

**POCKET  
NOTEBOOK**

# **POCKET MEDICINE**

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**FOURTH EDITION**

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**Edited by**

**Marc S. Sabatine**

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**The Massachusetts General Hospital  
Handbook of Internal Medicine**

Wolters Kluwer  
Health

Lippincott  
Williams & Wilkins



POCKET  
NOTEBOOK

*Pocket*  
**MEDICINE**

Fourth Edition

*Edited by*

**MARC S. SABATINE, M.D., M.P.H.**  
**ASSOCIATE PROFESSOR OF MEDICINE**  
**HARVARD MEDICAL SCHOOL**



*The Massachusetts General Hospital  
Handbook of Internal Medicine*



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# FOREWORD

## To the 1st Edition

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

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

DENNIS A. AUSIELLO, MD

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# 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 manner as possible, the key information a clinician needs for the initial approach to and management of the most common inpatient medical problems.

The tremendous response to the previous editions suggests we were able to help fill an important need for clinicians. With this fourth edition come several major improvements including: a thorough updating of every topic; the addition of several new topics (including acute aortic syndromes, sepsis, obstructive sleep apnea, hepatic vascular disease, optimal use of diuretics, viral respiratory infections, infections in susceptible hosts, intensive glycemic control, approach to the patient with joint pain, and alcohol withdrawal); incorporation of references to the most recent reviews and important studies published through the middle of 2010; and the addition of high-resolution chest radiographs, chest and abdominal CTs, and echocardiograms, and photomicrographs of peripheral blood smears and urinalyses. We welcome any suggestions for further improvement.

Of course medicine is far too vast a field to ever summarize in a textbook of any size. Long monographs have been devoted to many of the topics discussed herein. *Pocket Medicine* is meant only as a starting point to guide one during the initial phases of diagnosis and management until one has time to consult more definitive resources. Although the recommendations herein are as evidence-based as possible, medicine is both a science and an art. As always, sound clinical judgement must be applied to every scenario.

I am grateful for the support of the house officers, fellows, and attendings at the Massachusetts General Hospital. It is a privilege to work with such a knowledgeable, dedicated, and compassionate group of physicians. I always look back on my time there as Chief Resident as one of the best experiences I have ever had. I am grateful to several outstanding clinical mentors, including Hasan Bazari, Denny Ausiello, Larry Friedman, Nesli Basgoz, Mort Swartz, Eric Isselbacher, Bill Dec, Mike Fifer, and Roman DeSanctis, as well as the late Charlie McCabe and Peter Yurchak. Special thanks to my parents for their perpetual encouragement and love and, of course, to my wife, Jennifer Tseng, who, despite being a surgeon, is my closest advisor, my best friend, and the love of my life.

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

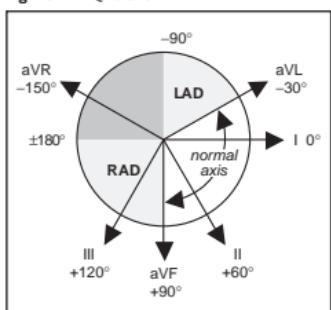
MARC S. SABATINE, MD, MPH

# ELECTROCARDIOGRAPHY

## Approach (a systematic approach is vital)

- Rate (? tachy, brady) and **rhythm** (? relationship between P and QRS)
- Intervals (PR, QRS, QT) and axis (? LAD or RAD)
- Chamber abnormality (? LAA and/or RAA, ? LVH and/or RVH)
- QRST changes (? Q waves, poor R-wave progression V<sub>1</sub>–V<sub>6</sub>, ST ↑/↓, or T-wave Δs)

Figure 1-1 QRS axis



### Left axis deviation (LAD)

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

### Right axis deviation (RAD)

- **Definition:** axis beyond  $+90^\circ$  (S > R in lead I)
- **Etiologies:** RVH, PE, COPD (usually not  $>+110^\circ$ ), septal defects, lateral MI, WPW
- **Left posterior fascicular block:** RAD ( $90$ – $180^\circ$ ) 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)

<b>Normal</b>		Initial depol. is left-to-right across septum (r in V <sub>1</sub> & q in V <sub>6</sub> ; nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB).
<b>RBBB</b>		<ol style="list-style-type: none"> <li>1. QRS <math>\geq 120</math> msec (110–119 = incomplete)</li> <li>2. rSR' in R precordial leads (V<sub>1</sub>, V<sub>2</sub>)</li> <li>3. Wide S wave in I and V<sub>6</sub></li> <li>4. <math>\pm</math> ST↑ or TWI in R precordial leads</li> </ol>
<b>LBBB</b>		<ol style="list-style-type: none"> <li>1. QRS <math>\geq 120</math> msec (110–119 = incomplete)</li> <li>2. Broad, slurred, monophasic R in I, aVL, V<sub>5</sub>–V<sub>6</sub> (<math>\pm</math> RS in V<sub>5</sub>–V<sub>6</sub> if cardiomegaly)</li> <li>3. Absence of Q in I, V<sub>5</sub>, and V<sub>6</sub> (may have narrow q in aVL)</li> <li>4. Displacement of ST &amp; Tw opposite major QRS deflection</li> <li>5. <math>\pm</math> PRWP, LAD, Qw's in inferior leads</li> </ol>

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, fosfarnet, atazanavir, ? TMP-SMX
  - Other:** antiemetics (droperidol, 5-HT<sub>3</sub> 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)

### 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  $\geq 20$  mm or S in V<sub>1</sub> or V<sub>2</sub>  $\geq 30$  mm or R in V<sub>5</sub> or V<sub>6</sub>  $\geq 30$  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  $\geq 90$  msec (1 point)

Intrinsicoid deflection (QRS onset to peak of R) in V<sub>5</sub> or V<sub>6</sub>  $\geq 50$  msec (1 point)

Sokolow-Lyon: S in V<sub>1</sub> + R in V<sub>5</sub> or V<sub>6</sub>  $\geq 35$  mm

Cornell: R in aVL + S in V<sub>3</sub>  $> 28$  mm in men or  $> 20$  mm in women

Other: R in aVL  $\geq 11$  mm (or, if LAD/LAFB,  $\geq 13$  mm and S in III  $\geq 15$  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<sub>1</sub> or R in V<sub>1</sub>  $\geq 7$  mm, S in V<sub>5</sub> or V<sub>6</sub>  $\geq 7$  mm, drop in R/S ratio across precordium
  - RAD  $\geq +110^\circ$  (LVH + RAD or prominent S in V<sub>5</sub> or V<sub>6</sub>  $\rightarrow$  biventricular hypertrophy)

### Ddx of dominant R wave in V<sub>1</sub> or V<sub>2</sub>

- Ventricular enlargement: RVH (RAD, RAA, deep S waves in I, V<sub>5</sub>, V<sub>6</sub>); HCMP
- Myocardial injury: true posterior MI (often IMI); Duchenne muscular dystrophy
- Abnormal depolarization: RBBB (QRS  $> 120$  msec, rSR'); WPW ( $\downarrow$  PR,  $\delta$  wave,  $\uparrow$  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<sub>1</sub>-V<sub>3</sub>); R wave in V<sub>3</sub>  $\leq 3$  mm
- Etiologies:
  - old anteroseptal MI (usually R wave V<sub>3</sub>  $\leq 1.5$  mm,  $\pm$  persistent ST  $\uparrow$  or TWI V<sub>2</sub> & V<sub>3</sub>)
  - 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:  $\geq 30$  msec or  $> 25\%$  height of the R wave in that complex
- Small (septal) q waves in I, aVL, V<sub>5</sub> & V<sub>6</sub> are normal, as can be isolated Qw in III, aVR, V<sub>1</sub>
- "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  $\pm$  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  $\downarrow$ ; Tw usually upright)
- HCMP, Takotsubo CMP, ventricular aneurysm, cardiac contusion
- Pulmonary embolism (occ. STE V<sub>1</sub>-V<sub>3</sub>; typically associated TWI V<sub>1</sub>-V<sub>4</sub>, RAD, RBBB)
- Repolarization abnormalities
  - LBBB ( $\uparrow$  QRS duration, STE discordant from QRS complex)
    - dx of STEMI in setting of LBBB:  $\geq 1$  mm STE concordant w/ QRS (Se 73%, Sp 92%)
    - or  $\geq 5$  mm discordant (Se 31%, Sp 92%) ("Sgarbossa criteria," NEJM 1996;334:481)
    - LVH ( $\uparrow$  QRS amplitude): Brugada syndrome (rSR', downsloping STE V<sub>1</sub>-V<sub>2</sub>)
    - Hyperkalemia ( $\uparrow$  QRS duration, tall Ts, no Ps)
- Early repolarization: most often seen in leads V<sub>2</sub>-V<sub>5</sub> and in young adults
  - J point  $\uparrow$  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  $\uparrow$  risk of VF, but absolute risk low (NEJM 2009;361:2529)

### ST depression (STD)

- Myocardial ischemia ( $\pm$  Tw abnl) or acute true posterior MI (V<sub>1</sub>-V<sub>3</sub>)
- Digitalis effect (downsloping ST  $\pm$  Tw abnl, does not correlate w/ dig levels)
- Hypokalemia ( $\pm$  U wave)
- Repolarization abnl in a/w LBBB or LVH (usually in leads V<sub>5</sub>, V<sub>6</sub>, I, aVL)

### T wave inversion (TWI; generally $\geq 1$ mm; deep if $\geq 5$ mm) (Circ 2009;119:e241)

- Ischemia or infarct; Wellens' sign (deep early precordial TWI)  $\rightarrow$  proximal LCA lesion
- Myopericarditis; CMP (incl Takotsubo & ARVD); MVP; PE (especially if TWI V<sub>1</sub>-V<sub>4</sub>)
- Repolarization abnl in a/w LVH/RVH ("strain pattern"), BBB
- Post-tachycardia or post-pacing
- Electrolyte, digoxin, PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, or core temperature disturbances
- Intracranial bleed ("cerebral T waves," usually w/  $\uparrow$  QT)
- Normal variant in children (V<sub>1</sub>-V<sub>4</sub>) and leads in which QRS complex predominantly  $\ominus$ ; 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

# CHEST PAIN

## Cardiac Causes

Disorder	Typical Characteristics & Diagnostic Studies
<b>Unstable angina</b>	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 ( <i>Annals EM</i> 2005;45:581). ± ECG Δs (ST ↓↑, T-WI).
<b>MI</b>	Same as angina but ↑ intensity & duration. ⊕ troponin or CK-MB.
<b>Pericarditis &amp; Myo-pericarditis</b>	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.
<b>Aortic dissection</b>	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. ( <i>JAMA</i> 2002;287:2262)

## Pulmonary Causes

Disorder	Typical Characteristics & Diagnostic Studies
<b>Pneumonia</b>	Pleuritic; dyspnea, fever, cough, sputum. ↑ RR, crackles. CXR infiltrate.
<b>Pleuritis</b>	Sharp, pleuritic pain. ± Pleuritic friction rub.
<b>PTX</b>	Sudden onset, sharp pleuritic pain. Hyperresonance, ↓ BS. PTX on CXR.
<b>PE</b>	Sudden onset pleuritic pain. ↑ RR & HR, ↓ S <sub>a</sub> O <sub>2</sub> , ECG Δs (RAD, RBBB, TWI V <sub>1</sub> -V <sub>4</sub> , occ STE V <sub>1</sub> -V <sub>3</sub> ). ⊕ CTA.
<b>PHT</b>	Exertional pressure, dyspnea. ↓ S <sub>a</sub> O <sub>2</sub> , loud P <sub>2</sub> , right-sided S <sub>3</sub> and/or S <sub>4</sub> .

## GI Causes

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

## Musculoskeletal and Miscellaneous Causes

Disorder	Typical Characteristics & Diagnostic Studies
<b>Costochondritis</b>	Localized sharp pain. ↑ w/ movement. Reproduced by palpation.
<b>Herpes zoster</b>	Intense unilateral pain. Dermatomal rash & sensory findings.
<b>Anxiety</b>	"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<sub>7</sub>-V<sub>9</sub>) 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, <sup>99m</sup>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** ( $HR \times BP$ ), HR recovery ( $HR_{peak} - HR_{1\text{ min later}}$ ; 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 – ( $5 \times \text{max ST dev}$ ) – ( $4 \times \text{angina index}$ ) [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 test 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 ( $\pm$  bicarb, acetylcysteine; see "CIAKI"); blood bank sample
- ASA 325 mg; consider clopidogrel preRx (300–600 mg  $\geq$ 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:  $\downarrow$  mortality c/w med Rx (albeit pre statins & ACEI/ARB) in Pts w/ 3VD, LM, or 2VD w/ critical prox LAD, and espec. if  $\downarrow$  EF (but viable myocardium);  $\downarrow$  repeat revasc and trend toward  $\downarrow$  D/MI but  $\uparrow$  stroke c/w PCI in LM/3VD (NEJM 2009;360:961); CABG vs. PCI being studied in DM (FREEDOM trial)
- PCI:  $\downarrow$  angina c/w med Rx; does *not*  $\downarrow$  D/MI (COURAGE, NEJM 2007;356:1503); prompt revasc (PCI or CABG) did not  $\downarrow$  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  $\downarrow$  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,  $\downarrow$  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  $<0.8 \rightarrow \downarrow$  # stents &  $\downarrow$  D/MI/revasc (NEJM 2009;360:213)

**PCI**

- Balloon angioplasty (POBA):** effective, but c/b dissection & elastic recoil & neointimal hyperplasia  $\rightarrow$  restenosis; now reserved for small lesions & ? some SVG lesions
- Bare metal stents (BMS):**  $\downarrow$  elastic recoil  $\rightarrow$  33–50%  $\downarrow$  restenosis & repeat revasc (to ~10% by 12 mos) c/w POBA; requires ASA lifelong & clopidogrel  $\times \geq 4$  wks
- Drug-eluting stents (DES):**  $\downarrow$  neointimal hyperplasia  $\rightarrow$  ~75%  $\downarrow$  restenosis, ~50%  $\downarrow$  repeat revasc (to <5% by 1 y), no  $\uparrow$  D/MI c/w BMS (NEJM 2008;359:1330); 2nd gen. everolimus DES promising (NEJM 2010;362:1728); require ASA lifelong & clopidogrel  $\times \geq 1$  y (Circ 2007;115:813)
- Anticoagulant:** UFH (short-acting, rapidly reversible, but need to ✓ PTT/ACT), LMWH (no need for monitoring, but t<sub>1/2</sub> 8–12 h), bivalirudin ( $\downarrow$  bleeding, but  $\pm\uparrow$  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  $\downarrow$  Hct  $\pm$  back pain;  $\uparrow$  HR &  $\downarrow$  BP late; Dx: abd/pelvic CT (I<sup>-</sup>); 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
  - $\downarrow$  perfusion to LE (embolization, dissection, thrombus): loss of distal pulse; Dx: angiogram; 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 antipt 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  $\uparrow$  angina (10% p/w ACS).
  - Due to combination of elastic recoil and neointimal hyperplasia;  $\downarrow$  w/ DES vs. BMS.

# ACUTE CORONARY SYNDROMES

ACS 1-6

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<sub>2</sub> 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<sub>4</sub>, new MR murmur 2° papillary muscle dysfxn, paradoxical S<sub>2</sub>
- Signs of heart failure: ↑ JVP, crackles in lung fields, ⊕ S<sub>3</sub>, 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 <sub>1</sub> –V <sub>2</sub>	Proximal LAD
Anterior	V <sub>3</sub> –V <sub>4</sub>	LAD
Apical	V <sub>5</sub> –V <sub>6</sub>	Distal LAD, LCx, or RCA
Lateral	I, aVL	LCx
Inferior	II, III, aVF	RCA (~85%), LCx (~15%)
RV	V <sub>1</sub> –V <sub>2</sub> & V <sub>4R</sub> (most Se)	Proximal RCA
Posterior	ST depression V <sub>1</sub> –V <sub>3</sub>	RCA or LCx

If ECG non-dx and suspicion high, consider add'l lateral (posterior) leads (V<sub>7</sub>–V<sub>9</sub>) to further assess LCx territory. Check right-sided precordial leads in patients with IMI to help detect RV involvement (STE in V<sub>4R</sub> 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)
<b>History</b>	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)
<b>Exam</b>	HoTN, diaphoresis, CHF, transient MR	PAD or CVD	pain reproduced on palp.
<b>ECG</b>	new STD ( $\geq 1$ 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
<b>Biomarkers</b>	$\oplus$ 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  $\leq 70$ ;  $\emptyset$  prior CAD, CVD, PAD;  $\emptyset$  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	
<b>Nitrates (SL, PO, topical, or IV)</b>	$\downarrow$ anginal sx, no $\downarrow$ in mortality
<b><math>\beta</math>-blockers: PO; IV if ongoing pain, HTN or <math>\uparrow</math> HR (w/o s/s CHF) eg, metoprolol 5 mg IV q5 min <math>\times 3</math> then 25–50 mg PO q6h titrate to HR 50–60</b>	13% $\downarrow$ in progression to MI ( <i>JAMA</i> 1988;260:2259) <i>Contraindicated</i> if HR $< 50$ , SBP $< 90$ , moderate or severe CHF, 2 <sup>o</sup> /3 <sup>o</sup> AVB, severe bronchospasm
<b>CCB (nondihydropyridines)</b>	If cannot tolerate $\beta\beta$ b/c bronchospasm
<b>ACEI or ARB</b>	Especially if CHF or EF $< 0.40$ and if SBP $> 100$
<b>Morphine</b>	Consider if persistent sx or pulmonary edema Should not be used to mask persistent CP
<b>Oxygen</b>	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

<b>Aspirin</b> 162–325 mg $\times 1$ (1 <sup>st</sup> dose crushed/chewed) then 75–325 mg/d	50–70% $\downarrow$ D/MI ( <i>NEJM</i> 1988;319:1105) If ASA allergy, use clopidogrel instead (and desensitize to ASA)
<b>Clopidogrel</b> (ADP receptor blocker) 300 mg $\times 1 \rightarrow 75$ mg/d (requires $\sim 6$ h to steady-state) 600 mg $\times 1 \rightarrow 150$ mg/d $\times 7$ d may $\downarrow$ D/MI/stroke by 15% in PCI Pts (CURRENT/OASIS-7, ESC 2009)	Give in addition to ASA, 20% $\downarrow$ CVD/MI/stroke $\uparrow$ benefit if given upstream prior to PCI but need to wait $> 5$ d after d/c clopi prior to CABG ( <i>NEJM</i> 2001;345:494; <i>Lancet</i> 2001;358:257) $\sim 30\%$ pop have $\downarrow$ fxn CYP2C19 allele $\rightarrow \downarrow$ plt inhib & $\uparrow$ ischemic events ( <i>NEJM</i> 2009;360:354)
<b>Prasugrel</b> (ADP receptor blocker) 60 mg $\times 1 \rightarrow 10$ mg/d (? 5 mg/d if $< 60$ kg)	More rapid ( $\sim 30$ min) and potent plt inhib c/w clopi. 19% $\downarrow$ CVD/MI/stroke in ACS w/ planned PCI vs clopi, but $\uparrow$ bleeding ( <i>NEJM</i> 2007;359:2001). Particularly efficacious in DM ( <i>Circ</i> 2008;118:1626). Avoid if $> 75$ y; contraindic. if h/o TIA/CVA.
<b>Ticagrelor</b> (ADP receptor blocker) 180 mg $\times 1 \rightarrow 90$ mg bid reversible ( $\sim$ nl plt fxn after 72 h) under review at FDA	More rapid ( $\sim 30$ min) and potent plt inhib c/w clopi. 16% $\downarrow$ CVD/MI/stroke & 22% $\downarrow$ death c/w clopi, but with $\uparrow$ non-CABG bleeding ( <i>NEJM</i> 2009;361:1045). $\uparrow$ frequency of dyspnea.
<b>GP IIb/IIIa inhibitors (GPI)</b> 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 $\uparrow$ risk of bleeding ( <i>NEJM</i> 2009;360:2176)

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

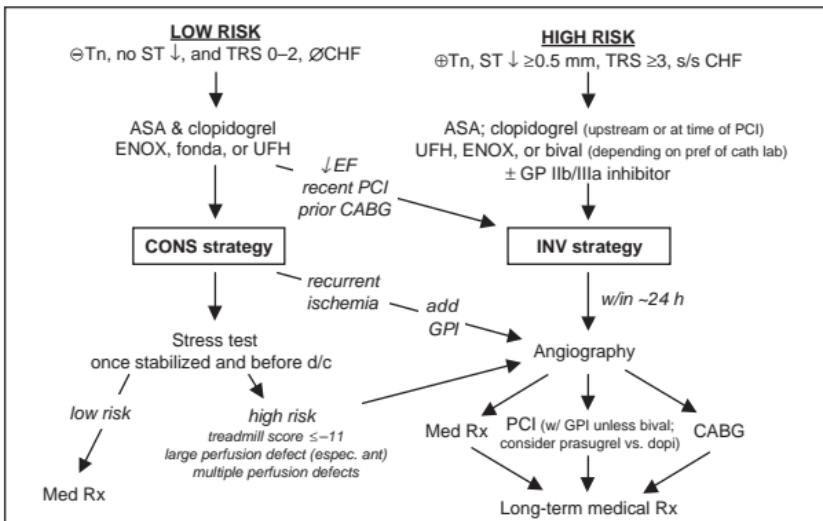
Anticoagulant Therapy	
<b>UFH</b> 60 U/kg IVB (max 4000 U) 12 U/kg/h (max 1000 U/h)	24% ↓ D/MI (JAMA 1996;276:811) titrate to aPTT 1.5–2x cntl (~50–70 sec)
<b>Enoxaparin</b> (low-molecular-weight heparin) 1 mg/kg SC bid × 2–8 d (± 30 mg IVB) (qd if CrCl <30)	Consider instead of UFH. ~10% ↓ D/MI (JAMA 2004;292:89). Benefit greatest if conservative strategy. Can perform PCI on enoxaparin.
<b>Bivalirudin</b> (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).
<b>Fondaparinux</b> (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
<i>Historical</i>		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%
<i>Presentation</i>		6–7	41%
Severe angina (≥2 episodes w/in 24 h)	1	Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH, GP IIb/IIIa inhibitors, and early angiography (JACC 2003;41:895)	
ST deviation ≥0.5 mm	1		
⊕ cardiac marker (troponin, CK-MB)	1		
<b>RISK SCORE = Total points</b>	<b>(0–7)</b>		

Figure 1-2 Approach to UA/NSTEMI



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

## Contraindications to Fibrinolysis

**Absolute Contraindications**

- Any prior ICH
- Intracranial neoplasm, aneurysm, AVM
- Nonhemorrhagic stroke or closed head trauma w/in 3 mo
- Active internal bleeding or known bleeding diathesis
- Suspected aortic dissection

**Relative Contraindications**

- Hx of severe HTN or SBP >180 or DBP >110 on presentation (? absolute contra. if low-risk MI)
- Ischemic stroke >3 mos prior
- Prolonged CPR (>10 min)
- Trauma or major surgery w/in 3 wk
- 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**

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

Clopidogrel: 600 mg pre-PCI, 300 mg if lysis (not if >75 y) → 75 mg/d  
Prasugrel & ticagrelor as above

**GP IIb/IIIa inhibitors**

Lysis: no indication (Lancet 2001;357:1905)  
Peri-PCI: 60% ↓ D/MI/UR (NEJM 2001;344:1895)

abciximab, eptifibatide, tirofiban

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

Anticoagulant Therapy	
<b>UFH</b> 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)
<b>Enoxaparin</b> 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)
<b>Bivalirudin</b> 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)
<b>Fondaparinux</b> 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	
<b>β-blockers</b> 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) <b>Contraindic.</b> if HR <60 or >110, SBP <120, mod/severe CHF, late present, 2°/3° AVB, severe bronchospasm
<b>Nitrates</b> SL or IV	? ~5% ↓ mortality (Lancet 1994;343:1115;1995;345:669) Use for relief of sx, control of BP, or Rx of CHF <b>Contraindic.</b> in hypovolemia, sx RV infarcts, sildenafil
<b>Oxygen</b>	Use if necessary to keep $S_aO_2 > 90\%$ .
<b>Morphine</b>	Relieves pain, ↓ anxiety, venodilation → ↓ preload
<b>ACE inhibitors</b> 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 <b>Contraindicated</b> in severe hypotension or renal failure
<b>ARBs</b>	Appear = ACEI (VALIANT, NEJM 2003;349:20)
<b>Insulin</b>	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<sub>2</sub> demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O<sub>2</sub> 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<sup>2</sup>, 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)

### IMI 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 V4R; 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  $\times$  6–24 h, then reassess;  $\uparrow \beta\text{B}$  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
<b>LV thrombus</b>	~30% incid. (esp. lg antero-apical MI)	Anticoagulate $\times$ 3–6 mo
<b>Ventricular aneurysm</b>	Noncontractile outpouching of LV; 8–15% incid.; persistent STE.	Surgery if recurrent CHF, thromboemboli, arrhythmia
<b>Ventricular pseudoaneurysm</b>	Rupture $\rightarrow$ sealed by thrombus and pericardium	Surgery
<b>Pericarditis</b>	10–20% incid.; 1–4 d post-MI ⊕ pericardial rub; ECG $\Delta$ s rare	High-dose aspirin, NSAIDs Minimize anticoagulation
<b>Dressler's syndrome</b>	<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 <sub>3</sub> and/or basilar rales	17%
III	pulmonary edema	30–40%
IV	cardiogenic shock	60–80%

Forrester Class Mortality								
	PCWP (mmHg)							
	<18	>18						
CI	<table border="1"> <tr> <td>&gt;2.2</td><td>3%</td><td>9%</td></tr> <tr> <td><math>\leq 2.2</math></td><td>23%</td><td>51%</td></tr> </table>	>2.2	3%	9%	$\leq 2.2$	23%	51%	
>2.2	3%	9%						
$\leq 2.2$	23%	51%						

(NEJM 1976;295:1356)

(Am J Cardiol 1967;20:457)

## 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  $\uparrow$  ~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):  $\geq 12$  mos (? longer if DES); some PPIs may interfere with biotransformation of clopidogrel and  $\therefore$  plt inhibition, but no convincing evidence to date of impact on clinical outcomes (*Lancet* 2009;374:989; COGENT, TCT 2009)
- $\beta$ -blocker:** 23%  $\downarrow$  mortality after acute MI
- Statins:** high-intensity lipid-lowering (eg, atorvastatin 80 mg, *NEJM* 2004;350:1495)
- ACEI:** life-long if CHF,  $\downarrow$  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 antiocoagulants: beyond indic. for AF and LV thrombus, comb. of warfarin (goal INR 2–2.5) + ASA  $\downarrow$  D/MI/CVA c/w ASA alone, but  $\uparrow$  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  $\leq 30\text{--}40\%$  (NYHA II–III) or  $\leq 30\text{--}35\%$  (NYHA I); need to wait  $\geq 40$  d after MI (*NEJM* 2004;351:2481 & 2009; 361:1427)

### Risk factors and lifestyle modifications

- Low chol. (<200 mg/dl) & low fat (<7% saturated) diet; LDL goal <70 mg/dL; ? fish oil (*BMJ* 2008;337: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 ( $\geq 30$  mins 3–4  $\times$  per wk); Weight loss with BMI goal 18.5–24.9 kg/m<sup>2</sup>
- Influenza vaccination (*Circ* 2006;114:1549)

**Rationale**

- Cardiac output (CO) =  $SV \times HR$ ; 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)  $\Delta$  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**

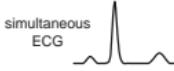
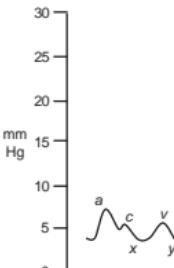
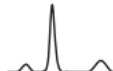
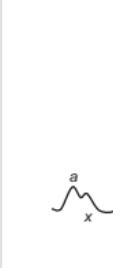
- **Central venous access:** pneumo/hemothorax (1–3%), arterial puncture, air embolism
- **Advancement:** atrial or ventricular arrhythmias (3% VT), RBBB (5%), catheter knotting, cardiac perforation/tamponade, PA rupture
- **Maintenance:** infection (especially if catheter >3 d old), thrombus, pulmonary infarction (≤1%), PA rupture/pseudoaneurysm (esp. w/ PHT), balloon rupture

**Intracardiac pressures**

- Transmural pressure (= preload) = measured intracardiac pressure-intrathoracic pressure
- Intrathoracic pressure (usually slightly  $\ominus$ ) 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  $\oplus$  pressure vent.)
- If ↑ intrathoracic pressure (eg, PEEP), measured PCWP overestimates true transmural pressures. Can approx by subtracting ~½ PEEP (convert cmH<sub>2</sub>O to mmHg by  $\times \frac{3}{4}$ ).
- PCWP: LV preload best estimated at  $a$  wave; risk of pulmonary edema from avg PCWP

**Cardiac output**

- **Thermodilution:** saline injected in RA.  $\Delta$  in temp over time measured at thermistor (in PA) is integrated  $\approx 1/CO$ . Inaccurate if ↓ CO, sev TR, or shunt.
- **Fick method:**  $O_2$  consumption (L/min) = CO (L/min)  $\times$  arteriovenous  $O_2$  difference. CO derived by dividing  $O_2$  consumption by observed AV  $O_2$  difference [ $10 \times 1.34 \text{ ml O}_2/\text{g Hb} \times \text{Hb g/dl} \times (S_vO_2 - S_eO_2)$ ]. Can estimate  $O_2$  consumption using wt-based formula, but best to measure (espec if ↑ metabolism, eg, sepsis). If  $SvO_2 > 80\%$ , 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 $\leq$ 6	syst 15–30 diast 1–8	syst 15–30 mean 9–18 diast 6–12	mean $\leq$ 12
Waves	 	 	 	 
Comment	<p>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</p>	<p>RVEDP occurs right before upstroke and <math>\geq</math> mean RA pressure unless there is TS or TR</p>	<p>Waveform should contain notch (closure of pulmonic valve). Peak during T wave PA systolic = RV systolic unless there is a gradient (eg, PS).</p>	<p>Similar to RA except dampened and delayed. a wave after QRS, <math>\pm</math> distinct c wave, v wave after T (helps distinguish PCWP w/ large v waves 2° MR from PA).</p>

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  $\approx$  LVEDP  $\approx$  LAP  $\approx$  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**  $\approx$  wall stress during LV ejection =  $[(\text{SBP} \times \text{radius}) / (2 \times \text{wall thick.})]$   
and  $\therefore \propto$  MAP and  $\propto$  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 ↑ (&  $\therefore$  CO ↓): temporize w/ pressors until can ↑ CO (see below)  
MAP <60 & SVR low/nl (&  $\therefore$  inappropriate vasoplegia): vasopressors (eg, norepinephrine [ $\alpha$ ,  $\beta$ ], dopamine [D,  $\alpha$ ,  $\beta$ ], phenylephrine [ $\alpha$ ], or vasopressin [V<sub>1</sub>] if refractory)
- **Optimize contractility**  $\propto$  CO for given preload & afterload; goal **CI = (CO / BSA) >2.2**  
if too low despite optimal preload & vasodilators (as MAP permits):  $\oplus$  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  $\pm$  RVAD

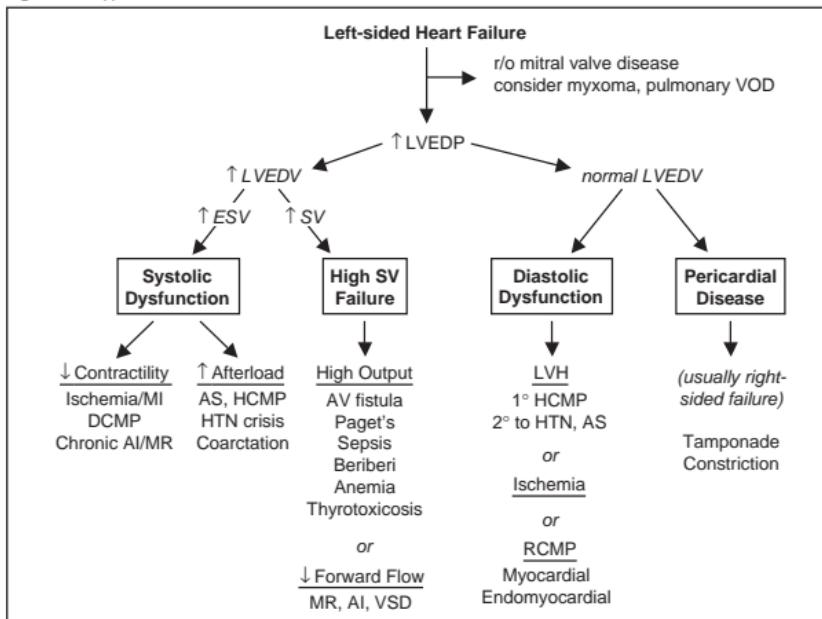
# HEART FAILURE

HF 1-14

## 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;345:574)  
rales, dullness at base 2° pleural effus. (often absent due to lymphatic compensation)  
± hepatomegaly, ascites and jaundice, peripheral edema

### Perfusion ("warm" vs. "cold")

- narrow pulse pressure (<25% of SBP) → CI <2.2 (91% Se, 83% Sp; JAMA 1989;261:884)  
pulsus alternans, cool & pale extremities, ↓ UOP, muscle atrophy
- ± Other: Cheyne-Stokes resp., abnl PMI (diffuse, sustained, or lifting depending on cause of HF),  $S_4$  (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, LHV, 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** ( $\beta$ B, 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"

Lasix w/ monitoring of UOP; high-dose (IVB 2.5× PO dose) vs. low-dose (IVB 1× PO dose) → ↑ UOP but transient ↑ in renal dysfxn; Ø clear diff between cont vs. intermittent (DOSE, ACC 2010)

Morphine ( $\downarrow$  sx, venodilator,  $\downarrow$  afterload)

Nitrates (venodilator)

Oxygen ± noninvasive ventilation (see "Mechanical Ventilation")

Position (sitting up & legs dangling over side of bed →  $\downarrow$  preload)

- For **low perfusion**, see below

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

- Tailored Rx w/ PAC (qv); goals of MAP >60, CI >2.2 (MVO<sub>2</sub> >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  $\leq$ 5  $\mu$ g/kg/min; mild ↓ PVR; desensitization over time
  - dopamine: splanchnic vasodil. → ↑ GFR & natriuresis; vasoconstrict. at  $\geq$ 5  $\mu$ g/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 ↓ impedance 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	
<b>A</b>	High risk for HF Ø 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>B</b>	⊕ Structural heart dis. Asx	Prior MI, ↓ EF, LHV or asx valvular dis.	All measures for stage A ACEI & $\beta$ B if MI/CAD or ↓ EF
<b>C</b>	⊕ Structural heart dis. ⊕ Symptoms of HF (prior or current)	Overt HF	All measures for stage A ACEI, $\beta$ B, diuretics, Na restrict Consider aldactone, ICD, CRT Consider nitrate/hydral, digoxin
<b>D</b>	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)

<b>Treatment of Chronic Heart Failure with Reduced Ejection Fraction</b>	
Diet, exercise	Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
<b>ACEI</b>	↓ mortality: 40% in NYHA IV, 16% in NYHA II/III, 20% in asx, post-MI, EF ≤40% ( <i>NEJM</i> 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% ( <i>SOLVD-P</i> , <i>NEJM</i> 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
<b>ATII receptor blockers (ARBs)</b>	Consider as alternative if cannot tolerate ACEI (eg, b/c cough) Noninferior to ACEI ( <i>VALIANT</i> , <i>NEJM</i> 2003;349:1893) Good alternative if ACEI intol ( <i>CHARM-Alternative</i> , <i>Lancet</i> 2003;362:772) As with ACEI, higher doses more efficacious ( <i>Lancet</i> 2009;374:1840) ? ↓ HF ( <i>Val-HEFT</i> , <i>NEJM</i> 2001;345:1667) and ↓ mort. when added to ACEI ( <i>CHARM-Added</i> , <i>Lancet</i> 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. ( <i>NEJM</i> 1986;314:1547); infer. to ACEI ( <i>NEJM</i> 1991;325:303) 40% ↓ mort. in blacks on standard Rx ( <i>A-HEFT</i> , <i>NEJM</i> 2004;351:2049)
<b>β-blocker</b> (data for carvedilol, metoprolol, bisoprolol)	EF will transiently ↓, then ↑. Contraindic. in decompensated HF. 35% ↓ mort. & 40% ↓ rehosp. in NYHA II–IV ( <i>JAMA</i> 2002;287:883) Carvedilol superior to low-dose metoprolol ( <i>Lancet</i> 2003;362:7)
<b>Aldosterone antagonists</b>	Consider if HF severe or post-MI, adeq. renal fxn; watch for ↑ K 30% ↓ mort. in NYHA III/IV & EF ≤35% ( <i>RALES</i> , <i>NEJM</i> 1999;341:709) 15% ↓ mort. in HF post-MI, EF ≤40% ( <i>EPHESUS</i> , <i>NEJM</i> 2003;348:1309)
<b>Cardiac resynchronization therapy (CRT)</b>	Consider if EF ≤35%, QRS ≥120 ms, and symptomatic 36% ↓ mort. & ↑ EF in NYHA III–IV ( <i>CARE-HF</i> , <i>NEJM</i> 2005;352:1539) ↓ HF if EF <30% & NYHA I/II, espec if QRS ≥150 ms, no Δ in mortality ( <i>NEJM</i> 2009;361:1329) No single measure of dyssynchrony on echo improves Pt selection for CRT ( <i>Circ</i> 2008;117:2608)
<b>ICD</b>	Use for 1° prevention if sx & EF ≤35% or for 2° prevention ↓ mort. in Pts w/ MI & EF ≤30% ( <i>NEJM</i> 2002;346:877); no Δ mort. early post-MI ( <i>NEJM</i> 2004;351:2481; 2009;361:1427), ∴ wait ≥40 d 23% ↓ mort. in all DCMP, EF ≤35% ( <i>SCD-HeFT</i> , <i>NEJM</i> 2005;352:225) ↓ arrhythmic death in nonisch DCMP ( <i>DEFINITE</i> , <i>NEJM</i> 2004;350:2151)
Diuretics	Loop ± thiazides diuretics (sx relief; no mortality benefit)
Digoxin	23% ↓ HF hosp., no Δ mortality ( <i>NEJM</i> 1997;336:525) ? ↑ mort. in women, ? related to ↑ levels ( <i>NEJM</i> 2002;347:1403) ? optimal dig concentration 0.5–0.8 ng/mL ( <i>JAMA</i> 2003;289:871)
Ω-3 fatty acids	9% ↓ mortality ( <i>Lancet</i> 2008;372:1223)
Anticoagulation	Consider if AF, LV thrombus, large akinetic LV segment, EF <30%
Heart rhythm	Catheter ablation of AF → ↑ in EF, ↓ sx ( <i>NEJM</i> 2004;351:2373) No mortality benefit to AF rhythm vs. rate ctrl ( <i>NEJM</i> 2008;358:2667) For sx AF, pulm vein isolation improves sx c/w AVN ablation & CRT ( <i>NEJM</i> 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

CMP  
1-17

## 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;326:77)
- **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<sup>2</sup>, 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<sub>1</sub>–V<sub>3</sub>, 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<sub>3</sub>, ± 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  $\geq 15$  mm) and/or RV hypertrophy disproportionate to hemodynamic load
- Prevalence: 1 case/500 population; 50% sporadic, 50% familial
- Differentiate from  $2^\circ$  LVH: hypertension (espc. elderly women; NEJM 1985;312:277), AS, elite athletes (wall thickness usually  $< 13$  mm & symmetric and nl/ $\uparrow$  rates of tissue Doppler diastolic relaxation; NEJM 1991;324:295), Fabry dis. ( $\uparrow$  Cr, skin findings)

## Pathology

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

## Pathophysiology

- Subaortic outflow obstruction: narrowed tract  $2^\circ$  hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (may be fixed, variable, or nonexistent) and papillary muscle displacement. Gradient ( $\nabla$ ) worse w/  $\uparrow$  contractility (digoxin,  $\beta$ -agonists),  $\downarrow$  preload, or  $\downarrow$  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:  $\uparrow$  chamber stiffness + impaired relaxation
- Ischemia: small vessel dis., perforating artery compression (bridging),  $\downarrow$  coronary perfusion
- Syncope:  $\Delta s$  in load-dependent CO, arrhythmias

## Clinical manifestations (70% are asymptomatic at dx)

- **Dyspnea** (90%): due to  $\uparrow$  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)  $\rightarrow$  palpitations, syncope, sudden cardiac death

## Physical exam

- Sustained PMI, S<sub>2</sub> paradox. split if severe outflow obstruction,  $\oplus$  S<sub>4</sub> (occ. palpable)
- **Systolic crescendo-decrescendo murmur** at LLSB:  $\uparrow$  w/ **Valsalva** & standing
- $\pm$  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  $\downarrow$  w/ Valsalva and  $\downarrow$  carotid pulses

## Diagnostic studies

- CXR: cardiomegaly (LV and LA)
- ECG: LVH, anterolateral and inferior pseudo-Qw,  $\pm$  apical giant TWI (apical variant)
- **Echo**: no absolute cutoffs for degree of LVH but septum / post wall  $\geq 1.3$  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  $\nabla$ ; **Brockenbrough sign** =  $\downarrow$  pulse pressure post-extrasystolic beat (in contrast to AS, in which pulse pressure  $\uparrow$  postextrasystole)

## Treatment (NEJM 2004;350:1320)

- Heart failure
  - ⊖ **inotropes/chronotropes**:  $\beta$ -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* ( $\nabla > 50$  mmHg):
    - a) Alcohol septal ablation (NEJM 2002;347:1326)  
triphasic  $\nabla$  response: acute  $\downarrow \rightarrow \pm$  partial  $\uparrow$  back to 50% of baseline  $\rightarrow \downarrow$  over months by 1 y resting  $\nabla \sim 15$  mmHg & stress-induced  $\nabla \sim 31$  mmHg (J Interv Card 2006;19:319)  
complications: transient (& occ. delayed)  $3^\circ$  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,  $\beta$ B, phenylephrine
  - AF: rate control with  $\beta$ -blockers, maintain SR with disopyramide, amiodarone
  - Sudden cardiac death: ICD (JACC 2003;42:1687). Major risk factors include history of VT/VF,  $\oplus$  FHx SCD, unexplained syncope, NSVT,  $\downarrow$  SBP or relative HoTN ( $\uparrow$  SBP  $< 20$  mmHg) w/ exercise, LV wall  $\geq 30$  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%), batrial enlargement (40%), thickened atrial septum, valve thickening (65%), diastolic dysfxn, small effusion

normal voltage & normal septal thickness has NPV ~90%

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

**sarcoidosis:** age at present. ~30 y; more common in blacks, N. Europeans, women

5% of those with sarcoid w/ overt cardiac involvement; cardiac w/o systemic in 10%  
ECG: AVB (75%), RBBB (20–60%), VT

Echo: regional WMA (particularly basal septum) with thinning or mild hypertrophy  
nuclear imaging: gallium uptake in areas of sestamibi perfusion defects

**hemochromatosis:** presents in middle-aged men (particularly N. European)

storage diseases: Gaucher's, Fabry, Hurler's, glycogen storage diseases

diabetes mellitus

#### • **Endomyocardial processes**

chronic eosinophilic: Löffler's endocarditis (temperate climates; ↑ eos.; mural thrombi that embolize); endomyocardial fibrosis (tropical climates; var. eos.; mural thrombi)

toxins: radiation, anthracyclines

serotonin: carcinoid, serotonin agonists, ergot alkaloids

metastatic cancer

### **Pathology & pathophysiology**

- Path: normal or ↑ wall thickness ± infiltration or abnormal deposition
- ↓ myocardial compliance → 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<sub>3</sub> and S<sub>4</sub>, ± 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, batrial 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

# VALVULAR HEART DISEASE

## AORTIC STENOSIS (AS)

### Etiology

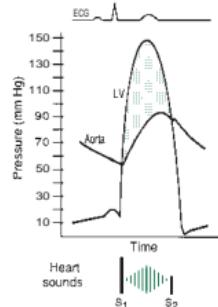
- Calcific:** predominant cause in Pts >70 y; risk factors include HTN, ↑ chol., ESRD
- Congenital** (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- Rheumatic heart disease** (AS usually accompanied by AI and MV disease)
- AS mimickers:** subvalvular (HCMP, subAo membrane),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

### Clinical manifestations (usually indicates AVA < 1 cm<sup>2</sup> or concomitant CAD)

- Angina:** ↑ O<sub>2</sub> demand (hypertrophy) + ↓ O<sub>2</sub> supply (↓ cor perfusion pressure) ± CAD
- Syncope** (exertional): peripheral vasodil. w/ fixed CO → ↓ MAP → ↓ cerebral perfusion
- Heart failure:** outflow obstruction + 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<sup>2</sup> 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<sub>2</sub> or inaudible A<sub>2</sub>, small and delayed carotid pulse ("pulsus parvus et tardus"), LV heave, ⊕ S<sub>4</sub> (occasionally palpable)



### Diagnostic studies

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

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

Classification of Aortic Stenosis				
Stage	Mean Gradient (mmHg)	Jet Vel. (m/s)	AVA (cm <sup>2</sup> )	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*	↓

\*AVAI index (AVA relative to BSA) <0.6 cm<sup>2</sup>/m<sup>2</sup> 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<sup>2</sup>, 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 Δ, 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<sup>2</sup> (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

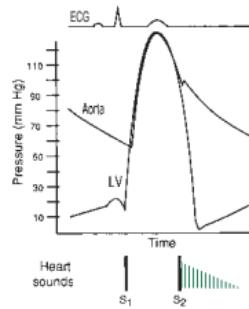
aortic inflammation: giant cell, Takayasu's, ankylosing spond., reactive arthritis, syphilis

### 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<sub>1</sub> (early closure of MV); ± S<sub>3</sub> (≠ ↓ 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<sup>2</sup>, 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)

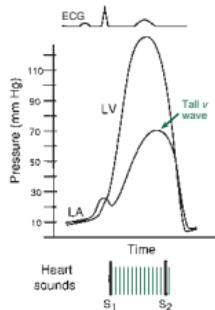
- Leaflet abnormalities:** myxomatous degeneration (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs
- Functional:** inferoapical papillary muscle displacement due to ischemic LV remodeling or other causes of DCMP; LV annular dilation due to LV dilation
- 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)]
- HCM: (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<sub>1</sub>, widely split S<sub>2</sub> (A<sub>2</sub> early b/c ↓ LV afterload, P<sub>2</sub> late if PHT); ± S<sub>3</sub>
- 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 cr 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 <sup>2</sup> )	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 (dobutamine), 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: Ø 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

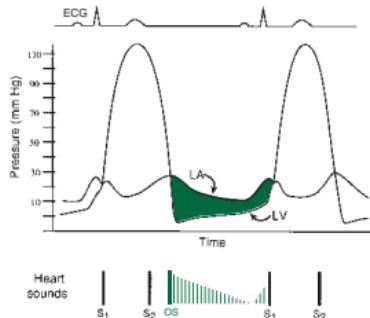
- Rheumatic heart disease (RHD):** fusion of commissures → "fish mouth" valve from autoimmune rxn to β strep infxn; seen largely in developing world today
- Mitral annular calcification (MAC):** encroachment upon leaflets → functional MS
- Congenital, infectious endocarditis w/ large lesion, myxoma, 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<sub>2</sub>–OS interval (tighter valve → ↑ LA pressure → shorter interval)
- Loud S<sub>1</sub> (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 (ΔV), 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: ΔV 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 <sup>2</sup> )	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 ΔV 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, ΔV ↓ 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 V)
- 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

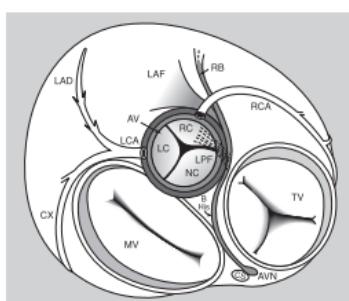
### Endocarditis prophylaxis (see “Endocarditis”)

- 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 2x 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

# PERICARDIAL DISEASE

## GENERAL PRINCIPLES

### Anatomy

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

### Disease states

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

## PERICARDITIS AND PERICARDIAL EFFUSION

Etiologies of Pericarditis ( <i>Lancet</i> 2004;363:717)	
<b>Infectious</b> (50%)	Viral: Coxsackie, echo, adeno, EBV, VZV, HIV, influenza Bacterial (from endocarditis, pneumonia, or s/p cardiac surgery): <i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>S. aureus</i> , <i>Borrelia</i> (Lyme) Tuberculous (extension from lung or hematogenous) Fungal: <i>Histo</i> , <i>Coccidioides</i> , <i>Candida</i> ; Parasitic: <i>Entamoeba</i> , <i>Echino</i>
<b>Neoplastic</b> (35%)	Common: metastatic (lung, breast, lymphoma, leukemia, renal cell) Rare: primary cardiac & serosal tumors (mesothelioma)
<b>Autoimmune</b>	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, Churg-Strauss, Wegener's Drug-induced: procainamide, hydralazine, INH, CsA
<b>Uremia</b>	Develops in ~20% of Pts, especially if on HD. May be transudative.
<b>Cardiovascular</b>	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
<b>Radiation</b>	>4,000 cGy to mediastinum; acute or delayed; may be transudative
<b>Idiopathic</b>	Most presumed to be undiagnosed viral
<b>Effusions w/o pericarditis</b>	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 (*EJH* 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:  $TP > 3 \text{ g/dL}$ ,  $TP_{\text{eff}}/TP_{\text{serum}} > 0.5$ ,  $LDH_{\text{eff}}/LDH_{\text{serum}} > 0.6$ , or  $\text{glc} < 60 \text{ mg/dL}$
  - 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)  $\pm$  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: ?  $\uparrow$  rate of relapse, and  $\uparrow$  osteoporosis, Cushing's (Circ 2008;118:667).
- Avoid anticoagulants
- Infectious effusion  $\rightarrow$  pericardial drainage (preferably surgically) + systemic antibiotics
- Acute idiopathic effusion self-limited in 70–90% of cases
- Recurrent effusion  $\rightarrow$  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 ( $\uparrow$  compliance) and accommodate fluid

### Pathophysiology (NEJM 2003;349:684)

- $\uparrow$  intrapericardial pressure, compression of heart chambers,  $\downarrow$  venous return  $\rightarrow$   $\downarrow$  CO
- Diastolic pressures  $\uparrow$  & equalize in all cardiac chambers  $\rightarrow$  minimal flow of blood from RA to RV when TV opens  $\rightarrow$  blunted y descent
- $\uparrow$  ventricular interdependence  $\rightarrow$  pulsus paradoxus (pathologic exaggeration of nl physi)
  - Inspiration  $\rightarrow$   $\downarrow$  intrapericardial & RA pressures  $\rightarrow$   $\uparrow$  venous return  $\rightarrow$   $\uparrow$  RV size  $\rightarrow$  septal shift to left. Also,  $\uparrow$  pulmonary vascular compliance  $\rightarrow$   $\downarrow$  pulm venous return.
  - Result is  $\downarrow$  LV filling  $\rightarrow$   $\downarrow$  LV stroke volume & blood pressure.

