 2002;347:1403) ? optimal dig concentration 0.5–0.8 ng/mL (*JAMA* 2003;289:871)
Ω-3 fatty acids	9% ↓ mortality (*Lancet* 2008;372:1223)
Anticoagulation	*Consider if AF, LV thrombus, large akinetic LV segment, EF <30%*
Heart rhythm	Catheter ablation of AF → ↑ in EF, ↓ sx (*NEJM* 2004;351:2373) No mortality benefit to AF rhythm vs. rate cntl *(NEJM 2008;358:2667)* For sx AF, pulm vein isolation improves sx c/w AVN ablation & CRT (*NEJM* 2008;359:1778)

(*Lancet* 2009;373:941; *Circ* 2009;119:e391; *NEJM* 2010;362:228)

Heart failure with preserved EF ("Diastolic HF") (*JACC* 2009;53:905)

- 40–60% of Pts w/ HF have normal or only min. impaired systolic fxn (EF ≥40%) (*NEJM* 2006;355:251, 260), w/ mortality rates similar to those w/ systolic dysfxn
- ~30% of population >45 y w/ diastolic dysfxn 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, HCMP, infiltrative CMP, RCMP, aging, hypothyroidism
- Precipitants of pulmonary edema: volume overload (poor compliance of LV → sensitive to even modest ↑ in volume); ischemia (↓ relaxation); tachycardia (↓ filling time in diastole), AF (loss of atrial boost to LV filling); HTN (↓ afterload → ↓ stroke volume)
- Dx w/ clinical s/s of HF w/ preserved systolic *and* impaired diastolic fxn 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
- Treatment: diuresis for volume overload, BP control, prevention of tachycardia and ischemia. No clear benefit of ACEI/ARB in Pts with isolated diastolic HF (*Lancet* 2003;362:777; *NEJM* 2008;359:2456). May underscore heterogeneity of Pt population.

CARDIOMYOPATHIES

Diseases with mechanical and/or electrical dysfunction of the myocardium

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;362:77)
- **Idiopathic** (~25% of DCMP, ? undiagnosed infectious, alcoholic, or genetic cause)
- **Infectious myocarditis** (10–15%, autoimmune response to infxn; *NEJM* 2009;360:1526)
  - Viruses (coxsackie, adeno, echovirus, CMV): ranging from subacute (dilated LV w/ mild-mod 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, megaesophagus or colon (*NEJM* 1993;329:639)
- **Toxic**
  - Alcohol (5%) typically 7–8 drinks/d × >5 y, but much interindividual variability
  - Anthracyclines (risk ↑ >550 mg/m^2, may manifest late), cyclophosphamide, trastuzumab
  - Cocaine, antiretrovirals, lead, carbon monoxide poisoning, radiation
- **Infiltrative** (5%): often mix of DCMP + RCMP (qv) with 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_1–V_3, ϵ 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_3**, ± 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%)
- Echocardiogram: LV dilatation, ↓ EF, *regional or global* LV HK, ± RV HK, ± mural thrombi
- Laboratory evaluation: TFTs, iron studies, HIV, SPEP, 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* 2007;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 & hemodyn compromise (r/o GCM, ANEM); arrhythmia or RCMP 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 (? IVIg), & 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 nl/↑ 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

Pathophysiology
- Subaortic outflow obstruction: narrowed tract 2° hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (may be fixed, variable, or nonexistent) and papillary muscle displacement. Gradient (∇) worse w/ ↑ contractility (digoxin, β-agonists), ↓ 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 ↑ LVEDP, MR, and diastolic dysfunction
- **Angina** (25%) even w/o epicardial CAD; microvasc. dysfxn (*NEJM* 2003;349:1027)
- **Arrhythmias** (AF in 20–25%; VT/VF) → palpitations, syncope, sudden cardiac death

Physical exam
- Sustained PMI, S_2 paradox. split if severe outflow obstruction, ⊕ S_4 (occ. palpable)
- **Systolic crescendo-decrescendo murmur** at LLSB: ↑ **w/ Valsalva** & standing
- ± mid-to-late or holosystolic murmur of MR at apex
- Bisferiens 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 giant TWI (apical variant)
- **Echo**: no absolute cutoffs for degree of LVH but septum / post wall ≥1.3 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 ∇; *Brockenbrough sign* = ↓ pulse pressure post-extrasystolic beat (in contrast to AS, in which pulse pressure ↑ postextrasystole)

Treatment (*NEJM* 2004;350:1320)
- Heart failure
  - ⊖ **inotropes/chronotropes**: β-blockers, CCB (verapamil), disopyramide. Careful use of diuretics. Vasodilators only if systolic dysfxn. Avoid digoxin.
  - If refractory to drug therapy and there is *obstructive* physiology (∇ >50 mmHg):
    - a) Alcohol septal ablation (*NEJM* 2002;347:1326) triphasic ∇ response: acute ↓ → ± partial ↑ back to 50% of baseline → ↓ over months by 1 y resting ∇ ~15 mmHg & stress-induced ∇ ~31 mmHg (*J 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% (*Circ* 2005;112:482)
    - c) ? 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* 2007;50:2101): 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 sesta MIBI 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 → nl EDV but ↑ EDP → ↑ systemic & pulm. venous pressures
- ↓ ventricular cavity size → ↓ SV and ↓ CO

Clinical manifestations (*Circ* 2000;101:2490)
- **Right-sided > left-sided heart failure** with peripheral edema > pulmonary edema
- **Diuretic "refractoriness"**
- **Thromboembolic events**
- Poorly tolerated tachyarrhythmias; VT → syncope/sudden cardiac death

Physical exam
- ↑ JVP, ± Kussmaul's sign (classically seen in *constrictive pericarditis*)
- Cardiac: ± S_3 and S_4, ± murmurs of MR and TR
- Congestive hepatomegaly, ± ascites and jaundice, peripheral edema

Diagnostic studies
- CXR: normal ventricular chamber size, enlarged atria, ± pulmonary congestion
- ECG: low voltage, pseudoinfarction pattern (Qw), ± arrhythmias
- Echo: symmetric wall thickening, biatrial enlarge., ± mural thrombi, ± cavity oblit.
  - w/ diast dysfxn: ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio, ↓ decel. time
- Cardiac MRI: 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

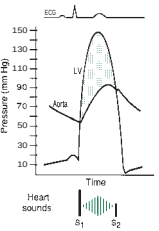
- **Calcific**: predominant cause in Pts >70 y; risk factors include HTN, ↑ chol., ESRD
- **Congenital** (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- **Rheumatic heart disease** (AS usually accompanied by AI and MV disease)
- AS mimickers: subvalvular (HCMP, subAo membrane),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

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

- **Angina**: ↑ O_2 demand (hypertrophy) + ↓ O_2 supply (↓ cor perfusion pressure) ± CAD
- **Syncope** (*exertional*): peripheral vasodil. w/ fixed CO → ↓ MAP → ↓ cerebral perfusion
- **Heart failure**: outflow obstruct + diastolic dysfxn → pulm. edema; 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 cm^2 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 = Gallavardin 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-peaking* murmur, paradoxically split S_2 or inaudible A_2, small and delayed carotid pulse ("*pulsus parvus et tardus*"), LV heave, ⊕ S_4 (occasionally palpable)



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

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 gradiant (∇) across AoV, AVA, *r/o CAD* (in ~50% of calcific AS)
- **Dobutamine challenge** during echo or cath if low EF and ∇<30 to differentiate:
  afterload mismatch: 20% ↑ SV & ↑ ∇, no Δ AVA (implies contractile reserve & ↑ EF post-AVR)
  pseudostenosis: 20% ↑ SV, no Δ in ∇, ↑ AVA (implies low AVA *artifact* of LV dysfxn)
  limited contractile reserve: no Δ SV, ∇, or AVA (implies EF prob. will not improve w/ AVR)

Classification of Aortic Stenosis

Stage	Mean Gradient (mmHg)	Jet Vel. (m/s)	AVA (cm^2)	LVEF
Normal	0	1	3–4	normal
Mild	<25	<3	>1.5	normal
Moderate	25–40	3–4	1.0–1.5	normal
Severe, compensated	>40	>4	<1.0*	normal
Severe, decompensated	Variable	Variable	<1.0*	↓

*AVA index (AVA relative to BSA) <0.6 cm^2/m^2 also qualifies for severe AS.

Treatment (*Circ* 2008;118:e523 & *Lancet* 2009;373:956)

- 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 cm^2, 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 sev AS *and* undergoing CV surgery.
- Medical therapy: used in sx Pts who are not operative candidates
  careful diuresis, control HTN, maintain SR; digoxin if low EF or AF
  avoid venodilators (nitrates) and ⊖ inotropes (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 ∇, *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 cm^2 (*JACC* 2010;55:1080); RCTs ongoing

AORTIC INSUFFICIENCY (AI)

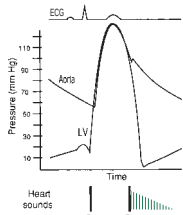
Etiology *(Circ 2006;114:422)*

- **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**
  - aortic aneurysm or dissection, annuloaortic ectasia, Marfan syndrome
  - aortic inflammation: giant cell, Takayasu's, ankylosing spond., reactive arthritis, syphilis

Clinical manifestations

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

Physical 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 S_1 (early closure of MV); ± S_3 (≠ ↓ EF but rather just volume overload in AI)

Classic Eponymous Signs in Chronic AI *(South Med J 1981;74:459)*

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

Diagnostic studies

- ECG: 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 cm^2, 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
  - IV 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)

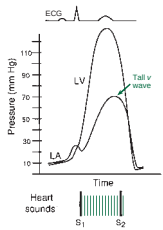
- **Leaflet abnormalities**: **myxomatous degeneration (MVP)**, endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs
- **Functional**: inferoapical **papillary muscle displacement due to ischemic LV remodeling** or other causes of DCMP; LV **annular dilation** due to LV dilation
- Ruptured chordae tendinae: myxomatous, endocarditis, spontaneous, trauma
- Acute papillary muscle *dysfxn* b/c of ischemia or *rupture* during MI [usu. *posteromedial* papillary m. (supplied by PDA only) vs. anterolateral (suppl. by diags & OMs)]
- HCMP: (see "Cardiomyopathy")

Clinical manifestations

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

Physical 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)
  ant. leaflet abnl → post. jet heard at spine
  post. leaflet abnl → ant. jet heard at sternum
- Lat. displ. hyperdynamic PMI, obscured S_1, widely split S_2 (A_2 early b/c ↓ LV afterload, P_2 late if PHT); ± S_3
- Carotid upstroke brisk (vs. diminished and delayed in AS)



Diagnostic studies

- 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

Classification of Mitral Regurgitation

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

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

Treatment (*Circ* 2008;118:e523; *NEJM* 2009;361:2261)

- Acute decompensation (consider ischemia and endocarditis as precipitants)
  IV afterload reduction (nitroprusside), ± inotropes (dobuta), 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)
  sx 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
  if in AF, Maze procedure or pulm vein isolation may → NSR and prevent future stroke
- In Pts undergoing CABG w/ mod/sev fxnal ischemic MR, consider annuloplasty ring
- Percutaneous MV repair: edge-to-edge clip may be noninferior to surgery (EVEREST II, ACC 2010); annuloplasty band placed in coronary sinus (*Circ* 2006;113:851) under study
- Medical: ∅ benefit (incl ACEI) in asx Pts; indicated if sx but not an operative candidate
  ↓ **preload** (↓ CHF and MR by ↓ MV orifice): diuretics, nitrates (espec if ischemic/fxnal MR)
  if LV dysfxn: ACEI, βB (carvedilol), ± biV pacing; maintain SR

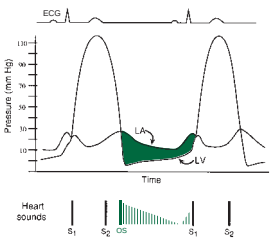
MITRAL STENOSIS (MS)

Etiology

- **Rheumatic heart disease** (RHD): *fusion of commissures* → "fish mouth" valve from autoimmune rxn 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, ↑ 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 S_2–OS interval (tighter valve → ↑ LA pressure → shorter interval)
- Loud S_1 (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)
- **Echo**: estimate pressure gradient (∇), 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**: ∇ from simultaneous PCWP & LV pressures, calculated MVA; LA pressure tall *a* wave and blunted *y* descent; ↑ PA pressures

Classification of Mitral Stenosis			
Stage	**Mean gradient (mmHg)**	**MV area (cm^2)**	**PA Systolic (mmHg)**
Normal	0	4–6	<25
Mild	<5	1.5–2	<30
Moderate	5–10	1–1.5	30–50
Severe	>10	<1	>50

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 ∇ 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)	
AVR w/o risk factors	d/c warfarin 48–72 h before surg; restart 24 h after surg
MVR or AVR w/ risk factors	Preop: d/c warfarin, start UFH when INR <2 4–6 h preop: d/c UFH; postop: restart UFH & warfarin ASAP

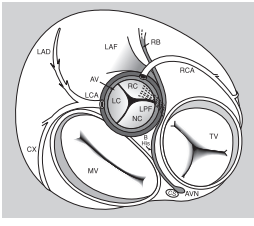
Procedures include noncardiac surgery, invasive procedures, and major dental work (*Circ* 2008;118:e523)

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
  thrombosis: surgery if left-sided valve & either severe sx or lg (? >1 cm) clot burden; 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/o 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)



AV = aortic valve
AVN = AV node
B His = bundle of His
CS = coronary sinus
Cx = circumflex artery
LAD = left anterior descending artery
LAF = left anterior fascicle
LCA = left coronary artery
LPF = left posterior fascicle
MV = mitral valve
RB = right bundle
RC/LC/NC = right/left/noncoronary cusp
RCA = right coronary artery
TV = tricuspid valve

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)	
Infectious (50%)	Viral: Coxsackie, echo, adeno, EBV, VZV, HIV, influenza Bacterial (from endocarditis, pneumonia, or s/p cardiac surgery): *S. pneumococcus*, *N. meningitidis*, *S. aureus*, *Borrelia* (Lyme) Tuberculous (extension from lung or hematogenous) Fungal: *Histo*, *Coccidio*, *Candida*; Parasitic: *Entamoeba*, *Echino*
Neoplastic (35%)	*Common:* metastatic (lung, breast, lymphoma, leukemia, renal cell) *Rare:* primary cardiac & serosal tumors (mesothelioma)
Autoimmune	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, Churg-Strauss, Wegener's Drug-induced: procainamide, hydralazine, INH, CsA
Uremia	Develops in ~20% of Pts, especially if on HD. May be transudative.
Cardiovascular	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
Radiation	>4,000 cGy to mediastinum; acute or delayed; may be transudative
Idiopathic	Most presumed to be undiagnosed viral
Effusions w/o pericarditis	CHF, cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis.; Transudative.

Clinical manifestations *(NEJM 2004;351:2195)*
- **Pericarditis**: chest pain that is pleuritic, positional (↓ 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 LLSB w/ diaphragm of stethoscope (leathery sound w/ up to 3 components: atrial contraction, ventricular contraction, 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;25:587; Circ 2006;113:1622)*
- ECG: may show diffuse STE (*concave up*) & PR depression (except in aVR: ST ↓ & PR ↑), TWI; classically and in contrast to STEMI, 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 (∴ 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

- Pericardiocentesis if suspect infxn or malignancy or if effusion large (>2 cm)
  ✓ cell counts, TP, 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_{eff}/TP_{serum} >0.5, LDH_{eff}/LDH_{serum} >0.6, or glc <60 mg/dL
  high Se (~90%) but *very low* Sp (~20%); overall low utility (*Chest* 1997;111:1213)
- Pericardial bx if suspicion remains for malignancy or tuberculosis

Treatment of pericarditis (*EHJ* 2004;25:587; *Circ* 2006;113:1622)
- NSAIDs (eg, ibuprofen 600–800 mg tid) ± colchicine 0.5 mg bid (*Circ* 2005;112:2012)
  sx usually subside 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 → pulsus paradoxus (pathologic exaggeration of nl physio)
  Inspiration → ↓ intrapericardial & RA pressures → ↑ venous return → ↑ RV size → septal shift to left. Also, ↑ pulmonary vascular compliance → ↓ pulm venous return. Result is ↓ LV filling → ↓ LV stroke volume & blood pressure.

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
- **Pulsus paradoxus** (Se 82%, Sp 70%) = ↓ SBP ≥10 mmHg during inspiration
  ⊕LR 3.3 (5.9 if pulsus >12), ⊖LR 0.03
  Ddx = PE, hypovolemia, severe obstructive lung disease, constriction (~1/3), CHF
  Can be absent if pre-existing ↑ LVEDP, cardiac arrhythmia, or regional tamponade
- Distant heart sounds (28%), ± pericardial friction rub (30%)
- Tachypnea but clear lungs

Diagnostic studies
- ECG: ↓ voltage (seen in 42%), electrical alternans, ± signs of pericarditis
- CXR: ↑ cardiac silhouette (89%)
- **Echocardiogram**: ⊕ **effusion**, IVC plethora, **septal shift** with inspiration, **diastolic collapse** of RA (Se 85%, Sp 80%) and/or RV (Se <80%, Sp 90%)
  respirophasic Δ's in transvalvular velocities (↑ across TV & ↓ across MV w/ inspir.)
  postsurgical tamponade may be localized and not easily visible
- Cardiac cath (right heart and pericardial): elevation (15–30 mmHg) and equalization of intrapericardial and diastolic pressures (RA, RV, PCWP), blunted *y* descent in RA ↑ in stroke volume postpericardiocentesis ultimate proof of tamponade
  if RA pressure remains elevated after drainage, may have effusive-constrictive disease (*NEJM* 2004;350:469) or myocardial dysfxn (eg, from concomitant myocarditis)

Treatment
- Volume (but be careful as overfilling can worsen tamponade) and ⊕ inotropes (avoid βB)
- **Pericardiocentesis** (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)
  - ventricles: **dip-and-plateau** or **square-root sign** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
  - *discordance* between LV & RV pressure peaks during respiratory cycle (*Circ* 1996;93:2007)
- CT or **MRI**: thickened pericardium (>4 mm on CT) with tethering

Treatment
- Diuresis for intravascular volume overload, surgical pericardiectomy

Constrictive Pericarditis vs. Restrictive Cardiomyopathy

Evaluation	Constrictive pericarditis	Restrictive cardiomyopathy
Physical exam	⊕ Kussmaul's sign Absent PMI ⊕ Pericardial knock	± Kussmaul's sign Powerful PMI, ± S_3 and S_4 ± **Regurg murmurs of MR, TR**
ECG	± Low voltage	Low voltage ± **Conduction abnormalities**
Echocardiogram	Normal wall thickness **Septal bounce during early diastole** Inspir. → ↑ flow across TV and ↓ flow across MV E′ (tissue velocity) nl/↑ Expir. hepatic vein flow reversal	± ↑ **wall thickness** **Biatrial enlargement** Inspir. → ↓ flow across TV & MV Slower peak filling rate Longer time to peak filling rate E′ ↓ Inspir. hepatic vein flow reversal
CT/MRI	**Thickened pericardium**	Normal pericardium
Cardiac catheterization	Prominent *x* and *y* descents Dip-and-plateau sign LVEDP = RVEDP RVSP <55 (Se 90%, Sp 29%) RVEDP >⅓ RVSP (Se 93%, Sp 46%) **Discordance** of LV & RV pressure peaks during respiratory cycle **Systolic area index** (ratio of RV to LV pressure–time area in inspir vs. expir) >1.1 (Se 97%, Sp 100%)	**LVEDP > RVEDP** (espec. w/ vol.) RVSP >55 mmHg RVEDP <⅓ RVSP Concordance of LV & RV pressure peaks during respiratory cycle Systolic area index ≤1.1 (*JACC* 2008;51:315)
Endomyocardial biopsy	Usually normal	± **Specific etiology of RCMP**

HYPERTENSION

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

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

- **Essential** (95%): onset 25–55 y; ⊕ FHx. Unclear mechanism but ? additive microvasc renal injury over time w/ contribution of hyperactive sympathetics (*NEJM* 2002;346:913) genetic loci under investigation (*Nat Genet* 2009;41:666 & 677)
- **Secondary**: Consider if Pt <20 or >50 y or if sudden onset, severe, refractory or ↑ HTN

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

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 diet, Na intake, smoking, alcohol, prescription and OTC medications, OCP
- 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)

Complications of HTN

- *Each ↑ 20 mmHg SBP or 10 mmHg DBP → 2× ↑ CV complications* (*Lancet* 2002;360:1903)
- Neurologic: **TIA/CVA**, ruptured aneurysms
- Retinopathy: I = arteriolar narrowing, II = copper-wiring, AV nicking, III = hemorrhages and exudates, IV = papilledema
- 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

- **Pharmacologic options** (if HTN *or* pre-HTN + diabetes or renal disease)
  Pre-HTN: ARB prevents onset of HTN, no ↓ in clinical events (*NEJM* 2006;354:1685)
  HTN: *choice of therapy controversial, concomitant disease may help guide*
  uncomplicated: ? thiazide better than ACEI or CCB in preventing CVD (*JAMA* 2002;288:2981; *NEJM* 2009;361:2153); β-blockers not first line (*Lancet* 2005;366:1545)
  + **high-risk CAD**: ACEI (*NEJM* 2000;342;145) or ARB (*NEJM* 2008;358:1547); ACEI + CCB superior to ACEI + thiazide (*NEJM* 2008;359:2417) or βB + diuretic (*Lancet* 2005;366:895)
  + **angina**: β-blockers, CCB
  + **post-MI**: βB (*JAMA* 1982;247:1707), ACEI (*NEJM* 1992;327:669), ± aldosterone antagonist
  + **HF**: ACEI/ARB, β-blockers, diuretics, aldosterone antagonist (see "Heart Failure")
  + **recurrent stroke prevention**: ACEI (*Lancet* 2001;358:1033); benefit of ARB unclear (*Lancet* 2002;359:995; *NEJM* 2008;359:1225).
  + **diabetes mellitus**: ACEI or ARB; can also consider diuretic, BB, or CCB
  + **chronic kidney disease**: ACEI/ARB (*NEJM* 1993;329:1456 & 2001;345:851, 861)
  most will require ≥2 drugs; if not at goal → optimize doses or add drug
- **Secondary causes**
  Renovasc: control BP w/ diuretic + ACEI/ARB (watch for ↑ Cr w/ bilat. RAS) or CCB
  Atherosclerosis risk-factor modification: quit smoking, ↓ chol.
  If refractory HTN, recurrent HF, UA, or worse CKD, revasc. indicated (*JACC* 2006;47:1)
  For atherosclerosis: stenting ↓ restenosis vs. PTA alone, but no clear improvement in BP or renal function vs. med Rx alone (*NEJM* 2009;361:1953; *Annals* 2009;150:840)
  For FMD (usually more distal lesions): PTA ± bailout stenting
  Surgery for complex lesions or aortic involvement
  Renal parenchymal: salt and fluid restriction, ± diuretics
  Endocrine etiologies: see "Adrenal Disorders"
- Pregnancy: methyldopa, labetalol; other βB and CCB probably safe

Hypertensive Crises

- **Hypertensive emergency**: ↑ BP → acute target-organ ischemia and damage
  neurologic damage: encephalopathy, hemorrhagic or ischemic stroke, papilledema
  cardiac damage: ACS, HF/pulmonary edema, aortic dissection
  renal damage: proteinuria, hematuria, acute renal failure; scleroderma renal crisis
  microangiopathic hemolytic anemia; preeclampsia-eclampsia
- **Hypertensive urgency**: SBP >180 or DBP >120 (?110) w/ min./no target-organ damage

Precipitants

- Progression of essential HTN ± medical noncompliance (especially clonidine)
- Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia
- Endocrine: pheochromocytoma, Cushing's
- Sympathomimetics: cocaine, amphetamines, MAO inhibitors + foods rich in tyramine
- Cerebral injury (do *not* treat HTN in acute ischemic stroke unless Pt getting lysed, extreme, BP, ie, >220/120, or Ao dissection, active ischemia, or CHF; *Stroke* 2003;34:1056)

Treatment (*Chest* 2007;131:1949)

- Tailor goals to clinical context (eg, more rapid lowering for Ao dissection)
- Emergency: ↓ MAP by ~25% in *mins to 2 h* w/ IV agents (may need arterial line for monitoring); goal DBP <110 w/in 2–6 h, as tolerated
- Urgency: ↓ BP in *hours* using PO agents; goal normal BP in ~1–2 d
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

Drugs for Hypertensive Crises

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

*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;111:816 & 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 & thoracoabd rare)
  Risk factors: **HTN**; **atherosclerosis**; **aortitis** (Takayasu's, GCA, spondyloarthritis, 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 ♂ than ♀; most infrarenal
  Risk factors = risk factors for atherosclerosis: **smoking**, HTN, hyperlipidemia, age, FHx

Pathophysiology (*NEJM* 2009;361:1114; *Nat 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 and all men 65–75 y w/ prior tobacco use (*J Vasc Surg* 2004;39:267; *Annals* 2005;142:203;)

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; ? macrolides 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)
  ↓ short-term mortality, bleeding, and length of stay, but, long-term graft complications (2–5%/y; leak, rupture) necessitating periodic surveillance and no Δ in overall mortality (*JAMA* 2009;302:1535; *NEJM* 2010;362:1863 & 1881). Consider for high-risk operative Pts or in descending thoracic aneurysms >5.5 cm (*JACC* 2010;55:986).
  In Pts unfit for surgery: ↓ aneurysm mortality but no Δ in overall mortality over medical Rx (*NEJM* 2010;362:1872). EVAR noninferior (? superior) to open repair in ruptured AAA w/ favorable anatomy (*Ann Surg* 2009;250:818).

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**: intimomedial 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; *Loeys-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

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

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

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, labetalol) to blunt reflex ↑ HR & inotropy that will occur in response to vasodilators
  ***then* ↓ SBP with IV vasodilators** (eg, nitroprusside)
  control pain with MSO_4 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

Type	Features
1°	Prolonged PR (>200 ms), all atrial impulses conducted (1:1).
2° Mobitz I (Wenckebach)	Progressive ↑ PR until impulse not conducted (→ "grouped beating"). 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.
2° Mobitz II	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.
3° (complete)	No AV conduction. Escape, if present, narrow (jxnal) or wide (vent.)

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

AV dissociation

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

SUPRAVENTRICULAR TACHYCARDIAS (SVTs)

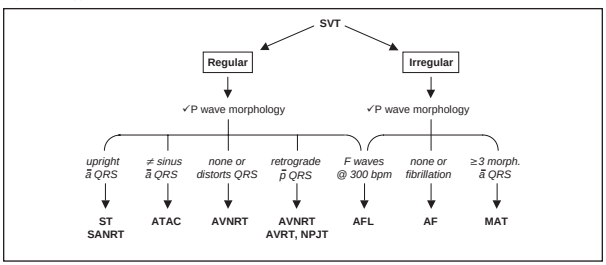
Arise above the ventricles, ∴ ***narrow QRS*** *unless aberrant conduction or pre-excitation.*

Etiologies of SVT *(NEJM 1995;332:162; 2006;354:1039)*

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

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 V_1) 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 & V_1) → 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

Figure 1-4 Approach to SVT



Treatment of SVT		
Rhythm	**Acute treatment**	**Long-term treatment**
Unstable	**Cardioversion** per ACLS	n/a
ST	Treat underlying stressor(s)	n/a
AT	β-blockers, CCB, or amiodarone	β-blockers or CCB, ± antiarrhythmics ? Radiofrequency ablation
AVNRT or AVRT	**Vagal maneuvers** **Adenosine** (caution in AVRT*) **CCB** or β-blockers	*For AVNRT* (see *next section for AVRT*): **Radiofrequency ablation** CCB or β-blockers (chronic or prn) ± Class IC antiarrhythmics (if nl heart)
NPJT	**CCB**, **β-blockers**, **amiodarone**	Rx underlying dis. (eg, dig tox, ischemia)
AF	**β-blockers**, **CCB**, **digoxin**, **AAD**	See "Atrial Fibrillation"
AFL	**β-blockers**, **CCB**, **digoxin**, **AAD**	Radiofrequency ablation β-blockers or CCB ± antiarrhythmics
MAT	CCB or β-blockers if tolerated	Treat underlying disease process ? AVN ablation + PPM

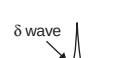
*Avoid adenosine & nodal agents if accessory pathway + preexcited tachycardia, see below. (*JACC* 2003;42:1493)

- *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)

Definitions

- **Accessory pathway** (bypass tract) of conducting myocardium connecting atria & ventricles, allowing impulses to bypass normal AVN delay
- **Preexcitation (WPW) pattern**: ↓ PR interval, ↑ QRS width w/ δ wave (slurred onset, *can be subtle*), ST & Tw abnl (can mimic old IMI); only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde then ECG will be normal during SR; "concealed" bypass tract)
- **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, βB, ? CCB; caution w/ adenosine (can precip. AF); *have defibrillator ready*
- **AF/AFL** w/ conduction down accessory pathway: need to Rx arrhythmia *and* ↑ pathway refractoriness; use **procainamide**, ibutilide, flecainide *or* cardiovert; avoid CCB & βB (ineffective) and dig/adenosine (can ↓ refractoriness of pathway → ↑ vent. rate → VF)
- **Long term**: Rx tachycardias w/ radiofrequency ablation or antiarrhythmics (IA, IC) consider pathway ablation if asx but AVRT or AF inducible on EPS (*NEJM* 2003;349:1803) risk of SCD related to how short R-R interval is in AF and if SVT inducible w/ exercise

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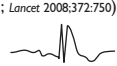
Wide-Complex Tachycardias (WCTs)

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 V_1 = RBBB-type vs. downward = LBBB-type
- Etiologies in a structurally *abnormal* heart: **prior MI** (scar); **CMP**; **myocarditis**; **arrhythmogenic RV CMP (ARVC)**: incomplete RBBB, ε wave (terminal notch in QRS) & TWI in $V_{1–3}$ 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 (responds to verapamil)

Polymorphic ventricular tachycardia (PMVT)
- QRS morphology changes from beat to beat
- Etiologies: **ischemia**; **CMP**; catecholaminergic;
  torsades de pointes (TdP, "twisting of the points", PMVT + ↑ QT): ↑ QT *acquired* (eg, meds, lytes, 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 $V_{1–3}$ (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 SVT
- 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 atypical for BBB
    RBBB-type: absence of tall R' (or presence of monophasic R) in V_1, r/S ratio <1 in V_6
    LBBB-type: onset to nadir >60–100 ms in V_1, q wave in V_6
  concordance (QRS in all precordial leads w/ same pattern/direction)

Long-term management (*JACC* 2006;48:1064)
- Workup: **echo** to ✓ LV fxn, **cath** or **stress test** to r/o ischemia, ? MRI and/or RV bx to look for infiltrative CMP or ARVC, ? **EP study** to assess inducibility
- **ICD**: 2° prevention after documented VT/VF arrest (unless due to reversible cause)
  1° 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 ↓ discharge rate by 40% (*Lancet* 2010;375:31)

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

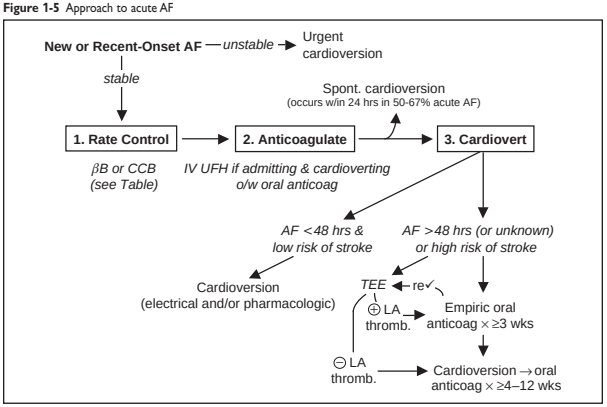
Pathophysiology (*NEJM* 1998;339:659; & *Circ* 1995;92:1954)

- 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



(Adapted from *NEJM* 2004;351:2408; & *JACC* 2006;48:e149)

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

Agent		Acute (IV)	Maint. (PO)	Comments
CCB	**Verapamil**	5–10 mg over 2′ may repeat in 30′	120–360 mg/d in divided doses	↓ BP (Rx w/ Ca gluc) Watch for CHF
	Diltiazem	0.25 mg/kg over 2′ may repeat after 15′ 5–15 mg/h infusion	120–360 mg/d in divided doses	Preferred if COPD Can ↑ dig levels
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 CrCl)	Consider in HF or low BP Poor exertional HR ctrl
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; ∴ procainamide 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

Antiarrhythmic Drugs (AAD) for AF

Agent		Conversion	Maintenance	Comments
III	Amiodarone	5–7 mg/kg IV over 30–60' → 1 mg/min to achieve 10-g load	200–400 mg qd (most effective drug)	↑ QT but TdP rare Pulm, liver, thyroid toxicity ✓ PFTs, LFTs, TFTs
	Dronedarone	n/a	400 mg bid	↑ QT, contraindic severe CHF ↓ side effects c/w amio ↓ efficacy but also ↓ CV mort
	Ibutilide	1 mg IV over 10' may repeat × 1	n/a	Contraindic. if ↓ K or ↑ QT ↑ QT, 3–8% risk of TdP Mg 1–2 g IV to ↓ risk TdP
	Dofetilide	0.5 mg PO bid	0.5 mg bid	↑ QT, ↑ risk of TdP Renally adjust dose
	Sotalol	n/a	90–160 mg bid	✓ for ↓ HR, ↑ QT Renally adjust dose
IC	Flecainide	300 mg PO × 1	100–150 mg bid	PreRx w/ AVN blocker
	Propafenone	600 mg PO × 1	150–300 mg tid	*Contraindic. if structural or ischemic heart disease*
IA	Procainamide	10–15 mg/kg IV over 1 h	1–2 g bid of slow release	↓ BP; ↑ QT ± PreRx w/ AVN blocker

(*JACC* 2006;48:e149; *NEJM* 2007;357:987 & 2009;360:668; *JACC* 2009;54:1089)

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

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 to 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;293:2634 & 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 of ICH (*Lancet* 2009;374:534)

Anticoagulation (*JACC* 2006;48:e149; *Chest* 2008;133:546S)

- Risk of stroke ~4.5% per year in nonvalvular AF; risk factors include:
  CHADS$_2$: **C**HF (1 point), **H**TN (1), **A**ge >**75 y** (1), **D**M (1), **prior S**troke/**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
  ASA+clopi inferior to warfarin but ↓ stroke (& ↑ 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**
  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

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* 2005;352:1004): ↑ sympathetic tone → vigorous contraction of LV → mechanoreceptors in LV trigger ↑ vagal tone (hyperactive Bezold-Jarisch reflex) → ↓ HR (cardioinhibitory) and/or ↓ BP (vasodepressor)
  cough, deglutition, defecation & micturition → ↑ vagal tone and thus can be precipitants
  related disorder: carotid sinus hypersensitivity
- **Orthostatic hypotension** (10%)
  hypovolemia, diuretics, deconditioning
  vasodilators (espec. if combined w/ ⊖ chronotropes)
  autonomic neuropathy (1° = Parkinson's, Shy-Drager, Lewy body dementia, POTS; 2° = diabetes, EtOH, amyloidosis, renal failure) (*NEJM* 2008;358:615)
- **Cardiovascular**
  Arrhythmia (15%)
    Bradyarrhythmias: SSS, high-grade AV block, ⊖ chronotropes, PPM malfunction
    Tachyarrhythmias: 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 HCMP (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, HCMP, PHT), positional Δ (orthostatic hypotension), stressors such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, N/V, cough/micturition/defecation/swallowing (neurocardiogenic), head turning or shaving (carotid sinus hypersens.); arm exercise (subclavian steal)
  prodrome (eg, diaphoresis, nausea, blurry vision): cardiac <~5 sec, vasovagal >~5 sec
  associated sx: chest pain, palp., neurologic, 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; ⊖ chronotropes (eg, β-blockers and CCB)
  proarrhythmic or QT prolonging: class IA, IC or III antiarrhythmics, 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, S_3), murmurs, LVH (S_4, LV heave), PHT (RV heave, ↑ P_2)
  vascular exam: ✓ for asymmetric pulses, carotid bruits, carotid sinus massage
  neurologic exam: focal findings, evidence of tongue biting; fecal occult blood test
- **ECG** (abnormal in ~50%, definitively 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, ε wave (ARVC)

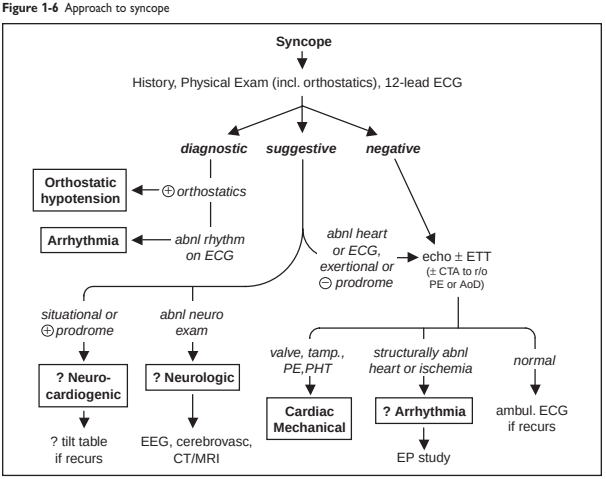
Other diagnostic studies (consider ordering based on results of H&P and ECG)

- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope
  Holter monitoring (continuous ECG 24–48 h): useful if *frequent* events
    arrhythmia + sx (4%); asx but 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 (*AJC* 2003;92:1231)

- Echo: r/o structural heart disease (eg, CMP [incl HCMP & ARVD], valvular disease [incl AS, MS, 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



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

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

- Arrhythmia, cardiac mechanical, or neurologic syncope: treat underlying disorder
- Vasovagal syncope: ? midodrine, fludrocortisone, disopyramide, SSRI
  ? 16 oz of H_2O before at-risk situations (*Circ* 2003;108:2660)
  no proven benefit w/ β-blockers (*Circ* 2006;113:1164) or PPM (*JAMA* 2003;289:2224)
- 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

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

- 22% overall recurrence rate if idiopathic, else 3% recurrence
- Cardiac syncope: 2-fold ↑ in mort., 20–40% 1-y SCD rate, median survival ~6 y
- Unexplained syncope w/ 1.3-fold ↑ in mort., but noncardiac or unexplained syncope w/ nl ECG, no h/o VT, no HF, age <45 → low recurrence rate and <5% 1-y SCD rate
- Vasovagal syncope: Pts not at increased risk for death, MI, or stroke
- ✓ state driving laws and MD reporting requirements. Consider appropriateness of Pt involvement in exercise/sport, operating machinery, high-risk occupation (eg, pilot).

Pacemaker Code				
A, atrial; V, vent.; I, inhibition; D, dual; R, rate-adaptive	**1st letter**	**2nd letter**	**3rd letter**	**4th letter**
	Chamber paced	Chamber sensed	Response to sensed beat	Program features

Common Pacing Modes	
VVI	Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia.
DDD	A & V sensing & pacing (RA & RV leads). Sensed A beat inhibits A pacing & *triggers V pacing* → tracking of intrinsic atrial activity. Maintains AV synchrony.
Magnet (place over generator)	Pacing at fixed rate regardless of intrinsic activity. Use to ✓ ability to capture when output inhibited by intrinsic rhythm. Use if Pt hemodynamically unstable due to inappropriate PPM inhibition or PPM-induced tachycardia.

Indications for Pacing (*Circ* 2008;117:2820)	
AV block	Symptomatic 3° or 2° AVB; ? asx 3° or type II 2° AVB HR <40; pauses ≥3 sec while awake; alternating L and R BBB
Sinus node	SB or pauses a/w sxs or ? if sx w/o clear assoc. Chronotropic incompet.
Acute MI	See "STEMI"
Tachy-arrhythmia	Sx recurrent SVT that can be term. by pacing after failing drugs & ablation Sustained pause-dependent VT; ? high-risk Pts w/ congenital long QT
Syncope	Carotid sinus hypersensitivity with asystole >3 sec ? Neurocardiogenic syncope w/ prominent cardioinhib. response ? Syncope with bi- or trifascicular block and not likely 2° to other causes
CMP	Sx DCMP (BiV pacing); ? refractory sx HCMP w/ signif outflow obstruction

Permanent Pacemaker (PPM) Complications		
Issue	**Manifestation**	**Description**
Failure to pace	Bradycardia	Battery depletion, lead fracture/dislodgment, ↑ pacing threshold due to local tissue rxn/injury, or myopotential sensing → inappropriate inhibition
Failure to sense	Inapprop. pacing	Lead dislodgment or sensing threshold too high
PM-mediated tachycardia	Tachycardia	Seen w/ DDD.V depol. → retrograde A activation → sensed by A lead → triggers V pacing → etc.
PM syndrome	Palpit, HF	Seen w/ VVI. Due to loss of AV synchrony.

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

- 3-lead pacemaker (RA, RV, coronary sinus); R >S in V_1 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% + QRS ≥120 ms; no clear benefit 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/o 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 (wait ≥40 d if post-MI or ≥9 mos for non-ischemic CMP; *NEJM* 2009;361:1427); for HCMP, 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 ~½ of Pts w/ *S. aureus* bacteremia (even w/o s/s and w/ ⊖ TTE/TEE)
- Treatment: abx and removal of system

Clinical Assessment	
Active Cardiac Conditions	**Clinical Risk Factors**
• MI w/in 30 d or current unstable or severe angina • Decompensated HF • Significant arrhythmia (eg, high-grade AVB, Mobitz II, 3° AVB, new or sx VT, SVT w/ HR >100, sx brady) • Severe AS or sx MS	• h/o CAD • h/o HF • h/o Cerebrovascular dis. • Diabetes mellitus • Renal insuffic. (Cr >2 mg/dL)

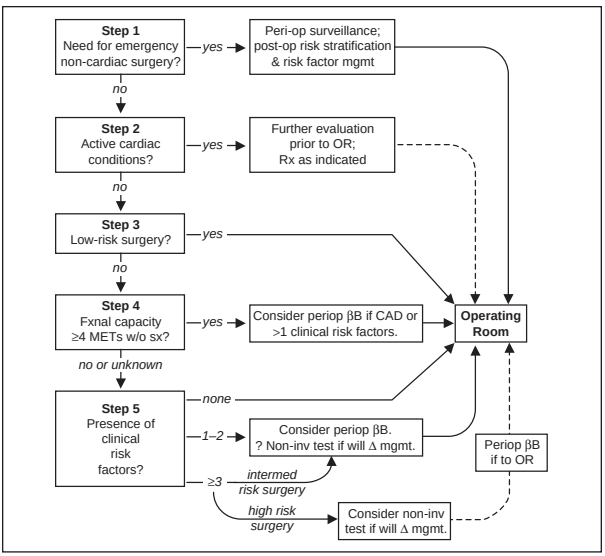
Surgery-Specific Risk		
High (>5% risk)	**Intermediate (1–5%)**	**Low (<1%)**
• Aortic or other major vascular • Peripheral vasc.	• Intrathoracic; intraperitoneal; prostate • CEA; head & neck • Orthopedic	• Endoscopic • Breast; superficial • Cataract; ambulatory

Functional Capacity		
1–4 METs	**4–10 METs**	**>10 METs**
• ADLs • Walk indoors • Walk 1–2 level blocks	• Climb a flight of stairs/hill • Walk briskly; heavy housework • Golf, doubles tennis	• Strenuous sports

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

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** (eg, 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 ↓ 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 (*Circ* 2009;120:2123; *JAMA* 2010;303:551)

- 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

Pathophysiology	Etiologies
Airway obstruction (↑ resistance to airflow)	**Asthma**, **COPD**, **bronchiectasis** (dilated, collapsible airways, impaired clearance of secretions, ± hemoptysis; infxn #1 cause; Rx: mucolytics, bronchodilators, ± abx), CF (chronic resp infxns, bronchiectasis, infertility, pancreatitis), tumor or foreign body
Parenchymal disease (↑ resistance to expansion)	**Pulmonary edema**: *cardiogenic* (LV systolic or diastolic dysfxn) or *noncardiogenic* (ALI/ARDS) **ILD**
Vascular (V/Q mismatch)	Large vessel: **PE**, tumor emboli Small vessel: **PHT**, vasculitis, ILD, emphysema
Bellows (↑ resistance to CW/diaphragm expansion; weakness of respiratory muscles)	**Pleural disease**: effusion, fibrosis **Chest wall/diaphragm**: kyphoscoliosis, ↑ abd girth **Neuromuscular disorders** Hyperinflation (COPD, asthma)
Stimulation of receptors	Chemoreceptors: **hypoxemia**, metabolic acidosis Mechanoreceptors: **ILD**, **pulmonary edema**, PHT, PE
↓ O_2 carrying cap. (but nl P_aO_2)	**Anemia**, methemoglobinemia, CO poisoning
Psychological	Anxiety, panic attack, depression, somatization

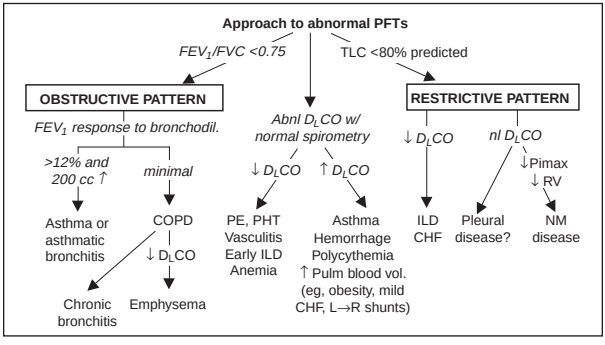
Evaluation

- Cardiopulmonary exam, S_aO_2, CXR (see Appendix & Radiology inserts), ECG
  predictors of CHF: h/o CHF, PND, S_3, CXR w/ venous congestion, AF (*JAMA* 2005;294:1944)
  dyspnea w/ nl CXR → CAD, asthma, PE, PHT, early ILD, anemia, acidosis, NM disease
- Based on results of initial evaluation: 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% ↓ FEV_1 → asthma
- **Lung volumes**: evaluate for restrictive disease including NM causes
- **D_LCO**: evaluates functional surface area for gas exchange; helps differentiate causes of obstructive and restrictive diseases and screens for vascular disease & early ILD

Figure 2-1 Approach to abnormal PFTs



ASTHMA

Definition and epidemiology
- Chronic inflam. 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* with *episodic exacerbation*
- Precipitants (**triggers**)
  respiratory irritants (smoke, perfume, etc.) & *allergens* (pets, dust mites, pollen, etc.)
  infections (URI, bronchitis, sinusitis)
  drugs (eg, ASA & NSAIDs via leukotrienes, βB via bronchospasm, MSO_4 via histamine)
  emotional stress, cold air, exercise
- 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**: ↓ FEV_1, ↓ FEV_1/FVC, coved flow-volume loop; lung volumes: ± ↑ RV & TLC
  ⊕ bronchodilator response (↑ FEV_1 ≥12%) strongly suggestive of asthma
  methacholine challenge (↓ FEV_1 ≥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 lysophospholipase);
  Δ in sputum eos count may guide outPt 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° to 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 **β_2-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 β_2-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.
- *Long-acting* inh **β_2-agonists** (eg, salmeterol): improves PEF when added to inh steroid (*Lancet* 2009;374:1754). Except for control of exercise-induced asthma, should *not* be used w/o inh steroid (may ↑ mortality; *Chest* 2006;129:15 & *Annals* 2006;144:904). Clinical relevance of β_2-receptor pharmacogenetic interaction not validated (*Lancet* 2009;374:1754).
- **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
- **Leukotriene modifiers**: some Pts very responsive, especially aspirin-sensitive (*AJRCCM* 2002;165:9) and exercise-induced asthma (*Annals* 2000;132:97). Transcription of genes for 5-lipoxygenase pathway predicts response (*Nat Genet* 1999;22:168).
- **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 (eg, desensitization): may be useful if significant allergic component
- TNF antagonists may be helpful in Pts w/ refractory asthma (*NEJM* 2006;354:697)
- Anti-IL5 found to spare steroids in uncontrolled Pts w/ sputum eos (*NEJM* 2009;360:985)
- Bronchial thermoplasty (exp'tal): radiofrequency destruction of airway smooth muscle
  no Δ in FEV_1, 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** = daily sx $\leq$2/wk, $\varnothing$ nocturnal sx or limitation of activity, reliever med $\leq$2/wk, nl PEF or FEV_1; partly controlled = 1–2 of the above present in a wk; uncontrolled = $\geq$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 $\rightarrow$ $\downarrow$ need for PO steroids (*AJRCCM* 2009;180:598)

Asthma Stepwise Therapy

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

ICS, inh corticosteroid; LABA, long-acting β_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, pulsus paradoxus, abdominal paradox
  - Assess for barotrauma: asymmetric breath sounds, tracheal deviation, subcutaneous air $\rightarrow$ pneumothorax, precordial (Hamman's) crunch $\rightarrow$ pneumomediastinum
- Diagnostic studies
  - *ABG:* not always considered essential because exam and S_aO_2 provide equivalent info; low P_aCO_2 initially; nl or high P_aCO_2 *may* signify tiring; may respond to bronchodilator
  - *PEF:* used to follow clinical course; *CXR:* not essential unless suspicion for PNA or PTX

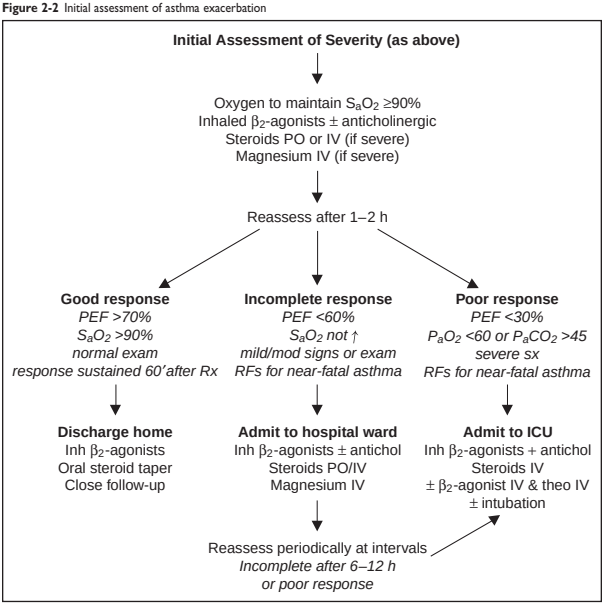
Severity of Asthma Exacerbation

Feature	Mild	Moderate	Severe
Breathless w/ . . .	Walking	Talking	At rest
Talking in . . .	Sentences	Phrases	Words
Mental status	$\pm$ Agitated	Agitated	Agitated
RR	$\uparrow$	$\uparrow$	>30
Accessory muscles	$\varnothing$	$\oplus$	$\oplus$
Wheeze	Moderate, end-expir	Loud	Usually loud
HR	<100	100–120	>120
Pulsus paradoxus	Normal (<10)	10–25	>25
PEF	>80%	60–80%	<60%
S_aO_2	>95%	91–95%	<90%
P_aO_2	Normal	>60	<60
P_aCO_2	<45	<45	>45

Presence of several parameters (not necessarily all) indicates classification (GINA 2009)
Resp arrest imminent: drowsy, abdominal paradox, wheezes inaudible (b/c $\varnothing$ air movement), bradycardia, loss of abdominal paradox (respiratory muscle fatigue).

Acute Pharmacologic Treatment		
Agent	**Dose**	**Comments**
Oxygen	Titrate to achieve S_aO_2 >90%	
Albuterol	MDI 4–8 puffs q20min *or* nebulizer 2.5–5 mg q20min *continuous* nebulizer if severe	First-line therapy
Corticosteroids	prednisone 60 mg PO *or* methylprednisolone 80 mg IV	IV not superior to PO (*JAMA* 1988;260:527)
Ipratropium	MDI 4–8 puffs q30min *or* nebulizer 0.5 mg q30min × 3	↑ bronchodilation when combined w/ albuterol (*Chest* 2002;121:1977)
Magnesium	2 g IV over 20 min (*Lancet* 2003;361:2114)	↑ PEF & FEV_1

Figure 2-2 Initial assessment of asthma exacerbation



(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 β_2.agonists, psych issues, h/o noncompliance.

Other treatments

- Epinephrine (0.3–0.5 mL SC of 1:1000 dilution): no advantage over inhaled β_2-agonists
- Abx: not needed w/o evidence of bacterial infection. Evidence of improved sx & FEV_1 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 H_2O (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

Definition and epidemiology (*NEJM* 2004;350:26)

- Progressive airflow limitation caused by airway and parenchymal inflammation

Emphysema vs. Chronic Bronchitis

	Emphysema	Chronic Bronchitis
Definition	Dilation/destruction of parenchyma (path definition)	Productive cough >3 mo/y × ≥2 y (clinical definition)
Pathophysiology	Tissue destruction Matched V/Q defects Mild hypoxemia	Small airways affected V/Q mismatch Severe hypoxemia, hypercapnia PHT, cor pulmonale
Clinical manifestations	Severe, constant dyspnea Mild cough	Intermittent dyspnea Copious sputum production
Physical exam	"Pink puffer" Tachypneic, noncyanotic, thin Diminished breath sounds	"Blue bloater" Cyanotic, obese, edematous Rhonchi & wheezes

Pathogenesis (*Lancet* 2003;362:1053)

- **Cigarette smoke** (centrilobular emphysema, affects 15–20% of smokers)
- Recurrent airway infections
- α_1-antitrypsin defic.: early-onset panacinar emphysema, 1–3% of COPD cases. Suspect if age <45, lower lungs affected, extrathoracic manifestations (liver disease [not if MZ subtype], FMD, pancreatitis). ✓ serum AAT level (nb, acute phase reactant).