### Clinical manifestations

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

### Physical exam (JAMA 2007;297:1810)

- **Beck's triad** (present in minority): **distant heart sounds,  $\uparrow$  JVP, hypotension**
- $\uparrow$  JVP (76%) w/ blunted y descent
- Reflex tachycardia (77%), hypotension (26%; occasionally hypertensive), cool extremities
- **Pulsus paradoxus** (Se 82%, Sp 70%) =  $\downarrow$  SBP  $\geq 10 \text{ mmHg}$  during inspiration
  - $\ominus$  LR 3.3 (5.9 if pulsus  $>12$ ),  $\ominus$  LR 0.03
  - Ddx = PE, hypovolemia, severe obstructive lung disease, constriction (~1/3), CHF
  - Can be absent if pre-existing  $\uparrow$  LVEDP, cardiac arrhythmia, or regional tamponade
- Distant heart sounds (28%),  $\pm$  pericardial friction rub (30%)
- Tachypnea but clear lungs

### Diagnostic studies

- ECG:  $\downarrow$  voltage (seen in 42%), electrical alternans,  $\pm$  signs of pericarditis
- CXR:  $\uparrow$  cardiac silhouette (89%)
- **Echocardiogram:**  $\oplus$  effusion, IVC plethora, **septal shift** with inspiration, **diastolic collapse** of RA (Se 85%, Sp 80%) and/or RV (Se  $<80\%$ , Sp 90%)
  - respirophasic  $\Delta$ 's in transvalvular velocities ( $\uparrow$  across TV &  $\downarrow$  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
  - $\uparrow$  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  $\oplus$  inotropes (avoid  $\beta$ B)
- **Pericardiocentesis** (except if due to aortic or myocardial rupture, in which cases consider removing just enough fluid to reverse PEA while awaiting surgery)

## CONSTRICITIVE 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**,  $\oplus$  **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:  $\pm$  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 pericardectomy

Constrictive Pericarditis vs. Restrictive Cardiomyopathy		
Evaluation	Constrictive pericarditis	Restrictive cardiomyopathy
Physical exam	$\oplus$ Kussmaul's sign Absent PMI $\oplus$ Pericardial knock	$\pm$ Kussmaul's sign Powerful PMI, $\pm$ S <sub>3</sub> and S <sub>4</sub> $\pm$ <b>Regurg murmur of MR, TR</b>
ECG	$\pm$ Low voltage	Low voltage $\pm$ <b>Conduction abnormalities</b>
Echocardiogram	Normal wall thickness <b>Septal bounce during early diastole</b> Inspir. → ↑ flow across TV and ↓ flow across MV E' (tissue velocity) nl/t Expir. hepatic vein flow reversal	$\pm$ ↑ wall thickness <b>Biatrial enlargement</b> Inspir. → ↓ flow across TV & MV Slower peak filling rate Longer time to peak filling rate E' ↓ Inspir. hepatic vein flow reversal
CT/MRI	<b>Thickened pericardium</b>	Normal pericardium
Cardiac catheterization	Prominent x and y descents Dip-and-plateau sign LVEDP = RVEDP RVSP < 55 (Se 90%, Sp 29%) RVEDP > 1/3 RVSP (Se 93%, Sp 46%) <b>Discordance of LV &amp; RV pressure peaks during respiratory cycle</b> <b>Systolic area index</b> (ratio of RV to LV pressure-time area in inspir vs. expir) $> 1.1$ (Se 97%, Sp 100%)	<b>LVEDP &gt; RVEDP</b> (espec. w/ vol.) RVSP > 55 mmHg RVEDP < 1/3 RVSP Concordance of LV & RV pressure peaks during respiratory cycle Systolic area index $\leq 1.1$ (JACC 2008;51:315)
Endomyocardial biopsy	Usually normal	$\pm$ <b>Specific etiology of RCMP</b>

# 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 microvascular 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
<b>RENAL</b>	<b>Renal parenchymal</b> (2–3%)	h/o DM, polycystic kidney disease, glomerulonephritis	CrCl, albuminuria See "Renal Failure"
	<b>Renovascular</b> (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)
<b>ENDO</b>	<b>Hyperaldo or Cushing's</b> (1–5%)	Hypokalemia Metabolic alkalosis	See "Adrenal Disorders"
	Pheochromocytoma (<1%)	Paroxysmal HTN, H/A, palp.	
<b>OTHER</b>	Myxedema (<1%)	See Thyroid Disorders	TFTs
	Hypercalcemia (<1%)	Polyuria, dehydration, Δ MS	ICa
<b>Obstructive sleep apnea</b> (qv)			
<b>Medications:</b> OCP, steroids, licorice; NSAIDs (espec. COX-2); Epo; cyclosporine Coarctation of aorta: ↓ LE pulses, systolic murmur, radiofemoral delay; abnl TTE, CXR 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, glic, 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'ng 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 CRISIS

- **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 & thoracoabdominal 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  $\propto [(\Delta P \times r) / (\text{wall thickness})]$
- **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:**  $\beta$ -blockers ( $\downarrow$  dP/dt)  $\downarrow$  aneurysm growth (NEJM 1994;330:1335); **ACEI** a/w  $\downarrow$  risk of rupture (Lancet 2006;368:659), **ARB** may  $\downarrow$  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  $\geq 5.5$  cm; descending  $>6$  cm; Marfan Pt  $\geq 4.0$ – $4.5$  cm; growing  $>0.5$  cm/y; aneurysm  $\geq 4.5$  cm and planned AoV surgery
  - AAA:**  $\geq 5$  cm; rapidly growing; infrarenal/juxtarenal  $\geq 5.5$  cm (NEJM 2002;346:1437)
- **Endovascular aneurysm repair (EVAR)** (NEJM 2008;358:494)
  - $\downarrow$  short-term mortality, bleeding, and length of stay, but, long-term graft complications (2–5%/y; leak, rupture) necessitating periodic surveillance and no  $\Delta$  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:  $\downarrow$  aneurysm mortality but no  $\Delta$  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  $\uparrow$  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  $\uparrow$  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  $\sim 0.1$  cm/y for TAA,  $\sim 0.4$  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); arachnodactyl, joint disloc., pectus, ectopia lentis, MVP; Ehlers-Danlos type IV (type III procollagen); translucent skin; bowel or uterine rupture; Loey-Dietz; annuloaortic ectasia, familial AoD; PCKD
- **Congenital aortic anomaly:** bicuspid aortic valve or coarctation (eg, in Turner's)
- **Aortitis:** Takayasu's, giant cell arteritis, Behcet'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<sub>4</sub> 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 → LMI, 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 <b>AV node</b> 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 <b>His-Purkinje system</b> 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  $\geq 2$  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* ( $A \approx V$  rate, ∴ some P's non-conducting)

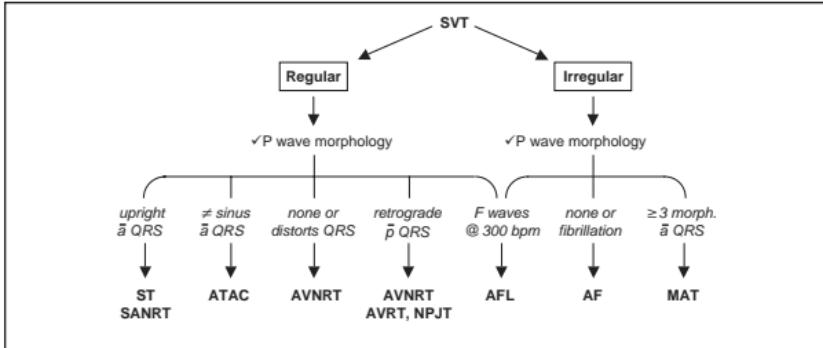
## SUPRAVENTRICULAR TACHYCARDIAS (SVTs)

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)	
<b>Onset</b>	Abrupt onset/offset suggests reentry (AVNRT, AVRT, SANRT)
<b>Rate</b>	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
<b>Rhythm</b>	Irregular → AF, AFL w/ variable block, or MAT
<b>P wave morphology</b>	Before QRS → ST, AT (P different from sinus), MAT ( $\geq 3$ 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 <sub>1</sub> ) 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 <sub>1</sub> ) → AFL
<b>Response to vagal stim. or adenosine</b>	↑ 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**

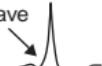
Rhythm	Acute treatment	Long-term treatment
Unstable	<b>Cardioversion</b> per ACLS	n/a
ST	Treat underlying stressor(s)	n/a
AT	$\beta$ -blockers, CCB, or amiodarone	$\beta$ -blockers or CCB, $\pm$ antiarrhythmics ? Radiofrequency ablation
AVNRT or AVRT	<b>Vagal maneuvers</b> <b>Adenosine</b> (caution in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

\*Avoid adenosine &amp; 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 IML); 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**

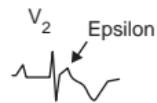
- AVRT:** vagal maneuvers, βB, ? CCB; caution w/ adenosine (can precip. AF); have defibrillator ready
- AF/AFL** w/ conduction down accessory pathway: need to Rx arrhythmia and ↑ pathway refractoriness; use procainamide, ibutilide, flecainide or cardiovert; avoid CCB & βB (ineffective) and digadenosine (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

**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<sub>1</sub> = 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<sub>1-3</sub> 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<sub>1-3</sub> (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<sub>1</sub>, r/S ratio <1 in V<sub>6</sub>
  - LBBB-type: onset to nadir >60–100 ms in V<sub>1</sub>, q wave in V<sub>6</sub>
  - 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 (espc 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)

# atrial fibrillation

## Classification (JACC 2006;48:e149)

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

## Epidemiology and Etiologies (Annals 2008;149:ITC5-2)

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

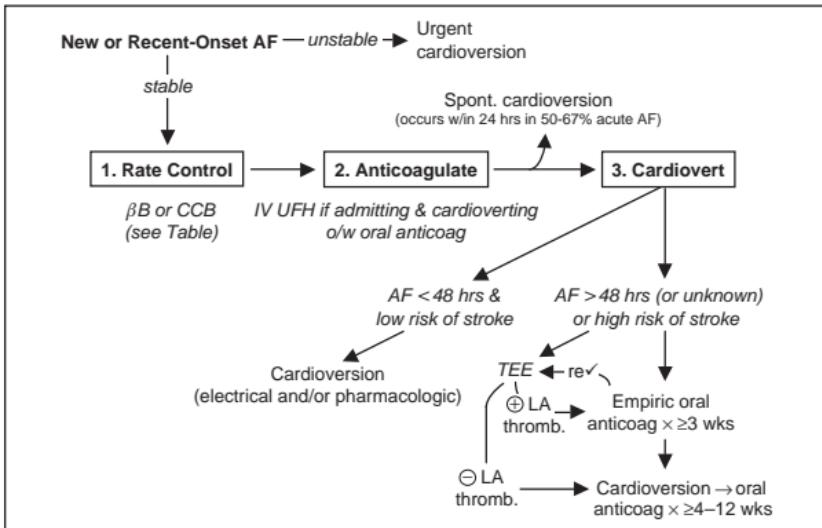
## Pathophysiology (NEJM 1998;339:659; & Circ 1995;92:1954)

- 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
	Propranolol	1 mg q2'	80–240 mg/d in divided doses  Preferred if CAD
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.g., 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
IC	Sotalol	n/a	90–160 mg bid	✓ for ↓ HR, ↑ QT Renally adjust dose
	Flecainide	300 mg PO × 1	100–150 mg bid	PreRx w/ AVN blocker
IA	Propafenone	600 mg PO × 1	150–300 mg tid	Contraindic. if structural or ischemic heart disease
	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;133:5465)

- Risk of stroke ~4.5% per year in nonvalvular AF; risk factors include:
  - CHADS<sub>2</sub>:** CHF (1 point), HTN (1), Age >75 y (1), DM (1), **prior Stroke/TIA** (2)
  - echo: EF ≤35%, dense spontaneous echo contrast in LAA, ? ↑ LA size, ? Ao athero
- Risk of stroke ↑ in valvular AF, ~ anticoagulate all
- Rx options: **warfarin** (INR 2–3) → 68% ↓ stroke (heparin → warfarin bridge if h/o stroke)
  - ASA (81–325 mg/d): better than placebo (21% ↓ stroke) but inferior to warfarin
  - 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<sub>3</sub>), murmurs, LVH (S<sub>4</sub>, LV heave), PHT (RV heave, ↑ P<sub>2</sub>)  
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)

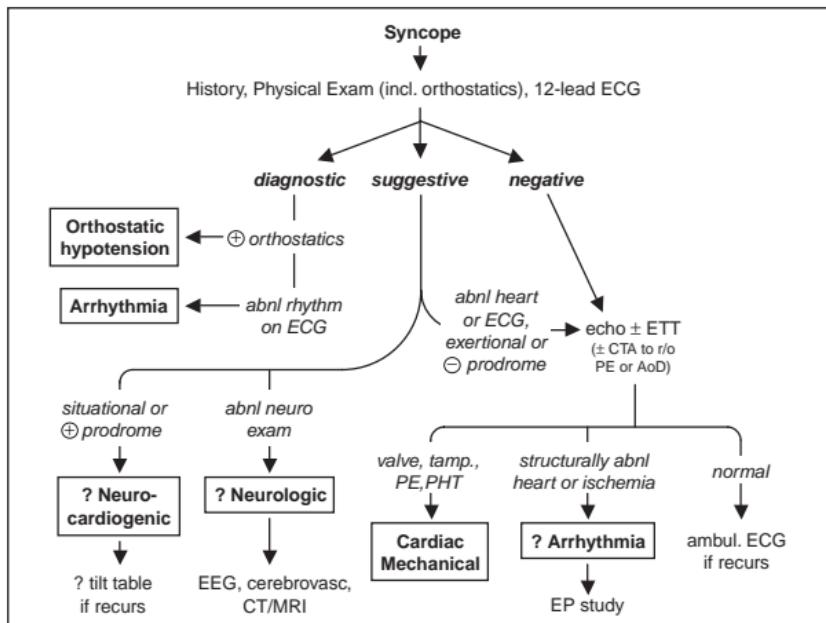
- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope  
Holter monitoring (continuous ECG 24–48 h): useful if frequent events arrhythmia + sx (4%); asx but signif. arrhythmia (13%); sx but no arrhythmia (17%)
- Event recorder (activated by Pt to record rhythm strip): useful for infrequent events, 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%; reproduc. ≤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<sub>2</sub>O 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).

# INTRACARDIAC DEVICES

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

Common Pacing Modes	
<b>VVI</b>	Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia.
<b>DDD</b>	A & V sensing & pacing (RA & RV leads). Sensed A beat inhibits A pacing & triggers V pacing → tracking of intrinsic atrial activity. Maintains AV synchrony.
<b>Magnet</b> (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)	
<b>AV block</b>	Symptomatic 3° or 2° AVB; ? asx 3° or type II 2° AVB HR <40; pauses ≥3 sec while awake; alternating L and R BBB
<b>Sinus node</b>	SB or pauses a/w sx or ? if sx w/o clear assoc. Chronotropic incompt.
<b>Acute MI</b>	See "STEMI"
<b>Tachy-arrhythmia</b>	Sx recurrent SVT that can be term. by pacing after failing drugs & ablation
<b>Syncope</b>	Sustained pause-dependent VT; ? high-risk Pts w/ congenital long QT 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
<b>CMP</b>	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<sub>1</sub> 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* bacteraemia (even w/o s/s and w/ ⊖ TTE/TEE)
- Treatment: abx and removal of system

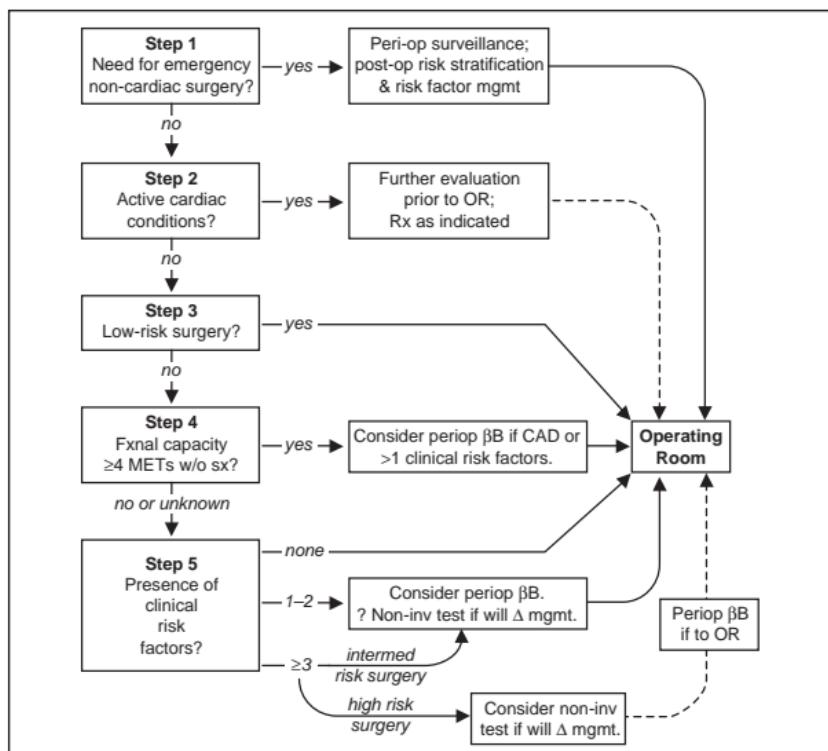
# CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

PREOP EVAL 1-40

Clinical Assessment		
Active Cardiac Conditions		Clinical Risk Factors
<ul style="list-style-type: none"> <li>MI w/in 30 d or current unstable or severe angina</li> <li>Decompensated HF</li> <li>Significant arrhythmia (eg, high-grade AVB, Mobitz II, 3° AVB, new or sx VT, SVT w/ HR &gt;100, sx brady)</li> <li>Severe AS or sx MS</li> </ul>		<ul style="list-style-type: none"> <li>h/o CAD</li> <li>h/o HF</li> <li>h/o Cerebrovascular dis.</li> <li>Diabetes mellitus</li> <li>Renal insuffic. (Cr &gt;2 mg/dL)</li> </ul>
Surgery-Specific Risk		
High (>5% risk)	Intermediate (1-5%)	Low (<1%)
<ul style="list-style-type: none"> <li>Aortic or other major vascular</li> <li>Peripheral vasc.</li> </ul>	<ul style="list-style-type: none"> <li>Intrathoracic; intraperitoneal; prostate</li> <li>CEA; head &amp; neck</li> <li>Orthopedic</li> </ul>	<ul style="list-style-type: none"> <li>Endoscopic</li> <li>Breast; superficial</li> <li>Cataract; ambulatory</li> </ul>
Functional Capacity		
1-4 METs	4-10 METs	>10 METs
<ul style="list-style-type: none"> <li>ADLs</li> <li>Walk indoors</li> <li>Walk 1-2 level blocks</li> </ul>	<ul style="list-style-type: none"> <li>Climb a flight of stairs/hill</li> <li>Walk briskly; heavy housework</li> <li>Golf, doubles tennis</li> </ul>	<ul style="list-style-type: none"> <li>Strenuous sports</li> </ul>
Noninvasive Testing Result		
High risk	Intermediate risk	Low risk
<b>Ischemia at &lt;4 METs manifested by ≥ 1 of:</b> <ul style="list-style-type: none"> <li>Horiz/down ST ↓ ≥ 1 mm or STE</li> <li>≥ 5 abnl leads or &gt; 3 min after exert</li> <li>SBP ↓ 10 mmHg or typical angina</li> </ul>	<b>Ischemia at 4-6 METs manifested by ≥ 1 of:</b> <ul style="list-style-type: none"> <li>Horiz/down ST ↓ ≥ 1 mm</li> <li>3-4 abnl leads</li> <li>1-3 min after exert</li> </ul>	<b>No ischemia or at &gt;7 METs w/</b> <ul style="list-style-type: none"> <li>ST ↓ ≥ 1 mm or</li> <li>1-2 abnl leads</li> </ul>

## Preoperative evaluation

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



## Pre-operative testing and therapy

- ECG if  $\geq 1$  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/  $\geq 3$  risk factors & it will  $\Delta$  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  $\Delta$  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  $\downarrow$  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  $\ominus$  ETT or  $\oplus$  ETT & revascularized). If no revasc, wait 6 mo before elective surgery.
- Preop statins:  $\downarrow$  ischemia & CV events in Pts undergoing vascular surg (NEJM 2009;361:980)

## Perioperative $\beta$ -blocker use (Circ 2009;120:2123; JAMA 2010;303:551)

- Conflicting evidence regarding efficacy of  $\beta$ B for  $\downarrow$  periop events. Some studies have shown  $\downarrow$  cardiac death & MI (NEJM 1996;335:1713 & 1999;341:1789) whereas another  $\downarrow$  MI but  $\uparrow$  death & stroke and  $\uparrow$  bradycardia/HoTN (Lancet 2008;371:1839).
- Consider periop  $\beta$ B if CAD,  $\oplus$  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  $\sim 55$ –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  $\Delta$ s or chest pain suggestive of ACS

# NOTES

# DYSPNEA

Pathophysiology	Etiologies
<b>Airway obstruction</b> (↑ resistance to airflow)	<b>Asthma, COPD, bronchiectasis</b> (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
<b>Parenchymal disease</b> (↑ resistance to expansion)	<b>Pulmonary edema:</b> cardiogenic (LV systolic or diastolic dysfxn) or noncardiogenic (ALI/ARDS) <b>ILD</b>
<b>Vascular</b> (V/Q mismatch)	Large vessel: <b>PE</b> , tumor emboli Small vessel: <b>PHT</b> , vasculitis, ILD, emphysema
<b>Bellows</b> (↑ resistance to CW/diaphragm expansion; weakness of respiratory muscles)	<b>Pleural disease:</b> effusion, fibrosis <b>Chest wall/diaphragm:</b> kyphoscoliosis, ↑ abd girth <b>Neuromuscular disorders</b> Hyperinflation (COPD, asthma)
<b>Stimulation of receptors</b>	Chemoreceptors: <b>hypoxemia</b> , metabolic acidosis Mechanoreceptors: <b>ILD, pulmonary edema, PHT, PE</b>
↓ O <sub>2</sub> carrying cap. (but nl P <sub>a</sub> O <sub>2</sub> )	<b>Anemia</b> , methemoglobinemia, CO poisoning
<b>Psychological</b>	Anxiety, panic attack, depression, somatization

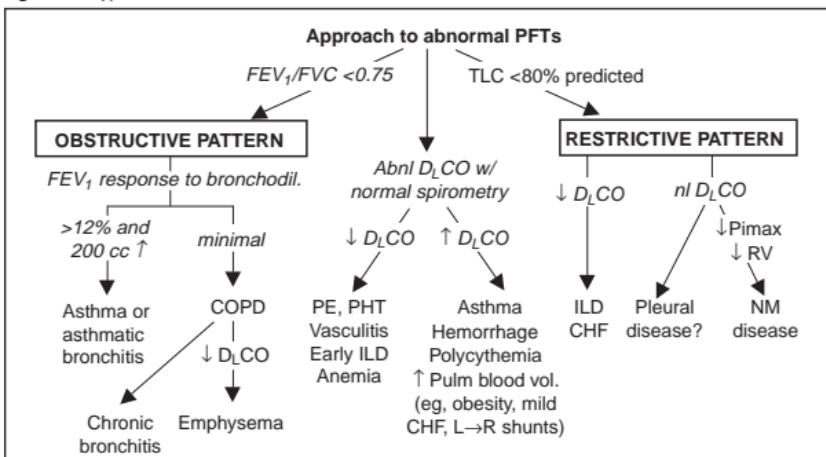
## Evaluation

- Cardiopulmonary exam, S<sub>3</sub>O<sub>2</sub>, CXR (see Appendix & Radiology inserts), ECG predictors of CHF: h/o CHF, PND, S<sub>3</sub>, 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 (*EJH* 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<sub>1</sub> → asthma
- Lung volumes:** evaluate for restrictive disease including NM causes
- D<sub>L</sub>CO:** evaluates functional surface area for gas exchange; helps differentiate causes of obstructive and restrictive diseases and screens for vascular disease & early ILD

Figure 2-1 Approach to abnormal PFTs



# 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,  $\beta$ B via bronchospasm, MSO<sub>4</sub> 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<sub>1</sub>, ↓ FEV<sub>1</sub>/FVC, coved flow-volume loop; lung volumes: ± ↑ RV & TLC
  - ⊕ bronchodilator response (↑ FEV<sub>1</sub> ≥12%) strongly suggestive of asthma
  - methacholine challenge (↓ FEV<sub>1</sub> ≥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  $\beta_2$ -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  $\beta_2$ -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  $\beta_2$ -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  $\beta_2$ -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<sub>1</sub>, but ↓ 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 ≤2/wk, Ø nocturnal sx or limitation of activity, reliever med ≤2/wk, nl PEF or FEV<sub>1</sub>; partly controlled = 1–2 of the above present in a wk; uncontrolled = ≥3 of the above present in a wk
- Step up treatment as needed to gain control, step down as tolerated
- If PEF ↓ 15% × 2 d or ↓ 30%, quadrupling inh steroid dose → ↓ need for PO steroids (AJRCCM 2009;180:598)

Asthma Stepwise Therapy				
Step 1	Step 2	Step 3	Step 4	Step 5
Rapid-acting β <sub>2</sub> -agonists prn				
Controller options	Select one	Select one	Do one or more	Add one or both
	<b>Low-dose ICS</b>	<b>Low-dose ICS + LABA</b>	Δ <b>low-dose ICS to med/high dose (w/LABA)</b>	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<sub>2</sub>-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 → pneumothorax, precordial (Hamman's) crunch → pneumomediastinum
- Diagnostic studies
  - ABG: not always considered essential because exam and S<sub>a</sub>O<sub>2</sub> provide equivalent info; low P<sub>a</sub>CO<sub>2</sub> initially; nl or high P<sub>a</sub>CO<sub>2</sub> may signify tiring; may respond to bronchodilator
  - PEF: used to follow clinical course; CXR: not essential unless suspicion for PNA or PTX

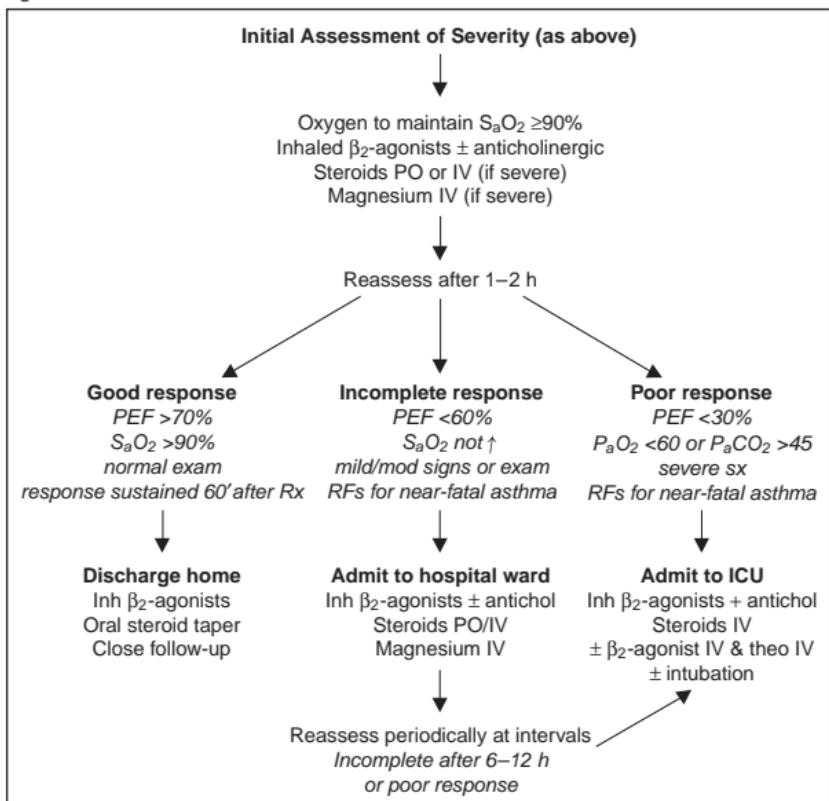
Severity of Asthma Exacerbation			
Feature	Mild	Moderate	Severe
Breathless w/ ...	Walking	Talking	At rest
Talking in ...	Sentences	Phrases	Words
Mental status	± Agitated	Agitated	Agitated
RR	↑	↑	>30
Accessory muscles	Ø	⊕	⊕
Wheeze	Moderate, end-expir	Loud	Usually loud
HR	<100	100–120	>120
Pulsus paradoxus	Normal (<10)	10–25	>25
PEF	>80%	60–80%	<60%
S <sub>a</sub> O <sub>2</sub>	>95%	91–95%	<90%
P <sub>a</sub> O <sub>2</sub>	Normal	>60	<60
P <sub>a</sub> CO <sub>2</sub>	<45	<45	>45

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

**Resp arrest imminent:** drowsy, abdominal paradox, wheezes inaudible (b/c Ø 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 ( <i>JAMA</i> 1988;260:527)
Ipratropium	MDI 4–8 puffs q30min or nebulizer 0.5 mg q30min × 3	↑ bronchodilation when combined w/ albuterol ( <i>Chest</i> 2002;121:1977)
Magnesium	2 g IV over 20 min ( <i>Lancet</i> 2003;361:2114)	↑ PEF & FEV <sub>1</sub>

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<sub>2</sub>-agonists, psych issues, h/o noncompliance.

### Other treatments

- Epinephrine (0.3–0.5 mL SC of 1:1000 dilution): no advantage over inhaled β<sub>2</sub>-agonists
- Abx: not needed w/o evidence of bacterial infection. Evidence of improved sx & FEV<sub>1</sub> 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 (*Respir Care* 2008;53:740).
- Invasive ventilation:** large ET tube, keep P<sub>plat</sub> < 30 cm H<sub>2</sub>O (predicts barotrauma better than PIP), maximize exp time, and use no PEEP to avoid hyperinflation (*Respir Care* 2008;53:740) paralysis, inhalational anesthetics, bronchoalveolar lavage w/ mucolytic, heliox (need 60–80% helium), and ECMO have been used with success

# CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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

- Progressive airflow limitation caused by airway and parenchymal inflammation

Emphysema vs. Chronic Bronchitis		
	Emphysema	Chronic Bronchitis
<b>Definition</b>	Dilation/destruction of parenchyma (path definition)	Productive cough >3 mo/y ≥ 2 y (clinical definition)
<b>Pathophysiology</b>	Tissue destruction Matched V/Q defects Mild hypoxemia	Small airways affected V/Q mismatch Severe hypoxemia, hypercapnia PHT, cor pulmonale
<b>Clinical manifestations</b>	Severe, constant dyspnea Mild cough	Intermittent dyspnea Copious sputum production
<b>Physical exam</b>	"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
- $\alpha_1$ -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<sub>1</sub>, ↓ FVC, ↓ FEV<sub>1</sub>/FVC, expir scooping of flow-volume loop  
Hyperinflation: ↑↑ RV, ↑ TLC, ↑ RV/TLC  
**Abnormal gas exchange:** ↓ DLCO (in emphysema)
- ABG: ↓ PaO<sub>2</sub>, ± ↑ PaCO<sub>2</sub> (in chronic bronchitis, usually only if FEV<sub>1</sub> < 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,  $\beta_2$ -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<sub>1</sub> 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<sub>1</sub>, ↓ COPD admits (Annals 2007;146:545)
- Corticosteroids (inhaled):** ~20% ↓ in exacerbations if FEV<sub>1</sub> < 2.0 L (Chest 2009;136:1029) may slow FEV<sub>1</sub> loss, but more so in combo with  $\beta_2$ -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<sub>1</sub>, but ? ↓ exacerbation rate (Lancet 2008;371:2013)
- Oxygen:** if PaO<sub>2</sub> ≤ 55 mm Hg or SaO<sub>2</sub> ≤ 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, bupropion) → 50% ↓ in lung function decline (AJRCCM 2002;166:675) and ↓ long-term mortality (Annals 2005;142:223)
- Rehabilitation:** ↓ dyspnea and fatigue, ↑ exercise tolerance, ↑ QoL (Chest 2007;131:45)
- Experimental**
  - Lung volume reduction surgery: ↑ exer. capacity, ↓ mort. if FEV<sub>1</sub> > 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<sub>1</sub> 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<sub>1</sub>:** <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<sub>1</sub>): 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<sub>1</sub> (*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 <sub>1</sub> /FVC > 70%	FEV <sub>1</sub> ≥ 80%	Bronchodilator prn
II: Mod		FEV <sub>1</sub> 50–80%	Standing LA dilator (tiotropium >β ag) Rehabilitation
III: Severe		FEV <sub>1</sub> 30–50%	Above + inh steroid if ↑ exacerbations
IV: Very Severe		FEV <sub>1</sub> <30% or FEV <sub>1</sub> <50% and chronic respiratory failure	Above + O <sub>2</sub> if chronic resp failure Experimental as indicated

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

**EXACERBATION**

COPD Exacerbation Treatment ( <i>NEJM</i> 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 ( <i>Cochrane</i> 2009;CD001288). Consider: Methylprednisolone 125 mg IV q6h × 72 h then: Prednisone 60 mg PO qd w/ 20 mg taper q3–4d ( <i>NEJM</i> 1999;340:1941) or prednisone 40 mg × 10d or prednisone 30 mg qd × 2 wks if pH >7.26 ( <i>Lancet</i> 1999;354:456)	↓ treatment failure, ↓ hospital stay, ↑ FEV <sub>1</sub> but no mortality benefit, ↑ complications ( <i>Cochrane</i> 2009;CD001288)  OutPt Rx after ED visit ↓ relapse ( <i>NEJM</i> 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.	<i>H. flu</i> , <i>M. catarrhalis</i> , <i>S. pneumoniae</i> freq. precipitants. Dyspnea, ↑ sputum production, ↑ purulence → abx may improve outcome ( <i>Annals</i> 1987;106:196) ↑ PEF & chance of clinical resolution ( <i>JAMA</i> 1995;273:957) ↓ subseq exacerbation ( <i>Thorax</i> 2008;63:96) ≤5d course likely enough for mild-mod exacerbation ( <i>Thorax</i> 2008;63:41; <i>JAMA</i> 2010;303:2035)
Oxygenation	↑ F <sub>i</sub> O <sub>2</sub> to achieve P <sub>a</sub> O <sub>2</sub> ≥55–60 or S <sub>a</sub> O <sub>2</sub> 90–93%	<b>Watch for CO<sub>2</sub> retention</b> (due to ↑V/Q mismatch, loss of hypoxic resp. drive, Haldane effect) but must maintain oxygenation!
Noninvasive positive-pressure ventilation	Initiate early if mod/severe dyspnea, ↓ pH / ↑ P <sub>a</sub> CO <sub>2</sub> , 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 ( <i>NEJM</i> 1995;333:817; <i>Annals</i> 2003;138:861; <i>Cochrane</i> 2004;CD004104; <i>ERJ</i> 2005;25:348)	
Endotracheal intubation	Consider if P <sub>a</sub> O <sub>2</sub> <55–60, ↑ing P <sub>a</sub> CO <sub>2</sub> , ↓ing pH, ↑ RR, respiratory fatigue, Δ MS, or hemodynamic instability	
Other measures	Mucolytics overall not supported by data ( <i>Chest</i> 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, Behcet'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	Bronchogenic carcinoma (75%): adeno & large cell (peripheral) squamous & small cell (central)
Hamartoma (10%)	Metastatic (20%): breast, head & neck, colon, testicular, renal, sarcoma, melanoma
Bronchogenic cyst, AVM, pulm infarct	Carcinoid, primary sarcoma
Echinococcosis, ascariasis, aspergilloma	
Wegener's, rheumatoid nodule	
Lipoma, fibroma, amyloidoma, pneumonitis	

## 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 ( $\leq 1$ ppd)	current ( $> 1$ ppd)
Smoking cessation	none, quit $\geq 7$ 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  
Ø Ca  $\rightarrow$  ↑ likelihood malignant; laminated  $\rightarrow$  granuloma; “popcorn”  $\rightarrow$  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  $\rightarrow$  resect
- **Video-assisted thorascopic surgery (VATS):** for percutaneously inaccessible lesions;  
highly sensitive and allows resection; has replaced thoracotomy
- Transbronchial bx: most lesions too small to reliably sample w/o endobronchial U/S (*Chest* 2003;123:604); bronch w/ brushings low-yield unless invading bronchus
- PPD, fungal serologies, ANCA

**Management**

- **Low-risk:** serial CT (q3mo  $\times$  4, then q6mo  $\times$  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  $\rightarrow$  VATS
- **High-risk** (and surgical candidate): VATS  $\rightarrow$  lobectomy if malignant

## OBSTRUCTIVE SLEEP APNEA (OSA)

**Definition and pathophysiology**

- Repetitive pharyngeal collapse during sleep causing apnea ( $\geq 10$  s) or hypopnea (airflow reduction)  $\pm$  desaturation, arousals from sleep  $\rightarrow$  daytime sleepiness
- Apnea-hypopnea index (AHI) = avg # apneas and hypopneas per hr of sleep
- Sleep-induced loss of activity of pharyngeal dilator muscles  $\rightarrow$  pharyngeal collapse  $\rightarrow$  arousal  $\rightarrow$  activation of sympathetic nervous system; phenotypes vary across OSA Pts
- Apnea  $\rightarrow$  negative intrathoracic pressure  $\rightarrow$  ↑ preload, ↑ afterload  $\rightarrow$  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  $\oplus$ , 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 retrognathia collapse. Offer if refusing CPAP.
- Avoid alcohol and sedatives
- Surgery (eg, uvulopalatopharyngoplasty, UPPP) of limited benefit (*Chest* 1997;111:265)

# INTERSTITIAL LUNG DISEASE

## WORKUP OF ILD

### Rule out mimickers of ILD

- Congestive heart failure ( $\checkmark$  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  $\Delta$ s, 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, asbestos, infections, XRT
- PFTs: restrictive pattern ( $\downarrow$  volumes),  $\downarrow$  DLCO,  $\downarrow$  PaO<sub>2</sub> (especially w/ exercise); if also obstructive, consider sarcoid
- Serologies:  $\checkmark$  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; $\uparrow$ 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  
 $^{18}\text{FDG}$  PET can be used to identify extent and potentially targets for dx bx  
 $\uparrow$  **ACE** (Se 60%, 90% w/ active dis., Sp 80%, false  $\oplus$  in granulomatous diseases)
- To assess extent: CXR, PFTs, full ophtho exam, ECG, CBC (lymphopenia,  $\uparrow$  eos), Ca, 24-h urine for Ca, LFTs;  $\pm$  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  $\Delta$  long-term course); hydroxychloroquine for extensive skin disease; anti-TNF, MTX, AZA, mycophenolate, or cyclophosphamide for chronic/refractory disease
- Prognosis:  $\sim\frac{2}{3}$  spontaneously remit w/in 10 y (60–80% of stage I, 50–60% stage II, 30% stage III), w/ relapses uncommon;  $\sim\frac{1}{3}$  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 (espc. 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 actinomycetes); pigeon fancier's lung (proteins from feathers and excreta of birds); humidifier lung (thermophilic bacteria)  
Pathophysiology: immunologic rxn; either acute (6 h after exposure) or chronic

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

- **Rheumatologic disease**

Scleroderma: fibrosis in ~67%; PHT seen in ~10% of CREST Pts  
PM-DM: ILD & weakness of respiratory muscles; MCTD: PHT & fibrosis  
SLE & RA: pleuritis and pleural effusions more often than ILD; SLE can cause DAH

- **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 ( $\frac{2}{3}$ ) & massive (even w/o marked ascites)
- Nephrotic syndrome: usually small, bilateral, asymptomatic (r/o PE b/c hypercoag)
- Other: PE (usually exudate), malignancy (lymphatic obstruction), myxedema, CAPD

## Exudates

- **Lung parenchymal infection (25%)**

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

- **Malignancy (15%)**: primary lung cancer most common, metastases (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;  $\oplus$  eosinophils  
Drug-induced (eg, nitrofurantoin, methysergide, bromocriptine, amiodarone):  $\oplus$  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  $LDH_{eff} > \frac{2}{3} ULN$  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  $\leq 1.2$ , Se 87%, Sp 92%; serum-effusion TP gradient  $\leq 3.1$ , Se 84%, Sp 91%;  $chol_{eff} > 45 \text{ mg/dL}$  and  $LDH_{eff} > 200$ , 90% Se, 98% Sp (no serum required)

CHF effusions: TP may ↑ with diuresis or chronicity → "pseudoexudate"; use albumin gradient  $\leq 1.2$ ,  $chol_{eff} > 60 \text{ mg/dL}$  (Se 54%, Sp 92%), or clinical judgment to help distinguish (Chest 2002;122:1524)

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

complicated =  $\oplus$  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  $\geq 1,500$  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<sub>eff</sub> 1–20% → cancer, PE, trauma; Hct<sub>eff</sub>/Hct<sub>blood</sub>  $>50\%$  → 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  $\geq 150$  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<sub>19</sub>50, 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-proBNP<sub>eff</sub>; 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<sup>+</sup>), ADA or IFN-γ release assay; consider thoracoscopy.

#### Characteristics of Pleural Fluid (not diagnostic criteria)

Etiology	Appear	WBC diff	RBC	pH	Glc	Comments
<b>CHF</b>	clear, straw	<1,000 lymphs	<5,000	normal	= serum	bilateral, cardiomegaly
<b>Cirrhosis</b>	clear, straw	<1,000	<5,000	normal	= serum	right-sided
<b>Uncomplicated parapneumonic</b>	turbid	5–40,000 polys	<5,000	normal to ↓	= serum ( $>40$ )	
<b>Complicated parapneumonic</b>	turbid to purulent	5–40,000 polys	<5,000	↓↓	↓↓ ( $<40$ )	need drainage
<b>Empyema</b>	purulent	25–100,000 polys	<5,000	↓↓↓	↓↓	need drainage
<b>Tuberculosis</b>	serosang.	5–10,000 lymphs	<10,000	normal to ↓	normal to ↓	⊕ AFB ⊕ ADA
<b>Malignancy</b>	turbid to bloody	1–100,000 lymphs	<100,000	normal to ↓	normal to ↓	⊕ cytology
<b>Pulmonary embolism</b>	sometimes bloody	1–50,000 polys	<100,000	normal	= serum	no infarct → transudate
<b>Rheumatoid arthritis/SLE</b>	turbid	1–20,000 variable	<1,000	↓	RA ↓↓ SLE nl	↑ RF, ↓ C <sub>19</sub> 50 ↑ imm. complex
<b>Pancreatitis</b>	serosang. to turbid	1–50,000 polys	<10,000	normal	= serum	left-sided, ↑ amylase
<b>Esophageal rupture</b>	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

# VENOUS THROMBOEMBOLISM (VTE)

VTE  
2-13

## 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
<b>Low</b> VTE <10%	Minor surgery in mobile Pt; fully mobile medical Pt	Early, aggressive ambulation
<b>Moderate</b> VTE 10–40%	Most surgery Pts; sick or bedrest medical Pts	<b>UFH</b> 5,000 U SC bid or tid; <b>LMWH</b> , fonda (if HIT $\oplus$ ); mechanical Ppx if high bleed risk
<b>High</b> VTE 40–80%	Ortho surgery, trauma, spinal cord injury	<b>LMWH</b> , 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,  $\oplus$  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

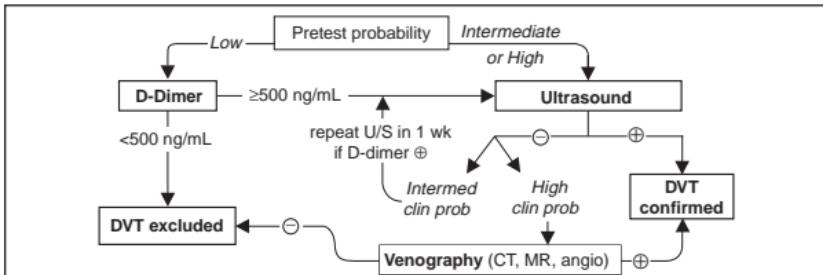
Pretest Probability of DVT	
Major points	Minor points
<ul style="list-style-type: none"> <li>• Active cancer</li> <li>• Paralysis, paresis, immobilization of foot</li> <li>• Bed rest <math>\times</math> &gt;3 d or major surg. w/in 4 wk</li> <li>• Localized tenderness along veins</li> <li>• Swelling of thigh and calf</li> <li>• Swelling of calf &gt;3 cm c/w asx side</li> <li>• <math>\oplus</math> FHx of DVT (<math>\geq 2</math> 1° relatives)</li> </ul>	<ul style="list-style-type: none"> <li>• Trauma to symptomatic leg w/in 60 d</li> <li>• Pitting edema in symptomatic leg</li> <li>• Dilated superficial veins (nonvaricose) in symptomatic leg only</li> <li>• Hospitalization w/in previous 6 mo</li> <li>• Erythema</li> </ul>
<b>High probability (~85% <math>\oplus</math> DVT)</b> ≥3 major + no alternative dx ≥2 major + ≥2 minor + no alternative dx	<b>Low probability (~5% <math>\oplus</math> DVT)</b> 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
<b>Intermediate prob (~33% <math>\oplus</math> DVT)</b> 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<sub>2</sub>
- Massive: syncope, HoTN, PEA; ↑ JVP, R-sided S<sub>3</sub>, 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

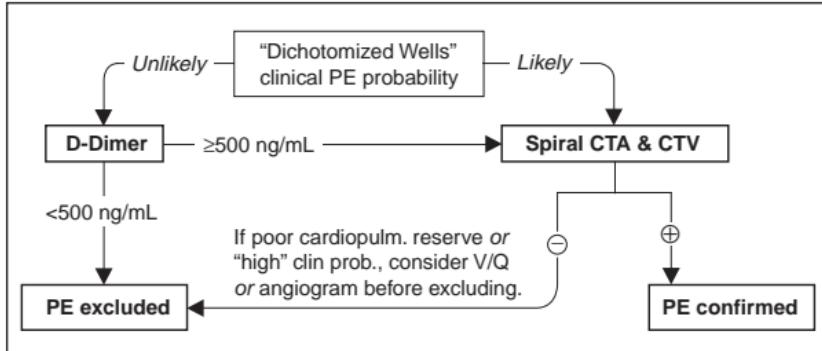
“Dichotomized Wells” Pretest Probability Assessment* (Use for CTA)		
Score ≤4: PE “Unlikely”	Score >4: PE “Likely”	

(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<sub>i</sub>Q<sub>III</sub>T<sub>III</sub> & TWI V<sub>1</sub>–V<sub>4</sub> (McGinn-White pattern, *Chest* 1997;111:537)
- ABG: hypoxemia, hypocapnia, respiratory alkalosis, ↑ A-a gradient (*Chest* 1996;109:78) 18% w/ room air P<sub>a</sub>O<sub>2</sub> 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 &amp; 2006;354:22; JAMA 2005;293:2012 &amp; 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 × ctrl (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 ( $\text{CrCl} < 25$ ),? 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  $\geq 2 \times \geq 24$  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;351:1655)

- Smooth muscle & endothelial cell proliferation: ↑ VEGF, ET-1, 5-HT; ↓ PGI<sub>2</sub>, 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<sub>2</sub> (TXA<sub>2</sub>), serotonin (5-HT), endothelin-1 (ET-1)
  - ↓ vasodilators: prostacyclin (PGI<sub>2</sub>), nitric oxide (NO), vasoactive peptide (VIP)
- In situ thrombosis: ↑ TXA<sub>2</sub>, 5-HT, PAI-1; ↓ PGI<sub>2</sub>, NO, VIP, tissue plasminogen activator

Etiologies of Pulmonary Hypertension (Revised WHO Classification)	
Pulmonary arterial HTN (PAH)	<ul style="list-style-type: none"><li>Idiopathic (IPAH): mean age of onset 36 y (♂ older than ♀); ♀:♂ = ~2:1, usually mild ↑ in PAP</li><li>Familial (FPAH)</li><li>Associated conditions (APAH)<ul style="list-style-type: none"><li>Connective tissue disorders: CREST, SLE, MCTD, RA, PM, Sjögren</li><li>Congenital L→R shunts: ASD, VSD, PDA</li><li>Portopulmonary HTN (?<sup>2</sup> vasoactive substances not filtered in ESLD; ≠ hepatopulmonary syndrome)</li><li>HIV; drugs &amp; toxins: anorexic agents, rapeseed oil, L-tryptophan</li><li>Other: thyroid dis., glycogen storage dis., Gaucher disease, HHT, hemoglobinopathies, chronic myeloprolif d/o, splenectomy</li></ul></li><li>Pulmonary veno-occlusive disease: ?<sup>2</sup> chemo, BMT; orthopnea, CHF, pl eff, nl PCWP; art vasodil. worsen CHF (AJRCCM 2000;162:1964)</li><li>Pulmonary capillary hemangiomatosis</li></ul>
Left heart disease	<ul style="list-style-type: none"><li>Left atrial or ventricular (diastolic or systolic) dysfunction</li><li>Left-sided valvular heart disease (eg, MS/MR)</li></ul>
Lung diseases and/or chronic hypoxemia	<ul style="list-style-type: none"><li>COPD</li><li>ILD</li><li>Sleep apnea</li><li>Alveolar hypoventilation (eg, NM disease)</li><li>Chronic hypoxemia (eg, high altitude)</li><li>Developmental abnormalities</li></ul>
Chronic thrombotic or embolic disease	<ul style="list-style-type: none"><li>Obstruction of proximal or distal pulmonary arteries</li><li>Nonthrombotic emboli (tumor, foreign body, parasites)</li></ul>
Miscellaneous	<ul style="list-style-type: none"><li>Sarcoidosis, histiocytosis X, lymphangiomatosis, schistosomiasis</li><li>Compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis)</li></ul>

(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<sub>2</sub>, R-sided S<sub>4</sub>, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- ± RV failure: ↑ JVP, hepatomegaly, peripheral edema

## Diagnostic studies & workup (Circ 2009;119:2250)

- IPAH yearly incidence 1–2 per million, .. r/o 2° causes
- CXR and high-resolution chest CT: dilatation & pruning of pulmonary arteries, enlargement of RA and RV; r/o parenchymal lung disease
- ECG: RAD, RBBB, RAE ("P pulmonale"), RVH (Se 55%, Sp 70%)
- PFTs: ↓ DLCO, mild restrictive pattern; r/o obstructive and restrictive lung disease
- ABG & polysomnography: ↓ PaO<sub>2</sub> and SaO<sub>2</sub> (especially w/ exertion), ↓ PaCO<sub>2</sub>, ↑ A-a gradient; r/o hypoventilation and OSA
- TTE: ↑ RVSP (but over or under by ≥10 mm Hg in 1/2 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  $S_aO_2 > 90\text{--}92\%$  (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)

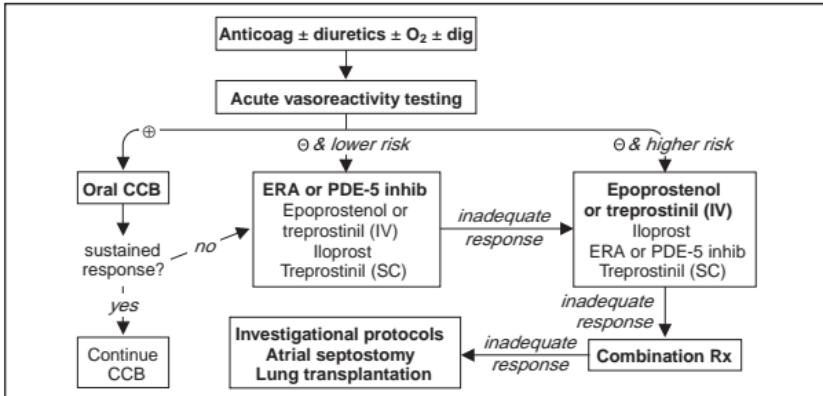
- Vasodilators**

acute vasoreactivity test: use inhaled NO, adenosine, or prostacyclin to identify Pts likely to have a long-term response to oral CCB ( $\oplus$  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
<b>Oral CCB</b> Nifedipine, diltiazem	If $\oplus$ acute vasoreactive response; $< \frac{1}{2}$ will be long-term responder (NYHA I/II & near-nl hemodynamics) & have ↓ mortality. Side effects: HoTN, lower limb edema. ( <i>NEJM</i> 1992;327:76; <i>Circ</i> 2005;111:3105)
<b>IV Prostacyclin</b> 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. ( <i>NEJM</i> 1996;334:296 & 1998;338:273; <i>Annals</i> 2000;132:425)
<b>Prostacyclin analogues</b> 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.). ( <i>NEJM</i> 2002;347:322; <i>AJRCM</i> 2002;165:800)
<b>Endothelin receptor antagonists (ERAs)</b> Bosentan, ambrisentan	↓ Smooth muscle remodeling, ↑ vasodilation, ↓ fibrosis. ↓ sx, ↑ 6MWT, ↓ clinical events. Side effects: ↑ LFTs, headache, anemia, edema, teratogen. ( <i>NEJM</i> 2002;346:896; <i>JACC</i> 2005;46:529; <i>Circ</i> 2008;117:3010)
<b>PDE-5 Inhibitor</b> Sildenafil, tadalafil	↑ cGMP → ↑ NO → vasodilation, ↓ smooth muscle proliferation ↓ sx, ↑ 6MWT, no Δ clinical outcomes. Low side effect profile: HA, vision Δ's, sinus congestion. ( <i>NEJM</i> 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<sub>2</sub> 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

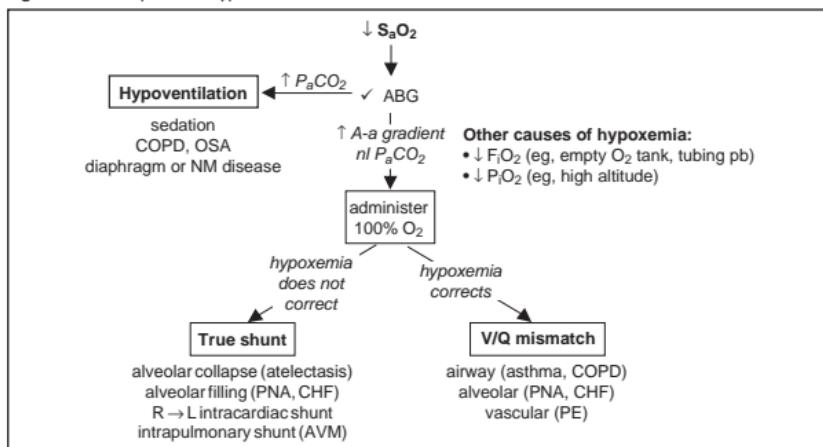
- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (*Chest* 2004;126:78-S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO (modified NYHA) class IV, 6MWT  $< 300$  m, peak VO<sub>2</sub>  $< 10.4$  mL/kg/min, ↑ RA or RV or RV dysfxn, RA 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

# RESPIRATORY FAILURE

$$\text{Hypoxemia} \rightarrow P_aO_2 = F_iO_2 \times (760 - 47) - \frac{P_aCO_2}{R}$$

- A-a gradient** =  $P_aO_2 - PaO_2$ : 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<sub>a</sub>O<sub>2</sub>** (mixed venous O<sub>2</sub> sat, nl 60–80%): measure O<sub>2</sub> consumption vs. delivery; low S<sub>a</sub>O<sub>2</sub> → ↓ O<sub>2</sub> delivery (↓ S<sub>a</sub>O<sub>2</sub>, nl S<sub>a</sub>O<sub>2</sub> but ↓ CO or anemia) or excessive O<sub>2</sub> consump.
- V/Q mismatch** and **shunt** represent spectrum w/ both coexisting in alveolar disease  
100% O<sub>2</sub> can overcome V/Q mismatch but not large shunt b/c sigmoidal Hg-O<sub>2</sub> curve

Figure 2-6 Workup of acute hypoxemia



### Chemical Causes of Cellular Hypoxia

Condition	Causes	Classic Features	P <sub>a</sub> O <sub>2</sub>	Pulse Ox Sat	CO-Ox Sat	Treatment (+ 100% O <sub>2</sub> )
Carbon monoxide	Fires, portable heaters, auto exhaust	Cherry-red skin (COHb color)	nl	nl	↓	Hyperbaric O <sub>2</sub>
Methemoglobinemia	Nitrates, sulfonamide, benzocaine, dapsone	Chocolate brown blood	nl	mild ↓	↓	Methylene blue
Cyanide	Nitroprusside, fires, industrial	Bitter almond odor; pink skin	nl	nl (↑ S <sub>a</sub> O <sub>2</sub> )	nl	Hydroxy-cobalamin

CO binds to Hb more avidly than does O<sub>2</sub>. Pulse ox misreads COHb as HbO<sub>2</sub> → falsely nl sat.

Oxidizing drugs Δ Hb (ferrous) to MethHb (ferric), which cannot carry O<sub>2</sub>. Pulse ox misreads MethHb as HbO<sub>2</sub>. Cyanide inhibits mitochondrial O<sub>2</sub> use → cellular hypoxia but pink skin and ↑ venous O<sub>2</sub> 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 <sub>a</sub> CO <sub>2</sub>			
"Won't breathe"		"Can't breathe"	
<b>Respiratory Drive</b>	<b>NM System</b>	<b>Lung/Airways</b>	<b>CW/Pleura</b>
↓ RR	↓ V <sub>T</sub>	↓ V <sub>T</sub> and/or ↑ V <sub>D</sub>	↓ V <sub>T</sub>
↓ P <sub>100</sub> Voluntary hypervent. NL PI <sub>max</sub> & A-a gradient	↓ PI <sub>max</sub> ↓ PE <sub>max</sub>	Abnl PFTs	Abnl PEx Abnl CXR/CT
<b>Chemoreceptors</b> metab. alkalosis <b>1° neurologic</b> brainstem stroke tumor 1° alveolar hypovent	<b>Neuropathies</b> cervical spine phrenic nerve GBS, ALS, polio <b>NMJ</b> MG, LE, botulism <b>Myopathies</b> diaphragm PM/DM; ↓ PO <sub>4</sub> musc dystrophies	<b>Lung parenchyma</b> emphysema ILD/fibrosis CHF, PNA <b>Airways</b> asthma, COPD bronchiectasis CF OSA	<b>Chest wall</b> obesity kyphosis scoliosis <b>Pleura</b> fibrosis effusion

↑ VCO<sub>2</sub> typically transient cause of ↑ P<sub>a</sub>CO<sub>2</sub>; 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
<b>Assist control (AC)</b>	Vent delivers a minimum number of supported breaths Additional Pt-initiated breaths trigger <i>fully-assisted</i> vent breaths ∴ Vent-triggered breaths identical to Pt-triggered breaths Tachypnea → ? respiratory alkalosis, breath-stacking, & auto-PEEP May be pressure targeted or volume targeted
<b>Synchronized intermittent mandatory vent (SIMV)</b>	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
<b>Pressure support vent (PSV)</b>	Support Pt-initiated breaths w/ a set inspiratory pressure & PEEP A mode of <i>partial</i> vent support because no set rate
<b>Continuous positive airway pressure (CPAP)</b>	Pt breathes spont. at his/her own rate while vent maintains constant positive airway pressure throughout respiratory cycle (7 cm H <sub>2</sub> O overcomes 7 Fr ETT)
<b>T piece</b>	No airway pressure, no rate set; patient breathes through ETT
<b>Other</b>	High-frequency vent (AJRCCM 2002;166:801; CCM 2003;S-31:S-317) ECMO and ECCO <sub>2</sub> R (Ann Surg 2004;240:595)

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

<b>Volume targeted</b>	Vent delivers a set $V_T$ Airway pressures depend on airway resist. & lung/chest wall compliance <b>Benefit:</b> ↑ 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) <b>Risk:</b> 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.
<b>Pressure targeted</b>	Vent delivers a fixed inspiratory pressure regardless of $V_T$ $V_T$ depends on airway resistance and lung/chest wall compliance <b>Benefit:</b> May ↑ patient comfort (PSV) requiring less sedation <b>Risk:</b> Pt at risk for ↓ volumes → inadequate $V_E$
<b>Other</b>	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
<b>General principles</b>	<b>Institutional/practitioner preference</b> and <b>patient comfort</b> usually dictate ventilator strategy; no strategy has proven superior <b>Common reasons for Δ include:</b> dyssynchrony, poor gas exchange, Δ mech. resp properties, Δ goals of care (eg, sedation, weaning, lung protection) <b>Alarms</b> can be set for ↑ volumes and ↑ airway pressures in pressure-targeted and volume-targeted strategies, respectively

### Step 3: Set or ✓ Remaining Variables

<b>F<sub>i</sub>O<sub>2</sub></b>	Fraction of inspired air that is oxygen
<b>Positive end-expiratory pressure (PEEP)</b>	<p>Positive pressure applied during exhalation via resistor in exhalation port</p> <p>Benefits: prevents alveoli collapse, ↓ intrapulmonary shunt, ↑ O<sub>2</sub></p> <p>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</p> <p>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</p> <p>Will ↓ preload and may ↓ CO, especially if hypovolemic</p> <p>Will ↑ work of breathing as must be overcome by Pt to trigger breaths; can prevent Pt from successfully triggering ventilator</p> <p>Can be detected if end-expiratory flow ≠ 0 before next breath</p> <p>Can measure by occluding expiratory port of vent at end-expiration</p> <p>Can ↓ by: ↑ exp time, ↓ RR, ↓ V<sub>T</sub>, Rx bronchospasm and secretions</p>
<b>Inspiratory time</b>	Normally I:E ratio is ~1:2; however, can alter I time (and consequently flow rate, see later); use in pressure-control mode
<b>Inspiratory flow rates</b>	↑ flow rate → ↓ I time → ↑ E time → .. may improve ventilation in obstructive disease, but may affect resp rate and bronchodilation/constriction
<b>Peak inspiratory pressure (PIP)</b>	<p>Dynamic measurement during inspiration; set in pressure-targeted mode</p> <p>Determined by airway resistance and lung/chest wall compliance</p> <p>↑ PIP w/o ↑ P<sub>plat</sub> → ↑ airway resist (eg, bronchospasm, plugging)</p> <p>↓ PIP → ↓ airway resistance or air leak in the system</p>
<b>Plateau pressure (P<sub>plat</sub>)</b>	<p>Static measurement at the end of inspiration when there is no flow</p> <p>Determined by resp system compliance (resist. not a factor since ∅ flow)</p> <p>↑ P<sub>plat</sub> → ↓ lung or chest wall compliance (eg, PTX, pulmonary edema, pneumonia, atelectasis), ↑ PEEP, or auto-PEEP</p> <p>P<sub>plat</sub> &lt;30 cm H<sub>2</sub>O ↓ barotrauma (↓ V<sub>T</sub>, ↓ PEEP or ↑ compl [eg, by diuresis])</p>

#### Initial Settings

Mode	Tidal volume	Respiratory rate	F <sub>i</sub> O <sub>2</sub>	PEEP
Assist control volume-targeted	4–8° mL/kg IBW	12–14 breaths/min	1.0 (ie, 100%)	? 5 cm H <sub>2</sub> O

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

### Noninvasive Ventilation

<b>Conditions</b>	<p>Cardiogenic pulmonary edema: may ↓ intub. &amp; mortality (<i>JAMA</i> 2005;294:3124; <i>Lancet</i> 2006;367:1155) although recent trial (w/ high crossover) did not show any benefit (<i>NEJM</i> 2008;359:142)</p> <p>COPD exacerbation w/ hypercapnia: ↓ intub. &amp; mortality (<i>Lancet</i> 2000;355:1931), but if pH &lt;7.3 → intubate</p> <p>High-risk extubation (age &gt;65, CHF, APACHE II &gt;12): NIV × 24 h directly after extubation → ↓ reintub and, if P<sub>a</sub>CO<sub>2</sub> &gt;45 during SBT, ↓ mortality (<i>AJRCCM</i> 2006;173:164). However, if used as rescue after failed extubation → ↑ mortality (<i>NEJM</i> 2004;350:2452).</p> <p>End-of-life care (<i>Respir Care</i> 2009;54:223)</p> <p>Immunosupp. w/ infiltrates: ↓ complic &amp; mort (<i>NEJM</i> 2001;344:481)</p>
<b>Indications</b> ( <i>Lancet</i> 2009;374:250)	<p><b>Clinical:</b> mod-severe dyspnea, RR &gt;24–30, signs of ↑ work of breathing, accessory muscle use, abd paradox</p> <p><b>Gas exchange:</b> P<sub>a</sub>CO<sub>2</sub> &gt;45 (&amp; significantly worse than baseline), hypoxemia, P<sub>a</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> &lt;200</p>
<b>Contraindications</b> ( <i>JAMA</i> 2002;288:932)	Claustrophobia, inability to fit mask, Δ MS, vomiting, unable to protect airway, extrapulm organ failure, hemodyn instab, sev UGIB
<b>Continuous positive airway pressure (CPAP)</b>	=PEEP No limit on O <sub>2</sub> delivered (ie, can give hi-flow → F <sub>i</sub> O <sub>2</sub> ≈1.0) Used if primary problem <b>hypoxemia</b> (eg, CHF)
<b>NPPV/bilevel positive airway pressure (BiPAP)</b>	=PSV + PEEP. Able to set both inspiratory (usually 8–10 cm H <sub>2</sub> O) and expiratory pressures (usually <5 cm H <sub>2</sub> O). Used if primary problem <b>hypoventilation</b> ; F <sub>i</sub> O <sub>2</sub> delivery limited
<b>Mask ventilation</b>	Tight-fitting mask connecting patient to a standard ventilator Can receive PS ~20–30 cm H <sub>2</sub> O, PEEP ~10 cm H <sub>2</sub> O, F <sub>i</sub> O <sub>2</sub> ~1.0 Used for short-term support (<24 h) for a reversible process

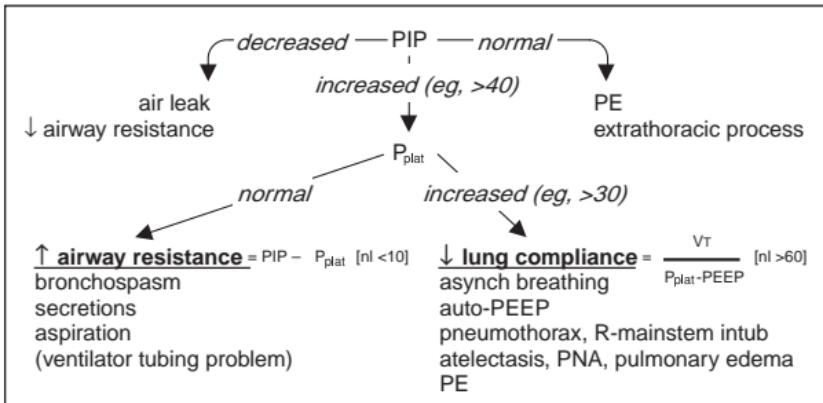
## Tailoring the ventilator settings

- To improve oxygenation: options include ↑ F<sub>i</sub>O<sub>2</sub>, ↑ PEEP
  - First, ↑ F<sub>i</sub>O<sub>2</sub>. If >0.6 and oxygenation remains suboptimal, then try ↑ PEEP:  
If ↑ P<sub>a</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> and P<sub>plat</sub> stable, suggests recruitable lung (ie, atelectasis). Continue to ↑ PEEP until either can ↓ F<sub>i</sub>O<sub>2</sub> to <0.6 or P<sub>plat</sub> ≥ 30 cm H<sub>2</sub>O. If PEEP 20 & F<sub>i</sub>O<sub>2</sub> 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see ARDS).
  - If ↑ PEEP → ØΔ or ↓ P<sub>a</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> or ↑ P<sub>a</sub>CO<sub>2</sub>, suggests additional lung not recruitable and instead overdistending lung → ↑ shunt & dead space; ∴ ↓ PEEP
- To improve ventilation: ↑V<sub>T</sub> or inspiratory pressure, ↑ RR (may need to ↓ I time). Nb, tolerate ↑ P<sub>a</sub>CO<sub>2</sub> (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<sub>a</sub>O<sub>2</sub> <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<sub>a</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> >200, PEEP ≤5, f/V<sub>T</sub> <105, V<sub>E</sub> <12 L/min, VC >10 mL/kg rapid shallow breathing index (f/V<sub>T</sub>) >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<sub>plat</sub> (>30 cm H<sub>2</sub>O, but lower better) → alveolar damage
- Oxygen toxicity (theoretical); proportional to duration + degree of ↑ oxygen (F<sub>i</sub>O<sub>2</sub> >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<sub>2</sub>RA/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:  $P_aO_2/FiO_2 \leq 200$  → ARDS;  $P_aO_2/FiO_2 \leq 300$  → 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:  $V_T/(P_{plat} - PEEP) < 50 \text{ mL/cm H}_2\text{O}$

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*
<b>Barotrauma/volutrauma:</b> alveolar overdistention → mechanical damage	$V_T \leq 6 \text{ mL/kg}$ , $P_{plat} \leq 30 \text{ cm H}_2\text{O}$ , tolerate ↑ $P_aCO_2$ (but keep pH >7.15), ↓ mortality (NEJM 2000;342:1301). Weight risk/benefit of sedation & paralysis.
<b>Biotrauma → SIRS</b>	Low $V_T$ , open lung strategy w/ high PEEP
<b>Atelectrauma:</b> repetitive alveoli recruitment & decruitment	<b>Titrate PEEP to prevent tidal alveolar collapse</b> 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 <sub>2</sub> O → ↓ 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 $S_aO_2 \geq 88\text{--}90\%$ & $P_{plat} \leq 30$
<b>Hyperoxia:</b> ? 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<sub>2</sub>O (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 glucose 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 ↑  $P_aO_2/FiO_2$ , 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<sub>2</sub>O × 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 protocalized, 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 → ↑  $P_aO_2/FiO_2$ , ↑ 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<sub>L</sub>CO, muscle wasting, weakness persists (NEJM 2003;348:683)

Definitions	
<b>Systemic Inflammatory Response Syndrome (SIRS)</b>	2 or more of the following: (1) Temp $>38$ or $<36^{\circ}\text{C}$ , (2) HR $>90$ , (3) RR $>20$ or $\text{PaCO}_2 <32$ , (4) WBC $>12,000$ or $<4000$ or $>10\%$ bands
<b>Sepsis</b>	SIRS + suspected infection
<b>Severe Sepsis</b>	Sepsis + organ dysfunction, hypoperfusion or hypotension Signs of hypoperfusion may incl. lactic acidosis, oliguria, ΔMS
<b>Septic Shock</b>	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)  $\text{O}_2$  sat  
Target MAP  $\geq 65$  mm Hg, CVP 8–12 mm Hg, & UOP  $\geq 0.5$  mL/kg/h using fluid (eg, 500 mL NS q30min) and vasopressors as needed  
Target  $\text{ScvO}_2 \geq 70\%$  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  $\Delta \leq 9$   $\mu\text{g}/\text{dL}$  (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  $\mu\text{g}$  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  $\Delta$  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)

# NOTES

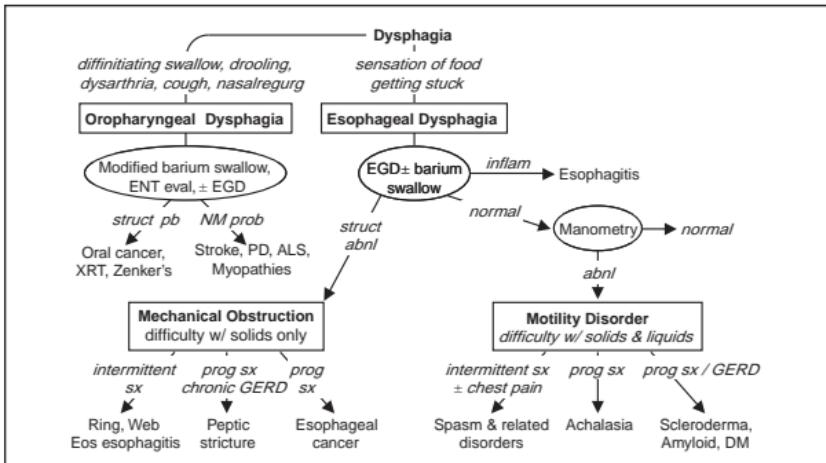
# ESOPHAGEAL AND GASTRIC DISORDERS

## DYSPHAGIA

### Definitions

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

Figure 3-1 Etiologies of and approach to dysphagia (NCP Gastrohep 2008;5:393)



### Achalasia

- Etiologies: idiopathic (most common), pseudoachalasia (due to GE jxn tumor), Chagas
- Sx: dysphagia (solid & liquid), chest pain ( $\frac{1}{3}$  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 ( $\pm$  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 > dysphagia; NSAID, KCl, bisphosp., doxy & tetracycline
- Eos esophagitis: EGD w/ ringed, corrugated eso, stricture, >15 eos/hpf on bx; Rx steroids

## GASTROESOPHAGEAL REFLUX DISEASE (GERD)

### Pathophysiology

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

### Clinical manifestations

- Esophageal: **heartburn**, atypical chest pain, regurgitation, water brash, dysphagia
- 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,  $\oplus$  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<sub>2</sub>RA, espec. if esophagitis (Cochrane 2007;2:003244), antacids PPI achieve relief in 80–90%; side effects: diarrhea, H/A, ↑ risk of *C. diff* & hip fx
- Surgical: fundoplication if refractory sx on meds: success >90%, but >1/2 on meds after 10 y

**Complications** (NEJM 2009;361:2548)

- Barrett's esophagus: 10–15% 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  $\oplus$  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  $\oplus$  wks to y
  - Stool antigen: Se & Sp >90%; use to confirm erad.; high false  $\oplus$  in acute GIB
  - EGD + rapid urease test (Se & Sp >95%) or histo: false  $\ominus$  if on abx, bismuth, PPI
- EGD req to def make dx; consider if fail empiric Rx or alarm features; bx GUs to r/o malign; relook in 6–12 wks if apparently benign ulcer is Ig or complicated or sx persist despite Rx

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

- **If *H. pylori*  $\oplus$ , eradicate:**
  - Triple Rx: clarith 500 bid + amox 1 g bid + PPI bid  $\times$  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  $\times$  5 d  $\rightarrow$  PPI + 2 different abx  $\times$  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*  $\ominus$ : 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 ? ↓ antiptl effect); (c)  $\geq 2$  of the following: age  $>60$ , steroids, or dyspepsia; prior to start test & Rx *H. pylori*
- Consider misoprostol; consider H<sub>2</sub>RA if ASA monotherapy (Lancet 2009;374:119)
- Consider  $\Delta$  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. telangiectasia: 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. telangiectasia)
- **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);  $\ominus$  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  $\geq 0.5$  mL/min and can Rx (coil, vaso, glue)
  - tagged RBC scan**: can localize bleeding rates  $\geq 0.1$  mL/min for surg but unreliable emergent exploratory laparotomy (last resort)

Etiology	Treatment Options
<b>Varices</b> ( <i>Hep</i> 2007;46:922; <i>NEJM</i> 2010;362:823)	<p><u>Pharmacologic</u></p> <p><b>octreotide</b> 50 <math>\mu</math>g IVB → 50 <math>\mu</math>g/h infusion (84% success). Usually <math>\times</math> 5 d, but most benefit w/in 24–48 h. Abx: cirrhotics w/ any GIB should receive prophylaxis: Ctx IV vs. norfloxacin PO (<i>Hep</i> 2004;39:746 &amp; <i>Gastro</i> 2006;131:1049)</p> <p><u>Nonpharmacologic</u></p> <p><b>endoscopic band ligation</b> (&gt;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 (portacaval/splenorenal shunts) rarely used now</p>
<b>PUD</b> ( <i>NEJM</i> 2000;343:310; 2007;356:1631; 2008;359:928; <i>Annals</i> 2010;152:101)	<p>If active bleeding or non-bleeding visible vessel (NBVV) on EGD <b>PPI</b> (eg, omeprazole 80 mg IVB → 8 mg/h) before EGD → ↓ need for endoscopic Rx and ↓ LOS continue IV dose <math>\times</math> 72 h following EGD: ↓ rebleed rate convert to PO after 72 h ? Octreotide if no access to EGD</p> <p><b>Endoscopic therapy (ET)</b>: epi inj + either bipolar cautery or hemoclip; rebleeding risk: 43% (NBVV) to 85% (active bleed) w/o ET vs. 15–20% w/ ET vs. &lt;7% w/ ET + PPI (most w/in 48 h) Clear liquids 6 h after ET if hemodynamically stable Arteriography w/ vasopressin or embolization; surgery (last resort)</p> <p>If adherent clot PPI as above <math>\pm</math> endo removal of clot (if experienced ctr) to r/o NBVV; rebleeding risk 22% w/o ET vs. 5% w/ ET</p> <p>If flat, pigmented spot or clean base No endo Rx indicated; rebleed risk &lt;10%: oral PPI BID Consider early hospital d/c (see criteria in <i>NEJM</i> 2008;359:928)</p> <p>If Pt on ASA for CV disease and PUD GIB endoscopically controlled, resume ASA when CV risk &gt; rebleeding risk, typically 7 d following index bleed (<i>Annals</i> 2010;152:101)</p>
<b>Mallory-Weiss</b>	Usually stops spontaneously; endoscopic Rx if active
<b>Esophagitis</b> <b>Gastritis</b>	PPI, H <sub>2</sub> -receptor antagonists
<b>Diverticular disease</b>	Usually stops spontaneously (~75%) Endoscopic Rx (eg, epinephrine injection, cautery, banding, or hemoclip), arterial vasopressin or embolization, surgery
<b>Angiodysplasia</b>	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  $\ominus$  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  $\ominus$  perform video capsule to evaluate small intestine (*Gastro* 2009;137:1197)  
If still  $\ominus$  consider <sup>99m</sup>Tc-pertechnetate scan ("Meckel's scan"), double-balloon enteroscopy, tagged RBC scan, and arteriography

# DIARRHEA, CONSTIPATION, AND ILEUS

## ACUTE DIARRHEA (<4 wk)

		Acute Infectious Etiologies
Pathogen		Epidemiology & Clinical Sx
<b>Noninflammatory</b>		<b>Predom. disruption small intestine absorp. &amp; secretion. Voluminous diarrhea, N/V. ⊕ fecal WBC &amp; FOB.</b>
<b>Preformed toxin</b>		"Food poisoning," <24 hr dur. <i>S. aureus</i> (meats & dairy), <i>B. cereus</i> (fried rice), <i>C. perfringens</i> (rewarmed meats).
<b>Viral</b>	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.
<b>Bacterial</b>	<i>E. coli</i> (toxigenic)	>50% of traveler's diarrhea; cholera-like toxin; <7 d.
	<i>Vibrio cholerae</i>	Contam H <sub>2</sub> O, fish, shellfish; 50 cases/y in U.S. gulf coast. Severe dehydration & electrolyte depletion.
<b>Parasitic</b> (± malab for mos after Rx)	<i>Giardia</i>	Streams/outdoor sports, travel, outbreaks. Bloating.
	<i>Cryptosporidium</i>	Water-borne outbreak; typically self-limited, can cause chronic infxn if immunosupp. Abd pain (80%), fever (40%). (NEJM 2002;346:1723)
	<i>Cyclospora</i>	Contaminated produce
<b>Inflammatory</b>		<b>Predom. colonic invasion. Small vol diarrhea. LLQ cramps, tenesmus, fever, typically ⊕ fecal WBC or FOB.</b>
<b>Bacterial</b>	<i>Campylobacter</i>	Undercooked poultry, unpasteurized milk, travel to Asia; carried by puppies & kittens. Prodrome; abd pain → "pseudoappendicitis"; c/b GBS, reactive arthritis.
	<i>Salmonella</i> (nontyphoidal)	Eggs, poultry, milk. Bacteremia in 5–10%. 10–33% of bacteremic pts >50 y develop aortitis.
	<i>Shigella</i>	Low inoculum; PTP spread. Abrupt onset; often gross blood & pus in stool; ↑ WBC.
	<i>E. coli</i> (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.
	<i>C. difficile</i>	See later
	<i>Vibrio parahaem.</i>	Undercooked seafood
	<i>Salmonella typhi</i>	Travel to Asia. Systemic toxicity, relative bradycardia, rose spot rash, ileus → pea-soup diarrhea, bacteremia.
	Other	<i>Yersinia</i> : undercooked pork; unpasteurized milk, abd pain → "pseudoappendicitis" (aka mesenteric adenitis) <i>Aeromonas, Pleisomonas, Listeria</i> (meats & cheeses)
<b>Parasitic</b>	<i>E. histolytica</i>	Contaminated food/water, travel (rare in U.S.); liver abscess
<b>Viral</b>	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, significant 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<sub>2</sub>O, 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<sub>2</sub>O) 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  $\times$  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)

- Axx 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  $\times$  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  $\times$  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  $\times$  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<sub>2</sub>RA, 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: +<sup>14</sup>C-xylose & H<sup>+</sup> 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)

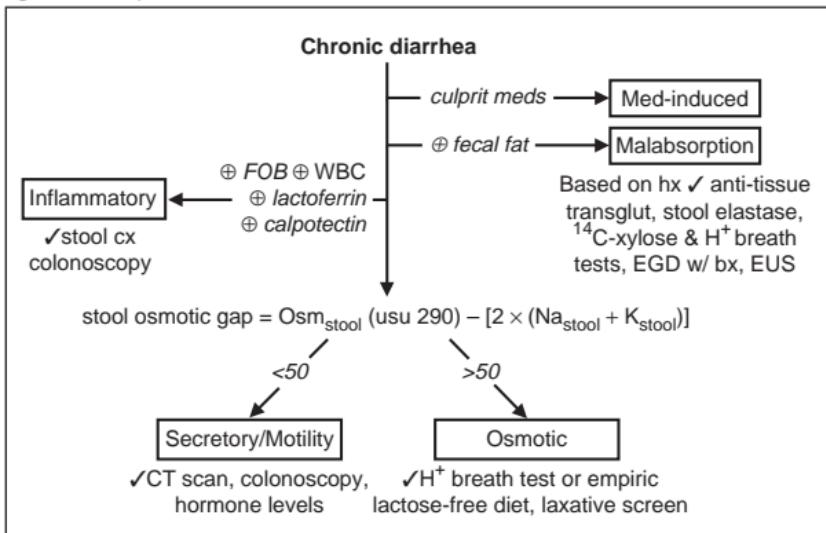
#### Secretory (normal osmotic gap, no Δ diarrhea after NPO, nocturnal diarrhea freq described)

- **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<sub>3</sub> antagonist) for women (↑ risk of ischemic colitis). Constipation: ↑ fiber 25 g/d, lubiprostone (Cl<sup>-</sup> channel activator); tegaserod (5-HT<sub>4</sub> 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, cystitis, colorectal cancer

**Diagnostic studies**

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

**Treatment** (*Am J Gastro* 2008;103:1550)

- Mild: outPt Rx indicated if Pt has few comorbidities and can tolerate POs  
PO abx: (MNZ + FQ) or amox/clav for 7–10 d; liquid diet until clinical improvement
- Severe: inPt Rx if cannot take POs, narcotics needed for pain, or complications  
NPO, IV fluids, NGT (if ileus)  
IV abx (GNR & anaerobic coverage): amp/gent/MNZ or piperacillin-tazobactam
- Abscesses >4 cm should be drained percutaneously or surgically
- Surgery: if progression despite med Rx, undrainable abscess, free perforation, or recurrent disease ( $\geq 2$  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 (espc during a flare; *Lancet* 2010;375:657), AIHA, seroneg arthrits, 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<sub>12</sub>, 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:** ileal 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	
<b>5-ASA</b>	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).
<b>Steroids</b>	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.
<b>Anti-TNF<math>\alpha</math></b>	Mod/Severe flare unresponsive to steroids, flare on immunomodulators. Infliximab: ~20% remission by 30 wks ( <i>NEJM</i> 2005;353:2462)
<b>CsA</b>	Severe flare: 2 mg/kg infusion × 24 h; ✓ Mg; avoid if low chol (seizures)
<b>Surgery</b>	J pouch anal anastomosis; ~6% fail; pouchitis: Rx w/ abx, probiotics
Crohn's Disease	
<b>Abx</b>	FQ/MNZ or amox/clav; best for perianal disease, limited data for colonic CD
<b>Steroids</b>	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
<b>Anti-TNF<math>\alpha</math></b>	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 ( <i>NEJM</i> 2010;362:1383).
<b>Other</b>	Surgery: diverting ileostomy, especially good for perineal disease anti- $\alpha$ 4 $\beta$ 1 integrin (natalizumab): rare risk of PML, restricted use in CD In clinical trials: anti-IL12/23 (ustekinumab), anti- $\alpha$ 4 $\beta$ 7 integrin (vedolizumab)

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

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

- **Anti-TNF $\alpha$ :** 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 bx 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.