Clinical manifestations

- Chronic cough, sputum production, dyspnea; later stages → freq exac., a.m. HA, wt loss
- Exacerbation triggers: infxn, other cardiopulmonary disease, incl. PE (*Annals* 2006;144:390)
  Infxn: overt tracheobronchitis/pneumonia from viruses, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, or triggered by changes in strain of colonizers (*NEJM* 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, pulsus paradoxus, cyanosis

Diagnostic studies

- CXR (see Radiology inserts): hyperinflation, flattened diaphragms, ± interstitial markings and bullae
- PFTs: **Obstruction**: ↓↓ FEV_1, ↓ FVC, ↓ FEV_1/FVC, expir scooping of flow-volume loop
  Hyperinflation: ↑↑ RV, ↑ TLC, ↑ RV/TLC
  Abnormal gas exchange: ↓ D_LCO (in emphysema)
- ABG: ↓ P_aO_2, ± ↑ P_aCO_2 (in chronic bronchitis, usually only if FEV_1 <1.5 L) and ↓ pH
- ECG: PRWP, S1S2S3, R-sided strain, RVH, ↑ P waves in lead II ("P pulmonale")

Chronic treatment (*Annals* 2007;147:633; *NEJM* 2010;362:1407)

- **Bronchodilators** (*first-line therapy*): anticholinergics, β_2-agonists, theophylline
  LA anticholinergic (tiotropium): ↓ exac, ↓ 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, ↓ FEV_1 decline, trend toward ↓ mort. (*NEJM* 2007;356:775)
  LABA + inh steroid: ? ↓ mort (*NEJM* 2007;356:775; *AJRCCM* 2008;177:19)
  Tiotropium + LABA + inh steroid: ↑ FEV_1, ↓ COPD admits (*Annals* 2007;146:545)
- **Corticosteroids** (inhaled): ~20% ↓ in exacerbations if FEV_1 <2.0 L (*Chest* 2009;136:1029)
  may slow FEV_1 loss, but more so in combo with β_2-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 FEV_1, but ? ↓ exacerbation rate (*Lancet* 2008;371:2013)
- **Oxygen**: if $P_aO_2 \leq 55$ mm Hg or $S_aO_2 \leq 89\%$ (during rest, exercise, or sleep) to prevent cor pulmonale and ↓ mortality (*Annals* 1980;93:391 & *Lancet* 1981;i:681)
- **Prevention**: Flu/Pneumovax; smoking cessation (eg, varenicline, buproprion) → 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;131:4S)
- Experimental
  Lung volume reduction surgery: ↑ exer. capacity, ↓ mort. *if* FEV_1 >20%, upper-lobe, low exer. capacity (*NEJM* 2003;348:2059); ? bronchoscopic (*Chest* 2006;129:518)
  Bronchoscopic opening of extra-anatomical airway passages to ↑ exp collateral flow
  Roflumilast (PDE-4 inhibitor): ↑ FEV_1 when added to standard Rx (*Lancet* 2009;374:685&695)
  Nocturnal BiPAP: may improve survival, ? decrease QoL (*Thorax* 2009;64:561)
- Lung transplant: ↑ QoL and ↓ sx (*Lancet* 1998;351:24), ? survival benefit (*Am J Transplant* 2009;9:1640)

Prognosis

- **FEV_1**: <60% predicted → 5-y mort ~10%; <40% → ~50%; <20% → ~90%
- **BODE** 10-pt scale (*Lancet* 2009;374:704); HR 1.62 for resp. mort, 1.34 mort for each 1-pt ↑
  BMI: ≤21 (+1)
  Obstruction (FEV_1): 50–64% (+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)
  superior to FEV_1 (*NEJM* 2004;350:1005); can predict survival from LVRS (*Chest* 2006;129:873)

COPD Staging and Recommended Therapies by GOLD Criteria				
Stage	**PFTs (of predicted)**		**Therapies**	
I: Mild	FEV_1/FVC <70%	FEV_1 ≥80%	RF reduction, Flu vaccine	Bronchodilator prn
II: Mod		FEV_1 50–80%		Standing LA dilator (tiotropium >β ag) Rehabilitation
III: Severe		FEV_1 30–50%		Above + inh steroid if ↑ exacerbations
IV: Very Severe		FEV_1 <30% *or* FEV_1 <50% and chronic respiratory failure		Above + O_2 if chronic resp failure Experimental as indicated

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

Exacerbation

COPD Exacerbation Treatment (*NEJM* 2002;346:988)		
Agent	**Dose**	**Comments**
Ipratropium	MDI 4–8 puffs q1–2h *or* Nebulizer 0.5 mg q1–2h	First-line therapy
Albuterol	MDI 4–8 puffs q1–2h *or* Nebulizer 2.5–5 mg q1–2h	Benefit if component of reversible bronchoconstriction
Corticosteroids	No consensus for optimal dose & duration (*Cochrane* 2009:CD001288). Consider: Methylprednisolone 125 mg IV q6h × 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 >7.26 (*Lancet* 1999;354:456)	↓ treatment failure, ↓ hospital stay, ↑ FEV_1 but no mortality benefit, ↑ complications (*Cochrane* 2009:CD001288) OutPt Rx after ED visit ↓ relapse (*NEJM* 2003;348:2618)
Antibiotics	Amoxicillin, TMP-SMX, doxycycline, clarithromycin, anti-pneumococcal FQ, etc., all reasonable (no single abx proven superior). Consider local flora and avoid repeat courses of same antibiotic.	*H. flu*, *M. catarrhalis*, *S. pneumo* freq. precipitants. Dyspnea, ↑ sputum production, ↑ purulence → abx may improve outcome (*Annals* 1987;106:196) ↑ PEF & chance of clinical resolution (*JAMA* 1995;273:957) ↓ subseq exacerbation (*Thorax* 2008;63:96) ≤5d course likely enough for mild-mod exacerbation (*Thorax* 2008;63:41; *JAMA* 2010;303:2035)
Oxygenation	↑ F_iO_2 to achieve P_aO_2 ≥55–60 *or* S_aO_2 90–93%	**Watch for CO_2 retention** (due to ↑ V/Q mismatch, loss of hypoxemic resp. drive, Haldane effect) *but must maintain oxygenation!*
Noninvasive positive-pressure ventilation	Initiate *early* if mod/severe dyspnea, ↓ pH / ↑ P_aCO_2, RR >25 Results in 58% ↓ intubation, ↓ LOS by 3.2 d, 59% ↓ mortality Contraindications: Δ MS, inability to cooperate or clear secretions, hemodynamic instability, UGIB (*NEJM* 1995;333:817; *Annals* 2003;138:861; *Cochrane* 2004;CD004104; *ERJ* 2005;25:348)	
Endotracheal intubation	Consider if P_aO_2 <55–60, ↑'ing P_aCO_2, ↓'ing pH, ↑ RR, respiratory fatigue, Δ MS, or hemodynamic instability	
Other measures	Mucolytics overall not supported by data (*Chest* 2001;119:1190) Monitor for cardiac arrhythmias	

HEMOPTYSIS

Definition and pathophysiology

- Expectoration of blood or blood-streaked sputum
- **Massive hemoptysis**: ~>600 mL/24–48 h; gas exchange more important than blood loss
- Massive hemoptysis usually from tortuous or invaded **bronchial arteries**

Etiologies	
Infection/ Inflammation	**Bronchitis** (most common cause of trivial hemoptysis) **Bronchiectasis** incl. **CF** (common cause of massive hemoptysis) Tuberculosis or aspergilloma (can be massive) Pneumonia or lung abscess
Neoplasm	Usually primary **lung cancer,** sometimes metastasis (can be massive)
Cardiovascular	**PE** (can be massive), pulmonary artery rupture (2° to instrumentation), CHF, mitral stenosis, trauma/foreign body, bronchovascular fistula
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	
Benign (70%)	**Malignant (30%)**
Granuloma (80%): TB, histo, coccidio **Hamartoma** (10%) Bronchogenic cyst, AVM, pulm infarct Echinococcosis, ascariasis, aspergilloma Wegener's, rheumatoid nodule Lipoma, fibroma, amyloidoma, pneumonitis	**Bronchogenic carcinoma** (75%): adeno & large cell (peripheral) squamous & small cell (central) **Metastatic** (20%): breast, head & neck, colon, testicular, renal, sarcoma, melanoma Carcinoid, primary sarcoma

Risk of Cancer			
Feature	**Low**	**Intermediate**	**High**
Diameter (cm)	<1.5	1.5–2.2	≥2.3
Nodule shape	smooth	scalloped	spiculated
Age (y)	<45	45–60	>60
Smoking	never	current (≤1 ppd)	current (>1 ppd)
Smoking cessation	none, quit ≥7 y	quit <7 y ago	never quit

(*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 thoracopic 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

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.
- **CPAP**: ↓↓ apnea/hypopnea, ↓ BP (*Lancet* 2002:359:204), ↓ sleepiness, ↑ performance (*AJRCCM* 2001;164:608), ↑ EF in Pts with heart failure (*NEJM* 2003;348:1233)
- 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/arthritis, 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 (↓ volumes), ↓ D_LCO, ↓ P_aO_2 (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

Sarcoidosis (*NEJM* 2007;357:2153 & *Clin Chest Med* 2008;29:533)

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

Clinical Manifestations	
Organ system	**Manifestations**
Pulmonary	Hilar LAN; fibrosis; pulm hypertension. Stages: I = bilat hilar LAN; II = LAN + ILD; III = ILD only; IV = diffuse fibrosis
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; ↑ lacrimal gland
Endo & renal (10%)	Nephrolithiasis, hypercalcemia (10%), hypercalciuria (40%) Due to vitamin D hydroxylation by Mϕ
Neuro (10% clin, 25% path)	CN VII palsy, periph neuropathies, CNS lesions, seizures
Cardiac (5% clin, 25% path)	Conduction block, VT, CMP
Liver, spleen, BM	Granulomatous hepatitis (25%), splenic & BM gran. (50%)
Constitutional	Fever, night sweats, anorexia & wt loss (a/w hepatic path)
Musculoskeletal	Arthralgias, periarticular swelling, bone cysts

- *Löfgren's syndrome*: erythema nodosum + hilar adenopathy + arthritis (good prognosis)
- Diagnostic studies: **LN bx** → **noncaseating granulomas** + multinucleated giant cells
  ^{18}FDG PET can be used to identify extent and potentially targets for dx bx
  ↑ **ACE** (Se 60%, 90% w/ active dis., Sp 80%, false ⊕ in granulomatous diseases)
- To assess extent: CXR, PFTs, full ophtho exam, ECG, CBC (lymphopenia, ↑ eos), Ca, 24-h urine for Ca, LFTs; ± Holter, echo, cardiac MRI, brain MRI, etc., based on s/s
- Rx: **steroids** (eg, prednisone 20–40 mg/d) if sx or extrathoracic organ dysfxn (improves sx, but doesn't Δ long-term course); hydroxychloroquine for extensive skin disease; anti-TNF, MTX, AZA, mycophenolate, or cyclophosphamide for chronic/refractory disease
- Prognosis: ~⅔ spontaneously remit w/in 10 y (60–80% of stage I, 50–60% stage II, 30% stage III), w/ relapses uncommon; ~⅓ have progressive disease

Iatrogenic

- **Amiodarone** (~10%; dose & duration depend.): chronic interstitial pneumonia ↔ ARDS; bx → vacuolized Mϕ 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;172:268)

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

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

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

- Rx for UIP/IPF: steroids + AZA; NAC 600 tid may slow ↓ lung fxn (*NEJM* 2005;353:2229)
- Steroids for other IIPs: NSIP (espec. 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 worker's: upper lobe coal macules; may progress to massive fibrosis
  - Silicosis: upper lobe opacities ± eggshell calcification of lymph nodes; ↑ risk of TB
  - Asbestosis: lower lobe fibrosis, calcified pleural plaques, DOE, dry cough, rales on exam. Asbestos exposure also → pleural plaques, benign pleural effusion, diffuse pleural thickening, rounded atelectasis, mesothelioma, lung Ca (esp in smokers).
  - Berylliosis: multisystemic granulomatous disease that mimics sarcoidosis
- **Hypersensitivity pneumonitides** (organic dusts): loose, noncaseating *granulomas*
  - Antigens: farmer's lung (spores of thermophilic actinomyces); pigeon fancier's lung (proteins from feathers and excreta of birds); humidifier lung (thermophilic bacteria)
  - Pathophysiology: immunologic rxn; either acute (6 h after exposure) or chronic

Collagen vascular diseases (*ERJ* 2001;18:69S; *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
- **Vasculitis** (can p/w *DAH*)
  - Wegener's granulomatosis (⊕ c-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 ± periph. 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 infilt + 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/bronchovasc thickening; sx >1 y; Rx: steroids

PLEURAL EFFUSION

Pathophysiology

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

Transudates

- **Congestive heart failure (40%)**: 80% bilateral, ± cardiomegaly on CXR
  occasionally exudative (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 (⅔) & massive (even w/o marked ascites)
- Nephrotic syndrome: usually small, bilateral, asymptomatic (r/o PE b/c hypercoag)
- Other: PE (usually exudate), malignancy (lymphatic obstruction), myxedema, CAPD

Exudates

- **Lung parenchymal infection (25%)**
  bacterial (parapneumonic): can evolve along spectrum of *exudative* (but sterile) → *fibropurulent* (infected fluid) → *organization* (fibrosis & formation of rigid pleural peel).
  Common causes: *Strep pneumo, Staph aureus, Strep milleri, Klebsiella, Pseudomonas, Haemophilus, Bacteroides, Peptostreptococcus*, mixed flora in aspiration pneumonia.
  mycobacterial: >50% lymphs 80% of the time, ADA >40, pleural bx ~70% Se
  fungal, viral (usually small), parasitic (eg, amebiasis, echinococcosis, paragonimiasis)
- **Malignancy (15%)**: primary lung cancer most common, metastases (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*
- **Collagen vascular disease**: RA (large), SLE (small), Wegener's, Churg-Strauss
- **Gastrointestinal diseases**: pancreatitis, esophageal rupture, abdominal abscess
- Hemothorax (Hct_{eff}/Hct_{blood} >50%): trauma, PE, malignancy, coagulopathy, leaking aortic aneurysm, aortic dissection, pulmonary vascular malformation
- Chylothorax (triglycerides >110): thoracic duct damage due to trauma, malignancy, LAM
- Other: post-CABG: left-sided; initially bloody, clears after several wks
  Dressler's syndrome (pericarditis & pleuritis post-MI), uremia, post-radiation therapy
  Asbestos exposure: benign; ⊕ eosinophils
  Drug-induced (eg, nitrofurantoin, methysergide, bromocriptine, amiodarone): ⊕ eos
  Uremia; post-XRT; sarcoidosis
  Meigs' syndrome = benign ovarian tumor → ascites & pleural effusion
  Yellow-nail syndrome: yellow nails, lymphedema, pleural effusion, bronchiectasis

Diagnostic studies

- **Thoracentesis** (*NEJM* 2006;355:e16)
  Indications: **all effusions >1 cm in decubitus view**
  if suspect due to CHF, can diurese and see if effusions resolve (75% do so in 48 h)
  asymmetry, fever, chest pain, or failure to resolve → thoracentesis
  parapneumonics should be tapped ASAP (*cannot* exclude infxn clinically)
  Diagnostic studies: ✓ total protein, LDH, glucose, cell count w/ differential, gram stain & culture, pH; remaining fluid for additional studies as dictated by clinical scenario
  Complications: PTX (5–10%), hemothorax (~1%), re-expansion pulm. edema (if >1.5 L removed), spleen/liver lac.; post-tap CXR not routinely needed (*Annals* 1996;124:816)
- **Transudate vs. exudate** (*Annals* 1972;77:507)
  Light's criteria: exudate = TP_{eff}/TP_{serum} >0.5 *or* LDH_{eff}/LDH_{serum} >0.6 *or* LDH_{eff} >⅔ ULN of LDH_{serum}; 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%; $chol_{eff}$ >45 mg/dL *and* LDH_{eff} >200, 90% Se, 98% Sp (no serum required)
  CHF effusions: *TP may* ↑ *with diuresis or chronicity* → "pseudoexudate"; use albumin gradient ≤1.2, $chol_{eff}$ >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 (*Am J Med* 2004;116:417)
  WBC & diff.: exudates tend to have ↑WBC vs. transudates but nonspecific
    neutrophils → parapneumonic, PE, pancreatitis
    lymphocytes (>50%) → cancer, TB, rheumatologic
    eos (>10%) → blood, air, drug rxn, asbestos, paragonimiasis, Churg-Strauss, PE
  RBC: Hct_{eff} 1–20% → cancer, PE, trauma; Hct_{eff}/Hct_{blood} >50% → hemothorax
  AFB: yield in TB 0–10% w/ stain, 11–50% w/ culture, ~70% w/ pleural bx
  adenosine deaminase (ADA): seen w/ granulomas, >70 suggests TB, <40 excludes TB
  cytology: ideally ≥150 mL and at least 60 mL should be obtained (*Chest* 2010;137:68)
  glucose: <60 mg/dL → malignancy, infection, RA
  amylase: seen in pancreatic disease and esophageal rupture (salivary amylase)
  rheumatoid factor, C_H50, ANA: *limited utility* in dx collagen vascular disease
  triglycerides: >110 → chylothorax, 50–110 → ✓ lipoprotein analysis for chylomicrons
  cholesterol: >60; seen in chronic effusions (eg, CHF, RA, old TB)
  creatinine: effusion/serum ratio >1 → urinothorax
- Chest CT; pleural biopsy; VATS
- Undiagnosed persistent pleural effusions (*Clin Chest Med* 2006;27:309)
  Transudative: most commonly CHF or hepatic hydrothorax. ✓ s/s CHF or cirrhosis, $NT\text{-}proBNP_{eff}$; consider intraperitoneal injection of technetium-99m sulfur colloid
  Exudative (ensure using Sp test listed above): most commonly malig, empyema, TB, PE. ✓ s/s malig, chest CT (I^+), ADA or IFN-γ release assay; consider thoracoscopy.

Characteristics of Pleural Fluid (*not* diagnostic criteria)

Etiology	Appear	WBC *diff*	RBC	pH	Glc	Comments
CHF	clear, straw	<1,000 *lymphs*	<5,000	normal	≈ serum	bilateral, cardiomegaly
Cirrhosis	clear, straw	<1,000	<5,000	normal	≈ serum	right-sided
Uncomplicated parapneumonic	turbid	5–40,000 *polys*	<5,000	normal to ↓	≈ serum (>40)	
Complicated parapneumonic	turbid to purulent	5–40,000 *polys*	<5,000	↓↓	↓↓ (<40)	need drainage
Empyema	purulent	25–100,000 *polys*	<5,000	↓↓↓	↓↓	need drainage
Tuberculosis	serosang.	5–10,000 *lymphs*	<10,000	normal to ↓	normal to ↓	⊕ AFB ⊕ ADA
Malignancy	turbid to bloody	1–100,000 *lymphs*	<100,000	normal to ↓	normal to ↓	⊕ cytology
Pulmonary embolism	*sometimes* bloody	1–50,000 *polys*	<100,000	normal	≈ serum	no infarct → transudate
Rheumatoid arthritis/SLE	turbid	1–20,000 *variable*	<1,000	↓	RA ↓↓↓ SLE nl	↑ RF, ↓ C_H50 ↑ imm. complex
Pancreatitis	serosang. to turbid	1–50,000 *polys*	<10,000	normal	≈ serum	left-sided, ↑ amylase
Esophageal rupture	turbid to purulent	<5,000 >50,000	<10,000	↓↓↓	↓↓	left-sided, ↑ amylase

Treatment

- Symptomatic effusion: therapeutic thoracentesis, treat underlying disease process
- Parapneumonic effusion (*Chest* 2000;118:1158)
  uncomplicated → antibiotics for pneumonia
  >½ hemithorax *or* complicated *or* empyema → tube thoracostomy
    (o/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, ↓ ascitic fluid volume, NIPPV)
  avoid chest tubes; prn thoracenteses, pleurodesis, TIPS or VATS closure of diaphragmatic defects if medical Rx fails; NIPPV for acute short-term management
  spontaneous bacterial empyema (SBEM) can occur (even w/o SBP being present), ∴ thoracentesis if suspect infection
  transplant is definitive treatment and workup should begin immediately

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 >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 ↓ risk (*NEJM* 2009;360:1851)

Thromboprophylaxis (*Chest* 2008;133:381S)

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

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 asx PE

Pretest Probability of DVT

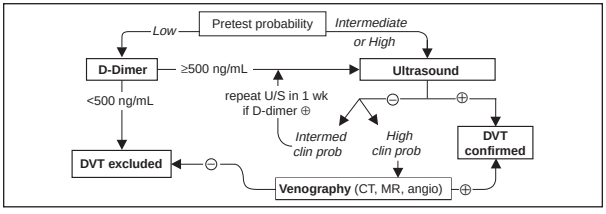
Major points	Minor points
• Active cancer • Paralysis, paresis, immobilization of foot • Bed rest × >3 d or major surg. w/in 4 wk • Localized tenderness along veins • Swelling of thigh *and* calf • Swelling of calf >3 cm c/w asx side • ⊕ FHx of DVT (≥2 1° relatives)	• Trauma to symptomatic leg w/in 60 d • Pitting edema in symptomatic leg • Dilated superficial veins (nonvaricose) in symptomatic leg only • Hospitalization w/in previous 6 mo • Erythema
High probability (~85% ⊕ DVT) ≥3 major + *no* alternative dx ≥2 major + ≥2 minor + *no* alternative dx	**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
Intermediate prob (~33% ⊕ DVT) neither high nor low probability	

(*Lancet* 1995;345:1326; *NEJM* 1996;335:1816)

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 2-3 Approach to suspected DVT



(*Lancet* 1995;345:1326 & 1997;350:1795; *NEJM* 1996;335:1816 & 2003;349:13; *Archives* 2002;162:907.)

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 P_2
- *Massive*: syncope, HoTN, PEA; ↑ JVP, R-sided S_3, Graham Steell (PR) murmur

"Modified Wells" Pretest Probability Scoring of PE	
Variable	**Point Score**
• PE as likely or more likely than alternate dx; clin. s/s of DVT	3 each
• HR >100 bpm; prior DVT or PE	1.5 each
• Immobilization (bed rest ≥3 d) or surgery w/in 4 wk	1.5
• Hemoptysis; malignancy	1 each

"Modified Wells" Pretest Probability Assessment (Use for V/Q)		
Score <2	Score 2–6	Score >6
Low probability	Intermediate probability	High probability

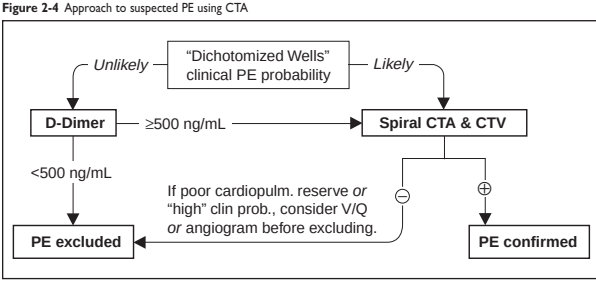
"Dichotomized Wells" Pretest Probability Assessment* (Use for CTA)	
Score ≤4: PE "Unlikely"	Score >4: PE "Likely"

(*Annals* 2001;135:98) (**JAMA* 2006;295:172)

Diagnostic studies—PE

- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, ↑ hemidiaphragm, Hampton hump, (wedge-shaped density abutting pleura); Westermark sign (avascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, $S_IQ_{III}T_{III}$ & TWI V_1–V_4 (McGinn-White pattern, *Chest* 1997;111:537)
- ABG: hypoxemia, hypocapnia, respiratory alkalosis, ↑ A-a gradient (*Chest* 1996;109:78) 18% w/ room air P_aO_2 85–105 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 dysfxn), but not dx (Se <50%)
- V/Q scan: high Se (~98%), low Sp (~10%). Sp improves to 97% for high prob VQ. Use if pretest prob of PE high and CT not available or contraindicated. Can also exclude PE if low pretest prob, low prob VQ, but 4% false ⊖ (*JAMA* 1990;263:2753).
- **CT angiography** (CTA; see Radiology inserts): Se. ~90% & Sp ~95% w/ MDCT, + CTV, good quality scans and experienced readers (*NEJM* 2006;354:2317); 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 Δ outcomes (*Lancet* 2008;371:1343)
- Pulmonary angio: ? gold standard (morbidity 5%, mortality <0.5%), infrequently performed
- MR angiography: Se 84% (segmental) to 100% (lobar) (*Lancet* 2002;359:1643)

Figure 2-4 Approach to suspected PE using CTA



Based on data from *NEJM* 2005;352:1760 & 2006;354:22; *JAMA* 2005;293:2012 & 2006;295:172

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;454S; *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)
- **Acute anticoagulation** *(initiate immediately if high clinical suspicion!)*
  - **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), ? extreme obesity, hemodynamic instability, or bleed risk (*Cochrane* 2004;CD001100)
    - No need to monitor anti-factor Xa unless concern re: dosing (eg, renal insuffic)
    - 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 ↑ 2×, no mort. diff. (*NEJM* 1998;338:409; *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 ≥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 at 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; ↓ PGI_2, NO, VIP; mutations in bone morphogenic 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 A_2 (TXA_2), serotonin (5-HT), endothelin-1 (ET-1)
  ↓ vasodilators: prostacyclin (PGI_2), nitric oxide (NO), vasoactive peptide (VIP)
- In situ thrombosis: ↑ TXA_2, 5-HT, PAI-1; ↓ PGI_2, NO, VIP, tissue plasminogen activator

Etiologies of Pulmonary Hypertension (Revised WHO Classification)	
Pulmonary arterial HTN (PAH)	• Idiopathic (IPAH): mean age of onset 36 y (♂ older than ♀); ♀:♂ = ~2:1, usually mild ↑ in PAP • Familial (FPAH) • Associated conditions (APAH) Connective tissue disorders: CREST, SLE, MCTD, RA, PM, Sjögren Congenital L→R shunts: ASD, VSD, PDA Portopulmonary HTN (? 2° vasoactive substances not filtered in ESLD; ≠ hepatopulmonary syndrome) HIV; drugs & toxins: anorexic agents, rapeseed oil, L-tryptophan Other: thyroid dis., glycogen storage dis., Gaucher disease, HHT, hemoglobinopathies, chronic myeloproliferative d/o, splenectomy • Pulmonary veno-occlusive disease: ? 2° chemo, BMT; orthopnea, CHF, pl eff, nl PCWP; art vasodil. *worsen* CHF (*AJRCCM* 2000;162:1964) • Pulmonary capillary hemangiomatosis
Left heart disease	• Left atrial or ventricular (diastolic or systolic) dysfunction • Left-sided valvular heart disease (eg, MS/MR)
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	• Sarcoidosis, histiocytosis X, lymphangiomatosis, schistosomiasis • Compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis)

(*Circulation* 2009;28:119:2250)

Clinical manifestations

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

Physical exam

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

Diagnostic studies & workup (*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: ↓ D_{LCO}, mild restrictive pattern; r/o obstructive and restrictive lung disease
- ABG & polysomnography: ↓ P_aO_2 and S_aO_2 (especially w/ exertion), ↓ P_aCO_2, ↑ 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 dysfxn, 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)

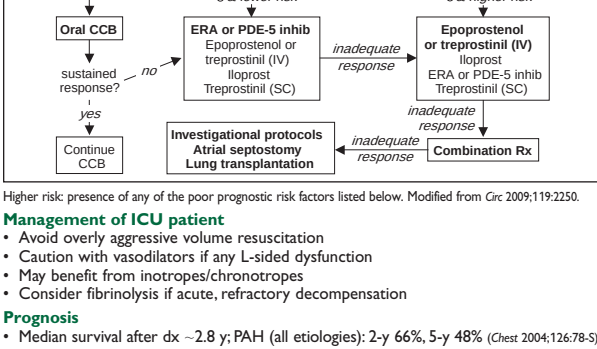
- Principles
  1) prevent and reverse vasoactive substance imbalance and vascular remodeling
  2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq. systemic DBP

- **Supportive**
  Oxygen: maintain S_aO_2 >90–92% (reduces vasoconstriction)
  Diuretics: ↓ RV wall stress and relieve RHF sx; *gentle* b/c RV is preload dependent
  Digoxin: control AF, ? counteract neg. inotropic effects CCB
  Dobutamine and inhaled NO for decompensated PHT
  Anticoagulation: ↓VTE risk of RHF; ? prevention of in situ microthrombi; ? 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 (⊕ vasoreactive response defined as ↓ PAP >10 mm Hg to a level <40 mm Hg with ↑ or stable CO); ~10% Pts are acute responders; no response → still candidates for other vasodilators (*NEJM* 2004;351:1425)

Vasodilators	Comments
Oral CCB Nifedipine, diltiazem	If ⊕ acute vasoreactive response; <½ will be long-term responder (NYHA I/II & near-nl hemodynamics) & have ↓ **mortality**. Side effects: HoTN, lower limb edema. (*NEJM* 1992;327:76, *Circ* 2005;111:3105)
IV Prostacyclin Epoprostenol; Flolan	Vasodilation, ↓ plt agg, ↓ smooth muscle proliferation; benefits ↑ w/ time (? vascular remodeling). ↑ 6MWT, ↑ QoL, ↓ **mortality**. Side effects: HA, flushing, jaw/leg pain, abd cramps, nausea, diarrhea, catheter infxn. (*NEJM* 1996;334:296 & 1998:338:273; *Annals* 2000;132:425)
Prostacyclin analogues Iloprost (inhaled) Treprostinil (IV or SC) Beraprost (PO)	Same mechanism as prostacyclin IV, but easier to take, ↓ side effects, and w/o risk of catheter infxn. ↓ sx, ↑ 6MWT; trend to ↓ clinical events w/ iloprost but not treprostinil. Beraprost w/o sustained outcome improvement (n/a in U.S.). (*NEJM* 2002;347:322; *AJRCCM* 2002;165:800)
Endothelin receptor antagonists (ERAs) Bosentan, ambrisentan	↓ Smooth muscle remodeling, ↑ vasodilation, ↓ fibrosis. ↓ sx, ↑ 6MWT, ↓ clinical events. Side effects: ↑ LFTs, headache, anemia, edema, teratogen. (*NEJM* 2002;346:896; *JACC* 2005;46:529; *Circ* 2008;117:3010)
PDE-5 Inhibitor Sildenafil, tadalafil	↑ cGMP → ↑ NO → vasodilation, ↓ smooth muscle proliferation ↓ sx, ↑ 6MWT, no Δ clinical outcomes. Low side effect profile: HA, vision Δ's, sinus congestion. (*NEJM* 2009;361:1864)

- Treat underlying causes of 2° PHT; can use vasodilators, although little evidence
- Refractory PHT
  balloon atrial septostomy: R→L shunt causes ↑ CO, ↓ S_aO_2, net ↑ tissue O_2 delivery
  lung transplant (single or bilateral); heart-lung needed if Eisenmenger physiology

Figure 2-5 Treatment of PAH



Higher risk: presence of any of the poor prognostic risk factors listed below. Modified from *Circ* 2009;119:2250.

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

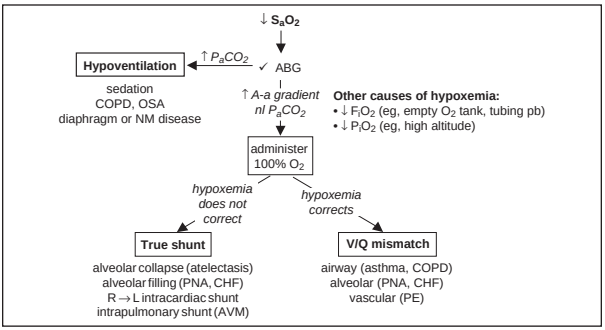
Prognosis

- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (*Chest* 2004;126:78-S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO (modified NYHA) class IV, 6MWT <300 m, peak VO_2 <10.4 mL/kg/min, ↑ RA or RV or RV dysfxn, RA >20 or CI <2.0, ↑ BNP (*Chest* 2006;129:1313)
- Lung transplant: 1-y survival 66–75%; 5-y survival 45–55% (*Chest* 2004;126:63-S)

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

- **A-a gradient = $P_AO_2 - P_aO_2$**: normal (*on room air*) = "4 + age/4" or "2.5 + (0.2 × age)" hypoxemia + normal A-a gradient → problem is excess P_aCO_2 (ie, hypoventilation)
- **S_vO_2** (mixed venous O_2 sat, nl 60–80%): measure O_2 consumption vs. delivery; low $S_vO_2 \rightarrow \downarrow O_2$ delivery ($\downarrow S_aO_2$, nl S_aO_2 but $\downarrow$ 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						
Condition	**Causes**	**Classic Features**	**P_aO_2**	**Pulse Ox Sat**	**CO-Ox Sat**	**Treatment** (+ 100% O_2)
Carbon monoxide	Fires, portable heaters, auto exhaust	Cherry-red skin (COHb color)	nl	nl	↓	Hyperbaric O_2
Methemo-globinemia	Nitrates, sulfonamide, benzocaine, dapsone	Chocolate brown blood	nl	mild ↓	↓	Methylene blue
Cyanide	Nitroprusside, fires, industrial	Bitter almond odor; pink skin	nl	nl (↑ S_vO_2)	nl	Hydroxy-cobalamin

CO binds to Hb more avidly than does O_2. Pulse ox misreads COHb as $HbO_2 \rightarrow$ falsely nl sat.
Oxidizing drugs Δ Hb (ferrous) to MetHb (ferric), which cannot carry O_2. Pulse ox misreads MetHb as HbO_2.
Cyanide inhibits mitochondrial O_2 use → cellular hypoxia but pink skin and ↑ *venous* O_2 sat.

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

↑ P_aCO_2			
"Won't breathe"	**"Can't breathe"**		
Respiratory Drive	**NM System**	**Lung/Airways**	**CW/Pleura**
↓ RR	↓ V_T	↓ V_T and/or ↑ V_D	↓ V_T
↓ P_{100} Voluntary hypervent. Nl PI_{max} & A-a gradient	↓ PI_{max} ↓ PE_{max}	Abnl PFTs	Abnl PEx Abnl CXR/CT
Chemoreceptors metab. alkalosis **1° neurologic** brainstem stroke tumor 1° alveolar hypovent **2° neurologic** sedatives CNS infection hypothyroidism	**Neuropathies** cervical spine phrenic nerve GBS, ALS, polio **NMJ** MG, LE, botulism **Myopathies** diaphragm PM/DM; ↓ PO_4 musc dystrophies	**Lung parenchyma** emphysema ILD/fibrosis CHF, PNA **Airways** asthma, COPD bronchiectasis CF OSA	**Chest wall** obesity kyphosis scoliosis **Pleura** fibrosis effusion

↑ VCO_2 typically transient cause of ↑ P_aCO_2; Ddx: exercise, fever, hyperthyroidism, ↑ work of breathing, ↑ carbs.

MECHANICAL VENTILATION

Indications

- Improve gas exchange
  - ↑ oxygenation
  - ↑ alveolar 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_iO_2, PEEP, I:E time, flow, airway pressures)

Step 1: Pick Ventilator Mode	
Mode	**Description**
Assist control (AC)	Vent delivers a minimum number of supported breaths Additional Pt-initiated breaths trigger *fully-assisted* vent breaths ∴ Vent-triggered breaths identical to Pt-triggered breaths Tachypnea → ? respiratory alkalosis, breath-stacking, & auto-PEEP May be pressure targeted or volume targeted
Synchronized intermittent mandatory vent (SIMV)	Vent delivers min. # supported breaths (synch. to Pt's efforts) Additional Pt-initiated breaths → V_T 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
Pressure support vent (PSV)	Support Pt-initiated breaths w/ a set inspiratory pressure & PEEP A mode of *partial* vent support because no set rate
Continuous positive airway pressure (CPAP)	Pt breathes spont. at his/her own rate while vent maintains constant positive airway pressure throughout respiratory cycle (7 cm H_2O overcomes 7 Fr ETT)
T piece	No airway pressure, no rate set; patient breathes through ETT
Other	High-frequency vent (*AJRCCM* 2002;166:801; *CCM* 2003;S-31:S-317) ECMO and $ECCO_2R$ (*Ann Surg* 2004;240:595)

Step 2: Choose Volume Targeted or Pressure Targeted	
Volume targeted	Vent delivers a set V_T 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 (PIP, P_{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 V_T. Volume support (VS) sample principle in spontaneous mode.
Pressure targeted	Vent delivers a fixed inspiratory pressure regardless of V_T V_T depends on airway resistance and lung/chest wall compliance **Benefit:** May ↑ patient comfort (PSV) requiring less sedation **Risk:** Pt at risk for ↓ *volumes* → inadequate V_E
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	
F_IO_2	Fraction of inspired air that is oxygen
Positive end-expiratory pressure (PEEP)	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, "breath stacking"); 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 ≠ 0 before next breath Can measure by occluding expiratory port of vent at end-expiration Can ↓ by: ↑ exp time, ↓ RR, ↓V_T, Rx bronchospasm and secretions
Inspiratory time	Normally I:E ratio is ~1:2; however, can alter I time (and consequently flow rate, see later); use in pressure-control mode
Inspiratory flow rates	↑ flow rate → ↓ I time → ↑ E time → ∴ may improve ventilation in obstructive disease, but may affect resp rate and bronchodilation/constriction
Peak inspiratory pressure (PIP)	Dynamic measurement during inspiration; set in pressure-targeted mode Determined by airway resistance and lung/chest wall compliance ↑ PIP w/o ↑ P_{plat} → ↑ airway resist (eg, bronchospasm, plugging) ↓ PIP → ↓ airway resistance or air leak in the system
Plateau pressure (P_{plat})	Static measurement at the end of inspiration when there is no flow Determined by resp system compliance (resist. not a factor since ∅ flow) ↑ P_{plat} → ↓ lung or chest wall compliance (eg, PTX, pulmonary edema, pneumonia, atelectasis), ↑ PEEP, or auto-PEEP P_{plat} <30 cm H_2O ↓ barotrauma (↓V_T, ↓ PEEP or ↑ compl [eg, by diuresis])

Initial Settings				
Mode	**Tidal volume**	**Respiratory rate**	**F_IO_2**	**PEEP**
Assist control volume-targeted	4–8* mL/kg IBW	12–16 breaths/min	1.0 (ie, 100%)	? 5 cm H_2O

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

Noninvasive Ventilation	
Conditions	Cardiogenic pulmonary edema: may ↓ intub. & mortality (*JAMA* 2005;294:3124; *Lancet* 2006;367:1155) although recent trial (w/ high crossover) did not show any benefit (*NEJM* 2008;359:142) COPD exacerbation w/ hypercapnia: ↓ intub. & mortality (*Lancet* 2000;355:1931), but if pH <7.3 → intubate High-risk extubation (age >65, CHF, APACHE II >12): NIV × 24 h directly after extubation → ↓ reintub and, if P_aCO_2 >45 during SBT, ↓ mortality (*AJRCCM* 2006;173:164). However, if used as *rescue* after failed extubation → ↑ mortality (*NEJM* 2004;350:2452). End-of-life care (*Resp Care* 2009;54:223) Immunosupp. w/ infiltrates: ↓ complic & mort (*NEJM* 2001;344:481)
Indications (*Lancet* 2009;374:250)	*Clinical*: mod-severe dyspnea, RR >24–30, signs of ↑ work of breathing, accessory muscle use, abd paradox *Gas exchange*: P_aCO_2 >45 (& significantly worse than baseline), hypoxemia, P_aO_2/F_IO_2 <200
Contraindications (*JAMA* 2002;288:932)	Claustrophobia, inability to fit mask, Δ MS, vomiting, unable to protect airway, extrapulm organ failure, hemodyn instab, sev UGIB
Continuous positive airway pressure (CPAP)	≈PEEP No limit on O_2 delivered (ie, can give hi-flow → F_IO_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). Used if primary problem ***hypoventilation***; F_IO_2 delivery limited
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_IO_2 ~1.0 Used for short-term support (<24 h) for a reversible process

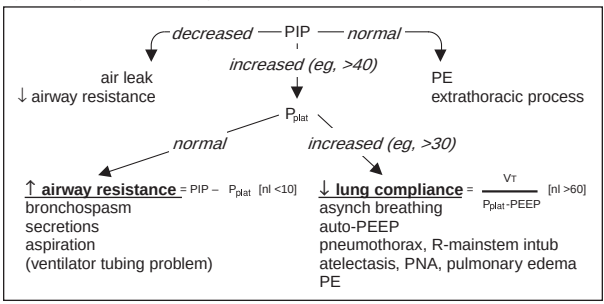
Tailoring the ventilator settings

- To improve oxygenation: options include ↑ F_IO_2, ↑ PEEP
  First, ↑ F_IO_2. If >0.6 and oxygenation remains suboptimal, then try ↑ PEEP:
  If ↑ P_aO_2/F_IO_2 *and* P_{plat} stable, suggests recruitable lung (ie, atelectasis). Continue to ↑ PEEP until either can ↓ F_IO_2 to <0.6 or P_{plat} ≥30 cm H_2O. If PEEP 20 & F_IO_2 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see ARDS).
  If ↑ PEEP → ∅Δ or ↓ P_aO_2/F_IO_2 *or* ↑ P_aCO_2, suggests additional lung *not* recruitable and instead overdistending lung → ↑ shunt & dead space; ∴ ↓ PEEP
- To improve ventilation: ↑ V_T or inspiratory pressure, ↑ RR (may need to ↓ I time). Nb, tolerate ↑ P_aCO_2 (permissive hypercapnia) in ALI/ARDS (qv) as long as pH >7.15.

Acute ventilatory deterioration (usually ↑ PIP)

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

Figure 2-7 Approach to acute ventilatory deterioration



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

Weaning from the ventilator

- 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, S_aO_2 <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: P_aO_2/F_IO_2 >200, PEEP ≤5, f/V_T <105, V_E <12 L/min, VC >10 mL/kg
  rapid shallow breathing index (f/V_T) >105 predicts failure; NPV 0.95 (*NEJM* 1991;324:1445)
- SBT = CPAP or T piece × 30–120 min (*AJRCCM* 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 ↑ P_{plat} (>30 cm H_2O, but lower better) → alveolar damage
- Oxygen toxicity (theoretical); proportional to duration + degree of ↑ oxygen (F_IO_2 >0.6)
- Alterations in cardiac output (eg, PEEP can ↓ preload → hypotension)
- Ventilator-associated pneumonia (~1%/day, mortality rate ~30%)
  typical pathogens: MRSA, *Pseudomonas*, *Acinetobacter*, and *Enterobacter* species
  preventive strategies (*AJRCCM* 2005;171:388): wash hands, semirecumbent position, non-nasal intub, enteral nutrition rather than TPN, routine suction of subglottic secretions, avoid unnecessary abx & transfusions, routine oral antiseptic, stress-ulcer prophylaxis w/ ? sucralfate (↓VAP, ↑ GIB) vs. H_2RA/PPI, ? silver-coated tubes (*JAMA* 2008;300:805)
- Laryngeal
  edema: for Pts vent >36 h; ? predicted by ⊕ cuff leak test. Methylprednisolone 20 mg IV q4h starting 12 h pre-extub → ↓↓ edema and 50% ↓ in reintubation (*Lancet* 2007;369:1003)
  ulceration: consider *tracheostomy* for patients in whom expect >14 d of mech. vent → ↓ duration mech. vent, ↓ # ICU days (*BMJ* 2005;330:1243); no benefit to performing at ~1 wk vs. waiting until ~2 wk (*JAMA* 2010;303:1483)

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**: $P_aO_2/F_iO_2 \leq 200$ → ARDS; $P_aO_2/F_iO_2 \leq 300$ → 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: $V_T/(P_{plat} - PEEP)$ <50 mL/cm H_2O

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

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

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

Mechanisms of VILI	Ventilator Strategies*
Barotrauma/volutrauma: alveolar overdistention → mechanical damage	**V_T ≤6 mL/kg, P_{plat} ≤30 cm H_2O,** tolerate ↑ P_aCO_2 (but keep pH >7.15), ↓ mortality (*NEJM* 2000;342:1301). Weight risk/benefit of sedation & paralysis.
Biotrauma → SIRS	Low V_T, open lung strategy w/ high PEEP
Atelectrauma: repetitive alveoli recruitment & decruitment	**Titrate PEEP to prevent tidal alveolar collapse** Variable benefit in different studies, Pt subgps. No benefit at given V_T if titrated to P_aO_2 alone (*NEJM* 2004;351:327; *JAMA* 2008;299:637). If titrated to P_{plat} 28–30 cm H_2O → ↓ time on vent, better lung mechanics (*JAMA* 2008;299:646), ? ↓ mortality (*JAMA* 2010;303:865). If able to ↑ PEEP w/o ↑ P_{plat}, suggests "recruitability." ∴ ↑ PEEP if → ↑ S_aO_2; target S_aO_2 ≥88–90% & P_{plat} ≤30
Hyperoxia: ? injury; worsened V/Q matching	↑ **PEEP** rather than F_iO_2 (keep <0.60) O_2 -induced injury only theoretical in humans

*See ARDSnet.org for ventilator protocol.

- **Fluid balance**: target CVP 4–6 cm H_2O (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 ↑ P_aO_2/F_iO_2, no ↓ mort or vent-free days (*BMJ* 2007;334:779); inhaled prostacyclins similar physiologically, similar effect
  - *Prone ventilation:* ↑ P_aO_2, but ↑ complications and no ↓ mortality (*JAMA* 2009;302:1977)
  - *High-frequency oscillatory ventilation:* no mort benefit (*AJRCCM* 2002;166:801), can transiently ↑ P_aO_2 (*Chest* 2007;131:1907)
  - *Lung recruitment:* apply CPAP 40–45 cm H_2O × 2 min to recruit lung and then ↑ PEEP to maintain; sicker Pts had ↑ recruitable lung (*NEJM* 2006;354:1775, 1839)
  - *ECMO:* may be useful in refractory ARDS, but no good trial c/w protocolized, low-V_T ARDS ventilation (*Ann Surg* 2004;240:595; *Chest* 1997;112:759; *Lancet* 2009;374:1351)
  - *Esoph manometry:* adjust PEEP according to esoph pressure (≈pleural pressure) to maintain positive transpulm pressure → ↑ P_aO_2/F_iO_2, ↑ 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, ↓ D_LCO, muscle wasting, weakness persists (*NEJM* 2003;348:683)

Definitions	
Systemic Inflammatory Response Syndrome (SIRS)	2 or more of the following: (1) Temp >38 or <36°C, (2) HR >90, (3) RR >20 or P_aCO_2 <32, (4) WBC >12,000 or <4000 or >10% bands
Sepsis	SIRS + suspected infection
Severe Sepsis	Sepsis + organ dysfunction, hypoperfusion or hypotension Signs of hypoperfusion may incl. lactic acidosis, oliguria, ΔMS
Septic Shock	Sepsis-induced hypotension despite adequate fluid resuscitation, along with signs of hypoperfusion

(*Chest* 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) O_2 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 $S_{cv}O_2$ ≥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 (↓ 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 (*Chest* 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;288:862)
- No mortality benefit to early (<72 h) empiric corticosteroids in all Pts w/ septic shock, regardless of ACTH stim; faster resolution of shock, more 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* 2001;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 contraindic. (*Crit Care Med* 2008;36:296)

Intensive Glycemic Control

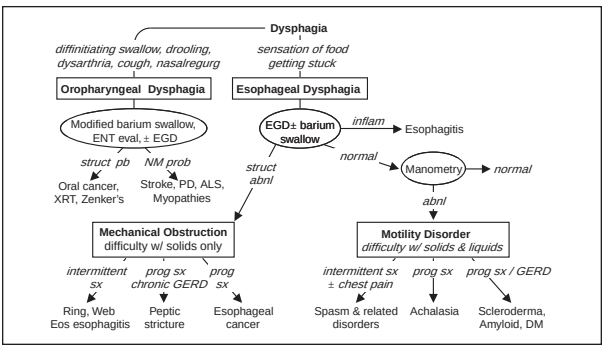
- No evidence of improved outcomes in MICU population w/ intensive glycemic control
- Intensive glycemic control to goal 80–110 mg/dL in *surgical* ICU population → mortality benefit, greatest if >3-d ICU stay (*NEJM* 2001;345:1359)
- More recently, intensive glycemic control → either no Δ or ↑ increased 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)

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)



Achalasia

- Etiologies: idiopathic (most common), pseudoachalasia (due to GE jxn tumor), Chagas
- Sx: dysphagia (solid & liquid), chest pain (⅓ of Pts), regurgitation
- Dx: barium swallow → 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 (pharyngoesoph jxn); dx w/ barium swallow; Rx endo/surg
- Infx esophagitis: odynophagia > dysphagia; often immunosupp w/ *Candida*, HSV, CMV
- Pill esophagitis: odynophagia > dypshagia; 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
- Extraesophageal: **cough**, asthma (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) > H_2RA, 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 >½ on meds after 10 y

Complications (*NEJM* 2009;361:2548)
- Barrett's esophagus: 10–15% of Pts 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

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 ↓ing b/c ↓ incidence of *H. pylori* and potent acid suppression Rx. However, incidence of hospitalization for complications unΔ'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** & **NSAIDs**: 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 & penetration, 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 GUs to r/o malig; 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 (*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 (see above)

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 H_2RA if ASA monotherapy (*Lancet* 2009;374:119)
- Consider Δ to COX-2 inhibit (↓ PUD & UGIB but ↑ CV events) if low CV risk & not on ASA
- 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 → r/o splenic vein thrombosis.
- **Gastritis/gastropathy/duodenitis** (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, angioectasias, 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, vasovagal, 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 >50,000
- **Triage**: consider ICU if unstable VS or poor end organ perfusion
  Intubation for emergent EGD, if ongoing hematemesis, shock, poor resp status, Δ MS
  ? OutPt management if SBP ≥110, HR <100, Hb ≥13 (♂) or ≥12 (♀), BUN <18, ∅ melena, syncope, heart failure, liver disease (*Lancet* 2009;373:42)

Workup

- **History**: *where* (anatomic location) & *why* (etiology)
  acute or chronic, prior GIB, # of episodes, other GI dx
  hematemesis, vomiting *prior* to hematemesis (Mallory-Weiss), melena, hematochezia
  abdominal pain, wt loss, anorexia, Δ 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 GI or aortic surgery
- **Physical exam**: *VS most important, orthostatic Δs, 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, telangiectasias (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; **plt**, **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 UGIB (can be confused w/ bile); *nonbloody bile* → ? lower source, but does not exclude active UGIB (~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 → ↑ Dx/Rx yield (*Am J Gastro* 2006;101:1211)
- LGIB: *first* r/o UGIB 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)

Etiology	Treatment Options
Varices (*Hep* 2007;46:922; *NEJM* 2010;362:823)	*Pharmacologic* **octreotide** 50 μg IVB → 50 μg/h infusion (84% success). Usually × 5 d, but most benefit w/in 24–48 h. Abx: cirrhotics w/ any GIB should receive prophylaxis: Cftx IV vs. norfloxacin PO (*Hep* 2004;39:746 & *Gastro* 2006;131;1049) *Nonpharmacologic* **endoscopic band ligation** (>90% success) arteriography with coiling/glue occasionally for gastric varices balloon tamponade (Sengstaken-Blakemore) if bleeding severe; mainly used as rescue procedure and bridge to TIPS TIPS for esophageal variceal hemorrhage refractory to above, or for gastric varices; c/b encephalopathy, shunt occlusion surgery (portocaval/splenorenal shunts) rarely used now
PUD (*NEJM* 2000;343:310; 2007;356:1631; 2008;359:928; *Annals* 2010;152:101)	*If active bleeding or non-bleeding visible vessel (NBVV) on EGD* **PPI** (eg, omeprazole 80 mg IVB → 8 mg/h) before EGD → ↓ need for endoscopic Rx and ↓ LOS continue IV dose × 72 h following EGD: ↓ rebleed rate convert to PO after 72 h ? Octreotide if no access to EGD **Endoscopic therapy** (ET): epi inj + either bipolar cautery or hemoclip; rebleeding risk: 43% (NBVV) to 85% (active bleed) w/o ET vs. 15–20% w/ ET vs. <7% w/ ET+ PPI (most w/in 48 h) Clear liquids 6 h after ET if hemodynamically stable Arteriography w/ vasopressin or embolization; surgery (last resort) *If adherent clot* PPI as above ± endo removal of clot (if experienced ctr) to r/o NBVV; rebleeding risk 22% w/o ET vs. 5% w/ ET *If flat, pigmented spot or clean base* No endo Rx indicated; rebleed risk <10%: oral PPI BID Consider early hospital d/c (see criteria in *NEJM* 2008;359:928) If Pt on ASA for CV disease and PUD GIB endoscopically controlled, resume ASA when CV risk > rebleeding risk, typically 7 d following index bleed (*Annals* 2010;152:101)
Mallory-Weiss	Usually stops spontaneously; endoscopic Rx if active
Esophagitis Gastritis	PPI, H_2-receptor antagonists
Diverticular disease	Usually stops spontaneously (~75%) Endoscopic Rx (eg, epinephrine injection, cautery, banding, or hemoclip), arterial vasopressin or embolization, surgery
Angiodysplasia	Usually stops spontaneously (~85%) Endo Rx (cautery or argon plasma), arterio w/ vasopressin, surgery

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 ^{99m}Tc-pertechnetate scan ("Meckel's scan"), double-balloon enteroscopy, tagged RBC scan, and arteriography

ACUTE DIARRHEA (<4 WK)

Acute Infectious Etiologies		
Pathogen		**Epidemiology & Clinical Sx**
Noninflammatory		**Predom. disruption small intestine absorp. & secretion. Voluminous diarrhea, N/V. ⊖ fecal WBC & FOB.**
Preformed toxin		"Food poisoning," <24 h dur. *S. aureus* (meats & dairy), *B. cereus* (fried rice), *C. perfringens* (rewarmed meats).
Viral	Rotavirus	Outbreak person to person (PTP), daycare; lasts 4–8 d.
	Norovirus	~50% of all diarrhea. Winter outbreaks; PTP & food/water; no immunity. Lasts 1–3 d. Vomiting prominent.
Bacterial	*E. coli* (toxigenic)	>50% of traveler's diarrhea; cholera-like toxin; <7 d.
	Vibrio cholerae	Contam H_2O, fish, shellfish; 50 cases/y in U.S. gulf coast. Severe dehydration & electrolyte depletion.
Parasitic (± malab for mos after Rx)	*Giardia*	Streams/outdoor sports, travel, outbreaks. Bloating.
	Cryptosporidia	Water-borne outbreak; typically self-limited, can cause chronic infxn if immunosupp. Abd pain (80%), fever (40%). (*NEJM* 2002;346:1723)
	Cyclospora	Contaminated produce
Inflammatory		**Predom. colonic invasion. Small vol diarrhea. LLQ cramps, tenesmus, fever, typically ⊕ fecal WBC or FOB.**
Bacterial	*Campylobacter*	Undercooked poultry, unpasteurized milk, travel to Asia; carried by puppies & kittens. Prodrome; abd pain → "pseudoappendicitis"; c/b GBS, reactive arthritis.
	Salmonella (nontyphoidal)	Eggs, poultry, milk. Bacteremia in 5–10%. 10–33% of bacteremic Pts >50 y develop aortitis.
	Shigella	Low inoculum; PTP spread. Abrupt onset; often gross blood & pus in stool; ↑↑ WBC.
	E. coli (O157:H7 & inv/ hemorrhagic non-O157:H7)	Undercooked beef, unpasteurized milk, raw produce; PTP. O157 & non-O157 sp. (40%) produce *Shiga* toxin → HUS (typically in children). Gross blood in stool.
	C. difficile	See later
	Vibrio parahaem.	Undercooked seafood
	Salmonella typhi	Travel to Asia. Systemic toxicity, relative bradycardia, rose spot rash, ileus → pea-soup diarrhea, bacteremia.
	Other	*Yersinia*: undercooked pork; unpasteurized milk, abd pain → "pseudoappendicitis" (aka mesenteric adenitis) *Aeromonas*, *Pleisomonas*, *Listeria* (meats & cheeses)
Parasitic	*E. histolytica*	Contaminated food/water, travel (rare in U.S.); liver abscess
Viral	CMV	Immunosuppressed; dx by shell vial cx of colon bx

Evaluation (*NEJM* 2009;361:1560 & *Gastro* 2009;136:1874)

- **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 H_2O, 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/ H_2O) 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

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

Diagnosis
- **Stool ELISA**: detects toxin A and/or B; fast (2–6 h); Se 90–95% if A+B tested. If high clinical suspicion and 1st test ⊖ consider repeating × 1 (*CID* 2008;46:S12).
- 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 postcessation of sx 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. boulardii, 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)

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

Medications (cause ↑ secretion, ↑ motility, Δ flora, ↑ cell death, or inflammation)
- PPI, colchicine, abx, H_2RA, SSRIs, ARBs, NSAIDs, 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 s/s: 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 ceph × 10–14 d → Bactrim for ≥1 y
- **Bacterial overgrowth**: ↑ small intestinal bacteria from incompetent/absent ileocecal valve, s/p RYGB, scleroderma, diabetes, s/p vagotomy → fat & CHO malabsorption. Dx: ⊕ ^{14}C-xylose & H^+ breath tests; Rx: cycled 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)

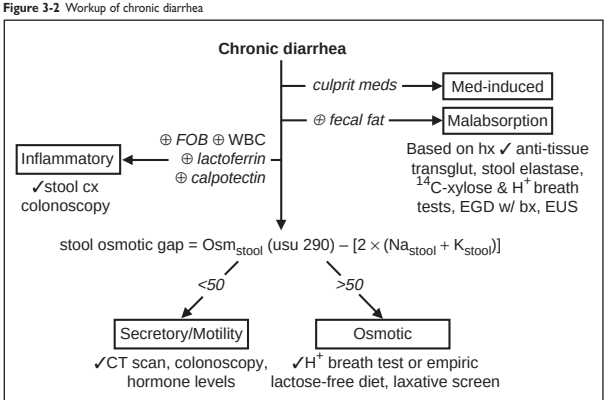
Secretory (normal osmotic gap, no Δ diarrhea after NPO, nocturnal diarrhea freq described)

- **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/ Δ freq of stool, (iii) onset w/ Δ in form of stool
  Rx sx-guided (*AJG* 2009;104:51). *Pain*: antispasmodics, TCA, SSRI. *Bloating*: rifaximin, probiotics. *Diarrhea*: loperamide, alosetron (5-HT_3 antagonist) for women (↑ risk of ischemic colitis). *Constipation*: ↑ fiber 25 g/d, lubiprostone (Cl^- channel activator); tegaserod (5-HT_4 agonist) withdrawn due to CV risk.
- Scleroderma; diabetic autonomic neuropathy; hyperthyroidism; amyloidosis; s/p vagotomy

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)
  Lubiprostone (see IBS). Methylnaltrexone for opioid-induced *(NEJM 2008;358:2332)*.