# INTESTINAL ISCHEMIA

## ACUTE MESENTERIC ISCHEMIA (25%)

### Etiologies

- **SMA embolism** (50%): from LA (AF), LV (↓ EF), or valves; SMA most prone to embolism
- **Nonocclusive mesenteric ischemia** (25%): transient intestinal hypoperfusion due to ↓ CO, atherosclerosis, sepsis, drugs that ↓ gut perfusion (pressors, cocaine, dig, diuretic)
- **SMA thrombosis** (10%): usually at site of atherosclerosis, often at origin of artery
- **Venous thrombosis** (10%): hypercoagulable states, portal hypertension, IBD, malignancy, inflammation (pancreatitis, peritonitis), pregnancy, trauma, surgery
- **Focal segmental ischemia of the small bowel (<5%):** vascular occlusion to small segments of the small bowel (vasculitis, atheromatous emboli, strangulated hernias, XRT)

### Clinical manifestations

- Occlusive: sudden abd pain out of proportion to abdominal tenderness on exam at least initially (2–4 h) until severe ischemia → frank infarction w/ peritoneal signs
- Nonocclusive: abd distension & pain, though up to 25% may be pain-free, + 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

## 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, ↑ glucose
- 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 US**: typically not useful to visualize pancreas (obscured by bowel gas), but helpful to investigate biliary etiology, ie, gallstones and BD dilatation; can see pseudocyst
  - MRI/MRCP: can detect necrosis; also used to assess for stones & ductal disruption
  - Endoscopic US (EUS): limited role acutely; useful for occult biliary disease (microlithiasis)

## Treatment (Lancet 2008;371:143)

- Supportive therapy: in mild cases, bowel rest is usually sufficient
  - Fluid resuscitation** (may need up to 10 L/d if hemodynamically severe pancreatitis)
  - 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<sup>o</sup> 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](http://www.mdcalc.com/apache-ii-score-for-icu-mortality)): severe if score ≥8

Ranson's Criteria		Prognosis	
At diagnosis	At 48 hours	# of criteria	Mortality
age >55	Hct ↓ >10%	≤2	<5%
WBC >16,000/mm <sup>3</sup>	BUN ↑ >5 mg/dL	3–4	15–20%
glucose >200 mg/dL	base deficit >4 mEq/L	5–6	40%
AST >250 U/L	Ca <8 mEq/L	≥7	>99%
LDH >350 U/L	P <sub>a</sub> O <sub>2</sub> <60 mmHg		
	fluid sequestration >6 L		

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

CT Grade	Description	Points	Necrosis	Points	Total Index	Mortality
A	Normal pancreas c/w mild pancreatitis	0	<33%	2	0–3	3%
B	Enlarged pancreas but w/o inflammation	1	33–50%	4	4–6	6%
C	Pancreatic or peripancreatic inflammation	2	>50%	6	7–10	17%
D	Single peripancreatic fluid collection	3				
E	≥2 Peripancreatic fluid collections or gas in pancreas/retroperitoneum	4				

(*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<sup>2+</sup> in pancreas on KUB/CT
- ERCP/MRCP/EUS high Se for dx: stricture, dil ducts, honeycombing of parenchyma
- Treatment is low-fat diet and enzyme replacement

# ABNORMAL LIVER TESTS

LFTs 3-15

## 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 ( $\uparrow\uparrow$  LDH → ischemia/toxic)
- **Alkaline phosphatase (A $\phi$ ):** enzyme bound in hepatic canalicular membrane besides liver; also found in bone, intestines, kidney, and placenta  
confirm liver origin with: ↑ 5'-NT, ↑ GGT, or A $\phi$  heat fractionation  
↑ levels seen with biliary obstruction or intrahepatic cholestasis (eg, hepatic infiltration)

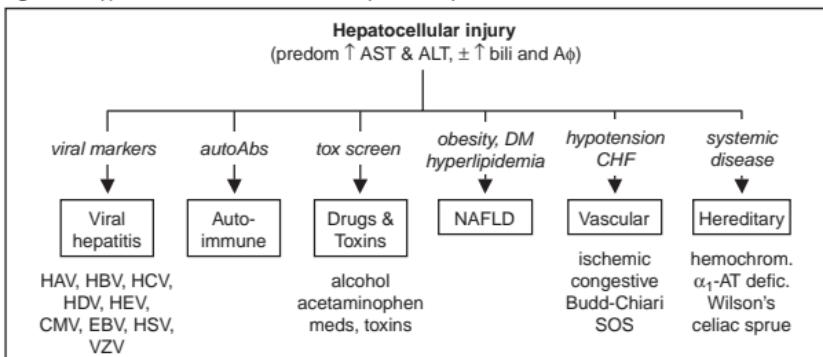
## Tests of hepatic function

- **Albumin:** marker for liver protein synthesis, ↓ slowly in liver failure ( $t_{1/2} \sim 20$  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

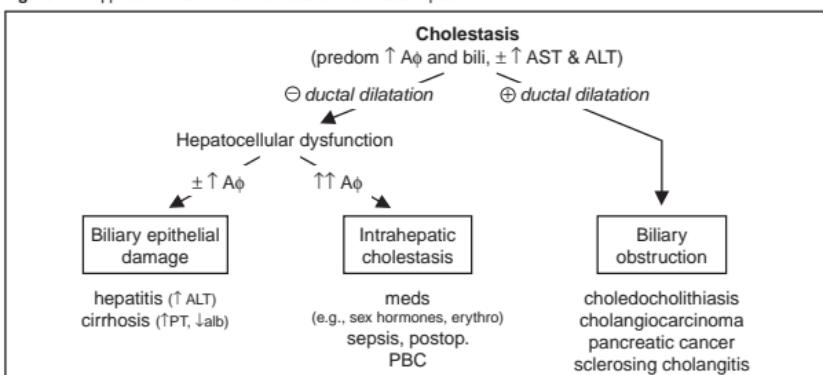
- **Hepatocellular:** ↑ aminotransferases, ± ↑ bilirubin or A $\phi$   
 $\uparrow\uparrow$  ALT & AST (>1000): severe viral hepatitis, acetaminophen, ischemia, Wilson's, AIH
- **Cholestasis:** ↑ A $\phi$  and bilirubin, ± ↑ aminotransferases
- **Isolated hyperbilirubinemia:** ↑ bilirubin (direct or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

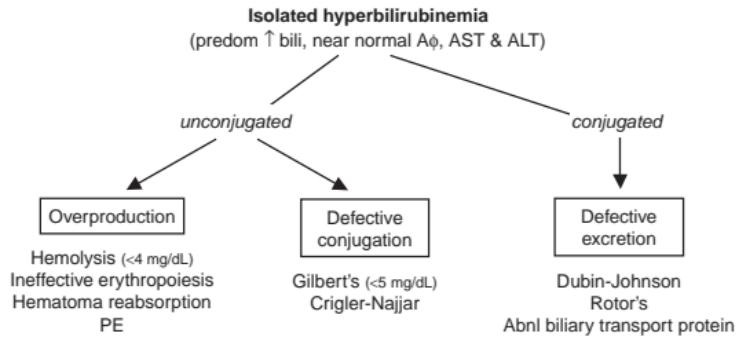


- **Acute workup:** toxins (EtOH, acetaminophen) & vascular abnl (U/S w/ Doppler)  
viral tests: HAV IgM, HBV sAg, HCV RNA, HEV Ab, ± EBV, CMV, HSV, VZV  
autoimmune (ANA, ASMA, ALKM) & ceruloplasmin
- **Chronic workup:** HBV sAg, HCV Ab; Fe, TIBC; glc, HbA1c, TG; ANA, ASMA, ALKM; anti-tissue transglutaminase; ceruloplasmin & α<sub>1</sub>-AT; TSH; vascular abnl (U/S w/ Doppler)

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

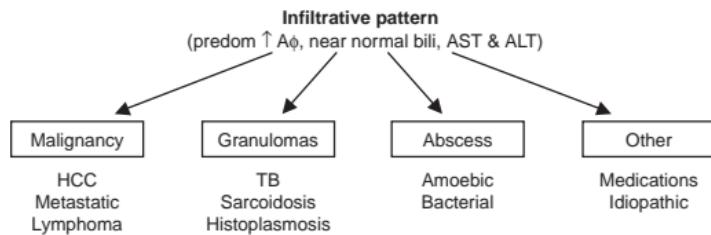


**Figure 3-5** Approach to abnormal liver tests with isolated hyperbilirubinemia



LFTs 3-16

**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<sub>1</sub>-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	Irbesartan	Azathioprine
Allpurinol	Omeprazole	Steroids	Mirtazapine	Captopril
Amiodarone	Paroxetine	Chlorpromazine	Phenothiazine	Carbamazepine
Baclofen	Pyrazinamide	Clopidogrel	Terbinafine	Clindamycin
Bupropion	Rifampin	OCP	Tricyclics	Enalapril
Fluoxetine	Risperidone	Erythromycins		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)

# HEPATITIS

## VIRAL

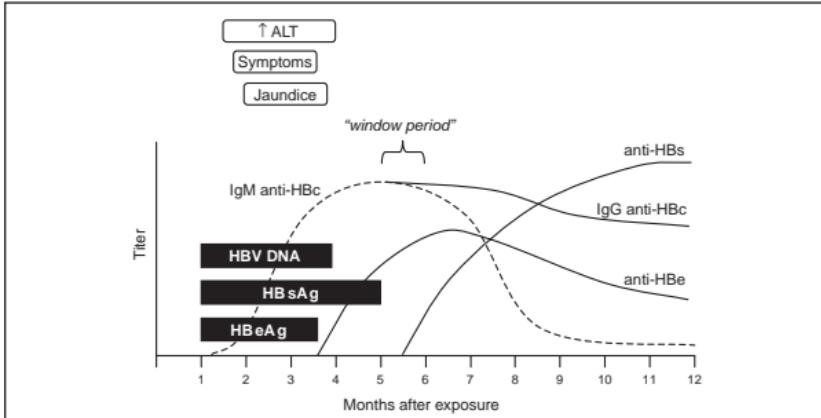
### Hepatitis A (ssRNA; accounts for 30–45% of acute viral hepatitis)

- Transmission: fecal-oral route; contaminated food, water, shellfish; day-care ctr outbreaks
- Incubation: 2–6 wks; no chronic carrier state
- Sx: ↓ appetite, malaise, fever, N/V, RUQ pain, ± jaundice; rarely fulminant
- Diagnosis: acute hepatitis = + IgM anti-HAV; past exposure = + IgG anti-HAV ( $\ominus$  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 ppv: 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 & 1<sup>st</sup> 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  $\ominus$ , anti-HBs not yet +, anti-HBc only clue to infection
  - IgG anti-HBc: indicates previous (HBsAg  $\ominus$ ) 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
<b>Acute hepatitis</b>	+	-	IgM	+	-	+
<b>Window period</b>	-	-	IgM	±	±	+
<b>Recovery</b>	-	+	IgG	-	±	-
<b>Immunization</b>	-	+	-	-	-	-
<b>Chronic hepatitis HBeAg +</b>	+	-	IgG	+	-	+
<b>Chronic hepatitis HBeAg -</b>	+	-	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  $\Delta$  MS or  $\uparrow$  INR (liver transplant ctr)
- Treatment for chronic HBV if: (1) HBeAg  $\oplus$  w/ DNA  $>20,000$  IU/mL & elevated ALT; (2) HBeAg  $\ominus$  w/ DNA  $>2,000$  IU/mL & elevated ALT or liver bx demonstrates stage  $\geq 2$  fibrosis (NEJM 2008;359:1486 & Hep 2009;50:661)
- PEG IFN $\alpha$ -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  $\uparrow$  CK & neuropathy; adefovir (add to lamivudine-resistant Pts) nephrotoxic & resistance occurs, too
- Goal: if HBeAg  $\oplus \rightarrow$  HBeAg  $\ominus$ , anti-HBe  $\oplus$ ; if HBeAg  $\ominus$  or  $\emptyset$  seroconversion  $\rightarrow$  indefinite
- If undergo liver transplant: HBIG + nucleoside analog effective in preventing reinfection
- HIV/HBV **coinfection:** Rx w/ 2 drugs active against both HBV & HIV (NEJM 2007;356:1445)
- If inactive carrier scheduled to receive immunosuppression/chemotherapy  $\rightarrow$  Rx
- Prevention: vaccinate high-risk Pts (3 doses 0, 1 & 6 mos)
- Postexposure (risk infxn ~30%) ppx: HBIG  $\rightarrow$  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%  $\rightarrow$  chronic hepatitis, 20–30% of whom develop cirrhosis (after ~20 y)  $\uparrow$  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):  $\oplus$  in 6 wks, does not = recovery or immunity; can be  $\ominus$  after recovery
  - HCV RNA:  $\oplus$  w/in 2 wks, marker of active infection
  - HCV RIBA: used to confirm  $\oplus$  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 =  $\oplus$  HCV RNA,  $\pm$  anti-HCV
- resolved hepatitis =  $\ominus$  HCV RNA,  $\pm$  anti-HCV
- chronic hepatitis =  $\oplus$  HCV RNA,  $\oplus$  anti-HCV
- Treatment indications (Hep 2009;49:1335)
  - Acute: if no spont clearance at 8–12 wks, consider PEG-IFN $\alpha$ -2a/b  $\times$  12–24 wks
  - Chronic: RNA  $\oplus$ , 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-IFN $\alpha$ -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  $\downarrow < 2$  log) stop Rx, as EVR best predictor of lack of SVR. If partial EVR (RNA  $\downarrow \geq 2$  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  $<400$ k IU/mL, rapid vir resp ( $\emptyset$  RNA at wk 4),  $\emptyset$  cirrhosis,  $\text{♀}$ , age  $<40$  y, wt  $<75$  kg, white/Hispanic,  $\emptyset$  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  $\rightarrow \oplus$ , 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  $\uparrow$  severity of infxn and  $\uparrow$  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/  $\uparrow$  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<sub>6</sub> 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](http://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 1 h → 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<sub>4</sub>, *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<sub>2</sub> 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%

**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,  $\oplus$  ANA, anti-smooth muscle Ab
- **Metabolic diseases** (~5%): hemochromatosis, Wilson's disease,  $\alpha_1$ -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 angioma & palmar erythema ( $\uparrow$  estradiol), Dupuytren's contractures, white nail lines (Muehrcke's lines) & proximal nail beds (Terry's nails),  $\uparrow$  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**

- $\uparrow$  bilirubin,  $\uparrow$  PT (poor correlation w/ bleeding; factor VIII nl as not synthesized by liver),  $\downarrow$  alb,  $\pm$   $\uparrow$  aminotransferases (AST > ALT if late) and  $\uparrow$  Ad (variable),  $\downarrow$  Na,  $\uparrow$  gamma glob
- Anemia (marrow suppression, hypersplenism, Fe and/or folate deficiencies), neutropenia (hypersplenism), thrombocytopenia (hypersplenism,  $\downarrow$  Tpo production by liver, EtOH tox)

**Workup**

- Abdominal U/S w/ Doppler: liver size ( $\uparrow$  L & caudate lobe), r/o HCC, ascites, ✓ patency of portal, splenic, and hepatic veins
- Assess fibrosis: biomarkers (FibroSURE = panel of 6 markers,  $\uparrow$  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,  $\alpha_1$ -AT, AMA
- $\pm$  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):  $\downarrow$  Na intake (1–2 g/d) in all free H<sub>2</sub>O restriction only if Na <125  
**Diuretics:** goal 1 L/d; urine Na/K >1 implies effective aldo block  
spironolactone (100 mg PO qd)  $\pm$  furosemide (40 mg PO qd);  $\uparrow$  doses in proportion  $\varnothing$  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  $\downarrow$  sx  
? albumin replacement:  $\downarrow$  chemical abnl; no  $\Delta$  mortality (*Gastro* 1988;94:1493)  
Beware LVP if SBP as  $\uparrow$  risk of ARF → consider dx tap to r/o SBP first

**Transjugular intrahepatic portosystemic shunt (TIPS)**

- $\downarrow$  ascites in 75%,  $\uparrow$  CrCl,  $\uparrow$  transplant-free survival (NEJM 2000;342:1701)  
 $\uparrow$  encephalopathy (.. TIPS contraindic. if > mild at baseline), no  $\Delta$  quality of life (*Gastro* 2003;124:634); by 1 y ~40% occlude (metal stent); new coated stent  $\downarrow$  (~20%) occlusion and ?  $\downarrow$  mortality (*Gastro* 2004;126:469)
- LVP 1st line Rx b/c TIPS complications (metal stent), but TIPS  $\downarrow$  mort (*Gastro* 2007;133:825)
- Hepatic hydrothorax: 2° diaphragmatic defect; often unilateral, R > L,  $\pm$  ascites  
Treatment:  $\varnothing$  chest tube due to  $\uparrow$  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 Ø 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/physician 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) encephalopathy (PSE)**

- Pathogenesis: failure of liver to detoxify NH<sub>3</sub> + other substances that cause cerebral edema and/or act as false neurotransmitters (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<sub>3</sub> 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<sub>3</sub> → NH<sub>4</sub><sup>+</sup>); goal 2–4 stools/d or **rifaximin** 400 mg tid (↓ gut bacteria → ↓ NH<sub>3</sub> 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<sub>Na</sub> <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)**  
Definition/etiology: abnl pulm gas exchange (A-a gradient ≥15 or P<sub>a</sub>O<sub>2</sub> <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<sub>2</sub>; potential embolization if large vessel on CT, liver transplant only definitive Rx
- **Portopulmonary hypertension:** ↑ PAP; unclear pathogenesis though some response to prostacyclin or to endothelin antagonists; poor prognosis
- **"Cirrhotic" cardiomyopathy:** ↓ inotropic & chronotropic response, ↓ systolic and diastolic fxn, prolonged QT, hyperkinetic circulation; ↑ troponin, BNP (Gut 2008;57:268)
- **Infxn:** Kupffer 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](http://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  $\geq 10$
- 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  $\leq 3$  lesions with largest  $\leq 3$  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

- Recessive disorders of iron sensing (hepcidin) and transport (transferrin) → tissue **iron overload**; nonhereditary: ineffective 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  $\times 100\%$ ; most Se & Sp), ↑ ferritin (acute phase reactant, so poor Sp; often nl in young Pts); MRI (shows “black liver” and can  $\checkmark$  iron stores). If ↑ iron saturation →  $\checkmark$  HFE gene mutation (C282Y/C282Y or C282Y/H63D are  $\oplus$ ). Liver bx to assess damage if: HFE  $\oplus$  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 ( $\downarrow$  intestinal iron transport); deferoxamine if phleb. contraindic.; genetic counseling

### Wilson's disease

- 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 ( $\oplus$  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*, A $\phi$ /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 ( $\downarrow$  toxicity w/ similar efficacy). **Zinc**:  $\downarrow$  intestinal Cu transport and can help delay disease; best used if asx or in conjunction w/ chelation (must give 4–5 h apart from chelators).

**$\alpha_1$ -antitrypsin deficiency ( $\alpha_1$ -AT)** (NEJM 2009;360:2749)

- Abnl  $\alpha_1$ -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  $\alpha_1$ -AT globulin on SPEP,  $\oplus$  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  $\alpha_1$ -AT, ∴ only COPD and not liver dz (no polymerization)
- Treatment: standard Rx for cirrhosis/chronic liver dis.;  $\alpha_1$ -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 IL12a & 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: ↑ A $\phi$ , ↑ bili, ↑ chol,  $\oplus$  anti-mitochondrial Ab (AMA) in 95%. If  $\ominus$  AMA, liver bx not needed due to high Se & Sp. 0.5% gen pop  $\oplus$  AMA & normal LFTs → 10% develop PBC at 6 y. If AMA  $\ominus$ , liver bx (Pts often  $\oplus$  ANA, anti-smooth muscle; same prognosis as  $\oplus$  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 independent 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, ↑ A $\phi$ ,  $\oplus$  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 US and CA 19-9; ? PET  
Liver transplantation: ~30% recurrence, though if UC, colectomy may ↓ recurrence

# HEPATIC VASCULAR DISEASE

## Portal vein thrombosis (PVT) (AI 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), pancreatitis, 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 ( $\text{I}^+$ ), angiography; “portal cavernoma” network of hepatopetal 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 riskVarices: screen at dx; no evidence for 1° ppx of bleed; if bleed endoscopic Rx and  $\beta\text{B}$ . If refractory bleed consider TIPS, shunt. Isolated gastric varices 2° splenic vein thrombosis: splenectomy is curative.

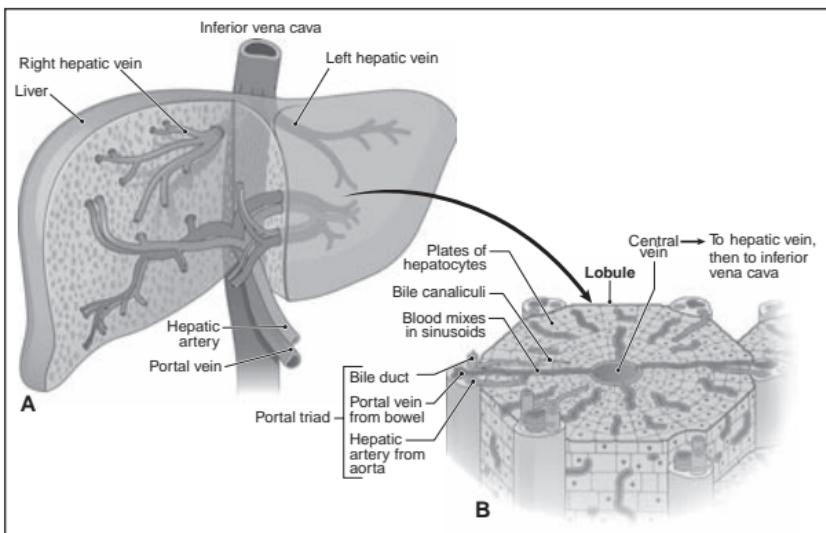
## Budd-Chiari syndrome (NEJM 2004;350:578)

- 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, 1/4 idiopathic
- Symptoms: hepatomegaly, RUQ pain, ascites, dilated venous collaterals
- Dx:  $\pm$  ↑ aminotransferases & AdP; Doppler U/S of hepatic veins (85% Se & Sp); CT ( $\text{I}^+$ ) 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 cyclophosphamide), XRT, Jamaican bush tea
- Clinical manifestations: hepatomegaly, RUQ pain, ascites, weight gain, ↑ bilirubin
- Dx: U/S w/ reversal of portal flow, but often not helpful; dx made clinically ( $\uparrow$  bili, wt gain/ascites, and RUQ pain) or, if necessary, by liver bx or HVPG ( $>10 \text{ mmHg}$ )
- Treatment (20% mortality): supportive; ? defibrotide (adenosine agonist  $\uparrow$  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.

# ASCITES

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

## 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;52:2307): 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)  $\geq 1.1$  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  $\geq 1.1$  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  $\geq 1.1$  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, Afp (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 <sup>3</sup>	Ascites culture
<b>Sterile</b>	<250 polys	⊖
<b>Spontaneous bacterial peritonitis (SBP)</b>	≥250 polys	⊕ (1 organism)
<b>Culture-⊖ neutrocytic ascites (CNNA)</b>	≥250 polys	⊖
<b>Nonneutrocytic baterascites (NNBA)</b>	<250 polys	⊕ (1 organism)
<b>Secondary</b>	≥250 polys	⊕ (polymicro)
<b>Peritoneal dialysis-associated</b>	≥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, Afp >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)

# BILIARY TRACT DISEASE

## CHOLELITHIASIS (GALLSTONES)

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

- >10% adults in the U.S. have gallstones
- Bile = bile salts, phospholipids, cholesterol; ↑ cholesterol saturation in bile + accelerated nucleation + 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, *Cryptosporidium*, *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, Alp, 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  $\oplus$  (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  $\downarrow$  operative time w/o  $\Delta$  rate of complications or conversion to open procedure (*Am J Surg* 2008;194:40).
- Cholecystostomy and percutaneous drainage if too sick for surgery
- Intraoperative cholangiogram or ERCP to r/o choledocholithiasis in Pts w/ jaundice, cholangitis, or stone in BD on U/S

### Complications

- Gangrenous cholecystitis: necrosis w/ risk of empyema and perforation
- Emphysematous cholecystitis: infection by gas-forming organisms (air in GB wall)
- Post CCY: bile duct leak, BD injury or retained stones, cystic duct remnant, sphincter of Oddi dysfxn

## CHOLEDOCHOLITHIASIS

### Definition

- Gallstone lodged in bile duct (BD)

### Epidemiology

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

### Clinical manifestations

- Asymptomatic (50%)
- RUQ/epigastric pain due to obstruction of bile flow  $\rightarrow$   $\uparrow$  BD pressure, jaundice, pruritis, nausea

### Diagnostic studies

- Labs:  $\uparrow$  bilirubin, A $\phi$ ; 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  $\rightarrow$  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  $\Delta$  MS; present in ~15% of Pts

### Diagnostic studies

- RUQ U/S
- Labs:  $\uparrow$  WBC, bilirubin, A $\phi$ , amylase;  $\oplus$  BCx
- ERCP; percutaneous transhepatic cholangiogram (if ERCP unsuccessful)

### Treatment

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

# ACID-BASE DISTURBANCES

## GENERAL

### Definitions

- Acidemia → pH < 7.36, alkalemia → pH > 7.44
- Acidosis → process that increases  $[H^+]$ ; alkalosis → process that decreases  $[H^+]$
- Primary disorders: metabolic acidosis or alkalosis, respiratory acidosis or alkalosis
- Compensation
  - respiratory: hyper- or hypoventilation alters  $P_aCO_2$  to counteract 1° metabolic process
  - renal: excretion/retention of  $H^+/HCO_3$  to counteract 1° respiratory process
  - respiratory compensation occurs in 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 <sub>4</sub>
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

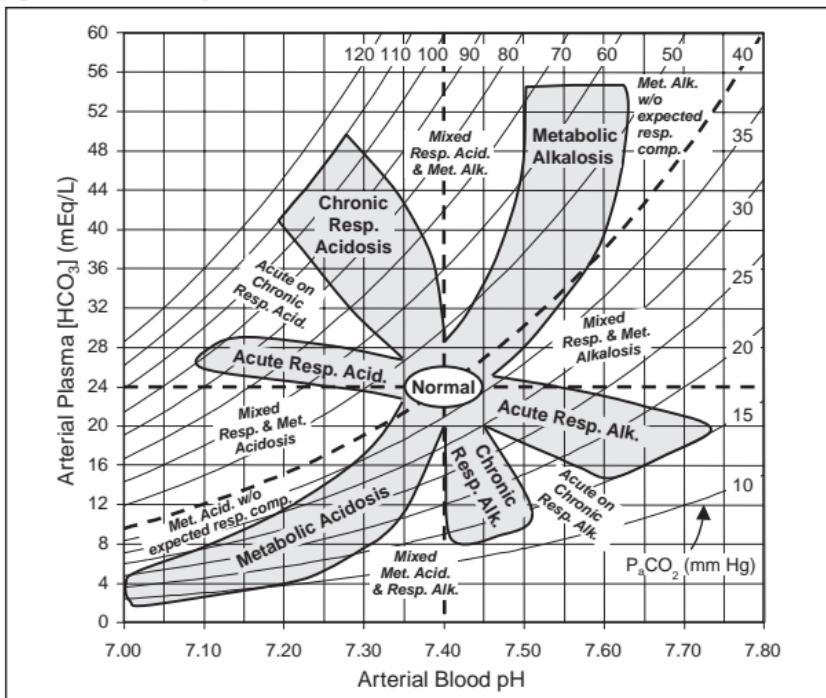
Primary Disorders				
Primary disorder	Problem	pH	$HCO_3$	$P_aCO_2$
Metabolic acidosis	gain of $H^+$ or loss of $HCO_3$	↓	↓↓	↓
Metabolic alkalosis	gain of $HCO_3$ or loss of $H^+$	↑	↑↑	↑
Respiratory acidosis	hypoventilation	↓	↑	↑↑
Respiratory alkalosis	hyperventilation	↑	↓	↓↓

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

### 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 ...
  - $\uparrow P_aCO_2 + \uparrow HCO_3 \rightarrow$  resp. acid. + met. alk.
  - $\downarrow P_aCO_2 + \downarrow HCO_3 \rightarrow$  resp. alk. + met. acid.
  - normal  $P_aCO_2$  &  $HCO_3$ , but  $\uparrow AG \rightarrow$  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  $\text{pH} \sim 0.04 \downarrow$ ,  $\text{PaCO}_2 \sim 8 \text{ mm Hg} \uparrow$ , and  $\text{HCO}_3 \sim 2 \text{ mEq} \uparrow$ . (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) =  $\text{Na} - (\text{Cl} + \text{HCO}_3)$  = unmeasured anions – unmeasured cations  
if ↑ glc, use measured *not* corrected Na  
expected AG is  $[\text{albumin}] \times 2.5$  (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 1 AG, ✓ delta-delta ( $\Delta\Delta = \Delta\text{AG}/\Delta\text{HCO}_3$ ) to assess if there is an additional metabolic acid-base disturbance;  $\Delta\text{AG} = (\text{calculated AG} - \text{expected AG})$ ,  $\Delta\text{HCO}_3 = (24 - \text{HCO}_3)$   
 $\Delta\Delta = 1 - 2 \rightarrow$  pure AG metabolic acidosis  
 $\Delta\Delta < 1 \rightarrow$  AG metabolic acidosis *and* simultaneous non-AG acidosis  
 $\Delta\Delta > 2 \rightarrow$  AG metabolic acidosis *and* simultaneous metabolic alkalosis

Etiologies of AG Metabolic Acidosis	
Ketoacidosis	Diabetes mellitus, alcoholism, starvation
Lactic acidosis	<b>Type A:</b> impairment in tissue oxygenation, eg, <b>circulatory or respiratory failure, sepsis, ischemic bowel, carbon monoxide, cyanide</b> <b>Type B:</b> no impairment in tissue oxygenation, eg, malignancy, alcoholism, meds (metformin, NRTIs, salicylates, propylene glycol) <b>D-lactic acidosis:</b> 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	<b>Methanol</b> (windshield fluid, antifreeze, solvents, fuel): metab to formic acid <b>Ethylene glycol</b> (antifreeze): metab to glycolic and oxalic acids <b>Propylene glycol</b> (pharmaceutical solvent, eg, IV diazepam & lorazepam; antifreeze): lactic acidosis <b>Salicylates:</b> metabolic acidosis (from lactate, ketones) + respiratory alkalosis due to stimulation of CNS respiratory center <b>Acetaminophen:</b> 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  $\beta$ -hydroxybutyrate ( $\beta$ OHB)  
nb, urine acetoacetate often not present in early ketoacidosis due to shunting to  $\beta$ OHB; ∴ acetoacetate may later turn  $\oplus$ , but does not signify worsening disease
- If  $\ominus$  ketones, ✓ renal function, lactate, toxin screen, and osmolal gap
- Osmolal gap (OG)** = measured osmoles – calculated osmoles  

$$\text{calculated osmoles} = (2 \times \text{Na}) + (\text{glucose}/18) + (\text{BUN}/2.8)$$

(can + [EtOH/4.6] if have EtOH level and want to test if other ingestions)  
 $\text{OG} > 10 \rightarrow$  suggests ingestion (see below)

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

**Etiologies of Non-AG Metabolic Acidosis**

GI losses of $\text{HCO}_3^-$	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 $\text{HCO}_3^-$ ; rapid correction of resp. alk. → transient acidosis until $\text{HCO}_3^-$ regenerated
Ureteral diversion	Colonic $\text{Cl}^-/\text{HCO}_3^-$ exchange, ammonium reabsorption

**Workup for non-AG metabolic acidosis**

- Evaluate history for causes (see above)
- ✓ **urine anion gap (UAG)** =  $(\text{U}_{\text{Na}} + \text{U}_{\text{K}}) - \text{U}_{\text{Cl}}$   
 $\text{UAG}$  = unmeasured anions – unmeasured cations; as  $\text{NH}_4^+$  is primary unmeasured cation, UAG is indirect assay for renal  $\text{NH}_4^+$  excretion (NEJM 1988;318:594)
- $\ominus$  UAG → ↑ renal  $\text{NH}_4^+$  excretion → appropriate renal response to acidemia  
Ddx: GI causes, type II RTA, ingestions or dilutional
- $\oplus$  UAG → failure of kidneys to secrete  $\text{NH}_4^+$   
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 ( $\text{U}_{\text{Na}} > 25$ ) & w/o AG met. acid. →  $\oplus$  UAG

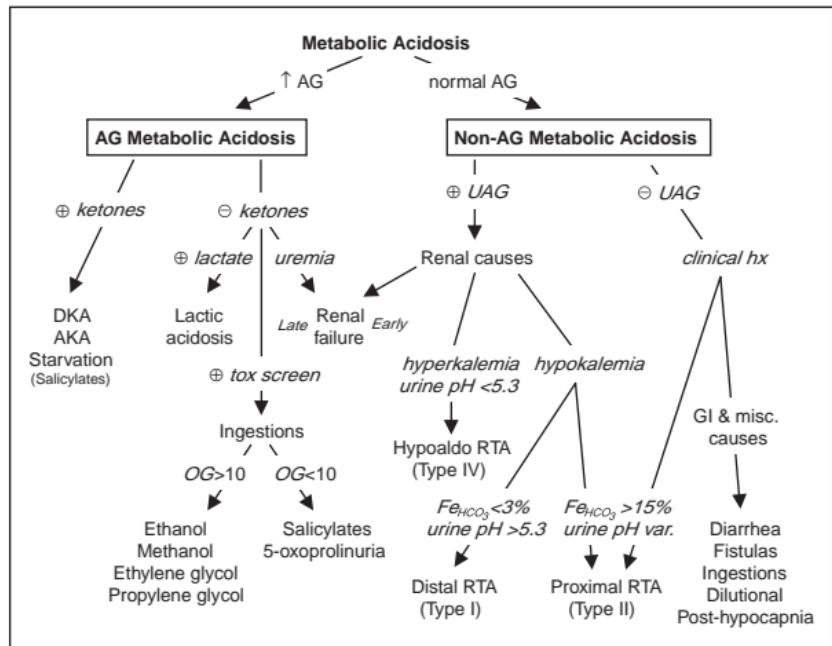
**Renal tubular acidoses (RTAs)**

- Proximal (Type II):** ↓ proximal reabsorption of  $\text{HCO}_3^-$   
 $1^\circ$  (Fanconi's syndrome = ↓ proximal reabsorption of  $\text{HCO}_3^-$ ,  $\text{PO}_4^-$ , glc, amino acids), paraprotein (multiple myeloma, amyloidosis), meds (acetazolamide, heavy metals, ifosfamide), renal transplant, ↓ Vit D, NRTIs
- Distal (Type I):** defective distal  $\text{H}^+$  secretion  
 $1^\circ$ , 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 → ↓  $\text{NH}_3$  synthesis/delivery → ↓ urine acid carrying capacity  
↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV  
normal renin, ↓ aldo synthesis:  $1^\circ$  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 <sub>3</sub> <sup>b</sup>	Serum K
Proximal	II	moderate	±	<5.3 <sup>a</sup>	>15%	↓
Distal	I	severe	⊕	>5.3	<3%	↓ <sup>c</sup>
Hypoaldo	IV	mild	⊕	<5.3	<3%	↑

<sup>a</sup>urine pH will rise above 5.3 in the setting of HCO<sub>3</sub> load<sup>b</sup>FeHCO<sub>3</sub> should be checked after an HCO<sub>3</sub> load<sup>c</sup>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<sub>4</sub> as needed
- Lactic acidosis: treat underlying condition, avoid vasoconstrictors
- Renal failure: hemodialysis
- Methanol & ethylene glycol: early fomepizole, vit. B<sub>6</sub> (ethylene glycol), folate (methanol), hemodialysis (especially if late presentation) (NEJM 2009;360:2216)
- Alkali therapy: NaHCO<sub>3</sub> (eg, 3 50-mmol amp in 1 L D<sub>5</sub>W) to get serum HCO<sub>3</sub> > 8 and pH > 7.2 (estimate mmol of HCO<sub>3</sub> needed as 8-[HCO<sub>3</sub>]<sub>serum</sub> × wt × 0.5) side effects: volume overload, hypernatremia, ↓ ICa, ↑ P<sub>a</sub>CO<sub>2</sub> (and ∴ possibly intracellular acidosis), overshoot; no proven benefit in lactic acidosis (Annals 1990;112:492)

## METABOLIC ALKALOSIS

### Pathophysiology

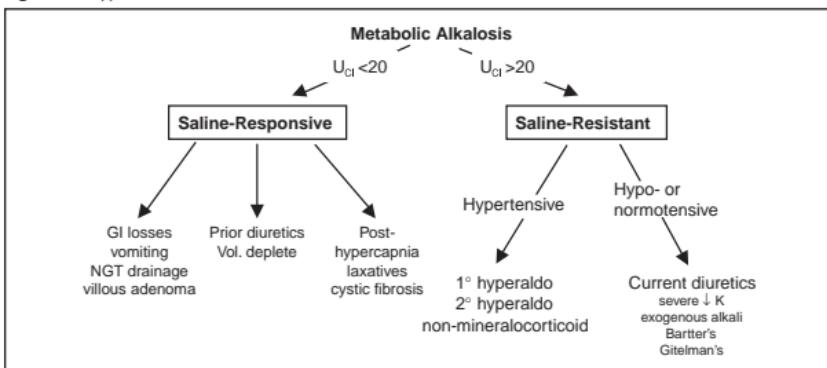
- Saline-responsive etiologies require *initiating event* and *maintenance factors*, whereas saline-resistant etiologies develop from various causes
- Initiating event*
  - loss of H<sup>+</sup> from GI tract or kidneys
  - exogenous alkali
- contraction alkalosis:** diuresis → excretion of HCO<sub>3</sub>-poor fluid → extracellular fluid “contracts” around fixed amount of HCO<sub>3</sub> → ↑ HCO<sub>3</sub> concentration
- posthypercapnia:** respiratory acidosis → renal compensation with HCO<sub>3</sub> retention; rapid correction of respiratory disorder (eg, with intubation) → transient excess HCO<sub>3</sub>
- Maintenance factors*
  - volume depletion** → ↑ proximal reabsorption of NaHCO<sub>3</sub> and ↑ aldosterone (see next)
  - hyperaldosteronism** (either 1° or 2°) → distal Na reabsorption in exchange for K<sup>+</sup> and H<sup>+</sup> excretion (and consequent HCO<sub>3</sub> retention)
  - hypokalemia** → transcellular K<sup>+</sup>/H<sup>+</sup> exchange; intracellular acidosis in renal proximal tubular cells promotes bicarbonate reabsorption and ammoniagenesis

Etiologies of Metabolic Alkalosis	
<b>Saline-responsive</b>	GI loss of $\text{H}^+$ : vomiting, NGT drainage, villous adenoma Diuretic use Posthypercapnia, laxatives, cystic fibrosis
<b>Saline-resistant</b>	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  $\text{U}_{\text{Cl}}$   
 $\text{U}_{\text{Cl}} < 20 \text{ mEq/L} \rightarrow$  saline-responsive  
 $\text{U}_{\text{Cl}} > 20 \text{ mEq/L} \rightarrow$  saline-resistant (unless currently receiving diuretics)  
 $(\text{U}_{\text{Na}}$  unreliable determinant of volume status as alkalemia  $\rightarrow \uparrow \text{HCO}_3$  excretion  $\rightarrow$   
 $\uparrow \text{Na}$  excretion; negatively charged  $\text{HCO}_3$  "drags"  $\text{Na}^+$  along)  
If  $\text{U}_{\text{Cl}} > 20$  and volume replete, ✓ **blood pressure**

Figure 4-3 Approach to metabolic alkalosis

**Treatment of severe metabolic alkalosis ( $\text{pH} > 7.6$ )**

- 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,  $\text{O}_2$  in chronic hypercapnia ( $\downarrow$  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  $\rightarrow \uparrow \text{RR} \rightarrow$  resp. alk., but eventual muscle fatigue  $\rightarrow$  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  $\uparrow$  minute ventilation

**RESPIRATORY ALKALOSIS****Etiologies (NEJM 2002;347:43)**

- Hypoxia  $\rightarrow$  hyperventilation:** pneumonia, pulm. edema, PE, restrictive lung disease
- Primary hyperventilation**  
CNS disorders, pain, anxiety  
drugs: salicylates, progesterone, methylxanthines  
pregnancy, sepsis, hepatic failure

# SODIUM AND WATER HOMEOSTASIS

## OVERVIEW

### General

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

### Key hormones

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

## HYPONATREMIA

### Pathophysiology

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

### Workup (NEJM 2000;342:1581)

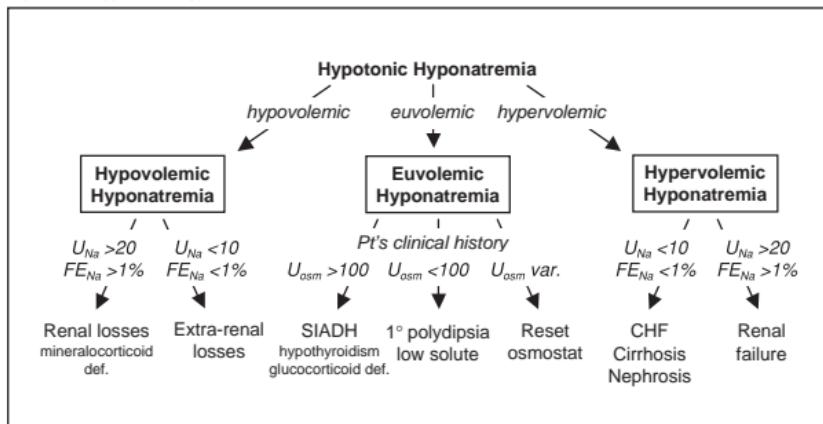
#### • Measure plasma osmolality

*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  $\uparrow$  glc  $> 100$  mg/dL  $\rightarrow \downarrow [Na]$  by 2.4 mEq/L

*Isotonic hyponatremia*: rare lab artifact from hyperlipidemia or hyperproteinemia

- For hypotonic hyponatremia,  $\checkmark$  **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 &  $\downarrow$  solute intake moreover,  $U_{osm} > 300 \neq$  SIADH; must determine if  $\uparrow ADH$  appropriate or inappropriate however,  $U_{osm}$  important when deciding on treatment (see below)
- If euvolemic and  $\uparrow U_{osm}$ , 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, inappropriately ↑  $U_{Osm}$ , 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** (splanchic 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<sub>2</sub>O;  $U_{Na} > 20$  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**

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

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<sub>2</sub>O 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<sub>2</sub>O) given to Pt with SIADH with  $U_{osm} = 616 \rightarrow 308$  mOsm solute excreted in 0.5 L H<sub>2</sub>O → net gain 0.5 L H<sub>2</sub>O → ↓  $[Na]_{serum}$

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

- Hypovolemic hyponatremia:** volume repletion with **normal saline** once volume replete → stimulus for ADH removed → kidneys will excrete free H<sub>2</sub>O → 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<sub>2</sub>O 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
    - demeclacycline: causes nephrogenic DI, ↓  $U_{osm}$

**Hypervolemic hyponatremia: free water restrict**

mobilize excess Na & H<sub>2</sub>O (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

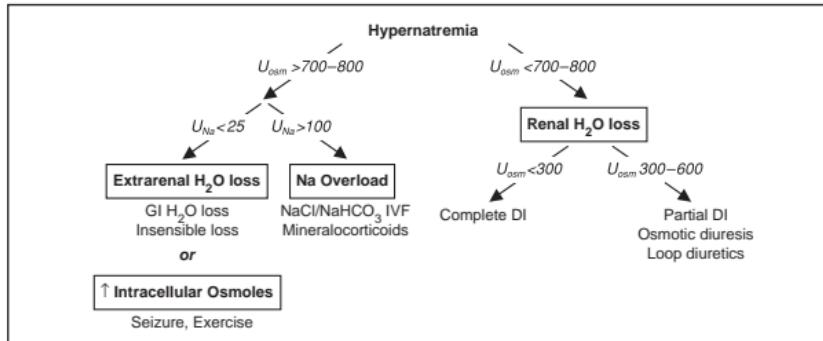
### Pathophysiology (NEJM 2000;342:1493)

- 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<sub>2</sub>O

### Workup

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

Figure 4-5 Approach to hypernatremia



### Extrarenal H<sub>2</sub>O loss (U<sub>osm</sub> >700–800)

- GI H<sub>2</sub>O loss:** vomiting, NGT drainage, osmotic diarrhea, fistula
- Insensible loss:** fever, exercise, ventilation

### Renal H<sub>2</sub>O loss (U<sub>osm</sub> <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<sub>osm</sub> >700–800)

- Na overload:** hypertonic saline (eg, resuscitation w/ NaHCO<sub>3</sub>), mineralocorticoid excess
- Seizures, ↑ exercise:** ↑ intracellular osmoles → H<sub>2</sub>O shifts → transient ↑ [Na]<sub>serum</sub>

### Treatment

- Restore access to H<sub>2</sub>O or supply daily requirement of H<sub>2</sub>O (≥1 L/d)**
- Replace free H<sub>2</sub>O deficit** (also replace concurrent volume deficit if appropriate):

$$\text{Free H}_2\text{O deficit (L)} = \frac{[\text{Na}]_{\text{serum}} - 140}{140} \times \text{TBW} \quad \text{TBW} = \text{wt (kg)} \times 0.6 \text{ (♂)} \text{ or } 0.5 \text{ (♀)} \\ \text{if elderly use } 0.5 \text{ (♂)} \text{ or } 0.45 \text{ (♀)}$$

shortcut: for typical 70-kg man, free H<sub>2</sub>O deficit (L) ~ ([Na]<sub>serum</sub> – 140)/3

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

e.g., 1 L D<sub>5</sub>W given to 70-kg man w/ [Na] = 160 mEq/L will ↓ [Na]<sub>serum</sub> 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<sub>2</sub>O will ↓ [Na] by ~0.5 mEq/L/h
- ½ NS (77 mEq/L) or ¼ NS (38 mEq/L) provides both volume & free H<sub>2</sub>O (500 or 750 mL of free H<sub>2</sub>O per L, respectively); can give free H<sub>2</sub>O via NGT/OGT
- Formulas provide only estimates; ∴ recheck serum Na frequently
- DI and osmotic diuresis:** see “Polyuria” section below
- Na overload:** D<sub>5</sub>W + 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)  $\times U_{osm}$   
 $>1000 \text{ mOsm/d} \rightarrow \text{osmotic diuresis}$   
 $<800 \text{ mOsm/d} \rightarrow \text{water diuresis}$

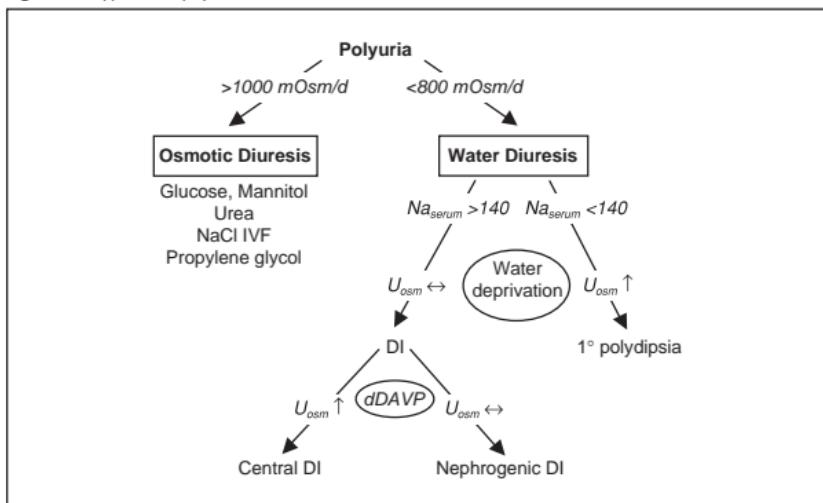
### Osmotic diuresis

- 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:
    - $U_{osm} \uparrow$  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<sub>2</sub>O
- **Osmotic diuresis:** address underlying cause, replace free H<sub>2</sub>O deficit (see “Hypernatremia” for formula to calculate) and ongoing losses
- **DI:**
  - central DI: desmopressin (dDAVP)
  - nephrogenic DI: treat underlying cause if possible; Na restriction + thiazide (mild volume depletion → ↓ 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<sub>12</sub>, AML crisis), hypothermia

### GI potassium losses ( $U_K < 25 \text{ mEq/d}$ or $< 15 \text{ mEq/L}$ 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 ( $U_K > 30 \text{ mEq/d}$ or $> 15 \text{ mEq/L}$ 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)  
nonaldo mineralocorticoid (eg, Cushing's, Liddle's, exogenous mineralocort., licorice)

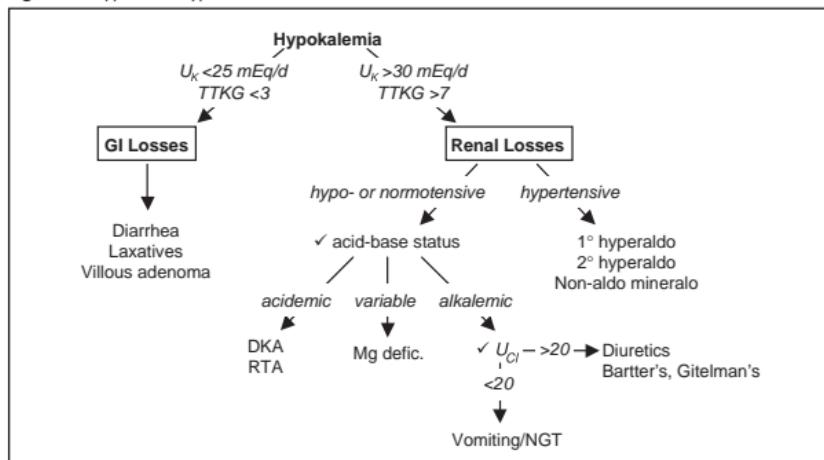
### Clinical manifestations

- 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  $U_K$  and **transtubular potassium gradient (TTKG)** =  $(U_K/P_K) / (U_{\text{osm}}/P_{\text{osm}})$   
 $U_K > 30 \text{ mEq/d}$  or  $> 15 \text{ mEq/L}$  or TTKG  $> 7$  → renal loss  
 $U_K < 25 \text{ mEq/d}$  or  $< 15 \text{ mEq/L}$  or TTKG  $< 3$  → extrarenal loss
- If renal losses, ✓ **BP, acid-base,  $U_{Cl}$**  ( $U_{Na}$  unreliable for volume status w/ alkalemia)

Figure 4-7 Approach to hypokalemia



**Treatment**

- If true potassium deficit: **potassium repletion** ( $\downarrow 1 \text{ mEq/L} = 200 \text{ mEq}$  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  $\rightarrow \uparrow$  insulin  $\rightarrow$  intracellular potassium shifts)
- Replete Mg as necessary

**HYPERKALEMIA****Transcellular shifts**

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

**Decreased GFR**

- Any cause of oligouric or anuric AKI or any cause of end stage renal disease

**Normal GFR but with  $\downarrow$  renal K excretion**

- Normal aldosterone function
  - $\downarrow$  EAV (K excretion limited by  $\downarrow$  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)
  - $\downarrow$  renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV
  - normal renin,  $\downarrow$  aldo synthesis: 1° adrenal disorders, ACEI, ARBs, heparin
  - $\downarrow$  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,  $\uparrow$  PR interval,  $\uparrow$  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,  $\uparrow$  plt or WBC)
- Rule out transcellular shift
- **Assess GFR**, if normal:
  - Consider  $\downarrow$  distal Na delivery and urine flow
  - $\checkmark$  transtubular K gradient (TTKG) =  $(U_K/P_K)/(U_{osm}/P_{osm})$ ,  $< 7$  c/w hypoaldo

**Treatment of Hyperkalemia**

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

<sup>a</sup>calcium chloride contains more calcium and is typically reserved for use in codes ( $\uparrow$  risk of tissue necrosis)

<sup>b</sup>increased risk of intestinal necrosis with postoperative ileus

- Rate of onset important to note when establishing a treatment plan
- Calcium helps prevent cardiac complications;  $\therefore$  should be initial Rx, esp. if ECG  $\Delta$ s
- Insulin, bicarbonate (esp. if acidemic), and  $\beta$ 2 agonists should follow to  $\downarrow$  plasma K
- Treatments that **eliminate total body K essential** as other Rx's will wear off with time; kayexalate  $\pm$  diuretics may be effective in many cases, but emergent hemodialysis should be considered in life-threatening situations

# RENAL FAILURE

## 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<sub>Na</sub>)** =  $(U_{Na}/P_{Na})/(U_{Cr}/P_{Cr})$ 
  - <1% → prerenal, contrast, or glomerulonephritis; >2% → ATN
  - In setting of diuretics, ✓ FE<sub>UN</sub> =  $(U_{UN}/P_{UN})/(U_{Cr}/P_{Cr})$ ; <35% → prerenal
- Renal US: 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 ( <i>Lancet</i> 2005;365:417)	
Etiologies	U/A, Sediment, Indices
<b>Prerenal</b> <ul style="list-style-type: none"> <li>↓ Effective arterial volume (<i>NEJM</i> 2007;357:797)           <ul style="list-style-type: none"> <li>Hypovolemia, ↓ cardiac contractility (eg, CHF), systemic vasodilatation (eg, sepsis)</li> </ul> </li> <li><b>Renal vasoconstriction</b> <ul style="list-style-type: none"> <li>NSAIDs, ACEI/ARB, contrast</li> <li>calcineurin inhibitors, hepatorenal, hypercalcemia</li> </ul> </li> <li><b>Large vessel:</b> RAS (bilateral + ACEI), thrombosis, embolism, dissection, vasculitis, compression</li> </ul>	<b>Bland</b> <ul style="list-style-type: none"> <li>Transparent hyaline casts</li> <li>FE<sub>Na</sub> &lt; 1%</li> <li>BUN/Cr &gt; 20</li> <li>U<sub>osm</sub> &gt; 500</li> </ul>
<b>Intrinsic</b> <ul style="list-style-type: none"> <li><b>Acute tubular necrosis (ATN)</b> <ul style="list-style-type: none"> <li><i>Ischemia:</i> progression of prerenal disease</li> <li><i>Toxins</i> <ul style="list-style-type: none"> <li>Drugs: AG, amphotericin, cisplatin</li> <li>Pigments: Hb, myoglobin (<i>NEJM</i> 2009;361:62)</li> <li>Proteins: Ig light chains</li> <li>Crystals: UA, ACV, MTX, indinavir, oral NaPO<sub>4</sub></li> </ul> </li> <li><i>Contrast-induced AKI (CIAKI):</i> ↓ RBF + toxin</li> </ul> </li> <li><b>Acute interstitial nephritis (AIN)</b> <ul style="list-style-type: none"> <li>Allergic: β-lactams, sulfa drugs, NSAIDs, PPIs</li> <li><i>Infection:</i> pyelonephritis, legionella</li> <li><i>Infiltrative:</i> sarcoid, lymphoma, leukemia</li> <li><i>Autoimmune:</i> Sjögren's, TINU syndrome, IgG4, SLE</li> </ul> </li> <li><b>Small vessel:</b> cholesterol emboli, thrombotic microangiopathy (HUS/TTP, DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)</li> <li><b>Glomerulonephritis</b> (see “Glomerular Disease”)</li> </ul>	<ul style="list-style-type: none"> <li>Pigmented granular muddy brown casts in ~75% (± in CIAKI)</li> <li>± RBCs &amp; protein from tubular damage</li> <li>FE<sub>Na</sub> &gt; 2% (except pigment &amp; CIAKI)</li> <li>U<sub>osm</sub> &lt; 350</li> </ul>
<b>Post</b> <ul style="list-style-type: none"> <li><b>Bladder neck:</b> BPH, prostate cancer, neurogenic bladder, anticholinergic meds</li> <li><b>Ureteral</b> (bilateral): malig, LAN, retroperitoneal fibrosis, nephrolithiasis</li> </ul>	<ul style="list-style-type: none"> <li>WBCs, WBC casts, ± RBCs</li> <li>⊕ urine eos in abx</li> <li>⊕ lymphs in NSAIDs</li> </ul>

### **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<sub>3</sub>: 3 mL/kg/h × 1 h before, 1 mL/kg/h × 6 h after (*JAMA* 2004;291:2328)
    - unclear if NaHCO<sub>3</sub> 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 ( $\uparrow K$ ,  $\uparrow PO_4$ ), & 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  $\Delta$  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](http://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 <sup>2</sup>	Goals
1 (nl or $\uparrow$ 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 ureemicus, metallic taste, susceptibility to drug O/D, decreased temperature
Skin	Uremic frost (white crystals in & on skin), pruritis, calciphylaxis, NSF
Neurologic	Encephalopathy ( $\Delta$ MS, $\downarrow$ 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	$\uparrow$ K, $\uparrow$ PO <sub>4</sub> , acidosis, $\downarrow$ 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<sub>4</sub>, ? moderate protein restriction, strict glucose 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  $\uparrow$  30% or K  $>5.4$  (after dietary  $\Delta$  & 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<sub>3</sub> <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<sub>4</sub>, ↓ 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<sub>4</sub> and ↓ Ca → calcium acetate (PhosLo) or calcium carbonate  
 if refractory ↑ PO<sub>4</sub> or in setting of ↑ Ca → sevelamer (Renagel), lanthanum (Fosrenol)  
 if severe ↑ PO<sub>4</sub> → aluminum hydroxide (Amphojel), *short-term use only*  
 calcitriol or paricalcitol if Ca-PO<sub>4</sub> 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 ( <i>may start here if inPt</i> ) ↑ 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

**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<sub>2</sub>O) via transmembrane pressure (TMP) gradient  
Solute removal via transmembrane concentration gradient and inversely proportional  
to size (∴ effective removal of K, urea, and Cr, but not PO<sub>4</sub>)
- Typical orders: duration, volume removal goals, K and Ca in dialysate bath, anticoagulation
- Complications: hypotension, arrhythmia, access complications, disequilibrium syndrome

Vascular Access		
	Advantages	Disadvantages
<b>AV Fistula</b>	Highest patency Lowest risk of bacteremia	Long maturation time (2–6 mo) Primary nonfunction (20%)
<b>AV Graft</b>	Easier to create than AVF Maturation time (2–3 wks)	Poor 1° patency, often requiring thrombectomy or angioplasty
<b>Catheter</b>	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<sub>4</sub>). 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<sub>3</sub> (requires heparin to prevent machine from clotting) **vs. citrate** (hepatically metabolized to HCO<sub>3</sub>; provides anticoagulation w/ in machine via Ca chelation; ∴ need Ca infusion to maintain serum Ca)
- Complications: hypotension, ↓ PO<sub>4</sub>, 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<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup>
  - 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

# GLOMERULAR DISEASE

## 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,  $\pm$  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 $\oplus$ Vasculitis (pauci-immune or minimal staining) ~40–45% of total						
Disease	Gran	Renal	Pulm	Asthma	ANCA Type*	ANCA $\oplus$
Wegener's granulomatosis	$\oplus$	80%	90% (+ ENT)	—	c-ANCA (anti-PR3)	90%
Microscopic polyangiitis	—	90%	50%	—	p-ANCA (anti-MPO)	70%
Churg-Strauss syndrome	$\oplus$	45%	70%	$\oplus$	p-ANCA (anti-MPO)	50%

\*Predominant ANCA type; either p- or c-ANCA can be seen in all three diseases. (NEJM 1997;337:1512)

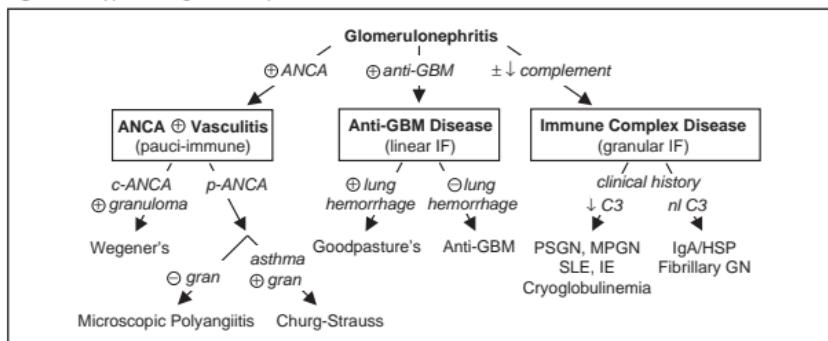
Anti-GBM Disease (linear staining) ~15% of total			
Disease	Glomerulonephritis	Pulm hemorrhage	Anti-GBM
Goodpasture's	$\oplus$	$\oplus$	$\oplus$
Anti-GBM disease	$\oplus$	—	$\oplus$

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

### Workup (Archives 2001;161:25)

- AGN/RPGN  $\pm$  lung hemorrhage is an emergency  $\rightarrow$  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:  $\downarrow$  Hct & Plts, schistocytes on smear,  $\uparrow$  LDH
  - cholesterol emboli (Lancet 2010;375:1650): purple toes, livedo,  $\downarrow$  C3/C4, eos, prior cath
  - AIN: rash, new drug exposure, urine WBCs (incl eos)  $\pm$  WBC casts
  - myeloma: anemia, hypercalcemia, lytic bone lesions, +SPEP/UPEP
- Renal biopsy with immunofluorescence (IF)  $\pm$  electron microscopy (EM)

Figure 4-8 Approach to glomerulonephritis



**Treatment**

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

**ASYMPTOMATIC GLOMERULAR HEMATURIA****Definition and Etiologies**

- Hematuria  $\pm$  proteinuria of glomerular origin w/o renal insufficiency or systemic disease (nonglomerular hematuria more common; see "Hematuria")
- 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  $\sim$  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,  $\pm$  fish oils (*NEJM* 1994;331:1194); steroids (*JASN* 2004;15:157)  $\pm$  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,  $\uparrow$  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<sub>2</sub> 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  $\pm$  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  $\rightarrow$  microalbuminuria  $\rightarrow$  dipstick  $\oplus$   $\rightarrow$  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;  $\pm$  oval fat bodies ("Maltese crosses," *NEJM* 2007;357:806)
- Measure proteinuria: 24-h urine collection or urine prot/Cr ratio (not accurate in AKI)
- r/o secondary causes:  $\uparrow$  Hb<sub>A1C</sub> + retinopathy  $\rightarrow$  presumpt. dx of diabetic nephropathy;  
 $\checkmark$  ANA, anti-dsDNA, C3, C4, SPEP/UPEP, fat pad bx, cryocrit, HBV, HCV, HIV, RPR, phospholipase A<sub>2</sub> receptor Ab
- Renal biopsy

**Treatment**

- General: protein suppl.; diuretics for edema; treat hyperlipidemia, Na restriction (<2 g/d)
- ACEI/ARB**: decrease proteinuria  $\rightarrow$  slow nonimmunologic progression of renal disease
- 1° glomerular dis: steroids  $\pm$  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 anticoag), infection (esp. encapsulated organisms b/c loss of Ig)

# URINALYSIS

Urine Dipstick	
Measurement	Significance and uses
<b>Specific Gravity</b>	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 $U_{osm}$
<b>pH</b>	range: 4.5–8.5; useful in evaluation of stones and RTAs, infection
<b>Protein</b>	detects albumin (marker for glomerular dysfxn); see “Proteinuria”
<b>RBC</b>	see “Hematuria”; also $\oplus$ with myoglobinuria (rhabdomyolysis)
<b>WBC</b>	suggests inflammation (UTI, interstitial nephritis, GN)
<b>Ketones</b>	detects acetoacetate (ie, ketoacidosis), but not $\beta$ -hydroxybutyrate
<b>Nitrite</b>	suggests presence of Enterobacteriaceae
<b>Bilirubin</b>	$\uparrow$ in biliary or hepatic disease
<b>Glucose</b>	$\oplus$ in hyperglycemia (>180 mg/dL), pregnancy, Fanconi’s syndrome

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

**Method:** centrifuge fresh sample  $\times$  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.

<b>Cells</b>	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
<b>Casts</b>	Proteins molded in lumen of renal tubule $\pm$ 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
<b>Crystals</b>	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
<b>Glomerular</b> (can be $>3$ g/d)	Disruption of filtration barrier → lose albumin	Glomerulonephritis Nephrotic syndrome
<b>Tubulointerstitial</b> (usually $<1-2$ g/d)	$\downarrow$ reabsorption of freely filtered proteins → lose globulins	ATN AIN Fanconi’s syndrome
<b>Overflow</b>	$\uparrow$ production of freely filtered proteins	Multiple myeloma Myoglobinuria
<b>Isolated</b>	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**

$1+ = 30 \text{ mg/dL}$ ,  $2+ = 100 \text{ mg/dL}$ ,  $3+ = 300 \text{ mg/dL}$ ,  $4+ > 2 \text{ g/dL}$  → interpretation depends on SG; eg,  $3+$  in very concentrated urine might not indicate heavy proteinuria  
Insensitive for microalbuminuria and myeloma light chains; false  $\oplus$  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

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<sub>3</sub> 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<sub>4</sub>, PTH, UA
- 24-h urine × 2 (>6 wk after acute setting) for Ca, PO<sub>4</sub>, 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 absorpt., 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, captoril

# NOTES

# ANEMIA

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

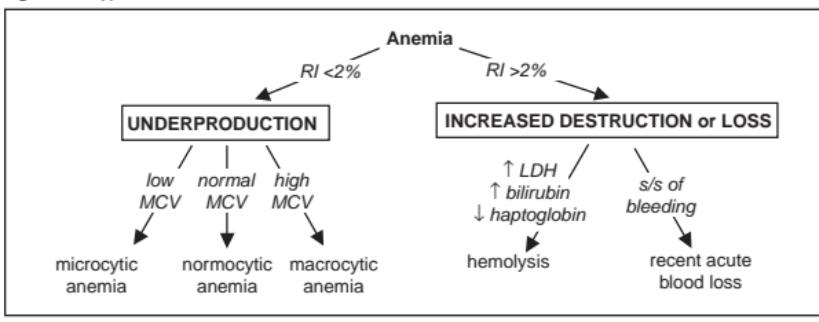
## Clinical manifestations

- Symptoms: ↓ O<sub>2</sub> 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<sub>12</sub> defic.), **koilonychia** (iron defic.), **neurologic abnormalities** (B<sub>12</sub> 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<sub>12</sub>, 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 GI**; 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<sub>4</sub>) disease = severe anemia, hemolysis, and splenomegaly  
0 α genes → Hb Bart's (γ<sub>4</sub>) = 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

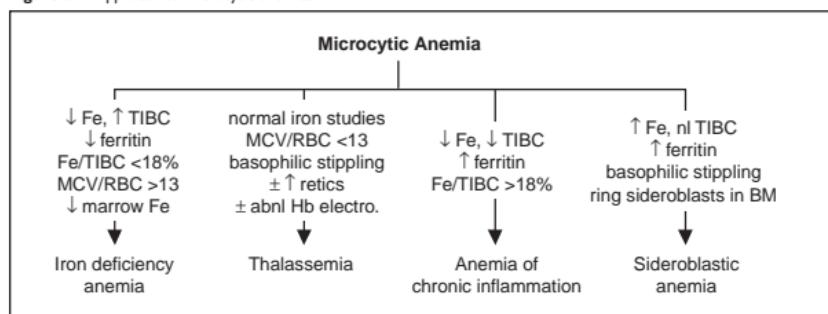
- Special clinical manifestations (in severe cases): chipmunk facies, pathologic fractures, hepatosplenomegaly (due to extramedullary hematopoiesis), high-output CHF, bilirubin gallstones, iron overload syndromes (from chronic transfusions)
- Diagnosis: MCV <70, normal Fe, MCV/RBC count <13, ± ↑ retics, basophilic stippling; Hb electrophoresis: ↑ HbA<sub>2</sub> ( $\alpha_2\delta_2$ ) 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<sub>2</sub> 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; IV Ig 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<sub>12</sub> deficiency**
- ✓ folate and **vitamin B<sub>12</sub>**, ↑ 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<sub>12</sub> defic.)
- Treatment: folate 1–5 mg PO qd for 1–4 mo or until complete hematologic recovery; critical to r/o B<sub>12</sub> deficiency first (see below)

### Vitamin B<sub>12</sub> deficiency

- B<sub>12</sub> 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<sub>12</sub>; ↑ homocysteine and methylmalonic acid; anti-IF Ab; Schilling test; ↑ gastrin in PA
- Treatment: 1 mg B<sub>12</sub> 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<sub>12</sub> deficiency but not neurologic changes (and can lead to "steal" of B<sub>12</sub> 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<sub>12</sub> 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 bruising

### Aplastic anemia = stem cell failure (*Lancet* 2005;365:1647)

- Epidemiology: 2–5 cases/10<sup>6</sup>/y; biphasic (major peak in adolescents, 2nd peak in elderly)
- Diagnosis: pancytopenia w/ ↓ retics, BM bx w/ cytogenetics showing hypocellularity
- Etiologies: **idiopathic** (1/2–2/3 of cases)
  - stem cell destruction**: **radiation, chemotherapy, chemicals** (eg, benzene)
  - idiosyncratic med rxn** (eg, chloramphenicol, NSAIDs, sulfa drugs, gold, carbamazepine, antithyroid)
  - viruses** (HHV-6, HIV, EBV, parvovirus B19); 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)

#### Myelophthistic 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	
Extrinsic	Immune-mediated	Autoimmune; drug-induced, tx rxn	Acquired
	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,  $\alpha$ - and  $\beta$ -spectrin, band 3, and pallidin have been identified
- Most common in N. European populations (1 in 5,000 births);  $\oplus$  FHx (75% of Pts)
- Anemia, jaundice, splenomegaly, pigmented gallstones
- Diagnosis: spherocytes on smear,  $\oplus$  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  $<37^{\circ}\text{C}$  → **complement fixation**  
→ intravascular hemolysis and acrocytosis on exposure to cold  
Etiologies: idiopathic, lymphoproliferative (eg, Waldenström's) disorders (monoclonal), *Mycoplasma pneumoniae* infection and infectious mononucleosis (polyclonal)
- Diagnosis: spherocytes on smear,  $\oplus$  **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 <sup>*</sup> system hyperplasia	Hemolytic anemia, sickle cell disease, <b>thalassemia major</b>
Immune hyperplasia	Infection (HIV, EBV, CMV, TB, <b>malaria</b> , <b>kala azar</b> , <b><i>Mycobacterium avium</i> complex</b> ), autoimmune disorders (SLE, RA with Felty's syndrome), sarcoidosis, serum sickness
Congestion	Cirrhosis, CHF, portal/splenic vein thrombosis, <b>schistosomiasis</b>
Infiltration (nonmalignant)	Lysosomal storage disorders ( <b>Gaucher's</b> , Niemann-Pick), glycogen storage diseases, histiocytosis X, splenic cysts
Neoplasm	<b>MPN (CML, PMF, PV, ET)</b> , <b>CMML</b> , acute leukemia, <b>lymphoma (NHL, HL, hairy cell leukemia)</b> , <b>PLL</b> , <b>Waldenström's</b> , T-LGL leukemia, multiple myeloma, amyloid

**boldface** = causes of massive splenomegaly; \*Reticuloendothelial

# DISORDERS OF HEMOSTASIS

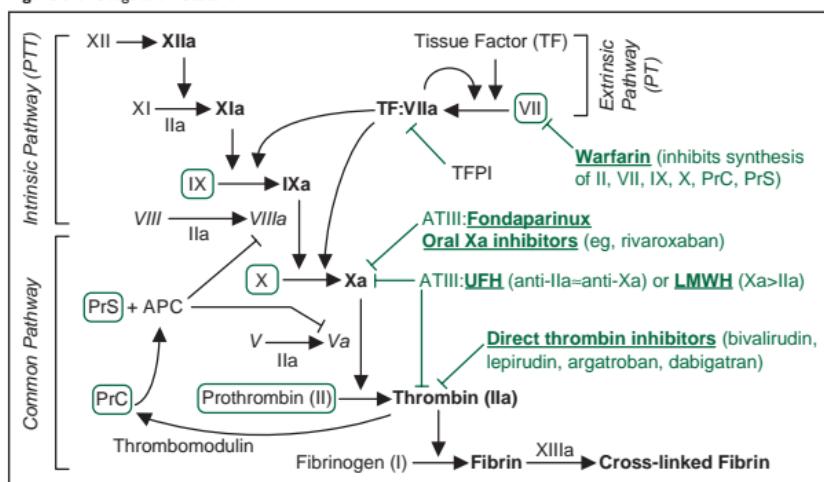
## Clinical Characteristics of Bleeding Disorders

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

### Purpura

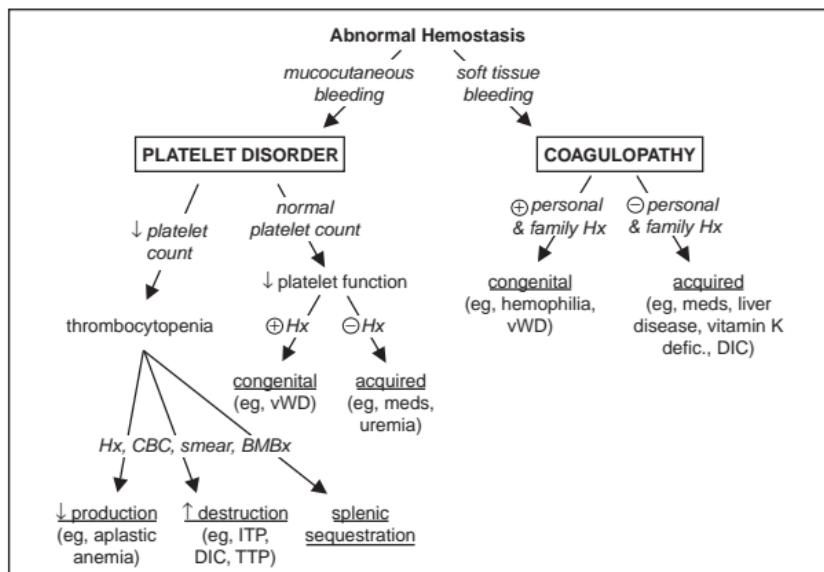
- **Nonblanching** purple/red lesions due to extravasation of RBCs into dermis
- **Nonpalpable** (macular;  $\leq 3$  mm in diameter = petechiae;  $> 3$  mm = ecchymoses)
  - platelet disorder:** thrombocytopenia, defect in platelet function
  - thromboemboli:** DIC, TTP, cholesterol or fat emboli
 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



# PLATELET DISORDERS

## THROMBOCYTOPENIA (Plt count < 150,000/ $\mu$ L)

Thrombocytopenia and Risk of Bleeding	
Platelet count (cells/ $\mu$ L)	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)

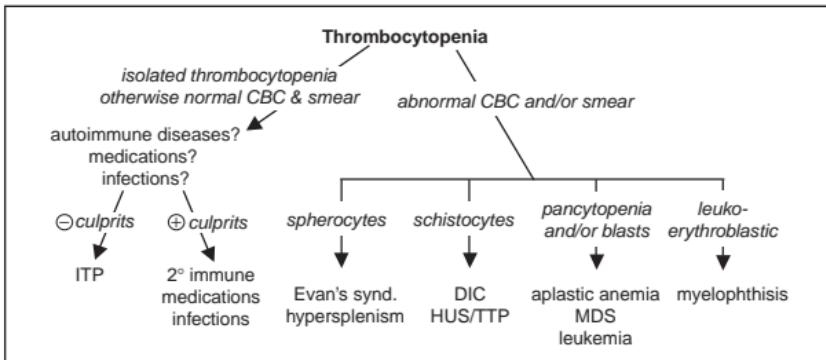
**non-immune-mediated:** **MAHA** (DIC, HUS, TTP), ticlopidine/clopidogrel, vasculitis, preeclampsia/HELLP syndrome, cardiopulmonary bypass, CVVH, IABP, cavernous hemangioma

- 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/ $\mu$ L); 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/ $\mu$ L 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	<b>Steroids:</b> 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 $\mu$ g/kg/d IV	For Rh(D) $\oplus$ Pts w/ spleen Ab-coated RBCs overwhelm Mφ FcR
	<b>IVIg</b> (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	<b>Splenectomy</b>	Persistent disease >6 mo ~65% long-term remission
	Rituximab (anti-CD20) $\pm$ dex	anti-B-cell Ab
	Romiplostim or eltrombopag	TPO-R agonists → ↑ plt prod
	Azathioprine, cyclophosphamide Danazol, vincristine	Immunosuppressants ↓ plt clearance
Bleeding	Aminocaproic acid	Inhibits plasmin activation
	Methylprednisolone 1g/d IV × 3 d	See above
	IVIg	See above
Refractory	Platelet transfusion	Given w/ IVIg or anti-Rh(D)
	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
<b>Mechanism</b>	Direct effect of heparin (nonimmune)	Immune (Ab)-mediated IgG against plt factor 4—heparin complex
<b>Incidence</b>	10–20%	1–3% with UFH, 0–0.8% LMWH
<b>Onset</b>	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
<b>Platelet nadir</b>	>100,000/ $\mu$ L	~60,000/ $\mu$ L, ↓ >50%
<b>Sequelae</b>	None	Thrombotic events (HITT) in 30–50% Rare hemorrhagic complications
<b>Management</b>	Can continue heparin and observe	<b>Discontinue heparin</b> 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 ( $\oplus$  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:**  $\oplus$  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
<b>Adhesion</b>	Bernard-Soulier; vWD	Uremia; acquired vWD
<b>Aggregation</b>	Afibrinogenemia Glanzmann's thrombasthenia	Ticlopidine, clopidogrel, GP IIb/IIIa Dysproteinemias (myeloma)
<b>Granule release</b>	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

# COAGULOPATHIES

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

## Further coagulation tests

- 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, immuno-supp. 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, ↓ hapt; 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 & Fibrinolitics			
Anticoag.	t <sub>1/2</sub>	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 <b>vit. K</b> 2.5 mg PO (superior to SC, ~IV at 24 h) or Ø Rx; if INR >10 give 5 mg (Archives 2003;163:2469; Annals 2009;150:293) Bleeding: <b>vit. K</b> 10 mg IV + <b>FFP</b> 2–4 units IV q 6–8°
Fibrinolytic	20–90', LK	↓ fbgn ↑ FDP	<b>Cryoprecipitate</b> , <b>FFP</b> , ± 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  $\oplus$  FHx

Inherited Hypercoagulable States			
Risk factor	Prevalence	VTE	Comments
Factor V Leiden	3–7%	4.3x	Activated protein C (APC) resist.
Prothrombin mutation	2%	2.8x	G20210A $\rightarrow$ $\uparrow$ prothrombin level
Hyperhomocysteinemia	5–10%	2.5x	Inherited or acquired
Protein C deficiency	0.02–0.05%	11x	
Protein S deficiency	0.01–1%	32x	Warfarin-induced skin necrosis risk
Antithrombin III def.	0.04%	17.5x	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.	<b>Factor V Leiden</b> Prothrombin mutation $\downarrow$ 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: <b>antiphospholipid syndrome</b> , 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  $\therefore$  levels best assessed  $\geq 2$  wk after completing anticoagulation course
- Age-appropriate malignancy screening ( $\oplus$  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  $\geq 1$  clinical &  $\geq 1$  laboratory criteria  
Clinical: thrombosis (any) or complication of pregnancy ( $\geq 3$  spont abortions before 10 wk or  $\geq 1$  fetal loss after 10 wk or premature birth before 34 wk)  
Laboratory:  $\oplus$  moderate-high titer anticardiolipin (ACL), lupus anticoagulant (LA) or  $\beta 2$ -glycoprotein-I ( $\beta 2$ -GP-I) Ab on  $\geq 2$  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  $\rightarrow$  high mortality**
- Antiphospholipid antibodies (APLAs)**
  - $\checkmark$  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;  $\therefore \uparrow$  **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
  - $\beta 2$ -GP-I: Ab against  $\beta 2$ -glycoprotein-I, IgG or IgM
  - False  $\oplus$  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  $\rightarrow$  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)

# DISORDERS OF LEUKOCYTES

## Neutrophilia ( $>7500\text{--}10,000/\mu\text{L}$ )

Infection	Usually bacterial; $\pm$ toxic granulations, Döhle bodies
Inflammation	Burn, tissue necrosis, MI, PE, collagen vascular disease
Drugs and toxins	Corticosteroids, $\beta$ -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	$>50,000/\mu\text{L}$ + left shift, not due to leukemia; unlike CML, $\uparrow$ LAP

## Lymphocytosis ( $>4000\text{--}5000/\mu\text{L}$ )

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 ( $>500/\mu\text{L}$ )

Infection	Usually TB, SBE, <i>Listeria</i> , <i>Brucella</i> , rickettsiae, fungi, parasites
Inflammation	IBD, sarcoidosis, collagen vascular diseases
Neoplasm	Hodgkin's disease, leukemias, MPD, carcinomas

## Eosinophilia ( $>500/\mu\text{L}$ )

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 <i>FIP1L1-PDGFRα</i> fusion ( <i>NEJM</i> 2003;348:1201) <i>D816kit</i> -positive systemic mastocytosis ( <i>Lancet</i> 2003;362:535)

## Basophilia ( $>150/\mu\text{L}$ )

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.

# TRANSFUSION THERAPY

Blood Products and Indications	
Packed red blood cells (PRBCs)	For acute blood loss or to ↑ O <sub>2</sub> -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/ $\mu$ L or <20,000/ $\mu$ L with infection or ↑ bleeding risk or <50,000/ $\mu$ L with active bleeding or preprocedure. 6 U pooled donor plts = 1 single donor plt apheresis unit (reduces alloimmunization) → ↑ plt count by ~30–60,000/ $\mu$ L. <b>Contraindicated</b> in TTP/HUS, HELLP, HIT. Refractory: ↑ <5000/ $\mu$ L 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.”

# MYELODYSPLASTIC SYNDROMES (MDS)

## Myeloid neoplasm overview (*Blood* 2009;114:937)

- Myeloid neoplasms are classified into 5 categories based on bone marrow morphology, clinical characteristics and genetics (WHO 2008 system)

WHO 2008 Myeloid Neoplasm Categories	
Acute myeloid leukemia	Dysplastic clonal myeloid stem cell (SC) disorder w/ $\geq 20\%$ blasts in the bone marrow or peripheral blood
Myelodysplastic syndromes	Dysplastic clonal myeloid SC disorder $\rightarrow$ 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, CMMI, atypical CML)
Myeloid/lymphoid malig. a/w eos and PDGFR or FGFR1 $\Delta$	Consider imatinib Rx for PDGFR rearrangement

## Myelodysplastic syndromes (MDS) overview (*NEJM* 2009;361:1872)

- 5-14
- Acquired clonal stem cell disorder  $\rightarrow$  ineffective hematopoiesis  $\rightarrow$  **cytopenias, dysmorphic blood cells and precursors**, variable risk of **leukemic transformation**
  - Epidemiology:  $< 100$  cases/ $10^6$ /y; median age  $\sim 65$  y; male predominance (1.8x)
  - **Idiopathic** or 2° to chemo w/ **alkylating agents, topo II inhib.**;  $\uparrow$  risk w/ radiation, benzene
  - Clinical manifestations: **anemia** (85%), neutropenia (50%), thrombocytopenia (25%)
  - Diagnosis: dysplasia (usually multilineage) in peripheral smear (ovalomacrococytes, **pseudo-Pelger-Hüet anomaly**) and bone marrow ( $\geq 10\%$  dysplasia with blasts  $\pm$  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 ( $\geq 20\%$  blasts) and CMMI (monocyte count  $> 1 \times 10^9/L$ ); r/o 2° BM  $\Delta$ s due to defic. of B<sub>12</sub>, 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	$\geq 10\%$ dysplastic cells in one myeloid lineage $< 5\%$ blasts; $< 15\%$ RS
Refractory anemia with ring sideroblasts (RARS)	$< 5\%$ blasts, $\geq 15\%$ RS
Refractory cytopenias with multilineage dysplasia (RCMD)	$\geq 10\%$ dysplasia $\geq 2$ 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, $\pm$ 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 CMMI 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  $\rightarrow$  supportive care = transfusions, G-CSF, epo, abx if needed
  - Low/intermediate risk  $\rightarrow$  Epo (esp if Epo level  $< 500$ ); lenalidomide (esp for 5q- syndrome; *NEJM* 2005;352:549); DNA demethylating agents (azacitidine or decitabine)
  - Intermediate/high risk  $\rightarrow$  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)  $\rightarrow$  can consider **immunosuppression** (CsA, ATG, prednisone)
- Prognosis: IPSS correlates with **survival** and **progression to AML**

International Prognostic Scoring System (IPSS)		Score	Risk group	Total score	Median survival
	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	–	–	–

(*Blood* 1997;89:2079) LDH may add further prognostic value to traditional IPSS score (*Leukemia* 2005;19:2223)

**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 (PMF); chronic myelogenous leukemia (CML), BCR-ABL1 $\oplus$ ; chronic neutrophilic leukemia; chronic eosinophilic leukemia, not otherwise specified; mastocytosis; myeloproliferative neoplasms, unclassifiable
- Gain of fxa 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  $\pm$  ↑ granulocytes and platelets in the absence of physiologic stimulus

**Etiologies of erythrocytosis**

- Relative ↑ RBC ( $\downarrow$  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<sub>2</sub> or PaO<sub>2</sub>, 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
- $\pm$  ↑ WBC, platelets, basophils; ↑ uric acid, leukocyte alkaline phosphatase, vitamin B<sub>12</sub>
- 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  $\geq 60$ , prior thrombosis) or sx thrombocytosis (plt  $> 1.5 \times 10^6/\mu\text{L}$ )
- Supportive: allopurinol (gout), H<sub>2</sub>-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 ( $>450,000/\mu\text{L}$ )  $\pm$  ↑ 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  $> 10^6/\mu\text{L}$ , <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 × 10 <sup>6</sup> /μL and no CV risk factors	Consider for vasomotor symptoms	No
Int.	Neither low nor high	±	Consider if plt >1.5 × 10 <sup>6</sup> /μL
High	Age ≥60 or h/o thrombosis or plt >1.5 × 10 <sup>6</sup> /μL	⊕	<b>Hydroxyurea</b> 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 (qy)

**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<sub>4</sub>, ↓ 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
Karyotype	t(15;17) in APL; t(8;21); inv(16); t(16;16)	-5; -7; 3q26 aberrations, t(6;9); 11q23 aberrations; complex karyotype
Gene mutations	NPM1; 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<sup>2</sup>) superior to standard dose (45 mg/m<sup>2</sup>) (*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 ± leukapheresis 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-RAR $\alpha$**  (>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/ $\mu$ L 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/ $\mu$ L, 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  $\ominus$ ) 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/ $\mu$ L), 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<sub>4</sub>, 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 (slg); 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%) <sup>*</sup>	>24	β2-microglobulin: higher levels correlate with disease stage, tumor burden and a poorer prognosis.	
Unmutated (<2%) <sup>*</sup>	<8		

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

# LYMPHOMA

## Definition

- Malignant disorder of lymphoid cells that reside predominantly in lymphoid tissues
- Hodgkin lymphoma (HL)** is distinguished from **non-Hodgkin's lymphoma (NHL)** by the presence of **Reed-Sternberg (RS) cells**

## Clinical manifestations

- Lymphadenopathy (nontender)
  - HL:** superficial (usually **cervical/suprACLAVICULAR**)  $\pm$  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** ( $>38^\circ$ ), **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 A<sub>d</sub> elevated

### Ann Arbor Staging System with Cotswolds Modifications

Stage	Features
I	Single lymph node (LN) region
II	$\geq 2$ 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

<b>Lymphocyte rich</b>	5%	Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis
<b>Nodular sclerosis</b>	60–80%	Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I/II at dx
<b>Mixed cellularity</b>	15–30%	Pleomorphic; older age; male predominance; $\geq 50\%$ stage III/VI at presentation; intermediate prognosis
<b>Lymphocyte depletion</b>	<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  $\oplus$
  - 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
<b>Mature B Cell</b>	Diffuse large B-cell lymphoma (DLBCL) Follicular lymphoma CLL/small lymphocytic lymphoma Mantle cell Marginal zone lymphoma (nodal, extranodal (MALT), splenic) Burkitt's lymphoma Hairy cell leukemia (p/w fatigue, ↓ monos, massive splenomegaly; ⊕ TRAP)	IGH-BCL2  t(11;14) BCL1-IgH → cyclin D1 dysreg AP12-MALT1 & BCL-10-Ig enhancer  8q24, c-MYC
<b>Mature T Cell &amp; NK Cell</b>	Peripheral T cell lymphoma Mycosis fungoides (cutaneous lymphoma) / Sézary syndrome (+ LAN) Anaplastic large cell lymphoma Angioimmunoblastic T cell lymphoma	Some ALK1 ⊕

(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;  $\geq 2$  extranodal site +  $\uparrow$  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  $\pm$  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:  $\downarrow$  response to chemotherapy, but long median survival

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

(Blood 2004;104:1258)

- Aggressive:  $\uparrow$  chance of cure, but overall worse prognosis

<b>International Prognostic Index (IPI) for Aggressive NHL</b>		
Factors: age $> 60$ , stage III/IV, $\geq 2$ extranodal sites, performance status $\geq 2$ , LDH $> \text{nl}$		
# 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  $\oplus$  imparts 60–100 $\times$  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  $\pm$  RT
  - Primary effusion lymphoma (<5%): HHV8 driven; also can be seen in other immuno-supp. Pts such as s/p solid organ transplant or w/ chronic HBV. Treat with standard CHOP (often CD20-), but poor prognosis.

# PLASMA CELL DYSCRASIAS

## MULTIPLE MYELOMA (MM)

### Definition and epidemiology

- Malignant neoplasm of **plasma cells** producing a monoclonal Ig = "**M protein**"
- ~20,580 new cases and ~10,580 deaths/y in U.S. (2009); median age at diagnosis 66 y
- African American:Caucasian ratio =2:1

### Clinical manifestations

- Anemia** (normocytic) due to bone marrow involvement and autoimmune Ab
- Bone pain** and **hypercalcemia** due to ↑ osteoclast activity → lytic lesions, pathologic fx
- Recurrent infections** due to relative hypogammaglobulinemia as clonal plasma cells suppress nl immunoglobulin
- Renal disease:** multiple mechanisms include toxic effect of filtered light chains → **renal failure** (cast nephropathy) or **type II RTA**; amyloidosis or light chain deposition disease → **nephrotic syndrome**: hypercalcemia, urate nephropathy, type I cryoglobulinemia
- Neurologic: cord compression; POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome
- Hyperviscosity: usually when IgM >4 g/dL, IgG >5 g/dL, or IgA >7 g/dL
- Coagulopathy: inhibition of or Ab against clotting factor; Ab-coated platelets
- Amyloidosis (see "Amyloidosis")

### Diagnostic and staging evaluation (NCCN Version 3.2010)

- Six 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/ $\mu$ L
  - 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
- $\beta$ 2-microglobulin and LDH levels reflect tumor burden**
- Bone marrow bx:** better prognosis = hyperdiploidy; worse prognosis = del. of chromosome 17p13 (~10% of Pts) & certain translocations
- Skeletal survey** (plain radiographs) to identify lytic bone lesions and areas at risk for pathologic fracture; **bone scan is not useful for detecting lytic lesions**

### Multiple Myeloma Staging Systems

Stage	ISS Criteria	Durie-Salmon Criteria	Median survival
I	$\beta$ 2-microglobulin <3.5 mg/L and albumin >3.5g/dL	<i>all of the following:</i> 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	$\beta$ 2-microglobulin >5.5 mg/L	<i>any of the following:</i> 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** ( $\uparrow$  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  $\uparrow$  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**  $\uparrow$  survival (NEJM 2003;349:2495), + thalidomide  $\rightarrow$   $\uparrow$  response rate but no  $\Delta$  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  $\rightarrow$  infxn, myelosuppression; thalidomide  $\rightarrow$  thromboembolism, bradycardia, periph. neuropathy, neutropenia, rash (Blood 2008;111:3968); bortezomib  $\rightarrow$  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  $\rightarrow$  MM, WM, amyloidosis, or malign. lymphoproliferative dis.
- Abnormal serum-free light chain ratio:  $\uparrow$  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,  $\Delta$  MS
    - cardiopulmonary: congestive heart failure, pulmonary infiltrates
  - type I cryoglobulinemia  $\rightarrow$  Raynaud's phenomenon**
  - platelet dysfxn  $\rightarrow$  mucosal bleeding
- **IgM deposition** (skin, intestine, kidney); amyloidosis and glomerulopathy
- **Autoantibody activity of IgM**
  - chronic AIHA (prominent rouleaux; 10% Coombs'  $\oplus$  = 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  $\oplus$  UPEP)
- Bone marrow biopsy:  $\uparrow$  plasmacytoid lymphocytes;  $\beta$ -2-microglobulin for prognostic eval
- **Relative serum viscosity:** defined as ratio of viscosity of serum to H<sub>2</sub>O (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 chemoradiotoxicities** 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
<b>Regimen-related</b>	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		
<b>Immune-mediated</b>	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			
Class of pathogen and associated prophylaxis	Time after transplant and associated risk factors		
	Days 0-30 Mucositis Organ dysfunction Neutropenia	Days 30-90 Acute GVHD ↓ cellular immunity	>90 days Chronic GVHD ↓ cellular & humoral immunity
<b>Viral</b> 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		
<b>Bacterial</b> antibiotics (eg, fluoroquinolone) while neutropenic	Gram + cocci (coagulase-negative staph., <i>S. aureus</i> , <i>S. viridans</i> ) GNRs ( <i>Enterobacteriaceae</i> , <i>Pseudomonas</i> , <i>Legionella</i> , <i>S. maltophilia</i> )		
<b>Fungal</b> fluconazole or posaconazole (NEJM 2007;356:335) to d 75 for <i>Candida</i>	<i>Candida</i> spp.  <i>Aspergillus</i> spp.		
<b>Parasitic</b> TMP-SMX to d 180 (or off immunosuppression) for PCP	<i>T. gondii</i> <i>P. carinii</i> <i>S. stercoralis</i>		

\*Primarily among persons who are seropositive before transplant

# LUNG CANCER

## Pathology and genetics (NEJM 2008;359:1367)

- Non-small cell lung cancer (NSCLC, ~85%)

Adenocarcinoma: typically peripheral; tumor cells can have mutations in KRAS,

EGFR, p53, & LKB 1, and EML4-ALK fusion protein

Squamous cell: typically central; tumor cells can have mutations in p53, MET, & LKB 1, 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  $\propto$  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 $\oplus$ nodes	ipsilat. hilar	ipsilat. mediast.	contralat. or supraclav.	
T1	T $\leq$ 2 cm (T1a) or T > 2–3 cm (T1b)	IA	IIA			
T2	T $\leq$ 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](http://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  $\oplus$  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 $\pm$ radiation $\pm$ chemo	40-50
IIIA	15	Mediast. spread but resectable	Chemoradiation $\pm$ surgical resection	25-30
IIIB	15	Unresectable	Chemoradiation $\pm$ biologic $\pm$ surgery (selected cases)	10-20
IV	40	Metastatic	Chemo $\pm$ 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](http://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 $\pm$ PCI	1-2 y
Extensive	60-70	Beyond one radiation port	Chemotherapy $\pm$ PCI	~1 y

# BREAST CANCER

## Epidemiology and genetics (Risk assessment tool: [www.cancer.gov/bcrisktool](http://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  $\oplus$  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,  $\oplus\oplus$  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 indeterm. 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  $\oplus$ , node  $\ominus$  Pts (NEJM 2004;351:2817; 2006;355:560)

Simplified Staging System for Breast Cancer				
Stage	Characteristics	Description	5-y surv	
I	Tumor $\leq$ 2 cm	Operable	90%	
IIA	Tumor $>$ 2 cm or mobile axillary nodes	locoregional	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	45%	
IIIC	Infraclavicular or supraclavicular nodes	locoregional	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  $\geq 4 \oplus$  LN, tumor  $>$  5 cm or  $\oplus$  surgical margins  $\rightarrow$  ↓ 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)  $\rightarrow$  small ↑ survival, ? related to length of amenorrhea (NEJM 2007;357:1496 & 2010;362:2053).