Adynamic ileus

- Definition: loss of intestinal peristalsis in absence of mechanical obstruction
  Ogilvie's = acute colonic adynamic ileus in presence of competent ileocecal valve
- 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

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** → ↑ stool transit time and ↓ stool volume → ↑ intraluminal pressure → herniation at site of relative muscle weakness where vasa recta penetrate to supply blood to colonic mucosa and submucosa

Epidemiology

- Prevalence higher w/ ↑ age (10% if <40 y; 50–66% if >80 y); "Westernized" societies
- **Left side** (90%, mostly sigmoid) > 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 → fecalith formation → obstruction → compromise of diverticulum's blood supply, infection, perforation
- **Uncomplicated**: microperforation → localized infection
- **Complicated** (25%): macroperforation → abscess, peritonitis, fistula (65% w/ bladder), obstruction, stricture

Clinical manifestations

- **LLQ abdominal pain**, **fever**, nausea, vomiting, constipation
- PEx ranges from LLQ tenderness ± palpable mass to peritoneal signs & septic shock
- Ddx includes IBD, infectious colitis, PID, tubal pregnancy, cystitits, colorectal cancer

Diagnostic studies

- Plain abdominal radiographs to r/o free air, ileus, or obstruction
- **Abdominal CT** (I^+O^+): >95% Se & Sp; assess complicated disease (abscess, fistula)
- Colonoscopy *contraindicated* acutely ↑ risk of perforation; do 6 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 abcess, 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 ± 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 → weakening of vascular wall → 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; ~20% recur

Diagnostic studies

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

Treatment

- Colonoscopy: epinephrine injection ± 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

Epidemiology & Pathophysiology (*Lancet* 2007;369:1627 & *NEJM* 2009;361:2066)
- 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 with ↓ Hct, ↑ ESR, fever, hypotension, >6 bloody BMs per day, distended abdomen with absent bowel sounds
- Extracolonic (>25%): erythema nodosum, pyoderma gangrenosum, aphthous ulcers, uveitis, episcleritis, thromboembolic events (espec during a flare; *Lancet* 2010;375:657), AIHA, seroneg 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 + descending colon, 50–70%), and pancolitis (20%)
- Appearance: granular, friable mucosa with 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 perf. 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%; continual active disease in ~18%. Rate of colectomy at 10 y is 24%.
- Mortality rate of severe UC flare is <2%, & overall life expectancy in UC = non-UC Pts

CROHN'S DISEASE (*Lancet* 2007;369:1641)

Clinical manifestations
- **Smoldering disease with abd pain,** fevers, malaise, wt loss
- Mucus-containing, **non-grossly bloody diarrhea;** n/v, bloating, obstipation
- ↓ albumin, ↑ ESR/CRP, ↓ Hct (due to Fe, B_{12}, 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 with *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** with 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, enterocutaneous
- **Abscess**: fever, tender abd mass, ↑ WBC; *steroids mask sx*, ∴ need high-level suspicion
- **Malabsorption**: illeal disease/resection: ↓ bile acids abs → gallstones; ↓ fatty acid abs → Ca oxalate kidney stones; ↓ fat soluble vitamin abs → Vit D deficiency → osteopenia

Prognosis
- Highly 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 ↓

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 → maintain remission; mucosal healing 1° goal
- Convention has been step-up Rx (least → most toxic). Recent shift to early and/or combined immunomodulation to improve disease outcome (*Lancet* 2008;371:660 & *NEJM* 2010;362:1383).

Induction of Remission (Acute Flare Treatment)	
Ulcerative Colitis	
5-ASA	For mild dis. (≤4 BMs/d w/o systemic toxicity). *PR* if disease distal to splenic flexure. *PO* if more extensive: 2.4–4.8 g/d mesalamine (released in ileum/colon), olsalazine (colon), sulfasalazine (avoid if sulfa allergy).
Steroids	Mod dis. (≤6 BMs/d w/ minimal systemic tox) → PO prednisone. Severe dis. (>6 BMs/d w/ systemic tox) → IV. PR only in mild distal dis.
Anti-TNFα	Mod/Severe flare unresponsive to steroids, flare on immunomodulators. Infliximab: ~20% remission by 30 wks (*NEJM* 2005;353:2462)
CsA	Severe flare: 2 mg/kg infusion × 24 h; ✓ Mg; avoid if low chol (seizures)
Surgery	J pouch anal anastamosis; ~6% fail; pouchitis: Rx w/ abx, probiotics
Crohn's Disease	
Abx	FQ/MNZ or amox/clav; best for perianal disease, limited data for colonic CD
Steroids	*Mild dis.* (tolerating POs, w/o >10% wt loss): consider budesonide w/ ileal dis. (1st-pass metabolism limits systemic adverse effects) *Mod dis.* (wt loss, abd pain, nausea, anemia): PO prednisone *Severe dis.* (fever, obstruction, cachexia): IV pred ~1 mg/kg w/o immunomod at 1 y ~30% remission, 30% steroid-depend, 40% surgery
Anti-TNFα	Indic as above for UC, though *early Rx* prior to steroid failure gaining favor. Infliximab (chimeric), adalimumab (humanized), or certolizumab (pegylated). Inflixi + AZA → ~60% steroid-free clin remission by 6 mos (*NEJM* 2010;362:1383).
Other	Surgery: diverting ileostomy, especially good for perineal disease anti-α4β1 integrin (natalizumab): rare risk of PML, restricted use in CD In clinical trials: anti-IL12/23 (ustekinamab), anti-α4β7 integrin (vedolizumab)

Maintenance of Remission (Chronic Treatment)	
Ulcerative Colitis	
5-ASA	Effective in maintaining remission in mild/mod UC
6MP/AZA	Takes 2–4 mos before treatment response
Anti-TNFα	Infliximab: ↓ colectomy rates & ↑ mucosal healing
Crohn's Disease	
6MP/AZA	As above w/ UC; also effective for maintenance in Pts w/ fistulae
Anti-TNFα	↓ surg, ↓ hosp, ↑mucosal healing; ~30% remission at 1 y If flare on infliximab: ↑ dose, ↑ freq, or Δ to adalimumab (*Annals* 2007;146:829)
MTX	15–25 mg IM/SC or PO qwk; 1–2 mos to take effect (*NEJM* 2000;342:1627)

Complications of therapy (*Clin Gastro Hep* 2009;7:874)

- **Anti-TNFα**: reactivation TB; must doc ⊖ PPD prior to Rx. If ↑ LFTs, must exclude viral hepatitis. Small ↑'d risk of NHL. Other: infusion rxn; lupus-like rxn, psoriasis, MS, CHF.
- **6MP/AZA**: BM suppression, lymphoma, pancreatitis, hepatitis; ✓ TPMT genotype prior to dosing to ↓ risk of generation of toxic metabolites
- **5-ASA**: diarrhea, abd pain, pancreatitis

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 bxs 8 y 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.

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, ⊕ N/V; 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% ↑WBC; ↑ amylase & 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 to >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 overdistension 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

PANCREATITIS

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 microlithiasis
- **Alcohol** (30%): ♂>♀, usually chronic, w/ acute flares
- Drugs (occur via hypersensitivity, toxic metab, or direct toxicity): furosemide, thiazides, sulfa, DDI, asparaginase, estrogen, 6-MP/AZA, 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% with asx ↑ 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**, radiating to back, constant, some relief w/ leaning forward
- Nausea and vomiting
- Ddx: acute cholecystitis, perforated viscus such as DU, intestinal obstruction, mesenteric ischemia, IMI, AAA leak, distal aortic dissection, ruptured ectopic pregnancy

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
    - false ⊖: acute on chronic (eg, alcoholic); hypertriglyceridemia (↓ amylase activity)
    - false ⊕: other abd or salivary gland process, acidemia, renal failure, macroamylasemia (amylase binds to other proteins in serum, cannot be filtered out)
  - ↑ **lipase**: more specific than amylase
    - false ⊕: renal failure, other abd process, diabetic ketoacidosis, HIV, macrolipasemia

  ALT >3 × ULN suggests gallstone pancreatitis (*Am J Gastro* 1994;89:1863); Aϕ, bili not helpful
  Other labs (see Prognosis): ↑WBC, ↑ or ↓ Hct, ↑ BUN, ↓ Ca, ↑ glc
- 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 b/c theoretical concern of ↑ necrosis w/ IV contrast; defer if concomitant ARF).
  Abd U/S: 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/MRCP: can detect necrosis; also used to assess for stones & ductal disruption
  Endoscopic U/S (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)
  Nutrition: enteral preferred over TPN if NPO >7 d; ↓ infectious complications & disease severity, & trend toward ↓ mortality (*BMJ* 2004;328:1407). Ideally NJ tube, but NG okay.
  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 suggested by persistent pain & elevation of amylase or lipase, or mass on exam most resolve spont.; if >6 cm or persists >6 wks + pain → endo/perc/surg drainage
- **Sterile pancreatic necrosis** (20%): area of nonviable pancreatic tissue
  ? prophylactic abx (see above); supportive measures, surgery if Pt unstable
- **Infection** (5% of all cases, 30% of severe): usually 2° 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 with 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 (*Gastro* 2007;132:2022)

- 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) identifies Pts 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

Ranson's Criteria	
At diagnosis	**At 48 hours**
age >55	Hct ↓ >10%
WBC >16,000/mm^3	BUN ↑ >5 mg/dL
glucose >200 mg/dL	base deficit >4 mEq/L
AST >250 U/L	Ca <8 mEq/L
LDH >350 U/L	P_aO_2 <60 mmHg
	fluid sequestration >6 L

Prognosis	
# of criteria	**Mortality**
≤2	<5%
3–4	15–20%
5–6	40%
≥7	>99%

(*Am J Gastro* 1982;77:633)

CT Grade	Description	Points
A	Normal pancreas c/w mild pancreatitis	0
B	Enlarged pancreas but w/o inflammation	1
C	Pancreatic or peripancreatic inflammation	2
D	Single peripancreatic fluid collection	3
E	≥2 Peripancreatic fluid collections or gas in pancreas/retroperitoneum	4

Necrosis	Points
<33%	2
33–50%	4
>50%	6

Total Index	Mortality
0–3	3%
4–6	6%
7–10	17%

(*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. ⊕ fecal fat, ↓'d stool elastase & chymotrypsin, Ca^{2+} 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

Tests of hepatocellular injury or cholestasis

- **Aminotransferases** (AST, ALT): intracellular enzymes released 2° necrosis/inflammation
  ALT more specific for liver than is AST (heart, skeletal muscle, kidney, brain, RBC/WBC)
  ALT > AST → viral hepatitis or fatty liver/nonalcoholic steatohepatitis (pericirrhotic)
  AST:ALT >2:1 → alcoholic hepatitis, cirrhosis, NAFLD; nonhepatic source
  ALT/AST >15× ULN → etiologies of acute liver failure (↑↑↑ LDH → ischemia/toxic)
- **Alkaline phosphatase** (Aϕ): enzyme bound in hepatic canicular membrane besides liver, also found in bone, intestines, kidney, and placenta
  confirm liver origin with: ↑ 5'-NT, ↑ GGT, or Aϕ heat fractionation
  ↑ levels seen with biliary obstruction or intrahepatic cholestasis (eg, hepatic infiltration)

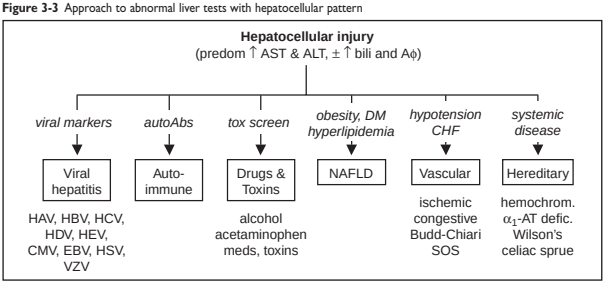
Tests of hepatic function

- **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 (most sensitive to detect parenchymal disease); either conjugated (direct) or unconjugated (indirect)

Patterns of liver injury

- **Hepatocellular**: ↑↑ aminotransferases, ± ↑ bilirubin or Aϕ
  ↑↑↑ ALT & AST (>1000): severe viral hepatitis, acetaminophen, ischemia, Wilson's, AIH
- **Cholestasis**: ↑↑ Aϕ and bilirubin, ± ↑ aminotransferases
- **Isolated hyperbilirubinemia**: ↑↑ bilirubin (direct or indirect), nl Aϕ and aminotransferases
- **Infiltrative**: ↑ Aϕ, ± ↑ 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



- **Acute workup**: toxins (EtOH, acetaminophen) & vascular abnl (U/S w/ Doppler)
  viral tests: HAV IgM, HBV sAg, HCV RNA, HEV Ab, ± EBV, CMV, HSV, VZV
  autoimmune (ANA, ASMA, ALKM) & ceruloplasmin
- **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

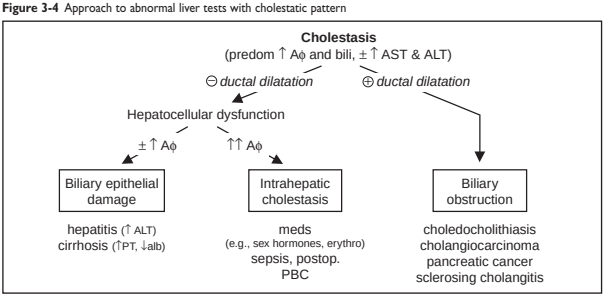


Figure 3-5 Approach to abnormal liver tests with isolated hyperbilirubinemia

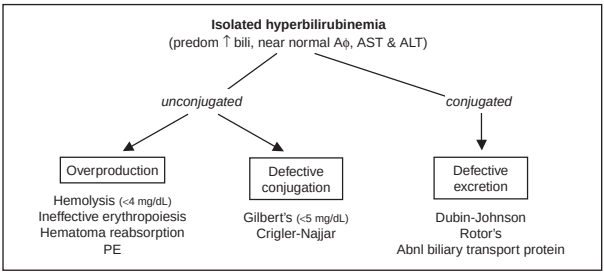
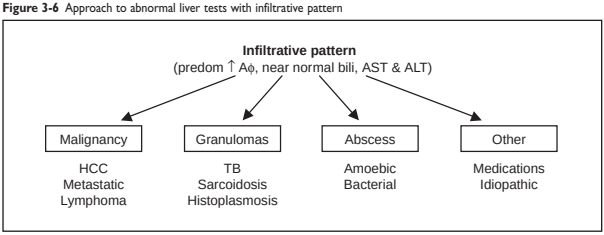


Figure 3-6 Approach to abnormal liver tests with infiltrative pattern



Abnormal liver tests in asymptomatic patients (*Gastro* 2002;123:1364)

- Careful review of history (**meds**, **ETOH**/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 ↑ Aϕ (✓ GGT) or AST>ALT (✓ 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, α_1-AT; ✓ U/S & consider liver bx
  - If still ⊖ → liver bx if ALT or AST >2× ULN 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 ⊖: Aϕ >1.5× ULN → consider bx; Aϕ <1.5× ULN → observe
- **Isolated hyperbilirubinemia**: ✓ conjugated vs. unconjugated
  - conjugated → perform abdominal U/S → MRCP if dilatation or obstruction; if nl ultrasound ✓ AMA and consider MRCP or liver bx
  - unconjugated → ✓ Hct, retic count, smear, LDH, haptoglobin

Common medications that cause abnormal liver tests

Hepatocellular		Cholestatic		Mixed
Acarbose	Methotrexate	Amox/Clav	Estrogens	Amitriptyline
Acetaminophen	NSAID	Anabolic Steroids	Irbesartan	Azathioprine
Allopurinol	Omeprazole	Chlorpromazine	Mirtazapine	Captopril
Amiodarone	Paroxetine	Clopidogrel	Phenothiazine	Carbamazepine
Baclofen	Pyrazinamide	OCP	Terbinafine	Clindamycin
Bupropion	Rifampin	Erythromycins	Tricyclics	Enalapril
Fluoxetine	Risperidone			Nitrofurantoin
HAART	Sertraline			Phenobarbital
Isoniazid	Statins			Phenytoin
Ketoconazole	Tetracyclines			Sulfonamides
Lisinopril	Trazodone			Trazodone
Losartan	Valproic Acid			Verapamil

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

VIRAL

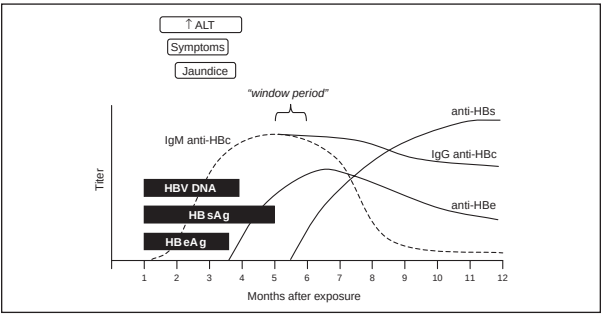
Hepatitis A (ssRNA; accounts for 30–45% of acute viral hepatitis)

- 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%), 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



(Adapted from Friedman LS, Keeffe EB. Serologic course of HBV. *Handbook of Liver Disease* 2004; Hoofnagle JH, DiBisceglie AM. Serologic diagnosis of acute and chronic viral hepatitis. *Semin Liver Dis* 1991;11:73.)

Diagnosis	HbsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV DNA
Acute hepatitis	⊕	⊖	IgM	⊕	⊖	⊕
Window period	⊖	⊖	IgM	±	±	⊕
Recovery	⊖	⊕	IgG	⊖	±	⊖
Immunization	⊖	⊕	⊖	⊖	⊖	⊖
Chronic hepatitis *HBeAg* ⊕	⊕	⊖	IgG	⊕	⊖	⊕
Chronic hepatitis *HBeAg* ⊖	⊕	⊖	IgG	⊖	⊕	±*

*__Precore mutant:__ HBeAg not 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 IFNα-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 immunosuppresion/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, EtOH, HIV; HCC in 2–5% of cirrhotics/y
- Extrahepatic syndromes: cryoglobulinemia, porphyria cutanea tarda (blistering rash in sun-exposed areas), MPGN, MGUS, IPF, 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-IFNα-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)
- Drugs: **PEG-IFNα-2a** + **ribavirin** *(Gastro 2010;138:108)*. Goal is *sustained virologic response* (SVR) = absence of viremia 24 wks after completion of Rx. PIs (telaprevir, boceprevir) promising *(NEJM 2009;360:1827 & 1839; 2010;362:1292)*.
- 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 dysfxn, marrow suppression (can give EPO & GCSF), hemolysis (ribavirin), sexual dysfxn
- Contraindic.: 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
- Pathogenesis: requires HBV to cause either simultaneous or superimposed infection
- Natural hx: in HBV ↑ severity of infxn and ↑ progression to cirrhosis; clears w/ HBV
- Serologic/virologic tests: anti-HDV; follow HDV RNA during Rx (high relapse rate)

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); Mediterranean
- Overlap syndrome: autoimmune hepatitis + PBC or PSC

Diagnosis and Treatment

- ¾ female; 40% present acutely (occ fulminant); 34% asymptomatic; ALT can be >1,000
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs, ⊕ hemolytic anemia
- Dx: scoring system combining serologies, ↑ IgG, ∅ viral hepatitis, & characteristic liver bx (lymphoplasmocytic infiltrate & interface hepatitis) has high Sp & mod Se (*Hep* 2008;48:169)
- Rx: if LFTs 10× ULN, or if 5× ULN w/ IgG 2× ULN, or bridging/multiacinar necrosis on bx
- **Prednisone** ± azathioprine → 65% remission w/in 3 y; 50% relapse on withdrawal of meds at 6 mos; up to 90% by 3 y; ∴ most will require long-term Rx
- Liver transplant for ESLD; recurs in ~40% of Pts, but generally easily treated

OTHER CAUSES OF HEPATITIS OR HEPATOTOXICITY

Alcoholic hepatitis (*NEJM* 2009;360:2758)

- Sxs: can range from asx hepatomegaly to decompensation w/ ascites, encephalopathy, and death. AST & ALT usually <300–500 w/ AST:ALT >2:1, in part b/c concomitant B_6 defic (ALT can be normal); ↓ plt, ↑ iron sat, ↑'d Tbili & INR indicate severe hepatitis.
- Rx: if discriminant fxn (= 4.6 × [PT-control] + Tb in mg/dL) >32 or encephalopathy methylprednisolone 32 mg/d × 4 wks → 4–6 wk taper; ↓ death (*NEJM* 1992;326:507) contraindications: GIB, chronic HBV, sepsis
  pentoxifylline 400 mg tid ↓ mortality due to reduction in HRS (*Coch* 2009;4:CD007339)
- Lille model predicts nonresponse to corticosteroids & mortality, powered by Δ Tb from day 1→7; nonresponders have 6-mo survival of 25% (www.lillemodel.com & *Hep* 2007;45:1348)

Acetaminophen hepatotoxicity (*Clin Liv Dis* 2007;11:525 & *NEJM* 2008;359:285)

- Normal metabolism via glucuronidation and sulfation → nontoxic metabolites
- Overdose (usually >10 g): CYP2E1 hydroxylation → reactive electrophilic species (NAPQI) that are scavenged by glutathione until reserves exhausted → hepatotoxicity
- CYP2E1 *induced* by fasting and alcohol allowing for "therapeutic misadventure" in malnourished alcoholics taking even low doses (2–6 g) of acetaminophen
- Liver dysfunction may not be apparent for 2–6 d
- Rx: NG lavage, activated charcoal if w/in 4 h. Consider early transfer to transplant ctr.
  N-acetylcysteine: administer up to 72 h after ingestion, if time of ingestion unknown, *or* if chronic ingestion >4 g per day
  Rumack-Matthew nomogram predicts risk of hepatotoxicity from a given serum level of acetaminophen when time of ingestion is known (see Appendix)
  Low threshold to start NAC even w/ low or undetectable serum acetaminophen levels
  PO NAC (preferred): 140 mg/kg loading dose → 70 mg/kg q4h × 17 additional doses
  IV NAC: 150 mg/kg over 1h → 50 mg/kg over 4 h → 100 mg/kg over 16 h; risk of anaphylaxis; use if unable to tolerate POs, GIB, preg, fulminant hepatic failure

Ischemic hepatitis

- "Shock liver" w/ AST & ALT >1000 + ↑↑ LDH; delayed ↑↑ Tbili
- 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
- Prevalence: 20–30% of U.S. population. Risk factors: DM & metabolic syndrome (hyperinsulinemia, obesity, ↑ TGs), HAART, tamoxifen, amiodarone, TPN, rapid wt loss. Variants in apolipoprotein C3 gene a/w ↑ TG & risk of NAFLD (*NEJM* 2010;362:1082).
- 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 wks; subfulminant = develops between 8 wks 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, amiodarone, PTU, valproate
  - Toxins: fluorinated hydrocarbons, CCl_4, *Amanita phalloides*
- **Vascular**: ischemic hepatitis, Budd-Chiari syndrome, hepatic SOS, 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 = ΔMS; 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 O_2 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% of Pts): 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)

Treatment (*Hep* 2005;41;1179 & *Nat Rev Gastro Hep* 2009;6:542)
- **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; ? recomb. factor VIIa; 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, Cr >3.4, 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** (~10%): chronic HBV, HCV, HDV infection
- **Autoimmune hepatitis**: female, ↑ IgG, ⊕ ANA, anti–smooth muscle Ab
- **Metabolic diseases** (~5%): hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency
- **Biliary tract diseases** (~5%): primary biliary cirrhosis, secondary biliary cirrhosis (calculus, 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 portal HTN (ascites, varices); 35% p/w fever (SBP, acute EtOH); 25% p/w hematemesis

Physical exam
- Liver: *initially* enlarged, palpable (L lobe predom), firm; *eventually* shrunken and nodular
- Signs of liver failure: jaundice (bili >2), spider angiomata & palmar erythema (↑ estradiol), Dupuytren's contractures, white nail lines (Muehrcke's lines) & proximal nail beds (Terry's nails), ↑ parotid & lacrimal glands, gynecomastia, testicular atrophy, asterixis, encephalopathy, fetor hepaticus, clubbing, hypertrophic osteoarthropathy
- Signs of portal hypertension: splenomegaly, ascites, dilated superficial abdominal veins (caput medusae), epigastric Cruveilhier-Baumgarten venous hum

Laboratory studies
- ↑ **bilirubin**, ↑ **PT** (poor correlation w/ bleeding; factor VIII nl as not synthesized by liver), ↓ **alb**, ± ↑ aminotransferases (AST > ALT if late) and ↑ Aϕ (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, ✓ patency of portal, splenic, and hepatic veins
- 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, α_1-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 H_2O 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
  ∅ NSAID as interferes w/ 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: 2° 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)

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 GIB
- Can p/w encephalopathy, abd pain, fever, *but often (25%) asx*; ∴ consider paracentesis in all hospitalized cirrhotics w/ ascites
- Micro: 70% GNR (*E. coli*, *Klebs*), 30% GPC (*Enterococcus*, *S. pneumo*), nosocomial (fungi, *Pseud*)
- Rx: cefotaxime 2 gm IV q8h (or amox/clav) × 5 d; if ∅ 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
- Ppx: if h/o SBP or AFTP <1.5 + Na <130, Cr >1.2 or Child-Pugh B (*Am J Gastro* 2009;4:993)
  norfloxacin 400 mg PO qd or Bactrim DS qd; beware quinolone resistance

Gastroesophageal varices ± UGIB (see also "GIB"; *NEJM* 2010;362:823)

- At risk if HVPG >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
  nonselective β-blockers: ~50% ↓ risk of bleeding ± ↓ mortality
  no benefit in preventing varices (*NEJM* 2005;353:2254), but do ↓ progression in size
  nadolol or propanolol (ideally titrate to HVPG; often titrate to 25% ↓ HR)
  EGD not req. to document improvement
  endoscopic band ligation (EBL): ↓ bleeding & mortality ≈ βB (*Am J Gastro* 2007;102:2842)
  q1–2wk until gone → survey EGD at 3 mo → q6–12mo; adding βB only ↑ side effects
  βB vs EBL: choice based on Pt/physican preference, βB often 1st (*Hep* 2008;47:1764)
- 2° prevention: for all Pts after 1st bleed b/c ~50% rebleed & ~30% mortality
  βB + EBL > either alone (*Annals* 2008;149:109); if refractory → TIPS or liver transplant

Portosystemic (hepatic) encenphalopathy (PSE)

- Pathogenesis: failure of liver to detoxify NH_3 + other substances that cause cerebral edema and/or act as false neurotrasmitters (GABA-like)
- Precipitants: ↑ dietary protein, constipation, GIB, med noncompliance, infection, azotemia, ↓K, Δ volume/water, hypoxia, HCC, portosystemic shunt, meds, portal vein thrombosis
- Stages: (1) confusion; (2) drowsiness; (3) stupor; (4) coma
- Dx: asterixis can be seen; NH_3 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: $NH_3 \rightarrow NH_4^+$); goal 2–4 stools/d *or* **rifaximin** 400 mg tid (↓ gut bacteria → ↓ NH_3 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 Δs
- Definition: progressive azotemia (Cr >1.5 or >1.5 × base) 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 cirrhotics 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, U_{Na} <10 mEq/L 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 + terlipressin (*Gastro* 2008;134:1352 & 1360); ? TIPS; definitive Rx = *liver transplant*

Other complications

- **Hepatopulmonary syndrome** (*NEJM* 2008;358:2378)
  Defintion/etiology: abnl pulm gas exchange (A-a gradient ≥15 or P_aO_2 <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: O_2; 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**: ↓ inotopic & chronotropic response, ↓ systolic and diastolic fxn, prolonged QT, hyperkinetic circulation; ↑ troponin, BNP (*Gut* 2008;57:268)
- **Infxns:** Kuppfer cell (hepatic mϕ) dysfxn, ↓ opsonic activity; vaccinate for HAV & HBV, influenza yearly, pneumonia
- **Hepatocellular carcinoma**: incidence ~3.5%/y (↑ 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* 2007;5:508), though CT/MRI more sensitive
- Diabetes (15–30%): due to altered glc & insulin metabolism

Prognosis

Modified Child-Turcotte-Pugh Scoring System			
	Points scored		
	1	2	3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Grade I or II	Grade III or IV
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (sec > control) or INR	<4 <1.7	4–6 1.8–2.3	>6 >2.3
	Classification		
	A	B	C
Total points	5–6	7–9	10–15
1-y survival	100%	80%	45%

- **MELD** (Model for End-Stage Liver Disease): used to stratify Pts on liver transplant list & to predict 3-mo survival in Pts w/ various underlying forms of liver disease & complications. Based on Cr, INR, & total bili. Calculator: www.mayoclinic.org/meld/mayomodel6.html. If MELD <21 additional predictors of mortality include Na <130 (*NEJM* 2008;359:1018 & *Clin Gastro Hep* 2009;7:1236), refractory ascites, ↑ HVPG, and low quality of life.

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

Hereditary hemochromatosis (*Lancet* 2007;370:1855; *Hepatology* 2008;48:991)

- Recessive disorders of iron sensing (hepcidin) and transport (transferrin) → tissue **iron overload**; nonhereditary: ineffect. erythropoiesis ± transfusions
- *HFE* mutations (85% of cases), typically C282Y homozygotes (~0.5% of N. European Caucasians), rarely C282Y/H63D compound heterozygotes; *HJV* mut. → juvenile onset. C282Y homozygotes: 28% of ♂ develop sx (88% lab abnl), and 1% of ♀ develop sx (due to menses ↓ Fe load → later presentation). C282Y/H63D: only 1.5% manifest dis.
- Sx: fatigue & arthralgias. In *advanced disease* (rare): bronze skin (melanin + iron), hypogonadism (espec. in juvenile onset), DM, arthropathy (MCP), CHF, infxns (*Vibrio*, *Listeria*, *Yersinia*), cirrhosis (↑ risk if EtOH/fatty liver disease; 15% risk of HCC). Disease also a/w ALS & porphyria.
- Dx: iron sat >45% (iron/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 ⊕). Liver bx to assess damage if: HFE ⊕ *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 (↓ intestinal iron transport); deferoxamine if phleb. contraindic.; genetic counseling

Wilson's disease (*Lancet* 2007;369:397 & *Hepatology* 2008;6:2089)

- 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 (⊕ 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*, Alϕ/bili <4 + AST/ALT >2 better Se & Sp than urine Cu or ceruloplasmin (*Hepatology* 2008;4:1167). 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 asx or in conjuction w/ chelation (must give 4–5 h apart from chelators).

α_1-antitrypsin deficiency (α_1-AT) (*NEJM* 2009;360:2749)

- Abnl α_1-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 α_1-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 α_1-AT, ∴ only COPD and not liver dz (no polymerization)
- Treatment: standard Rx for cirrhosis/chronic liver dis.; α_1-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 IL12α & 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: ↑ Aϕ, ↑ bili, ↑ 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, ↑ Aϕ, ⊕ 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

Portal vein thrombosis (PVT) (*Al Phar Ther* 2009;30:881)

- Definition: thrombosis, constriction, or invasion of portal vein → portal HTN → varices. Isolated splenic vein thrombosis (eg, 2° to pancreatitis) → isolated gastric varices.
- Etiologies: cirrhosis, neoplasm (pancreas, HCC), abdominal infxn → pylephlebitis (infected thrombosis of PVT), hypercoag state (incl MPS), panceatitis, IBD, surgery, trauma
- Clinical manifestations
  - **acute PVT**: can p/w pain; often asx and dx as incidental finding on U/S or CT if mesenteric vein involved may p/w intestinal infarct; if fevers consider pylephlebitis
  - **chronic PVT**: asx/incidental finding; may p/w s/s of **portal HTN** → hematemesis 2° variceal bleeding, splenomegaly, mild encephalopathy; ascites rare unless cirrhosis
- Diagnostic studies: LFTs usually normal; U/S w/ Doppler, MRA, CT (I^+), angiography; "portal cavernoma" network of hepatopedal collaterals in chronic PVT—can rarely cause biliary obstruction and cholestatic 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 > bleed risk
  - Varices: screen at dx; no evidence for 1° ppx of bleed; if bleed endoscopic Rx and βB. If refractory bleed consider TIPS, shunt. Isolated gastric varices 2° splenic vein thrombosis: splenectomy is curative.

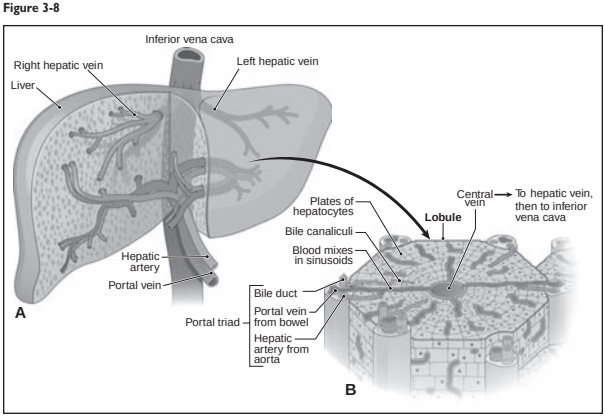
Budd-Chiari syndrome (*NEJM* 2004;350:578)

- 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 & Aϕ; Doppler U/S of hepatic veins (85% Se & Sp); CT (I^+) or 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 → warfarin), 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, chemo (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



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

Pathophysiology

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

Etiologies	
Portal hypertension related SAAG ≥1.1	**Nonportal hypertension related SAAG <1.1**
Sinusoidal	**Peritonitis:** TB, ruptured viscus (↑ amy)
cirrhosis (81%), including SBP	**Peritoneal carcinomatosis**
acute hepatitis	Pancreatitis
extensive malignancy (HCC or mets)	Vasculitis
Postsinusoidal	Hypoalbuminemic states: nephrotic syndrome, protein-losing enteropathy
right-sided CHF incl. constriction & TR	Meigs' syndrome (ovarian tumor)
Budd-Chiari syndrome, SOS	Bowel obstruction/infarction
Presinusoidal (a/w varices > ascites)	Postoperative lymphatic leak
portal or splenic vein thrombosis, schisto	

Symptoms

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

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

- Physical exam: flank dullness (NPV ~90%; >1500 mL needed), shifting dullness (Se ~83%)
- Radiologic: **U/S** detects >100 mL; MRI/CT scan (also help with Ddx)
- **Paracentesis** (*NEJM* 2006;355:e21; *Dig Dis Sci* 2007;52:3307): perform in all Pts w/ new ascites and consider in all hospitalized cirrhotics w/ ascites; complic. <1% (bleeding, but risk not related to PT or plt count; *Hepatology* 2004;40:484); U/S ↑ success but does not ↓ complic.
- **Serum-ascites albumin gradient (SAAG)**: ~95% acc. for portal HTN (*Annals* 1992;117:215)
  ≥1.1 g/dL → portal hypertension related; <1.1 g/dL → non–portal hypertension related
  if portal HTN + another cause (seen 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, Aϕ (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

Type	Ascites cell count/mm^3	Ascites culture
Sterile	<250 polys	⊖
Spontaneous bacterial peritonitis (SBP)	≥250 polys	⊕ (1 organism)
Culture-⊖ neutrocytic ascites (CNNA)	≥250 polys	⊖
Nonneutrocytic bacterascites (NNBA)	<250 polys	⊕ (1 organism)
Secondary	≥250 polys	⊕ (polymicro)
Peritoneal dialysis-associated	≥100, poly predom.	⊕

- **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, Aϕ >240
  Rx: 3rd-gen. ceph + metronidazole; urgent abdominal imaging ± ex lap
- **Peritoneal dialysis-associated**: cloudy fluid, abd pain, fever, nausea
  pathogens: 70% GPC, 30% GNR; Rx: vanc + gent (IV load, then administer in PD)

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 + gallbladder hypomotility → 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;302:2001)

Types of gallstones

- Cholesterol (90%): 2 subtypes
  - mixed: contain >50% cholesterol; typically smaller, multiple stones
  - pure: 100% cholesterol; larger, yellow, white appearance
- Pigment (10%)
  - *Black:* unconjugated 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, Aϕ, 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 piperacillin-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

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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, Aϕ; 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, Aϕ, amylase; ⊕ BCx
- ERCP; percutaneous transhepatic cholangiogram (if ERCP unsuccessful)

Treatment
- **Antibiotics** (broad spectrum) to cover common bile pathogens (see above) ampicillin + gentamicin (or levofloxacin) ± MNZ (if severe); carbapenems; pip/tazo
- ~80% respond to conservative Rx and abx → biliary drainage on elective basis
- ~20% require **urgent biliary decompression** via ERCP (papillotomy, stone extraction, and/or stent insertion). If sphincterotomy cannot be performed (larger stones), decompression by biliary stent or nasobiliary catheter can be done; otherwise percutaneous transhepatic biliary drainage or surgery.

GENERAL

Definitions

- **Acidemia** → pH <7.36, **alkalemia** → pH >7.44
- **Acidosis** → process that increases $[H^+]$; **alkalosis** → process that decreases $[H^+]$
- Primary disorders: metabolic acidosis or alkalosis, respiratory acidosis or alkalosis
- Compensation
  respiratory: hyper- or hypoventilation alters P_aCO_2 to counteract 1° metabolic process
  renal: excretion/retention of H^+/HCO_3 to counteract 1° respiratory process
  respiratory compensation occurs in min; renal compensation takes hrs to days
  compensation never fully corrects pH; if pH normal, consider mixed disorder

Consequences of Severe Acid-Base Disturbances		
Organ System	**Acidemia (pH <7.20)**	**Alkalemia (pH >7.60)**
Cardiovascular	↓ contractility, arteriolar vasodilation ↓ MAP & CO; ↓ response to catecholamines ↑ risk of arrhythmias	Arteriolar vasoconstriction ↓ coronary blood flow ↑ risk of arrhythmias
Respiratory	Hyperventilation, ↓ resp muscle strength	Hypoventilation
Metabolic	↑ K	↓ K, ICa, Mg, PO_4
Neurologic	Δ MS	Δ MS, seizures

(*NEJM* 1998;338:26 & 107)

Workup

- Determine **primary disorder**: ✓ pH, P_aCO_2, HCO_3
- Determine if **degree of compensation** is appropriate

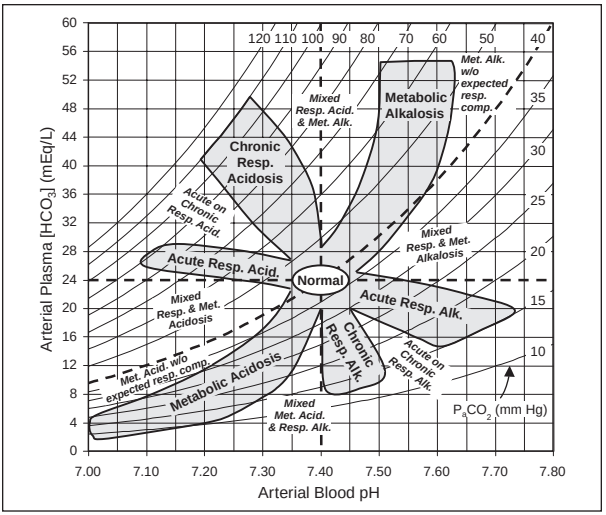
Primary Disorders				
Primary disorder	**Problem**	**pH**	**HCO_3**	**P_aCO_2**
Metabolic acidosis	gain of H^+ or loss of HCO_3	↓	⇓	↓
Metabolic alkalosis	gain of HCO_3 or loss of H^+	↑	⇑	↑
Respiratory acidosis	hypoventilation	↓	↑	⇑
Respiratory alkalosis	hyperventilation	↑	↓	⇓

Compensation for Acid/Base Disorders	
Primary disorder	**Expected compensation**
Metabolic acidosis	↓ $P_aCO_2 = 1.25 \times \Delta HCO_3$ or $P_aCO_2 = (1.5 \times HCO_3) + 8 \pm 2$ (also, P_aCO_2 = last two digits of pH)
Metabolic alkalosis	↑ $P_aCO_2 = 0.75 \times \Delta HCO_3$
Acute respiratory acidosis	↑ $HCO_3 = 0.1 \times \Delta P_aCO_2$ (also, ↓ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory acidosis	↑ $HCO_3 = 0.4 \times \Delta P_aCO_2$ (also, ↓ pH = $0.003 \times \Delta P_aCO_2$)
Acute respiratory alkalosis	↓ $HCO_3 = 0.2 \times \Delta P_aCO_2$ (also, ↑ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory alkalosis	↓ $HCO_3 = 0.4 \times \Delta P_aCO_2$

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

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

Figure 4-1 Acid-Base nomogram



NB, If ABG not available, can use VBG, but note that pH ~0.04 ↓, $PaCO_2$ ~8 mm Hg ↑, and HCO_3 ~2 mEq ↑. (Adapted from Brenner BM, ed. *Brenner & Rector's The Kidney*, 8th ed., 2007; Ferri F, ed. *Practical Guide to The Care of the Medical Patient*, 7th ed., 2007)

METABOLIC ACIDOSIS

Initial workup

- ✓ **anion gap** (AG) = Na − (Cl + HCO_3) = unmeasured anions − unmeasured cations
  if ↑ glc, use measured *not* corrected Na
  expected AG is [albumin] × 2.5 (ie, 10 if albumin is 4 g/dL, 7.5 if albumin is 3 g/dL)
  ↑ AG → ↑ unmeasured anions such as organic acids, phosphates, sulfates
  ↓ AG → ↓ alb or ↑ unmeasured cations (Ca, Mg, K, Li, bromine, immunoglobulin)
- If ↑ AG, ✓ **delta-delta** ($\Delta\Delta = \Delta AG/\Delta HCO_3$) to assess if there is an additional metabolic acid-base disturbance; ΔAG = (calculated AG − expected AG), ΔHCO_3 = (24 − HCO_3)
  $\Delta\Delta$ = 1–2 → pure AG metabolic acidosis
  $\Delta\Delta$ < 1 → AG metabolic acidosis *and* simultaneous non-AG acidosis
  $\Delta\Delta$ > 2 → AG metabolic acidosis *and* simultaneous metabolic alkalosis

Etiologies of AG Metabolic Acidosis	
Ketoacidosis	**Diabetes mellitus**, alcoholism, starvation
Lactic acidosis	**Type A**: impairment in tissue oxygenation, eg, **circulatory or respiratory failure**, **sepsis**, ischemic bowel, carbon monoxide, cyanide **Type B**: no impairment in tissue oxygenation, eg, malignancy, alcoholism, meds (metformin, NRTIs, salicylates, propylene glycol) **D-lactic acidosis**: short bowel syndrome → precip by glc ingest → metab by colonic bacteria to D-lactate; not detected by standard lactate assay
Renal failure	Accumulation of organic anions such as phosphates, sulfates, urate, etc.
Ingestions	**Methanol** (windshield fluid, antifreeze, solvents, fuel): metab to formic acid **Ethylene glycol** (antifreeze): metab to glycolic and oxalic acids **Propylene glycol** (pharmaceutical solvent, eg, IV diazepam & lorazepam; antifreeze): lactic acidosis **Salicylates**: metabolic acidosis (from lactate, ketones) + respiratory alkalosis due to stimulation of CNS respiratory center **Acetaminophen**: glutathione depletion → ↑ endogenous organic acid 5-oxoproline in susceptible host (malnourished, female, renal failure)

Workup for AG metabolic acidosis

- ✓ for **ketonuria** (dipstick acetoacetate) or plasma β-hydroxybutyrate (βOHB)
  nb, urine acetoacetate often not present in early ketoacidosis due to shunting to βOHB; ∴ acetoacetate may later turn ⊕, but does not signify worsening disease
- If ⊖ ketones, ✓ **renal function, lactate, toxin screen,** and **osmolal gap**
- **Osmolal gap** (OG) = measured osmoles − calculated osmoles
  calculated osmoles = (2 × Na) + (glucose/18) + (BUN/2.8)
  (can + [EtOH/4.6] if have EtOH level and want to test if other ingestions)
  OG >10 → suggests ingestion (see below)

Ingestions			
AG	**OG**	**Ingestion**	**Other manifestations**
↑	nl	Acetaminophen	Hepatitis
		Salicylates	Fever, tachycardia, tinnitus; met. acid. + resp. alk.
↑	↑	Ethanol	Alcoholic fetor, ΔMS, hepatitis; keto + lactic acid. ± met. alk. (vomiting)
		Methanol	ΔMS, blurred vision, pupillary dilation, papilledema
		Ethylene glycol	ΔMS, cardiopulmonary failure, hypocalcemia, Ca oxalate crystals → renal failure; urine fluoresces under UV light
		Propylene glycol	AKI
nl	↑	Isopropyl alcohol	ΔMS, fruity breath (acetone)

Etiologies of Non-AG Metabolic Acidosis	
GI losses of HCO_3	Diarrhea, intestinal or pancreatic fistulas or drainage
RTAs	*See section on renal tubular acidoses below*
Early renal failure	Impaired generation of ammonia
Ingestions	Acetazolamide, sevelamer, cholestyramine, toluene
Dilutional	Due to rapid infusion of bicarbonate-free intravenous fluids
Post-hypocapnia	Respiratory alkalosis → renal wasting of HCO_3; rapid correction of resp. alk. → transient acidosis until HCO_3 regenerated
Ureteral diversion	Colonic Cl^-/HCO_3^- exchange, ammonium reabsorption

Workup for non-AG metabolic acidosis

- Evaluate history for causes (see above)
- ✓ **urine anion gap** (UAG) = $(U_{Na} + U_K) - U_{Cl}$
  UAG = unmeasured anions − unmeasured cations; as NH_4^+ is primary unmeasured cation, UAG is indirect assay for renal NH_4^+ excretion *(NEJM 1988;318:594)*
- ⊖ UAG → ↑ renal NH_4^+ excretion → appropriate renal response to acidemia
  Ddx: GI causes, type II RTA, ingestions or dilutional
- ⊕ UAG → failure of kidneys to secrete NH_4^+
  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 (U_{Na} >25) & w/o AG met. acid. → ⊕ UAG

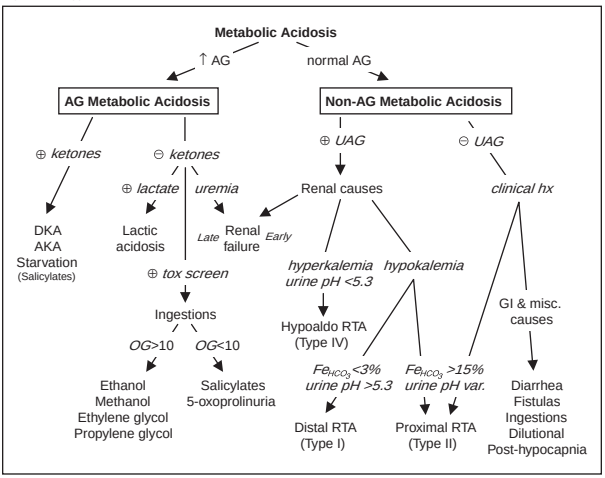
Renal tubular acidoses (RTAs)

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

Renal Tubular Acidosis						
Location	**Type**	**Acidosis**	**UAG**	**U pH**	**$FeHCO_3$[b]**	**Serum K**
Proximal	II	moderate	±	<5.3[a]	>15%	↓
Distal	I	severe	⊕	>5.3	<3%	↓[c]
Hypoaldo	IV	mild	⊕	<5.3	<3%	↑

[a]urine pH will rise above 5.3 in the setting of HCO_3 load
[b]$FeHCO_3$ should be checked after an HCO_3 load
[c]see above for causes of distal RTA (Type I) associated with hyperkalemia

Figure 4-2 Approach to metabolic acidosis



Treatment of severe metabolic acidoses (pH <7.2) *(NEJM 1998;338:26)*

- DKA: insulin & IVF; AKA: dextrose, IVF, replete K, Mg, PO_4 as needed
- Lactic acidosis: treat underlying condition, avoid vasoconstrictors
- Renal failure: hemodialysis
- Methanol & ethylene glycol: early fomepizole, vit. B_6 (ethylene glycol), folate (methanol), hemodialysis (especially if late presentation) *(NEJM 2009;360:2216)*
- Alkali therapy: $NaHCO_3$ (eg, 3 50-mmol amp in 1 L D_5W) to get serum HCO_3 >8 and pH >7.2 (estimate mmol of HCO_3 needed as $8-[HCO_3]_{serum} \times wt \times 0.5$)
  side effects: volume overload, hypernatremia, ↓ ICa, ↑ P_aCO_2 (and ∴ possibly intracellular acidosis), overshoot; no proven benefit in lactic acidosis *(Annals 1990;112:492)*

METABOLIC ALKALOSIS

Pathophysiology

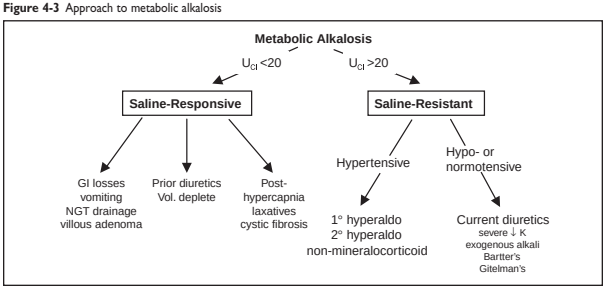
- Saline-responsive etiologies require *initiating event* and *maintenance factors*, whereas saline-resistant etiologies develop from various causes
- *Initiating event*
  loss of H^+ from GI tract or kidneys
  exogenous alkali
  contraction alkalosis: diuresis → excretion of HCO_3-poor fluid → extracellular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

Etiologies of Metabolic Alkalosis	
Saline-responsive	**GI loss of H^+**: vomiting, NGT drainage, villous adenoma **Diuretic use** Posthypercapnia, laxatives, cystic fibrosis
Saline-resistant	*Hypertensive* **(mineralocorticoid excess)** 1° hyperaldosteronism (eg, Conn's) 2° hyperaldosteronism (eg, renovascular dis., renin-secreting tumor) non-aldo (Cushing's, Liddle's, exogenous mineralocorticoids, licorice) *Normotensive* severe hypokalemia exogenous alkali load Bartter's syndrome (loop-like), Gitelman's syndrome (thiazide-like)

Workup

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

Figure 4-3 Approach to metabolic alkalosis



Treatment of severe metabolic alkalosis (pH >7.6)

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

Respiratory Acidosis

Etiologies

- **CNS depression**: sedatives, CNS trauma, O_2 in chronic hypercapnia (↓ hypoxemic drive)
- **Neuromuscular disorders**: myasthenia gravis, Guillain-Barré, poliomyelitis, 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 → ↑ RR → resp. alk., but eventual muscle fatigue → resp. acid.): pneumonia, pulmonary edema, restrictive lung disease
- Thoracic cage abnormalities: pneumothorax, flail chest, kyphoscoliosis
- Post infusion of bicarbonate in acidemic Pt w/ limited ability to ↑ minute ventilation

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

OVERVIEW

General

- Disorders of serum sodium are generally due to Δs in *total body water*, not sodium
- Hyper- or hypoosmolality → rapid water shifts → Δs in brain cell volume → Δ MS, seizures

Key hormones

- **Antidiuretic hormone (ADH)**: primary hormone that regulates *sodium concentration*
  stimuli for secretion: hyperosmolality, ↓↓ effective arterial volume (EAV)
  action: insertion of aquaporin-2 channels in collecting ducts → passive water reabsorption
  urine osmolality is an indirect functional assay of the ADH-renal axis
  U_{osm} range: 60 mOsm/L (no ADH) to 1200 mOsm/L (maximal ADH)
- **Aldosterone**: primary hormone that regulates *total body sodium* (and ∴ volume)
  stimuli for secretion: hypovolemia (via renin and angiotensin II), hyperkalemia
  action: iso-osmotic reabsorption of sodium in exchange for potassium or H^+

HYPONATREMIA

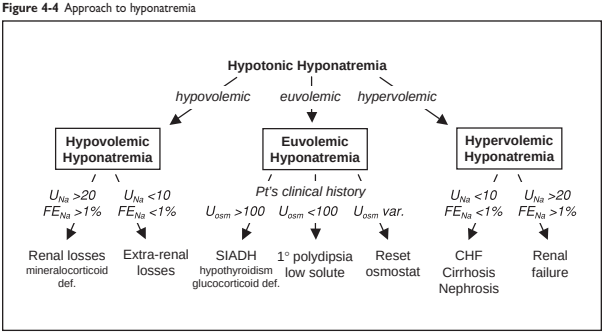
Pathophysiology

- **Excess of water relative to sodium**; almost always due to ↑ **ADH**
- ↑ ADH may be *appropriate* (eg, hypovolemia or hypervolemia with ↓ EAV)
- ↑ ADH may be *inappropriate* (SIADH)
- Rarely, ↓ ADH (appropriately suppressed), but kidneys unable to maintain nl $[Na]_{serum}$
  primary polydipsia: ingestion of massive quantities (usually >12 L/d) of free H_2O overwhelms diluting ability of kidney (normal solute load ~750 mOsm/d, min U_{osm} = 60 mOsm/L → excrete in ~12 L; if H_2O ingestion exceeds this, H_2O retention)
  "tea & toast" and *"beer potomania"*: ↓↓ daily solute load, ↑ free H_2O → insufficient solute to excrete H_2O intake (eg, if only 250 mOsm/d, minimum U_{osm} = 60 mOsm/L → excrete in ~4 L; if H_2O ingestion exceeds this, H_2O retention)

Workup *(NEJM 2000;342:1581)*

- Measure **plasma osmolality**
  Hypotonic hyponatremia most common scenario; true excess of free H_2O relative to Na
  Hypertonic hyponatremia: excess of another effective osmole (eg, glc, mannitol) that draws H_2O intravascularly; each 100 mg/dL ↑ glc >100 mg/dL → ↓ [Na] by 2.4 mEq/L
  Isotonic hyponatremia: rare lab artifact from hyperlipidemia or hyperproteinemia
- For hypotonic hyponatremia, ✓ **volume status** (vital signs, orthostatics, JVP, skin turgor, mucous membranes, peripheral edema, BUN, Cr, uric acid)
- **U_{osm}** diagnostically useful in limited circumstances, because almost always >300
  exceptions: U_{osm} <100 in 1° polydipsia & ↓ solute intake
  moreover, U_{osm} >300 ≠ SIADH; must determine if ↑ ADH appropriate or inappropriate
  however, U_{osm} important when deciding on *treatment* (see below)
- If euvolemic and ↑ U_{osm}, evaluate for glucocorticoid insufficiency and hypothyroidism

Figure 4-4 Approach to hyponatremia



Hypovolemic hypotonic hyponatremia (ie, ↓↓ total body Na, ↓ TBW)
- **Renal losses** (U_{Na} >20 mEq/L, FE_{Na} >1%): diuretics (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_{Na} <10 mEq/L, FE_{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, inapprop ↑ U_{Osm}, **normal U_{Na}**, ↓ BUN & UA)
  malignancy: lung, brain, GI, GU, lymphoma, leukemia, thymoma, 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_{osm} <100, ↓ uric acid): usually requires intake >12 L/d
- **Low solute**: "tea & toast"; "beer potomania"
- Reset osmostat: chronic malnutrition (↓ intracellular osmoles) or pregnancy (hormonal effects) → ADH physiology reset to regulate a lower $[Na]_{serum}$

Hypervolemic hypotonic hyponatremia (ie, ↑ total body Na, ↑↑ TBW)
- **CHF** (↓ CO → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Cirrhosis** (splanchnic arterial vasodilation and ascites → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Nephrotic syndrome** (hypoalbuminemia → edema → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- **Advanced renal failure** (diminished ability to excrete free H_2O; U_{Na} >20 mEq/L)

Treatment
- **Goals of treatment**
  Asymptomatic hyponatremia: correct $[Na]_{serum}$ 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**

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

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

  eg, 1 L hypertonic saline (513 mEq Na) given to 70-kg man w/ [Na] = 110 mEq/L will ↑ $[Na]_{serum}$ by 9.4 mEq
  however, above assumes entire infusate retained *without any output of Na or H_2O*
  if Pt is euvolemic, 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_2O) given to Pt with SIADH with U_{osm} = 616 → 308 mOsm solute excreted in 0.5 L H_2O →
  net gain 0.5 L H_2O → ↓ $[Na]_{serum}$
  ∴ normal saline can *worsen* hyponatremia 2° SIADH if U_{osm} > $infusate_{osm}$
- **Hypovolemic hyponatremia**: volume repletion with **normal saline**
  once volume replete → stimulus for ADH removed → kidneys will excrete free H_2O → serum Na will correct rapidly
- **SIADH** (*NEJM* 2007;356:2064): **free water restrict** + treat underlying cause
  hypertonic saline (± loop diuretic) if sx or Na fails to ↑ w/ free H_2O restriction
  1 L hypertonic saline will raise $[Na]_{serum}$ by ~10 mEq (see above)
  ~50 mL/h will ↑ [Na] by ~0.5 mEq/L/h; 100–200 mL/h will ↑ [Na] by ~1–2 mEq/L/h
  formula only provides estimate; ∴ recheck serum Na frequently
  salt tabs: particularly if chronic and no CHF
  aquaresis: conivaptan (IV V1a & V2 vasopressin receptor antag) or tolvaptan (oral V2 antag); used for symptomatic SIADH resistant to above Rx
  demeclocycline: causes nephrogenic DI, ↓ U_{osm}
- **Hypervolemic hyponatremia**: **free water restrict**
  mobilize excess Na & H_2O (loop diuretics) & ↑ EAV (vasodilators to ↑ CO in CHF, colloid infusion in cirrhosis)
  aquaresis: tolvaptan (*NEJM* 2006;355:2099), consider in symptomatic hyponatremia resistant to above Rx, monitor for overcorrection

HYPERNATREMIA

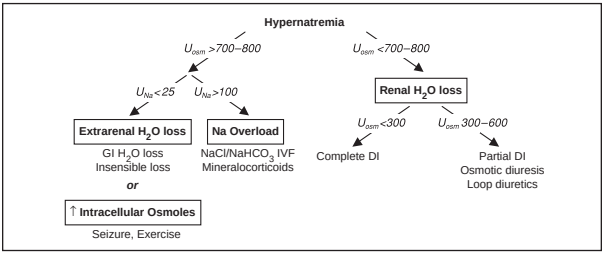
Pathophysiology (*NEJM* 2000;342:1493)

- 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 MS, elderly): hypernatremia is a powerful thirst stimulus, ∴ usually only develops in Pts w/o access to H_2O

Workup

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

Figure 4-5 Approach to hypernatremia



Extrarenal H_2O loss (U_{osm} >700–800)

- **GI H_2O loss**: vomiting, NGT drainage, osmotic diarrhea, fistula
- **Insensible loss**: fever, exercise, ventilation

Renal H_2O loss (U_{osm} <700–800)

- **Diuresis**: osmotic (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 (U_{osm} >700–800)

- **Na overload**: hypertonic saline (eg, resuscitation w/ $NaHCO_3$), mineralocorticoid excess
- **Seizures**, **↑exercise**: ↑ intracellular osmoles → H_2O shifts → transient ↑ $[Na]_{serum}$

Treatment

- **Restore access to H_2O** or supply daily requirement of H_2O (≥1 L/d)
- **Replace free H_2O deficit** (also replace concurrent volume deficit if appropriate):

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

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

shortcut: for typical 70-kg man, free H_2O deficit (L) ~ ($[Na]_{serum}$ − 140)/3

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

eg, 1 L D_5W given to 70-kg man w/ [Na] = 160 mEq/L will ↓ $[Na]_{serum}$ by 3.7 mEq

- **Rate of ↓ of Na should not exceed 0.5 mEq/L/h** to avoid cerebral edema
  shortcut: in 70-kg man, 125 mL/h of free H_2O will ↓ [Na] by ~0.5 mEq/L/h
- ½ NS (77 mEq/L) or ¼ NS (38 mEq/L) provides both volume & free H_2O (500 or 750 mL of free H_2O per L, respectively); can give free H_2O via NGT/OGT
- Formulas provide only estimates; ∴ recheck serum Na frequently
- **DI and osmotic diuresis**: see "Polyuria" section below
- **Na overload**: D_5W + 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_{osm}
- 24-h osmole excretion rate = 24-h UOP (actual or estimate) × U_{osm}
  - >1000 mOsm/d → osmotic diuresis
  - <800 mOsm/d → water diuresis

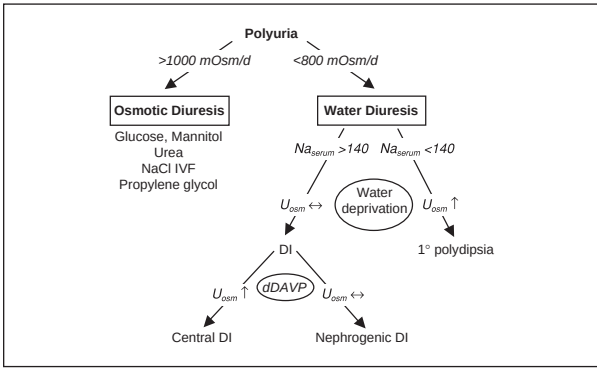
Osmotic diuresis

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

Water diuresis

- Etiologies: **diabetes insipidus** (DI) (Na_{serum} >140) or **1° polydipsia** (Na_{serum} <140) see "Hypernatremia" above for list of causes of central and nephrogenic DI
- Workup of DI: U_{osm} <300 (complete) or 300–600 (partial)
  - **water deprivation test** (start in a.m., ✓ Na_{serum}, P_{osm}, U_{osm}, UOP q1–2h)
  - Deprive until P_{osm} >295, then ✓ U_{osm}. If U_{osm} <300, then administer vasopressin (5 U SC) or dDAVP (10 μg intranasal), then check U_{osm} in 1–2 hrs:
    - U_{osm} ↑ by >50% = central DI
    - U_{osm} unchanged = nephrogenic DI
  - ✓ ADH level before and after water deprivation to evaluate proper response

Figure 4-6 Approach to polyuria



Treatment

- **1° polydipsia**: treat psychiatric illness, check meds, restrict access to free H_2O
- **Osmotic diuresis**: address underlying cause, replace free H_2O deficit (see "Hypernatremia" for formula to calculate) and ongoing losses
- **DI**:
  - central DI: desmopressin (dDAVP)
  - nephrogenic DI: treat underlying cause if possible; Na restriction + thiazide (mild volume depletion → ↓ delivery of filtrate to dysfxnal diluting segment of kidney)
  - pregnancy-induced DI: due to vasopressinase from placenta, ∴ Rx w/ dDAVP

POTASSIUM HOMEOSTASIS

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 → hypokalemia; reversed by β-blockers
  Digoxin → blocks Na-K ATPase → hyperkalemia
  Massive necrosis (eg, tumor lysis, rhabdo, ischemic bowel) → release of intracellular K
  Hypo- or hyperkalemic periodic paralysis: rare disorders due to channel mutations

HYPOKALEMIA

Transcellular shifts
- Alkalemia, insulin, catecholamines, hypokalemic periodic paralysis, acute ↑ in hematopoiesis (megaloblastic anemia Rx w/ B_{12}, AML crisis), hypothermia

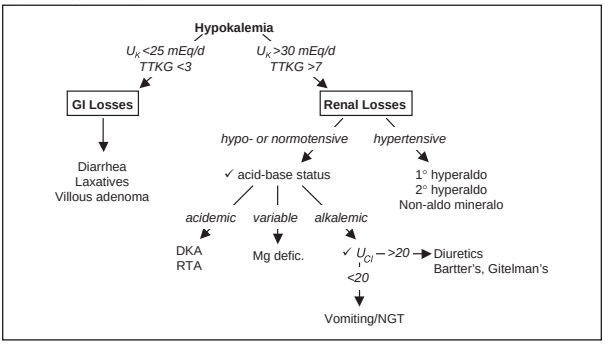
GI potassium losses (U_K <25 mEq/d or <15 mEq/L or TTKG <3)
- GI losses *plus* metabolic acidosis: diarrhea, laxative abuse, villous adenoma
- Vomiting & NGT drainage usually manifest as *renal losses* due to 2° hyperaldo & met. alk.

Renal potassium losses (U_K >30 mEq/d or >15 mEq/L or TTKG >7)
- Hypotensive or normotensive
  acidosis: DKA, RTA [proximal RTA (type II) and some distal RTAs (type I)]
  alkalosis
    diuretics, vomiting/NGT drainage (via 2° hyperaldosteronism)
    Bartter's syndrome (loop of Henle dysfxn → furosemide-like effect; *NEJM* 1999;340:1177)
    Gitelman's syndrome (distal convoluted tubule dysfxn → thiazide-like effect)
  Mg 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)
  nonaldosterone 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
- ✓ 24-hr $\mathbf{U_K}$ and **transtubular potassium gradient** (TTKG) = $(U_K/P_K) / (U_{osm}/P_{osm})$
  U_K >30 mEq/d or >15 mEq/L or TTKG >7 → renal loss
  U_K <25 mEq/d or <15 mEq/L or TTKG <3 → extrarenal loss
- If renal losses, ✓ **BP**, **acid-base**, $\mathbf{U_{Cl}}$ (U_{Na} unreliable for volume status w/ alkalemia)

Figure 4-7 Approach to hypokalemia



Treatment
- *If true potassium deficit:* **potassium repletion** (↓ 1 mEq/L ≈ 200 mEq total body loss) KCl 40 mEq PO q4–6h if nonurgent, KCl 10 mEq/h IV if urgent, recheck K freq
- Beware of excessive potassium repletion if transcellular shift cause of hypokalemia
- Treat underlying cause (if hydration needed, avoid dextrose-containing solutions as dextrose → ↑ insulin → intracellular potassium shifts)
- Replete 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 oliguric or anuric AKI or any cause of end stage renal disease

Normal GFR but with ↓ renal K excretion
- Normal aldosterone function
  - ↓ EAV (K excretion limited by **↓ distal Na delivery & urine flow**): CHF, cirrhosis excessive K intake: in conjunction with impairment in K excretion or transcellular shift
- **Hypoaldosteronism**: same as etiologies of hypoaldo RTA (type IV)
  - ↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV
  - normal renin, ↓ aldo synthesis: 1° adrenal disorders, ACEI, ARBs, heparin
  - ↓ response to aldosterone
    - meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors
    - tubulointerstitial disease: sickle cell, SLE, amyloid, diabetes

Clinical manifestations
- Weakness, nausea, paresthesias, palpitations
- ECG: peaked T waves, ↑ PR interval, ↑ QRS width, loss of P wave, sine wave pattern, PEA/VF (ECG: low sensitivity, cardiac arrest can be first electrical manifestation!)

Workup *(Crit Care Med 2008;36:3246)*
- Rule out pseudohyperkalemia (IVF with K, hemolysis during venipuncture, ↑ plt or WBC)
- Rule out transcellular shift
- **Assess GFR**, if normal:
  - Consider ↓ distal Na delivery and urine flow
  - ✓ transtubular K gradient (TTKG) = $(U_K/P_K)/(U_{osm}/P_{osm})$, <7 c/w hypoaldo

Treatment of Hyperkalemia

Intervention	Dose	Onset	Comment
Calcium gluconate **Calcium chloride**[a]	1–2 amps IV	<3 min	transient effect (30–60 min) stabilizes cell membrane
Insulin	reg. insulin 10 U IV + 1–2 amps $D_{50}W$	15–30 min	transient effect (30–60 min) drives K into cells
Bicarbonate (esp. if acidemic)	1–3 amps IV	15–30 min	transient effect (60 min) drives K into cells in exchange for H
β2 agonists	albuterol 10–20 mg inh. or 0.5 mg IV	30–90 min	transient effect (~2 h) drives K into cells
Kayexalate[b]	30–90 g PO/PR	1–2 h	↓ total body K (over ~6 h) exchanges Na for K in gut
Diuretics	furosemide ≥40 mg IV	30 min	↓ total body K
Hemodialysis			↓ total body K

[a]calcium chloride contains more calcium and is typically reserved for use in codes (↑ risk of tissue necrosis)
[b]increased 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 acidemic), and β2 agonists should follow to ↓ plasma K
- Treatments that **eliminate total body K essential** as other Rxs will wear off with time; kayexalate ± 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_{Na})** = $(U_{Na}/P_{Na})/(U_{Cr}/P_{Cr})$
  <1% → prerenal, contrast, or glomerulonephritis; >2% → ATN
  In setting of diuretics, ✓ $FE_{UN} = (U_{UN}/P_{UN})/(U_{Cr}/P_{Cr})$; <35% → prerenal
- Renal U/S: r/o obstruction & eval kidney size to estimate chronicity of kidney disease
- Serologies (if indicated): see "Glomerular Disease"
- Renal bx: may be necessary if cause remains unclear

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

Etiologies		U/A, Sediment, Indices
Prerenal	↓ **Effective arterial volume** (*NEJM* 2007;357:797) Hypovolemia, ↓ cardiac contractility (eg, CHF), systemic vasodilatation (eg, sepsis) **Renal vasoconstriction** NSAIDs, ACEI/ARB, contrast calcineurin inhibitors, hepatorenal, hypercalcemia **Large vessel**: RAS (bilateral + ACEI), thrombosis, embolism, dissection, vasculitis, compression	Bland Transparent hyaline casts FE_{Na} <1% BUN/Cr >20 U_{osm} >500
Intrinsic	**Acute tubular necrosis (ATN)** *Ischemia*: progression of prerenal disease *Toxins* Drugs: AG, amphotericin, cisplatin Pigments: Hb, myoglobin (*NEJM* 2009;361:62) Proteins: Ig light chains Crystals: UA, ACV, MTX, indinavir, oral $NaPO_4$ *Contrast-induced AKI (CIAKI)*: ↓ RBF + toxin	Pigmented granular muddy brown casts in ~75% (± in CIAKI) ± RBCs & protein from tubular damage FE_{Na} >2% (except pigment & CIAKI) U_{osm} <350
	Acute interstitial nephritis (AIN) *Allergic:* β-lactams, sulfa drugs, NSAIDs, PPIs *Infection:* pyelonephritis, legionella *Infiltrative:* sarcoid, lymphoma, leukemia *Autoimmune*: Sjögren's, TINU syndrome, IgG4, SLE	WBCs, WBC casts, ± RBCs ⊕ urine eos in abx ⊕ lymphs in NSAIDs
	Small vessel: cholesterol emboli, thrombotic microangiopathy (HUS/TTP, DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)	± RBCs ⊕ urine eos in chol emboli
	Glomerulonephritis (see "Glomerular Disease")	Dysmorphic RBCs & RBC casts
Post	**Bladder neck**: BPH, prostate cancer, neurogenic bladder, anticholinergic meds **Ureteral** (bilateral): malig, LAN, retroperitoneal fibrosis, nephrolithiasis	Bland ± RBCs if nephrolithiasis

Contrast-induced acute kidney injury (CIAKI)
- Risk factors: CKD, DM, CHF, age, hypotension, ↑ 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
- Prevention (*NEJM* 2006;354:379; *JAMA* 2006;295:2765; *Circ* 2006;113:1799)
  N-acetylcysteine 1,200 mg PO bid on day prior to and day of contrast (*NEJM* 2006;354:2773)
  Prehydration/posthydration (*NEJM* 1994;331:1416) unless contraindic. to IVF (eg, CHF) isotonic $NaHCO_3$: 3 mL/kg/h × 1 h before, 1 mL/kg/h × 6 h after (*JAMA* 2004;291:2328) unclear if $NaHCO_3$ more effective than saline, hydration is the key (*Annals* 2009;151:631) benefit additive to N-acetylcysteine (*Circ* 2007;115:1211)
  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
  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)

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, ↑ PO_4), & acid/base status
- If obstruction is diagnosed and relieved, watch for:
  Hypotonic diuresis (2° buildup of BUN, tubular damage); Rx w/ IVF (eg, ½ NS)
  Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly
- 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

Chronic Kidney Disease (CKD)

Definition and Etiologies (*Annals* 2009;150:ITC2-1 & *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)

Stages of CKD		
Stage	**GFR** mL/min/1.73 m^2	**Goals**
1 (nl or ↑ GFR)	>90	Dx/Rx of underlying condition & comorbidities, slow progression; cardiovascular risk reduction
2 (mild)	60–89	Estimate progression
3 (moderate)	30–59	Evaluate and treat complications
4 (severe)	15–29	Prepare for renal replacement therapy (RRT)
5 (kidney failure)	<15 or dialysis	Dialysis if uremic

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), pruritis, calciphylaxis, NSF
Neurologic	Encephalopathy (Δ MS, ↓ memory & attention), seizures, neuropathy, impaired sleep, restless leg syndrome
Cardiovascular	Pericarditis, accelerated atherosclerosis, hypertension, hyperlipidemia, volume overload, CHF, cardiomyopathy (especially LVH)
Hematologic	Anemia, bleeding (due to platelet dysfunction)
Metabolic	↑ K, ↑ PO_4, acidosis, ↓ Ca, 2° hyperparathyroidism, osteodystrophy

Treatment (*Annals* 2009;150:ITC2-1, *NEJM* 2010;362:57)

- **General**: nephrology referral when GFR <30 and access planning (avoid subclavian lines; preserve an arm for access by avoiding blood draws, BP measurements, IVs)
- **Dietary restrictions**: Na (if HTN), K (if oliguric or hyperkalemic), PO_4, ? moderate protein restriction, strict glc control in DM
- **BP Control**: goal <130/80, start with ACEI (or ARB), effective in diabetic & nondiabetic CKD (*NEJM* 2004;351:1952). ACEI + ARB unresolved (*Annals* 2008;148:30 & *Lancet* 2008;372:547). 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 HCO_3 <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

- **2° Hyperparathyroidism**: ↑ PO_4, ↓ Ca, ↓ calcitriol → ↑ PTH → renal osteodystrophy

CKD Stage	3	4	5
Target PTH (pg/mL)	35–70	70–110	150–300

  phosphorus binders (*take with meals!*) (*NEJM* 2010;362:1312)
    if ↑ PO_4 and ↓ Ca → calcium acetate (PhosLo) or calcium carbonate
    if refractory ↑ PO_4 or in setting of ↑ Ca → sevelamer (Renagel), lanthanum (Fosrenol)
    if severe ↑ PO_4 → aluminum hydroxide (Amphojel), *short-term use only*
  calcitriol or paricalcitol if Ca-PO_4 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)
  parathyroidectomy
- **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 ~2× as potent as PO dose
  torsemide & bumetanide ~90% bioavailability; use ethacrynic acid if sulfa allergy
  40 mg furosemide PO ≈ 20 mg furosemide IV ≈ 20 mg torsemide PO ≈ 1 mg bumetanide
  dose furosemide bid-qid; qd dosing can lead to initial diuresis → antinatriuresis
  ? ↑ diuresis w/ contin. infusion (bolus → titrate drip) vs. bolus alone (*Annals* 1991;115:360)
  ? ↑ diuresis w/ co-administration of albumin if ↓ serum albumin (*Crit Care Med* 2005;33:1681)

Thiazide diuretics (*NEJM* 2009;361:2153)
- **Drugs**: hydrochlorothiazide (HCTZ), chlorothiazide (Diuril), metolazone (Zaroxolyn)
- **Mechanism**: inhibit Na-Cl cotransporter in the distal convoluted tubule (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.

Approach to Diuresis (if inadequate diuresis, go to next step)	
Step	**Action**
1	**Loop diuretic PO**: ✓ response at 3 h, redose at 2× prior dose if needed
2	**Add thiazide diuretic PO** (potentiates response to loop diuretic)
3	**Loop diuretic IV**: bolus bid-qid ± thiazide (*may start here if inPt*) ↑ dose needed w/ ↑ Cr; initial effective IV lasix dose ≈ 30 × Cr (ie, if Cr = 4 → 120 mg IV lasix)
4	**Loop diuretic infusion**: bolus + continuous IV infusion ± thiazide
5	**RRT**: consider ultrafiltration, CVVH, or HD

Disease state specific regimens
- Renal insufficiency: loop diuretic (↑ dose to achieve effective delivery to ThAL) ± thiazide
- CHF: loop diuretic (↑ frequency over ↑ dose) + thiazide (watch K & Mg)
- Nephrotic syndrome: urinary albumin binds secreted loop diuretic, use 2–3 × normal dose
- Cirrhosis: spironolactone (blocks 2° hyperaldosteronism) + lasix in 2.5:1 ratio
- Severe metabolic alkalosis: acetazolamide & treat underlying cause

Adverse effects
- Loop: ↓ Na, ↓ K, ↓ Mg, ↓ Ca, hyperuricemia, ototoxicity
- 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, $Na + H_2O$) via transmembrane pressure (TMP) gradient
  Solute removal via transmembrane concentration gradient and inversely proportional to size ($\therefore$ effective removal of K, urea, and Cr, but not PO_4)
- Typical orders: duration, volume removal goals, K and Ca in dialysate bath, anticoagulation
- Complications: hypotension, arrhythmia, access complications, disequilibrium syndrome

Vascular Access

	Advantages	Disadvantages
AV Fistula	Highest patency Lowest risk of bacteremia	Long maturation time (2–6 mo) Primary nonfunction (20%)
AV Graft	Easier to create than AVF Maturation time (2–3 wks)	Poor 1° patency, often requiring thrombectomy or angioplasty
Catheter	Immediate use Use as bridge to AVF/AVG	Highest risk of bacteremia ↓ blood flow → ↓ HD efficiency

Continuous Veno-Venous Hemofiltration (CVVH) (*NEJM* 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, PO_4). 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: **HCO_3** (requires heparin to prevent machine from clotting) **vs. citrate** (hepatically metabolized to HCO_3; provides anticoagulation w/ in machine via Ca chelation; $\therefore$ need Ca infusion to maintain serum Ca)
- Complications: hypotension, ↓ PO_4, 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)

Peritoneal Dialysis (PD) (*Perit Dial Int* 2001;21:25)

- 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^+, Ca^{2+}, Mg^{2+}
  infuse 10 min, dwell 30 min–5.5 h, drain 20 min
- Can use overnight cycler device that infuses & drains more rapidly, with shorter dwells, while Pt sleeps. Called automated or continuous cycling peritoneal dialysis (APD, CCPD).
- Complications
  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

GLOMERULONEPHRITIS (GN)

Definition (*NEJM* 1998;339:888 & *Lancet* 2005;365:1797)

- *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 asx 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)	—	c-ANCA (anti-PR3)	90%
Microscopic polyangiitis	—	90%	50%	—	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)

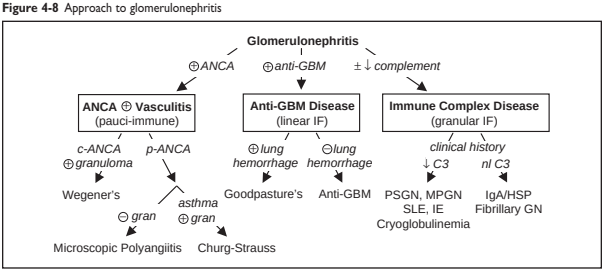
Anti-GBM Disease (linear staining) ~15% of total			
Disease	**Glomerulonephritis**	**Pulm hemorrhage**	**Anti-GBM**
Goodpasture's	⊕	⊕	⊕
Anti-GBM disease	⊕	—	⊕

Immune Complex (IC) Disease (granular staining) ~40–45% of total	
Renal-limited diseases	**Systemic diseases**
Poststreptococcal GN (PSGN, usually 10–14 d, ⊕ ASLO, ↓ C3)	**SLE** (⊕ ANA, anti-dsDNA, ↓ C3, ↓ C4)
Membranoproliferative GN (MPGN, ↓ C3)	**Cryoglobulinemia** (⊕ cryocrit, ⊕ RF, HCV Ab, ↓ C3, ↓ C4)
Fibrillary glomerulonephritis (normal C3)	**Endocarditis** (fever, ⊕ BCx, valvular disease, ↓ C3)
IgA nephropathy (normal C3)	**Henoch-Schönlein purpura** (IgA nephropathy + systemic vasculitis, 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



Treatment
- ANCA ⊕ or anti-GBM: **steroids** *ASAP* + cyclophos; ± plasmapheresis (*JASN* 2007;18:2180)
- SLE nephritis: IV cyclophosphamide + steroids → azathioprine or MMF (*JAMA* 2005;293:3053); induction with MMF (no cyclophosphamide) may be as effective (*NEJM* 2005;353:2219)
- Other IC disease: ? steroids ± alkylating agents; treat underlying systemic disease

Asymptomatic Glomerular Hematuria

Definition and Etiologies
- Hematuria ± proteinuria of glomerular origin w/o renal insufficiency or systemic disease (nonglomerular hematuria more common; see "Hematuria")
- Ddx: any cause of GN, 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: asx hematuria (30–40%), gross hematuria ~1–3 d after URI (30–40%), chronic GN (10%), nephrotic syndrome (5%), RPGN (<5%)
- Though clinical presentation can be highly suggestive, definitive dx only w/ bx
- Prognosis: 25–30% will reach ESRD w/in 20–25 y of presentation
- Treatment: ACEI/ARB, ± fish oils (*NEJM* 1994;331:1194); steroids (*JASN* 2004;15:157) ± cytotoxic therapy for crescentic GN and nephrotic sx, consider for progressive chronic GN

Nephrotic Syndrome

Definition
- Proteinuria >3.5 g/d, albumin <3.5 mg/dL, edema, ↑ cholesterol

Primary glomerular diseases (grouped by pathology)
- **Focal segmental glomerulosclerosis** (40%)
  idiopathic, HIV (collapsing variant), pamidronate, 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, syphilis), autoimmune (espec. SLE), carcinomas, drugs (NSAIDs, penicillamine)
- **Minimal change disease** (20%, more common in children)
  idiopathic, NSAIDs, Hodgkin's disease & other lymphoproliferative disorders
- **Membranoproliferative GN** (5%, *mixed* nephrotic/nephritic features)
  Type I: infection (especially HCV ± cryos; IE, HBV, other chronic infxns), immune complex disease (SLE, cryos, Sjögren's), lymphoproliferative disorders, idiopathic
  Type II: very rare; autoAb blocks inactivation of C3 convertase = *C3 nephritic factor*
- **Fibrillary-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 ⊕ → 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: ↑ Hb_{A1C} + 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 dis: 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)

Urine Dipstick	
Measurement	**Significance and uses**
Specific Gravity	estimate U_{osm}: each 0.001 above 1 ≈30 osm (SG 1.010 → U_{osm} ≈300) SG and U_{osm} useful in evaluating AKI, dysnatremias, polyuria heavy substances (glucose, contrast) increase SG more than U_{osm}
pH	range: 4.5–8.5; useful in evaluation of stones and RTAs, infection
Protein	detects albumin (marker for glomerular dysfxn); see "Proteinuria"
RBC	see "Hematuria"; also ⊕ with myoglobinuria (rhabdomyolysis)
WBC	suggests inflammation (UTI, interstitial nephritis, GN)
Ketones	detects acetoacetate (ie, ketoacidosis), but *not* β-hydroxybutyrate
Nitrite	suggests presence of Enterobacteriaceae
Bilirubin	↑ in biliary or hepatic disease
Glucose	⊕ in hyperglycemia (>180 mg/dL), pregnancy, Fanconi's syndrome

Urine Sediment (microscopic examination) *(Am J Kidney Dis 2008;51:1052)*	
Method: centrifuge fresh sample × 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

Etiologies of Proteinuria		
Category	**Description**	**Etiologies**
Glomerular (can be >3 g/d)	Disruption of filtration barrier → lose albumin	Glomerulonephritis Nephrotic syndrome
Tubulointerstitial (usually <1–2 g/d)	↓ reabsorption of freely filtered proteins → lose globulins	ATN AIN Fanconi's syndrome
Overflow	↑ production of freely filtered proteins	Multiple myeloma Myoglobinuria
Isolated	By def'n: asx, normal renal fxn, sed, & imaging, no h/o renal disease	Functional (fever, exercise, CHF) Orthostatic (only when upright) Idiopathic (transient or persistent)

- **Urine dipstick**
  1+ ≈30 mg/dL, 2+ ≈100 mg/dL, 3+ ≈300 mg/dL, 4+ >2 g/dL → interpretation depends on SG; eg, 3+ in very concentrated urine might not indicate heavy proteinuria
  Insensitive for microalbuminuria and myeloma light chains; false ⊕ with contrast
- **Spot urine**: protein (mg/dL)/creatinine (mg/dL) ≈g/d of proteinuria *(NEJM 1983;309:1543)*
  unlike urine dipstick, will accurately measure myeloma light chains
- Orthostatic proteinuria: typically in adolescents; ~90% of young ♂ with isolated proteinuria have orthostatic proteinuria; typically resolves spontaneously

Hematuria

Etiologies of Hematuria	
Extrarenal (far more common)	**Intrarenal**
Nephrolithiasis	Nephrolithiasis or crystalluria
Neoplasm: transitional cell, prostate	Neoplasm
Infection: cystitis, urethritis, prostatitis	Trauma / exercise
Foley trauma	Vascular: renal infarcts, renal vein thromb., sickle cell disease and trait
BPH	Glomerular disease (IgA, thin BM > others)
Schistosoma haematobium	PKD (*NEJM* 2008;359:1477)

- Wide, overlapping ages for various etiologies, but general guide for common causes:
  <20 y: GN, UTI, congenital; 20–60 y: UTI, nephrolithiasis, cancer
  >60 y ♂: prostatitis, cancer; UTI; >60 ♀: UTI, cancer

Workup (*NEJM* 2003;348:2330 & *BMJ* 2009;338:a3021)
- **Urine dipstick**: ⊕ if >3 RBCs; ⊕ dipstick and ⊖ sediment → myo- or hemoglobinuria
- **Urine sediment**: dysmorphic RBCs or RBC casts → GN → consider renal bx
- If no evidence of glomerulonephritis:
  r/o UTI
  Urine cytology (Se ~70%, Sp ~95%; ∴ ✓ am void × 3 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
  2° hypercalciuria: 1° hyperparathyroidism, type 1 RTA, sarcoid
  2° hyperoxaluria: Crohn's, ileal disease w/ intact colon, gastric bypass
  Diet: ↑ 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 NH_3 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; urinalysis of 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, PO_4, PTH, UA
- 24-h urine × 2 (>6 wk after acute setting) for Ca, PO_4, 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

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

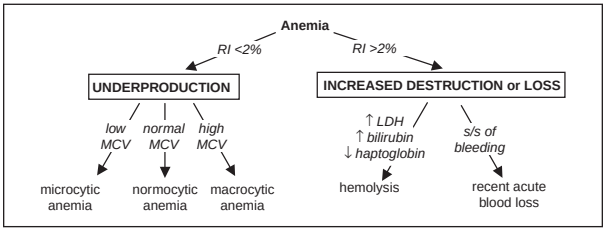
Clinical manifestations

- Symptoms: ↓ O_2 delivery → fatigue, exertional dyspnea, angina (if CAD)
- Signs: pallor (mucous membranes, palmar creases), tachycardia, orthostatic hypotension
- Other findings: **jaundice** (hemolysis), **splenomegaly** (thalassemia, neoplasm, chronic hemolysis), **petechiae/purpura** (bleeding disorder), **glossitis** (iron, folate, vitamin B_{12} defic.), **koilonychia** (iron defic.), **neurologic abnormalities** (B_{12} defic.)

Diagnostic evaluation

- History: bleeding, systemic illness, drugs, exposures, alcohol, diet (including **pica**), FHx
- CBC w/ diff.; RBC params incl. retics, MCV (nb, mixed disorder can → nl MCV), RDW
- **Reticulocyte index** (RI) = [reticulocyte count × (Pt's Hct/nl Hct)]/maturation factor
  maturation factors for a given Hct: 45% = 1, 35% = 1.5, 25% = 2, 20% = 2.5
  RI >2% → adequate marrow response; RI <2% → hypoproliferation
- **Peripheral smear**: select area where RBCs evenly spaced and very few touch each other; ✓ RBC size, shape, inclusions (see Appendix & Peripheral Smear inserts), WBC morphology, plt count
- Additional labs as indicated: hemolysis labs (if RI >2%), iron/TIBC, ferritin, folate, B_{12}, LFTs, BUN and Cr, TFTs, Hb electrophoresis, enzyme analyses, gene mutation screens
- **Bone marrow (BM) aspirate and biopsy (bx)** with cytogenetics as indicated

Figure 5-1 Approach to anemia



MICROCYTIC ANEMIAS

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., epo). 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

Thalassemias (*NEJM* 2005;353:1135)

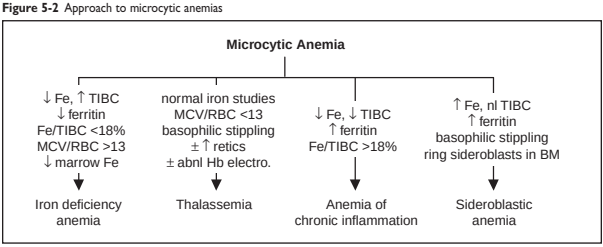
- ↓ synthesis of α- or β-globin chains of Hb → ≠ subunits → destruction of RBCs and erythroid precursors; ∴ anemia from hemolysis *and* ineffective erythropoiesis
- **α-thalassemia**: deletions in α-globin gene complex on chr. 16 (nl 4 α genes)
  3 α → α-thal-2 trait = silent carrier; 2 α → α-thal-1 trait or α-thal minor = mild anemia
  1 α → HbH (β_4) disease = severe anemia, hemolysis, and splenomegaly
  0 α genes → Hb Barts (γ_4) = intrauterine hypoxia and hydrops fetalis
- **β-thalassemia**: mutations in β-globin gene 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 <70, **normal Fe**, **MCV/RBC count** <**13**, ± ↑ retics, basophilic stippling; **Hb electrophoresis**: ↑ HbA_2 ($\alpha_2\delta_2$) 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; ↑ Fe, nl TIBC, ↑ ferritin, basophilic stippling, RBC **Pappenheimer bodies** (Fe-containing inclusions), **ring sideroblasts** (w/ iron-laden mitochondria) in BM
- Treatment: treat reversible causes; trial of pyridoxine, supportive transfusions for severe anemia; high-dose pyridoxine for some hereditary cases

Figure 5-2 Approach to microcytic anemias



NORMOCYTIC ANEMIAS

Pancytopenia (see below)

Anemia of chronic inflammation (ACI; *NEJM* 2005;352:1011; 2009;361:1904)
- ↓ 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 ± 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 ↓ O_2 demand with thyroid, pituitary, adrenal, or parathyroid disease → ↓ epo; can be normocytic or macrocytic

Sideroblastic anemia (see above)

Pure red cell aplasia
- Destructive antibodies or lymphocytes → ineffective erythropoiesis
- Associated with thymoma, CLL, and parvovirus infection
- Diagnostic studies: **lack of erythroid precursors on BM bx**, other lines normal
- Treatment: thymectomy if thymus enlarged; IVIg 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 **B_{12} deficiency**
- ✓ **folate** and **vitamin B_{12}**, ↑ LDH & indirect bilirubin (due to ineffective erythropoiesis)
- Smear: **neutrophil hypersegmentation**, **macro-ovalocytes**, anisocytosis, poikilocytosis

Folate deficiency

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

Vitamin B_{12} deficiency

- B_{12} present only in foods of animal origin; total body stores sufficient for **2–3 y**
- Binds to **intrinsic factor** (IF) secreted by gastric parietal cells; absorbed in terminal ileum
- Etiologies: malnutrition (alcoholics, vegans), **pernicious anemia** (PA, autoimmune disease against gastric parietal cells, a/w polyglandular endocrine insufficiency and ↑ risk of gastric carcinoma), other causes of ↓ absorption (gastrectomy, sprue, Crohn's disease), ↑ competition (intestinal bacterial overgrowth, fish tapeworm)
- Clinical manifestations: **neurologic** changes (**subacute combined degeneration**) affecting peripheral nerves, posterior and lateral columns of the spinal cord, and cortex → numbness, paresthesias, ↓ vibratory and positional sense, ataxia, dementia
- Dx: ↓ B_{12}; ↑ homocysteine and methylmalonic acid; anti-IF Ab; Schilling test; ↑ gastrin in PA
- Treatment: 1 mg B_{12} IM qd × 7 d → q wk × 4–8 wk → q month for life
  neurologic abnormalities are reversible if treated w/in 6 mo
  folate can reverse *hematologic* abnormalities of B_{12} deficiency but not *neurologic* changes (and can lead to "steal" of B_{12} stores → worsening of neuro complications)
  oral supplementation (2 mg qd) appears feasible as well (*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/B_{12} defic. or cirrhosis
- **Reticulocytosis**
- **Other causes**: hypothyroidism; MDS; meds that impair DNA synthesis (zidovudine, 5-FU, hydroxyurea, Ara-C); hereditary orotic aciduria; Lesch-Nyhan 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/10^6/y; biphasic (major peak in adolescents, 2nd peak in elderly)
- Diagnosis: pancytopenia w/ ↓ retics, BM bx w/ cytogenetics showing hypocellularity
- Etiologies: **idiopathic** (½–⅔ of cases)
  stem cell destruction: **radiation**, **chemotherapy**, **chemicals** (eg, benzene)
  idiosyncratic **med rxn** (eg, chloramphenicol, NSAIDs, sulfa drugs, gold, carbamazepine, antithyroid)
  viruses (HHV-6, HIV, EBV, parvovirus B19); also **posthepatitis** (non A, B, or C)
  immune disorders (SLE, GVHD post HSCT, thymoma)
  PNH (see below); Fanconi's anemia (congenital disorder w/ pancytopenia, macrocytic anemia, ↑ risk of MDS, AML, & SCC of head & neck, and multiple physical anomalies); telomerase (hTERT) mutation (*NEJM* 2005;352:1413)

- Treatment and prognosis
  - **allogeneic HSCT**: for *young* Pts → ~80% long-term survival and significantly ↓ risk of malignant evolution, but has risk of transplant-related morbidity & mortality; if possible avoid transfusions (and alloimmunization) pretransplant
  - **immunosuppression** (CsA/tacrolimus, ATG): 70–80% respond, with 80–90% 5-y survival in responders; 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) (qv)

Paroxysmal nocturnal hemoglobinuria (PNH)

- Acquired clonal stem cell disorder = inactivating somatic mutation of *PIG-A* gene → inability to form GPI-anchor for CD55 & CD59 (inhib of complement) → complement-mediated RBC lysis, plt aggreg., & hypercoagulability
- Clinical: intravascular **hemolytic anemia**, **hypercoagulability** (venous > arterial; esp. intraabdominal, cerebral), smooth muscle dystonias, **deficient hematopoiesis** (cytopenias); a/w aplastic anemia, MDS, and evolution to AML
- Dx: peripheral blood **flow cytometry** (↓ 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

Location	Mechanism	Examples	Mode
Intrinsic	Enzyme deficiency	G6PD deficiency	Hereditary
	Hemoglobinopathies	Sickle cell anemia, thalassemia	
	Membrane abnormalities	Hereditary spherocytosis	
		PNH	Acquired
Extrinsic	Immune-mediated	Autoimmune; drug-induced, tx rxn	
	Traumatic	MAHA; prostheses (valves, TIPS)	
	Direct infections, toxins	Malaria, babesiosis; snake & spider venoms; Wilson's; hypotonic infusions	
	Entrapment	Hypersplenism	

(*Lancet* 2000;355:1169 & 1260)

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)

Sickle cell anemia (*NEJM* 1999;340:1021; *Hematology ASH Educ Program* 2004;35)

- 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** causes ↑ HbF → ↓ painful crises, acute chest episodes and may ↓ mortality (*NEJM* 2008;358:1362); allogeneic HSCT may have a role in young Pts w/ severe disease (*Blood* 2000;95:1918) and adults (*NEJM* 2009;361:2309)
- Supportive care: 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)

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% of Pts)
- Anemia, jaundice, splenomegaly, pigmented gallstones
- Diagnosis: spherocytes on smear, ⊕ osmotic fragility test (~80% Se), ↓ eosin-5-maleimide (EMA) binding (92% Se; 99% Sp)
- Treatment: folate, splenectomy for moderate and severe HS

Paroxysmal nocturnal hemoglobinuria (see above)

Autoimmune hemolytic anemia (AIHA)

- Acquired, antibody-mediated RBC destruction
- **Warm AIHA**: **IgG** Abs opsonize RBCs *at body temp* → removal by spleen
  Etiologies: idiopathic, lymphoproliferative 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, IVIg, 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, mech. 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

Causes of Splenomegaly

Etiology	Comments
RE* system hyperplasia	Hemolytic anemia, sickle cell disease, **thalassemia major**
Immune hyperplasia	Infection (HIV, EBV, CMV, TB, **malaria**, **kala azar**, ***Mycobacterium avium*** complex), autoimmune disorders (SLE, RA with Felty's syndrome), sarcoidosis, serum sickness
Congestion	Cirrhosis, CHF, portal/splenic vein thrombosis, **schistosomiasis**
Infiltration (nonmalignant)	Lysosomal storage disorders (**Gaucher's**, Niemann-Pick), glycogen storage diseases, histiocytosis X, splenic cysts
Neoplasm	**MPN (CML**, **PMF**, **PV**, **ET)**, **CMML**, **acute leukemia**, **lymphoma (NHL**, **HL**, **hairy cell leukemia**, **CLL**, **PLL**, **Waldenstrom's)**, T-LGL leukemia, multiple myeloma, amyloid

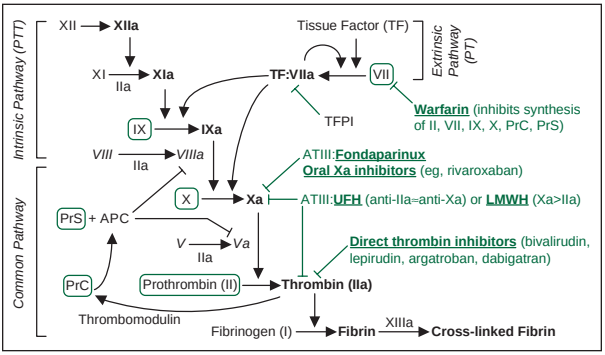
boldface = causes of massive splenomegaly; *Reticuloendothelial

Clinical Characteristics of Bleeding Disorders		
Feature	**Platelet/Vascular Defect**	**Coagulation Defect**
Site	Skin, mucous membranes	Deep in soft tissues (muscles, joints)
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas
Bleeding	After minor cuts: yes After surgery: immediate, mild	After minor cuts: unusual After surgery: delayed, severe

Purpura

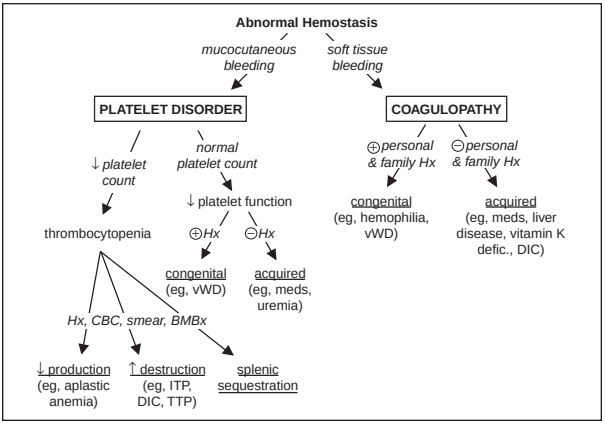
- **Nonblanching** purple/red lesions due to extravasation of RBCs into dermis
- **Nonpalpable** (macular; ≤3 mm in diameter = petechiae; >3 mm = ecchymoses)
  platelet disorder: thrombocytopenia, defect in platelet function
  thromboemboli: DIC, TTP, cholesterol or fat emboli
  trauma or vascular fragility (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



THROMBOCYTOPENIA (Plt count <150,000/μL)

Thrombocytopenia and Risk of Bleeding	
Platelet count (cells/μL)	**Risk**
>100,000	No ↑ risk
50,000–100,000	Risk with major trauma; can proceed with general surgery
20,000–50,000	Risk with minor trauma or surgery
<20,000	Risk of *spontaneous* bleeding (less so with ITP)
<10,000	Risk of severe, life-threatening bleeding

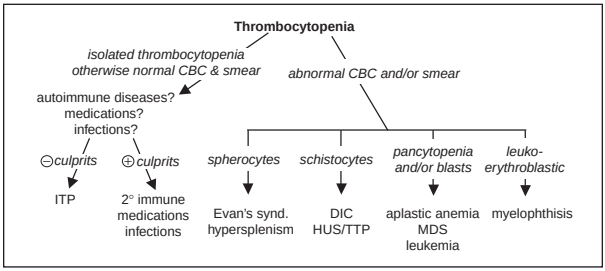
Etiologies

- ↓ **production**
  - **hypocellular bone marrow**: aplastic anemia (qv), rarely MDS, drugs (eg, thiazides, antibiotics), alcohol, cirrhosis
  - **hypercellular bone marrow**: MDS, leukemia, severe megaloblastic anemia
  - **marrow replacement**: myelofibrosis, hematologic and solid malignancies, granulomas
- ↑ **destruction**
  - **immune-mediated** (distinguish primary from secondary; *Blood* 2009;113:2386)
    - Primary (idiopathic): immune thrombocytopenic purpura (**ITP**, see below)
    - Secondary: 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**
  - ↑ destruction → 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: ↑ 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, TSH, parvovirus, & CMV PCR. *Anti-plt Ab tests not useful.*
- Clinical manifestations: insidious onset of mucocutaneous bleeding; ♀:♂ = 3:1
- Treatment: goals based on individual Pt
  rarely indicated if plt >50,000/μL unless bleeding, trauma/surgery, anticoag, comorbidities
  steroids, IVIg and splenectomy mainstay of initial Rx, but TPO-receptor agonists (eg, romiplostim and eltrombopag) likely to play increasing role

Treatment of Primary ITP in Adults		
Approach	**Treatment**	**Notes**
First-line	**Steroids:** prednisone 0.5–2 mg/kg/d PO tapered ~4 wk vs. dexamethasone 40 mg PO × 4 d	70–90% initial response ~20% sustained remission ↓ Mϕ FcR & ↓ anti-plt Ab
	Anti-Rh(D) Ig 75 μg/kg/d IV	For Rh(D) ⊕ Pts w/ spleen Ab-coated RBCs overwhelm Mϕ FcR
	IVIg (1 g/kg/d IV × 2–3 d) *consider if need rapid ↑ in plt*	Up to 80% initial response Blocks Mϕ FcR, ↓ anti-plt Ab
Second-line	**Splenectomy**	Persistent disease >6 mo ~65% long-term remission
	Rituximab (anti-CD20) ± dex	anti–B-cell Ab
	Romiplostim or eltrombopag	TPO-R agonists → ↑ plt prod
	Azathioprine, cyclophosphamide	Immunosuppressants
	Danazol, vincristine	↓ plt clearance
Bleeding	Aminocaproic acid	Inhibits plasmin activation
	Methylprednisolone 1g/d IV × 3 d	See above
	IVIg	See above
	Platelet transfusion	Given w/ IVIg or anti-Rh(D)
Refractory	Romiplostim or eltrombopag	See above
	Autologous HSCT	Limited data, investigational

(*NEJM* 2006;355:1672 & 2007;357:2237; *Lancet* 2008;371:395 & 2009;373:641; *Blood* 2010;115:168)

Overview of Heparin-Induced Thrombocytopenias		
Feature	**Type I**	**Type II**
Mechanism	Direct effect of heparin (nonimmune)	Immune (Ab)-mediated IgG against plt factor 4—heparin complex
Incidence	10–20%	1–3% with UFH, 0–0.8% LMWH
Onset	After 1–4 d of heparin therapy	After 4–10 d; but can occur in <24 h if prior exposure w/in 100 d (persistent Ab). Postop highest risk. Can occur after heparin d/c
Platelet nadir	>100,000/μL	~60,000/μL, ↓ >50%
Sequelae	None	Thrombotic events (HITT) in 30–50% Rare hemorrhagic complications
Management	Can continue heparin and observe	**Discontinue heparin** Alternative anticoagulation

(*NEJM* 2001;344:1286; *Chest* 2008;133:340S & 2009;135:1651)

- Pathophysiology (type II): Ab binds heparin-PF4 → immune complex binds to plt → **plt activation**, further PF4 release → plt aggregates removed from circulation → **thrombocytopenia**; procoagulants released by plts and tissue factor released by endothelial cells damaged by HIT Abs → **prothrombotic state**
- Diagnosis: need to meet *clinical and pathologic* criteria (⊕ HIT Ab alone ≠ HIT)
  Clinical: plt <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)
  Pathologic: ⊕ HIT Ab using PF4-heparin ELISA (~90% Se, re✓ if high suspicion), may confirm w/ fxnal plt aggregation (serotonin-release) assay (>90% Sp)

- Treatment of type II (*NEJM* 2006;355:809; *Chest* 2008;133:340S)
  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): anticoagulate 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;133:340S)

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 & plts → 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, HSCT, 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"

DISORDERS OF PLATELET FUNCTION

Mechanisms and Etiologies of Platelet Function Abnormalities		
Function	**Inherited**	**Acquired**
Adhesion	Bernard-Soulier; vWD	Uremia; acquired vWD
Aggregation	Afibrinogenemia Glanzmann's thrombasthenia	Ticlopidine, clopidogrel, GP IIb/IIIa Dysproteinemias (myeloma)
Granule release	Chediak-Higashi syndrome Hermansky-Pudlak syndrome	Drugs (ASA, NSAIDs); liver disease; MPN; cardiopulmonary bypass

Tests of platelet function
- 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 (vWD) (*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,** ± ↑ PTT, ± ↓ 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

Uremic Bleeding
- Uremia → platelet dysfunction including ↓ aggregation, impaired adhesiveness
- Treatment: **dDAVP**, cryoprecipitate, correct anemia (improves plt aggregation and adhesion by increasing plt interactions with endothelium), consider holding anti-plt agents

Screening Test Abnormalities in Inherited and Acquired Coagulopathies				
PT	**PTT**	**Factors**	**Inherited**	**Acquired**
↑	↔	VII	FVII defic.	**Vit. K defic.**; **liver dis.**; factor inhib.
↔	↑	VIII or IX	Hemophilias, vWD	**Antiphospholipid Ab**; factor inhib.
↑	↑	I, II, V, or X	Fbgn, FII, or FV defic.	**DIC**; **liver dis.**; factor inhib.

Further coagulation tests

- Mixing study: useful if ↑ PT or PTT; mix Pt's plasma 1:1 w/ normal plasma and retest
  PT/PTT normalizes → factor **deficiency**; PT/PTT remains elevated → factor **inhibitor**
- Coagulation factor levels: useful if mixing study suggests factor deficiency
  DIC → all factors consumed; ∴ ↓ 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 fibrin)

Hemophilias (*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 VIIa 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 VIIa**, porcine factor concentrates, activated prothrombin complex; others → high-purity human factor, plasmapheresis, immunosupp. 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, ↓ hapto; *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 (↓ stores), **warfarin**

Properties and Antidotes for Anticoagulants & Fibrinolytics			
Anticoag.	**$t_{1/2}$**	**Labs**	**Rx for O/D w/ serious bleeding***
UFH	60–90′, RES	↑ PTT	**Protamine** IV 1 mg/100 U UFH (max 50 mg). For infusions, dose to reverse 2× UFH given per h
Bivalirudin	25′, K	↑ PTT	Dialysis
Lepirudin	80′, K	↑ PTT	Dialysis
Argatroban	45′, L	↑ PTT	? Dialysis
Enoxaparin, Dalteparin	2–7°, K	(anti-Xa)	? Protamine (reversal incomplete)
Fondaparinux	24°, K	(anti-Xa)	? Dialysis
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	↓ fbgn ↑ FDP	**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			
Risk factor	**Prevalence**	**VTE**	**Comments**
Factor V Leiden	3–7%	4.3×	Activated protein C (APC) resist.
Prothrombin mutation	2%	2.8×	G20210A → ↑ prothrombin level
Hyperhomocysteinemia	5–10%	2.5×	Inherited or acquired
Protein C deficiency	0.02–0.05%	11×	Warfarin-induced skin necrosis risk
Protein S deficiency	0.01–1%	32×	
Antithrombin III def.	0.04%	17.5×	May be relatively heparin-resistant

Prevalence is in Caucasians. (*NEJM* 2001;344:1222; *Hematology ASH Educ Prog* 2007;127)

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

Diagnostic evaluation

- 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 nephrotic syndrome, PNH (especially if mesenteric thrombus).
- Consider *JAK2* mutation screen if suspect myeloprolif 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 (⊕ 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: nontreponemal 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 (lifelong for most Pts)
  - Intensity of anticoagulation controversial (*Arthritis Rheum* 2007;57:1487)
  - INR 2–3 for an initial *venous* thrombosis (*NEJM* 2003;349:1133; *J Thromb Haemost* 2005;3:848)
  - 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)

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*, rickettsiae, 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 fasciitis, PAN
Endocrine	Adrenal insufficiency
Neoplasm	Hodgkin's lymphoma, CML, mycosis fungoides, carcinomas, mastocytosis
Atheroembolic disease	Cholesterol emboli syndrome
Hypereosinophilic syndrome	Multiorgan system involvement including heart and CNS, associated with FIP1L1-PDGFRA fusion (*NEJM* 2003;348:1201) *D8 16kit*-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 Toxoplasmosis
Immunologic	Collagen vascular disease, drug hypersensitivity (eg, phenytoin), serum sickness, histiocytosis X, Castleman's and Kawasaki disease
Neoplasm	Lymphoma, leukemia, amyloidosis, metastatic carcinoma
Other	Sarcoidosis; lipid storage diseases
Factors that favor biopsy	Age (>40 y), size (>2 cm), location (supraclavicular is always abnormal), duration (>1 m). Consistency (hard *vs.* rubbery *vs.* soft) & tenderness are not reliable.

Blood Products and Indications	
Packed red blood cells (PRBCs)	For acute blood loss or to ↑ O_2-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 & 2001;345:1230). 1 U PRBC → ↑ Hb by ~1 g/dL. Large-volume transfusion PRBC → ↓ Ca, ↑ K, ↓ plt, ↑coags (may need concurrent transfusion plt & FFP).
Platelets (plts)	Plts <10,000/μL *or* <20,000/μL with infection *or* ↑ bleeding risk *or* <50,000/μL with active bleeding or preprocedure. 6 U pooled donor plts ≈ 1 single donor plt apheresis unit (reduces alloimmunization) → ↑ plt count by ~30–60,000/μL. *Contraindicated* in TTP/HUS, HELLP, HIT. Refractory: ↑ <5000/μL 30–60 min posttransfusion. Suggests *alloimmunization* → trial ABO-matched plts. If still refractory ✓ panel reactive Abs (PRA) to assess utility HLA-matched plts.
Fresh frozen plasma (FFP)	Contains all coagulation factors. For bleeding due to deficiency of multiple coagulation factors (eg, DIC, TTP/HUS, liver disease, warfarin excess, dilution) *or* PT >17 sec preprocedure.
Cryoprecipitate	Enriched for fibrinogen, vWF, VIII, and XIII. For bleeding in vWD, factor XIII deficiency or fibrinogen <100 mg/dL.
Irradiated	Prevents donor T-cell proliferation. Use if risk of transfusion-assoc GVHD (HSCT, heme malig, congenital immunodef).
CMV-negative	From CMV-negative donors. For CMV-seronegative pregnant women, transplant candidates/recipients, SCID, AIDS Pts.
Leukoreduced	WBCs cause HLA alloimmunization and fever (cytokine release) and carry CMV. For chronically transfused Pts, potential transplant recipients, h/o febrile nonhemolytic transfusion reaction, cases in which CMV-negative products are desired but unavailable.
Intravenous immune globulin (IVIg)	Polyvalent IgG from >1000 donors. For postexposure prophylaxis (eg, HAV), certain autoimmune disorders (eg, ITP, Guillain-Barré, MG ? CIDP), congenital or acquired hypogammaglobulinemia (CVID, CLL).
Plasmapheresis and cytapheresis	Removes Ig molec wt subst. (eg, cryoglobulinemia, Goodpasture's, Guillain-Barré, hyperviscosity syndrome, TTP) or cells (eg, leukemia w/ hyperleukocytosis, sx thrombocytosis, sickle cell) from plasma.

Transfusion Complications			
Noninfectious	**Risk (per unit)**	**Infectious**	**Risk (per unit)**
Febrile	1:100	CMV	common
Allergic	1:100	Hepatitis B	1:220,000
Delayed hemolytic	1:1000	Hepatitis C	1:1,600,000
Acute hemolytic	<1:250,000	HIV	1:1,800,000
Fatal hemolytic	<1:100,000	Bacteria (PRBCs)	1:500,000
TRALI	1:5000	Bacteria (platelets)	1:12,000

(*NEJM* 1999;340:438; *JAMA* 2003;289:959)

Transfusion reactions

- For all reactions (except minor allergic): **stop transfusion**; send remaining blood product and fresh blood sample to blood bank
- **Acute hemolytic**: fever, hypotension, 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."