**Biologics**

trastuzumab (Herceptin; anti-HER2/neu mAb) ↑ survival in HER2 $\oplus$  tumors (15–20%), but ↑ cardiotoxicity w/ anthracyclines (NEJM 2007;357:39, 1673; Lancet 2007;369:29).

Usually used after anthracycline regimens or concurrently w/ taxane regimens.

lapatinib (tyrosine kinase inhib. of HER2 & EGFR): if mets, delays progression if failed trastuzumab (NEJM 2006;355:2733)

bevacizumab (anti-VEGF): if mets, delays progression (NEJM 2007;357:2666)

Hormonal (in ER/PR  $\oplus$  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**

<b>LCIS</b>	Close surveillance ± chemoprevention; ? prophylactic bilat. mastectomy
<b>DCIS</b>	Mastectomy or lumpectomy + RT; ALND not indicated; ± chemoprevention (NEJM 2004;350:1430)
<b>I</b>	Surgery + RT
<b>II</b>	+ Adjuvant chemo if ↑ risk: tumor $>$ 1 cm or $\oplus$ LN or ER/PR $\ominus$ (Lancet 1998;352:930) + Hormonal therapy if ER/PR $\oplus$ (or unknown status) (Lancet 2009;374:2055) + Trastuzumab if HER2 $\oplus$ and tumor $\geq$ 1 cm or $\oplus$ LN
<b>III</b>	Neoadjuvant chemo → surgery + RT ± adjuvant chemotherapy + Hormonal therapy for ER/PR $\oplus$ (or unknown status) tumors + Trastuzumab if HER2 $\oplus$
<b>IV</b>	ER/PR $\oplus$ : hormonal therapy ± chemotherapy ER/PR $\ominus$ : HER2 $\oplus$ → chemo + trastuzumab; HER2 $\ominus$ → 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  $\rightarrow$  ~90% ↓ risk & bilat. salpingo-oophorectomy ↓ risk of ovarian and breast cancer.

# PROSTATE CANCER

## Epidemiology and risk factors (NEJM 2003;349:366)

- Most common cancer in U.S. men; 2nd most common cause of cancer death in men
- Lifetime risk of prostate cancer dx ~16%; lifetime risk of dying of prostate cancer ~3%
- More common with ↑ age (rare if <45 y), in African Americans, and if + FHx

## Clinical manifestations (usually asymptomatic at presentation)

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

## Screening (NEJM 2009;360:1351)

- Mortality benefit from screening has not been established, with one recent trial showing a 20% ↓ mortality, but another no benefit (NEJM 2009;360:1310 & 1320)
- **Digital rectal exam (DRE)**: size, consistency, lesions
- **PSA**: 4 ng/mL cutpoint neither Se nor Sp; can ↑ with BPH, prostatitis, acute retention, after bx or TURP, and ejaculation (*no significant ↑ after DRE, cystoscopy*); 15% of men >62 y w/ PSA <4 & nl DRE have bx-proven T1 cancer (NEJM 2004;350:2239)
- Per American Cancer Soc., offer PSA + DRE screening to men age ≥50 (≥45 if high risk) with life expectancy ≥10 y; USPSTF has no rec. for PSA if <75 y, rec. against if ≥75 y

## Diagnostic and staging evaluation

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

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

\*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  $\oplus$  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  $\rightarrow$  1000s of polyps at young age  $\rightarrow$  ~100% lifetime risk;  $\uparrow$  risk of thyroid, stomach, SI cancers
- **Hereditary nonpolyposis colorectal cancer (HNPCC):** mutations in DNA mismatch repair genes  $\rightarrow$   $\uparrow$  tumor progression  $\rightarrow$  ~80% lifetime risk; predom. **right-sided** tumors;  $\uparrow$  risk of **endometrial**, ovarian, stomach, small bowel cancers.  
Amsterdam criteria:  $\geq 3$  family members w/ HNPCC-related cancer, one of which dx before age 50, affecting 2 successive generations.
- **Inflammatory bowel disease:**  $\uparrow$  risk with  $\uparrow$  extent and duration of disease
- Other factors a/w  $\uparrow$  risk of CRC: diet rich in animal fat, ? smoking, ? diabetes/obesity
- $\downarrow$  risk of adenomas w/ ASA & NSAIDs, incl. COX-2 (*NEJM* 2006;355:873, 885), but  $\uparrow$  bleeding and  $\uparrow$  CV events w/ COX-2;  $\downarrow$  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  $\rightarrow$  carcinoma sequence** reflects accumulation of multiple genetic mutations  $\uparrow$  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:  $\Delta$  **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  $\rightarrow$  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
- $\uparrow$  **risk:** earlier and/or more frequent screening.  $\oplus$  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  $\checkmark$  in 3–5 y.
- **Fecal occult blood test (FOBT):**  $\downarrow$  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:**  $\uparrow$  Se,  $\approx$  Sp c/w FOBT, but less Se than colonoscopy (*NEJM* 2004;351:2704)
- **CT colonography (CTC):** c/w colonoscopy, 90% Se for lesions  $\geq 1$  cm but considerably less for smaller lesions (*NEJM* 2008;359:1207). Strategy of CTC followed by colonoscopy for lesions  $\geq 6$  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  $\geq 6$  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 $\geq 12$ LN)
IIA	B	Into serosa	83%	Surgery; no established role for adjuvant chemo for colon cancer*
IIB	B	Into peritoneum	74%	Preop XRT or 5FU/XRT added for rectal cancer followed by postop chemo (FOLFOX)
IIC	B	Direct invasion	56%	
IIIA	C	$\leq 6 \oplus$ LNs	86%	Surgery + chemotherapy*
IIIB	C	Varying degrees of $\oplus$ LNs and local invasion	51–77%	<b>5-FU + leucovorin + oxaliplatin = FOLFOX (NEJM 2004;350:2343)</b>
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 $\pm$ bevacizumab or cetuximab (benefit limited to Pts w/o KRAS mutation) $\pm$ 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](http://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, ↑ Adf, anemia

## Diagnostic and staging evaluation

- Pancreatic protocol CT scan** (↑ 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
<b>Resectable</b> , 15–20%	No extrapancreatic dis. or bulky LN; Patent SMV & portal vein; celiac axis & SMA not involved	10–20 mo (favorable: tumor <3 cm, ⊖ marg., well-different.) 5–y ~30% node ⊕ vs. ~10% if ⊕
<b>Locally advanced</b> (unresect.), 40%	Extensive PV/SMV, celiac axis, or SMA involvement	8–12 mo
<b>Metastatic</b> , 40%	Usually liver & peritoneum; 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;23:165,1) 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  $\geq 38.3^{\circ}\text{C}$  ( $101^{\circ}\text{F}$ ) or  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) for  $\geq 1$  h
- **Neutropenia:** ANC  $< 500 \text{ cells}/\mu\text{L}$  or  $< 1,000 \text{ cells}/\mu\text{L}$  with predicted nadir  $< 500 \text{ cells}/\mu\text{L}$

**Pathophysiology and microbiology**

- Predisposing factors: catheters, skin breakdown, GI mucositis, obstruction (lymphatics, biliary tract, GI, urinary tract), immune defect a/w malignancy
- Most episodes thought to result from seeding of bloodstream by GI flora
- Neutropenic enterocolitis (typhlitis): RLQ pain, watery/bloody diarrhea, cecal wall thickening
- GNRs (especially *P. aeruginosa*) were historically most common
- Gram  $\ominus$  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)  $\downarrow$  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  $\rightarrow \checkmark$  stool (*C. difficile*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s  $\rightarrow$  CNS, sinus, chest, or abdomen/pelvis imaging
- Caveats: neutropenia  $\rightarrow$  impaired inflammatory response  $\rightarrow$  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  $< 39^{\circ}\text{C}$ , no tachypnea, no hypotension, no  $\Delta$  MS, no dehydration
- Studies: ANC  $> 100 \text{ cells}/\mu\text{L}$ , 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  $\beta$ -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  $\ominus \times 48$  h

**Modification to initial antibiotic regimen**

- Low-risk Pts who become afebrile w/in 3–5 d can be switched to PO antibiotics
- 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  $> 500 \text{ cells}/\mu\text{L}$
- 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  $1^{\circ}$  prophylaxis when expected FN incidence  $> 20\%$  or as  $2^{\circ}$  prophylaxis after FN has occurred in a previous cycle (to maintain dose-intensity for curable tumors). CSF  $\downarrow$  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  $\Delta$ s), **weakness, autonomic dysfunction** (urinary retention, ↓ anal sphincter tone), **sensory loss**

### Diagnostic evaluation

- Always take back pain in Pts with solid tumors very seriously
- Do not wait for neurologic signs to develop before initiating evaluation b/c duration & severity of 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<sub>4</sub> → ↓ Ca
- **Renal failure** (urate nephropathy)

### Prophylaxis

- Allopurinol 300 mg qd to bid PO or 200–400 mg/m<sup>2</sup> 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<sub>3</sub> to ↑ UA solubility & ↓ risk of urate nephropathy (controversial: may cause metabolic alkalosis or Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub> 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

# NOTES

# PNEUMONIA

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

## 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:  $S_aO_2$  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): Confusion, Uremia, RR ≥30, BP <90/60, age ≥65
  - SMART-COP** (CID 2008;47:375): SBP <90, Multilobar infiltrates, Alb <3.5 g/dL, RR ≥30, Tachycardia (HR >125 bpm), Confusion,  $O_2$  sat <90%, pH <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 <sub>a</sub> O <sub>2</sub> <60 or S <sub>a</sub> O <sub>2</sub> <90 (+10), pleural effusion (+10)

(NEJM 1997;336:243)

Treatment	
Clinical scenario	Empiric treatment guidelines*
<b>Outpatient</b>	No recent abx: macrolide or doxycycline Recent abx: (macrolide + [high-dose amox ± clav or 2nd-gen. ceph.]) or respiratory FQ
<b>Community-acquired, hospitalized</b>	(3rd-gen. ceph. + macrolide) or respiratory FQ
<b>Community-acquired, hospitalized, ICU</b>	(3rd-gen. ceph. or amp-sulbactam) + (macrolide or FQ) (assuming no risk for <i>Pseudomonas</i> )
<b>Hosp-acquired &amp; risk for MDR pathogens</b>	(Antipseudomonal PCN or ceph. or carbapenem) + (FQ or [gentamicin + azithromycin]) + vancomycin
<b>Immunosuppressed</b>	As above ± TMP-SMX ± steroids to cover PCP
<b>Aspiration</b>	(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 amantadine
- Oseltamivir dosed 75 mg PO bid × 5 d, effective only if started w/in 48 h of sx, but used anytime in immunosupp. & considered in all Pts w/ or predisposed to severe influenza
- Consider inhaled ribavirin for RSV in immunosupp. (eg, BMT, lung tx); limited adult data

### Prevention

- Inactivated **influenza vaccine**: available for seasonal and select pandemic flu, incl. H1N1 rec if >50 y, at risk for complic., HCW, caretakers of high-risk Pts; for all if surplus
- Isolation, droplet precautions for inPts strongly recommended
- Prophylaxis for high-risk contacts of confirmed influenza: oseltamivir 75 mg PO daily × 10 d

# FUNGAL INFECTIONS

## Candida species

- **Microbiology:** normal GI flora; *C. albicans* & nonalbicans spp. (consider azole resistance if prior Rx or nonalbicans; *C. parapsilosis* more likely to be echinocandin resistant)
- **Risk factors:** neutropenia, immunosupp., broad-spectrum abx, intravascular catheters (esp. if TPN), IVDU, abd surgery, DM, renal failure
- **Clinical manifestations**
  - Mucocutaneous: cutaneous (eg, red, macerated lesions in intertriginous zones); oral thrush (exudative, erythematous, or atrophic; if unexplained, r/o HIV); esophageal (odynophagia; ± oral thrush); vulvovaginal, balanitis
  - Candiduria: typically colonization due to broad-spectrum abx and/or indwelling catheter
  - Candidemia (#4 cause of nosocomial bloodstream infxn): r/o retinal involvement (req ↑ Rx); endocarditis rare but serious (esp. w/ nonalbicans & prosthetic valve)
  - Hepatosplenic: intestinal seeding of portal & venous circulation; seen in acute leukemias
  - 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, mafungin) 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 cryptococcosis. With any evidence of cryptococcal disease, exonerate CNS infxn w/ LP.
- Treatment:  
CNS disease (or non-CNS disease in immunosupp. Pts):  
**HIV**  $\oplus$ : 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)  $\times \geq 2$  wk; Consolidation: fluconazole 800 mg/d  $\times \geq 8$  wk; Maintenance:  $\geq 12$  mo antifungal Rx and until immune recovery on ARVs  
**Transplant**: Induction: liposomal ampho B and flucytosine  $\times \geq 2$  wks; Consolidation: fluconazole 400 mg/d  $\times \geq 8$  wk; Maintenance: fluconazole  $\times 6$ –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)	<b>Encapsulated bacteria:</b> <i>S. pneumo</i> , <i>H. flu</i> , <i>N. meningitidis</i> <b>Other bacteria:</b> <i>E. coli</i> and other GNRs
Granulocytopenia or neutropenia (includes DM, ESRD → functional impairment)	<b>Bacteria:</b> Gram positive: coag neg Staph, <i>S. aureus</i> , viridans Strep, <i>S. pneumo</i> , other Strep; <i>Corynebacterium</i> spp., <i>Bacillus</i> spp. Gram negative: <i>E. coli</i> , <i>Klebsiella</i> , <i>Pseudomonas</i> <b>Fungi:</b> Yeast: <i>Candida albicans</i> and other <i>Candida</i> spp.; Molds: <i>Aspergillus</i> , <i>Mucor</i> spp., and others (these also require CMI)
Impaired cell-mediated immunity (CMI) (eg, HIV, chronic steroids, posttransplant, DM, ESRD)	<b>Bacteria:</b> <i>Salmonella</i> spp., <i>Campylobacter</i> , <i>Listeria</i> , <i>Yersinia</i> , <i>Legionella</i> , <i>Rhodococcus</i> , <i>Nocardia</i> , TB, other mycobacteria <b>Fungi:</b> <i>Candida</i> , <i>Crypto</i> , <i>Histo</i> , <i>Coccidio</i> , <i>Aspergillus</i> , and other molds, <i>Pneumocystis</i> <b>Viruses:</b> HSV, VZV, CMV, EBV, JC virus, BK virus <b>Parasites:</b> Protozoa: <i>Toxoplasma</i> , <i>Cryptosporidium</i> , <i>Isospora</i> , <i>Babesia</i> ; Helminths: <i>Strongyloides</i>
Organ dysfunction	<b>Splenectomy:</b> <i>S. pneumo</i> , <i>H. flu</i> , <i>N. meningitidis</i> (vaccinate against these 3, ideally prior to splenectomy); <i>Capnocytophaga</i> , <i>Babesia</i> <b>Liver (esp. cirrhosis):</b> <i>Vibrio</i> spp., encapsulated bacteria <b>ESRD:</b> impaired granulocyte fxn and CMI as above <b>Iron overload (or deferoxamine Rx):</b> <i>Yersinia</i> , <i>Mucor</i>
Biologics (eg, TNF inhibitors, anti-B-cell Rx)	<b>Bacteria:</b> sepsis, TB, other mycobacteria <b>Fungi:</b> <i>Pneumocystis</i> , <i>Histo</i> , <i>Coccidio</i> , other endemic fungi <b>Viruses:</b> JC virus (PML), EBV, HSV, VZV, HBV <b>Parasites:</b> <i>Strongyloides</i> reactivation

# URINARY TRACT INFECTIONS (UTI)

UTI  
6.5

## 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:  $\geq 10^5$  CFU/mL in asx women,  $\geq 10^3$  CFU/mL in men,  $\geq 10^2$  CFU/mL in sx or catheterized Pts (hydration may falsely dilute counts)
  - pyuria &  $\ominus$  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*
<b>Cystitis</b>	FQ or TMP-SMX PO $\times$ 3 d (uncomp.) or $\times$ 10–14 d (complicated) Asx bacteriuria in pregnancy or prior to urologic surgery → abx $\times$ 3 d
<b>Catheterized Pts</b>	Abx as above and remove or exchange catheter
<b>Urethritis</b>	Treat for both <i>Neisseria</i> and <i>Chlamydia</i> <i>Neisseria</i> : ceftriaxone 125 mg IM $\times$ 1 <i>Chlamydia</i> : doxy 100 mg PO bid $\times$ 7 d or azithromycin 1 g PO $\times$ 1
<b>Prostatitis</b>	FQ or TMP-SMX PO $\times$ 14–28 d (acute) or 6–12 wks (chronic)
<b>Pyelonephritis</b>	Outpatient: FQ or oral ceph. PO $\times$ 14 d Inpatient: ceftriaxone IV or FQ PO or aminoglycoside or ampicillin/sulbactam $\times$ 14 d (Δ IV → PO when Pt improved clinically and afebrile $\times$ 24–48 h and then complete 14-d course)
<b>Renal abscess</b>	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.

# SOFT TISSUE AND BONE INFECTIONS

## 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
- Erysipelas:** raised erythematous lesion with **clear demarcation** from normal skin
- Folliculitis:** superficial inflammation of hair follicles, limited to epidermis
- Furunculosis:** infxn of follicle extending to dermis (mult. coalescent furuncles = carbuncle)

### Microbiology and treatment (CID 2005;41:1373)

- Impetigo:** Strep or Staph; Rx = topical mupirocin or other top. antibacterial usually sufficient
- Erysipelas:** mainly Grp A Strep; Rx = PCN unless Staph suspected
- Folliculitis/furunculosis:** *S. aureus*, *Pseud.* ("hot tub folliculitis"); Rx = warm compress ± I&D; abx controversial, give if assoc. cellulitis, lymphangitis, systemic sx, immunosupp.

## “DIABETIC FOOT”

Infected neuropathic foot ulcer

### Microbiology

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

### Clinical manifestations

- Ulcer with surrounding erythema and warmth ± purulent drainage
- Tenderness may be absent due to neuropathy
- ± Crepitus (indicating gas and ∴ mixed infection w/ GNR & anaerobes or *Clostridium*)
- ± Underlying osteomyelitis
- ± Systemic toxicity (fever, chills, leukocytosis, hyperglycemia)
- #1 cause of DM-related hosp. days; #1 proximal cause of non-traumatic amputations in U.S.

**Diagnostic studies**

- Superficial swabs from ulcers *not* helpful (only yield superficial colonizing organisms)
- Wound cx (eg, curettage at base of ulcer after débridement) has ↑ Se
- Blood cx should be obtained in all Pts, ⊕ in 10–15%
- **Osteomyelitis should always be ruled out** (see below for specific imaging tests) 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: Ig, **Gram  $\oplus$**  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  $\pm$  fistula to superficial skin
- $\pm$  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  $\oplus$  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  $\oplus$  if contiguous focus w/ periosteal reaction, Charcot changes
  - radionuclide imaging: very Se but non-Sp (false  $\oplus$  if soft-tissue inflammation)

## Treatment

- **Antibiotics** (based on cx data)  $\times$  4–6 wks
- **Surgery** should be considered for any of the following: acute osteo that fails to respond to medical Rx, chronic osteo, complications of pyogenic vertebral osteo (eg, early signs of cord compression, spinal instability, epidural abscess), or infected prosthesis

## EPIDURAL ABSCESS

### Etiology

- Hematogenous spread (2/3): skin infection, soft tissue (dental abscess), or endocarditis
- Direct extension (1/3): vertebral osteomyelitis, sacral decubitus ulcer, spinal anesthesia or surgery, lumbar puncture
- Risk factors: diabetes, renal failure, alcoholism, IVDU, immunosuppression
- **S. aureus** most common pathogen

## Clinical manifestations

- **Back pain** (unremitting including midline) + often **fever**  $\pm$  nerve root or cord signs

## Diagnostic studies

- **MRI**
- Aspiration of abscess fluid for Gram stain & cx or operative Gram stain & cx
- Blood cx (frequently  $\ominus$ )

## Treatment

- **Antibiotics  $\pm$  surgery** (decompressive laminectomy and débridement) for failure to improve on medical Rx or early s/s of cord compression (w/ vertebral osteo and epidural abscess, may see paraplegia 48–72 h after first signs)

# INFECTIONS OF THE NERVOUS SYSTEM

## ACUTE BACTERIAL MENINGITIS

### Definition

- Bacterial infection of the subarachnoid space

Microbiology in Adult Meningitis	
Etiology	Comments
<b>S. pneumoniae</b> (30–60%)	Look for distant infection (eg, Osler's triad = meningitis, pneumonia, endocarditis). Drug-resistant <i>S. pneumoniae</i> (DRSP): ~40% PCN-resistant (even <i>intermed</i> resist problematic for Rx) ~<10% 3rd-gen. ceph.-resistant Vaccine reduces rate of invasive disease
<b>N. meningitidis</b> (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.
<b>H. influenzae</b> (<5%)	↓ Incidence in children because of <i>H. influenzae</i> type b vaccine. Look for predisposing factors in adults (eg, CSF leak, recent neurosurgical procedure, trauma, mastoiditis).
<i>L. monocytogenes</i> (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 <i>poly-predominant</i> pleocytosis.
GNRs (1–10%)	Usually nosocomial or postprocedure or in elderly or immunosuppressed
Staphylococci (5%)	Seen with indwelling CSF shunt ( <i>S. epidermidis</i> ) or following neurosurgery or head trauma ( <i>S. aureus</i> )
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)
- ± Fundoscopic 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 <sub>2</sub> O)	WBC/mm <sup>3</sup> 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 <i>S. pneumoniae</i> ; Vanco, which has poorer CSF penetration, in case Cftx-resistant <i>S. pneumoniae</i> ) If >50 y old or alcoholic: + ampicillin 2 g IV q4h for <i>Listeria</i> 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/ <i>S. pneumoniae</i> & 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 <i>N. meningitidis</i> is ruled out

\*When possible, organism-directed Rx, guided by suspect. or local patterns of drug resistance should be used.

## Prognosis

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

## ASEPTIC MENINGITIS

## Definition

- Negative bacterial microbiologic data**, CSF pleocytosis with ⊖ appropriate blood and CSF cultures (aseptic meningitis can be neutrophilic, though less common)
- Aseptic = less likely to be bacterial, but can be infectious or noninfectious

## Etiologies (Neurology 2006;66:75)

- Viral**: enteroviruses (most common), HIV, HSV (type 2 > 1), VZV, mumps, lymphocytic choriomeningitis virus, encephalitis viruses, adenovirus, polio, CMV, EBV
- Parameningeal focus of infection** (eg, brain abscess, epidural abscess, septic thrombophlebitis of dural venous sinuses, or subdural empyema)
- TB, fungal, spirochetal** (Lyme, syphilis, leptospirosis), **rickettsial**, *Coxiella*, *Ehrlichia*
- Partially treated bacterial meningitis
- Medications**: TMP/SMX, NSAIDs, IV Ig and antilymphocyte globulins, penicillin, isoniazid
- Systemic illness**: SLE, sarcoidosis, Behcet'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/immunosuppr.); 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

**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**,  $\Delta$  MS,  $\pm$  seizures and focal neuro findings (latter atypical for viral meningitis)

**Diagnostic studies** (etiology 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  $\pm$  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  $\times$  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 immunosuppr.
- 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/  $\uparrow$  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 immunosuppr.
- Valacyclovir or famciclovir  $\times$  ~7 d in normal host; acyclovir 10 mg/kg IV q8h if disseminated or high-risk Pt (medically ill, immunosuppr., V1 zoster w/ any ophthalmic s/s, etc).
- Prevention: vaccine approved for Pts  $>60$  y ( $\downarrow$  lifetime risk from 20% to 10%, also  $\downarrow$  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
<ul style="list-style-type: none"><li><b>Sustained bacteremia</b> by an organism known to cause endocarditis (or 1 BCx or <math>\oplus</math> serology for <i>Coxiella</i>)*</li><li><b>Endocardial involvement</b> document by either <math>\oplus</math> <b>echocardiogram</b> (vegetation, abscess, prosthetic dehiscence) or <b>new valvular regurgitation</b></li></ul>	<ul style="list-style-type: none"><li>Predisposing condition (see above)</li><li>Fever</li><li><b>Vascular phenomena:</b> septic arterial or pulmonary emboli, mycotic aneurysms, ICH, Janeway lesions</li><li><b>Immune phenomena:</b> <math>\oplus</math> RF, GN, Osler's nodes, Roth spots</li><li><math>\oplus</math> <b>blood cx</b> not meeting major criteria</li></ul>

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  $\geq$ 92% (CID 2000;30:633). \*Serologic or molecular tests for other known agents of culture  $\ominus$  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 ( $\leq$ 60 d post)	Late ( $>$ 60 d post)
<i>S. viridans</i> et al.	36%	13%	<5%	20%
<i>Enterococcus</i>	11%	5%	8%	13%
<i>S. aureus</i>	28%	68%	36%	20%
<i>S. epidermidis</i>	9%	<5%	17%	20%
GNR	<5%	<5%	6%	<5%
Other	<5%	<5%	10%	10%
Culture $\ominus$	11%	<5%	17%	12%

Culture  $\ominus$  = 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,  $\oplus$  RF,  $\uparrow$  ESR

## Physical exam

- HEENT:** **Roth spots** (retinal hemorrhage + pale center), **petechiae** (conjunctivae, palate)
- Cardiac:** **murmur** (85%), **new valvular regurgitation** (40–85%)  $\pm$  thrill (fistulated valve or ruptured chordae), muffled prosthetic valve sounds. Frequent exams for  $\Delta$  murmurs.
- Abdomen:** tender splenomegaly
- Musculoskeletal:** arthritis, vertebral tenderness
- Extremities** (typically seen in SBE, not ABE)
  - Janeway lesions** (septic emboli  $\rightarrow$  non-tender, hemorrhagic macules on palms or soles)
  - Osler's nodes** (immune complexes  $\rightarrow$  tender nodules on pads of digits)  
*proximal* nail bed splinter hemorrhages (8–15%); petechiae (33%); clubbing
- Neuro:**  $\Delta$  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  $\geq 1$  h apart. ✓ BCx (at least 2 sets) after appropriate abx have been initiated to document clearance; repeat q24–48h until  $\ominus$ .
- CBC w/ diff ( $\uparrow$  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  $\ominus$  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  $\ominus$  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  $\rightarrow$  abx should be started promptly after culture data obtained  
SBE  $\rightarrow$  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  $\pm$  gent  
**native valve SBE:** ceftriaxone (or amp if ? enterococcus; eg, older ♂ or ob/gyn) + gent  
**PVE:** early ( $\leq 60$  d): vanco + cefepime + gent; intermediate (60–365 d): vanco + gent; late ( $> 1$  y): vanco + ceftriaxone + gent  
**native or prosthetic valve, culture  $\ominus$ :** 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  $\ominus$ ; 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  $\rightarrow$  4 wks of abx; sx  $> 3$  mos  $\rightarrow$   $\geq 6$  wks. Uncomplicated right-sided NVE  $\rightarrow$  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  $\downarrow$  incidence of recurrent infection in prosthesis, as well as to improve structural integrity of tissue that will receive prosthesis
- Severe valvular dysfunction  $\rightarrow$  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,  $\uparrow$  veg. size, or persistent sepsis (eg,  $\oplus$  BCx (? or fever) after  $\sim 1$  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*  $\rightarrow$  30–45% mortality; IVDU *S. aureus* (typically right-sided)  $\rightarrow$  10–15% mortality; SBE  $\rightarrow$  10–15% mortality
- PVE  $\rightarrow$  23% mortality
- Aortic valve worse prognosis than mitral valve

Endocarditis Prophylaxis	
<b>Cardiac conditions*</b>	<b>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</b> (Prophylaxis no longer rec. in acquired valvular dysfxn, bicuspid AoV, MVP with leaflet thickening or regurgitation, HCMP)
<b>Procedures*</b>	<b>Dental:</b> that involve manipulation of gingival tissue or periapical region of teeth or perforation of oral mucosa (eg, extractions, periodontal procedures, implants, root canal, cleanings) <b>Respiratory:</b> incision or biopsy of respiratory mucosa (Prophylaxis no longer rec. for GI or GU procedures)
<b>Regimens</b>	<b>Oral: amoxicillin 2 g 30-60 min before</b> 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. pneumoniae*, *Neisseria*  
lower risk: coag-neg staph (~10%), diphtheroids, & *Propionibacterium* (~0%)
- Time to growth: <24 h → higher risk, >72 h → lower risk (except for slow-growing organisms such as HACEK group)
- Confirmatory cultures: draw prior to first abx dose in stable Pts if possible
- Factors favoring endocarditis: bacteremia that is high-grade w/o identifiable source, persisting after line removal or drainage of focal source, in hosts at risk for endocarditis, or w/ organisms known to cause IE (Duke criteria); emboli

### Treatment

- 1° infxn: antibiotics based on Gram stain/culture results; tailor abx to sensitivities  
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)	
<b><i>S. aureus</i></b>	<b>Risk of endocarditis in bacteremia:</b> ~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. <b>Preferred abx:</b> MSSA → nafcillin or oxacillin; MRSA → vancomycin
<b>Coag-neg staphylococci</b>	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
<b>Enterococcus</b>	D/c catheter & Rx × 7–14 d
<b>GNR</b>	<b>D/c catheter &amp; Rx × 7–14 d.</b> Abx based on suspect.
<b>Fungi</b>	<b>D/c catheter &amp; Rx × 14 d</b> 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 ( $10 \times$  ↑ 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  $\oplus$  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  $\pm$  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  $\oplus$  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 $\oplus$ test
>5 mm	HIV $\oplus$ or immunosupp (eg, prednisone 15 mg/d $\times$ $>1$ 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 ( $\uparrow$ in induration by $>10$ mm in last 2 y)
>15 mm	Everyone else
False $\ominus$	Faulty application, anergy (including from active TB), acute TB (2–10 wk to convert), acute non-TB infections, malignancy
False $\oplus$	Improper reading, cross-reaction with nontuberculous mycobacteria (NTM), BCG vaccination (although usually $<10$ mm by adulthood)
Booster effect	$\uparrow$ induration due to immunologic boost by prior skin test in previously sensitized individual (by TB or NTM, or BCG). Test goes from $\ominus$ $\rightarrow$ $\oplus$ but does <i>not</i> represent true conversion due to <i>recent</i> infection. 2nd test is Pt's true baseline. Can be 1 y after initial test.

(NEJM 2002;347:1860)

- **IFN- $\gamma$  release assays (IGRA):** (Ag-stimulated IFN- $\gamma$  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**,  $\pm$  effusion,  $\pm$  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**  $\pm$  pericardial and peritoneal effusions (tuberculous polyserositis).
- **Reactivation TB pulmonary dis.:** apical infiltrate  $\pm$  volume loss  $\pm$  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  $\pm$  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  $>8\text{--}10\%$ /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** ( $\uparrow$  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 fibrocavitory apical disease in reactivation vs. middle & lower lobe consolidation in  $1^{\circ}$  TB, but distinction imperfect and HIV  $\oplus$  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  $\oplus$  based on screening guidelines listed above, or any exposed HIV  $\oplus$  Pt
  - R/O active disease** in any Pt w/ suggestive s/s before starting INH. If HIV  $\oplus$ , 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 $\times$ 6–9 mo
HIV $\oplus$	INH 300 mg PO qd + pyridoxine 25 mg PO qd $\times$ 9 mo
Contact case INH-resistant	RIF $\times$ 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  $5\times$  normal (risk  $\uparrow$  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  $\ominus$  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  $\oplus$  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 $\downarrow$ by concomitant vit B <sub>6</sub> ), 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  $\uparrow$  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
<b>Pulmonary TB ≥4% INH-resist. in community (includes most of U.S.)</b>	INH + RIF + PZA + (EMB) until suscept. known If sensitive to INH & RIF → INH + RIF + PZA $\times$ 2 mos, then → INH + RIF $\times$ 4 mos If resistant, see next row
<b>Drug-resistant TB (INH-R, RIF-R, or MDR/XDR)</b>	Consult ID specialist ( <i>NEJM</i> 2008;359:636)
<b>Extrapulmonary TB</b>	Consult ID specialist
<b>TB in HIV <math>\oplus</math> patient</b>	Consult ID specialist

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

**Definition**

- AIDS: HIV + CD4 count <200/mm<sup>3</sup> 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, lyses, LFTs, fasting glucose 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
<b>NRTI</b> 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) lipodystrophy (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 ( <i>Lancet</i> 2008;371:1417) TDF: acute or chronic renal insufficiency
<b>NNRTI</b> delavirdine (DLV; Rescriptor) efavirenz (EFV; Sustiva) etravirine (ETR; Intelence) nevirapine (NVP; Viramune)	Class: rash, hepatitis, mixed CYP450 inducer/inhibitor EFV: CNS effects (incl depression) ETR: rare hypersensitivity NVP: rash and hypersensitivity [risk factors are female, CD4 >250, pregnancy (∴ avoid)]
<b>PI</b> amprenavir (APV; Agenerase) atazanavir (ATV; Reyataz) darunavir (DRV; Prezista) fosamprenavir (FPV; Lexiva) indinavir (IDV; Crixivan) lopinavir/ritonavir (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 ( <i>NEJM</i> 2007;356:1723) IDV, ATV: crystalluria → nephrolithiasis DRV: rash (10%) DRV & TPV: possible sulfa cross-reactivity
<b>FI</b> enfuvirtide (T20; Fuzeon)	injection site reaction
<b>EI</b> maraviroc (MVC; Selzentry)	dizziness, hepatotoxicity
<b>II</b> 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/mm<sup>3</sup>** (also gen rec. at 350–500/mm<sup>3</sup>, 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 ( $\pm$  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 (El) under study in naïve & Rx'd Pts, ✓ CCR5 tropism assay (NEJM 2008;359:1429)
- Viral load should  $\downarrow$  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 ( $\geq$ 5 mm) or IGRA or high-risk exposure	INH + vitamin B <sub>6</sub> $\times$ 9 mo
Pneumocystis jiroveci	CD4 count <200/mm <sup>3</sup> 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/mm <sup>3</sup> and ⊕ Toxoplasma serology	TMP-SMX DS qd or dapsone 50 mg qd + pyrimethamine 50 mg qwk + leucovorin 25 qwk
MAC	CD4 count <50/mm <sup>3</sup>	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  $\times$  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 <i>P. jiroveci</i> (PCP)
Diffuse interstitial infiltrates	<i>P. jiroveci</i> , TB, viral or disseminated fungal PNA
Focal consolidation or masses	Bacterial or fungal PNA, TB, Kaposi's sarcoma
Cavitory lesions	TB, aspergillosis, and other fungal PNA Bacterial PNA (including MRSA, <i>Nocardia</i> , and <i>Rhodococcus</i> )
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, ↓ PaO<sub>2</sub>, ↑ A-a ∇, ↑ LDH, ⊕ PCP sputum stain, ⊕ beta-glucan Rx if PaO<sub>2</sub> >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 PaO<sub>2</sub> <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 → altretinoin 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
- **Neurosphylis:** 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)	⊕ <i>Toxoplasma</i> 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, cryptococcosis, 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 lymphadenitis with CD4 <100–150, bacteremia usually when CD4 <50
- Treatment: clarithromycin + ethambutol ± rifabutin

**Cytomegalovirus (CMV)**

- Usually reactivation
- Clinical manifestations: retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis
- Treatment: valganciclovir, ganciclovir, foscarnet, or cidofovir

# TICK-BORNE DISEASES

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
<b>Stage 1 (early localized) wks after infection</b>	Due to local effects of spirochete. General: <b>flu-like illness</b> Derm (~80%): <b>erythema migrans</b> (EM) = erythematous patches w/ central clearing, size 6–38 cm; lymphocytomas; regional LAN
<b>Stage 2 (early disseminated) wks to mos after infection</b>	Due to spirochetemia and immune response General: fatigue, malaise, LAN, HA; fever uncommon Derm: <b>multiple (1–100) annular lesions</b> ≈ EM Rheum (~10%): <b>migratory arthralgias</b> (knee & hip) & <b>myalgias</b> Neurologic (~15%): cranial neuropathies (esp. <b>CN VII</b> ), aseptic meningitis, mononeuritis multiplex (± pain), transverse myelitis Cardiac (~8%): <b>heart block</b> , myopericarditis
<b>Stage 3 (late persistent) mos to y after infection</b>	Due to chronic infection or autoimmune response Derm: <b>acrodermatitis chronica atrophicans</b> , panniculitis Rheum (~60%): joint pain, <b>recurrent mono- or oligoarthritis of large joints</b> (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  $\oplus$  due to other spirochetal diseases, SLE, RA, EBV, HIV, etc.; false  $\ominus$  due to early abx therapy or w/in 6 wks of infxn confirm  $\oplus$  ELISA results w/ **Western blot** ( $\uparrow$  Sp)
- ✓ CSF if suspected neuro disease:  $\oplus$  intrathecal Ab if  $(\text{IgG}_{\text{CSF}}/\text{IgG}_{\text{serum}})/(\text{alb}_{\text{CSF}}/\text{alb}_{\text{serum}}) > 1$

### Treatment (NEJM 2006;354:2794)

- Prophylaxis (best prevention is tick avoidance): protective clothing, tick ✓ q24h, DEET Chemoprophylaxis w/ doxycycline 200 mg PO  $\times 1$  only if *all* of the following:
  - Ixodes scapularis* tick attached  $\geq 36$  h
  - Local Lyme carriage in ticks  $\geq 20\%$  (peak season in New England, mid-Atl, MN, WI)
  - Abx can be given w/in  $\leq 72$  h
  - No contraindication 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)  $\times 30$  d
- Antibiotics: if clin. manifestations *and*  $\oplus$  serology (? and h/o tick bite if nonendemic area) local or early disseminated w/o neuro or cardiac involvement: **doxycycline** 100 mg PO bid  $\times 2$  wks (range: 10–21 d); alternative (eg, pregnancy, doxy allergy): amox 500 mg PO tid or cefuroxime 500 mg PO bid  $\times 14$ –21 d neuro (other than isolated CN VII palsy), cardiac, chronic arthritis: **ceftriaxone** 2 g IV daily  $\times 2$ –4 wks; alternative (eg, severe  $\beta$ -lactam allergy): doxy 100–200 mg PO bid  $\times 2$ –4 wks
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias

## ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

### Microbiology & Epidemiology

- Infection with *Rickettsia rickettsii* (Gram  $\ominus$  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,  $\Delta$  MS, myalgias, N/V, occasionally abdominal pain
- Rash (2–5 d after onset) = centripetal: starts on ankles and wrists  $\rightarrow$  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  $\oplus$

### Treatment

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

## EHRLICHIOSIS/ANAPLASMOSIS

### Microbiology

- Infection with Gram  $\ominus$  obligate intracellular bacterium
- Human monocytic ehrlichiosis (*Ehrlichiosis chaffeensis*) (HME)
- Human granulocytic anaplasmosis (*Anaplasma 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,  $\uparrow$  aminotransferases, LDH, Ad

### 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  $\times$  10 d); should defervesce in  $\leq$ 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 asymptomatic 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,  $\downarrow$  cellular immunity,  $\uparrow$  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  $\oplus$  by 2nd week.
- Streptomycin or gentamicin  $\times$  7–14 d

# FEVER OF UNKNOWN ORIGIN (FUO)

FUO  
6-23

## Definition

- Fever  $>101^{\circ}\text{F}$  or  $>38.3^{\circ}\text{C}$  on more than one occasion
- Duration  $\geq 3$  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%	<b>Tuberculosis:</b> 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 <b>Intra-abdominal abscess:</b> hepatic, splenic, subphrenic, pancreatic, perinephric, pelvic, prostatic abscess or prostatitis, appendicitis <b>Endocarditis:</b> consider HACEK orgs, <i>Bartonella</i> , <i>Legionella</i> , <i>Coxiella</i> <b>Osteomyelitis:</b> dental abscess, sinusitis, paraspinal abscess CMV, EBV, Lyme, malaria, <i>Babesia</i> , ameba, fungus, typhoid
Connective tissue disease ~30%	<b>Giant cell arteritis:</b> headache, scalp pain, jaw claudication, visual disturbances, myalgias, arthralgias, $\uparrow$ ESR <b>Adult-onset Still's disease (juvenile RA):</b> fevers w/ evanescent truncal rash, pharyngitis, LAN, very high ferritin <b>Polyarteritis nodosa, other vasculitides:</b> RA, SLE, PMR, psoriatic arthritis, reactive arthritis
Neoplasm ~20%	<b>Lymphoma:</b> LAN, HSM, $\downarrow$ Hct or plt, $\uparrow$ LDH; leukemia, myelodysplasia <b>Renal cell carcinoma:</b> microscopic hematuria, $\uparrow$ Hct <b>Hepatocellular, pancreatic, and colon cancers, sarcomas:</b> 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; $\uparrow$ WBC & ESR during attacks); other defects in innate immunity

(Archives 2003;163:545; Medicine 2007;86:26)

## Workup

- History: thorough hx, ROS, PMHx and PSHx, fever curve (consider holding antipyretics), infectious contacts, travel, pets, occupation, meds, TB hx
- Careful physical exam w/ attention to skin/mucous memb., LAN, murmurs, HSM, arthritis
- Laboratory evaluation  
CBC with diff, lyses, BUN, Cr, LFTs, ESR, CRP, ANA, RF, cryoglobulin, LDH, CK, SPEP BCx  $\times 3$  sets (off abx; hold for HACEK, RMSF, Q fever, *Brucella*), U/A, UCx, PPD or IGRA, HIV Ab  $\pm$  PCR, heterophile Ab (specific EBV serologies if neg), CMV antigenemia, Hep serologies if LFTs abnl
- Discontinue unnecessary meds (only 20% w/ med-induced FUO have eos or rash), reassess 1–3 wks after meds d/c'd
- Imaging studies: CXR, chest & abd CT (oral & IV contrast), ? tagged WBC or gallium scan, ? FDG PET, ? echo, ? lower extremity Doppler US
- Pursue abnormalities raised by above w/u (eg, bx, MRI, etc., for dx, not screening)
- Duke's criteria for endocarditis (qv) have good Se & Sp in Pts with FUO
- Consider temporal artery bx if  $\uparrow$  ESR and age  $>60$ , particularly if other s/s
- ? Bone marrow aspirate & bx (esp if signs of marrow infiltration) or liver bx (espec. if  $\uparrow$  A $\phi$ ): 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,  $\uparrow$  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

# NOTES

## 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<sub>4</sub> 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* hyponatremia (severe if ↓ access to H<sub>2</sub>O)
- 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, Ø mass effect, no hormonal effects, can f/u 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**: transphenoidal 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 glucose 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

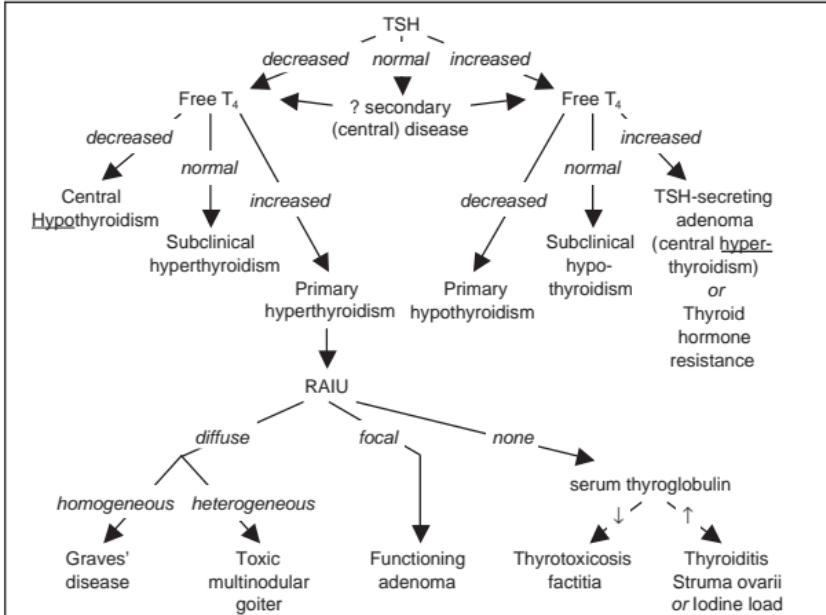
### Polyglandular Autoimmune (PGA) Syndromes

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

# THYROID DISORDERS

Diagnostic Studies in Thyroid Disorders	
Test	Comments
<b>Thyroid-stimulating hormone (TSH)</b>	Most sensitive test to detect 1° hypo- and hyperthyroidism May be inappropriately normal in central etiologies ↓d by dopamine, steroids, severe illness
T <sub>3</sub> and T <sub>4</sub> immunoassays	Measure <i>total</i> serum concentrations (∴ influenced by TBG)
<b>Free T<sub>4</sub> immunoassay (FT<sub>4</sub>)</b>	Free T <sub>4</sub> , not influenced by TBG, increasingly popular
Thyroxine-binding globulin (TBG)	↑ TBG (∴ ↑ T <sub>4</sub> ): estrogens, OCP, pregnancy, hepatitis, opioids, hereditary ↓ TBG (∴ ↓ T <sub>4</sub> ): androgens, glucocorticoids, nephritic syndrome, cirrhosis, acromegaly, nicotinic acid, hereditary
Reverse T <sub>3</sub>	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 <i>after</i> total thyroidectomy and radioiodine therapy
<b>Radioactive iodine uptake (RAIU) scan</b>	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 <b>no uptake</b> = 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<sub>4</sub>, ↑ 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<sub>4</sub>, 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<sub>4</sub>; ↑ 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<sub>4</sub> IV, then 50–100 µg IV qd; b/c peripheral conversion impaired, may also give 5–10 µg T<sub>3</sub> IV q8h if unstable w/ bradycardia and/or hypothermia (T<sub>3</sub> 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<sub>4</sub>** 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) thyroiditis
- **Toxic adenomas** (single or multinodular goiter)
- TSH-secreting pituitary tumor or pituitary resistance to thyroid hormone (↑ TSH, ↑ free T<sub>4</sub>)
- 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<sub>4</sub> and FT<sub>3</sub>; ↓ 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 hypercalcioruria ± hypercalcemia, ↑ A<sub>f</sub>, anemia