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, CMML, atypical CML)
Myeloid/lymphoid malig. a/w eos and *PDGFR* or *FGFR1* Δ	Consider imatinib Rx for *PDGFR* rearrangement

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/10^6/y; median age ~65 y; male predominance (1.8x)
- **Idiopathic** or 2° to chemo w/ **alkylating agents**, **topo II inhib.**;↑ risk w/ radiation, benzene
- Clinical manifestations: **anemia** (85%), neutropenia (50%), thrombocytopenia (25%)
- Diagnosis: dysplasia (usually multilineage) in peripheral smear (ovalomacrocytes, **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 × 10^9/L); r/o 2° BM Δs due to defic. of B_{12}, folate, copper; viral infections (eg, HIV); chemotherapy; alcohol abuse; lead or arsenic toxicity

WHO 2008 Classification Systems for MDS	
Classification	**Bone Marrow Features**
Refractory cytopenias 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 cytopenias with multilineage dysplasia (RCMD)	≥10% dysplasia ≥2 lines <5% blasts, w/ 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
Refractory anemia with excess blasts – 2 (RAEB-2)	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* 2005;352:549); DNA demethylating agents (azacitidine or decitabine)
  Intermediate/high risk → DNA demethylating agents, combination **chemo** (akin to AML therapy) or **allogeneic HSCT** (HLA-matched sibling donor preferred) if age <55 (consider reduced-intensity transplant for ages 55–75)
  Hypoplastic MDS (rare) → can consider **immunosuppression** (CsA, ATG, prednisone)
- Prognosis: IPSS correlates with **survival** and **progression to AML**

International Prognostic Scoring System (IPSS)					
	Score				
	0	0.5	1	1.5	2
Blasts (%)	<5	5–10	–	11–20	21–30
Karyotype	Good	Int.	Poor	–	–
Cytopenias	0 or 1	2 or 3	–	–	–

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)

General (*NEJM* 2006;355:2452; *Nat Rev Clin Oncol* 2009;6:627)
- 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–⊕; 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 ~100%, ET ~50%, PMF ~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 (Gaisböck's syndrome)
- *Absolute* ↑ RBC: 1° (PV, other MPD) or 2° due to **hypoxia**; **carboxyhemoglobinemia**; **inappropriate erythropoietin** (renal, hepatic, cerebellar tumors); Cushing's syndrome

Clinical manifestations (common between PV and ET)
- Symptoms → often termed "vasomotor symptoms"
  - **hyperviscosity** (erythrocytosis): headache, dizziness, tinnitus, blurred vision
  - **thrombosis** (hyperviscosity, thrombocytosis): transient visual disturbances (amaurosis, ocular migraine); Budd-Chiari syndrome; erythromelalgia = intense burning, pain, and erythema of extremities due to microvascular thrombi; ↑ risk of **DVT**, **MI**, **stroke.** Risk of thrombosis is highly correlated with elevated WBC in PV and ET (see below).
  - **bleeding** (abnormal platelet function): easy bruising, epistaxis, GI bleeding
  - ↑ histamine from basophils → **pruritus**, peptic ulcers; ↑ uric acid (cell turnover) → gout
- Signs: **plethora**, **splenomegaly**, hypertension, engorged retinal veins

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**
  If Epo ↑, then ✓ SaO_2 or PaO_2, carboxyhemoglobin
- ***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 B_{12}
- 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 × $10^6/\mu L$)
- Supportive: allopurinol (gout), H_2-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 THROMBOCYTHEMIA (ET)

Definition
- ↑ in platelets (>450,000/μL) ± ↑ RBC and granulocytes

Etiologies of thrombocytosis
- 1° = ET or other MPN; myelodysplastic syndromes (5q-syndrome)
- 2° = **reactive thrombocytosis**: inflammation (RA, IBD, vasculitis), infection, acute bleeding, iron deficiency, postsplenectomy, neoplasms (particularly Hodgkin's disease)
- Of Pts w/ plt >$10^6/\mu L$, <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

Treatment of ET			
Risk	**Features**	**ASA 81 mg qd**	**Cytoreduction**
Low	Age <60 *and* no h/o thrombosis *and* plt $<1.5 \times 10^6/\mu L$ *and* no CV risk factors	Consider for vasomotor symptoms	No
Int.	Neither low nor high	±	Consider if plt $>1.5 \times 0^6/\mu L$
High	Age ≥60 *or* h/o thrombosis *or* plt $>1.5 \times 10^6/\mu L$	⊕	**Hydroxyurea** superior to **anagrelide** (*NEJM* 2005;353:33) Goal plt <400,000/μL

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")

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 (*Blood* 2009;114:937)

- **Peripheral smear**: anemia, thrombocytopenia, variable WBC (50% p/w ↑ WBC, 50% p/w normal or ↓ 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, ↑ PO_4, ↓ 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)

4 Major Subtypes	Examples
With recurrent genetic abnormalities	t(8;21); inv(16); t(15;17); 11q23 anomalies
With myelodysplasia-related change	w/ or w/o antecedent MDS or MPN
Therapy-related	eg, alkylating agents or topoisomerase inhibitors
Not otherwise specified	w/ min differentiation; w/o maturation; w/ maturation; myelomonocytic; monoblastic/monocytic; erythroid; megakaryoblastic

AML Genetics (*JCO* 2005;23:6285; *Blood* 2007;109:431 & Grimwade, *Blood* 2010;epub)

	Favorable Prognosis	Unfavorable Prognosis
Karytope	t(15;17) in APL; t(8;21); inv(16); t(16;16)	–5; –7; 3q26 aberrations, t(6;9); 11q23 aberrations; complex karyotype
Gene mutations	*NPM1*; *CEBPA*	*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/m^2) superior to standard dose (45 mg/m^2) (*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;301:2349)
- 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 & neutropenia; 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)

Classification
- Lymphoblastic neoplasms may present as acute leukemia (ALL) with >**20% BM blasts,** or as lymphoblastic lymphoma (LBL) w/ mass lesion & <20% BM blasts. ALL and LBL are considered the same disease with different clinical presentations.
- Morphology: **no granules** (granules seen in myeloid lineage)
- Cytochemistry: ⊕ terminal deoxynucleotidyl transferase (TdT) in 95% of ALL
- Cytogenetics (*JCO* 2005;23:6306): t(9;22) = Philadelphia chrom (Ph) ~25% of adults w/ ALL
- Immunohistochemistry: 3 major phenotypes (Burkitt's usually treated differently)

WHO Immunophenotype Classification of ALL

WHO Type	Adult Freq	Immunohistochemistry
Precursor B-cell	75%	⊕ TdT, ⊕ CD19; variable CD10, CD20
Precursor T-cell	20%	⊕ TdT, ⊕ T-cell Ag (CD2, 3, 5, 7) ⊖ CD10, ⊖ mature T-cell Ag (CD4, 8)
Burkitt's Lymphoma*	5%	⊖ TdT, ⊕ surface Ig

*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 ⊖) now 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, thrombocytosis, **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 inhib**: 1st line Rx chronic phase; continued indef in responders
  - imatinib, dasatinib & nilotinib are selective inhib of BCR-ABL (*Blood* 2008;112:4808)
  - **imatinib** active in chronic, accelerated, blastic phases (but less as disease advances)
    - imatinib resistance is associated with *BCR-ABL* mutation or amplification
  - **dasatanib** 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, cytopenias, ↓ PO_4, 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

Response	Definition	Goal time
Hematologic	WBC <10K, Plt <450, <5% myelocytes & metamyelocytes, <20% basos, no immature cells in blood, no extramedullary involvement	3 mo
Cytogenetic	Absence of the Ph chromosome in metaphase cells	12 mo
Molecular	3-log reduction by quantitative PCR	12–18 mo

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
- ↑ 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+, CD19+, CD20+, CD23+. CD38+ or ZAP70+ a/w unmutated Ig variable heavy chain region & worse prognosis
- **Bone marrow**: normo- or hypercellular; infiltrated w/ small B-cell lymphocytes (≥30%)
- **Lymph nodes**: infiltrated w/ small lymphocytic or diffuse small cleaved cells = SLL
- **Cytogenetics**: 11q22-23 & 17p13 unfavorable; trisomy 12 neutral; 13q14 favorable

CLL Staging

Rai System		Median survival	Binet System	
Stage	Description		Description	Stage
0	Lymphocytosis *only*	>10 y	<3 node areas	A
I	⊕ lymphadenopathy	7 y	>3 node areas	B
II	⊕ hepatosplenomegaly			
III	⊕ anemia (not AIHA)	1–2 y	Anemia or thrombocytopenia	C
IV	⊕ thrombocytopenia (not ITP)			

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)
  ≈ survival w/ single agents, although higher response rate w/ F (*NEJM* 2000;343:1750)
  combination regimens (ie, FR, FC, FCR, PCR) superior to monoRx (*Lancet* 2007;370:230)
- 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

Factor	Years	Factor	Years
Cytogenetics		*CD38 expression*	
17p-	2.5	Low (<20–30%)	8
11q-	6.6	High (>20–30%)	Unclear
Trisomy 12 or Normal	9	*Zap-70 expression*	
13q-	11	Low (<20–30%)	24.3
IgVH gene status		High (>20–30%)	9.3
Mutated (>2%)*	>24	β2-microglobulin: higher levels correlate with	
Unmutated (<2%)*	<8	disease stage, tumor burden and a poorer prognosis.	

*% difference c/w germline. *NEJM* 2004;351:893 & 2005;353:1793; *Blood* 2007;109:4679; *JCO* 2009;27:1637.

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**) ± mediastinal lymphadenopathy; **nodal** disease with **orderly, anatomic spread** to adjacent nodes
  - **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; ✓ 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 Aϕ elevated

Ann Arbor Staging System with Cotswolds Modifications

Stage	Features
I	Single lymph node (LN) region
II	≥2 LN regions on the same side of the diaphragm
III	LN regions on both sides of the diaphragm
IV	Disseminated involvement of one or more extralymphatic organs

Modifiers: A = no symptoms; B = fever, night sweats or weight loss; X = bulky disease = greatest transverse diam. of mediastinal mass / max diam. of chest wall >1/3 on CXR or >10 cm if in abd; E = involves single contiguous extranodal site; H = hepatic; S = splenic

HODGKIN LYMPHOMA (HL)

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

Lymphocyte rich	5%	Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis
Nodular sclerosis	60–80%	Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I/II at dx
Mixed cellularity	15–30%	Pleomorphic; older age; male predominance; ≥50% stage III/VI at presentation; intermediate prognosis
Lymphocyte depletion	<1%	Diffuse fibrosis and large numbers of RS cells; older, male patients; disseminated at dx; seen in HIV; worst prognosis

- **Nonclassical** (5%): nodular lymphocyte predominant (NLP); involves peripheral LN
  80% present in 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)		
Negative Prognostic Indicators	**Total # of Indicators**	**5-y PFS**
Albumin <4 g/dL	0	84%
Hb <10.5 g/dL	1	77%
Male	2	67%
Age >45 y	3	60%
Stage IV	4	51%
WBC ≥ 15k/μL	≥5	42%
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		
Type	**Examples**	**Associated genetic abnl**
Mature B Cell	Diffuse large B-cell lymphoma (DLBCL)	
	Follicular lymphoma	*IGH-BCL2*
	CLL/small lymphocytic lymphoma	
	Mantle cell	*t(11;14) BCL1-IgH* → cyclin D1 dysreg
	Marginal zone lymphoma (nodal, extranodal (MALT), splenic)	*AP12-MALT1* & *BCL-10-Ig enhancer*
	Burkitt's lymphoma	*8q24, c-MYC*
	Hairy cell leukemia (p/w fatigue, ↓ monos, massive splenomegaly; ⊕ TRAP)	
Mature T Cell & NK Cell	Peripheral T cell lymphoma	
	Mycosis fungoides (cutaneous lymphoma) / Sézary syndrome (+ LAN)	
	Anaplastic large cell lymphoma	Some *ALK1* ⊕
	Angioimmunoblastic T cell lymphoma	

(*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 I^{131} tositumomab and Y^{90} 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;359:613);
  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

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

(*Blood* 2004;104:1258)

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

International Prognostic Index (IPI) for Aggressive NHL		
Factors: age >60, stage III/IV, ≥2 extranodal sites, performance status ≥2, LDH >nl		
# Factors	**Complete Response**	**5-y Overall Survival**
0–1	87%	73%
2	67%	51%
3	55%	43%
4–5	44%	26%
Revised IPI Prognosis in Patients Rx'd with CHOP-R		
Factors	**% at dx**	**4-y Overall Survival**
0	10%	94%
1–2	45%	79%
3–5	45%	55%

(*NEJM* 1993;329:987; Blood 2007;109:1857).

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

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) = lytic bone lesions, 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;356:2582)*
  - solitary bone plasmacytoma: 1 lytic lesion w/o M protein, plasmacytosis, or other ROTI
  - extramedullary plasmacytoma: usually upper respiratory tract
  - plasma cell leukemia: plasma cell count >2000/μL
  - nonsecretory MM: no M protein, but marrow plasmacytosis & ROTI
- Ddx 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
- β2-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

Stage	ISS Criteria	Durie-Salmon Criteria	Median survival
I	**β2-microglobulin** <3.5 mg/L *and* **albumin** >3.5g/dL	*all of the following:* Hb >10 g/dL; Ca ≤12 mg/dL; 0–1 lytic bone lesions; IgG <5 g/dL or IgA <3 g/dL or urine light chain <4 g/24 h	61 mo
II	fulfilling criteria for neither I nor III		55 mo
III	**β2-microglobulin** >5.5 mg/L	*any of the following:* Hb <8.5 g/dL; Ca >12 mg/dL; >5 lytic bone lesions; IgG >7 g/dL or IgA >5 g/dL or urine light chain >12 g/24 h	30 mo for IIIA 15 mo for IIIB
Subclassification by serum Cr: A <2 mg/dL; B ≥2 mg/dL			

Treatment (*NEJM* 2004;351:1860; *Lancet* 2009;374:324; *NEJM* 2009;360:2645)
- Treatment not indicated for smoldering MM or asx stage I disease
- In general, Pts divided into two groups: transplant eligible vs. not eligible
- If *not* transplant eligible: **systemic chemotherapy** (↑ median survival, but not curative) regimens include melphalan + prednisone + either thalidomide/lenalidomide (*Lancet* 2007;370:1209) or proteasome inhibitor if high risk (bortezomib; *NEJM* 2008;359:906) lenalidomide + dexamethasone for relapsing/refractory MM (*NEJM* 2007;357:2123, 2133)
- If transplant *eligible*: **high-dose chemo** + **auto-HSCT.** Not curative, but ↑ survival c/w conv. chemo (*NEJM* 2009;360:2645). Offer if <70 y w/ good performance status. Many chemo regimens used incl. thalidomide or lenalidomide + dex, bortezomib + dex, vincristine/doxorubicin/dex, etc.
  Double auto-HSCT ↑ survival (*NEJM* 2003;349:2495), + thalidomide → ↑ response rate but no Δ in overall survival (*NEJM* 2006;354:1021)
- Local radiation for solitary or extramedullary plasmacytoma
- Adjunctive Rx
  bone: **bisphosphonates** (*NEJM* 1996;334:488; & *JCO* 2007;25:2464); XRT for sx bony lesions
  renal: avoid NSAIDs & IV contrast; consider plasmapheresis for acute renal failure
  hyperviscosity syndrome: plasmapheresis
  infections: consider IVIg for recurrent infections
- Common **toxicities** of Rx: melphalan + prednisone → infxn, myelosuppression; thalidomide → thromboembolism, bradycardia, periph. neuropathy, neutropenia, rash (*Blood* 2008;111:3968); bortezomib → periph. neuropathy

Monoclonal Gammopathy of Uncertain Significance (MGUS)

Definition and epidemiology (*NEJM* 2006;355:2765)
- M protein <3 g/dL, no urinary Bence Jones proteins, marrow plasmacytosis <10%, no ROTI
- Prevalence ~3% in population >50 y of age, ~5% in population >70 y of age, and 7.5% in population >85 y of age (*NEJM* 2006;354:1362)

Management
- ✓ CBC, Ca, Cr, SPEP and UPEP with immunofixation to exclude MM
- Close observation: repeat SPEP in 6 mos and then yearly thereafter if stable

Prognosis (*NEJM* 2002:346:564)
- ~1%/y or ~25% lifetime risk → MM, WM, amyloidosis, or malign. lymphoproliferative dis.
- Abnormal serum-free light chain ratio: ↑ risk of progression to MM (*Blood* 2005;105:812)

Waldenström's Macroglobulinemia (WM)

Definition (*JCO* 2005;23:1564; *Blood* 2007;109:5096)
- 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, Δ MS
  cardiopulmonary: congestive heart failure, pulmonary infiltrates
  type I **cryoglobulinemia → Raynaud's phenomenon**
  platelet dysfxn → mucosal bleeding
- **IgM deposition** (skin, intestine, kidney); amyloidosis and glomerulopathy
- **Autoantibody activity of IgM**
  chronic AIHA (prominent **rouleaux**; 10% Coombs' ⊕ = AIHA)
  peripheral neuropathy: may be due to IgM against myelin-associated glycoprotein

Diagnostic evaluation
- SPEP + immunofixation with IgM >3 g/dL; 24-h urine for UPEP (only 20% have ⊕ UPEP)
- Bone marrow biopsy: ↑ plasmacytoid lymphocytes; β2-microglobulin for prognostic eval
- **Relative serum viscosity**: defined as ratio of viscosity of serum to H_2O (nl ratio 1.8) hyperviscosity syndrome when relative serum viscosity >**5–6**

Treatment (*NCCN Version* 3.2010)
- Hyperviscosity: **plasmapheresis**
- Symptoms (eg, progressive anemia): systemic chemotherapy w/ chlorambucil, fludarabine, cladribine, rituximab, bortezomib or combination therapy
- Thalidomide and HSCT are investigational modalities

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplantation of donor pluripotent cells that can reconstitute all recipient blood lineages

Categories of Stem Cell Transplantation		
Feature	**Allogeneic (Allo)**	**Autologous (Auto)**
Donor-recipient relationship	Immunologically distinct	Donor is also recipient
Graft-versus-host disease	Yes	No
Graft-versus-tumor effect	Yes	No
Risk of graft contam. w/ tumor	No	Yes
Relapse risk (leukemia)	Lower	Higher
Transplant-related mortality	Higher	Lower

- **Types of Allo HSCT**: *based on donor/recipient matching of major HLA antigens on Chr. 6* (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
  Umbilical cord blood: HSC processed at birth & stored; ↓ risk of GVHD; tolerate mismatch
- **Graft-versus-host disease (GVHD)**: *undesirable* side effect of allo HSCT allogeneic T cells view host cells as foreign; ↑ incid. w/ mismatch or unrelated donors
- **Graft-versus-tumor (GVT)** effect: *desirable* consequence of allo HSCT; allogeneic 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, CLL, MDS, lymphoma)
- **Nonmalignant disease**: allo HSCT replaces abnl lymphohematopoietic system w/ one from nl donor (eg, immunodef., aplastic anemia, hemoglobinopathies, ? autoimmune dis.)

Transplantation procedure

- **Preparative regimen**: *chemotherapy* and/or *immunosuppression* prior to transplantation
  myeloablative (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			
Timing	**<30 d**	**30–90 d**	**>90 d**
Regimen-related	Pancytopenia		Growth failure
	Mucositis, rash, alopecia		Hypogonadism/infertility
	Nausea, vomiting, diarrhea		Hypothyroidism
	Peripheral neuropathies		Cataracts
	Hemorrhagic cystitis		Avascular necrosis of bone
	Veno-occlusive disease		2nd malignancy
	Interstitial pneumonitis		
Immune-mediated	Acute GVHD		Chronic GVHD
	Primary graft failure		Secondary graft failure

- **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
  Treatment: high-dose corticosteroids (limited data)
- **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 allogeneic 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

	Time after transplant and associated risk factors		
Class of pathogen and associated prophylaxis	**Days 0–30** Mucositis Organ dysfunction Neutropenia	**Days 30–90** Acute GVHD ↓ cellular immunity	**>90 days** Chronic GVHD ↓ cellular & humoral immunity
Viral acyclovir to d 365 (HSV/VZV); valganciclovir or ganciclovir if CMV ⊕ (monitor until d 100 or until no longer immunesupp.)	Respiratory and enteral viruses HSV*	CMV*, HHV 6 & 7 EBV-related lymphoma	VZV*, BK/JC
Bacterial antibiotics (eg, fluoroquinolone) while neutropenic	Gram ⊕ cocci (coagulase-negative staph., *S. aureus*, *S. viridans*) GNRs (*Enterobacteriaceae*, *Pseudomonas*, *Legionella*, *S. maltophilia*)		Encapsulated bacteria
Fungal fluconazole or posaconazole (*NEJM* 2007;356:335) to d 75 for *Candida*	*Candida* spp.		
	Aspergillus spp.		
Parasitic TMP-SMX to d 180 (or off immunosuppression) for PCP		*T. gondii* *P. carinii* *S. stercoralis*	*T. gondii* *P. carinii*

*Primarily among persons who are seropositive before transplant

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 asx at presentation and are detected incidentally by imaging
- **Endobronchial growth** of 1° tumor: **cough**, **hemoptysis**, **dyspnea**, wheezing, post–obstructive pneumonia; more common with squamous or small cell (central location)
- **Regional spread**
  - **pleural effusion**, pericardial effusion, hoarseness (recurrent laryngeal nerve palsy), dysphagia (esophageal compression), stridor (tracheal obstruction)
  - **Pancoast's syndrome**: apical tumor → brachial plexus involvement (C8, T1, T2) → Horner's syndrome, shoulder pain, rib destruction, atrophy of hand muscles
  - **SVC syndrome** (*NEJM* 2007;356:1862): central tumor → SVC compression → face or arm swelling (>80%), venous distention of neck & chest wall (~60%), dyspnea/cough (~50%), HA (~10%); Rx = steroids & diuretics, XRT ± chemo 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**
    - PTH-rP (squamous cell) → **hypercalcemia**
  - *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), or sputum cytology (for central lesions)
- **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					
	N stage	N0	N1	N2	N3
T/M stage	**Definition**	no ⊕ nodes	ipsilat. hilar	ipsilat. mediast.	contralat. or supraclav.
T1	T ≤2 cm (T1a) or T >2–3 cm (T1b)	IA	IIA		
T2	T ≤5 cm (T2a) or T 5–7 cm (T2b)	IB/IIA	IIA/B		
T3	T >7 cm or invasion of chest wall, diaph., mediast. pleura, pericard.	IIB	IIIA		
T4	Invasion of mediast., heart, great vessels, trachea, esoph, vertebrae; separate tumor nodule ipsilat lobe			IIIB	
M1a	Nodules contralat lobe; pleural nodules or malignant effusion	IV			
M1b	Distant metastasis				

NSCLC treatment (*NCCN 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 IIIB 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)
  no single regimen proven superior (*NEJM* 2002;346:92)
  palliative radiation used to control local symptoms caused by tumor or metastasis
  solitary brain metastasis: surgical resection + whole brain irradiation may ↑ survival
- **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, ♀, nonsmokers, bronchioalveolar histology)
  ALK inhibitors in clinical trials for *EML4-ALK* ⊕ NSCLC

NSCLC Simplified Staging Schema, Treatment, and 5-y Survival				
Stage	**% at dx**	**Definition**	**Treatment**	**5-y (%)**
I	10-20	Isolated lesion	Surgery + chemo	>60
II	10–20	Hilar node spread	Surgery ± radiation ± chemo	40–50
IIIA	15	Mediast. spread but resectable	Chemoradiation ± surgical resection	25–30
IIIB	15	Unresectable	Chemoradiation ± biologic ± surgery (selected cases)	10–20
IV	40	Metastatic	Chemo ± biologic and/or supportive care Palliative radiation	1

NSCLC prognosis

- Gene expression data may aid in prognosis (*NEJM* 2006;355:570 & 2007;356:11)
- 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 chemotherapy 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				
Stage	**% at dx**	**Definition**	**Treatment**	**Median survival**
Limited	30–40	Confined to ipsilat. hemithorax w/in one radiation port	Radiation + chemotherapy ± PCI	1–2 y
Extensive	60–70	Beyond one radiation port	Chemotherapy ± PCI	~1 y

BREAST CANCER

Epidemiology and genetics (Risk assessment tool: www.cancer.gov/bcrisktool/)

- 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 ⊕ 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;346:2025)
- 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, limited to one duct, bloody, associated with mass)
- Special types: **Paget's** disease → unilateral nipple eczema + nipple discharge; **inflammatory** breast cancer → skin erythema and edema *(peau d'orange)*
- Metastases: lymph nodes, bone, liver, lung, brain

Screening

- **Self breast exam** (SBE): no proven mortality benefit (*JNCI* 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;299:3151)
- 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 mammo in high-risk Pts; consider annually if >20% lifetime risk (eg, ⊕⊕ 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 → **mammo** (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;356:1295); 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
  In situ carcinoma: no invasion of surrounding stroma
  Ductal (DCIS): ↑ risk of invasive cancer in *ipsilateral* breast (~30%/10 y)
  Lobular (LCIS): marker of ↑ risk of invasive cancer in *either* breast (~1%/y)
  Invasive carcinoma: infiltrating ductal (70–80%); invasive lobular (5–10%); tubular, medullary, and mucinous (10%, better prognosis); papillary (1–2%); other (1–2%)
  Inflammatory breast cancer (see above): not a histologic type but a clinical reflection of tumor invasion of dermal lymphatics; very poor prognosis
  Paget disease: ductal cancer invading nipple epidermis ± associated mass
- **Biomarkers**: 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 ⊕, node ⊖ Pts (*NEJM* 2004;351:2817; 2006:355:560)

Simplified Staging System for Breast Cancer			
Stage	**Characteristics**	**Description**	**5-y surv**
I	Tumor ≤2 cm	Operable locoregional	90%
IIA	Tumor >2 cm or *mobile* axillary nodes		80%
IIB	Tumor >5 cm		65%
IIIA	Internal mammary or *fixed* axillary nodes	Locally advanced	50%
IIIB	Direct extension to chest wall or skin	Inoperable locoregional	45%
IIIC	Infraclavicular or supraclavicular nodes		40%
IV	Distant metastases	Metastatic	15%

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) after 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). http://www.adjuvantonline.com/index.jsp can guide use of chemo and/or hormonal Rx.
  - *Chemotherapy* (*Lancet* 2008;371:29): in adjuvant setting usually **anthracycline**-based (eg, adriamycin + cyclophosphamide). Sequential Rx w/ taxane (eg, docetaxel) → small ↑ survival, ? related to length of amenorrhea (*NEJM* 2007;357:1496 & 2010;362:2053).
  - *Biologics*
    - trastuzumab (Herceptin; anti-HER2/*neu* mAb) ↑ survival in HER2⊕ tumors (15–20%), but ↑ cardiotoxicity w/ anthracyclines (*NEJM* 2007;357:39, 1673; *Lancet* 2007;369:29). Usually used after anthracyline regimens or concurrently w/ taxane regimens.
    - lapatinib (tyrosine kinase inhib. of HER2 & EGFR): if mets, delays progression if failed trastuzumab (*NEJM* 2006;355:2733)
    - bevacizumab (anti-VEGF): if mets, delays progression (*NEJM* 2007;357:2666)
  - *Hormonal (in ER/PR ⊕ or unknown status)*
    - **tamoxifen**: 41% ↓ recurrence and 34% ↓ breast cancer mortality in *postmenopausal* Pts (*Lancet* 2005;365:1687)
    - **aromatase inhibitors (AI)** (anastrozole, letrozole, exemestane): ~18% ↓ recurrence c/w tamoxifen in *postmenopausal* Pts (*Lancet* 2005;365:60; *NEJM* 2005;353:2747)
    - 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	
LCIS	Close surveillance ± chemoprevention; ? prophylactic bilat. mastectomy
DCIS	Mastectomy or lumpectomy + RT; ALND *not* indicated; ± chemoprevention (*NEJM* 2004;350:1430)
I **II**	Surgery + RT + Adjuvant chemo if ↑ risk: tumor >1 cm *or* ⊕ LN *or* ER/PR ⊖ (*Lancet* 1998;352:930) + Hormonal therapy if ER/PR ⊕ (or unknown status) (*Lancet* 2009;374:2055) + Trastuzumab if HER2⊕ and tumor ≥1 cm or ⊕ LN
III	Neoadjuvant chemo → surgery + RT ± adjuvant chemotherapy + Hormonal therapy for ER/PR ⊕ (or unknown status) tumors + Trastuzumab if HER2⊕
IV	ER/PR ⊕: hormonal therapy ± chemotherapy ER/PR ⊖: HER2⊕ → chemo + trastuzumab; HER2 ⊖ → chemotherapy Bony mets: bisphosphonates ↓ skeletal complic. (*NEJM* 1998;339:357)

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)
  - Raloxifene: ↓ risk of invasive breast cancer & vertebral fx, ↑ risk of stroke & DVT/PE (*NEJM* 2006;355:125); ≈ tamoxifen in prevention of breast cancer w/ ↓ risk of DVT/PE & cataracts, trend towards ↓ uterine cancer (*JAMA* 2006;295:2727)
- BRCA1/2 carriers: intensified surveillance as described above. Prophylactic bilat. mastectomy → ~90% ↓ risk & bilat. salpingo-oophorectomy ↓ risk of ovarian *and* breast 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

Stage	Tumor	Nodes, Mets	Treatment
I	T1a = non-palp., not visible on imaging	N0, M0, Gleason 2–4	**Active surveillance** (consider if life expect. <10 y) **Radiation** (external or brachy; *NEJM* 2006;355:1583) **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).
II	T1/T2 = w/ in prostate	N0, M0	
III	T3 = extends thru capsule	N0, M0	**Radiation** + androgen deprivation (see below) (*Lancet* 2009;373:301)
IV	T4 = invades adjacent structures	N0, M0	**Radiation** (for M0 disease) **Androgen deprivation** (*NEJM* 2009;360:2516) **GnRH analogues** (leuprolide, goserelin) antiandrogens (flutamide, bicalutamide) 2nd-line: androgen synthesis inhibitor (ketoconazole, aminoglutethimide), antiandrogen withdrawal (see below) **Chemo** (docetaxel + prednisone) if refractory
	Any T	N1, M0	
	Any T	Any N, M1*	

*__Bisphosphonates__ (alendronate, zolendronate) & palliative radiation for bone mets

Prognosis

- PSA level, Gleason grade, and age are predictors of metastatic disease
- In surgically treated Pts, 5-y relapse-free survival >90% if disease confined to organ, ~75% if extension through capsule, and ~40% if seminal vesicle invasion
- Compared to active surveillance surgery ↓ prostate cancer mortality & overall mortality in Pts <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% of Pts have ⊕ FHx. Risk depends on # of 1st degree relatives (w/ CRC *or* polyp) and their age at dx; ~5% have an identifiable germline mutation
  - **Familial adenomatous polyposis (FAP)**: mutation 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.
- **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
- ↓ risk of adenomas w/ ASA & NSAIDs, incl. COX-2 (*NEJM* 2006;355:873, 885), but ↑ bleeding and ↑ CV events w/ COX-2; ↓ COX-2-expressing CRC after prolonged ASA (*NEJM* 2007;356:2131 & *Lancet* 2007;369:1603); currently *not* recommended (*Annals* 2007;146:361)

Pathology and Genetics (*Hematol Oncol Clin North Am* 2002;16:127)

- **Adenoma → carcinoma sequence** reflects accumulation of multiple genetic mutations ↑ risk of malignancy with large (>2.5 cm), villous, sessile adenomatous polyps Adenomas typically observed ~10 y prior to onset of cancer (both sporadic and familial)
- 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 abd pain; obstruction atypical due to larger lumen, liquid stool, and polypoid tumors (*vs*. annular distal tumors)
- Metastases: nodes, **liver**, lung, peritoneum → RUQ tenderness, ascites, supraclavicular LN
- Associated with *Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis

Screening (*NEJM* 2009;361:1179)

- **Average risk**: colonoscopy starting at age 50 & repeat q10y strongly preferred method
- ↑ **risk**: earlier and/or more frequent screening. ⊕ FHx: age 40 or 10 y before index dx, then q5y. IBD: 8–10 y after dx, then q1–2y. Known or suspected familial syndrome: genetic counseling & very early screening (eg, age 20-25), 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 (*NEJM* 1992;326:653). 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). However, in high-risk Pts, Se only 85% for advanced neoplasia ≥6 mm (*JAMA* 2009;301:2453). ∴ ? consider CTC if avg risk (w/o personal or FH of polyps/CRC) (*Gastro* 2008;134:1578) or if cannot obtain colonoscopy.

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

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

Treatment Based on TNM and Modified Dukes Staging of Colorectal Cancer

TNM	Dukes	Path. Criteria	5-y surv.	Treatment
I	A	Into submucosa or muscularis	94–97%	Surgery alone (resection and analysis of ≥12 LN)
IIA	B	Into serosa	83%	Surgery; no established role for adjuvant chemo for colon cancer*
IIB	B	Into peritoneum	74%	
IIC	B	Direct invasion	56%	Preop XRT or 5FU/XRT added for rectal cancer followed by postop chemo (FOLFOX)
IIIA	C	≤6 ⊕ LNs	86%	Surgery + chemotherapy*
IIIB	C	Varying degrees of ⊕ LNs and local invasion	51–77%	**5-FU** + **leucovorin** + **oxaliplatin** = FOLFOX (*NEJM* 2004;350:2343)
IIIC	C		15–47%	Preop XRT or chemorad added for rectal cancer (*NEJM* 2006;355:1114)
IV	D	Distant metastases	5%	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

NCCN Clinical Practice Guidelines in Oncology, www.nccn.org. 5-y survival data shown are approximately equivalent for colon and rectal cancers, shown as average, w/ ranges for TNM substaging, adapted from relative survival in SEER data (*JCO* 2010;28:256,264). * 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;350:2335); cetuximab is an anti-EGFR mAb (*NEJM* 2004:351:337).

PANCREATIC TUMORS

Pathology and genetics (*Annu 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 cancer death in U.S. men and women
- 80% of pancreatic adenocarcinomas occur in Pts 60–80 y
- Acquired risk factors: **smoking** (RR ~1.5), 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 (*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, ↑ Aϕ, anemia

Diagnostic and staging evaluation

- **Pancreatic protocol CT scan** (I^+ w/ 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

Clinical (Radiologic) Staging & Prognosis of Pancreatic Adenocarcinoma

Stage, % at dx	**Criteria**	**Median Survival**
Resectable, 15–20%	No extrapanc. dis. or bulky LAN Patent SMV & portal vein; celiac axis & SMA not involved	10–20 mo (favorable: tumor <3 cm, ⊖ marg., well-differen.) 5-y ~30% node ⊖ vs. ~10% if ⊕
Locally advanced (unresect.), 40%	Extensive PV/SMV, celiac axis, or SMA involvement	8–12 mo
Metastatic, 40%	Usually liver & periton.; occ lung	3–6 mo

Treatment of pancreatic adenocarcinoma (*NEJM* 2010;362:1605)

- Resectable: surgery ± adjuvant (neoadjuvant or postoperative) therapy
  - pancreaticoduodenectomy = **Whipple procedure** = resection of pancreatic head, duodenum, CBD and gallbladder ± partial gastrectomy
  - adjuvant therapy: ↑ survival but choice of regimen controversial (chemo vs. chemo/XRT and gemcitabine vs. 5FU; *NEJM* 2004;350:2713; *JCO* 2005;23:4532; *JAMA* 2007;297:267)
- Locally advanced: optimal strategy controversial. Gemcitabine alone (*Ann Oncol* 2008;19:1592; *Br J Cancer* 2007;96:1183; *JCO* 2009;27:2269); ? gemcitabine + XRT (*JCO* 2008;26:214s).
- Metastatic: **gemcitabine** (*JCO* 1997;15:2403); adding erlotinib (*JCO* 2005;23:16S,1) or capecitabine (*JCO* 2009;27:5513) may give modest benefit. Offer clinical trials.
- Palliative and supportive care
  - obstructive jaundice or gastric outlet obstruction: endoscopic stenting or surgical bypass
  - pain: opiates, celiac plexus neurolysis, radiation therapy
  - weight loss: pancreatic enzyme replacement, nutrition consult, end-of-life discussions

Cystic lesions of the pancreas (*NEJM* 2004;351:1218; *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 ≥38.3°C (101°F) or ≥38°C (100.4°F) for ≥1 h
- **Neutropenia:** ANC <500 cells/μL or <1,000 cells/μL with predicted nadir <500 cells/μL

Pathophysiology and microbiology
- Predisposing factors: catheters, skin breakdown, GI mucositis, obstruction (lymphatics, biliary tract, GI, urinary tract), immune defect a/w malignancy
- Most episodes thought to result from seeding of bloodstream by GI flora
- Neutropenic enterocolitis (typhlitis): RLQ pain, watery/bloody diarrhea, cecal wall thickening
- GNRs (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
- Levofloxacin (500 mg qd) ↓ febrile episodes & bacterial infections in chemo-related high-risk neutropenic patients; no difference in mortality (*NEJM* 2005;353:977, 988)

Diagnostic evaluation
- Exam: skin, oropharynx, lung, perirectal area, surgical & catheter sites; avoid DRE
- Labs: CBC with differential, electrolytes, BUN/Cr, LFTs, U/A
- Micro: blood (peripheral & through each indwelling catheter port), urine, & sputum cx; for localizing s/s → ✓ stool (*C. difficile*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s → CNS, sinus, chest, or abdomen/pelvis imaging
- Caveats: neutropenia → impaired inflammatory response → *exam and radiographic findings may be subtle*; absence of neutrophils by Gram stain does *not* r/o infection

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

Initial antibiotic therapy (*Clin Infect Dis* 2002;34:730)
- Empiric 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 ⊖ × 48 h

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

Duration of therapy
- Known source: complete standard course (eg, 14 d for bacteremia)
- Unknown source: continue antibiotics until afebrile *and* ANC >500 cells/μL
- Less clear when to d/c abx when Pt is afebrile but prolonged neutropenia

Role of hematopoietic growth factors (*JCO* 2005;23:4198 & 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 Δs*), **weakness**, **autonomic dysfunction** (urinary retention, ↓ anal sphincter tone), **sensory loss**

Diagnostic evaluation

- Always take back pain in Pts with solid tumors very seriously
- Do *not* wait for neurologic signs to develop before initiating evaluation b/c duration & severity of neurologic dysfunction before Rx are best predictors of neurologic outcome
- Urgent **whole-spine MRI** 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 + XRT superior to XRT alone for neuro recovery in solid tumors (*Lancet* 2005;366:643)
- 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, ↑ PO_4 → ↓ Ca
- **Renal failure** (urate nephropathy)

Prophylaxis

- Allopurinol 300 mg qd to bid PO or 200–400 mg/m^2 IV (adjusted for renal fxn) & aggressive hydration prior to beginning chemotherapy or 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 (see below)

Treatment

- *Avoid* IV contrast and NSAIDs
- Allopurinol + aggressive IV hydration ± diuretics to ↑ UOP
- Consider alkalinization of urine w/ isotonic $NaHCO_3$ to ↑ UA solubility & ↓ risk of urate nephropathy (controversial: may cause metabolic alkalosis or $Ca_3(PO4)_2$ precipitation).
- Rasburicase (0.15–0.2 mg/kg/d × 3–7 d) for severe ↑ UA, espec in aggressive malig; UA level must be drawn on ice to quench ex vivo enzyme activity (*JCO* 2003;21:4402; *Acta Haematol* 2006;115:35)
- Treat hyperkalemia, hyperphosphatemia, and symptomatic hypocalcemia
- Hemodialysis may be necessary; early renal consultation for Pts w/ renal insuffic. or ARF

CANCER OF UNKNOWN PRIMARY SITE

Evaluation of Cancer of Unknown Primary

Path	Possible Sources	Markers	Imaging	Additional Path
Adeno.	Colon, upper GI, panc. HCC Breast Ovarian, prostate Lung	CEA, CA19-9 AFP CA-15-3 CA125, PSA	Endoscopy/EUS Abd/Pelvic CT Mammography Pelvic U/S Chest CT	CDX1, CK7/20 ER/PR, GCDFP CA-125, PSAP TTF1, CK7
Squam.	Lung Head & Neck Esophageal Cervix, Anus	None	Chest CT Laryngoscopy Endoscopy	TTF1, CK7
Poorly Differen.	Germ cell Lymphoma Thyroid GIST, Sarcoma Neuroendocrine	hCG, AFP LDH Thyroglob.	Testicular U/S PET Thyroid U/S Abd/Pelvic CT	PLAP, isochrom 12p LCA, flow, cytogenetics Thyroglobulin c-KIT, desmin, vimentin NSE, chromogranin *Consider EM for all*

Additional studies for each possible source listed in same row.

- Bony mets: breast, lung, thyroid, kidney, prostate

Microbiology of Pneumonia	
Clinical Setting	**Etiologies**
Community-acquired (*CID* 2007;44:527)	***S. pneumoniae*** *Mycoplasma*, *Chlamydia*, viral (espec. in young & healthy) *H. influenzae*, *M. catarrhalis* (espec. in COPD'ers) *Legionella* (espec. in elderly, smokers, ↓ immunity) *Klebsiella* & other GNR (espec. in alcoholics & aspirators) *S. aureus* (espec. post-viral infection) Influenza A & B et al. (see "Viral Respiratory Infections") (no organism identified in 40–60% cases)
Hospital-acquired	GNR including *Pseudomonas*, *Klebsiella*, *E. coli*, *Enterobacter*, *Serratia*, *Acinetobacter*, & *S. aureus* (including MRSA) Acid suppression may ↑ risk of acquiring PNA (*JAMA* 2009;301:2120)
Immunosuppressed	*Above* + PCP, fungi, *Nocardia*, atypical mycobacteria, CMV, HSV
Aspiration (*NEJM* 2001;334:665)	*Chemical pneumonitis* due to aspiration of gastric contents *Bacterial pneumonia* ≥24–72 h later, due to aspiration of oropharyngeal microbes outpatients: typical oral flora (*Strep*, *S. aureus*, anaerobes) inpatients or chronically ill: GNR and *S. aureus*

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, extrapulm 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. pneumo*, *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 (DFA 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: $\mathbf{S_aO_2}$ or P_aO_2, CBC w/ diff, lytes, 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 (Se 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 ⊕
  Induced sputum for PCP if HIV ⊕ or known ↓ cell-mediated immunity; HIV test if 15–54 y
- Bronchoscopy: consider if Pt immunosupp., 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 pneumonitis, PE, CHF, ARDS, DAH, ILD; **consider CT**
  Parapneumonic effusion/empyema: esp. seen w/ *Strep pneumo*, GrpA Strep; if CXR neg, **consider CT** (dx 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 f/u 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): **C**onfusion, **U**remia, **R**R ≥30, **B**P <90/60, age ≥**65**
  SMART-COP (*CID* 2008;47:375): **S**BP <90, **M**ultilobar infiltrates, **A**lb <3.5 g/dL, **R**R ≥30, **T**achycardia (HR >125 bpm), **C**onfusion, $\mathbf{O_2}$ sat <90%, **p**H <7.35 (arterial)

PORT Score, Prognosis, and Recommended Triage			
Class	**Score**	**Mortality**	**Suggested Triage**
I	Age <50, no comorbidities	<1%	Outpatient
II	≤70	<1%	Outpatient
III	71–90	2.8%	? Brief inpatient
IV	91–130	8.2%	Inpatient
V	>130	29.2%	ICU
Variables	**Points**		
Demograph.	Men (age in y), women (age – 10), nursing home resident (+10)		
Coexist. probs	Neoplasm (+30), liver dis. (+20), CHF (+10), CVA (+10), renal dis. (+10)		
Exam	Δ MS (+20), RR >30 (+20), SBP <90 (+20), T <35°/>40° (+15), HR >125 (+10)		
Laboratory	pH <7.35 (+30), BUN >30 (+20), Na <130 (+20), glc >250 (+10), Hct <30 (+10), P_aO_2 <60 or S_aO_2 <90 (+10), pleural effusion (+10)		

(*NEJM* 1997;336:243)

Treatment	
Clinical scenario	**Empiric treatment guidelines***
Outpatient	No recent abx: macrolide *or* doxycycline Recent abx: (macrolide + [high-dose amox ± clav *or* 2nd-gen. ceph.]) *or* respiratory FQ
Community-acquired, hospitalized	(3rd-gen. ceph. + macrolide) *or* respiratory FQ
Community-acquired, hospitalized, ICU	(3rd-gen. ceph. *or* amp-sulbactam) + (macrolide *or* FQ) (assuming no risk for *Pseudomonas*)
Hosp-acquired & risk for MDR pathogens	(Antipseudomonal PCN or ceph. or carbapenem) + (FQ *or* [gentamicin + azithromycin]) + vancomycin
Immunosuppressed	As above ± TMP-SMX ± steroids to cover PCP
Aspiration	(3rd-gen. ceph. *or* FQ) ± (clindamycin *or* metronidazole)
Route of therapy	InPts should initially be treated w/ IV abx Δ to PO when clinically responding and able to take POs

*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;302:1896)

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, adeno) on nasal washing or sputum/BAL
- Rapid influenza test on nasal swab: Se ~50–70% (? lower for pandemic flu), Sp >95%
- DFA (Se ~85%), RT-PCR (gold standard) avail. for influenza (PCR distinguishes type)

Treatment

- Seasonal influenza: M2 inhib. (amantadine, rimantadine) effective only against some type A; neuraminidase inhib. (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

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 & prosthetic valve)
  - Hepatosplenic: intestinal seeding of portal & venous circulation; seen in acute leukemics
  - Hematogenous dissemination → lung, brain, meninges, etc

Empiric Treatment	
Mucocutaneous	Clotrimazole, nystatin, fluconazole, itraconazole
Candiduria	Fluconazole or intravesical ampho B if sx, severely immunosupp., or will undergo GU procedure
Candidemia w/o neutropenia	Echinocandin *or* fluconazole *or* ampho B
Febrile neutropenia	Echinocandin (eg, micafungin) *or* Ampho B
Remove intravascular catheters (*CID* 2009;48:503)	

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**: often asx, acute PNA, chronic pneumonia; extrapulmonary: verrucous & ulcerated skin lesions, bone & GU involvement, CNS
- **Treatment**: itraconazole; ampho B if severe or immunosupp. (*CID* 2008;46:1801)

Aspergillus (*Chest* 2002;121:1988; *CID* 2008;46:327; *NEJM* 2009;360:1870)

- **ABPA**; **hypersensitivity pneumonitis**: see "Interstitial Lung Disease"
- **Aspergilloma**: usually in pre-existing cavity (from TB, etc.); most asx, but can lead to hemoptysis; sputum cx ⊕ in <50%; CT → mobile intracavitary mass with air crescent Rx: antifungals w/o benefit; embolization or surgery for persistent hemoptysis
- **Necrotizing tracheitis**: white necrotic pseudomembranes in Pts w/ AIDS or lung Tx
- **Chronic necrotizing**: seen in COPD, mild immunosupp; subacute sputum, fever, wt loss; CT: infiltrate ± nodule ± thick pleura; lung bx → invasion; Rx = voriconazole > ampho B
- **Invasive/disseminated**: seen if immunosupp. (neutropenia, s/p transplant, steroid Rx, AIDS esp. w/ steroids or neutropenia); s/s PNA w/ *chest pain* & *hemoptysis*; CT: nodules, halo sign, air crescent sign; lung bx if dx inconclusive; Rx = voriconazole > ampho B

Zygomycetes (eg, *Mucor*, *Rhizopus*)

- **Epidemiology**: **diabetes mellitus** (70%), heme malignancy, s/p transplant, chronic steroids, deferoxamine or iron overload
- **Clinical manifestations**: **rhinocerebral** = periorbital/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, ampho. 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 wks; *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*.
- **Antibody detection**: *Histo*, *Blasto*, *Coccidio*, *Aspergillus*. Se variable.
- **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 infxns
  - **1,3-β-D-glucan**: Se for many fungal infxns (*Candida, Aspergillus, Histo, Coccidio, Fusarium, Pneumocystis, Sporothrix*; but *not Crypto, Blasto, Mucor, Rhizopus*); not Sp
  - **Galactomannan** (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 Pts will fit into more than one category (eg, DM, ESRD, extremes of age)

Predisposition	Classic infectious etiologies
Humoral immune dysfunction (eg, CVID, myeloma)	**Encapsulated bacteria**: *S. pneumo*, *H. flu*, *N. meningitidis* **Other bacteria**: *E. coli* and other GNRs
Granulocytopenia or neutropenia (includes DM, ESRD → functional impairment)	**Bacteria**: Gram positive: coag neg *Staph*, *S. aureus*, viridans *Strep*, *S. pneumo*, other *Strep*; *Corynebacterium* spp., *Bacillus* spp. Gram negative: *E. coli*, *Klebsiella*, *Pseudomonas* **Fungi**: Yeast: *Candida albicans* and other *Candida* spp.; Molds: *Aspergillus*, *Mucor* spp., and others (these also require CMI)
Impaired cell-mediated immunity (CMI) (eg, HIV, chronic steroids, posttransplant, DM, ESRD)	**Bacteria**: *Salmonella* spp., *Campylobacter*, *Listeria*, *Yersinia*, *Legionella*, *Rhodococcus*, *Nocardia*, TB, other mycobacteria **Fungi**: *Candida*, *Crypto*, *Histo*, *Coccidio*, *Aspergillus*, and other molds, *Pneumocystis* **Viruses**: HSV, VZV, CMV, EBV, JC virus, BK virus **Parasites**: Protozoa: *Toxoplasma*, *Cryptosporidium*, *Isospora*, *Babesia;* Helminths: *Strongyloides*
Organ dysfunction	**Splenectomy**: *S. pneumo*, *H. flu*, *N. meningitidis* (vaccinate against these 3, ideally prior to splenectomy); *Capnocytophaga*, *Babesia* **Liver (esp. cirrhosis)**: *Vibrio* spp., encapsulated bacteria **ESRD**: impaired granulocyte fxn and CMI as above **Iron overload (or deferoxamine Rx)**: *Yersinia*, *Mucor*
Biologics (eg, TNF inhibitors, anti-B-cell Rx)	**Bacteria**: sepsis, TB, other mycobacteria **Fungi**: *Pneumocystis, Histo, Coccidio,* other endemic fungi **Viruses**: JC virus (PML), EBV, HSV, VZV, HBV **Parasites**: *Strongyloides* reactivation

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 asx women, ≥10^3 CFU/mL in men, ≥10^2 CFU/mL in sx or catheterized Pts (hydration may falsely dilute counts)
  - pyuria & ⊖ UCx = sterile pyuria → urethritis, nephritis, renal tuberculosis, foreign body
- Pregnant women & those undergoing urologic surgery: *screen for asx 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

Clinical scenario	Empiric treatment guidelines*
Cystitis	FQ or TMP-SMX PO × 3 d (uncomp.) or × 10–14 d (complicated) Asx bacteriuria in pregnancy or prior to urologic surgery → abx × 3 d
Catheterized Pts	Abx as above and remove or exchange catheter
Urethritis	Treat for both *Neisseria* and *Chlamydia* *Neisseria:* ceftriaxone 125 mg IM × 1 *Chlamydia:* doxy 100 mg PO bid × 7 d *or* azithromycin 1 g PO × 1
Prostatitis	FQ or TMP-SMX PO × 14–28 d (acute) or 6–12 wks (chronic)
Pyelonephritis	Outpatient: FQ *or* oral ceph. PO × 14 d Inpatient: ceftriaxone IV *or* FQ PO *or* aminoglycoside *or* ampicillin/sulbactam × 14 d (Δ IV → PO when Pt improved clinically and afebrile × 24–48 h and then complete 14-d course)
Renal abscess	Drainage + antibiotics as for pyelonephritis

*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.

Cellulitis

Infection of superficial and deep dermis and subcutaneous fat

Microbiology (*NEJM* 2004;350:904; *CID* 2005;41:1373)

- Primarily *Strep* and *Staph*, including MRSA; may include GNRs in diabetics/immunosupp.
- **Community-acquired MRSA** (**CA-MRSA**, *NEJM* 2005;352:1485 & 2006;355:666):
  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 susceptible 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 → *Pseudomonas*; gardening → *Sporothrix*; salt water → *V. vulnificus* (classically from raw oysters), *Erysipelothrix*; fresh water → *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 → TMP-SMX + agent for strep (eg, PCN, amox, clinda) or doxy (active against MRSA + strep)
- **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
- **Erisypelas**: 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
- **Erisypelas**: 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, immunsosupp.

"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) probing to bone via ulcer/tract has high Sp but low Se; **bone bx** most reliable

Treatment *(NEJM 1994;331:854, CID 2004;39:885)*
- Bedrest, elevation, non–weight-bearing status, **wound care**, **antibiotics**

Severity of infection	Empiric antibiotics
Mild	PCNase-resistant PCN *or* 1st-gen. ceph. (TMP-SMX if MRSA suspected)
Chronic non-limb & non-life-threatening	(FQ + clindamycin) *or* ampicillin-sulbactam *or* ticarcillin-clavulanate *or* (ceftriaxone + clinda) *or* ertapenem; add vanco *or* TMP-SMX *or* doxycycline if suspect MRSA
Life-threatening	Vanco + one of the following: imipenem *or* (piperacillin/tazobactam) *or* (aztreonam + metronidazole)

- **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** Δs 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: **lg**, **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

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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)

Acute Bacterial Meningitis

Definition
- Bacterial infection of the subarachnoid space

Microbiology in Adult Meningitis

Etiology	Comments
S. pneumoniae (30–60%)	Look for distant infection (eg, Osler's triad = meningitis, pneumonia, endocarditis). Drug-resistant *S. pneumoniae* (DRSP): ~40% PCN-resistant (even *intermed* resist problematic for Rx) ~<10% 3rd-gen. ceph.-resistant Vaccine reduces rate of invasive disease
N. meningitidis (10–35%)	Primarily in children and young adults; may be associated with petechiae or purpura. Deficiencies in terminal complement predispose to recurrent meningococcemia & rarely, meningitis. Vaccine rec for all adolescents, college freshmen living in dorm, military recruits, s/p splenectomy, or C5–9 deficiency.
H. influenzae (<5%)	↓ Incidence in children because of *H. influenzae* type b vaccine. Look for predisposing factors in adults (eg, CSF leak, recent neurosurgical procedure, trauma, mastoiditis).
L. monocytogenes (5–10%)	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.
GNRs (1–10%)	Usually nosocomial or postprocedure or in elderly or immunosuppressed
Staphylococci (5%)	Seen with indwelling CSF shunt (*S. epidermidis*) or following neurosurgery or head trauma (*S. aureus*)
Mixed infection	Suspect parameningeal focus or CSF leak

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°; ⊕ if passive extension of knee results in resistance), **Brudzinski's sign** (Pt supine and limbs supine; ⊕ if passive neck flexion → involuntary hip and/or knee flexion)
  nb, Kernig's and Brudzinski's signs ⊕ in only ~5% of Pts (*CID* 2002;35:46)
- ± 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					
Condition	**Appearance**	**Pressure (cm H_2O)**	**WBC/mm^3** *Predom type*	**Glc (mg/dL)**	**TP (mg/dL)**
Normal	Clear	9–18	0–5 *lymphs*	50–75	15–40
Bacterial	Cloudy	18–30	100–10,000 *polys*	<45	100–1000
TB	Cloudy	18–30	<500 *lymphs*	<45	100–200
Fungal	Cloudy	18–30	<300 *lymphs*	<45	40–300
Aseptic	Clear	9–18	<300 *polys → lymphs*	50–100	50–100

- 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	
Clinical scenario	**Empiric treatment guidelines***
Normal adult	**Ceftriaxone 2 g IV q12h + Vancomycin 15–20 mg/kg IV q12h** (nb, Cftx in case PCN-resistant *S. pneumo*; Vanco, which has poorer CSF penetration, in case Cftx-resistant *S. Pneumo*) If >50 y old or alcoholic: + ampicillin 2 g IV q4h for *Listeria* TMP/SMX + vancomycin if β-lactam allergic
Immunosuppressed	Ampicillin + ceftazidime 2 g IV q8h + vancomycin + acyclovir
CSF shunts, recent neurosurgery, or head trauma	Vancomycin + ceftazidime 2 g IV q8h (*NEJM* 2010;362:146)
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. pneumo* & GCS 8–11. Consider steroids in all bacterial meningitis prior to organism identification. Must start before or w/ 1st dose of abx (*NEJM* 2002;347:1549).	
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. pneumo* 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, IVIg 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: antimycobacterial 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 (*Lancet* 2002;359:507; *Neurology* 2006;66:75; *CID* 2008;47:303)
- **HSV-1** (~9%): all ages/seasons; MRI: temporal lobe lesions/edema; EEG: temporal focus
- **VZV** (~9%): 1° or reactivation; ± vesicular rash; all ages (favors elderly), all seasons
- **Arboviruses** (~9%): Eastern/Western equine, 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, adeno/enterovirus, 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 ± 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 valvular 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

Major	Minor
• **Sustained bacteremia** by an organism known to cause endocarditis (or 1 BCx or ⊕ serology for *Coxiella*)*	• Predisposing condition (see above)
• **Endocardial involvement** document by *either* ⊕ **echocardiogram** (vegetation, abscess, prosthetic dehiscence) *or* **new valvular regurgitation**	• Fever • **Vascular phenomena**: septic arterial or pulmonary emboli, mycotic aneurysms, ICH, Janeway lesions • **Immune phenomena**: ⊕ RF, GN, Osler's nodes, Roth spots • ⊕ **blood cx** not meeting major criteria
Definitive (ie, highly probable): 2 major *or* 1 major + 3 minor *or* 5 minor criteria Possible: 1 major + 1 minor *or* 3 minor criteria	

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

Microbiology of Endocarditis

	Native valve endocarditis (NVE)		Prosthetic valve endocarditis (PVE)	
Etiology	**Non-IVDA**	**IVDA**	**Early** (≤60 d post)	**Late** (>60 d post)
S. viridans et al.	**36%**	**13%**	<5%	**20%**
Enterococcus	**11%**	5%	8%	13%
S. aureus	**28%**	**68%**	**36%**	**20%**
S. epidermidis	9%	<5%	**17%**	**20%**
GNR	<5%	<5%	**6%**	<5%
Other	<5%	<5%	10%	10%
Culture ⊖	11%	<5%	17%	12%
Culture ⊖ = nutritionally-deficient streptococci, HACEK (*Haemophilus parainfluenzae & aphrophilus, Actinobacillus, Cardiobacterium, Eikenella*, and *Kingella*), *Bartonella*, *Coxiella*, *Chlamydia*, *Legionella*, *Brucella*				

(*JAMA* 2007;297:1354; *Annals* 2007;147:829; *Archives* 2009;169:463)

Clinical manifestations (*Archives* 2009;169:463)

- **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 ABE; anemia in 90% SBE), ESR, RF, BUN/Cr, U/A & UCx
- **ECG** (on admission and at regular intervals) to assess for new conduction abnormalities
- **Echocardiogram**: obtain TTE if low clinical suspicion, expect good image quality; TEE if (i) mod-to-high 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:e394)

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

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

- **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: **ceftriaxone** (*or* amp if ? enterococcus; eg, older ♂ or ob/gyn) + **gent**
  PVE: *early* (≤60 d): **vanco** + **cefepime** + **gent**; *intermediate* (60–365 d): **vanco** + **gent**; *late* (>1 y): **vanco** + **ceftriaxone** + **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 (*EHJ* 2009;30:2369; *Circ* 2010;121:1005 & 1141)

- Try for as many days of abx as possible, in hopes of ↓ 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 AI 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 approp. 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 contraindic 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*	**Prosthetic valve**; **previous NVE**; **congenital heart disease** (CHD) including 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 dysfxn, bicuspid AoV, MVP with leaflet thickening or regurgitation, HCMP)
Procedures*	**Dental**: that involve manipulation of gingival tissue or periapical region of teeth or perforation of oral mucosa (eg, extractions, periodontal procedures, implants, root canal, cleanings) **Respiratory**: incision or biopsy of respiratory mucosa (Prophylaxis no longer rec. for GI or GU procedures)
Regimens	Oral: **amoxicillin 2 g 30–60 min before** Unable to take PO: amp 2 g IM/IV or cefazolin or cftx 1 g IM/IV PCN-allergic: clindamycin 600 mg PO/IM/IV

*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 (includes *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. pneumonia*, *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
  empiric therapy for GPC: vanco to cover coag-neg staph and MRSA while awaiting sensi

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

*Complicated infections w/ suppurative thrombophlebitis, osteomyelitis, or endocarditis require longer treatment

- **2° infxn**: assess for primary source of infection and treat underlying infection. Source 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 1° TB (at site of infection)
- Hematogenous spread: latent infection ± 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 5-TU (0.1 mL) intermed. strength PPD intradermally → wheal; examine 48–72 h
- **How to interpret PPD**: determine max diameter of induration by palpation

Size of reaction	Persons considered to have ⊕ test
>5 mm	HIV ⊕ or immunosupp (eg, prednisone 15 mg/d × >1 mo) Close contacts 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 y)
>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)

- **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* 2008;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 1° infxn, and reactivation. Risk of progression from infxn to disease >8–10%/y. Can occur at any CD4 count, but more likely to disseminate at lower CD4 counts. Reinfection (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

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, bronchoscopic 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 5× 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/ extrapulm TB (eg, tuberculoma, LAN), likely due to hypersensitivity response to killing of bacilli. More frequent/severe w/ concurrent immune reconstitution (eg, HIV ⊕ Pts started on ARVs, Pts taken off immunosuppressants, etc). *Must r/o treatment failure* (repeat Cx, imaging, etc).

Antituberculous Medications

Drug	Dose	Adverse effects*
Isoniazid (INH)	300 mg PO qd	Hepatitis, periph neuropathy (risk ↓ by concomitant vit B_6), lupus-like synd.
Rifampin (RIF)	600 mg PO qd	Orange discoloration of urine/tears, GI upset, hepatitis, hypersensitivity, fever
Pyrazinamide (PZA)	25 mg/kg PO qd	Hepatitis, hyperuricemia, arthritis
Ethambutol (EMB)	15–25 mg/kg PO qd	Optic neuritis
Streptomycin (SM)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Amikacin (AMK)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Quinolone (moxifloxacin)	400 mg PO qd	GI upset

*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*

Scenario	Regimen
Pulmonary TB **≥4% INH-resist. in community** (includes most of U.S.)	INH + RIF + PZA + (EMB) until suscept. known If *sensitive* to INH & RIF → INH + RIF + PZA × 2 mos, *then* → INH + RIF × 4 mos If *resistant*, see next row
Drug-resistant TB (INH-R, RIF-R, or MDR/XDR)	*Consult ID specialist* (*NEJM* 2008;359:636)
Extrapulmonary TB	*Consult ID specialist*
TB in HIV ⊕ patient	*Consult ID specialist*

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

Definition
- AIDS: HIV + CD4 count <200/mm^3 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; 1° screen test
- **Western blot**: ⊕ if ≥2 bands from diff regions of HIV genome; >99% Sp; confirmatory after ⊕ ELISA
- **Rapid preliminary tests**: 4 Ab tests; use saliva, plasma, blood, or serum; 99% Se & 96–99% Sp (*Annals* 2008;149:153); 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)

	Drugs	Side Effects
NRTI	abacavir (ABC; Ziagen) didanosine (ddI; Videx) emtricitabine (FTC; Emtriva) lamivudine (3TC; Epivir) stavudine (d4T; Zerit) tenofovir (TDF; Viread) zidovudine (AZT; Retrovir)	*Class:* GI intol. common (less w/ 3TC, ABC, TDF) lipoatrophy (less w/ 3TC, ABC, FTC, TDF) lactic acidosis (less w/ 3TC, ABC, FTC, TDF) ABC: hypersensitivity (3%), ✓ HLA-B*5701 AZT: BM suppression (esp macrocytic anemia) ddI & d4T: peripheral neuropathy & pancreatitis ddI & ABC: MI (*Lancet* 2008;371:1417) TDF: acute or chronic renal insufficiency
NNRTI	delaverdine (DLV; Rescriptor) efavirenz (EFV; Sustiva) etravirine (ETR; Intelence) nevirapine (NVP; Viramune)	*Class:* rash, hepatitis, mixed CYP450 inducer/inhib EFV: CNS effects (incl depression) ETR: rare hypersensitivity NVP: rash and hypersensitivity [risk factors are female, CD4 >250, pregnancy (∴ avoid)]
PI	amprenavir (APV; Agenerase) atazanavir (ATV; Reyataz) darunavir (DRV; Prezista) fosamprenavir (FPV; Lexiva) indinavir (IDV; Crixivan) lopinavir/riton. (LPV/r; Kaletra) nelfinavir (NFV; Viracept) ritonavir (RTV; Norvir) saquinavir (SQV; Invirase) tipranavir (TPV; Aptivus)	*Class:* GI intolerance inhibit CYP450 (∴ caution w/ simva & lovastatin) type II DM hepatotoxicity truncal obesity; hyperlipidemia (less w/ ATV) MI (*NEJM* 2007;356:1723) IDV, ATV: crystalluria → nephrolithiasis DRV: rash (10%) DRV & TPV: possible sulfa cross-reactivity
FI	enfurvitide (T20; Fuzeon)	injection site reaction
EI	maraviroc (MVC; Selzentry)	dizziness, hepatotoxicity
II	raltegravir (RAL; Isentress)	GI intol, CPK elevation

NRTI, nucleoside/tide reverse transcriptase inhibitor; NNRTI, nonnucleoside RTI; PI, protease inhibitor; FI, fusion inhibitor; EI, entry inhibitor (CCR5 antagonist); II, integrase inhibitor

- ***ARVs should be given in consultation w/ 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-infxn requiring Rx, or HIV-assoc. sx (systemic, neurocognitive, mucocutaneous, etc.)
- Genotypic resistance testing recommended for all Pts in U.S. starting ARV
- Regimens for treatment-naïve Pts (DHHS guidelines Dec 1, 2009; http://aidsinfo.nih.gov)
  [NNRTI + 2 NRTI] *or* [PI (± low-dose ritonavir) + 2 NRTI] or [II + 2 NRTI]
  efavirenz + tenofovir + emtricitabine (*NEJM* 2006;354:251; 2008;358:2095; 2009;361:2230)
  ritonavir-boosted atazanavir + tenofovir + emtricitabine
  ritonavir-boosted darunavir + tenofovir + emtricitabine
  raltegravir + tenofovir + emtricitabine (*NEJM* 2008;359:339; *Lancet* 2009;374:796)
- Maraviroc (EI) 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 b/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)

OI Prophylaxis (*MMWR* March 24, 2009)

OI	Indication	1° Prophylaxis
Tuberculosis	⊕ PPD (≥5 mm) *or* IGRA *or* high-risk exposure	INH + vitamin B_6 × 9 mo
Pneumocystis jiroveci	CD4 count <200/mm³ *or* CD4% <14% *or* thrush	TMP-SMX DS or SS qd or DS tiw *or* dapsone 100 mg qd *or* atovaquone 1500 mg qd *or* pentamidine 300 mg inh q4wk
Toxoplasmosis	CD4 count <100/mm³ *and* ⊕ *Toxoplasma* serology	TMP-SMX DS qd *or* dapsone 50 mg qd + pyrimethamine 50 mg qwk + leucovorin 25 qwk
MAC	CD4 count <50/mm³	azithro 1200 mg qwk *or* clarithro 500 mg bid
Stop 1° prophylaxis if CD4 >initiation threshold >3–6 mo on ARVs		
Stop 2° prophylaxis (maintenance therapy of existing OI; drugs and doses differ for different OIs) if there has been clinical resolution or stabilization and CD4 thresholds have been exceeded × 3–6 mo		

Complications of HIV/AIDS

CD4 count	Complications
<500	Constitutional symptoms Mucocutaneous: Kaposi's sarcoma; seborrheic dermatitis; oral hairy leukoplakia; lymphoma; oral, esophageal, & recurrent vaginal candidiasis; HSV; VZV Recurrent bacterial infections TB (pulmonary and extrapulmonary)
<200	*Pneumocystis jiroveci* pneumonia (PCP), *Toxoplasma, Bartonella Cryptococcus, Histoplasma, Coccidioides*
<50–100	CMV, MAC Invasive aspergillosis, bacillary angiomatosis (disseminated *Bartonella*) CNS lymphoma, PML

Fever

- Etiologies (*Infect Dis Clin North Am* 2007;21:1013)
  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, BCx, 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; sputum 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

Radiographic pattern	Common causes
Normal	Early *P. jiroveci* (PCP)
Diffuse interstitial infiltrates	*P. jiroveci*, TB, viral or disseminated fungal PNA
Focal consolidation or masses	Bacterial or fungal PNA, TB, Kaposi's sarcoma
Cavitary lesions	TB, aspergillosis, and other fungal PNA Bacterial PNA (including MRSA, *Nocardia*, and *Rhodococcus*)
Pleural effusion	TB, bacterial or fungal PNA Kaposi's sarcoma, lymphoma

- ***Pneumocystis jiroveci* (PCP) pneumonia (CD4 <200)**
  constitutional sx, fever, night sweats, dyspnea on exertion, nonproductive cough
  CXR w/ interstitial pattern, ↓ P_aO_2, ↑ A-a $\overline{\nabla}$, ↑ LDH, ⊕ PCP sputum stain, ⊕ beta-glucan
  Rx if P_aO_2 >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 P_aO_2 <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
- **Kaposi's sarcoma** (HHV-8): can occur at any CD4 count, but incidence ↑ as CD4 count ↓
  usually occurs in MSM
  mucocutaneous: red-purple nodular lesions
  pulmonary: nodules, infiltrates, effusions, LAN
  GI: GI bleeding, obstruction, obstructive jaundice
  Rx: limited disease → alitretinoin gel, XRT, cryo, or intralesional vinblastine; systemic → chemotherapy
- **Cervical cancer**
- **Anal cancer**
- ↑ Rates of liver (a/w HBV, HCV), gastric, and lung cancer (*Lancet* 2007;370:59; *CID* 2007;45:103)

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, Δ?MS, CN palsy ± other classic meningeal 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
  workup: MRI, stereotactic brain bx if suspect non-*Toxoplasma* etiology (toxoplasma sero ⊖) or if Pt fails to respond to 2-wk trial of empiric toxoplasmosis Rx (of those who ultimately respond, 50% do so by d 3, 86% by d 7, 91% by d 14; *NEJM* 1993;329:995)

Etiology	Imaging Appearance	Diagnostic studies
Toxoplasmosis	enhancing lesions, typically in basal ganglia (can be multiple)	⊕ *Toxoplasma* serology (Se ~85%)
CNS lymphoma	enhancing ring lesion (single 60% of the time)	⊕ CSF PCR for EBV ⊕ SPECT or PET scan
Progressive multifocal leukencephalopathy (PML)	Multiple nonenhancing lesions in white matter	⊕ CSF PCR for JC virus
Other: bacterial abscess, nocardiosis, cryptococcoma, tuberculoma, CMV, HIV	Variable	Biopsy

- **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 lymphadentitis 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

Distinguishing Features of Tick-Borne Illnesses					
Disease	**Rash**	**↓ WBC**	**Anemia**	**↓ Plts**	**↑ LFTs**
Lyme	Erythema migrans	–	–	–	–
RMSF	Petechiae, palms/soles	–	–	+++ (late)	+
Ehrlichia	–	+	–	++	++
Babesia	–	–	++ (hemolytic)	++	+

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	
Stage	**Manifestations**
Stage 1 (early localized) wks after infection	Due to local effects of spirochete. *General:* **flu-like illness** *Derm* (~80%): **erythema migrans** (EM) = erythematous patches w/ central clearing, size 6–38 cm; lymphocytomas; regional LAN
Stage 2 (early dissem.) wks to mos after infection	Due to spirochetemia and immune response *General:* fatigue, malaise, LAN, HA; fever uncommon *Derm:* **multiple (1–100) annular lesions ≈ EM** *Rheum* (~10%): **migratory arthralgias** (knee & hip) **& myalgias** *Neurologic* (~15%): cranial neuropathies (esp. **CN VII**), aseptic meningitis, mononeuritis multiplex (± pain), transverse myelitis *Cardiac* (~8%): **heart block**, myopericarditis
Stage 3 (late persistent) mos to y after infection	Due to chronic infection *or* autoimmune response *Derm:* **acrodermatitis chronica atrophicans**, panniculitis *Rheum* (~60%): joint pain, **recurrent mono- or oligoarthritis of large joints** (classically knee), synovitis *Neurologic:* subacute encephalomyelitis, polyneuropathy, dementia

(*Lancet* 2003;362:1639; *CID* 2006;43:1089; *NEJM* 2007;357:1422)

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 ⊕ due to other spirochetal diseases, SLE, RA, EBV, HIV, etc.; false ⊖ due to early abx therapy or w/in 6 wks of infxn confirm ⊕ ELISA results w/ **Western blot** (↑ Sp)
- ✓ CSF if suspected neuro disease: ⊕ intrathecal Ab if $(IgG_{CSF}/IgG_{serum})/(alb_{CSF}/alb_{serum}) > 1$

Treatment (*NEJM* 2006;354:2794)
- Prophylaxis (best prevention is tick avoidance): protective clothing, tick ✓ q24h, DEET
  Chemoprophylaxis w/ doxycycline 200 mg PO × 1 *only* if *all* of the following:
  1. *Ixodes scapularis* tick attached ≥36 h
  2. Local Lyme carriage in ticks ≥20% (peak season in New England, mid-Atl, MN, WI)
  3. Abx can be given w/in ≤72 h
  4. No contraindic 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)
  Regardless of ppx, monitor for fever, flu-like sx, rash (erythema migrans) × 30 d
- Antibiotics: *if* clin. manifestations *and* ⊕ serology (*? and* h/o 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 x 2–4 wks
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias

ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

Microbiology & Epidemiology
- Infection with *Rickettsia rickettsii* (Gram ⊖ obligate intracellular bacterium)
- Transmitted by *Dermacentor variabilis*, *Dermacentor andersoni*
- Coastal mid-Atl, New Engl, midwest, northwest, southeast, Canada, Mexico, Central & South America
- Peak incidence spring and early summer

Clinical manifestations (typically w/in 1 week of tick exposure)
- **Fever**, **HA**, Δ MS, 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 w/ 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 ⊕

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

EHRLICHIOSIS/ANAPLASMOSIS

Microbiology
- Infection with Gram ⊖ obligate intracellular bacterium
- **Human monocytic ehrlichiosis** (*Ehrlichiosis chaffeensis*) (HME)
- **Human granulocytic anaplasmosis** (*Anaplama phagocytophilum*) (HGA)
- Transmission: HME by *Amblyomma americanum*, *Dermacentor variabilis;* HGA by *Ixodes*

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 w/in 3 wks of tick exposure)
- Fever, myalgias, malaise, HA, occasional cough, dyspnea; onset often acute
- Laboratory: leukopenia, thrombocytopenia, renal failure, ↑ aminotransferases, LDH, Aϕ

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

Clinical manifestations (typically w/in 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, LAN, very high ferritin **Polyarteritis nodosa**, **other vasculitides** RA, SLE, PMR, psoriatic arthritis, reactive arthritis
Neoplasm ~20%	**Lymphoma**: LAN, HSM, ↓ Hct or plt, ↑ LDH; leukemia, myelodysplasia **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, lytes, BUN, Cr, LFTs, ESR, CRP, ANA, RF, cryoglobulin, LDH, CK, SPEP
  BCx × 3 sets (off abx; hold for HACEK, RMSF, Q fever, *Brucella*), U/A, 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 U/S
- 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 ↑ Aϕ): even w/o localizing s/s, yield may be up to 24% (path and culture) (*Archives* 2009;169:2018)
- 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 dysfxn, loss of axillary & pubic hair, wt loss, amenorrhea
  - **Mass effect**: headache, visual field Δs, cranial nerve palsies, galactorrhea
  - **Apoplexy** (pituitary hemorrhage or infarction, usually w/ underlying pituitary adenoma): sudden headache, N/V, visual field Δs, cranial nerve palsies, meningismus, Δ MS, hypoglycemia, hypotension
- Diagnostic studies
  - **Hormonal studies**
    - *chronic:* ↓ target gland hormone + ↓ or normal trophic pituitary hormone
    - *acute:* target gland hormonal studies may be *normal*
    - *partial hypopituitarism is more common than panhypopituitarism*
  - **Pituitary MRI**
- Treatment
  - Replace deficient target gland hormones
  - Most important deficiencies to recognize and treat in inpatients are *adrenal insufficiency* and *hypothyroidism;* if both present, treat with glucocorticoids first, then replace thyroid hormone so as not to precipitate adrenal crisis

↓ ACTH

- Adrenal insufficiency similar to 1° (see "Adrenal Disorders") *except:*
  - no salt cravings or hypokalemia (b/c aldo 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 T_4 in addition to TSH, as TSH may be low or *inappropriately normal*

↓ PRL

- Inability to lactate

↓ GH

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

↓ 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 H_2O)
- 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) ± mass effect: headache, visual Δs, diplopia, cranial neuropathies
- 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 (↓ 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, macroglossia, hoarseness, sleep apnea, amenorrhea, impotence, diabetes mellitus, acanthosis/skin tags, ↑ sweating, HTN/CMP, colonic polyps
- Diagnostic studies: *no utility in checking random GH levels because of pulsatile secretion*
  ↑ **IGF-1** (somatomedin C); ± ↑ PRL; 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× ↑ mortality, risk of pituitary insufficiency, colon cancer

Cushing's disease (↑ ACTH): 10–15% of adenomas; see "Adrenal Disorders"

Central hyperthyroidism (↑ TSH, ↑ α-subunit): extremely rare; see "Thyroid Disorders"

↑ FSH & LH: usually non-fxn, presents as *hypopituitarism* b/c of compression effects

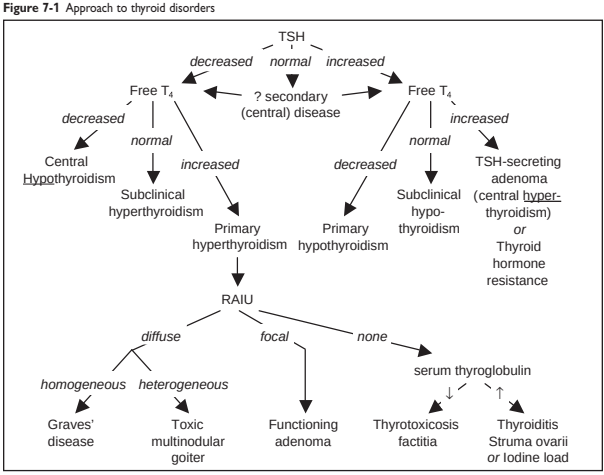
DISORDERS OF MULTIPLE ENDOCRINE SYSTEMS

Multiple Endocrine Neoplasia (MEN) Syndromes	
Type	**Features**
1 (*MENIN* inactiv.)	Parathyroid hyperplasia/adenomas → hypercalcemia (~100% penetrance) Pancreatic islet cell neoplasia (gastrin, VIP, insulin, glucagon) Pituitary adenomas (fxn or non-fxn)
2A (*RET* proto-oncogene)	Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Parathyroid hyperplasia → hypercalcemia (15–20%)
2B (*RET* proto-oncogene)	Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Mucosal and gastrointestinal neuromas

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

Diagnostic Studies in Thyroid Disorders	
Test	**Comments**
Thyroid-stimulating hormone (TSH)	*Most sensitive test* to detect 1° hypo- and hyperthyroidism May be inappropriately normal in central etiologies ↓'d by dopamine, steroids, severe illness
T_3 and T_4 immunoassays	Measure *total* serum concentrations (∴ influenced by TBG)
Free T_4 immunoassay (FT_4)	Free T_4, not influenced by TBG, increasingly popular
Thyroxine-binding globulin (TBG)	↑ TBG (∴ ↑ T_4): estrogens, OCP, pregnancy, hepatitis, opioids, hereditary ↓ TBG (∴ ↓ T_4): androgens, glucocorticoids, nephritic syndrome, cirrhosis, acromegaly, nicotinic acid, hereditary
Reverse T_3	Inactive, ↑'d in sick euthyroid syndrome
Thyroid antibodies	Antithyroid peroxidase (TPO) seen in Hashimoto's (high titer), painless thyroiditis and Graves' disease (low titer) Thyroid-stimulating Ig (TSI) and thyrotropin-binding inhibitory immunoglobulin (TBII) seen in Graves' disease
Thyroglobulin	↑'d in goiter, hyperthyroidism and thyroiditis ↓'d in factitious ingestion of thyroid hormone Tumor marker for thyroid cancer only *after* total thyroidectomy and radioiodine therapy
Radioactive iodine uptake (**RAIU**) scan	Useful to differentiate causes of hyperthyroidism ↑ **uptake** homogeneous = Graves' disease heterogeneous = multinodular goiter 1 focus of uptake w/ suppression of rest of gland = hot nodule **no uptake** = subacute painful or silent thyroiditis, exogenous thyroid hormone, struma ovarii, recent iodine load, or antithyroid drugs

Figure 7-1 Approach to thyroid disorders



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
- ⊕ antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) Abs in >90%

Clinical manifestations (*Lancet* 2004;363:793)
- **Early**: weakness, fatigue, arthralgias, myalgias, headache, depression, cold intolerance, weight gain, constipation, menorrhagia, dry skin, coarse brittle hair, brittle nails, carpal tunnel syndrome, delayed DTRs ("hung up" reflexes), diastolic HTN, hyperlipidemia
- **Late**: slow speech, hoarseness, loss of outer third of eyebrows, **myxedema** (nonpitting skin thickening due to ↑ glycosaminoglycans), periorbital puffiness, bradycardia, pleural, pericardial, & peritoneal effusions, atherosclerosis
- **Myxedema coma**: hypothermia, hypotension, hypoventilation, Δ MS

Diagnostic studies
- ↓ **FT_4**; ↑ **TSH** in primary hypothyroidism; ⊕ antithyroid Ab in Hashimoto's thyroiditis
- May see hyponatremia, hypoglycemia, anemia, ↑ LDL, ↓ HDL, and ↑ CK
- Screening recommended for pregnant women

Treatment of overt hypothyroidism
- Levothyroxine (1.5–1.7 μg/kg/d), re ✓ TSH q5–6wks and titrate until euthyroid; sx can take mos to resolve; *lower starting dose* (0.3–0.5 μg/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 μg/kg T_4 IV, then 50–100 μg IV qd; b/c peripheral conversion impaired, may also give 5–10 μg T_3 IV q8h if unstable w/ bradycardia and/or hypothermia (T_3 more arrhythmogenic); must give empiric *adrenal replacement therapy* first as ↓ adrenal reserves in myxedema coma

Subclinical hypothyroidism (*NEJM* 2001;345:260)
- Mild ↑ 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

Etiologies (*Lancet* 2003;362:459)
- **Graves' disease** (60–80% of thyrotoxicosis)
- **Thyroiditis**: thyrotoxic phase of subacute (granulomatous) thyroiditis or painless (lymphocytic) thryoiditis
- **Toxic adenomas** (single or multinodular goiter)
- TSH-secreting pituitary tumor or pituitary resistance to thyroid hormone (↑ TSH, ↑ free T_4)
- Misc: amiodarone, iodine-induced, thyrotoxicosis factitia, struma ovarii (3% of ovarian dermoid tumors and teratomas), hCG-secreting tumors (eg, choriocarcinoma), large deposits of metastatic follicular thyroid cancer

Graves' disease (*NEJM* 2008;358:2594)
- Female:male ratio is 5–10:1, most Pts between 40 and 60 y at dx
- ⊕ **thyroid antibodies**: TSI or TBII (⊕ in 80%), anti-TPO, antithyroglobulin; ANA
- Clinical manifestations in addition to those of hyperthyroidism (see 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, osteoporosis, stare 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
- ↑ **FT_4** and **FT_3**; ↓**TSH** (except in TSH-secreting tumors)
- **RAIU scan** is very useful study to differentiate causes (see table on page 7-3)
- Rarely need to ✓ for autoantibodies except in pregnancy (to assess risk of fetal Graves')
- May see hypercalciuria ± hypercalcemia, ↑ Aϕ, anemia

Treatment
- β-blockers: control tachycardia (propranolol also ↓ $T_4 \rightarrow T_3$ 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 Pts w/ cardiovascular disease or elderly w/ antithyroid drugs to prevent ↑ thyrotoxicosis, stop 3 d before to allow RAI uptake; >75% of treated Pts become hypothyroid
  - **surgery**: less commonly chosen for Graves', usually for Pts w/ obstructive goiter or ophthalmopathy
- Toxic adenoma or toxic multinodular goiter: RAI or surgery (methimazole preRx for surgery, in selected patients before RAI)
- Thyroid storm: β-blocker, PTU, iopanoic acid or iodide (for Wolff-Chaikoff effect) >1 h after PTU, ± steroids (↓ $T_4 \rightarrow T_3$)
- 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 T_4** 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 postsurgical)
- **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 Pts w/ severe nonthyroidal illness (∴ in acute illness, ✓ TFTs only if ↑ concern for thyroid disease); *may* have acquired transient central hypothyroidism
- If thyroid dysfxn suspected in critically ill Pt, TSH alone not reliable; must measure total T_4, FT_4, & T_3
- Mild illness: ↓ $T_4 \rightarrow T_3$ conversion, ↑ $rT_3 \Rightarrow \downarrow T_3$; in severe illness: ↓TBG & albumin, ↑↑ rT_3 $\Rightarrow \downarrow\downarrow T_3$, ↑ degradation of T_4, central ↓TSH $\Rightarrow$ **$\downarrow\downarrow T_3$, $\downarrow\downarrow T_4$, $\downarrow FT_4$, $\downarrow$ TSH**
- Recovery phase: ↑ TSH followed by recovery of T_4 and then T_3
- Replacement thyroxine *not* helpful or recommended for critically ill Pts w/ ↓ T_3 and T_4 unless other s/s of hypothyroidism

AMIODARONE AND THYROID DISEASE
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 T_4 & T_3
  (2) inhibits $T_4 \rightarrow T_3$ conversion
  (3) ? direct/immune-mediated thyroid destruction

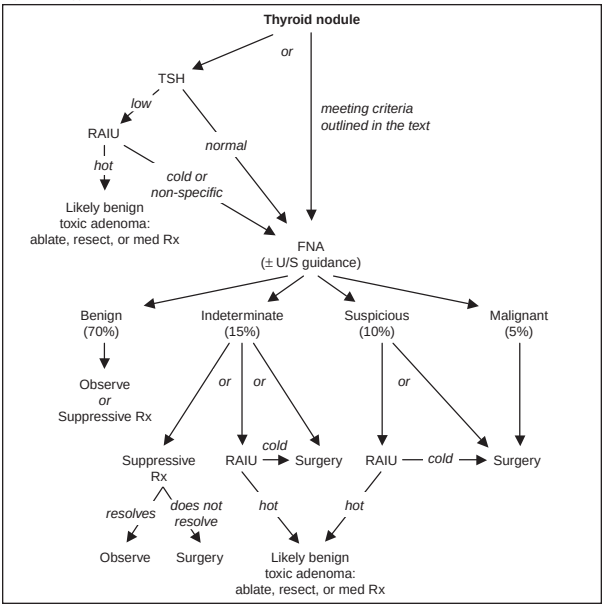
- Normal individuals: ↓T_4; then escape Wolff-Chaikoff effect and have ↑T_4, ↓T_3, ↑TSH; then TSH normalizes (after 1–3 mos)
- Susceptible individuals (eg, subclinical Hashimoto's, ∴ ✓ anti-TPO) do *not* escape effects
- Treatment: thyroxine to normalize TSH; may need larger than usual dose

Hyperthyroidism (3% of Pts on amio; ~10–20% of Pts *in iodine-deficient areas*)
- Type 1 = underlying multinodular goiter or autonomous thyroid tissue
  pathophysiology: Jod-Basedow effect (iodine load → ↑ **synthesis** of T_4 and T_3 in autonomous tissue)
  diagnostic studies: ↑ thyroid blood flow on Doppler U/S; treatment: methimazole
- Type 2 = destructive thyroiditis
  pathophysiology: ↑ **release** of preformed T4 & T3 → hyperthyroidism → hypothyroidism → recovery
  diagnostic studies: ↓ flow on Doppler U/S; treatment: steroids
- Type 1 vs. 2 often difficult to distinguish and Rx for both initiated (*JCEM* 2001;86:3)

Thyroid Nodules

- Prevalence 5–10% (50–60% if screen with U/S), ~5% malignant
- Features associated w/ ↑ 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 w/ 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

Figure 7-2 Approach to thyroid nodules (*Endocr Pract* 2006;12:63)



Cushing's Syndrome (Hypercortisolism)

Definitions

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

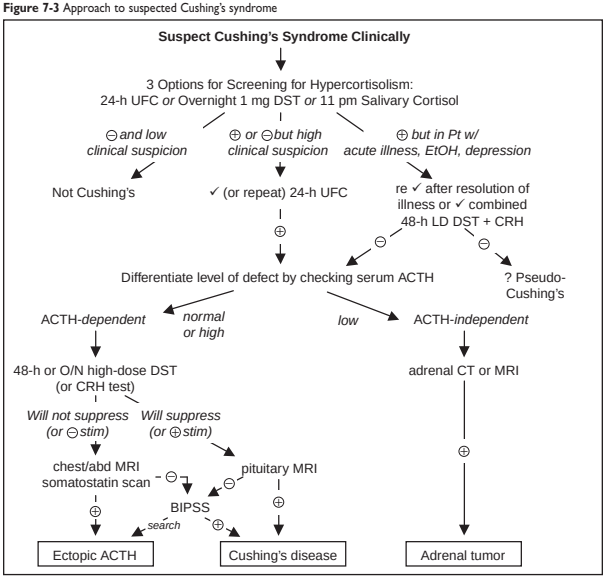
Etiologies of hypercortisolism

- 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, pheo

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 (if ↑ ACTH), fungal skin infxns, nephrolithiasis, polyuria

Figure 7-3 Approach to suspected Cushing's syndrome



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 (suppress if <10% of base)
48-h HD DST = 2 mg q6h × 2 d; ✓ 24-h UFC as per LD DST
O/N HD DST = 8 mg at 11 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 bilat 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-remediable aldosteronism (GRA; ACTH-dep. rearranged promoter)
- **Secondary** (extra-adrenal disorders, ↑ aldosterone is renin dependent)
  Primary reninism: renin-secreting tumor (rare)
  Secondary reninism
    renovascular disease: RAS, malignant hypertension
    edematous states w/ ↓ effective arterial volume: CHF, cirrhosis, nephrotic syndrome
    hypovolemia, diuretics, T2D, Bartter's (defective Na/K/2Cl transporter ≈ receiving loop diuretic), Gitelman's (defective renal Na/Cl transporter ≈ receiving thiazide diuretic)
- **Nonaldosterone mineralocorticoid excess** mimics hyperaldosteronism
  11β-HSD deficiency (→ lack of inactivation of cortisol, which binds to otherwise nonselective mineralocorticoid receptor)
  Black licorice (glycyrrhizinic acid inhibits 11β-HSD), extreme hypercortisolism (overwhelming 11β-HSD), exogenous mineralocorticoids
  Liddle's syndrome (constitutively activated/overexpressed distal tubular renal Na channel)

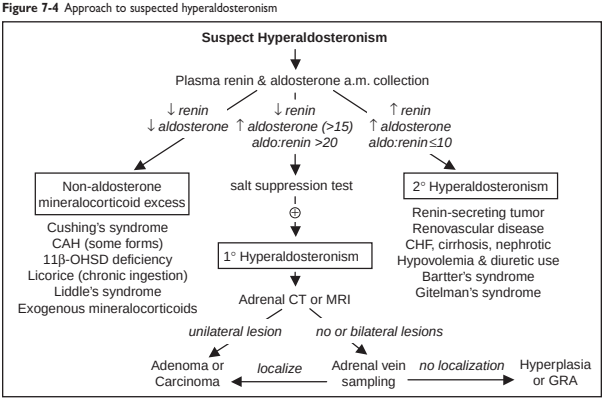
Clinical manifestations

- **Mild to moderate HTN** (11% of Pts w/ HTN refractory to 3 drugs; *Lancet* 2008;371:1921), headache, muscle weakness, polyuria, polydipsia; no peripheral edema because of "escape" from Na retention; malignant HTN is rare
- Classically **hypokalemia** (but often normal), metabolic alkalosis, mild hypernatremia

Diagnostic studies

- 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 aldo after sodium load)
  oral salt load (+ KCl) × 3 d, ✓ 24-h urine (⊕ if aldo >12 μg/d while Na >200 mEq/d) *or* 2L NS over 4 h, measure aldo at end of infusion (⊕ if aldo >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-hydroxycorticosteroid levels)
- Other lab abnormalities: hypoglycemia, eosinophilia, lymphocytosis, ± neutropenia
- ACTH: ↑ in 1°, ↓ or low-normal in 2°
- Imaging studies to consider
  pituitary MRI to detect anatomical abnormalities
  adrenal CT: small, noncalcified adrenals in autoimmune, enlarged in metastatic disease, hemorrhage, infection, or deposition (although they may be normal-appearing)

Adrenal insufficiency & critical illness (*NEJM* 2003;348:727; *JAMA* 2009;301:2362)
- 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 (⅔ a.m. ⅓ 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° 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, homogenous and hypodense appearance; unenhanced CT <10 Hounsfield units or CT contrast-medium washout >50% at 10 min. Can follow such incidentalomas w/ periodic scans.
  - *Suspicious features:* size >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.

Laboratory Findings in Calcium Disorders			
Ca	**PTH**	**Disease**	**PO_4**
↑	↑↑	Hyperparathyroidism (1° and 3°)	↓
	↑ or nl	Familial hypocalciuric hypercalcemia	↓
	↓	Malignancy	var.
		Vitamin D excess	↑
		Milk-alkali syndrome, thiazides	↓
		↑ Bone turnover	↑
↓	↑↑	Pseudohypoparathyroidism	↑
	↑	Vitamin D deficiency	↓
		Chronic renal failure (2° hyperpara)	↑
	var.	Acute calcium sequestration	var.
	↓	Hypoparathyroidism	↑

Pitfalls in measuring calcium

- Physiologically active Ca is free or ionized (ICa). Serum Ca reflects total calcium (bound + unbound) and ∴ influenced by albumin (main Ca-binding protein)
- Corrected Ca (mg/dL) = measured Ca (mg/dL) + {0.8 × [4 - albumin (gm/dL)]}
- Alkalosis will cause more Ca to be bound to albumin (∴ total Ca may be normal but ↓ ICa)
- Best to measure **ionized Ca directly**

HYPERCALCEMIA

Etiologies of Hypercalcemia	
Category	**Etiologies**
Hyperparathyroidism (HPT)	**1°: adenoma** (85%), hyperplasia (15–20%; spont. vs. MEN 1/2A), carcinoma (<1%) **3°**: after long-standing 2° hyperparathyroidism (as in renal failure) → autonomous nodule develops, requires surgery Lithium → ↑ PTH
Familial hypocalciuric hypercalcemia (FHH)	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_{Ca} [(24h U_{Ca}/serum Ca) / (24h U_{Cr}/serum Cr)] <0.01
Malignancy	PTH-related peptide (PTHrP) → humoral ↑ Ca of malignancy (e.g., squamous cell cancers, renal, breast, bladder) Cytokines & ↑ 1,25-$(OH)_2D_3$ (eg, hematologic malignancies) Local osteolysis (eg, breast cancer, myeloma)
Vitamin D excess	Granulomas (sarcoid, TB, histo, Wegener's) → ↑ 1-OH → ↑ 1,25-$(OH)_2$D. Vitamin D intoxication.
↑ Bone turnover	Hyperthyroidism, immobilization + Paget's disease, vitamin A
Miscellaneous	Thiazides; Ca-based antacids or massive dairy consumption (milk-alkali syndrome); adrenal insufficiency
Among inPts w/ hypercalcemia: 45% have cancer, 25% 1° HPT, 10% CKD → 3° HPT	

(*JCEM* 2005;90:6316)

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_4, and ↑ (Ca × PO_4) product. Dx by biopsy.
  Rx: aggressive wound care, keep Ca & PO_4 nl (goal <55), avoid vitamin D & Ca suppl.
  IV Na thiosulfate & parathyroidectomy controversial.
  Overall portends a poor prognosis

Diagnostic studies

- Hyperparathyroidism and malignancy account for 90% of cases of hypercalcemia
  hyperparathyroidism more likely if asx 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), PO_4; based on results consider checking PTHrP, 25-(OH)D, 1,25-$(OH)_2$D, Aϕ, U_{Ca}, SPEP, UPEP, ACE, CXR/CT, mammogram

Acute Treatment of Hypercalcemia			
Treatment	**Onset**	**Duration**	**Comments**
Normal saline (4–6 L/d)	h	during Rx	Natriuresis → ↑ renal Ca excretion
± **Furosemide**	h	during Rx	Use only if volume overloaded.
Bisphosphonates	1–2 d	var.	Inhibit osteoclasts, useful in malignancy; caution in renal failure; risk of jaw osteonecrosis
Calcitonin	h	2–3 d	Quickly develop tachyphylaxis
Glucocorticoids	days	days	? Useful in some malig, granulomatous disorders & vitamin D intox.

(*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	
Category	**Etiologies**
Hypoparathyroidism (*NEJM* 2008;359:391)	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
Pseudo-hypoparathyroidism	Ia and Ib: PTH end organ resistance (∴ ↑ serum PTH) Ia: + skeletal abnormalities, short stature, & retardation Pseudopseudohypoparathyroidism = Ia syndrome but *nl* Ca & PTH
Vitamin D deficiency or resistance	Nutritional/sunlight deprivation; GI disease/fat malabs.; drugs (anticonvulsants, rifampin, ketoconazole, 5-FU/leucovorin); genetic (1α-hydroxylase, VDR mutations)
Chronic renal failure	↓ 1,25-$(OH)_2$D production, ↑ PO_4 from ↓ clearance
Accelerated net bone Formation	Postparathyroidectomy, Rx of severe vit D deficiency or Paget's disease (*NEJM* 2006;355:593), osteoblastic metastases
Calcium sequestration	Pancreatitis, citrate excess (after blood transfusions), acute ↑↑ PO_4 (ARF, rhabdomyolysis, tumor lysis), bisphosphonates

Clinical manifestations

- **Neuromuscular irritability**: perioral paresthesias, cramps, ⊕ **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, ↓ PO_4 → ↓ bone/cartilage mineralization, growth failure, bone pain, muscle weakness
- **Renal osteodystrophy** (↓ vit D & ↑ PTH in renal failure): osteomalacia (↓ mineralization of bone due to ↓ Ca and 1,25-$(OH)_2$D) & osteitis fibrosa cystica (due to ↑ PTH)

Diagnostic studies

- Ca, alb, ICa, PTH, 25-(OH)D, 1,25-$(OH)_2$D (if renal failure or rickets), Cr, Mg, PO_4, Aϕ, U_{Ca}

Treatment (also treat concomitant vitamin D deficiency)

- 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:S33 & 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% ↓)
- ↑ Hb_{A1C} (no accepted criterion yet, ≥6.5% recommended by intl expert cmte)

Categories

- **Type 1:** islet cell destruction; absolute insulin deficiency; ketosis in absence of insulin
  prevalence 0.4%; usual onset in childhood but can occur throughout adulthood; ↑ risk if ⊕ FHx; HLA associations; anti-GAD, anti-islet cell & anti-insulin autoantibodies
- **Type 2**: insulin resistance + relative insulin deficiency
  prevalence 8%; onset generally later in life; ↑↑ risk if ⊕ FHx; no HLA associations
  risk factors: age, ⊕ FHx, obesity, sedentary lifestyle
- **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)
- **M**ature-**O**nset **D**iabetes of the **Y**oung (**MODY**): autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (*NEJM* 2001;345:971)
- **Secondary causes of diabetes**: exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF, resection), 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, ↓ Hb_{A1C} ~1.5% Wt neutral, N/V & diarrhea, rare lactic acidosis Contraindic. in renal (eg, Cr >1.5) or liver failure Consider first-line Rx w/ lifestyle mod. for all T2D w/ Hb_{A1C} ≥7%
Sulfonylureas (SU)	↑ insulin secretion, ↓ Hb_{A1C} ~1.5%. Hypoglycemia, wt gain.
Thiazolidinediones (TZD) (PPAR-γ agonists)	↑ insulin sens. in adipose & muscle. ↓ Hb_{A1C} ~1% Wt gain, hepatotoxicity, fluid retention & CHF, bone fractures ? ↑ MI w/ rosiglitazone (*NEJM* 2007;356:2457; *Lancet* 2009;373:2125) but not w/ pioglitazone (*JAMA* 2007;298:1180) Contraindic. in liver disease and NYHA III–IV, monitor LFTs
Glinides	↑ insulin secretion, ↓ Hb_{A1C} ~1.5% Hypoglycemia (but less than w/ SU), wt gain
Exenatide	↑ glc-depend insulin secretion (GLP-1 agonist), ↓ Hb_{A1C} ~0.5% Wt loss, N/V & diarrhea (30–45%), pancreatitis (rare)
α-glucosidase inhibitor	↓ intestinal CHO absorption, ↓ Hb_{A1C} 0.5–0.8%. GI distress (gas).
Pramlintide	Delays gastric emptying & ↓ glucagon, ↓ Hb_{A1C} 0.5% To be used as adjunctive Rx w/ insulin in T1D or T2D
DPP-4 inhibitor	Blocks degrad. of GLP-1 & GIP → ↑ insulin. ↓ Hb_{A1C} ~0.5%.
Insulin (Additional T1D options: insulin pump, pancreatic or islet cell transplant)	Hypoglycemia, wt gain 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 ↑ Hb_{A1c} high) and definitely start if combo oral Rx not adequate.

(*JAMA* 2002;287:360, 373; *Diabetes Care* 2009;32:193)

Insulin Preparations				
Preparation	**Onset**	**Peak**	**Duration**	**Side effects/Comments**
Lispro, aspart	5–15 min	60–90 min	2–4 h	Give immediately before meal
Regular	30–60 min	2–4 h	5–8 h	Give ~30 min before meal
NPH	1–2 h	4–8 h	12–18 h	Can cause protamine Ab prod
Glargine	2 h	No peak	20–24 h	Once daily (AM or PM)

(*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
  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 dysfxn, orthostasis
  mononeuropathy: sudden-onset peripheral or CN deficit (footdrop, CN III > VI > IV)
- **Accelerated atherosclerosis**: coronary, cerebral, and peripheral arterial beds
- **Infections**: UTI, osteomyelitis of foot, candidiasis, mucormycosis, necrotizing external otitis
- **Dermatologic**: necrobiosis lipoidica diabeticorum, lipodystrophy, acanthosis nigricans

Outpatient screening and treatment goals (*Diabetes Care* 2009;32:193 & S1:S13)
- ✓ Hb_{A1C} q3–6mo, goal <7% for most Pts (*NEJM* 2008;358:2545, 2560); microvascular & macrovascular complications ↓ by strict glycemic control in T1D (*NEJM* 1993;329:997 & 2005;353:2643) & T2D (*Lancet* 1998;352:837; *NEJM* 2008;359:1577; *Lancet* 2009;373:1765; *Annals* 2009;151:394)
- 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 (♂) or 60 (♀) 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), Hb_{A1C}
- 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 cntl, no plan for IV contrast, nl diet)
- InPt insulin: can use outPt regimen as guide; if insulin naïve:
  total daily insulin = wt (kg) ÷ 2, to start; adjust as needed
  give ½ of total daily insulin as basal insulin in long-acting form to target fasting glc
  give other ½ as short-acting boluses (standing premeal & sliding scale corrective insulin)
- Discharge regimen: similar to admission regimen unless poor outPt cntl or strong reason for Δ. Arrange early insulin and glucometer teaching, prompt outPt follow-up.

DIABETIC KETOACIDOSIS (DKA)

Precipitants (the 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); ↑ glucagon and ↓ insulin
- Hyperglycemia due to: ↑ gluconeogenesis, ↑ glycogenolysis, ↓ glucose uptake into cells
- Ketosis due to: insulin deficiency → mobilization and oxidation of fatty acids,
  ↑ substrate for ketogenesis, ↑ ketogenic state of the liver; ↓ ketone clearance

Clinical manifestations (*Diabetes Care* 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 (HCO_3 equivalents) and fluid resuscitation with chloride
- **Ketosis**: ⊕ **urine and serum ketones** (acetoacetate measured by nitroprusside, but predominant ketone is β-OH-butyrate; 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									
VS	UOP	pH	HCO_3	AG	Ketones	Glc	K	PO_4	IVF	Insulin

Note: Main ketone produced is β-OH-butyrate (βOHB), but ketone measured by nitroprusside is acetoacetate (Ac-Ac). As DKA is treated, βOHB → Ac-Ac, ∴ AG can decrease while measured ketones can increase.

Treatment of DKA	
Rule out possible precipitants	Infection, intra-abdominal process, MI, etc.
Aggressive hydration	NS 10–14 mL/kg/h, tailor to dehydration & CV status
Insulin	10 U IV push followed by 0.1 U/kg/h Continue insulin drip until AG normal If glc <250 and AG still high → add dextrose to IVF and continue insulin to metabolize ketones AG normal → SC insulin (overlap IV & SC 2–3 h)
Electrolyte repletion	K: add 20–40 mEq/L IVF if serum K <4.5 insulin promotes K entry into cells → ↓ serum K careful K repletion in Pts with renal failure HCO_3: ? replete if pH <7 or if cardiac instability PO_4: replete if <1

Hyperosmolar Hyperglycemic State

Definition, Precipitants, Pathophysiology (*Diabetes Care* 2003;26: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 D_{50} (50% dextrose)
- If no IV, can give glucagon 0.5–1 mg IM or SC (side effect: N/V)

Measurements

- Lipoproteins = lipids (cholesteryl 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

Category	Disorders
Endocrinopathies	Type 2 diabetes (↑ TG, ↓ HDL) Hypothyroidism (↑ LDL, ↑ TG); hyperthyroidism (↓ LDL) Cushing's syndrome & exogenous steroids (↑ TG)
Renal diseases	Renal failure (↑ TG); nephrotic syndrome (↑ LDL)
Hepatic diseases	Cholestasis, PBC (↑ LDL); liver failure (↓ LDL); acute hepatitis (↑ TG)
Lifestyle	Obesity (↑ TG, ↓ HDL); sedentary lifestyle (↓ HDL); alcohol (↑ TG, ↑ HDL); tobacco (↓ HDL)
Medications	Thiazides (↑ LDL); β-blockers (↑ TG, ↓ HDL) Estrogens (↑ TG, ↑ HDL); protease inhibitors (↑ TG)

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 $\varepsilon 2/\varepsilon 2$ + 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
- Xanthelasma: 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

Clinical risk	LDL Goal
High: CHD, CVD, PAD, AAA, DM, or ≥2 RFs & 10-y risk >20%	<100 mg/dL or <70 if very high risk (ACS, CAD + multiple RFs or + met syndrome)
Mod high: ≥2 RFs & 10-y risk 10–20%	<130 mg/dL (optional <100 mg/dL)
Mod: ≥2 RFs & 10-y risk <10%	<130 mg/dL
Lower: 0–1 RFs	<160 mg/dL

RFs: male ≥45 y or female ≥55 y, smoking, HTN, ⊕ FHx, HDL <40. If HDL >60, subtract 1 RF. Framingham 10-y CHD risk score at www.nhlbi.nih.gov/guidelines/cholesterol. (*JAMA* 2001;285:2486; *Circulation* 2004;110:227)

Drug Treatment

Drug	↓ LDL	↑ HDL	↓ TG	Side effects/comments
Statins	20–60%	5–10%	10–25%	↑ aminotransferases in 0.5–3%; ✓ LFTs before, at 8–12 wks, and then q6mos; risk dose-depend. Myalgias <10% (not always ↑ CK), myositis 0.5%, rhabdo <0.1%, risk dose-depend. Doubling of dose → 6% further ↓ LDL.
Ezetimibe	15–20%	—	—	Well tolerated; typically w/ statin
Fibrates	5–15%	5–15%	35–50%	Myopathy risk ↑ w/ statin. Dyspepsia, gallstones
Niacin	10–25%	~30%	40%	Flushing (Rx w/ ASA), pruritis, ↑ glc, gout, nausea, severe hepatitis (rare)
Resins	20%	3–5%	? ↑	Bloating, binds other meds
Ω-3 FA	5% ↑	3%	25–30%	Dyspepsia, diarrhea

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

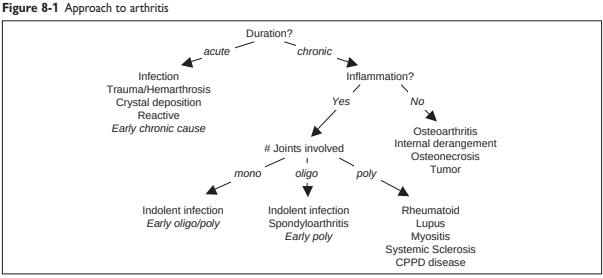
Key Physical Exam Findings in Joint Pain

	Joint		Soft tissues		
Physical exam	***Inflammatory Arthritis***	***Arthralgia***	***Bursitis***	***Tendonitis***	***Myofascial***
Inspection					
Swelling	yes	no	yes	yes	no
Erythema	varies	no	yes	usually	no
Palpation					
Warmth	yes	no	yes	usually	no
Tenderness	varies	varies	over bursa	over tendon	yes
ROM*					
ROM	limited	full or limited	full	full, often limited by pain	full
Pain w/ active or passive ROM	both	usually both	varies	active > passive	usually both

*Range of motion (ROM) of joint or joint associated with bursa or tendon

Approach to arthritis

Figure 8-1 Approach to arthritis



Etiologies of Arthritis by Joint

Shoulder	OA, calcific (Milwaukee shoulder), septic, CPPD
Elbow	Septic, spondyloarthritis, juvenile idiopathic arthritis (common nonarthritic causes of pain incl. olecranon bursitis and lateral epicondylitis)
Wrist	RA, CPPD, septic, gout, adult-onset Still's disease
1st CMC	OA
MCP	RA, CPPD, psoriatic, gout
PIP	OA, RA, psoriatic, gout
DIP	OA, psoriatic, gout
Hip	OA, septic, spondyloarthritis, osteonecrosis
Knee/ankle	OA, RA, gout, CPPD, psoriatic, septic, Lyme, spondyloarthritis, sarcoidosis
Toes	Gout, OA, spondyloarthritis, psoriatic

Comparison of Major Arthritides				
Feature	**OA**	**RA**	**Gout**	**Spondylo-arthritis**
Onset	gradual	gradual	acute	variable
Inflammation	⊖	⊕	⊕	⊕
Pathology	degeneration	pannus	microtophi	enthesitis
# of joints	poly	poly	mono to poly	oligo or poly
Type of joints	small or large	small	small or large	large
Locations typically involved	hips, knees, spine 1st CMC DIP, PIP	MCP, PIP wrists feet, ankles	MTP feet, ankles knees	sacroiliac spine large peripheral
Special articular findings	Bouchard's nodes Heberden's nodes	ulnar dev. swan neck boutonnière	urate crystals	en bloc spine enthesopathy (eg, Achilles)
Bone changes	osteophytes	osteopenia erosions	erosions	erosions ankylosis
Extra-articular features		SC nodules pulmonary cardiac splenomegaly	tophi olec. bursitis renal stones	uveitis conjunctivitis aortic insuff. psoriasis IBD
Lab data	normal	⊕ RF, anti-CCP	↑ UA	

Analysis of Joint Fluid				
Test	**Normal**	**Noninflammatory**	**Inflammatory**	**Septic**
Appearance	clear	clear, yellow	clear to opaque yellow-white	opaque
WBC/mm^3	<200	<2000	>2000	>2000 *usually >50K*
Polys	<25%	<25%	≥50%	≥75%
Culture	⊖	⊖	⊖	⊕
Conditions		OA, internal derangement	RA, crystal CTD spondyloarth.	infection

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 ⅓ of sero-⊕), myocarditis, nodules can cause valvular 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, mesganigal, 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 ⊕, 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; ⊕ ANA 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

Joint involvement	Score	Acute phase reactants	Score
1 med-large	0	Normal ESR & CRP	0
2–10 med-large	1	Abnormal ESR or CRP	1
1–3 small	2	**Duration of sx**	**Score**
4–10 small	3	<6 wk	0
>10 (≥1 small)	5	≥6 wk	1
Serology	**Score**	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.	
RF & ACPA ⊖	0		
Low-⊕ RF or ACPA	2		
High-⊕ RF or ACPA	3		

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 fxn and quality of life
- Initial therapy: **nonselective 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 **D**isease-**M**odifying **A**nti-**R**heumatic **D**rug **(DMARD)** w/in 3 mo if established disease and ongoing inflammation (*Annals* 2007;146:406); all take ≥1 mo to have an effect

DMARDs		
Class	**Drug**	**Side effects**
Antimetab	Methotrexate (MTX)	GI distress, myelosupression, hepatotoxicity. Supplement MTX w/ folate.
	Leflunomide	
	Azathioprine (AZA)	
Biologic	Anti-TNF: etanercept, infliximab, adalimumab, certolizumab, golimumab	TB, zoster, & other infxns. ∴ *screen for TB prior to starting Rx.* ? tumors. ? CHF & demyelinating CNS disease for anti-TNF.
	IL-1RA: anakinra	
	CTLA4-Ig: abatacept	
	IL-6R Ab: tocilizumab	
	Anti-CD20: rituximab	
Other	Hydroxychloroquine (HCQ)	Retinopathy, maculopapular rash
	Sulfasalazine (SAS)	Allergic rxn. Need folate suppl.
	Gold	
	Minocycline	
	Cyclosporine	Nephrotox, HTN, gum hyperplasia

(*NEJM* 2005;353:1114 & 2006;350:2572; *Arth Rheum* 2008;11:3319; *Lancet* 2008;371:987 & 2009;374:210)

- Treatment strategies (*Lancet* 2008;372:375 & 374:459; *Ann Rheum Dis* 2010;69:976 & 987)
  - **monotherapy** with MTX (a/w lower mortality; *Lancet* 2007;359:1173), sulfasalazine, leflunomide, or hydroxychloroquine, *or*
  - **combination** of DMARD + glucocorticoid or anti-TNF (*Arth 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
- Ddx: 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

	UA Overproduction	UA Underexcretion
Primary hyperuricemia	**Idiopathic** Rare inherited enzyme (HGPRT, PRPP) defic. Common genetic variants (*Lancet* 2008;372:1953)	**Idiopathic**
Secondary hyperuricemia	**↑ meat, seafood, EtOH intake** **Myelo- & lymphoproliferative dis.** Chronic hemolytic anemia Cytotoxic drugs, psoriasis Severe muscle exertion	**Dehydration** **↓ renal function** Drugs: **diuretics,** PZA, EMB, salicylates, CsA Keto- or lactic acidosis

(*Lancet* 2004;363:1277; *NEJM* 2004;350:1093; *Annals* 2005;143:499)

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/mm^3, >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

Acute Treatment for Gout

Drug	Mechanism	Comments
NSAIDs	↓ inflammation	Gastritis; ↓ dose in renal insufficiency
Colchicine (PO or IV)	inhibits polymerization of microtubules → prevention of chemotaxis and phagocytosis	Nausea, vomiting, and diarrhea IV and high PO doses → bone marrow suppression, myopathy, neuropathy ↓ dose in renal insufficiency
Corticosteroids (PO, IA, or IV) *or* **Corticotropin** (SC, IM, or IV)	↓ inflammation	For initial Rx, efficacy = NSAIDs Highly effective for recalcitrant cases Rule out joint infection first

(*NEJM* 2003;349:1647; *Lancet* 2008;371:1854)

Chronic treatment
- ↓ urate production by ↓ intake of meat and seafood (note: high-purine vegetables a/w ↑ risk); ↑ intake 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;65:1312)
- **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 Δ ↓ 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*
  location: **knees, wrists,** and MCP joints
  precipitants: surgery, trauma, or severe illness
- "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)
  WBC 2000–100,000/mm³, >50% polys
  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

SERONEGATIVE SPONDYLOARTHRITIS

General

Definition (*Annals* 2002;136:896)
- A spectrum of systemic inflammatory arthritides w/ 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, nonseptic picture

Pathogenesis (*Semin Arthritis Rheum* 2008;38:83)
- ↑ 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 *ARTS1* (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 jxn and another point 10 cm above, when going from standing to maximum forward flexion)
  - T-spine mobility (extension) and kyphosis severity measured by occiput-to-wall distance
- **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 sacroiliitis. Can develop *sausage digits* (dactylitis) of extremities.