## Treatment

- β-blockers: control tachycardia (propranolol also ↓ T<sub>4</sub> → T<sub>3</sub> 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<sub>4</sub> → T<sub>3</sub>)
- 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<sub>4</sub>** 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<sub>4</sub>, FT<sub>4</sub>, & T<sub>3</sub>
- Mild illness: ↓ T<sub>4</sub> → T<sub>3</sub> conversion, ↑ rT<sub>3</sub> ⇒ ↓ T<sub>3</sub>; in severe illness: ↓ TBG & albumin, ↑↑ rT<sub>3</sub> ⇒ ↓ T<sub>3</sub>, ↑ degradation of T<sub>4</sub>, central ↓ TSH ⇒ ↓ T<sub>3</sub>, ↓ T<sub>4</sub>, ↓ FT<sub>4</sub>, ↓ TSH
- Recovery phase: ↑ TSH followed by recovery of T<sub>4</sub> and then T<sub>3</sub>
- Replacement thyroxine *not* helpful or recommended for critically ill Pts w/ ↓ T<sub>3</sub> and T<sub>4</sub> 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)

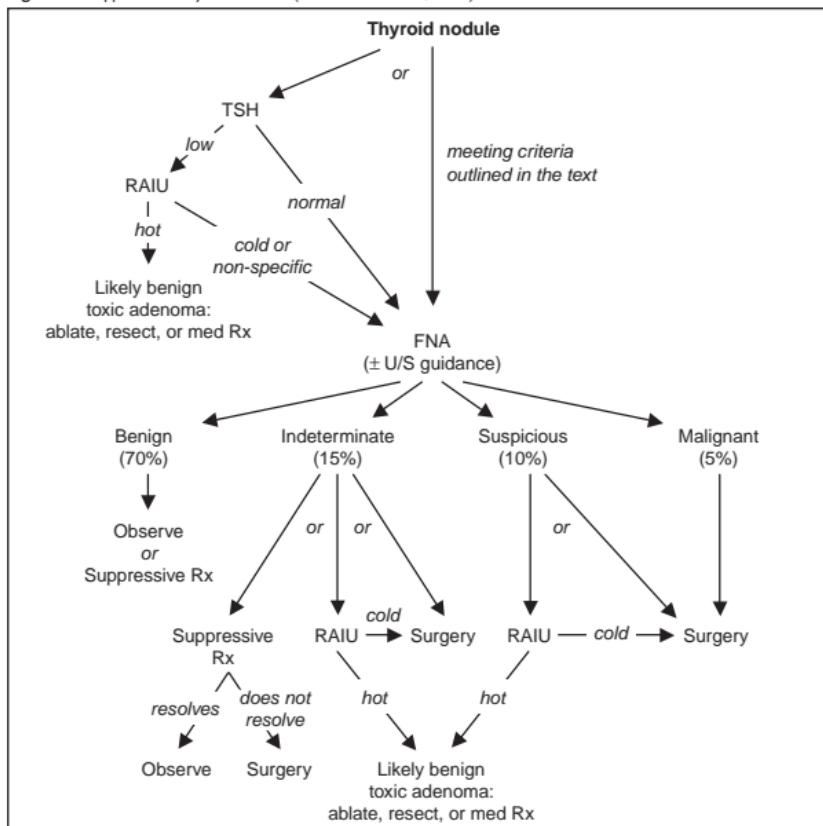
- Pathophysiology
  - (1) Wolff-Chaikoff effect: iodine load ↓ I<sup>-</sup> uptake, organification, and release of T<sub>4</sub> & T<sub>3</sub>
  - (2) inhibits T<sub>4</sub> → T<sub>3</sub> conversion
  - (3) ? direct/immune-mediated thyroid destruction

- Normal individuals: ↓ T<sub>4</sub>; then escape Wolff-Chaikoff effect and have ↑ T<sub>4</sub>, ↓ T<sub>3</sub>, ↑ 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<sub>4</sub> and T<sub>3</sub> in autonomous tissue)
    - diagnostic studies: ↑ thyroid blood flow on Doppler U/S; treatment: methimazole
  - Type 2 = destructive thyroiditis
    - pathophysiology: ↑ release of preformed T<sub>4</sub> & T<sub>3</sub> → 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)



# ADRENAL DISORDERS

## Cushing's Syndrome (Hypercortisolism)

### Definitions

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

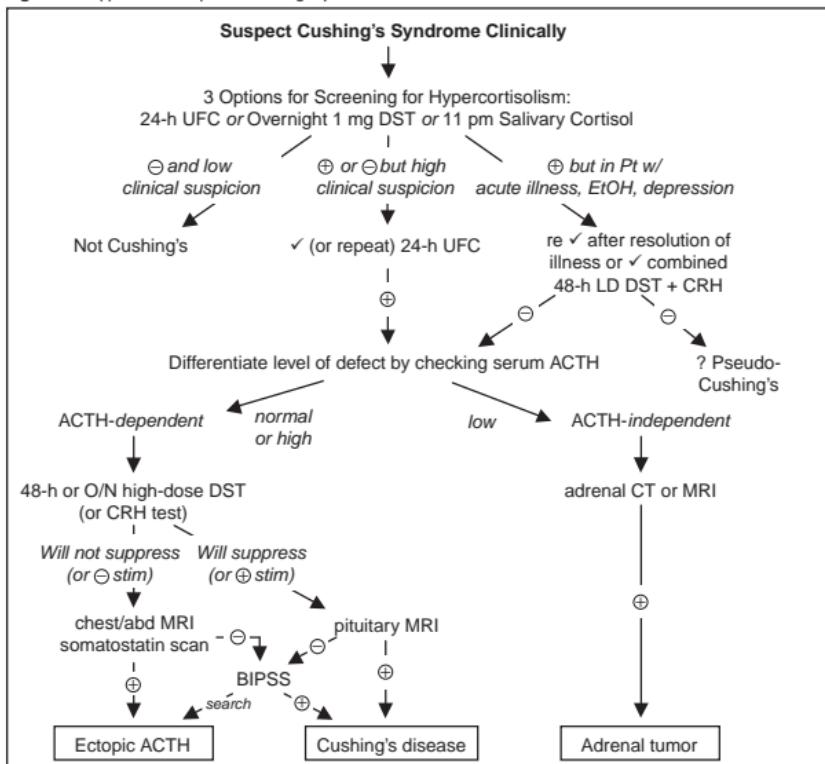
### Etiologies of hypercortisolism

- Most common cause is iatrogenic Cushing's syndrome caused by exogenous glucocorticoids
- **Cushing's disease** (60–70%): pituitary adenoma (usually microadenoma) or hyperplasia
- **Adrenal tumor** (15–25%): adenoma or (rarely) carcinoma
- **Ectopic ACTH** (5–10%): SCLC, carcinoid, islet cell tumors, medullary thyroid cancer, 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 ( $\pm$  metyrapone) to  $\downarrow$  cortisol
- Glucocorticoid replacement therapy  $\times$  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,  $\uparrow$  aldosterone is renin dependent)
  - Primary reninism: renin-secreting tumor (rare)
  - Secondary reninism
    - renovascular disease: RAS, malignant hypertension
    - edematous states w/  $\downarrow$  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
  - 11 $\beta$ -HSD deficiency ( $\rightarrow$  lack of inactivation of cortisol, which binds to otherwise nonselective mineralocorticoid receptor)
  - Black licorice (glycyrrhetic acid inhibits 11 $\beta$ -HSD), extreme hypercortisolism (overwhelming 11 $\beta$ -HSD), exogenous mineralocorticoids
  - Liddle's syndrome (constitutively activated/overexpressed distal tubular renal Na channel)

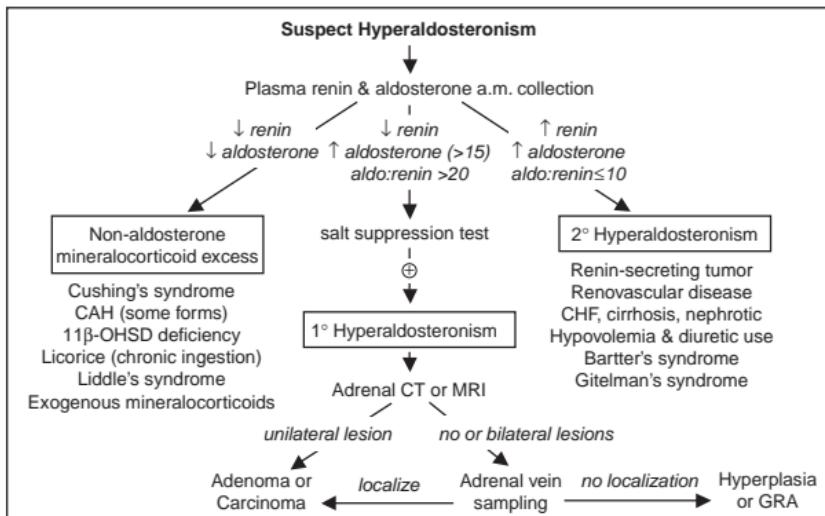
### Clinical manifestations

- 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;  $\therefore$  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  $\uparrow$  renin activity  $\rightarrow$   $\downarrow$  PAC/PRA ratio and  $\beta$ Bs may  $\uparrow$  PAC/PRA ratio;  $\therefore$  avoid.  $\alpha$ -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)  $\times$  3 d,  $\checkmark$  24-h urine ( $\oplus$  if aldo  $>12$   $\mu$ g/d while Na  $>200$  mEq/d) or 2L NS over 4 h, measure aldo at end of infusion ( $\oplus$  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 insuff.
- 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 ( $\frac{2}{3}$  a.m.  $\frac{1}{3}$  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 ( $\uparrow$  in paraganglioma), 10% malignant ( $\uparrow$  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<sup>h</sup> urinary fractionated metanephrenes & catechols: 90% Se, 98% Sp (JCEM 2003;88:553). Screening test of choice if low-risk (as false  $\oplus$  with severe illness, renal failure, OSA, labetalol due to assay interference, TCAs, medications containing sympathomimetics)
- Plasma free metanephrenes: 99% Se, 89% Sp (JAMA 2002;287:1427). Screening test of choice if high-risk, but  $\uparrow$  rate of false  $\oplus$  in low-preval. population.
- Adrenal CT or MRI; consider MIBG scintigraphy if CT/MRI  $\ominus$ , PET can be used to localize nonadrenal mass, but usually easy to find
- Consider genetic testing in appropriate circumstances (bilateral, young Pt,  $\oplus$  FHx, extra-adrenal)

### Treatment

- $\alpha$ -blockade first (usually phenoxybenzamine)  $\pm$   $\beta$ -blockade (often propranolol)  $\rightarrow$  surgery

## ADRENAL INCIDENTALOMAS

### Epidemiology

- 4% of Pts undergoing abdominal CT scan have incidentally discovered adrenal mass; prevalence  $\uparrow$  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 metanephrenes and catecholamines or plasma free metanephrenes.
- 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  $\uparrow$  size on repeat scan; irregular margins, heterogeneous, dense, or vascular appearance; h/o malignancy or young age (incidentaloma less common). Such incidentalomas warrant FNA biopsy, repeat scan in 3 mos, or resection.

# CALCIUM DISORDERS

Laboratory Findings in Calcium Disorders			
Ca	PTH	Disease	PO <sub>4</sub>
↑	↑↑	Hyperparathyroidism (1° and 3°)	↓
	↑ or nl	Familial hypocalciuric hypercalcemia	↓
	↓	Malignancy	var.
		Vitamin D excess	↑
		Milk-alkali syndrome, thiazides	↓
↓	↑↑	Bone turnover	↑
	↑	Pseudohypoparathyroidism	↑
	var.	Vitamin D deficiency	↓
		Chronic renal failure (2° hyperpara)	↑
	↓	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
<b>Hyperparathyroidism (HPT)</b>	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
<b>Familial hypocalciuric hypercalcemia (FHH)</b>	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 <sub>Ca</sub> [(24h U <sub>Ca</sub> /serum Ca) / (24h U <sub>Cr</sub> /serum Cr)] <0.01
<b>Malignancy</b>	PTH-related peptide (PTHRP) → humoral ↑ Ca of malignancy (e.g., squamous cell cancers, renal, breast, bladder) Cytokines & ↑ 1,25-(OH) <sub>2</sub> D <sub>3</sub> (eg, hematologic malignancies) Local osteolysis (eg, breast cancer, myeloma)
<b>Vitamin D excess</b>	Granulomas (sarcoid, TB, histo, Wegener's) → ↑ 1-OH → ↑ 1,25-(OH) <sub>2</sub> D. Vitamin D intoxication.
<b>↑ Bone turnover</b>	Hyperthyroidism, immobilization + Paget's disease, vitamin A
<b>Miscellaneous</b>	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<sub>4</sub>, and ↑ (Ca × PO<sub>4</sub>) product. Dx by biopsy. Rx: aggressive wound care, keep Ca & PO<sub>4</sub> nl (goal <55), avoid vitamin D & Ca suppl. IV Na thiosulfate & parathyroidectomy 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<sub>4</sub>; based on results consider checking PTHrP, 25-(OH)D, 1,25-(OH)<sub>2</sub>D, A<sub>d</sub>, U<sub>Ca</sub>, 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) <sub>2</sub> D production, ↑ PO <sub>4</sub> 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 <sub>4</sub> (ARF, rhabdomyolysis, tumor lysis), bisphosphonates

## Clinical manifestations

- Neuromuscular irritability:** perioral paresthesias, cramps,  $\oplus$  **Chvostek's** (tapping facial nerve → contraction of facial muscles),  $\oplus$  **Trousseau's** (inflation of BP cuff → carpal spasm), laryngospasm; irritability, depression, psychosis, ↑ ICP, seizures, ↑ QT
- Rickets and/or osteomalacia: chronic ↓ vit D → ↓ Ca, ↓ PO<sub>4</sub> → ↓ 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)<sub>2</sub>D) & osteitis fibrosa cystica (due to ↑ PTH)

## Diagnostic studies

- Ca, alb, ICa, PTH, 25-(OH)D, 1,25-(OH)<sub>2</sub>D (if renal failure or rickets), Cr, Mg, PO<sub>4</sub>, A<sub>d</sub>, U<sub>Ca</sub>

## 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  $\geq 126$  mg/dL  $\times 2$ ; random glc  $\geq 200$  mg/dL  $\times 2$  or  $\times 1$  if severe hyperglycemia and acute metabolic decompensation; or 75 g OGTT w/ 2-h glc  $\geq 200$  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<sub>A1C</sub> (no accepted criterion yet,  $\geq 6.5\%$  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)
- Mature-Onset Diabetes of the Young (MODY):** autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (*NEJM* 2001;345:971)
- Secondary causes of diabetes:** exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF resection), endocrinopathies (Cushing's disease, acromegaly), gestational, drugs (protease inhibitors, atypical antipsychotics)

**Clinical manifestations**

- Polyuria, polydipsia, polyphagia with unexplained weight loss; can also be asymptomatic

Diabetes Treatment Options	
Diet	Type 1: carb counting; Type 2: wt reduction diet + exercise
Metformin	↓ hepatic gluconeogenesis, ↓ Hb <sub>A1C</sub> ~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 <sub>A1C</sub> $\geq 7\%$
Sulfonylureas (SU)	↑ insulin secretion, ↓ Hb <sub>A1C</sub> ~1.5%. Hypoglycemia, wt gain.
Thiazolidinediones (TZD) (PPAR $\gamma$ agonists)	↑ insulin sens. in adipose & muscle. ↓ Hb <sub>A1C</sub> ~1% Wt gain, hepatotoxicity, fluid retention & CHF, bone fractures ? ↑ MI w/ rosiglitazone ( <i>NEJM</i> 2007;356:2457; <i>Lancet</i> 2009;373:2125) but not w/ pioglitazone ( <i>JAMA</i> 2007;298:1180) Contraindic. in liver disease and NYHA III–IV, monitor LFTs
Glinides	↑ insulin secretion, ↓ Hb <sub>A1C</sub> ~1.5% Hypoglycemia (but less than w/ SU), wt gain
Exenatide	↑ glc-depend insulin secretion (GLP-1 agonist), ↓ Hb <sub>A1C</sub> ~0.5% Wt loss, N/V & diarrhea (30–45%), pancreatitis (rare)
$\alpha$ -glucosidase inhibitor	↓ intestinal CHO absorption, ↓ Hb <sub>A1C</sub> 0.5–0.8%. GI distress (gas).
Pramlintide	Delays gastric emptying & ↓ glucagon, ↓ Hb <sub>A1C</sub> 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 <sub>A1C</sub> ~0.5%.
Insulin  (Additional T1D options: insulin pump, pancreatic or islet cell transplant)	Hypoglycemia, wt gain Generally combine intermed./long-acting (NPH or glargin) and short/rapid-acting (regular or lispro) insulin for all T1D. In T2D, consider starting if mono oral Rx not adequate (espec if ↑ Hb <sub>A1C</sub> 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 diabetorum, lipodystrophy, acanthosis nigricans

## Outpatient screening and treatment goals (Diabetes Care 2009;32:193 & S1:S13)

- ✓ Hb<sub>A1C</sub> 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/exacerbators (dextrose IV, glucocorticoids, postop, ↑ carb diet)
- Dx studies: BG fingersticks (fasting, qAC, qHS; or Q6h if NPO), Hb<sub>A1C</sub>
- 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 glucose
  - 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<sub>3</sub> equivalents) and fluid resuscitation with chloride
- Ketosis:**  $\oplus$  **urine and serum ketones** (acetoacetate measured by nitroprusside, but predominant ketone is β-OH-butrate; urine ketones may be  $\oplus$  in fasting normal Pts)
- ↑ serum glucose; ↑ BUN & Cr (dehydration ± artifact due to ketones interfering w/ some assays)
- Pseudohyponatremia: corrected Na = measured Na + [2.4 × (measured glucose - 100)/100]
- ↓ or ↑ K (but even if serum K is elevated, usually total body K depleted); ↓ total body phosphorus
- Leukocytosis, ↑ amylase (even if no pancreatitis)

Typical DKA "Flow sheet" Setup											
VS	UOP	pH	HCO <sub>3</sub>	AG	Ketones	Glc	K	PO <sub>4</sub>	IVF	Insulin	
Note: Main ketone produced is $\beta$ -OH-butyrate ( $\beta$ OHB), but ketone measured by nitroprusside is acetacetate (Ac-Ac). As DKA is treated, $\beta$ OHB $\rightarrow$ Ac-Ac, $\therefore$ 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 $\rightarrow$ add dextrose to IVF and continue insulin to metabolize ketones AG normal $\rightarrow$ 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 $\rightarrow$ ↓ serum K careful K repletion in Pts with renal failure $\text{HCO}_3$ : ? replete if pH <7 or if cardiac instability $\text{PO}_4$ : 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  $\rightarrow$  osmotic diuresis  $\rightarrow$  vol depletion  $\rightarrow$  prerenal azotemia  $\rightarrow$  ↑ 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 =  $2 \times \text{Na}$  (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<sub>50</sub> (50% dextrose)
- If no IV, can give glucagon 0.5–1 mg IM or SC (side effect: N/V)

# LIPID DISORDERS

## Measurements

- Lipoproteins = lipids (cholesteryl esters & triglycerides) + phospholipids + proteins include: chylomicrons, VLDL, IDL, LDL, HDL, Lp(a)
- Measure after 12-h fast; LDL 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 ( $\geq 3$  of following): waist  $\geq 40"$  (♂) or  $\geq 35"$  (♀); TG  $\geq 150$ ; HDL  $<40$  mg/dL (♂) or  $<50$  mg/dL (♀); BP  $\geq 130/85$  mm Hg; fasting glc  $\geq 100$  mg/dL (Circ 2009;120:1640)

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

## Primary dyslipidemias

- Familial hypercholesterolemia (FH, 1:500): defective LDL receptor;  $\uparrow$  chol, nl TG;  $\uparrow$  CAD
- Familial defective apoB100 (FDB, 1:1000): similar to FH
- Familial combined hyperlipidemia (FCH, 1:200): polygenic;  $\uparrow$  chol,  $\uparrow$  TG,  $\downarrow$  HDL;  $\uparrow$  CAD
- Familial dysbetalipoproteinemia (FDBL, 1:10,000): apoE ε2/ε2 + DM, obesity, renal disease, etc.;  $\uparrow$  chol and TG; tuberoeruptive and palmar striated xanthomas;  $\uparrow$  CAD
- Familial hypertriglyceridemia (FHTG, 1:500):  $\uparrow$  TG,  $\pm \uparrow$  chol,  $\downarrow$  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)  $\downarrow$  LDL  $\rightarrow$  21%  $\downarrow$  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  $\rightarrow$  47%  $\downarrow$  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
<b>High:</b> CHD, CVD, PAD, AAA, DM, or $\geq 2$ RFs & 10-y risk $>20\%$	$<100$ mg/dL or $<70$ if very high risk (ACS, CAD + multiple RFs or + met syndrome)
<b>Mod high:</b> $\geq 2$ RFs & 10-y risk 10–20%	$<130$ mg/dL (optional $<100$ mg/dL)
<b>Mod:</b> $\geq 2$ RFs & 10-y risk $<10\%$	$<130$ mg/dL
<b>Lower:</b> 0–1 RFs	$<160$ mg/dL

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

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

# ARTHRITIS—OVERVIEW

## Approach to patient with joint pain

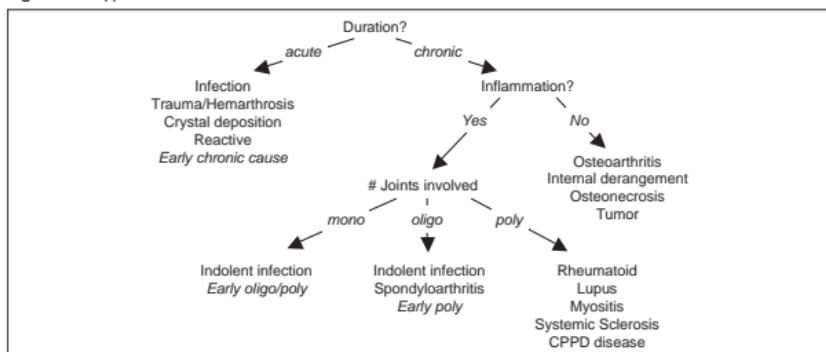
- Hx: distinguish **joint vs. soft tissue** pain, **inflammatory vs. noninflammatory** pain
  - Features suggestive of inflammatory pain: swelling in specific joint (w/o h/o trauma), persistence over days to weeks, morning stiffness, improvement of pain and stiffness w/ motion & exercise, improvement w/ NSAIDs or steroids
- Physical exam (see later): localize complaint and determine if there are objective signs of **inflammation** (arthritis, bursitis, tendinitis) or **noninflammatory pain** (arthralgia, myofascial pain)
- Osteoarthritis can p/w bony enlargement or crepitus, w/ or w/o noninflammatory effusion

Key Physical Exam Findings in Joint Pain					
	Joint		Soft tissues		
Physical exam	Inflammatory Arthritis	Arthralgia	Bursitis	Tendonitis	Myofascial
<b>Inspection</b>					
Swelling	yes	no	yes	yes	no
Erythema	varies	no	yes	usually	no
<b>Palpation</b>					
Warmth	yes	no	yes	usually	no
Tenderness	varies	varies	over bursa	over tendon	yes
<b>ROM*</b>					
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 Arthritis				
Feature	OA	RA	Gout	Spondyloarthritis
Onset	gradual	gradual	acute	variable
Inflammation	⊖	⊕	⊕	⊕
Pathology	degeneration	pannus	microtophi	enthesisitis
# 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 <sup>3</sup>	<200	<2000	>2000	>2000 usually >50K
Polys	<25%	<25%	≥50%	≥75%
Culture	⊖	⊖	⊖	⊕
Conditions		OA, internal derangement	RA, crystal CTD spondyloarth.	infection

# RHEUMATOID ARTHRITIS (RA)

RA  
8-3

## Definition and epidemiology

- Chronic, symmetric, debilitating, and destructive polyarthritis caused by inflammatory, proliferative synovial tissue (pannus) formation in affected joints
- Genetic factors: ↑ incidence in Pts w/ shared epitope on class II MHC DRB1 and DR4
- Environmental factors: smoking, silica dust exposure
- ↑ risk w/ shared epitope & smoke b/c gene-environment interaction (*Ann Rheum Dis* 2010;69:70)
- Prevalence = 1% of adults; female:male = 3:1; onset 35–50 y; worldwide

## Clinical manifestations (*Lancet* 2001;358:903)

- Pain, swelling, and impaired function of joints (typically PIPs, MCPs, wrists, knees, ankles, MTPs, and cervical spine) with **morning stiffness** for ≥ 1 h
- Polyarticular in 75% (60% small joints, 30% large joints, 10% both), monoarticular in 25% (knee, shoulder, wrist)
- Joint immobilization, muscle shortening, bone & cartilage destruction, joint deformities: **ulnar deviation**, **swan neck** (MCP flexion, PIP hyperextension, DIP flexion), **boutonnière** (PIP flexion, DIP hyperextension), **cock-up deformities** (toes)
- C1-C2 instability** → myelopathy, ∴ ✓ C-spine flex/ext films prior to elective intubation
- Rheumatoid nodules** (20–30%; usually in sero-⊕ Pts): SC nodules on extensor surfaces along tendon sheaths and in bursae; also occur in lung, heart, and sclera
- Constitutional symptoms: fever, weight loss, malaise
- Ocular: scleritis, episcleritis, keratoconjunctivitis sicca (associated Sjögren's)
- Pulmonary (20% of the time precedes joint manifestations)
  - ILD: COP fibrosis, nodules, Caplan's syndrome (pneumoconiosis + rheumatoid nodules)
  - pleural disease: pleuritis, pleural effusions (classically low glucose)
  - pulmonary hypertension
  - airway disease: obstruction (cricoarytenoid arthritis), bronchiolitis, bronchiectasis
- Cardiac: pericarditis (effusion in 1/3 of sero-⊕), 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, mesangial, MPGN); nephrotic syndrome due to AA amyloidosis; Rx-induced, including NSAIDs (AIN, membranous GN), gold, MTX
- Longstanding seropositive, erosive RA:
  - Felty's syndrome** (1%): neutropenia, RF ⊕, 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		
RF & ACPA ⊖	0	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.	
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 **Disease-Modifying Anti-Rheumatic Drug (DMARD)** w/in 3 mo if established disease and ongoing inflammation (*Annals* 2007;146:406); all take ≥ 1 mo to have an effect

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

# CRYSTAL DEPOSITION ARTHRITIDES

## GOUT

### Definition & Pathobiology (*Lancet* 2010;375:318)

- Monosodium urate (MSU) crystal deposition in joints and other tissues
- Activate cryopyrin inflammasome → IL-1 $\beta$  → 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
<b>Primary hyperuricemia</b>	<b>Idiopathic</b> Rare inherited enzyme (HGPRT, PRPP) defic. Common genetic variants ( <i>Lancet</i> 2008;372:1953)	<b>Idiopathic</b>
<b>Secondary hyperuricemia</b>	↑ meat, seafood, EtOH intake <b>Myelo- &amp; lymphoproliferative dis.</b> Chronic hemolytic anemia Cytotoxic drugs, psoriasis Severe muscle exertion	<b>Dehydration</b> ↓ 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<sup>3</sup>, >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

Gout 85

### Acute Treatment for Gout

Drug	Mechanism	Comments
<b>NSAIDs</b>	↓ inflammation	Gastritis; ↓ dose in renal insufficiency
<b>Colchicine (PO or IV)</b>	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
<b>Corticosteroids (PO, IA, or IV) or Corticotropin (SC, IM, or IV)</b>	↓ 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
- probencid** (uricosuric) for underexcretors (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-1 $\beta$  → 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/mm<sup>3</sup>, >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 blenorragica:** 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

## 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, subungual 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, antimarials, gold

## 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)

# INFECTIOUS ARTHRITIS & BURSITIS

## DIAGNOSIS AND EMPIRIC TREATMENT OF INFECTIOUS ARTHRITIS

### Diagnosis

- **Arthrocentesis** should be performed as soon as suspected
- Take care not to tap through an infected area thus introducing infxn into joint space
- Send fluid for cell count, gram stain, bacterial culture, crystals  
**WBC >50,000 with poly predominance** 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	<i>S. aureus</i> (most common)	Normal joints Prosthetic joints Damaged joints
	<i>S. epidermidis</i>	Prosthetic joints Post-joint procedure
	Streptococci	Healthy adults Splenic dysfunction
GN	Diplococci: <i>N. gonorrhoea</i>	Sexually active young adults
	Rods: <i>E. coli</i> , <i>Pseudomonas</i> , <i>Serratia</i>	IVDU GI infection Immunocompromised

## 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  $\oplus$  in ~75% of Staph, ~50% of GNR; culture  $\oplus$  in >90% of cases
- **Leukocytosis** with neutrophilic predominance  $\pm$  bandemia
- **Blood cultures**  $\oplus$  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 gonorrhoea*
- **Normal host** as well as Pts w/ deficiencies of terminal components of complement
- Female:male ratio = 4:1. ↑ incidence during menses, pregnancy, and postpartum period.  
    ↑ incidence in homosexual males. Rare after age 40 y.

### Clinical manifestations

- Preceded by **mucosal infection** (eg, endocervix, urethra, or pharynx) that is often asx
- Usually presents as two distinct syndromes:
  - Joint localized: purulent arthritis (40%) usually of knees, wrists, hands, or ankles
  - Bacteremia: triad of **polyarthritides**, **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

# CONNECTIVE TISSUE DISEASES

% 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 sabre” (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<sub>2</sub> 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 ↓ DLCO on PFTs; PHT revealed by echocardiography
- Skin bx not routine, but helpful to assess other possible causes for skin thickening

## Clinical Manifestations of Systemic Sclerosis

<b>Skin</b>	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
<b>Arteries</b>	Raynaud's phenomenon (80%); digital or visceral ischemia
<b>Renal</b>	Scleroderma renal crisis = sudden onset severe HTN, RPGN, MAHA Crescentic GN (rare) with $\oplus$ p-ANCA ( <i>J Rheum</i> 2006;33:1886)
<b>GI</b>	GERD and erosive esophagitis Esophageal dysmotility → dysphagia, odynophagia, aspiration Gastric dysmotility → early satiety and gastric outlet obstruction Small intestinal dysmotility → bloating, diarrhea, malabsorption
<b>Musculoskel</b>	Polyarthralgias & joint stiffness; muscle weakness, tendon friction rubs
<b>Cardiac</b>	Myocardial fibrosis, pericarditis; conduction abnormalities
<b>Pulmonary</b>	Pulmonary fibrosis (typically develops w/in 4 y); pulmonary arterial hypertension (typically develops after many yrs). #1 cause of mortality.
<b>Endocrine</b>	Amenorrhea and infertility common; thyroid fibrosis $\pm$ hypothyroidism

## Systemic Sclerosis

	Limited	Diffuse
<b>General</b>		Fatigue, weight loss
<b>Skin</b>	Thickening on distal extremities and face only	Thickening on extremities (incl. digits), face, and trunk
<b>Nails</b>	Capillary dropout $\pm$ dilatation	Capillary dropout & dilatation
<b>Pulmonary</b>	PAH > fibrosis	Fibrosis > PAH
<b>GI</b>	GERD, hypomotility, PBC	GERD, hypomotility
<b>Renal</b>		Renovascular HTN
<b>Cardiac</b>		Restrictive cardiomyopathy
<b>Other</b>	<b>CREST syndrome</b> = Calcinosis, Raynaud's Esophageal dysmotility Sclerodactyly, Telangiectasias	Raynaud's
<b>Antibodies</b>	Anticentromere (70%)	Anti-Scl 70 (40%)
<b>Prognosis</b>	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;  $\pm$  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  $\pm$  periorbital edema
  - Gottron's papules** (*pathognomonic*): violaceous often scaly areas symmetrically over dorsum of PIP and MCP joints, elbows, patellae, medial malleoli
  - subungual 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;  $\uparrow$  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

- $\uparrow$  **CK**, aldolase, SGOT, and LDH;  $\pm$   $\uparrow$  ESR & CRP
- Autoantibodies:  $\oplus$  ANA (>75%),  $\oplus$  RF (33%)
  - $\oplus$  anti-Jo-1 (25%), a/w nonerosive polyarthritis, Raynaud's, ILD, mechanic's hands
  - $\oplus$  anti-Mi-2 (5-10%), more common with DM, may have better prognosis
  - $\oplus$  anti-SRP (signal recognition peptide), seen in PM, indicates more aggressive disease
- EMG:**  $\uparrow$  spontaneous activity,  $\downarrow$  amplitude, polyphasic potentials with contraction
- Muscle biopsy:** all with muscle fiber necrosis, degeneration & regeneration
  - PM: endomysial inflam. (CD8 T cells) surrounds non-necrotic fibers,  $\uparrow$  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  $\pm$  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	$\uparrow$ CK	$\uparrow$ ESR	Biopsy
DM/PM	$\oplus$	$\ominus$	$\oplus$	$\pm$	as above
IBM	$\oplus$	$\ominus$	$\oplus$	$\ominus$	as above
Hypothyroidism	$\oplus$	$\pm$	$\oplus$	$\ominus$	mild necrosis inflammation atrophy
Steroid-induced	$\oplus$	$\ominus$	$\ominus$	$\ominus$	atrophy
PMR	$\ominus$ (limited by pain)	$\oplus$	$\ominus$	$\oplus$	normal
Fibromyalgia	$\ominus$ (limited by pain)	$\oplus$ (tender points)	$\ominus$	$\ominus$	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):  $\downarrow$  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 (~50x ↑ risk of lymphoma and WM in 1° Sjögren's)

### Diagnostic studies

- Autoantibodies:  $\oplus$  ANA (95%),  $\oplus$  RF (75%)  
Primary Sjögren's:  $\oplus$  anti-Ro (anti-SS-A, 56%) and  $\oplus$  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.  $\oplus$  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

- $\oplus$  ANA (95–99%),  $\oplus$  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,  $\ominus$  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,  $\alpha$ -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
<b>Constitutional</b> (84%)		Fever, malaise, anorexia, weight loss
<b>Cutaneous</b> (81%)	<b>1. Malar rash</b> (spares nasolabial folds) <b>2. Discoid rash</b> (erythematous papules w/ keratosis & plugging) <b>3. Photosensitivity</b> (rash, fever, N/V) <b>4. Oral/nasopharyngeal ulcers</b>	Alopecia Vasculitis Subacute cutaneous lupus Panniculitis (lupus profundus) Urticaria
<b>Musculoskeletal</b> (85–95%)	<b>5. Nonerosive arthritis:</b> episodic, oligoarticular, symmetrical, migratory	Arthralgias and myalgias Avascular necrosis of bone
<b>Cardiopulmonary</b> (33%)	<b>6. Serositis:</b> 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
<b>Renal</b> (77%)	<b>7. Proteinuria</b> (>500 mg/dL or 3+ on dipstick) or <b>urinary cellular casts</b>	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
<b>Neurologic</b> (54%)	<b>8. Seizures or psychosis</b> without other cause	Organic brain syndrome, PML Cranial or periph. neuropathies
<b>Gastrointestinal</b> (~30%)		Serositis (peritonitis, ascites) Vasculitis (bleeding, perf.) Abdominal pain Hepatitis, pancreatitis
<b>Hematologic</b>	<b>9. Hemolytic anemia</b> (DAT +) or <b>leukopenia</b> (<4000/mm <sup>3</sup> ), or <b>lymphopenia</b> (<1500/mm <sup>3</sup> ), or <b>thrombocytopenia</b> (<100,000/mm <sup>3</sup> )	Anemia of chronic disease Antiphospholipid syndrome (VTE w/ + ACL Ab or + LAC) Splenomegaly Lymphadenopathy
<b>Other</b>		Sicca syndrome Conjunctivitis or episcleritis Raynaud's (20%) Nailfold capillary changes
<b>Serologies</b>	<b>10. + ANA</b> <b>11. + anti-ds-DNA, anti-Sm, or antiphospholipid Abs</b>	↓ 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
<b>ANA</b>	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	
<b>Ro La</b>	15–35% ⊕ anti-Ro in ANA ⊖ SLE	Sjögren's/SLE overlap Neonatal lupus Photosensitivity Subacute cutaneous lupus	May appear yrs before overt disease
<b>ds-DNA</b>	70%; very specific for SLE Titers parallel disease activity, especially renal disease	Lupus nephritis Vasculitis	
<b>Sm</b>	30%; very specific for SLE	Lupus nephritis	
<b>U1-RNP</b>	40%	MCTD; Raynaud's Tend <i>not</i> to have nephritis	Appears mos before or at diagnosis
<b>histone</b>	SLE 80%, c/w 90% in DLE	Mild arthritis and serositis	At diagnosis

(NEJM 2003;349:1526)

### Treatment of SLE

Drug	Indication	Adverse Effects
<b>NSAIDs</b>	Arthralgias/arthritis, myalgias, mild serositis	Gastritis, UGIB Renal failure
<b>Hydroxychloroquine</b>	Mild disease complicated by serositis, arthritis, skin Δs	Retinal damage Stevens-Johnson synd. Myopathy
<b>Corticosteroids</b>	Low doses for mild disease High doses for major manifestations including renal, hematologic, CNS	Adrenal suppression, osteopenia, avascular necrosis of bone, myopathy
<b>Mycophenolate</b>	Nephritis (induction and/or maintenance; NEJM 2004:350:971 & 2005:353:2219)	Myelosuppression Immunosuppression/infxn, teratogen
<b>Cyclophosphamide</b>	Severe nephritis, vasculitis or CNS disease ( <i>induction ± maintenance</i> )	Myelosuppression Myeloproliferative disorders Immunosuppression/infxn Hemorrhagic cystitis, bladder cancer Infertility, teratogen
<b>Azathioprine (AZA)</b>	Mild nephritis (2nd line) Steroid-sparing agent	Myelosuppression Hepatotoxicity Lymphoproliferative disorders
<b>Methotrexate (MTX)</b>	Skin and joint disease Serositis	Myelosuppression Hepatotoxicity Pneumonitis ± fibrosis Alopecia, stomatitis
<b>Cyclosporine (CsA)</b>	Renal disease	Hyperplastic gums, HTN Hirsutism Renal impairment, anemia
<b>Rituximab</b>	? Refractory ITP or AIHA	B-cell depletion; PML (?)
<b>Belimumab</b>	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 (Cuppé 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**, GI/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)
  - weight loss ≥4 kg
  - livedo reticularis
  - testicular pain/tenderness
  - myalgias, weakness, leg tenderness
  - mononeuropathy or polyneuropathy
  - diastolic BP >90 mmHg
  - elevated BUN >40 mg/dL or Cr >1.5 mg/dL
  - Hepatitis B virus
  - Arteriographic abnormality (aneurysms, occlusion of visceral arteries)
  - 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 +
<b>Wegener's granulomatosis</b>	⊕	80%	90%	—	c-ANCA (anti-PR3)	90%
<b>Microscopic polyangiitis</b>	—	90%	50%	—	p-ANCA (anti-MPO)	70%
<b>Churg-Strauss syndrome</b>	⊕	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)
  - nasal or oral inflammation: oral ulcers, purulent or bloody nasal discharge
  - CXR showing nodules, fixed infiltrates, or cavities
  - microscopic hematuria or urinary red cell casts
  - 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 $\geq 2$ 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%  $\oplus$  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%  $\oplus$  ANCA** (c-ANCA or p-ANCA), **eosinophilia** (5–10 k/ $\mu$ L, 80%), **biopsy** → **microgranulomas**, fibrinoid necrosis, and thrombosis of small arteries and veins with **eosinophilic infiltrates**; CXR may show shifting pulmonary infiltrates
- Classification criteria (4 of 6 criteria is 85% Se & 99.7% Sp; Arth Rheum 1990;33:1094)
  - asthma
  - eosinophilia  $> 10\%$
  - mono- or polyneuropathy
  - migratory or transitory pulm. infiltrates
  - paranasal sinus abnormality
  - 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**  $\pm$  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)
  - palpable purpura
  - age  $\leq 20$  y at disease onset
  - bowel angina
  - biopsy showing granulocytes in the walls of arterioles or venules
- Treatment: supportive; steroids  $\pm$  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;  $\oplus$  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- $\alpha$ 2a
  - ocular: steroids, AZA, infliximab, IFN- $\alpha$ 2a, 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 $\oplus$ )	Autoimmune syndromes
Primary manifestations	Hyperviscosity $\pm$ 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  $\rightarrow$  immune complex (IC) formation
- Defective/insufficient IC clearance  $\rightarrow$  IC deposition with complement activation
- Promotes: platelet aggregation  $\rightarrow$  small vessel thromboses, inflammation  $\rightarrow$  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.
- $\oplus$  rheumatoid factor (RF)
- False elevations in WBC or plt count on automated CBC, due to cryoprecipitation
- $\downarrow$  C4 levels, variable C3 levels,  $\uparrow$  ESR
- Must keep blood warmed to  $37^\circ\text{C}$  at all times en route to lab; early cooling causes false  $\ominus$  cryoglobulin, loss of RF and  $\downarrow\downarrow$  complement
- In HCV-associated type 2 cryoglobulinemia:  $\oplus$  HCV RNA,  $\ominus$  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  $\beta$ -pleated sheets

Classification of Amyloidosis			
Type	Precursor	Causative diseases	Organ systems
<b>AL</b> (Primary) Most common ~2000 cases/y	Ig light chain (monoclonal)	MM Light chain disease ( $\lambda > \kappa$ ) MGUS, WM	<b>Renal, cardiac, GI, neuro, cutaneous, hepatic, pulmonary, musculoskeletal, heme</b>
<b>AA</b> (Secondary)	Serum amyloid (SAA)	Inflam: RA, IBD, FMF Chronic infxns: osteo, TB Neoplasms: renal, HD	<b>Renal, GI, hepatic, neuro, cutaneous</b>
<b>Hereditary</b>	Transthyretin, et al.	Mutant proteins	<b>Neurologic, cardiac</b>
<b>Senile</b>	TTR, ANP	Normal proteins; 2° aging	<b>Cardiac, aorta, GI</b>
<b>A<math>\beta</math>2M</b>	$\beta$ 2-microglobulin	Dialysis-associated $\beta$ 2m (normally renally excreted)	Musculoskeletal
<b>Organ-specific</b>	$\beta$ -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
<b>Renal</b>	Proteinuria or nephrotic syndrome	AL, AA
<b>Cardiac</b>	Cardiomyopathy (restrictive & dilated) $\downarrow$ QRS amplitude, conduction abnormalities, AF Orthostatic hypotension	AL, hereditary, senile, organ-specific
<b>GI</b>	Diarrhea, malabsorption, protein loss Ulceration, hemorrhage, obstruction Macroglossia $\rightarrow$ dysphonia and dysphagia	all systemic
<b>Neurologic</b>	Peripheral neuropathy with painful paresthesias Autonomic neuro $\rightarrow$ impotence, dysmotility, $\downarrow$ BP Carpal tunnel syndrome	hereditary, AL, organ-specific, A $\beta$ 2m
<b>Cutaneous</b>	Waxy, nonpruritic papules; periorbital ecchymoses “Pinch purpura” = skin bleeds with minimal trauma	AL
<b>Hepatic &amp; Splenic</b>	Hepatomegaly, usually without dysfunction Splenomegaly, usually without leukopenia or anemia	all systemic
<b>Endocrine</b>	Deposition with rare hormonal insufficiency	organ-specific
<b>Musculoskel</b>	Arthralgias and arthritis	AL, A $\beta$ 2m
<b>Pulmonary</b>	Airway obstruction	AL, AA
<b>Hematologic</b>	Factor X deficiency	AL

## Diagnostic studies

- If suspect AL  $\rightarrow$  ✓ SIEP (not SPEP or UPEP) & free light chains,  $\pm$  BM bx
- If suspect renal involvement ✓ U/A (proteinuria)
- If suspect cardiac involvement: ✓ ECG ( $\downarrow$  voltage, conduction abnl), echo (biventricular thickening with “granular sparkling” appearance;  $\uparrow$  wall w/o  $\uparrow$  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])  $\rightarrow$  apple-green birefringence on Congo red stain
- Genetic testing for hereditary forms

## Treatment

- AL: melphalan + dexamethasone, ? 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: ↓ PaO <sub>2</sub> , ↑ PaCO <sub>2</sub>
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	
TPP	

## 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
	Oriented	Follows commands	6
Spontaneous	Confused	Localizes pain	5
To voice	Inappropriate words	Withdraws from pain	4
To painful stimuli	Unintelligible sounds	Decorticate posturing	3
None	None	Decerebrate posturing	2
		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<sub>3</sub>, 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)

**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**

- Alcohol withdrawal, illicit drugs, meds (eg,  $\beta$ -lactams, bupropion, tramadol, metronidazole, meperidine, CsA, antidep., clozapine can lower seizure threshold)
- Brain tumor or penetrating trauma
- Cerebrovascular disease, including subdural hematomas, hypertensive encephalopathy
- Degenerative disorders of the CNS (eg, Alzheimer's)
- Electrolyte (hyponatremia) & other metabolic (eg, uremia, liver failure, hypoglycemia)

**Clinical manifestations**

- Aura** (sec to mins): premonition consisting of abnormal smells/tastes, unusual behavior, oral or appendicular automatisms
- Ictal period** (sec to mins): tonic and/or clonic movements of head, eyes, trunk, or extrem.
- Postictal period** (mins to h): slowly resolving period of confusion, disorientation, and lethargy. May be accompanied by focal neurologic deficits (Todd's paralysis).
- Status epilepticus:** continuous tonic-clonic seizure  $\geq 30$  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  $\oplus$  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 <sub>3</sub> , ↑ 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
Leviteracetam	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 Diazepam	0.1 mg/kg at 2 mg/min 0.2 mg/kg at 5 mg/min	Successive 2–4 mg IV pushes 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 Fosphenytoin	20 mg/kg at 50 mg/min 20 mg PE/kg at 150 mg/min + 5–10 mg/kg if still seizing	1.0–1.5 g IV over 20 min 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  $\gamma$ -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,  $\frac{1}{3}$  → delirium tremens
- Alcoholic hallucinosis:** isolated hallucinations (typically visual) 12–48 h after last drink
- Delirium tremens (DT):** disorientation, agitation, hallucinations, ↑ HR & BP, fever, diaphoresis; begins 48–96 h after last drink, lasts 5–7 d
- 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 $\leq 2$ 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 metab; good if cirrhosis)

Route: start IV, transition to PO

Dosing: typically start w/ diazepam 10–15 mg IV q10–15 min (or lorazepam 2–4 mg IV q15–20 min) until appropriate sedation achieved, then titrate to CIWA-Ar scale, evaluating q1h until score  $<8 \times 8$  h, then q2h  $\times 8$  h, 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  $\beta$ B / central  $\alpha_2$ -agonists (mask sx)
- Mechanical restraints as needed until chemical sedation achieved
- Volume resuscitation as needed; thiamine then glucose to prevent Wernicke's encephalopathy (ataxia, ophthalmoplegia, short-term memory loss); replete K, Mg, PO<sub>4</sub>
- 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  $\times$  24h, then 25–50 mg q6h  $\times$  2d

# STROKE

## ISCHEMIC (~70%)

### Etiologies

- Embolic (~75%): artery → artery, cardioembolic, paradoxical (*NEJM* 2007;357:2262), cryptogenic
- Thrombotic (~25%): lacunar (arteriolar, seen in HTN & DM) or large vessel
- Other: dissection, vasculitis, vasospasm, hyperviscosity, watershed

### Clinical Manifestations

*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)

- **ABCD<sup>2</sup>:** Age ≥60 y (+1); BP ≥140/90 (+1); Clin. features: unilateral weakness (+2), speech impairment w/o weakness (+1); Duration ≥60 (+2) or 10–59 min (+1); Diabetes (+1)
- Risk of stroke at 2 d: low risk (0–3) = 1.0%; moderate (4–5) = 4.1%; high (6–7) = 8.1%
- Risk of progression higher for TIAs due to large artery/lacunar dis. (vs. cardioembolic)

**Treatment of ischemic stroke** (NEJM 2008;359:1317; Lancet 2010;375:1695)

- **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,  $\emptyset$  hemorrhage, and  $\emptyset$  contraindication to lysis.  
For Pts Rx'd w/in 3 h, 12% absolute  $\uparrow$  in excellent functional outcome, 5.8%  
absolute  $\uparrow$  ICH, trend toward 4% absolute  $\downarrow$  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/  $\uparrow$  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**  $\downarrow$  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  $\uparrow$  bleeding (Lancet 2004;364:331)

dipyridamole + ASA  $\approx$  clopidogrel alone in risk of recurrent stroke, and  $\downarrow$  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  $\rightarrow$   $\uparrow$  ICP requiring elevated head of bed  $>30^\circ$ ; intubation & hyperventilation to  $P_{CO_2} \sim 30$  (transient benefit); osmotherapy with mannitol IV 1 gm/kg  $\rightarrow$  0.25 g/kg q6h;  $\pm$  hypertonic saline surgical decompression
- Statin  $\rightarrow$   $\downarrow$  in recurrent stroke &  $\downarrow$  MACE (Lancet 2002;360:7; NEJM 2006;355:549)

**Carotid revascularization**

- Carotid endarterectomy (if institutional morbidity & mortality  $\leq 6\%$ ) indicated for:  
sx stenosis  $\geq 70\%$  (? 50–69% if male, age  $\geq 75$  y, or recent sx)  $\rightarrow$  65%  $\downarrow$  stroke (NEJM 1991;325:445; Lancet 2004;363:915)  
asx stenosis  $\geq 70\%$  &  $<75$  y  $\rightarrow$   $\sim 50\% \downarrow$  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  $\uparrow$  risk of stroke:  $\geq 4$  mm separation, R  $\rightarrow$  L shunting at rest,  $\uparrow$  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  $\pm$  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  $\checkmark$  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  $\downarrow$  hematoma expansion and mortality at the expense of  $\uparrow$  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  $\downarrow$  risk of vasospasm, phenytoin for seizure prophylaxis, endovascular (Lancet 2005;366:783) or surgical correction of aneurysm/AVM to prevent rebleeding
- Cerebral venous thrombosis: paradoxically, requires anticoagulation with IV heparin

# WEAKNESS & NEUROMUSCULAR DYSFUNCTION

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<sub>12</sub> 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<sub>A1C</sub>, B<sub>12</sub>, 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<sub>a</sub>O<sub>2</sub> or S<sub>a</sub>O<sub>2</sub>)

### 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  $\oplus$  &  $\ominus$  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  $\ominus$  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.)
- $\pm$  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,  $\pm$  fibrillation potentials
- Muscle biopsy, molecular genetic testing (where indicated)

# HEADACHE

## Primary headache syndromes

- Tension: associated with muscle contraction in neck or lower head; treat with NSAIDs
- Migraine: see later
- Cluster: periodic, paroxysmal, brief, sharp, orbital headache that may awaken from sleep ± lacrimation, rhinorrhea, conjunctival injection, or unilateral Horner's syndrome.  
Acute treatments: oxygen, triptans; chronic prophylaxis: calcium-channel blocker.