- **Urethritis/cervicitis**: usually *Chlamydia* infection preceding arthritis, but also can see sterile urethritis in postdysenteric 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
  - stomatitis and superficial oral ulcers
- 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 Pts w/ psoriasis (and not necessarily those with severe skin disease)
- Arthritis may *precede* onset of skin disease, even by years; a/w nail changes
- 20–40% of Pts with psoriatic arthritis have spinal or sacroiliac involvement
- Men and women are affected equally and most Pts 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 Pts 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)

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 suspicious 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

Common microbes		Population	Initial antibiotic regimen
GPC	*S. aureus* (most common)	Normal joints Prosthetic joints Damaged joints	Nafcillin *or* Vancomycin if suspect MRSA (eg, hospitalized Pt)
	S. epidermidis	Prosthetic joints Post–joint procedure	Nafcillin *or* Vancomycin if suspect MRSA (eg, hospitalized Pt)
	Streptococci	Healthy adults Splenic dysfunction	Penicillin G or ampicillin
GN	Diplococci: *N. gonorrhea*	Sexually active young adults	Ceftriaxone or cefotaxime
	Rods: *E. coli*, *Pseudomonas*, *Serratia*	IVDU GI infection Immunocompromised	Cefepime or piperacillin/tazobactam + antipseudomonal aminoglycoside if suspect IVDU

Bacterial (Nongonococcal) 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 ⊕ in ~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 cases, 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 gonorrhea*
- **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, 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

% Autoantibodies in Patients with Rheumatic Diseases										
Disease	**ANA & Pattern**	**RF**	**dsDNA**	**Sm**	**Ro**	**La**	**Scl-70**	**Cent**	**Jo**	**RNP**
SLE	95–99 D, S, N	20	50–70	30	35	15	0	0	0	30–50
RA	15–35 D	85	<5	0	10	5	0	0	0	10
Sjögren's	>90 D, S	75	<5	0	55	40	0	0	0	15
Diffuse SSc	>90 N, S, D	30	0	0	5	1	40	<5	0	30
Limited SSc	>90 S, N, D	30	0	0	5	1	<5	70	0	30
PM-DM	75–95	33	0	0	0	0	10	0	25	0
MCTD	95–99 S, D	50	0	0	<5	<5	0	0	0	100

(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

see "Systemic Lupus Erythematosus" and "Rheumatoid Arthritis" for those diseases

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 O_2 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
  bibasilar **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 ↓ D_LCO 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	
Skin	Tightening and thickening of extremities, face, trunk (bx not req for dx) "Puffy" hands, carpal tunnel syndrome, sclerodactyly Nailfold capillary dilatation & dropout Immobile, pinched, "mouselike" facies and "purse-string" mouth Calcinosis cutis (subcutaneous calcification) Telangiectasias
Arteries	Raynaud's phenomenon (80%); digital or visceral ischemia
Renal	Scleroderma renal crisis = sudden onset severe HTN, RPGN, MAHA Crescentic GN (rare) with ⊕ p-ANCA (*J Rheum* 2006;33:1886)
GI	GERD and erosive esophagitis Esophageal dysmotility → dysphagia, odynophagia, aspiration Gastric dysmotility → early satiety and gastric outlet obstruction Small intestinal dysmotility → bloating, diarrhea, malabsorption
Musculoskel	Polyarthralgias & joint stiffness; muscle weakness, tendon friction rubs
Cardiac	Myocardial fibrosis, pericarditis; conduction abnormalities
Pulmonary	Pulmonary fibrosis (typically develops w/in 4 y); pulmonary arterial hypertension (typically develops after many yrs). #1 cause of mortality.
Endocrine	Amenorrhea and infertility common; thyroid fibrosis ± hypothyroidism

Systemic Sclerosis		
	Limited	**Diffuse**
General		Fatigue, weight loss
Skin	Thickening on distal extremities and face only	Thickening on extremities (incl. digits), face, *and trunk*
Nails	Capillary dropout ± dilatation	Capillary dropout & *dilatation*
Pulmonary	PAH > fibrosis	Fibrosis > PAH
GI	GERD, hypomotility, *PBC*	GERD, hypomotility
Renal		Renovascular HTN
Cardiac		Restrictive cardiomyopathy
Other	**CREST syndrome** = **C**alcinosis, **R**aynaud's **E**sophageal dysmotility **S**clerodactyly, **T**elangiectasias	Raynaud's
Antibodies	Anticentromere (70%)	Anti-Scl 70 (40%)
Prognosis	Survival >70% at 10 y	Survival 40–60% at 10 y

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
  hypomotility: metoclopramide or erythromycin; nonoperative Rx of pseudoobstruction
- 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)
  - dermatologic features without muscle disease = **DM sine myositis**
- 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
  PM: endomysial inflam. (CD8 T cells) surrounds non-necrotic fibers, ↑ MHC class I
  DM: perimysial, perivascular inflam. (B & CD4 T cells), complement in vessels
  IBM: same as PM with eosinophilic inclusions and rimmed vacuoles (EM)

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

Disease	Weakness	Pain	↑ CK	↑ ESR	Biopsy
DM/PM	⊕	⊖	⊕	±	as above
IBM	⊕	⊖	⊕	⊖	as above
Hypothyroidism	⊕	±	⊕	⊖	mild necrosis inflammation atrophy
Steroid-induced	⊕	⊖	⊖	⊖	atrophy
PMR	⊖ (limited by pain)	⊕	⊖	⊕	normal
Fibromyalgia	⊖ (limited by pain)	⊕ (tender points)	⊖	⊖	normal

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; xerotrachea; 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
2. Dry mouth
3. ⊕ Schirmer test or Rose-Bengal staining
4. Inflammatory foci on minor salivary gland bx
5. Objective ↓ in salivary gland function
6. Ab to Ro/SS-A or La/SS-B

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 → throbbing & pain

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*) exaggerated vascular reactivity ultimately leads to **tissue ischemia & injury**
- 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, α-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

Organ System	Am. Coll. Rheum. Criteria	Other Features
Constitutional (84%)		Fever, malaise, anorexia, weight loss
Cutaneous (81%)	**1. Malar rash** (spares nasolabial folds) **2. Discoid rash** (erythematous papules w/ keratosis & plugging) **3. Photosensitivity** (rash, fever, N/V) **4. Oral/nasopharyngeal ulcers**	Alopecia Vasculitis Subacute cutaneous lupus Panniculitis (lupus profundus) Urticaria
Musculoskeletal (85–95%)	**5. Nonerosive arthritis**: episodic, oligoarticular, symmetrical, migratory	Arthralgias and myalgias Avascular necrosis of bone
Cardiopulmonary (33%)	**6. Serositis**: pleuritis (37%) or pleural effusion, pericarditis (29%) or pericardial effusion	Pneumonitis, IPF, shrinking lung, PAH, DAH Myocarditis, CAD (*NEJM* 2003;349:2399, 2407) Libman-Sacks endocarditis
Renal (77%)	**7. Proteinuria** (>500 mg/dL or 3+ on dipstick) or **urinary** cellular **casts**	Nephrotic syndrome Lupus nephritis (ISN/RPS): I = min. mesangial II = mesangial prolif III = focal (active/chronic) prolif IV = diffuse prolif V = membranous VI = advanced sclerotic
Neurologic (54%)	**8. Seizures or psychosis** without other cause	Organic brain syndrome, PML Cranial or periph. neuropathies
Gastrointestinal (~30%)		Serositis (peritonitis, ascites) Vasculitis (bleeding, perf.) Abdominal pain Hepatitis, pancreatitis
Hematologic	**9. Hemolytic anemia** (DAT ⊕) *or* **leukopenia** (<4000/mm^3), *or* **lymphopenia** (<1500/mm^3), *or* **thrombocytopenia** (<100,000/mm^3)	Anemia of chronic disease Antiphospholipid syndrome (VTE w/ ⊕ ACL Ab or ⊕ LAC) Splenomegaly Lymphadenopathy
Other		Sicca syndrome Conjunctivitis or episcleritis Raynaud's (20%) Nailfold capillary changes
Serologies	**10. ⊕ ANA** **11. ⊕ anti-ds-DNA, anti-Sm, or antiphospholipid Abs**	↓ complement (during flare), ↑ ESR, ↑ CRP, ⊕ anti-Ro or anti-RNP, ⊕ RF, ⊕ anti-CCP

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)

Workup

- Detailed history and exam to assess for signs and symptoms of disease
- Autoantibodies: ANA, if ⊕ → ✓ anti-ds-DNA, anti-Sm, anti-Ro, anti-La, anti-U1-RNP
- Electrolytes, BUN, Cr, U/A, urine sediment, 24-h urine for CrCl and protein
- CBC, Coombs' test, PTT, APLA (anticardiolipin or lupus anticoagulant ⊕ in 20–40%), C3, C4

Autoantibodies in SLE			
AutoAb	**Frequency (approx)**	**Clinical Associations**	**Timeline**
ANA	95–99% if active disease 90% if in remission Homogeneous or speckled	Any or all of the broad spectrum of clinical manifestations Sensitive but not specific	May appear yrs before overt disease
Ro **La**	15–35% ⊕ anti-Ro in ANA ⊖ SLE	Sjögren's/SLE overlap Neonatal lupus Photosensitivity Subacute cutaneous lupus	
ds-DNA	70%; very specific for SLE Titers parallel disease activity, especially renal disease	Lupus nephritis Vasculitis	Appears mos before or at diagnosis
Sm	30%; very specific for SLE	Lupus nephritis	
U1-RNP	40%	MCTD; Raynaud's Tend *not* to have nephritis	
histone	SLE 80%, c/w 90% in DLE	Mild arthritis and serositis	At diagnosis

(*NEJM* 2003;349:1526)

Treatment of SLE		
Drug	**Indication**	**Adverse Effects**
NSAIDs	Arthralgias/arthritis, myalgias, mild serositis	Gastritis, UGIB Renal failure
Hydroxychloroquine	Mild disease complicated by serositis, arthritis, skin Δs	Retinal damage Stevens-Johnson synd. Myopathy
Corticosteroids	Low doses for mild disease High doses for major manifestations including renal, hematologic, CNS	Adrenal suppression, osteopenia, avascular necrosis of bone, myopathy
Mycophenolate	Nephritis (induction and/or maintenance; *NEJM* 2004;350:971 & 2005;353:2219)	Myelosuppression Immunosuppression/infxn, teratogen
Cyclophosphamide	Severe nephritis, vasculitis or CNS disease *(induction ± maintenance)*	Myelosuppression Myeloproliferative disorders Immunosuppression/infxn Hemorrhagic cystitis, bladder cancer Infertility, teratogen
Azathioprine (AZA)	Mild nephritis (2nd line) Steroid-sparing agent	Myelosuppression Hepatotoxicity Lymphoproliferative disorders
Methotrexate (MTX)	Skin and joint disease Serositis	Myelosuppression Hepatotoxicity Pneumonitis ± fibrosis Alopecia, stomatitis
Cyclosporine (CsA)	Renal disease	Hyperplastic gums, HTN Hirsutism Renal impairment, anemia
Rituximab	? Refractory ITP or AIHA	B-cell depletion; PML (?)
Belimumab	Refractory SLE; compassionate use only (*Arth Rheum* 2010;62:201)	B-cell depletion

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;82:299)

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

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; MRI/MRA; pathology → focal panarteritis, cellular infiltrate with granulomas and giant cells. MRI useful for monitoring.
- Classification criteria (3 of 6 is 90.5% Se & 97.8% Sp; *Arth Rheum* 1990;33:1129)
  1. age ≤40 y at dis. onset
  2. claudication of extremities
  3. ↓ brachial artery pulse
  4. systolic BP difference >10 mmHg between arms
  5. bruit over subclavian arteries or aorta
  6. arteriogram abnormality (Ao, primary branches, or prox. large arteries in extremities)
- Treatment: steroids, MTX, antiplatelet Rx, surgical/endovascular revasc (*Circ* 2008;69:70)

Giant cell arteritis (GCA) (*NEJM* 2003;349:160)
- Vasculitis affecting cranial branches of aortic arch, especially temporal artery (thus also called **temporal arteritis**), but can cause aortitis as well
- 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%) → optic neuritis, diplopia, amaurosis fugax, and blindness
  - facial arteries → **jaw claudication**
  - Raynaud's phenomenon; intermittent claudication of extremities; thoracic Ao aneurysm
- Dx studies: ↑ ESR (though in ~5% ESR <40 even before Rx); ↑ CRP, anemia (ESR related to fgbn & Ig in blood; Ddx for >100: malignancy esp. multiple myeloma, lymphoma; GCA or other vasculitis; ESRD; endocarditis, TB, osteomyelitis)
  - **temporal artery bx:** 3–5 cm, bilat. ↑ yield (*J Rheum* 2009;36:794); look for vasculitis, granul.
  - if suspect Ao involvement: MRI/MRA or CT-PET to identify stenoses, aneurysms, inflam.
- 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. temp artery tenderness or ↓ pulsation
  4. ↑ ESR >50 mm/h
  5. biopsy → vasculitis & granulomas
- **Polymyalgia rheumatica** (seen in 50% GCA Pts; 15% of Pts w/ PMR develop GCA)
  - no universal or validated diagnostic criteria exist; instead follow general guidelines:
    - age ≥50 y; ESR >40 mm/h (and/or elevated CRP)
    - *bilateral aching and morning stiffness* (>30 min × ≥1 mo), involving 2 of following 3 areas: neck or torso, shoulders or prox. arms, hips or prox. thighs; nighttime pain
  - exclude other causes of sx (eg, RA); CK should be normal
- 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**
- Clinical manifestations (Cupps and Fauci. *The Vasculitides*. Philadelphia: WB Saunders, 1981)
  - 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
  - GI (44%): **abd pain**, GIB/infarction, cholecystitis; GU (25%): ovarian or **testicular pain**
  - cutaneous 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 angio 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-Vessel Vasculitis

Disease	Gran.	Renal	Pulm.	Asthma	ANCA Type*	ANCA ⊕
Wegener's granulomatosis	⊕	80%	90%	—	c-ANCA (anti-PR3)	90%
Microscopic polyangiitis	—	90%	50%	—	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)

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 granulomatosis, drug-induced vasculitis, nonvasculitic rheumatic diseases
- **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×) 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)
  dermatologic: palpable purpura, petechiae, subcutaneous nodules
- Dx studies: **50%** ⊕ **ANCA** (c-ANCA or p-ANCA), **eosinophilia** (5–10 k/μL, 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. migratory or transitory pulm. infiltrates
  5. paranasal sinus abnormality
  6. 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** ± GIB 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; *Arth 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

Behçet'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
- Treatment (*Rheumatology* 2007;46:736; *Ann Rheum Dis* 2009;68:1528)
  - 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

CRYOGLOBULINEMIA

Definition & Types (*Blood Reviews* 2007;21:183)

- **Proteins that precipitate on exposure to the cold**, characterized by their composition

Types of Cryoglobulinemia			
Feature	**Type I (monoclonal)**	**Type II (mixed)**	**Type III (polyclonal)**
Proportion of cases	10–15%	50–60%	25–30%
Cryoglobulin	*monoclonal* Ig (usually IgM, or IgG)	*monoclonal* IgM usually w/ RF activity + *polyclonal* IgG	*polyclonal* Ig
Common etiologies	**MM, Waldenstrom's**	**HCV infection** (> 80% are HCV RNA ⊕)	**Autoimmune syndromes**
Primary manifestations	**Hyperviscosity** ± thrombosis	**IC-mediated vasculitis**, w/ multiorgan involvement. Type III can be asymptomatic	

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, myelodysplasia
- 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 asx 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			
Type	**Precursor**	**Causative diseases**	**Organ systems**
AL (Primary) Most common ~2000 cases/y	Ig light chain (monoclonal)	MM Light chain disease (λ >κ) MGUS, WM	**Renal**, **cardiac**, **GI**, **neuro**, **cutaneous**, hepatic, pulmonary, musculoskel, heme
AA (Secondary)	Serum amyloid (SAA)	Inflam: RA, IBD, FMF Chronic infxns: osteo, TB Neoplasms: renal, HD	**Renal**, **GI**, **hepatic**, neuro, cutaneous
Hereditary	Transthyretin, et al.	Mutant proteins	**Neurologic**, cardiac
Senile	TTR, ANP	*Normal* proteins; 2° aging	**Cardiac**, aorta, GI
Aβ$_2$M	β$_2$-microglobulin	Dialysis-associated β2m (normally renally excreted)	Musculoskeletal
Organ-specific	β-amyloid protein Peptide hormones	Localized production and processing	Neurologic Endocrine

(Adapted from *NEJM* 1997;337:898; 2003;349:583; 2007;356:2361)

Clinical Manifestations of Amyloidosis		
System	**Manifestations**	**Amyloid**
Renal	Proteinuria or nephrotic syndrome	AL, AA
Cardiac	Cardiomyopathy (restrictive & dilated) ↓ QRS amplitude, conduction abnormalities, AF Orthostatic hypotension	AL, hereditary, senile, organ-specific
GI	Diarrhea, malabsorption, protein loss Ulceration, hemorrhage, obstruction Macroglossia → dysphonia and dysphagia	all systemic
Neurologic	Peripheral neuropathy with painful paresthesias Autonomic neuro → impotence, dysmotility, ↓ BP Carpal tunnel syndrome	hereditary, AL, organ-specific, Aβ$_2$m
Cutaneous	Waxy, nonpruritic papules; periorbital ecchymoses "Pinch purpura" = skin bleeds with minimal trauma	AL
Hepatic & Splenic	Hepatomegaly, usually *without* dysfunction Splenomegaly, usually *without* leukopenia or anemia	all systemic
Endocrine	Deposition with rare hormonal insufficiency	organ-specific
Musculoskel	Arthralgias and arthritis	AL, Aβ$_2$m
Pulmonary	Airway obstruction	AL, AA
Hematologic	Factor X deficiency	AL

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 (↓ 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	
Primary Neurologic *(usually with focal signs)*	**Systemic** *(especially in elderly)*
Stroke	Cardiac: severe CHF, HTN encephalopathy
Seizure (postictal, status, nonconvulsive)	Pulmonary: ↓ P_aO_2, ↑ P_aCO_2
Infection: meningoencephalitis, abscess	GI: liver failure, constipation, Wilson's
Epidural/subdural hematoma	Renal: uremia, hyponatremia and hypernatremia
Concussion	Endocrine: ↓ glc, DKA, HHNS, ↑ Ca, hypothyroidism or hyperthyroidism, Addisonian crisis
Hydrocephalus	ID: pneumonia, UTI, sepsis
Complicated migraine	Hypothermia and hyperthermia
Venous thrombosis	Medications (espec. opiates & sedatives)
Transient global amnesia	Alcohol & toxins
CNS vasculitis	
TTP	

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 oculocephalic ("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			
Eye opening	**Best verbal response**	**Best motor response**	**Points**
		Follows commands	6
	Oriented	Localizes pain	5
Spontaneous	Confused	Withdraws from pain	4
To voice	Inappropriate words	Decorticate posturing	3
To painful stimuli	Unintelligible sounds	Decerebrate posturing	2
None	None	None	1
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, NH_3, 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

Coma Exam Checklist	
Cranial nerves	Pupillary response, extraocular movements, corneal reflex
Motor	Spontaneous limb movements, posturing
Sensory	Response to painful stimuli
Reflexes	Deep tendon reflexes, Babinski

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. ✓ PT and PTT.
  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)

SEIZURES

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; TIAs; narcolepsy; nonepileptic myoclonus; tics; asterixis

Etiologies

- **A**lcohol withdrawal, illicit drugs, meds (eg, β-lactams, bupropion, tramadol, metronidazole, meperidine, CsA, antidep., clozapine can lower seizure threshold)
- **B**rain tumor or penetrating trauma
- **C**erebrovascular disease, including subdural hematomas, hypertensive encephalopathy
- **D**egenerative disorders of the CNS (eg, Alzheimer's)
- **E**lectrolyte (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

Medication	Avg daily dose	Common Side Effects	
		Systemic	*Neurologic*
Phenytoin	300–400 mg	Gum hyperplasia	Dizziness, ataxia, diplopia, confusion, drowsiness
Carbamazepine	600–1800 mg	Aplastic anemia, ↓ WBC, rash, hepatotoxicity, ↓ Na	
Valproic acid	750–2000 mg	Hepatotoxicity, ↑ NH_3, ↑ wt, hair loss	Tremor, drowsiness
Phenobarbital	60–180 mg	Rash	Drowsiness
Ethosuximide	750–1250 mg	Rash, bone marrow suppression	Drowsiness, behavioral Δs
Gabapentin	900–2400 mg	GI upset, wt gain	Nystagmus, drowsiness
Lamotrigine	200–400 mg	Rash (Stevens-Johnson syndrome)	Tremor, HA, insomnia
Leviteracitam	1500–3000 mg	GI upset (rare)	Drowsiness, emotional lability
Oxcarbazepine	1200–2400 mg	Hyponatremia, rash	Drowsiness
Topiramate	100–400 mg	↓ wt, hypohidrosis, kidney stones, glaucoma	Cognitive slowing, fatigue
Zonisamide	200–400 mg	↓ wt, hypohidrosis, kidney stones	Abnormal thinking, fatigue

(*JAMA* 2004;291:605, 615)

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)

Step	Antiepileptic	Dosing regimen	Typical adult dose
1	**Lorazepam** or	0.1 mg/kg at 2 mg/min	Successive 2–4 mg IV pushes
	Diazepam	0.2 mg/kg at 5 mg/min	Successive 5–10 mg IV pushes
	Lorazepam marginally slower onset of action (3 vs. 2 min) but at least as efficacious (success 65%) & longer duration of effect (12–24 h vs. 15–30 min)		
2	**Phenytoin** or	20 mg/kg at 50 mg/min	1.0–1.5 g IV over 20 min
	Fosphenytoin	20 mg PE/kg at 150 mg/min + 5–10 mg/kg if still seizing	1.0–1.5 g PE IV over 5–10 min + 500 mg IV if still seizing
	Subsequent steps typically mandate intubation, EEG monitoring, and ICU admission		
3	Phenobarbital	20 mg/kg at 50–75 mg/min + 5–10 mg/kg if still seizing	1.0–1.5 g IV over 30 min + 500 g IV if still seizing
4	General anesthesia with midazolam, pentobarbital, or propofol		

PE, phenytoin equivalents. (*JAMA* 1983;249:1452; *NEJM* 1998;338:970 & 339:792)

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

CIWA-Ar Scale					
Points	**Anxiety**	**Agitation**	**Tremor**	**HA**	**Orientation**
0	None	None	None	None	Oriented
1		Somewhat	Not visible, but felt at fingertips	Very mild	Cannot do serial additions
2				Mild	Disorient. by ≤2 d
3				Moderate	Disorient. by >2 d
4	Guarded	Restless	Moderate w/ hands extended	Mod severe	Disoriented to person or place
5				Severe	n/a
6				Very severe	n/a
7	Panic	Pacing or thrashing	Severe	Extremely severe	n/a
Points	**N/V**	**Sweats halluc.**	**Auditory halluc.**	**Visual**	**Tactile disturb**
0	None	None	None	None	None
1		Moist palms	Very mild	Very mild photosens.	Very mild paresthesias
2			Mild	Mild photosens.	Mild paresth.
3			Moderate	Mod photosens.	Mod paresth.
4	Intermit. w/ dry heaves	Beads	Mod severe	Mod severe visual halluc.	Mod severe hallucinations
5			Severe	Severe	Severe
6			Very severe	Very severe	Very severe
7	Constant	Drenching	Cont.	Continuous	Continuous
SCORE: <8 none to minimal withdrawal; 8–15 mild; 16–20 moderate, >20 severe					

(Each criterion is a continuum that ranges from 0–7 points [except 0–4 for Orientation]; selected cells have text to provide guidance for assigning points.)

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 metabs; 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 α_2-agonists (mask sx)
- Mechanical restraints as needed until chemical sedation achieved
- Volume resuscitation as needed; thiamine *then* glc to prevent *Wernicke's encephalopathy* (ataxia, ophthalmoplegia, short-term memory loss); replete K, Mg, PO_4
- Prophylaxis: if min sx or asx (ie, CIWA score <8) but prolonged heavy EtOH consumption or h/o withdrawal seizures or DTs → chlordiazepoxide 25–100 mg (based on severity of EtOH use) q6h × 24h, then 25–50 mg q6h × 2d

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

Embolic: rapid onset, sx maximum at onset
Thrombotic: progression of sx over hrs to days possibly with stuttering course

Artery	Deficits
ICA/Ophth	Amaurosis fugax (transient monocular blindness)
ACA	Hemiplegia (leg > arm) Confusion, abulia, urinary incontinence, primitive reflexes
MCA	Hemiplegia (arm & face > leg); hemianesthesia; homonymous hemianopia Aphasia if dom. hemisphere: sup. div. → expressive; inf. → receptive Apraxia and neglect if nondominant hemisphere Drowsiness & stupor seen later (due to brain swelling)
PCA	Thalamic syndromes with contralateral hemisensory disturbance, aphasia Macular-sparing homonymous hemianopia
Vertebral	Wallenberg syndrome = numbness of ipsilateral face and contralateral limbs, diplopia, dysarthria, ipsilateral Horner's
Basilar	Pinpoint pupils, long tract signs (quadriplegia and sensory loss), cranial nerve abnormalities, cerebellar dysfunction
Cerebellar	Vertigo, nausea/vomiting, diplopia, nystagmus, ipsilateral limb ataxia
Lacunar	Pure hemiplegia, pure hemianesthesia, ataxic hemiparesis, or dysarthria + clumsy hand

Transient 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 Δs is <20% w/in 12 h)
  then, CT angio/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 ⊖ 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 ~4× ↑ 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 → warfarin** if: known or presumptive cardioembolic TIAs or if bridging to mechanical intervention (CEA, stenting) for large vessel atherothrombotic dis.
- **Antiplatelet 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)

- **ABCD²**: **A**ge ≥60 y (+1); **B**P ≥140/90 (+1); **C**lin. features: unilateral weakness (+2), speech impairment w/o weakness (+1); **D**uration ≥60 (+2) or 10–59 min (+1); **D**iabetes (+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;375:1695)

- **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, ∅ hemorrhage, and ∅ 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* 1995;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 poststroke → ↑ ICP requiring elevated head of bed >30°; intubation & hyperventilation to P_aCO_2 ~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)
- Superiority and even noninferiority of carotid *stenting* remains controversial (*NEJM* 2004;351:1493; *Lancet* 2006;368:1239; *NEJM* 2006;355:1660 & 2008;358:1572; *Lancet* 2010;375:985)

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

Feature	Upper Motor Neuron	Lower Motor Neuron	Myopathy
Distribution of weakness	Regional	Distal, segmental	Proximal, symmetric
Atrophy	None	Severe	Mild
Fasciculations	None	Common	None
Tone	↑	↓	Normal or ↓
Reflexes (DTRs)	+ + + +	0/ +	+ / + +
Babinski	Present	Absent	Absent

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, B_{12} defic

Clinical manifestations

- Weakness, fasciculations, numbness, dysesthesias (burning/tingling)
- ± Autonomic dysfxn (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 Hb_{A1C}, B_{12}, 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_aO_2 or S_aO_2)

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

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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": **P**ulsatile; duration 4–72 h**O**urs; **U**nilateral; **N**ausea & vomiting; **D**isabling
  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-HT_1 agonists ("triptans"); contraindic. 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

Ddx of back pain

- **Musculoskeletal**: musculoligamentous "strain" (experienced by up to 80% of population at some time), OA, RA, spondylolisthesis, vertebral compression fx, inflammatory spondyloarthritis (ankylosing spondylitis, reactive, psoriatic)
- **Spinal cord** (myelopathy) **/ nerve root** (radiculopathy):
  Degenerative/traumatic: disc herniation, spondylosis, 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, PO_4, Aϕ, 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
- Emergent neurosurgical and/or neurology consultation
- Urgent radiation therapy ± surgery for compression if due to metastatic disease
- High-dose steroids depending on cause:
  Tumor: dexamethasone 10–100 mg IV × 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

Conus Medullaris vs. Cauda Equina Syndromes

Features	Conus Medullaris	Cauda Equina
Localization	Cord (UMN) + nerve roots (LMN) Bilateral	Nerve roots (LMN) Unilateral
Pain	Mild, back > radicular	Severe, radicular > back
Sensory loss	Symmetric perianal	Asymmetric saddle/leg
Motor dysfxn	Mild symmetric weakness	Marked asymmetric weakness
Reflexes	↓ ankle but knee preserved May have ↓ reflexes, Babinski	↓ ankle, ↓ knee Babinski absent
Bowel-Bladder -Sexual dysfxn	Early retention, incontinence, ↓ anal tone, & impotence	sxs less frequent / occur late

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					
Disc	**Root**	**Pain / Paresthesias**	**Sensory loss**	**Motor loss**	**Reflex Loss**
C4–C5	C5	Neck, shoulder, upper arm	Shoulder	Deltoid, biceps, infraspinatus	Biceps
C5–C6	C6	Neck, shoulder, lat. arm, radial forearm, thumb & index finger	Lat. arm, radial forearm, thumb & index finger	Biceps, brachioradialis	Biceps, brachio-radialis, supinator
C6–C7	C7	Neck, lat. arm, ring & index fingers	Radial forearm, index & middle fingers	Triceps, extensor carpi ulnaris	Triceps, supinator
C7–T1	C8	Ulnar forearm and hand	Ulnar half of ring finger, little finger	Intrinsic hand muscles, wrist extensors, flexor dig profundus	Finger flexion
L3–L4	L4	Anterior thigh, inner shin	Anteromedial thigh and shin, inner foot	Quadriceps	Patella
L4–L5	L5	Lat. thigh and calf, dorsum of foot, great toe	Lat. calf and great toe	Extensor hallucis longus, ± foot dorsiflexion, invers. & evers.	None
L5–S1	S1	Back of thigh, lateral posterior calf, lat. foot	Posterolat. calf, lat. and sole of foot, smaller toes	Gastrocnemius ± foot eversion	Achilles

(Nb, lumbar disc protrusion tends to compress the nerve root that exits one vertebral level below the protrusion.)

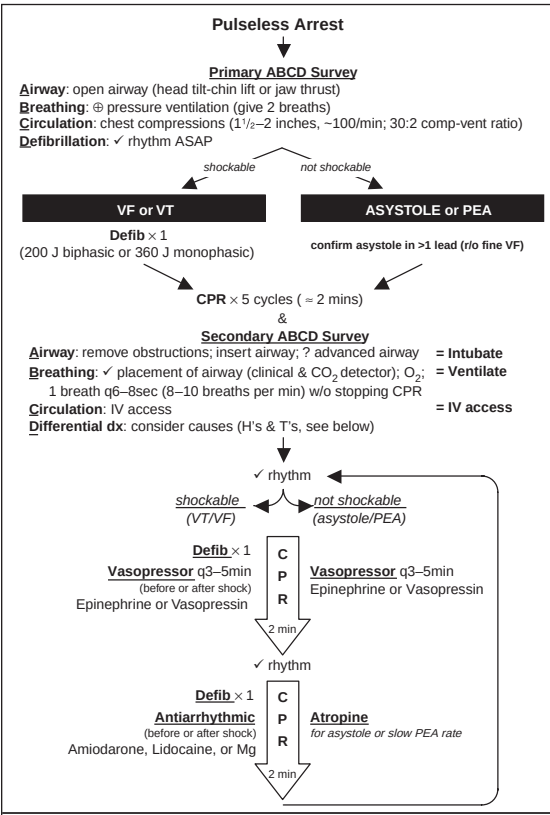
Neurogenic vs. Vascular Claudication		
Features	**Neurogenic Claudication**	**Vascular Claudication**
Cause	Lumbar spinal stenosis (with nerve root compression)	Peripheral artery disease (with limb ischemia)
Pain	Radicular back / buttock pain Maximal anterior thighs Radiating down legs	Cramping leg pain Most common in calves Radiating up legs
Worse with	Walking & standing Hyperextension / lying prone	Walking Biking
Better with	Bending forward, sitting	Rest (standing or sitting)
Other Sx	Numbness / paresthesias	Pale, cool extremity
Exam	± Focal weakness, ↓ reflexes ↓ Lumbar extension Preserved pulses	Diminished/absent pulses (dorsalis pedis / posterior tibialis) Pallor
Diagnostic studies	MRI lumbar spine CT myelogram (if no MRI) EMG/NCS	Arterial Doppler studies Ankle-brachial index (ABI) <0.90 Arteriography
Treatment	PT (flexion exercise), NSAIDs, steroid injections (ESI) Surgery (if other Rx fails)	Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization

(Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient. *NEJM* 2007;356:1241 & 2008;358:818.)

Treatment of nerve root compression

- 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)

Figure 10-1 ACLS VF/pulseless VT, asystole & PEA algorithms



MEDICATIONS

epinephrine: 1mg IV (10 mL of 1:10,000 solution) or 2 mg ETT q3–5min

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) q5–10min, max 3 mg/kg

atropine: 1 mg IV q3–5min × 3

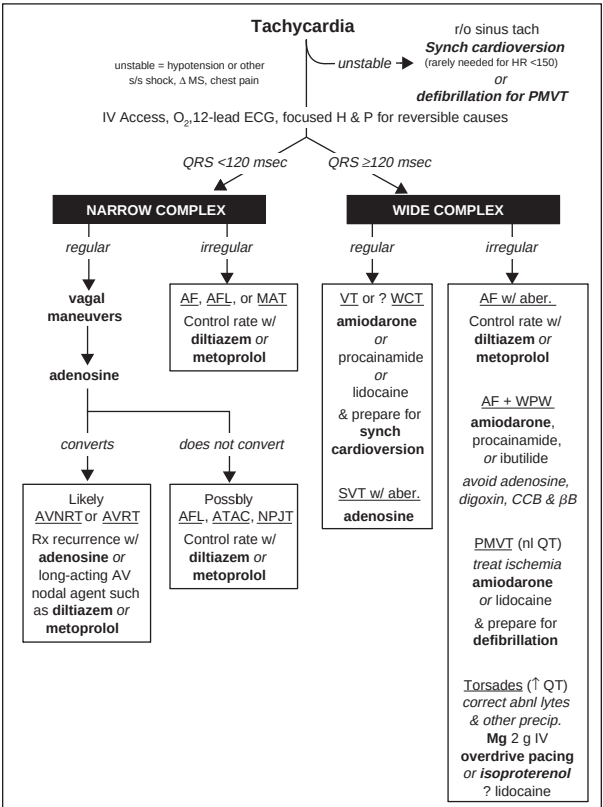
magnesium: 1–2 g IV for TdP

Treatment of reversible causes of PEA & asystole

Hypovolemia: volume infusion
Hypoxia: oxygenate
Hydrogen ions (acidosis): $NaHCO_3$
Hypokalemia: KCl
Hyperkalemia: Ca, $NaHCO_3$, insulin/glc
Hyoglycemia: glucose
Hypothermia: warming
Toxins/Tablets: med-specific
Tamponade: pericardiocentesis
Tension PTX: needle decompression
Thrombosis (ACS): PCI (or lysis), IABP
Thrombosis (PE): lysis, thrombectomy
Trauma (hypovol, ↑ ICP): per ATLS

(Adapted from ACLS 2005 Guidelines, *Circ* 2005;112(Suppl I):IV-58)

Figure 10-2 ACLS tachycardia algorithm



CARDIOVERSION

Ancillary equipment
- O_2 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

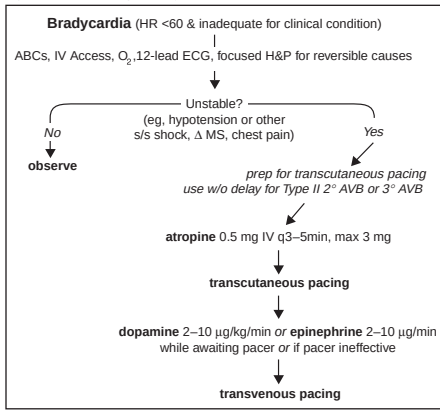
metoprolol 5 mg IV q5min × 3

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

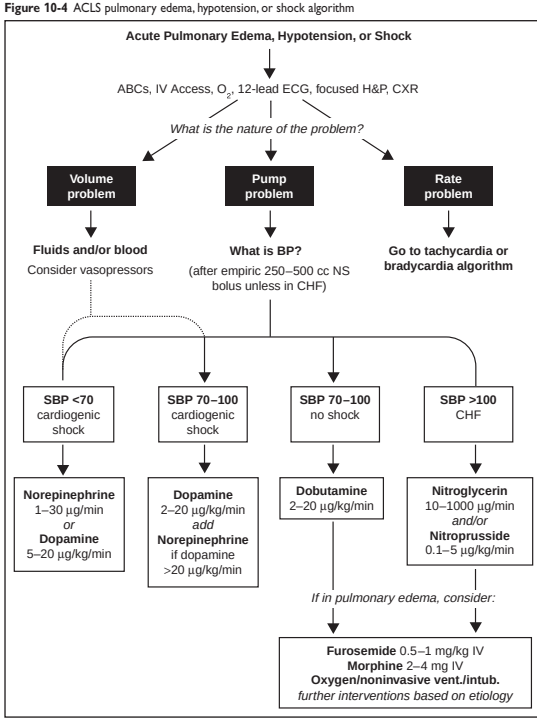
(Adapted from ACLS 2005 Guidelines, *Circ* 2005;112(Suppl I):IV-67)

Figure 10-3 ACLS bradycardia algorithms



(Adapted from ACLS 2005 Guidelines, *Circ* 2005;112(Suppl I):IV–67)

Figure 10-4 ACLS pulmonary edema, hypotension, or shock algorithm



(Adapted from ACLS 2005 Guidelines)

Drug	Class	Dose	
		per kg	average
Pressors, Inotropes, and Chronotropes			
Phenylephrine	α_1	10–300 μg/min	
Norepinephrine	$\alpha_1 > \beta_1$	1–40 μg/min	
Vasopressin	V_1	0.01–0.1 U/min (usually <0.04)	
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$	2–20 μg/min	
Isoproterenol	β_1, β_2	0.1–10 μg/min	
Dopamine	D β, D α, β, D	0.5–2 μg/kg/min 2–10 μg/kg/min >10 μg/kg/min	50–200 μg/min 200–500 μg/min 500–1000 μg/min
Dobutamine	$\beta_1 > \beta_2$	2–20 μg/kg/min	50–1000 μg/min
Milrinone	PDE	50 μg/kg over 10 min then 0.375–0.75 μg/kg/min	3–4 mg over 10 min then 20–50 μg/min
Inamrinone	PDE	0.75 mg/kg over 3 min then 5–15 μg/kg/min	40–50 mg over 3 min then 250–900 μg/min
Vasodilators			
Nitroglycerin	NO	10–1000 μg/min	
Nitroprusside	NO	0.1–10 μg/kg/min	5–800 μg/min
Nesiritide	BNP	2 μg/kg IVB then 0.01 μg/kg/min	
Labetalol	α_1, β_1, and β_2 blocker	20 mg over 2 min then 20–80 mg q10min or 10–120 mg/h	
Fenoldopam	D	0.1–1.6 μg/kg/min	10–120 μg/min
Epoprostenol	vasodilator	2–20 ng/kg/min	
Enalaprilat	ACE	0.625–2.5 mg over 5 min then 0.625–5 mg q6h	
Hydralazine	vasodilator	5–20 mg q20–30min	
Antiarrhythmics			
Amiodarone	K *et al.* (Class III)	150 mg over 10 min, then 1 mg/min × 6h, then 0.5 mg/min × 18h	
Lidocaine	Na channel (Class IB)	1–1.5 mg/kg then 1–4 mg/min	100 mg then 1–4 mg/min
Procainamide	Na channel (Class IA)	17 mg/kg over 60 min then 1–4 mg/min	1 g over 60 min then 1–4 mg/min
Ibutilide	K channel (Class III)	1 mg over 10 min, may repeat × 1	
Propranolol	β blocker	0.5–1 mg q5min then 1–10 mg/h	
Esmolol	$\beta_1 > \beta_2$ blocker	500 μg/kg then 25–300 μg/kg/min	20–40 mg over 1 min then 2–20 mg/min
Verapamil	CCB	2.5–5 mg over 1–2 min repeat 5–10 mg in 15–30 min prn 5–20 mg/h	
Diltiazem	CCB	0.25 mg/kg over 2 min reload 0.35 mg/kg × 1 prn then 5–15 mg/h	20 mg over 2 min reload 25 mg × 1 prn then 5–15 mg/h
Adenosine	purinergic	6 mg rapid push if no response: 12 mg → 12–18 mg	

Drug	Class	Dose	
		per kg	average
Sedation			
Morphine	opioid	1-unlimited mg/h	
Fentanyl	opioid	50–100 μg then 50-unlimited μg/h	
Thiopental	barbiturate	3–5 mg/kg over 2 min	200–400 mg over 2 min
Etomidate	anesthetic	0.2–0.5 mg/kg	100–300 mg
Propofol	anesthetic	1–3 mg/kg then 0.3–5 mg/kg/h	50–200 mg then 20–400 mg/h
Diazepam	BDZ	1–5 mg q1–2h then q6h prn	
Midazolam	BDZ	0.5–2 mg q5min prn or 0.5–4 mg then 1–10 mg/h	
Ketamine	anesthetic	1–2 mg/kg	60–150 mg
Haloperidol	antipsychotic	2–5 mg q20–30min	
Naloxone	opioid antag.	0.4–2 mg q2–3min to total of 10 mg	
Flumazenil	BDZ antag.	0.2 mg over 30 sec then 0.3 mg over 30 sec if still lethargic may repeat 0.5 mg over 30 sec to total of 3 mg	
Paralysis			
Succinylcholine	depolar. paralytic	0.6–1.1 mg/kg	70–100 mg
Tubocurare	nACh	10 mg then 6–20 mg/h	
Pancuronium	nACh	0.08 mg/kg	2–4 mg q30–90'
Vecuronium	nACh	0.08 mg/kg then 0.05–0.1 mg/kg/h	5–10 mg over 1–3 min then 2–8 mg/h
Cisatracurium	nACh	5–10 μg/kg/min	
Miscellaneous			
Aminophylline	PDE	5.5 mg/kg over 20 min then 0.5–1 mg/kg/h	250–500 mg then 10–80 mg/h
Insulin		10 U then 0.1 U/kg/h	
Glucagon		5–10 mg then 1–5 mg/h	
Octreotide	somatostatin analog	50 μg then 50 μg/h	
Phenytoin	antiepileptic	20 mg/kg at 50 mg/min	1–1.5 g over 20–30 min
Fosphenytoin	antiepileptic	20 mg/kg at 150 mg/min	1–1.5 g over 10 min
Phenobarbital	barbiturate	20 mg/kg at 50–75 mg/min	1–1.5 g over 20 min
Mannitol	osmole	1.5–2 g/kg over 30–60 min repeat q6–12h to keep osm 310–320	

ANTIBIOTICS

The following tables of spectra of activity for different antibiotics are generalizations. Sensitivity data at your own institution should be used to guide therapy.

Penicillins		
Generation	**Properties**	**Spectrum**
Natural (eg, penicillin)	Some GPC, GPR, GNC, most anaerobes (except *Bacteroides*)	Group A streptococci Enterococci, *Listeria, Pasteurella Actinomyces*, Syphilis
Anti-Staph (eg, nafcillin)	Active vs PCNase-producing Staph Little activity vs. Gram ⊖	Staphylococci (except MRSA) Streptococci
Amino (eg, ampicillin)	Penetrate porin channel of Gram ⊖ Not stable against PCNases	*E. coli, Proteus, H. influenzae Salmonella, Shigella Enterococci, Listeria*
Extended (eg, piperacillin)	Penetrate porin channel of Gram ⊖ More resistant to PCNases	Most GNR incl. *Enterobacter, Pseudomonas, Serratia*
Carbapenem (eg, imipenem)	Resistant to most β-lactamases	Most Gram ⊕ and ⊖ bacteria including anaerobes, but *not* MRSA or VRE
Monobactams (aztreonam)	Active vs. Gram ⊖ but not Gram ⊕	Gram ⊖ bacterial infxn in Pt w/ PCN or Ceph allergy
β-lact. Inhib. (eg, sulbactam)	Inhibit plasma-mediated β-lactamases	Adds Staph, *B. fragilis* and some GNR (*H. influenzae, M. catarrhalis*, some *Klebsiella*); intrinsic activity against *Acinetobacter* (sulbactam only)

Cephalosporins		
Resistant to most β-lactamases. No activity vs. MRSA or enterococci.		
Gen.	**Spectrum**	**Indications**
First (eg, cefazolin)	Most GPC (incl. Staph & Strep, not MRSA) Some GNR (incl. *E. coli, Proteus, Klebsiella*)	Used for surgical ppx & skin infxns
Second (eg, cefuroxime, cefotetan)	↓ activity vs. GPC, ↑ vs. GNR. 2 subgroups: Respiratory: *H. influenzae* & *M. catarrhalis* GI/GU: ↑ activity vs. *B. fragilis*	PNA/COPD flare Abdominal infxns
Third (eg, ceftriaxone)	Broad activity vs. GNR & some anaerobes Ceftazidime active vs. *Pseudomonas*	PNA, sepsis, meningitis
Fourth (eg, cefepime)	↑ resistance to β-lactamases (incl. of Staph and *Enterobacter*)	Similar to 3rd gen. MonoRx for nonlocalizing febrile neutropenia

Other Antibiotics	
Antibiotic	**Spectrum**
Vancomycin	Gram ⊕ bacteria incl. MRSA, PCNase-producing pneumococci and enterococci (except VRE)
Linezolid	GPC incl. MRSA & VRE (check susceptibility for VRE)
Daptomycin	
Quinopristin/ Dalfopristin	
Quinolones	Enteric GNR & atypicals. 3rd & 4th gen. ↑ activity vs. Gram ⊕.
Aminoglycosides	GNR. Synergy w/ cell-wall active abx (β-lactam, vanco) vs. GPC. ↓ activity in low pH (eg, abscess). No activity vs. anaerobes.
Macrolides	GPC, some respiratory Gram ⊖, atypicals
TMP/SMX	Some enteric GNR, PCP, *Nocardia, Toxoplasma*, most community-acquired MRSA
Clindamycin	Most Gram ⊕ (except enterococci) & anaerobes (incl. *B. fragilis*)
Metronidazole	Almost all anaerobic Gram ⊖, most anaerobic Gram ⊕
Doxycycline	*Rickettsia, Ehrlichia, Chlamydia, Mycoplasma, Nocardia,* Lyme
Tigecycline	Many GPC incl. MRSA & VRE; some GNR incl. ESBL but not *Pseudomonas* or *Proteus*. Approved for abdominal or skin/soft tissue infections. Check susceptibility if organism isolated.

CARDIOLOGY

Hemodynamic parameters	Normal value
Mean arterial pressure (MAP) $= \frac{SBP + (DBP \times 2)}{3}$	70–100 mmHg
Heart rate (HR)	60–100 bpm
Right atrial pressure (RA)	≤6 mmHg
Right ventricular (RV)	systolic 15–30 mmHg diastolic 1–8 mmHg
Pulmonary artery (PA)	systolic 15–30 mmHg mean 9–18 mmHg diastolic 6–12 mmHg
Pulmonary capillary wedge pressure (PCWP)	≤12 mmHg
Cardiac output (CO)	4–8 L/min
Cardiac index (CI) $= \frac{CO}{BSA}$	2.6–4.2 L/min/m^2
Stroke volume (SV) $= \frac{CO}{HR}$	60–120 mL/contraction
Stroke volume index (SVI) $= \frac{CI}{HR}$	40–50 mL/contraction/m^2
Systemic vascular resistance (SVR) $= \frac{MAP - \text{mean RA}}{CO} \times 80$	800–1200 dynes × sec/cm^5
Pulmonary vascular resistance (PVR) $= \frac{\text{mean PA} - \text{mean PCWP}}{CO} \times 80$	120–250 dynes × sec/cm^5

"Rule of 6s" for PAC: RA ≤6, RV ≤30/6, PA ≤30/12, WP ≤12. 1 mmHg = 1.36 cm water or blood.

Fick cardiac output

Oxygen consumption (L/min) = CO (L/min) × arteriovenous (AV) oxygen difference
CO = oxygen consumption / AV oxygen difference
Oxygen consumption must be measured (can estimate w/ 125 mL/min/m^2, but inaccurate)
AV oxygen difference = Hb (g/dl) × 10 (dl/L) × 1.36 (mL O_2/g of Hb) × (S_aO_2–S_vO_2)
S_aO_2 is measured in any arterial sample (usually 93–98%)
S_vO_2 (mixed venous O_2) is measured in RA, RV, or PA (assuming no shunt) (normal ~75%)

$$\therefore \textbf{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{\text{Hb (g/dl)} \times 13.6 \times (S_aO_2 - S_vO_2)}$$

Shunts

$$Q_p = \frac{\text{Oxygen consumption}}{\text{Pulm. vein } O_2 \text{ sat} - \text{Pulm. artery } O_2 \text{ sat}} \text{ (if no R} \rightarrow \text{L shunt, PV } O_2 \text{ sat} \approx S_aO_2)$$

$$Q_s = \frac{\text{Oxygen consumption}}{S_aO_2 - \text{mixed venous } O_2 \text{ sat}} \text{ (MVO_2 drawn proximal to potential L} \rightarrow \text{R shunt)}$$

$$\frac{Q_p}{Q_s} = \frac{S_aO_2 - MV\ O_2\ sat}{PV\ O_2\ sat - PA\ O_2\ sat} \approx \frac{S_aO_2 - MV\ O_2\ sat}{S_aO_2 - PA\ O_2\ sat} \text{ (if only L} \rightarrow \text{R and no R} \rightarrow \text{L shunt)}$$

Valve equations

Simplified Bernoulli equation: Pressure gradient (ΔP) = $4 \times v^2$ (where v = peak flow velocity)
Continuity eq., (conservation of flow): $Area_1 \times Velocity_1 = A_2 \times V_2$ (where 1 & 2 different points)

$$\text{or AVA (unknown)} = A_{\text{LV outflow tract}} \times \left(\frac{V_{LVOT}}{V_{AoV}}\right) \text{(all of which can be measured on echo)}$$

$$\text{Gorlin equation: Valve area} = \frac{CO/(\text{DEP or SEP}) \times HR}{44.3 \times \text{constant} \times \sqrt{\Delta P}} \text{ (constant = 1 for AS, 0.85 for MS)}$$

$$\text{Hakki equation: Valve area} \approx \frac{CO}{\sqrt{\Delta P}}$$

Chest Imaging (CXR & CT) Patterns		
Pattern	**Pathophysiology**	**Ddx**
Consolidation	Radiopaque material in air space & interstitium patent airway → "air bronchograms"	*Acute:* water **(pulm edema)**, pus **(PNA)**, **blood** *Chronic*: neoplasm (BAC, lymphoma), aspiration, inflammatory (BOOP, eosinophilic PNA), PAP, granuloma (TB/fungal, alveolar sarcoid)
Ground glass (CT easier than CXR)	Interstitial thickening or partial filling of alveoli (but vessels visible)	*Acute:* pulm edema, infxn (PCP, viral, resolving bact. PNA) *Chronic*: ILD w/o fibrosis: acute hypersens., DIP/RB, PAP w/ fibrosis: IPF
Septal lines Kerley A & B	Radiopaque material in septae	**Cardiogenic pulm edema**, interstitial PNA viral, mycoplasma), lymphangitic tumor
Reticular	Lace-like net (ILD)	**ILD** (espec. IPF, CVD, bleomycin, asbestos)
Nodules	Tumor Granulomas Abscess	*Cavitary*: **Primary or metastatic cancer**, **TB** (react. or miliary), **fungus**, Wegener's, RA **septic emboli**, PNA *Noncavitary:* any of above + **sarcoid**, hypersens. pneum., HIV, Kaposi's sarcoma
Wedge opac.	Peripheral infarct	**PE**, cocaine, angioinv. aspergillus, Wegener's
Tree-in-bud (best on CT)	Inflammation of small airways	**Bronchopneumonia**, endobronchial TB/MAI, viral PNA, aspiration, ABPA, CF, asthma, BOOP
Hilar fullness	↑ LN or pulm arteries	**Neoplasm** (lung, mets, lymphoma) **Infxn** (AIDS); **Granuloma** (sarcoid/TB/fungal) Pulmonary hypertension
Upper lobe	n/a	**TB**, fungal, sarcoid, hypersens. pneum., CF, XRT
Lower lobe	n/a	**Aspiration**, bronchiect., IPF, RA, SLE, asbestos
Peripheral	n/a	BOOP, IPF & DIP, eos PNA, asbestosis

CXR in heart failure

- ↑ cardiac silhouette (in systolic dysfxn, not in diastolic)
- Pulmonary venous hypertension: cephalization of vessels (vessels size > bronchi in upper lobes), peribronchial cuffing (fluid around bronchi seen on end → small circles), Kerley B lines (horizontal 1–2 cm lines at bases), ↑ vascular pedicle width, loss of sharp vascular margins, pleural effusions (~75% bilateral)
- Pulmonary edema: ranges from ground glass to consolidation; often dependent and central, sparing outer third ("bat wing" appearance)

Dead space = lung units that are ventilated but not perfused
Intrapulmonary shunt = lung units that are perfused but not ventilated

Alveolar gas equation: $P_AO_2 = [F_1O_2 \times (760 - 47)] - \frac{P_aCO_2}{R}$ (where R ≈ 0.8)

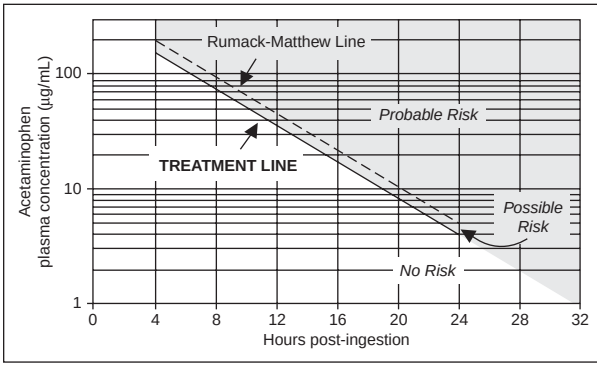
$$P_AO_2 = 150 - \frac{P_aCO_2}{0.8} \text{ (on room air)}$$

A-a gradient = $P_AO_2 - P_aO_2$ [normal A-a gradient ≈ 4 + (age/4)]
Minute ventilation (V_E) = tidal volume (V_T) × respiratory rate (RR) (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 $\left(\frac{V_D}{V_T}\right) = \frac{P_aCO_2 - P_{expired}CO_2}{P_aCO_2}$

$$\mathbf{P_aCO_2} = k = \times \frac{CO_2 \text{ Production}}{\text{alveolar ventilation}} = k \times \frac{\dot{V}_{CO_2}}{RR \times V_T \times \left(1 - \frac{V_D}{V_T}\right)}$$

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 + HCO_3) (normal = [alb] × 2.5; typically 12 ± 2 mEq)

Delta-delta (ΔΔ) = [Δ AG (ie, calc. AG - expected) / Δ HCO_3 (ie, 24 - measured HCO_3)]

Urine anion gap (UAG) = $(U_{Na} + U_K) - U_{Cl}$

Calculated osmoles = $(2 \times Na) + \left(\frac{glc}{18}\right) + \left(\frac{BUN}{2.8}\right) + \left(\frac{EtOH}{4.6}\right)$

Osmolal gap (OG) = measured osmoles – calculated osmoles (normal < 10)

Estimated creatinine clearance = $\frac{[140 - \text{age (yrs)}] \times \text{wt (kg)}}{\text{serum Cr (mg/dl)} \times 72}$ (× 0.85 in women)

Fractional excretion of Na (FE_{Na}, %) = $\left[\frac{\frac{U_{Na}(mEq/L)}{P_{Na}(mEq/L)} \times 100\%}{\frac{U_{Cr}(mg/mL)}{P_{Cr}(mg/dl)} \times 100\ (mL/dl)}\right] = \frac{\frac{U_{Na}}{P_{Na}}}{\frac{U_{Cr}}{P_{Cr}}}$

Corrected Na in hyperglycemia

estimate in all Pts: corrected Na = measured Na + $\left[2.4 \times \frac{(\text{measured glc} - 100)}{100}\right]$

however, Δ in Na depends on glc (*Am J Med* 1999;106:399)
Δ is 1.6 mEq per each 100 mg/dl ↑ in glc ranging from 100–440
Δ is 4 mEq per each 100 mg/dl ↑ in glc beyond 440

Total body water (TBW) = 0.60 × IBW (× 0.85 if female and × 0.85 if elderly)

Free H_2O deficit = TBW × $\left(\frac{[Na]_{serum} - 140}{140}\right) \approx \left(\frac{[Na]_{serum} - 140}{3}\right)$ (in 70 kg Pt)

Trans-tubular potassium gradient (TTKG) = $\frac{\frac{U_K}{P_K}}{\frac{U_{Osm}}{P_{Osm}}}$

Peripheral Smear Findings (also see Photo Inserts)	
Feature	**Abnormalities and diagnoses**
Size	normocytic vs. microcytic vs. macrocytic → see below
Shape	**anisocytosis** → unequal RBC size; **poikilocytosis** → irregular RBC shape acanthocytes = **spur** cells (irregular sharp projections) → liver disease **bite** cells (removal of Heinz bodies by phagocytes) → G6PD deficiency echinocytes = **burr** cells (even, regular projections) → uremia, artifact **pencil cell** → long, thin, hypochromic - very common in adv. iron deficiency **rouleaux** → hyperglobulinemia (eg, multiple myeloma) **schistocytes**, helmet cells → MAHA (eg, DIC, TTP/HUS), mechanical valve **spherocytes** → HS, AIHA; **sickle** cells → sickle cell anemia **stomatocyte** → central pallor appears as curved slit → liver disease, EtOH **target** cells → liver disease, hemoglobinopathies, splenectomy **tear drop** cells = dacryocytes → myelofibrosis, myelophthisic anemia, megaloblastic anemia, thalassemia
Intra-RBC findings	**basophilic stippling** (ribosomes) → abnl Hb, sideroblastic, megaloblastic **Heinz bodies** (denatured Hb) → G6PD deficiency, thalassemia **Howell-Jolly bodies** (nuclear fragments) → splenectomy or functional asplenia (eg advanced sickle cell) **nucleated** RBCs → hemolysis, extramedullary hematopoiesis
WBC findings	**blasts** → leukemia, lymphoma; **Auer rods** → acute myelogenous leukemia **hypersegmented** (>5 lobes) PMNs: megaloblastic anemia (B_{12}/folate def.) **pseudo-Pelger-Huët anomaly** (bilobed nucleus, "pince-nez") → MDS **toxic granules** (coarse, dark blue) and **Döhle bodies** (blue patches of dilated endoplasmic reticulum) → (sepsis, severe inflammation
Platelet	**clumping** → artifact, repeat plt count **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

(*NEJM* 2005;353:498)

Heparin for Thromboembolism 80 U/kg bolus 18 U/kg/h	
PTT	**Adjustment**
<40	bolus 5000 U, ↑ rate 300 U/h
40–49	bolus 3000 U, ↑ rate 200 U/h
50–59	↑ rate 150 U/h
60–85	no Δ
86–95	↓ rate 100 U/h
96–120	hold 30 min, ↓ rate 100 U/h
>120	hold 60 min, ↓ rate 150 U/h

(Modified from *Chest* 2008;133:141S)

Heparin for ACS 60 U/kg bolus (max 4000 U) 12 U/kg/h (max 1000 U/h)	
PTT	**Adjustment**
<40	bolus 3000 U, ↑ rate 100 U/h
40–49	↑ rate 100 U/h
50–75	no Δ
76–85	↓ rate 100 U/h
86–100	hold 30 min, ↓ rate 100 U/h
>100	hold 60 min, ↓ rate 200 U/h

(Modified from *Circ* 2007;116:e148 & *Chest* 2008;133:670)

✓ PTT q6h after every 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					
Day	**INR**				
	<1.5	**1.5–1.9**	**2–2.5**	**2.6–3**	**>3**
1–3	5 mg (7.5 mg if > 80 kg)		2.5–5 mg	0–2.5 mg	0 mg
4–5	10 mg	5–10 mg	0–5 mg		0–2.5 mg
6	Dose based on requirements over preceding 5 days				

(*Annals* 1997;126:133; *Archives* 1999;159:46)

or, go to www.warfarindosing.org

Warfarin-heparin overlap therapy

- Indications: when failure to anticoagulate carries ↑ risk of morbidity or mortality (eg, DVT/PE, intracardiac thrombus)
- Rationale: (1) Half-life of factor VII (3–6 h) is shorter than half-life of factor II (60–72 h);
  ∴ warfarin can elevate PT *before achieving a true antithrombotic state*
  (2) Protein C also has half-life less than that of factor II;
  ∴ theoretical concern of *hypercoagulable state* before antithrombotic state
- Method: (1) Therapeutic PTT is achieved using heparin
  (2) Warfarin therapy is initiated
  (3) Heparin continued until INR therapeutic for ≥2 d and ≥4–5 d of warfarin (roughly corresponds to ~2 half-lives of factor II or a reduction to ~25%)

OTHER

Ideal body weight (IBW) = [50 kg (men) or 45.5 kg (women)] + 2.3 kg/inch over 5 feet

Body surface area (BSA, m^2) = $\sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$

		Disease	
		present	absent
Test	⊕	a (true ⊕)	b (false ⊕)
	⊖	c (false ⊖)	d (true ⊖)

Prevalence = $\frac{\text{all diseased}}{\text{all patients}} = \frac{a + b}{a + b + c + d}$

Sensitivity = $\frac{\text{true positives}}{\text{all diseased}} = \frac{a}{a + c}$ **Specificity** = $\frac{\text{true negatives}}{\text{all healthy}} = \frac{d}{b + d}$

⊕ **Predictive value** = $\frac{\text{true positives}}{\text{all positives}} = \frac{a}{a + b}$

⊖ **Predictive value** = $\frac{\text{true negatives}}{\text{all negatives}} = \frac{d}{c + d}$

Accuracy = $\frac{\text{true positives} + \text{true negatives}}{\text{all patients}} = \frac{a + d}{a + b + c + d}$

⊕ **Likelihood ratio** = $\frac{\text{true positive rate}}{\text{false positive rate}} = \frac{Se}{1 - Sp}$

⊖ **Likelihood ratio** = $\frac{\text{false negative rate}}{\text{true negative rate}} = \frac{1 - Se}{Sp}$

Odds = $\frac{\text{probability}}{1 - \text{probability}}$ **Probability** = $\frac{\text{odds}}{\text{odds} + 1}$

Posttest odds = pretest odds × LR

NOTES

ABBREVIATIONS

5′-NT	5′-nucleotidase
6-MP	6-mercaptopurine
a/w	associated with
AAA	abdominal aortic aneurysm
AAD	antiarrhythmic drug
Ab	antibody
ABE	acute bacterial endocarditis
ABG	arterial blood gas
abnl	abnormal
ABPA	allergic bronchopulmonary aspergillosis
abx	antibiotics
AC	assist control
ACE	angiotensin converting enzyme
ACEI	ACE inhibitor
ACI	anemia of chronic inflammation
ACL	anticardiolipin antibody
ACLS	advanced cardiac life support
ACS	acute coronary syndrome
ACTH	adrenocorticotrophic hormone
ACV	acyclovir
ADA	adenosine deaminase
ADH	antidiuretic hormone
ADL	activities of daily living
AF	atrial fibrillation
AFB	acid-fast bacilli
AFL	atrial flutter
AFP	α-fetoprotein
AFTP	ascites fluid total protein
AG	aminoglycoside anion gap
Ag	antigen
AGN	acute glomerulonephritis
AI	aortic insufficiency
AIDS	acquired immunodeficiency syndrome
AIH	autoimmune hepatitis
AIHA	autoimmune hemolytic anemia
AIN	acute interstitial nephritis
AIP	acute interstitial pneumonia
AKI	acute kidney injury
ALF	acute liver failure
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
AMI	anterior myocardial infarction
AML	acute myelogenous leukemia
ANA	antinuclear antibody
ANCA	antineutrophilic cytoplasmic antibody
angio	angiogram
AoD	aortic dissection
AoV	aortic valve
APC	activated protein C
APL	acute promyelocytic leukemia
APLA	antiphospholipid antibody
APS	antiphospholipid antibody syndrome
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARV	antiretroviral
ARVC	arrhythmogenic RV cardiomyopathy
AS	aortic stenosis
ASA	aspirin
ASD	atrial septal defect
AST	aspartate aminotransferase
asx	asymptomatic
AT	atrial tachycardia
ATII	angiotensin II
ATIII	antithrombin III
ATN	acute tubular necrosis
ATRA	all-*trans*-retinoic acid
AV	atrioventricular
AVA	aortic valve area
AVB	atrioventricular block
AVNRT	AV nodal reentrant tachycardia
AVR	aortic valve replacement
AVRT	AV reciprocating tachycardia
AZA	azathioprine
Aϕ	alkaline phosphatase
b/c	because
BAL	bronchoalveolar lavage
βB	beta-blocker
BBB	bundle branch block
BCx	blood culture
BD	bile duct
BDZ	benzodiazepines
bili.	bilirubin
BiPAP	bilevel positive airway pressure
BiV	biventricular
BM	bone marrow bowel movement
BMD	bone mineral density
BMI	body mass index
BMS	bare metal stent
BNP	B-type natriuretic peptide
BOOP	bronchiolitis obliterans with organizing pneumonia
BP	blood pressure
BPH	benign prostatic hypertrophy
BRBPR	bright red blood per rectum
BS	breath sounds
BT	bleeding time
BUN	blood urea nitrogen
bx	biopsy
C′	complement
c/w	compared with consistent with
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CALLA	common ALL antigen
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CBD	common bile duct
CCB	calcium channel blocker
CCl_4	carbon tetrachloride
CCP	cyclic citrullinated peptide
CCS	Canadian Cardiovascular Society
CCY	cholecystectomy
CD	Crohn's disease
CEA	carcinoembryonic antigen carotid endarterectomy
ceph.	cephalosporin
CF	cystic fibrosis
Cftx	ceftriaxone
CFU	colony forming units
CHB	complete heart block
CHD	congenital heart disease
CHF	congestive heart failure

CI cardiac index
CIAKI contrast-induced acute kidney injury
CIDP chronic inflammatory demyelinating polyneuropathy
CK creatine kinase
CKD chronic kidney disease
CLL chronic lymphocytic leukemia
CMC carpalmetacarpal (joint)
CML chronic myelogenous leukemia
CMML chronic myelomonocytic leukemia
CMP cardiomyopathy
CMV cytomegalovirus
CN cranial nerve
CO carbon monoxide
cardiac output
COP cryptogenic organizing pneumonia
COPD chronic obstructive pulmonary disease
COX cyclooxygenase
CP chest pain
CPAP continuous positive airway pressure
CPP cerebral perfusion pressure
CPPD calcium pyrophosphate dihydrate
Cr creatinine
CRC colorectal cancer
CrCl creatinine clearance
CRP C-reactive protein
CRT cardiac resynchronization therapy
CsA cyclosporine A
CSF cerebrospinal fluid
CSM carotid sinus massage
CT computed tomogram
CTA CT angiogram
CTD connective tissue disease
CV cardiovascular
CVA cerebrovascular accident
CVD cerebrovascular disease
collagen vascular disease
CVID common variable immunodeficiency
CVP central venous pressure
CVVH continuous veno-venous hemofiltration
CW chest wall
cx culture
CXR chest radiograph

d day
D death
d/c discharge
discontinue
Δ MS change in mental status
DA dopamine
DAD diffuse alveolar damage
DAH diffuse alveolar hemorrhage
DAT direct antiglobulin test
DBP diastolic blood pressure
DCIS ductal carcinoma *in situ*
DCMP dilated cardiomyopathy
Ddx differential diagnosis
DES drug-eluting stent
DFA direct fluorescent antigen detection
DI diabetes insipidus
DIC disseminated intravascular coagulation
diff. differential
DIP desquamative interstitial pneumonitis
distal interphalangeal (joint)
DKA diabetic ketoacidosis
DL_{CO} diffusion capacity of the lung
DLE drug induced lupus
DM dermatomyositis
diabetes mellitus
DMARD disease-modifying anti-rheumatic drug
DOE dyspnea on exertion
DRE digital rectal exam
DSE dobutamine stress echo
DTRs deep tendon reflexes
DU duodenal ulcer
DVT deep vein thrombosis
dx diagnosis

EAD extreme axis deviation
EAV effective arterial volume
EBV Epstein-Barr virus
ECG electrocardiogram
echo echocardiogram
ECMO extracorporeal membrane oxygenation
ED emergency department
EDP end-diastolic pressure
EDV end-diastolic volume
EEG electroencephalogram
EF ejection fraction
EGD esophagogastroduodenoscopy
EGFR epidermal growth factor receptor
EI entry inhibitor
EIA enzyme-linked immunoassay
ELISA enzyme-linked immunosorbent assay
EM electron microscopy
EMB ethambutol
ENT ears, nose, & throat
EOM extraocular movement/muscles
EP electrophysiology
Epo erythropoietin
EPS electrophysiology study
ERCP endoscopic retrograde cholangiopancreatography
ERV expiratory reserve volume
ESP end-systolic pressure
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
ESV end-systolic volume
ET endotracheal tube
essential thrombocythemia
EtOH alcohol
ETT endotracheal tube
exercise tolerance test
EUS endoscopic ultrasound
EVAR endovascular aneurysm repair

FDP fibrin degradation product
FEV_1 forced expiratory volume in 1 second
FFP fresh frozen plasma
FHx family history
FI fusion inhibitor
FMD fibromuscular dysplasia
FMF familial Mediterranean fever
FNA fine needle aspiration
FOB fecal occult blood
FOBT fecal occult blood testing
FQ fluoroquinolone

FRC functional residual capacity
FSGS focal segmental glomerulosclerosis
FSH follicle stimulating hormone
FTI free thyroxine index
FUO fever of unknown origin
FVC forced vital capacity

G6PD glucose-6-phosphate dehydrogenase
GB gallbladder
GBM glomerular basement membrane
GBS Guillain-Barré syndrome
GCA giant cell arteritis
GCS Glasgow coma scale
G-CSF granulocyte colony stimulating factor
GE gastroesophageal
gen. generation
GERD gastroesophageal reflux disease
GFR glomerular filtration rate
GGT γ-glutamyl transpeptidase
GH growth hormone
GIB gastrointestinal bleed
GIST gastrointestinal stromal tumor
glc glucose
GN glomerulonephritis
GNR gram-negative rods
GnRH gonadotropin-releasing hormone
GPC gram-positive cocci
GPI glycoprotein IIb/IIIa inhibitor
GRA glucocorticoid-remediable aldosteronism
GU gastric ulcer
GVHD graft-versus-host disease

h hour
H2RA H_2-receptor antagonist
h/o history of
HA headache
HAV hepatitis A virus
Hb hemoglobin
HBIG hepatitis B immunoglobulin
HBV hepatitis B virus
HCC hepatocellular carcinoma
HCMP hypertrophic cardiomyopathy
Hct hematocrit
HCV hepatitis C virus
HCW health care worker
HD hemodialysis
HDL high-density lipoprotein
HDV hepatitis D virus
HELLP hemolysis, abnormal LFTs, low platelets
HEV hepatitis E virus
HF heart failure
HGPRT hypoxanthine-guanine phosphoribosyl transferase
HHS hyperosmolar hyperglycemic state
HIT heparin-induced thrombocytopenia
HK hypokinesis
HL Hodgkin lymphoma
HoTN hypotension
hpf high power field
HPT hyperparathyroidism
HR heart rate
HRT hormone replacement therapy
HS hereditary spherocytosis
HSCT hematopoietic stem cell transplantation
HSM hepatosplenomegaly
HSP Henoch-Schönlein purpura
HSV herpes simplex virus
HTN hypertension
HUS hemolytic uremic syndrome

I&D incision & drainage
IABP intraaortic balloon pump
IBD inflammatory bowel disease
IC inspiratory capacity
ICa ionized calcium
ICD implantable cardiac defibrillator
ICH intracranial hemorrhage
ICP intracranial pressure
ICU intensive care unit
IE infective endocarditis
IGF insulin-like growth factor
IGRA interferon-χ release assay
II integrase inhibitor
IIP idiopathic interstitial pneumonia
ILD interstitial lung disease
IMI inferior myocardial infarction
infxn infection
inh inhaled
INH isoniazid
INR international normalized ratio
IPF idiopathic pulmonary fibrosis
ITP idiopathic thrombocytopenic purpura
IVB intravenous bolus
IVC inferior vena cava
IVDU intravenous drug use(r)
IVF intravenous fluids
IVIg intravenous immunoglobulin

JVD jugular venous distention
JVP jugular venous pulse

LA left atrium
long-acting
lupus anticoagulant
LABA long-acting β_2-agonist
LAD left anterior descending coronary artery
left axis deviation
LAE left atrial enlargement
LAN lymphadenopathy
LAP leukocyte alkaline phosphatase
LAP left atrial pressure
LBBB left bundle branch block
LCA left coronary artery
LCIS lobular carcinoma *in situ*
LCx left circumflex coronary artery
LDH lactate dehydrogenase
LDL low-density lipoprotein
LE lower extremity
LES lower esophageal sphincter
LFTs liver function tests
LGIB lower gastrointestinal bleed
LH luteinizing hormone
LLQ left lower quadrant
LM left main coronary artery
LMWH low-molecular-weight heparin
LN lymph node
LOC loss of consciousness
LOS length of stay
LP lumbar puncture
lpf low power field
LR lactated Ringer's
LQTS long QT syndrome
LUSB left upper sternal border

LV left ventricle
LVAD LV assist device
LVEDP LV end-diastolic pressure
LVEDV LV end-diastolic volume
LVH left ventricular hypertrophy
LVOT left ventricular outflow tract
LVSD LV systolic dimension

MAC mitral annular calcification
Mycobacterium avium complex
MAHA microangiopathic hemolytic anemia
MAO monoamine oxidase
MAP mean arterial pressure
MAT multifocal atrial tachycardia
MCD minimal change disease
MCP metacarpal phalangeal (joint)
MCTD mixed connective tissue disease
MCV mean corpuscular volume
MDI metered dose inhaler
MDMA 3,4-methylenedioxymethamphetamine (Ecstasy)
MDS myelodysplastic syndrome
MEN multiple endocrine neoplasia
MG myasthenia gravis
MGUS monoclonal gammopathy of uncertain significance
MI myocardial infarction
min minute
min. minimal
MM multiple myeloma
MMEFR maximal mid-expiratory flow rate
MMF mycophenolate mofetil
MN membranous nephropathy
MNZ metronidazole
mod. moderate
MODS multiple organ dysfunction syndrome
mos months
MPN myeloproliferative neoplasm
MPGN membranoproliferative glomerulonephritis
MR magnetic resonance
mitral regurgitation
MRA magnetic resonance angiography
MRCP magnetic resonance cholangiopancreatography
MRI magnetic resonance imaging
MRSA methicillin-resistant *S. aureus*
MS mitral stenosis
MTb *Mycobacterium tuberculosis*
MTP metatarsal phalangeal (joint)
MTX methotrexate
MV mitral valve
MVA mitral valve area
MVP mitral valve prolapse
MVR mitral valve replacement
Mϕ macrophage

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 nasojejunal
nl normal
NM neuromuscular
NMJ neuromuscular junction
NNRTI non-nucleoside reverse transcriptase inhibitor
NNT number needed to treat
NO nitric oxide
NPJT nonparoxysmal junctional tachycardia
NPO nothing by mouth
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
NUD nonulcer dyspepsia
NVE native valve endocarditis

O/D overdose
o/w otherwise
OA osteoarthritis
OCP oral contraceptive pill
OG osmolal gap
OGT orogastric tube
OGTT oral glucose tolerance test
OI opportunistic infection
OM obtuse marginal coronary artery
OSA obstructive sleep apnea
OTC over-the-counter

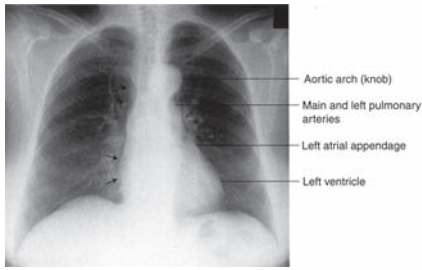
p/w present(s) with
PA pulmonary artery
PAC pulmonary artery catheter
PAD peripheral arterial disease
PAN polyarteritis nodosa
PASP pulmonary artery systolic pressure
PAV percutaneous aortic valvuloplasty
pb problem
PBC primary biliary cirrhosis
PCI percutaneous coronary intervention
PCN penicillin
PCP *Pneumocystis jiroveci* pneumonia
PCR polymerase chain reaction
PCT porphyria cutanea tarda
PCWP pulmonary capillary wedge pressure
PD Parkinson's disease
peritoneal dialysis
PDA patent ductus arteriosus
posterior descending coronary artery
PE pulmonary embolism
PEA pulseless electrical activity
PEEP positive end-expiratory pressure
PEF peak expiratory flow
PET positron emission tomography
PEx physical examination
PFO patent foramen ovale
PFT pulmonary function test
PGA polyglandular autoimmune syndrome
PHT pulmonary hypertension
PI protease inhibitor

PID	pelvic inflammatory disease
PIF	prolactin inhibitory factor
PIP	peak inspiratory pressure proximal interphalangeal (joint)
PKD	polycystic kidney disease
PM	polymyositis
PMF	primary myelofibrosis
PMHx	past medical history
PMI	point of maximal impulse
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear leukocyte
PMV	percutaneous mitral valvuloplasty
PMVT	polymorphic ventricular tachycardia
PNA	pneumonia
PND	paroxysmal nocturnal dyspnea
PNH	paroxysmal nocturnal hemoglobinuria
PMR	polymyalgia rheumatica
PO	oral intake
POBA	plain old balloon angioplasty
POTS	postural orthostatic tachycardia syndrome
PPD	purified protein derivative
PPH	primary pulmonary hypertension
PPI	proton pump inhibitors
P_{plat}	plateau pressure
PPM	permanent pacemaker
PPV	positive predictive value
Ppx	prophylaxis
PR	PR segment on ECG pulmonary regurgitation
PRBCs	packed red blood cells
PRL	prolactin
PRPP	phosphoribosyl-1-pyrophosphate
PRWP	poor R wave progression
PS	pressure support pulmonic stenosis
PSA	prostate specific antigen
PSC	primary sclerosing cholangitis
PSGN	post streptococcal glomerulonephritis
PSHx	past surgical history
PSV	pressure support ventilation
Pt	patient
PT	prothrombin time
PTA	percutaneous transluminal angioplasty
PTH	parathyroid hormone
PTH-rP	parathyroid hormone-related peptide
PTT	partial thromboplastin time
PTU	propylthiouracil
PTX	pneumothorax
PUD	peptic ulcer disease
PUVA	psoralen + ultraviolet A
PV	polycythemia vera portal vein
PVD	peripheral vascular disease
PVE	prosthetic valve endocarditis
PVR	pulmonary vascular resistance
PZA	pyrazinamide
qac	before every meal
qhs	every bedtime
QoL	quality of life
Qw	Q wave
r/i	rule in
r/o	rule out
RA	refractory anemia rheumatoid arthritis right atrium
RAD	right axis deviation
RAE	right atrial enlargement
RAI	radioactive iodine
RAIU	radioactive iodine uptake
RAS	renal artery stenosis
RBBB	right bundle branch block
RBC	red blood cell
RBF	renal blood flow
RCA	right coronary artery
RCMP	restrictive cardiomyopathy
RCT	randomized controlled trial
RDW	red cell distribution width
RE	reticuloendothelial
RF	rheumatoid factor risk factor
RHD	rheumatic heart disease
RI	reticulocyte index
RIBA	recombinant immunoblot assay
RMSF	Rocky Mountain spotted fever
ROS	review of systems
RPGN	rapidly progressive glomerulonephritis
RR	respiratory rate
RRT	renal replacement therapy
RT	radiation therapy
RTA	renal tubular acidosis
RUQ	right upper quadrant
RUSB	right upper sternal border
RV	residual volume right ventricle
RVAD	RV assist device
RVH	right ventricular hypertrophy
RVOT	RV outflow tract
RVSP	RV systolic pressure
Rx	therapy
s/e	side effect
s/p	status post
s/s	signs and symptoms
SA	sinoatrial
SAAG	serum-ascites albumin gradient
SAH	subarachnoid hemorrhage
SAS	sulfasalazine
SBE	subacute bacterial endocarditis
SBP	spontaneous bacterial peritonitis systolic blood pressure
SBT	spontaneous breathing trial
SC	subcutaneous
SCD	sudden cardiac death
SCID	severe combined immunodeficiency
SCLC	small cell lung cancer
Se	sensitivity
sec	second
SERM	selective estrogen receptor modulator
sev.	severe
SIADH	syndrome of inappropriate antidiuretic hormone
SIEP	serum immunoelectrophoresis
SIMV	synchronized intermittent mandatory ventilation
SLE	systemic lupus erythematosus
SMA	superior mesenteric artery
SMV	superior mesenteric vein

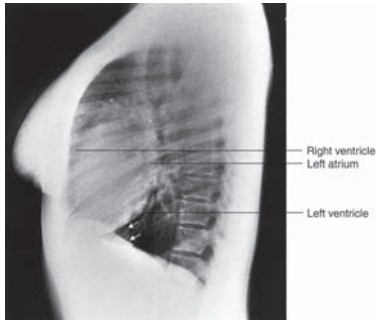
SOS	sinusoidal obstructive syndrome
Sp	specificity
SPEP	serum protein electrophoresis
SR	sinus rhythm
SSCY	*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*
SSRI	selective serotonin reuptake inhibitor
SSS	sick sinus syndrome
ST	sinus tachycardia
STD	sexually transmitted disease
	ST-segment depression
STE	ST-segment elevation
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
sx	symptom(s) or symptomatic
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
T_3RU	T_3 resin uptake
TAA	thoracic aortic aneurysm
TB	tuberculosis
TBG	thyroid binding globulin
TCA	tricyclic antidepressant
TCD	transcranial Doppler
TCN	tetracycline
TdP	torsades de pointes
TdT	terminal deoxynucleotidyl transferase
TEE	transesophageal echo
TFTs	thyroid function tests
TG	triglycerides
TGA	transposition of the great arteries
TIA	transient ischemic attack
TIBC	total iron binding capacity
TINU	tubulointerstitial nephritis and uveitis
TIPS	transjugular intrahepatic portosystemic shunt
TLC	total lung capacity
Tn	troponin
TP	total protein
TPN	total parenteral nutrition
Tpo	thrombopoietin
TPO	thyroid peroxidase
TR	tricuspid regurgitation
TRALI	transfusion-related acute lung injury
TRH	thyrotropin releasing hormone
TRS	TIMI risk score
TRUS	transrectal ultrasound
TS	tricuspid stenosis
TSH	thyroid stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TSS	toxic shock syndrome
	transsphenoidal surgery
TTE	transthoracic echo
TTKG	transtubular potassium gradient
TTP	thrombotic thrombocy-topenic 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
V_T	tidal volume
VT	ventricular tachycardia
VTE	venous thromboembolus
vWD	von Willebrand's disease
vWF	von Willebrand's factor
VZV	varicella zoster virus
w/	with
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

INDEX

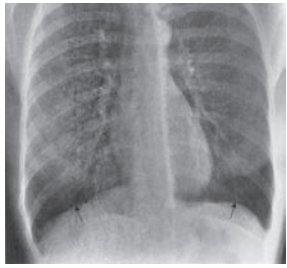
NOTES



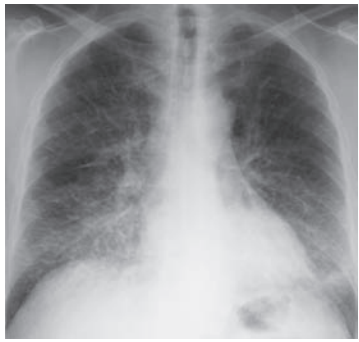
1 Normal PA CXR. The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicated the location of the superior vena cava. The left cardiac and great vessels border what might be considered as four skiing moguls. From cephalad to caudad, the moguls are the aortic arch, the main and left pulmonary arteries, the left atrial appendage, and the left ventricle. (*Radiology 101*, 3rd ed, 2009.)



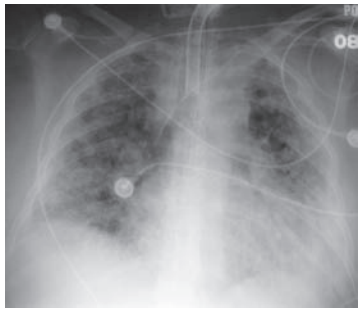
2 Normal lateral CXR. (*Radiology 101*, 3rd ed, 2009.)



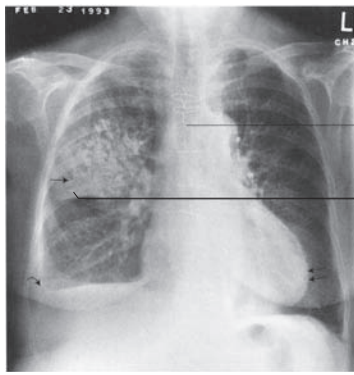
3 COPD: with hyperlucent, overinflated lungs and flat diaphragms. (*Radiology 101*, 3rd ed, 2009.)



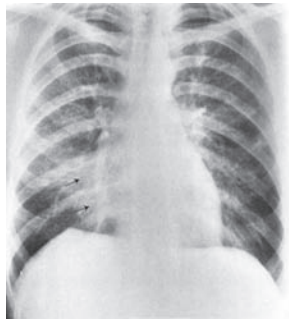
4 Interstitial pulmonary edema: with Kerley A, B, and C lines and cephalization of the vascular markings. (*Fund. Diag. Radiology* 3rd ed, 2006.)



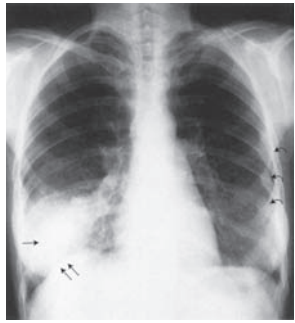
5 Alveolar pulmonary edema. (*Fund. Diag. Radiology* 3rd ed, 2006.)



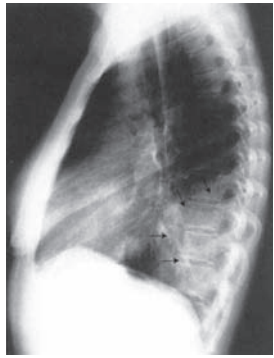
6 Right upper lobe pneumonia. (*Radiology 101*, 3rd ed, 2009.)



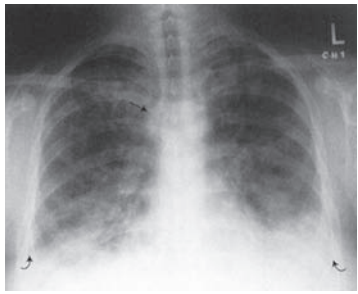
7 Right middle lobe pneumonia. (*Radiology 101*, 3rd ed, 2009.)



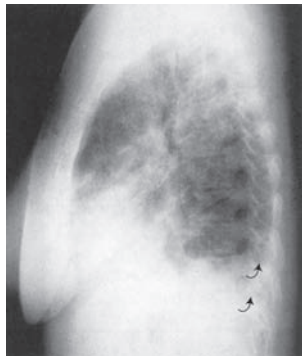
8 Right lower lobe pneumonia (PA). (*Radiology 101*, 3rd ed, 2009.)



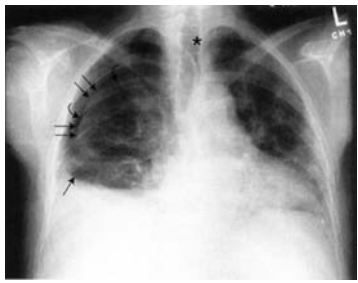
9 Right lower lobe pneumonia (lateral). (*Radiology 101*, 3rd ed, 2009.)



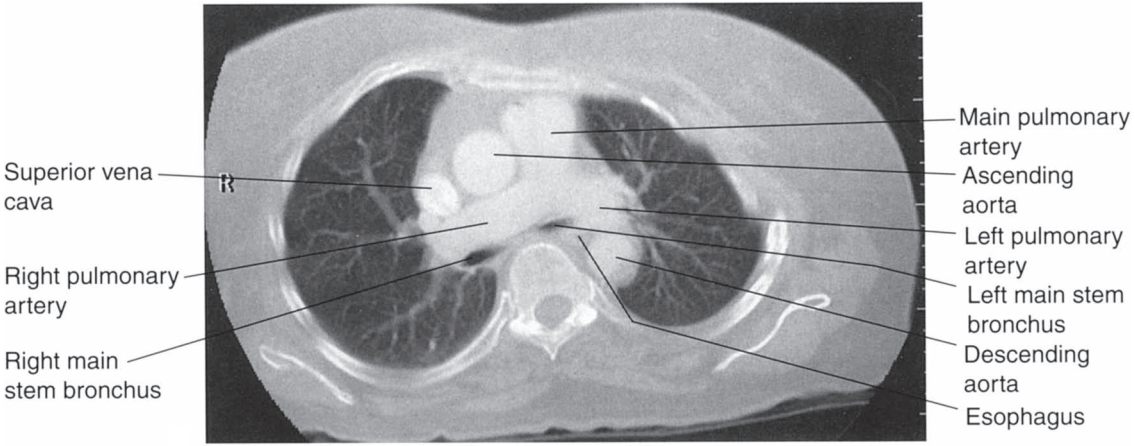
10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow) (PA). (*Radiology 101*, 3rd ed, 2009.)



11 Bilateral pleural effusions (curved arrows) (lateral). (*Radiology 101*, 3rd ed, 2009.)

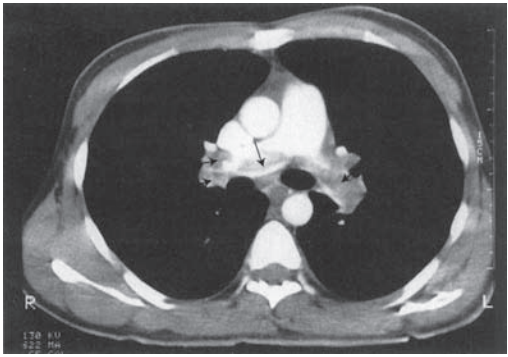


12 Pneumothorax. (*Radiology 101*, 3rd ed, 2009.)

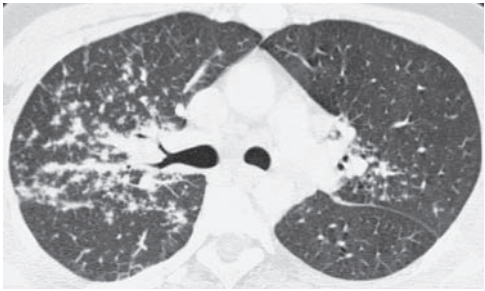


13 Normal chest CT at level of pulmonary arteries (parenchymal windows).
(*Radiology 101*, 3rd ed, 2009.)

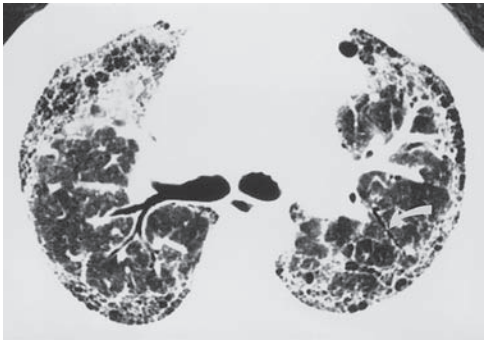
PHOTO INSERT P-5



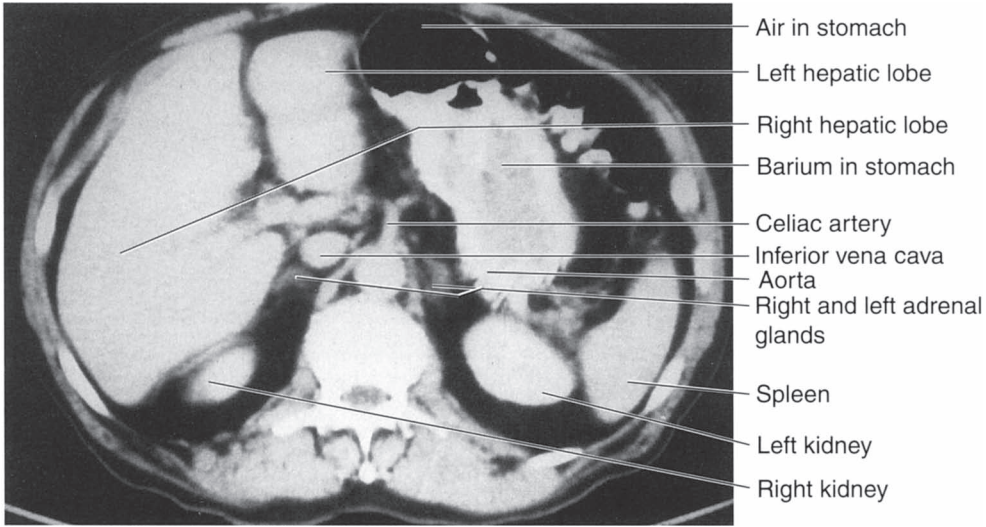
14 Bilateral PE (mediastinal windows). (*Radiology 101*, 3rd ed, 2009.)



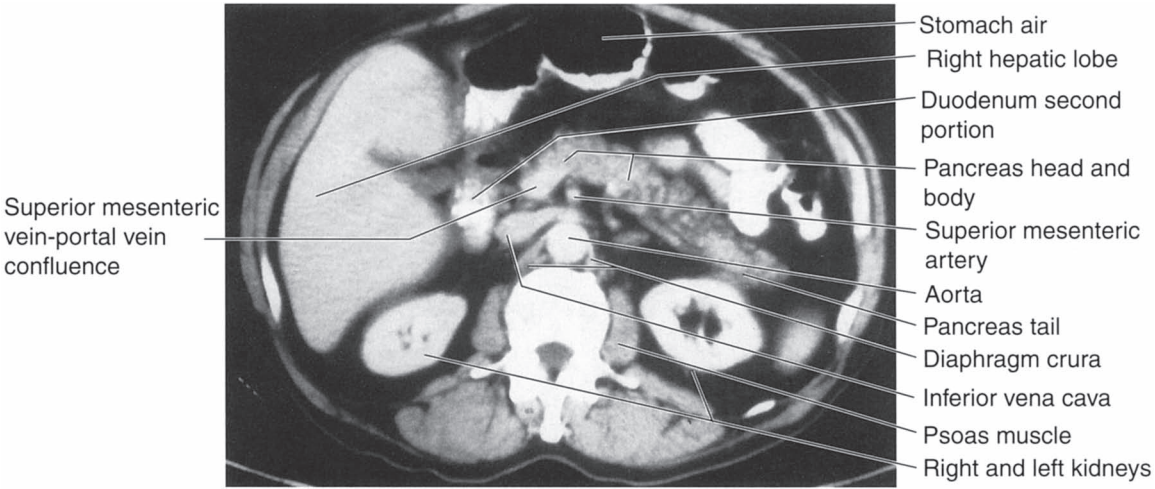
15 Sarcoidosis with perilymphatic nodules. (*Fund. Diag. Radiology* 3rd ed, 2006.)



16 Idiopathic pulmonary fibrosis. (*Fund. Diag. Radiology* 3rd ed, 2006.)

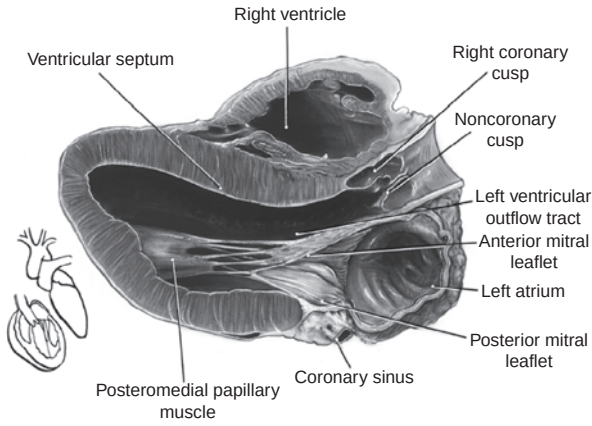


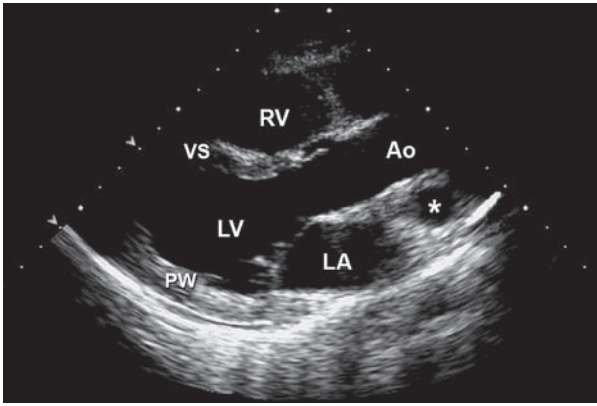
17 Normal abdomen CT at level of liver & spleen. (*Radiology 101*, 3rd ed, 2009.)



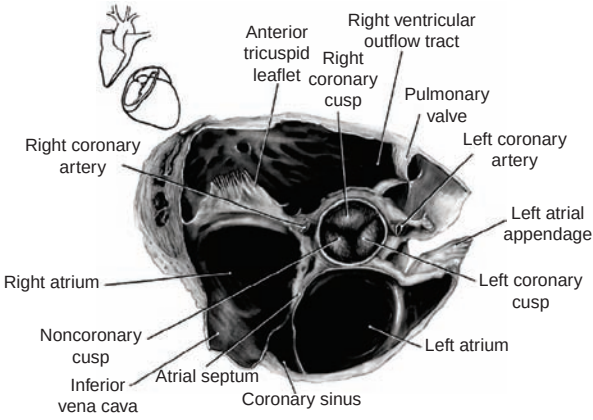
18 Normal abdomen CT at level of pancreas. (*Radiology 101*, 3rd ed, 2009.)

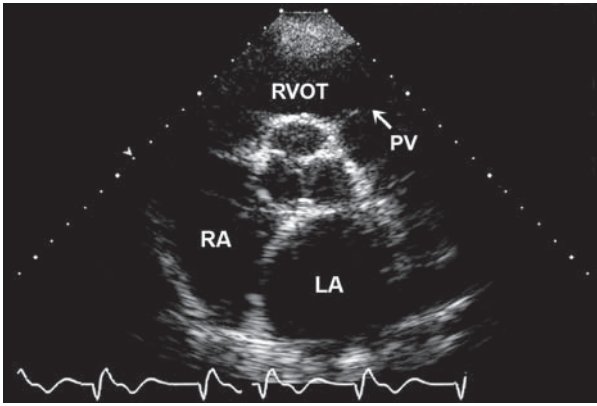
Photo Insert P-9



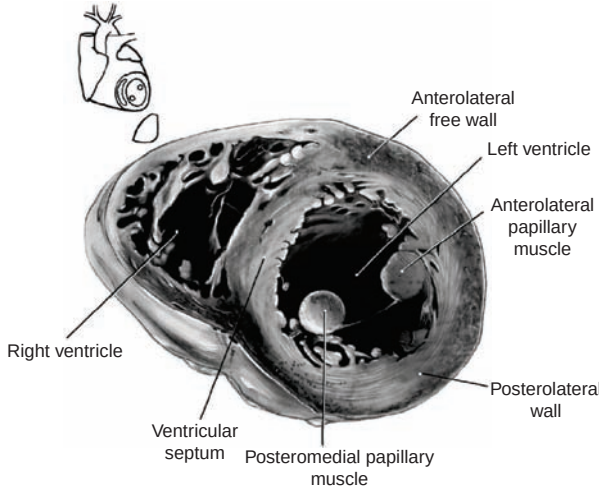


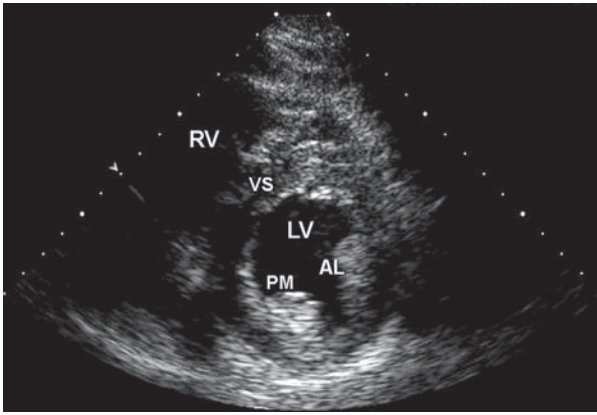
1 Parasternal long-axis view allows visualization of the right ventricle (RV), ventricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). *Pulmonary artery. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, *3rd ed*. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)



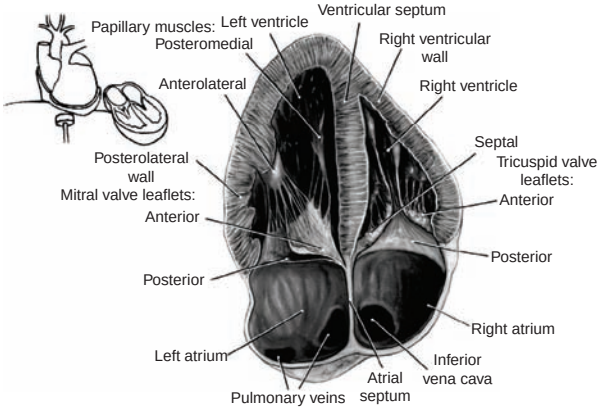


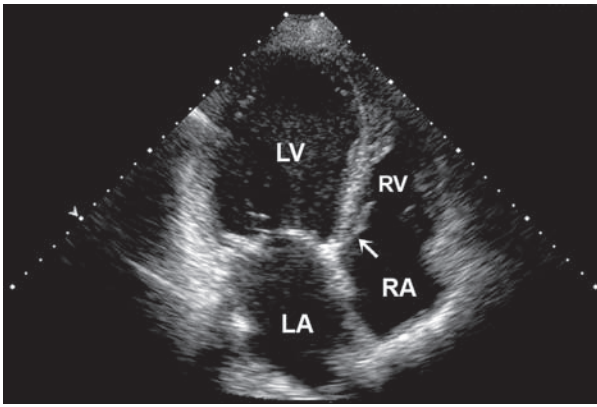
2 Parasternal short-axis view at the level of the aorta: LA, left atrium; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, *3rd ed*. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)





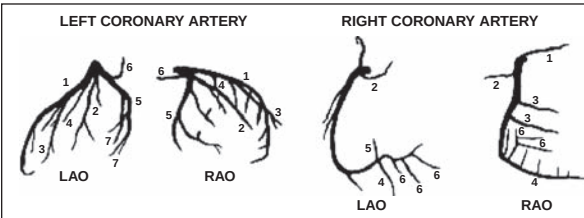
3 Parasternal short-axis view at the level of the papillary muscles: AL, anterolateral papillary muscle; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum; LV, left ventricle. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, *3rd ed*. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)





4 Apical four-chamber view: Note that at some institutions the image is reversed so that the left side of the heart appears on the right side of the screen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, *3rd ed*. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Coronary Angiography

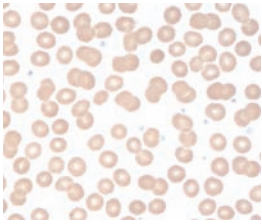


1. **Left anterior descending artery (LAD)**
2. Ramus medianus artery
3. Diagonal branches
4. Septal branches
5. **Left circumflex artery (LCx)**
6. Left atrial circumflex artery
7. Obtuse marginal branches

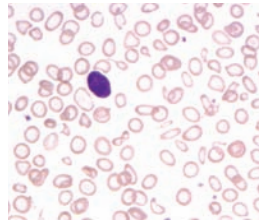
1. Conus artery
2. SA node artery
3. Acute marginal branches
4. Posterior descending artery (PDA)
5. AV node artery
6. Posterior left ventricular artery (PLV)

Coronary arteries. (From Grossman WG. *Cardiac Catheterization and Angiography*, 4th ed. Philadelphia: Lea & Febiger, 1991, with permission.)

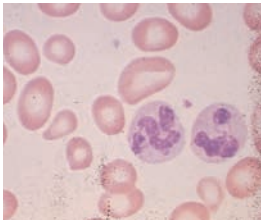
Peripheral Blood Smears



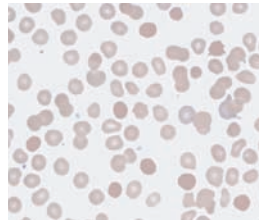
1 Normal smear.



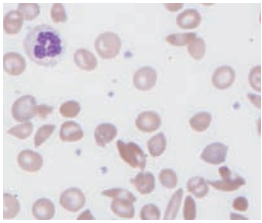
2 Hypochromic, microcytic anemia due to iron-deficiency.



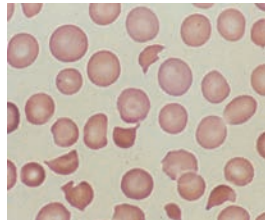
3 Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



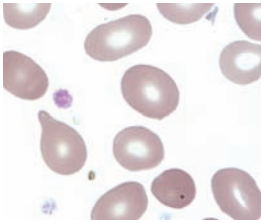
4 Spherocytes due to autoimmune hemolytic anemia.



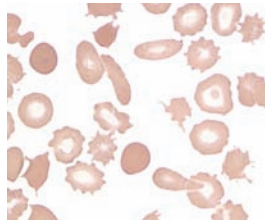
5 Sickle cell anemia.



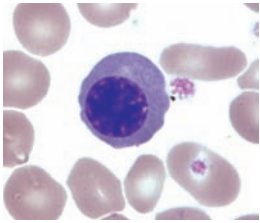
6 Schistocytes.



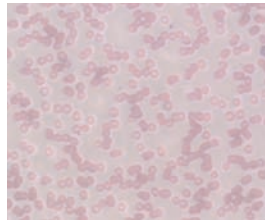
7 Teardrop shaped RBC (dacrocyte).



8 Acanthocytes.

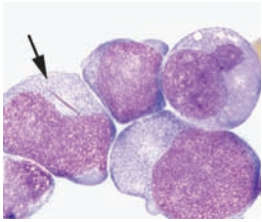


9 Nucleated RBC.

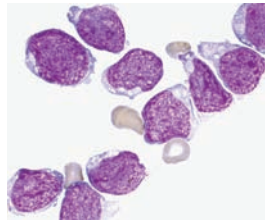


10 Rouleaux.

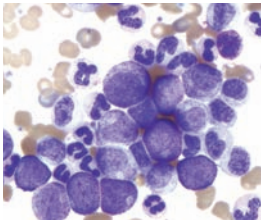
Leukemias



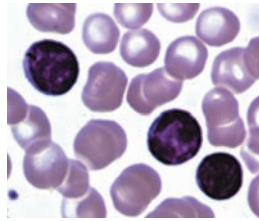
1 AML with Auer rod.



2 ALL.



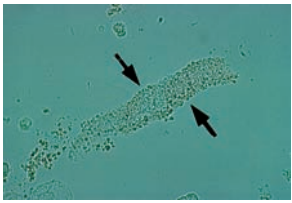
3 CML.



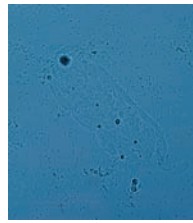
4 CLL.

All photos excluding Leukemias Fig. 4: From Wintrobe's *Clin. Hematol.* 12th ed, 2009: Leukemias Fig. 4 From Devita, Hellman, and Rosenberg's *Cancer: Princip. & Prac. of Oncol.* 8th ed, 2008.

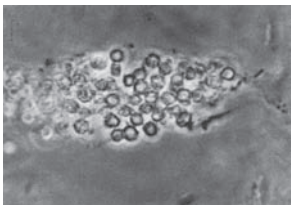
Urinalysis



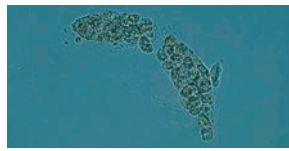
1 Granular cast. (*College of Am. Pathologist,* with permission.)



2 Hyaline cast. (*Clin. Lab. Medicine*, 2nd ed, 2002.)



3 RBC cast. (*Dis. of Kidney & Urinary Tract,* 8th ed, 2006.)



4 WBC cast. (*Clin. Lab. Medicine*, 2nd ed, 2002.)