## Secondary causes of headaches

- Vascular: stroke, intracerebral hemorrhage, SAH, subdural hematoma, AVM, unruptured aneurysm, arterial hypertension, venous thrombosis
- Infection: meningitis, encephalitis, abscess
- Brain tumor
- Pseudotumor cerebri (idiopathic intracranial hypertension)
- CSF disorder: ↑ (hydrocephalus) or ↓ (s/p LP)
- Trigeminal neuralgia
- Extracranial: sinusitis, TMJ syndrome, temporal arteritis
- Medication (analgesic) overuse

## Clinical evaluation (*JAMA* 2006;296:1274)

- History: quality, severity, location, duration, time of onset, precipitants/relieving factors
- Associated symptoms (visual Δs, nausea, vomiting, photophobia)
- Focal neurologic symptoms
- Head or neck trauma, constitutional symptoms
- Medications, substance abuse
- General and neurologic examination
- **Warning signs that should prompt neuroimaging:**  
worst ever, worsening over days, wakes from sleep  
vomiting, aggravated by exertion or Valsalva  
age >50 y, fever, abnl neurologic exam, aura, cluster-type headache, unilateral

## MIGRAINE

### Epidemiology

- Affects 15% of women and 6% of men; onset usually by 30 y

### Clinical manifestations (*Lancet* 2004;363:381; *JAMA* 2006;296:1274)

- Unilateral or bilateral, retro-orbital, throbbing or pulsatile headache; lasts 4–72 h
- Often accompanied by nausea, vomiting, photophobia
- “POUNDing”: **P**ulsatile; **O**nset duration 4–72 h**U**ltimate; **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<sub>1</sub> 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

# BACK AND SPINAL CORD DISEASE

## Ddx of back pain

- **Musculoskeletal:** musculoligamentous “strain” (experienced by up to 80% of population at some time), OA, RA, spondylolisthesis, vertebral compression fx, inflammatory 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<sub>4</sub>, A<sub>f</sub>, CSF
- **Neuroimaging:** low yield if nonradiating pain, high false  $\oplus$  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  $\pm$  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  $\pm$  surgery for compression if due to metastatic disease
- High-dose steroids depending on cause:
  - Tumor: dexamethasone 10–100 mg IV  $\times$  1 then 4–24 mg every 6 hr
  - Trauma: controversial (may have slight benefit but  $\uparrow$  risk of infection, poor healing)
    - ? methylprednisolone 30 mg/kg IV over 15 min then 45 min later: 5.4 mg/kg/h  $\times$  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	$\downarrow$ ankle but knee preserved May have $\downarrow$ reflexes, Babinski	$\downarrow$ ankle, $\downarrow$ knee Babinski absent
Bowel-Bladder -Sexual dysfxn	Early retention, incontinence, $\downarrow$ 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  $\pm$  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, brachioradialis, 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

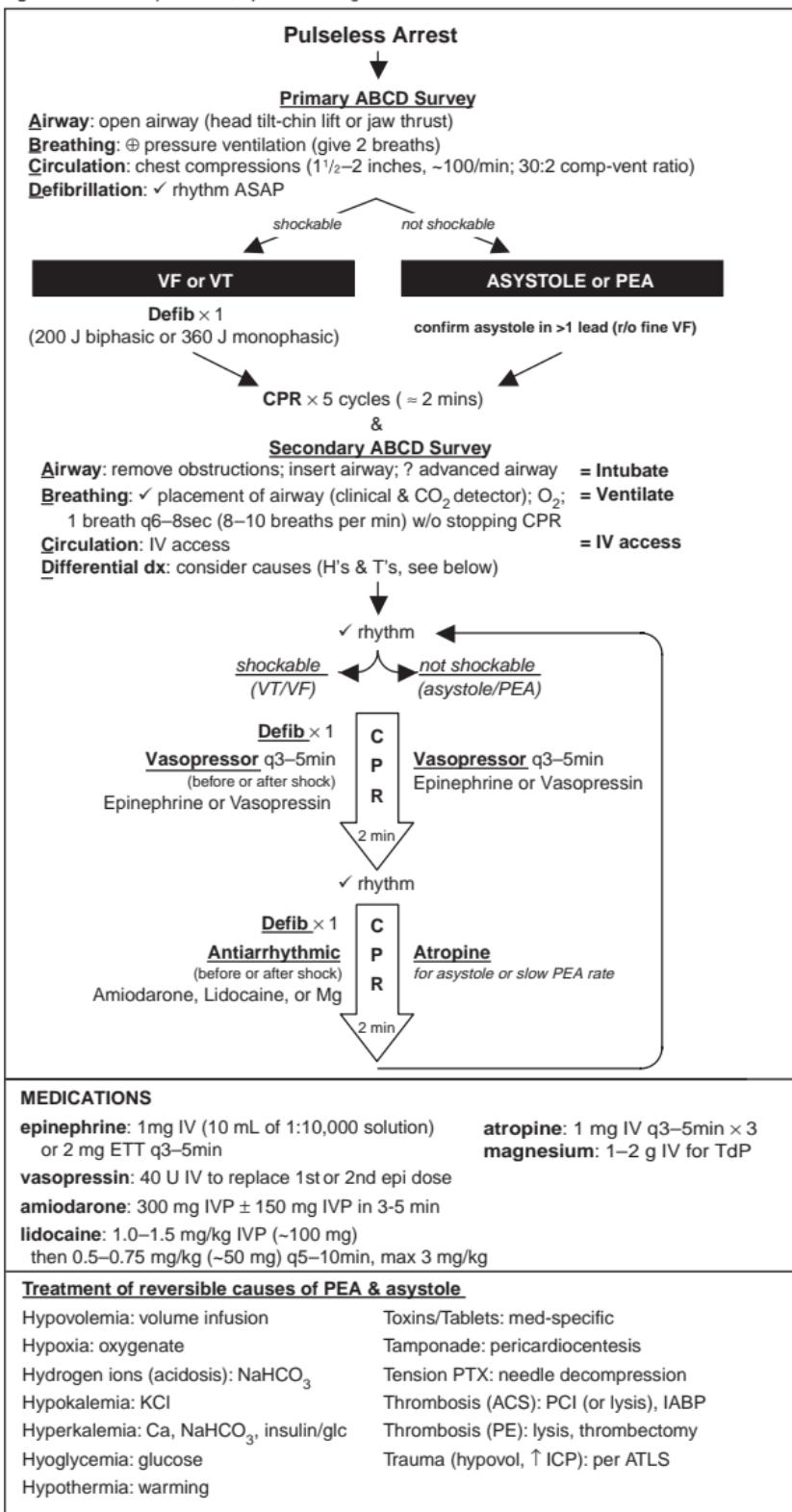
(Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient. NEJM 2007;356:1241 & 2008;358:818.)

### 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)

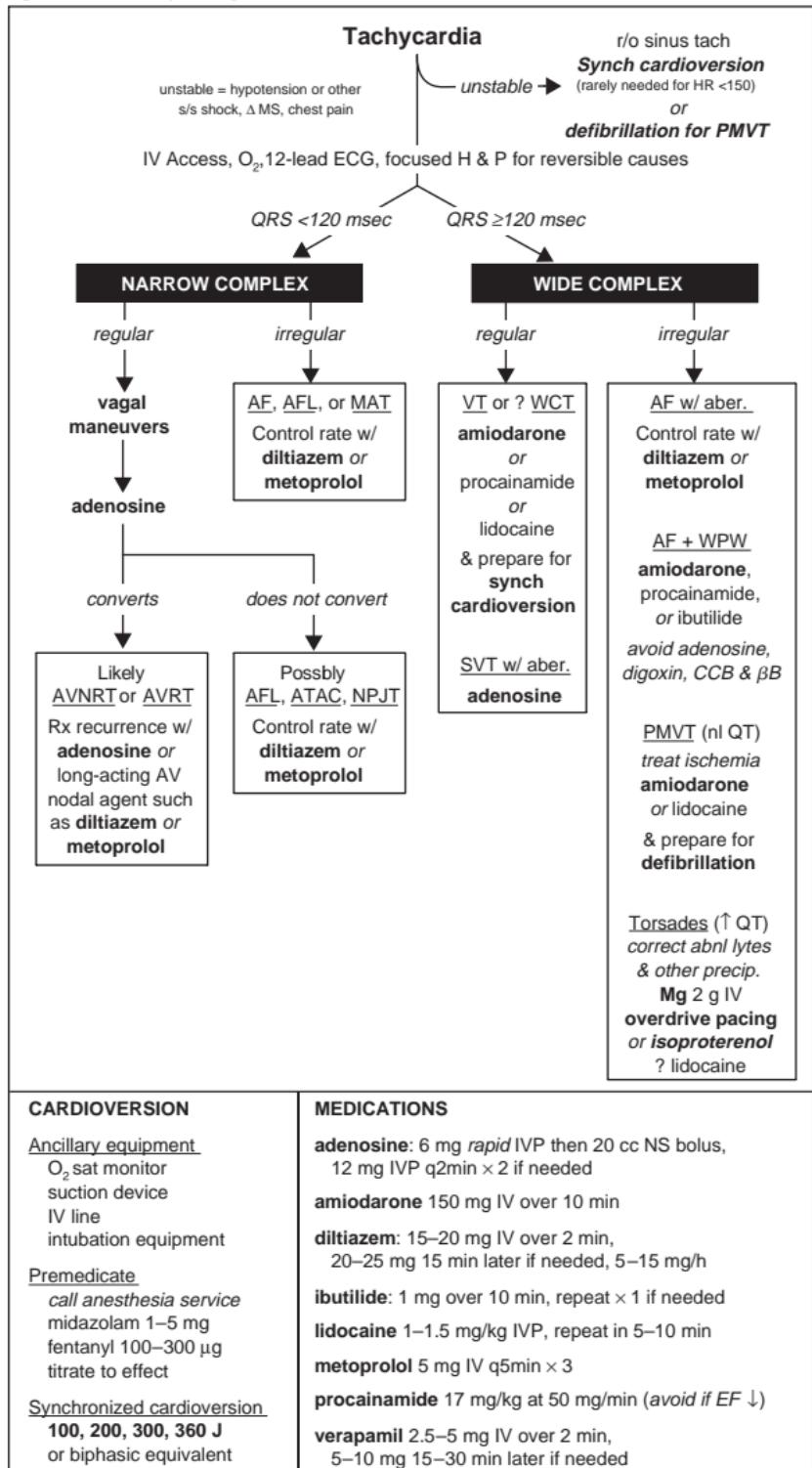
# ACLS ALGORITHMS

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



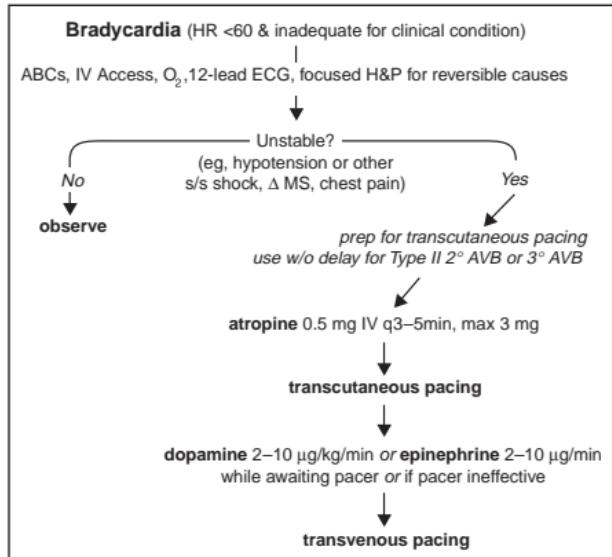
(Adapted from ACLS 2005 Guidelines, Circ 2005;112(Suppl 1):IV-58)

**Figure 10-2** ACLS tachycardia algorithm



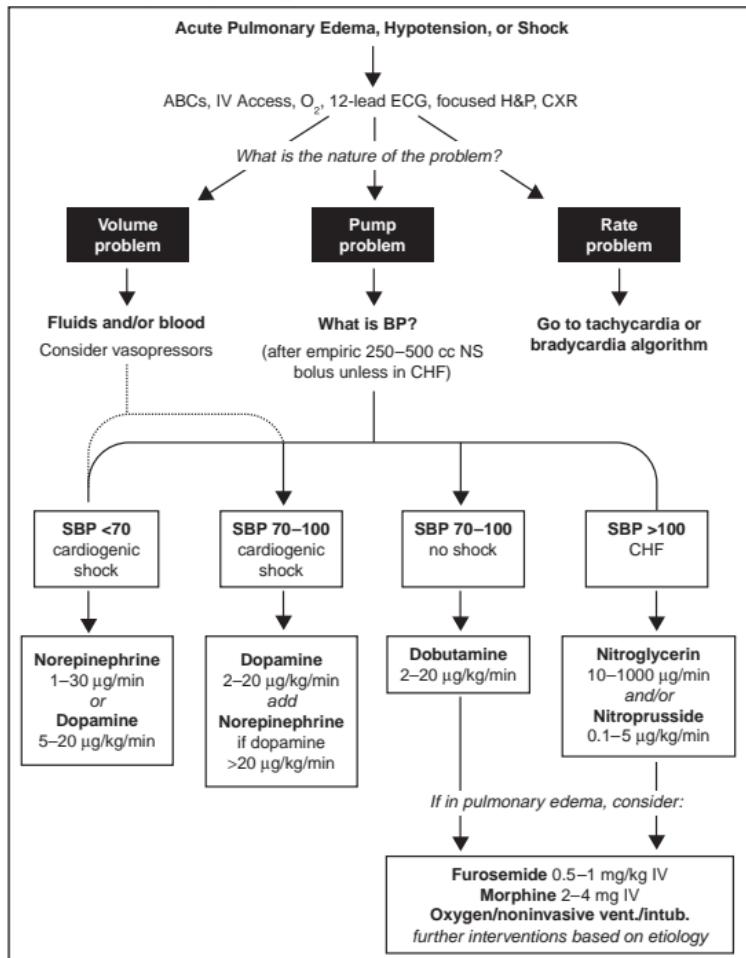
(Adapted from ACLS 2005 Guidelines, Circ 2005;112(Suppl 1):IV-67)

**Figure 10-3** ACLS bradycardia algorithms



(Adapted from ACLS 2005 Guidelines, *Circ* 2005;112(Suppl 1):IV-67)

**Figure 10-4** ACLS pulmonary edema, hypotension, or shock algorithm



(Adapted from ACLS 2005 Guidelines)

# ICU MEDICATIONS

Drug	Class	Dose	
		per kg	average
<b>Pressors, Inotropes, and Chronotropes</b>			
Phenylephrine	$\alpha_1$	10–300 $\mu\text{g}/\text{min}$	
Norepinephrine	$\alpha_1 > \beta_1$	1–40 $\mu\text{g}/\text{min}$	
Vasopressin	V <sub>1</sub>	0.01–0.1 U/min (usually <0.04)	
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$	2–20 $\mu\text{g}/\text{min}$	
Isoproterenol	$\beta_1, \beta_2$	0.1–10 $\mu\text{g}/\text{min}$	
Dopamine	D $\beta, D$ $\alpha, \beta, D$	0.5–2 $\mu\text{g}/\text{kg}/\text{min}$ 2–10 $\mu\text{g}/\text{kg}/\text{min}$ >10 $\mu\text{g}/\text{kg}/\text{min}$	50–200 $\mu\text{g}/\text{min}$ 200–500 $\mu\text{g}/\text{min}$ 500–1000 $\mu\text{g}/\text{min}$
Dobutamine	$\beta_1 > \beta_2$	2–20 $\mu\text{g}/\text{kg}/\text{min}$	50–1000 $\mu\text{g}/\text{min}$
Milrinone	PDE	50 $\mu\text{g}/\text{kg}$ over 10 min then 0.375–0.75 $\mu\text{g}/\text{kg}/\text{min}$	3–4 mg over 10 min then 20–50 $\mu\text{g}/\text{min}$
Inamrinone	PDE	0.75 mg/kg over 3 min then 5–15 $\mu\text{g}/\text{kg}/\text{min}$	40–50 mg over 3 min then 250–900 $\mu\text{g}/\text{min}$
<b>Vasodilators</b>			
Nitroglycerin	NO	10–1000 $\mu\text{g}/\text{min}$	
Nitroprusside	NO	0.1–10 $\mu\text{g}/\text{kg}/\text{min}$	5–800 $\mu\text{g}/\text{min}$
Nesiritide	BNP	2 $\mu\text{g}/\text{kg}$ IVB then 0.01 $\mu\text{g}/\text{kg}/\text{min}$	
Labetalol	$\alpha_1, \beta_1$ , and $\beta_2$ blocker	20 mg over 2 min then 20–80 mg q10min or 10–120 mg/h	
Fenoldopam	D	0.1–1.6 $\mu\text{g}/\text{kg}/\text{min}$	10–120 $\mu\text{g}/\text{min}$
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	
<b>Antiarrhythmics</b>			
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	$\beta$ blocker	0.5–1 mg q5min then 1–10 mg/h	
Esmolol	$\beta_1 > \beta_2$ blocker	500 $\mu\text{g}/\text{kg}$ then 25–300 $\mu\text{g}/\text{kg}/\text{min}$	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
<b>Sedation</b>			
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	
<b>Paralysis</b>			
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	
<b>Miscellaneous</b>			
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
<b>Natural</b> (eg, penicillin)	Some GPC, GPR, GNC, most anaerobes (except <i>Bacteroides</i> )	Group A streptococci Enterococci, <i>Listeria</i> , <i>Pasteurella</i> <i>Actinomyces</i> , <i>Syphilis</i>
<b>Anti-Staph</b> (eg, nafcillin)	Active vs PCNase-producing Staph Little activity vs. Gram $\ominus$	Staphylococci (except MRSA) Streptococci
<b>Amino</b> (eg, ampicillin)	Penetrate porin channel of Gram $\ominus$ Not stable against PCNases	<i>E. coli</i> , <i>Proteus</i> , <i>H. influenzae</i> <i>Salmonella</i> , <i>Shigella</i> Enterococci, <i>Listeria</i>
<b>Extended</b> (eg, piperacillin)	Penetrate porin channel of Gram $\ominus$ More resistant to PCNases	Most GNR incl. <i>Enterobacter</i> , <i>Pseudomonas</i> , <i>Serratia</i>
<b>Carbapenem</b> (eg, imipenem)	Resistant to most $\beta$ -lactamases	Most Gram $\oplus$ and $\ominus$ bacteria including anaerobes, but not MRSA or VRE
<b>Monobactams</b> (aztreonam)	Active vs. Gram $\ominus$ but not Gram $\oplus$	Gram $\ominus$ bacterial infxn in Pt w/ PCN or Ceph allergy
<b><math>\beta</math>-lact. Inhib.</b> (eg, sulbactam)	Inhibit plasma-mediated $\beta$ -lactamases	Adds Staph, <i>B. fragilis</i> and some GNR ( <i>H. influenzae</i> , <i>M. catarrhalis</i> , some <i>Klebsiella</i> ); intrinsic activity against <i>Acinetobacter</i> (sulbactam only)

Cephalosporins		
Resistant to most $\beta$ -lactamases. No activity vs. MRSA or enterococci.		
Gen.	Spectrum	Indications
<b>First</b> (eg, cefazolin)	Most GPC (incl. Staph & Strep, not MRSA) Some GNR (incl. <i>E. coli</i> , <i>Proteus</i> , <i>Klebsiella</i> )	Used for surgical ppx & skin infxns
<b>Second</b> (eg, cefuroxime, cefotetan)	$\downarrow$ activity vs. GPC, $\uparrow$ vs. GNR. 2 subgroups: Respiratory: <i>H. influenzae</i> & <i>M. catarrhalis</i> GI/GU: $\uparrow$ activity vs. <i>B. fragilis</i>	PNA/COPD flare Abdominal infxns
<b>Third</b> (eg, ceftriaxone)	Broad activity vs. GNR & some anaerobes Ceftazidime active vs. <i>Pseudomonas</i>	PNA, sepsis, meningitis
<b>Fourth</b> (eg, cefepime)	$\uparrow$ resistance to $\beta$ -lactamases (incl. of Staph and <i>Enterobacter</i> )	Similar to 3rd gen. MonoRx for nonlocalizing febrile neutropenia

Other Antibiotics	
Antibiotic	Spectrum
<b>Vancomycin</b>	Gram $\oplus$ bacteria incl. MRSA, PCNase-producing pneumococci and enterococci (except VRE)
<b>Linezolid</b>	
<b>Daptomycin</b>	GPC incl. MRSA & VRE (check susceptibility for VRE)
<b>Quinopristin/ Dalfopristin</b>	
<b>Quinolones</b>	Enteric GNR & atypicals. 3rd & 4th gen. $\uparrow$ activity vs. Gram $\oplus$ .
<b>Aminoglycosides</b>	GNR. Synergy w/ cell-wall active abx ( $\beta$ -lactam, vanco) vs. GPC. $\downarrow$ activity in low pH (eg, abscess). No activity vs. anaerobes.
<b>Macrolides</b>	GPC, some respiratory Gram $\ominus$ , atypicals
<b>TMP/SMX</b>	Some enteric GNR, PCP, <i>Nocardia</i> , <i>Toxoplasma</i> , most community-acquired MRSA
<b>Clindamycin</b>	Most Gram $\oplus$ (except enterococci) & anaerobes (incl. <i>B. fragilis</i> )
<b>Metronidazole</b>	Almost all anaerobic Gram $\ominus$ , most anaerobic Gram $\oplus$
<b>Doxycycline</b>	<i>Rickettsia</i> , <i>Ehrlichia</i> , <i>Chlamydia</i> , <i>Mycoplasma</i> , <i>Nocardia</i> , Lyme
<b>Tigecycline</b>	Many GPC incl. MRSA & VRE; some GNR incl. ESBL but not <i>Pseudomonas</i> or <i>Proteus</i> . Approved for abdominal or skin/soft tissue infections. Check susceptibility if organism isolated.

## CARDIOLOGY

Hemodynamic parameters	Normal value
<b>Mean arterial pressure (MAP)</b> = $\frac{\text{SBP} + (\text{DBP} \times 2)}{3}$	70–100 mmHg
<b>Heart rate (HR)</b>	60–100 bpm
<b>Right atrial pressure (RA)</b>	$\leq 6$ mmHg
<b>Right ventricular (RV)</b>	systolic 15–30 mmHg diastolic 1–8 mmHg
<b>Pulmonary artery (PA)</b>	systolic 15–30 mmHg mean 9–18 mmHg diastolic 6–12 mmHg
<b>Pulmonary capillary wedge pressure (PCWP)</b>	$\leq 12$ mmHg
<b>Cardiac output (CO)</b>	4–8 L/min
<b>Cardiac index (CI)</b> = $\frac{\text{CO}}{\text{BSA}}$	2.6–4.2 L/min/m <sup>2</sup>
<b>Stroke volume (SV)</b> = $\frac{\text{CO}}{\text{HR}}$	60–120 mL/contraction
<b>Stroke volume index (SVI)</b> = $\frac{\text{CI}}{\text{HR}}$	40–50 mL/contraction/m <sup>2</sup>
<b>Systemic vascular resistance (SVR)</b> = $\frac{\text{MAP} - \text{mean RA}}{\text{CO}} \times 80$	800–1200 dynes × sec/cm <sup>5</sup>
<b>Pulmonary vascular resistance (PVR)</b> = $\frac{\text{mean PA} - \text{mean PCWP}}{\text{CO}} \times 80$	120–250 dynes × sec/cm <sup>5</sup>

"Rule of 6s" for PAC: RA  $\leq 6$ , RV  $\leq 30/6$ , PA  $\leq 30/12$ , WP  $\leq 12$ . 1 mmHg = 1.36 cm water or blood.

### Fick cardiac output

Oxygen consumption (L/min) = CO (L/min)  $\times$  arteriovenous (AV) oxygen difference  
CO = oxygen consumption / AV oxygen difference

Oxygen consumption must be measured (can estimate w/ 125 mL/min/m<sup>2</sup>, but inaccurate)

AV oxygen difference = Hb (g/dL)  $\times$  10 (dL/L)  $\times$  1.36 (mL O<sub>2</sub>/g of Hb)  $\times$  (S<sub>a</sub>O<sub>2</sub> – S<sub>v</sub>O<sub>2</sub>)

S<sub>a</sub>O<sub>2</sub> is measured in any arterial sample (usually 93–98%)

S<sub>v</sub>O<sub>2</sub> (mixed venous O<sub>2</sub>) is measured in RA, RV, or PA (assuming no shunt) (normal ~75%)

$$\therefore \text{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{\text{Hb (g/dL)} \times 13.6 \times (\text{S}_a\text{O}_2 - \text{S}_v\text{O}_2)}$$

### Shunts

$$Q_p = \frac{\text{Oxygen consumption}}{\text{Pulm. vein O}_2 \text{ sat} - \text{Pulm. artery O}_2 \text{ sat}} \quad (\text{if no R} \rightarrow \text{L shunt, PV O}_2 \text{ sat} = \text{S}_a\text{O}_2)$$

$$Q_s = \frac{\text{Oxygen consumption}}{\text{S}_a\text{O}_2 - \text{mixed venous O}_2 \text{ sat}} \quad (\text{MVO}_2 \text{ drawn proximal to potential L} \rightarrow \text{R shunt})$$

$$\frac{Q_p}{Q_s} = \frac{\text{S}_a\text{O}_2 - \text{MV O}_2 \text{ sat}}{\text{PV O}_2 \text{ sat} - \text{PA O}_2 \text{ sat}} \approx \frac{\text{S}_a\text{O}_2 - \text{MV O}_2 \text{ sat}}{\text{S}_a\text{O}_2 - \text{PA O}_2 \text{ sat}} \quad (\text{if only L} \rightarrow \text{R and no R} \rightarrow \text{L shunt})$$

### Valve equations

Simplified Bernoulli equation: Pressure gradient ( $\Delta P$ ) =  $4 \times v^2$  (where  $v$  = peak flow velocity)  
Continuity eq., (conservation of flow): Area<sub>1</sub>  $\times$  Velocity<sub>1</sub> = Area<sub>2</sub>  $\times$  V<sub>2</sub> (where 1 & 2 different points)

or AVA (unknown) = A<sub>LV</sub> outflow tract  $\times \left( \frac{V_{\text{LVOT}}}{V_{\text{AOV}}} \right)$  (all of which can be measured on echo)

Gorlin equation: Valve area =  $\frac{\text{CO}/(\text{DEP or SEP}) \times \text{HR}}{44.3 \times \text{constant} \times \sqrt{\Delta P}}$  (constant = 1 for AS, 0.85 for MS)

Hakki equation: Valve area =  $\frac{\text{CO}}{\sqrt{\Delta P}}$

Chest Imaging (CXR & CT) Patterns		
Pattern	Pathophysiology	Ddx
Consolidation	Radiopaque material in air space & interstitium patent airway → "air bronchograms"	Acute: water ( <b>pulm edema</b> ), pus ( <b>PNA</b> ), 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	<b>Cardiogenic pulm edema</b> , interstitial PNA viral, mycoplasma, lymphangitic tumor
Reticular	Lace-like net (ILD)	<b>ILD</b> (espec. IPF, CVD, bleomycin, asbestos)
Nodules	Tumor Granulomas Abscess	<b>Cavitory:</b> Primary or metastatic cancer, TB (react. or miliary), fungus, Wegener's, RA septic emboli, PNA <b>Noncavitory:</b> any of above + <b>sarcoid</b> , hypersens. pneum., HIV, Kaposi's sarcoma
Wedge opac.	Peripheral infarct	<b>PE</b> , cocaine, angioinv. aspergillus, Wegener's
Tree-in-bud (best on CT)	Inflammation of small airways	<b>Bronchopneumonia</b> , endobronchial TB/MAI, viral PNA, aspiration, ABPA, CF, asthma, BOOP
Hilar fullness	↑ LN or pulm arteries	<b>Neoplasm</b> (lung, mets, lymphoma) <b>Infxn</b> (AIDS); <b>Granuloma</b> (sarcoid/TB/fungal) Pulmonary hypertension
Upper lobe	n/a	<b>TB</b> , fungal, sarcoid, hypersens. pneum., CF, XRT
Lower lobe	n/a	<b>Aspiration</b> , 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  $R \approx 0.8$ )

$$P_{AO_2} = 150 - \frac{P_aCO_2}{0.8} \text{ (on room air)}$$

**A-a gradient** =  $P_{AO_2} - P_aO_2$  [normal A-a gradient  $\approx 4 + (\text{age}/4)$ ]

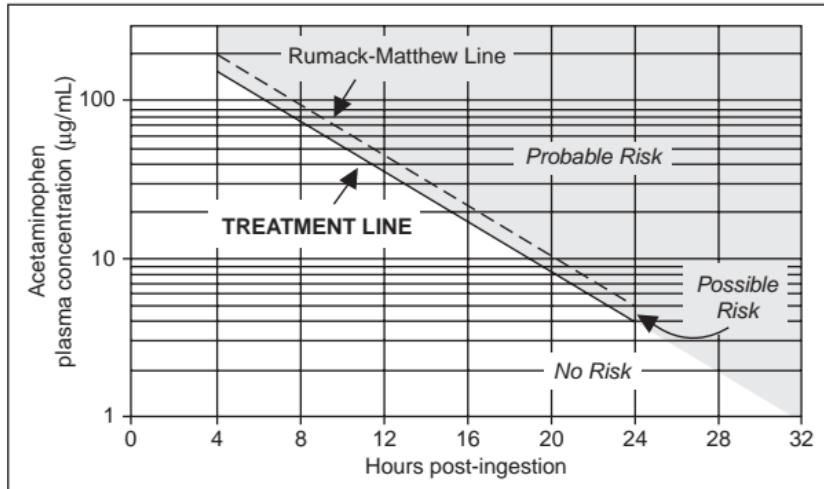
**Minute ventilation** ( $V_E$ ) = tidal volume ( $V_T$ ) × respiratory rate (RR) (normal 4–6 L/min)

**Tidal volume** ( $V_T$ ) = alveolar space ( $V_A$ ) + dead space ( $V_D$ )

$$\text{Fraction of tidal volume that is dead space} \left( \frac{V_D}{V_T} \right) = \frac{P_aCO_2 - P_{\text{expired}}CO_2}{P_aCO_2}$$

$$P_aCO_2 = k = \times \frac{\text{CO}_2 \text{ Production}}{\text{alveolar ventilation}} = k \times \frac{\dot{V}_{CO_2}}{RR \times V_T \times \left( 1 - \frac{V_D}{V_T} \right)}$$

Figure 10-5 Acetaminophen toxicity nomogram



(Adapted Archives 1981;141:382 & Guidelines for Management of Acute Acetaminophen Overdose. McNeil, 1999.)

## NEPHROLOGY

**Anion gap (AG)** =  $\text{Na} - (\text{Cl} + \text{HCO}_3)$  (normal =  $[\text{alb}] \times 2.5$ ; typically  $12 \pm 2 \text{ mEq}$ )

**Delta-delta ( $\Delta\Delta$ )** =  $[\Delta \text{ AG} \text{ (ie, calc. AG - expected)} / \Delta \text{ HCO}_3 \text{ (ie, 24 - measured HCO}_3)]$

**Urine anion gap (UAG)** =  $(\text{U}_{\text{Na}} + \text{U}_{\text{K}}) - \text{U}_{\text{Cl}}$

**Calculated osmoles** =  $(2 \times \text{Na}) + \left( \frac{\text{glc}}{18} \right) + \left( \frac{\text{BUN}}{2.8} \right) + \left( \frac{\text{EtOH}}{4.6} \right)$

**Osmolal gap (OG)** = measured osmoles – calculated osmoles (normal < 10)

**Estimated creatinine clearance** =  $\frac{[140 - \text{age (yrs)}] \times \text{wt (kg)}}{\text{serum Cr (mg/dl)} \times 72} \times 0.85 \text{ in women}$

**Fractional excretion of Na (FE<sub>Na</sub>, %)** = 
$$\left[ \frac{\frac{\text{U}_{\text{Na}}(\text{mEq/L})}{\text{P}_{\text{Na}}(\text{mEq/L})} \times 100\%}{\frac{\text{U}_{\text{Cr}}(\text{mg/mL})}{\text{P}_{\text{Cr}}(\text{mg/dl})} \times 100 \text{ (mL/dl)}} \right] = \frac{\frac{\text{U}_{\text{Na}}}{\text{P}_{\text{Na}}}}{\frac{\text{U}_{\text{Cr}}}{\text{P}_{\text{Cr}}}}$$

**Corrected Na in hyperglycemia**

estimate in all Pts: corrected Na = measured Na +  $\left[ 2.4 \times \frac{(\text{measured glc} - 100)}{100} \right]$

however,  $\Delta$  in Na depends on glc (Am J Med 1999;106:399)

$\Delta$  is 1.6 mEq per each 100 mg/dl  $\uparrow$  in glc ranging from 100–440

$\Delta$  is 4 mEq per each 100 mg/dl  $\uparrow$  in glc beyond 440

**Total body water (TBW)** =  $0.60 \times \text{IBW} (\times 0.85 \text{ if female and } \times 0.85 \text{ if elderly})$

**Free H<sub>2</sub>O deficit** =  $\text{TBW} \times \left( \frac{([\text{Na}]_{\text{serum}} - 140)}{140} \right) \approx \left( \frac{([\text{Na}]_{\text{serum}} - 140)}{3} \right) \text{ (in 70 kg Pt)}$

**Trans-tubular potassium gradient (TTKG)** = 
$$\frac{\text{U}_{\text{K}}}{\text{P}_{\text{K}}} \frac{\text{U}_{\text{Osm}}}{\text{P}_{\text{Osm}}}$$

Peripheral Smear Findings (also see Photo Inserts)	
<b>Feature</b>	<b>Abnormalities and diagnoses</b>
<b>Size</b>	normocytic vs. microcytic vs. macrocytic → see below
<b>Shape</b>	<b>anisocytosis</b> → unequal RBC size; <b>poikilocytosis</b> → irregular RBC shape acanthocytes = <b>spur</b> cells (irregular sharp projections) → liver disease <b>bite</b> cells (removal of Heinz bodies by phagocytes) → G6PD deficiency echinocytes = <b>burr</b> cells (even, regular projections) → uremia, artifact <b>pencil cell</b> → long, thin, hypochromic - very common in adv. iron deficiency <b>rouleaux</b> → hyperglobulinemia (eg, multiple myeloma) <b>schistocytes</b> , helmet cells → MAHA (eg, DIC, TTP/HUS), mechanical valve <b>spherocytes</b> → HS, AIHA; <b>sickle</b> cells → sickle cell anemia <b>stomatocyte</b> → central pallor appears as curved slit → liver disease, EtOH <b>target</b> cells → liver disease, hemoglobinopathies, splenectomy <b>tear drop</b> cells = dacrocytes → myelofibrosis, myelophthisic anemia, megaloblastic anemia, thalassemia
<b>Intra-RBC findings</b>	<b>basophilic stippling</b> (ribosomes) → abnl Hb, sideroblastic, megaloblastic <b>Heinz bodies</b> (denatured Hb) → G6PD deficiency, thalassemia <b>Howell-Jolly bodies</b> (nuclear fragments) → splenectomy or functional asplenia (eg advanced sickle cell) <b>nucleated</b> RBCs → hemolysis, extramedullary hematopoiesis
<b>WBC findings</b>	<b>blasts</b> → leukemia, lymphoma; <b>Auer rods</b> → acute myelogenous leukemia <b>hypersegmented</b> (>5 lobes) PMNs: megaloblastic anemia ( $B_{12}$ /folate def.) <b>pseudo-Pelger-Huët anomaly</b> (bilobed nucleus, "pince-nez") → MDS <b>toxic granules</b> (coarse, dark blue) and <b>Döhle bodies</b> (blue patches of dilated endoplasmic reticulum) → sepsis, severe inflammation
<b>Platelet</b>	<b>clumping</b> → artifact, repeat plt count <b>number</b> → periph blood plt count approximately 10,000 plt for every one plt seen at hpf (100 $\times$ ) <b>size</b> → MPV (mean platelet volume) enlarged in ITP

(NEJM 2005;353:498)

Heparin for Thromboembolism	
80 U/kg bolus	
18 U/kg/h	
<b>PTT</b>	<b>Adjustment</b>
<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)	
<b>PTT</b>	<b>Adjustment</b>
<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 &amp; 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](http://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

$$\text{Body surface area (BSA, m}^2\text{)} = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$$

		Disease	
		present	absent
Test	⊕	a (true ⊕)	b (false ⊕)
	⊖	c (false ⊖)	d (true ⊖)

$$\text{Prevalence} = \frac{\text{all diseased}}{\text{all patients}} = \frac{a + b}{a + b + c + d}$$

$$\text{Sensitivity} = \frac{\text{true positives}}{\text{all diseased}} = \frac{a}{a + c} \quad \text{Specificity} = \frac{\text{true negatives}}{\text{all healthy}} = \frac{d}{b + d}$$

$$\oplus \text{ Predictive value} = \frac{\text{true positives}}{\text{all positives}} = \frac{a}{a + b}$$

$$\ominus \text{ Predictive value} = \frac{\text{true negatives}}{\text{all negatives}} = \frac{d}{c + d}$$

$$\text{Accuracy} = \frac{\text{true positives} + \text{true negatives}}{\text{all patients}} = \frac{a + d}{a + b + c + d}$$

$$\oplus \text{ Likelihood ratio} = \frac{\text{true positive rate}}{\text{false positive rate}} = \frac{Se}{1 - Sp}$$

$$\ominus \text{ Likelihood ratio} = \frac{\text{false negative rate}}{\text{true negative rate}} = \frac{1 - Se}{Sp}$$

$$\text{Odds} = \frac{\text{probability}}{1 - \text{probability}} \quad \text{Probability} = \frac{\text{odds}}{\text{odds} + 1}$$

$$\text{Posttest odds} = \text{pretest odds} \times \text{LR}$$

# NOTES

# ABBREVIATIONS

<b>5'-NT</b>	5'-nucleotidase	<b>AST</b>	aspartate aminotransferase
<b>6-MP</b>	6-mercaptopurine	<b>asx</b>	asymptomatic
<b>a/w</b>	associated with	<b>AT</b>	atrial tachycardia
<b>AAA</b>	abdominal aortic aneurysm	<b>ATII</b>	angiotensin II
<b>AAD</b>	antiarrhythmic drug	<b>ATIII</b>	antithrombin III
<b>Ab</b>	antibody	<b>ATN</b>	acute tubular necrosis
<b>ABE</b>	acute bacterial endocarditis	<b>ATRA</b>	all-trans-retinoic acid
<b>ABG</b>	arterial blood gas	<b>AV</b>	atrioventricular
<b>abnl</b>	abnormal	<b>AVA</b>	aortic valve area
<b>ABPA</b>	allergic bronchopulmonary aspergillosis	<b>AVB</b>	atrioventricular block
<b>abx</b>	antibiotics	<b>AVNRT</b>	AV nodal reentrant tachycardia
<b>AC</b>	assist control	<b>AVR</b>	aortic valve replacement
<b>ACE</b>	angiotensin converting enzyme	<b>AVRT</b>	AV reciprocating tachycardia
<b>ACEI</b>	ACE inhibitor	<b>AZA</b>	azathioprine
<b>ACI</b>	anemia of chronic inflammation	<b>A<math>\phi</math></b>	alkaline phosphatase
<b>ACL</b>	anticardiolipin antibody	<b>b/c</b>	because
<b>ACLS</b>	advanced cardiac life support	<b>BAL</b>	bronchoalveolar lavage
<b>ACS</b>	acute coronary syndrome	<b><math>\beta</math>B</b>	beta-blocker
<b>ACTH</b>	adrenocorticotrophic hormone	<b>BBB</b>	bundle branch block
<b>ACV</b>	acyclovir	<b>BCx</b>	blood culture
<b>ADA</b>	adenosine deaminase	<b>BD</b>	bile duct
<b>ADH</b>	antidiuretic hormone	<b>BDZ</b>	benzodiazepines
<b>ADL</b>	activities of daily living	<b>bili.</b>	bilirubin
<b>AF</b>	atrial fibrillation	<b>BiPAP</b>	bilevel positive airway pressure
<b>AFB</b>	acid-fast bacilli	<b>BiV</b>	biventricular
<b>AFL</b>	atrial flutter	<b>BM</b>	bone marrow
<b>AFP</b>	$\alpha$ -fetoprotein	<b>BMD</b>	bowel movement
<b>AFTP</b>	ascites fluid total protein	<b>BMI</b>	bone mineral density
<b>AG</b>	aminoglycoside	<b>BMS</b>	body mass index
<b>Ag</b>	anion gap	<b>BNP</b>	bare metal stent
<b>AGN</b>	antigen	<b>BOOP</b>	B-type natriuretic peptide
<b>AI</b>	acute glomerulonephritis	<b>BP</b>	bronchiolitis obliterans with organizing pneumonia
<b>AIDS</b>	aortic insufficiency	<b>BPH</b>	blood pressure
	acquired immunodeficiency syndrome	<b>BRBPR</b>	benign prostatic hypertrophy
<b>AIH</b>	autoimmune hepatitis	<b>BS</b>	bright red blood per rectum
<b>AIHA</b>	autoimmune hemolytic anemia	<b>BT</b>	breath sounds
<b>AIN</b>	acute interstitial nephritis	<b>BUN</b>	bleeding time
<b>AIP</b>	acute interstitial pneumonia	<b>bx</b>	blood urea nitrogen
<b>AKI</b>	acute kidney injury	<b>C'</b>	biopsy
<b>ALF</b>	acute liver failure	<b>c/w</b>	
<b>ALL</b>	acute lymphoblastic leukemia	<b>CABG</b>	complement
<b>ALS</b>	amyotrophic lateral sclerosis	<b>CAD</b>	compared with
<b>ALT</b>	alanine aminotransferase	<b>CALLA</b>	consistent with
<b>AMA</b>	anti-mitochondrial antibody	<b>CAPD</b>	coronary artery bypass grafting
<b>AMI</b>	anterior myocardial infarction	<b>CBC</b>	coronary artery disease
<b>AML</b>	acute myelogenous leukemia	<b>CBD</b>	common ALL antigen
<b>ANA</b>	antineuclear antibody	<b>CCB</b>	chronic ambulatory peritoneal dialysis
<b>ANCA</b>	antineutrophilic cytoplasmic antibody	<b>CCI<sub>4</sub></b>	complete blood count
		<b>CCP</b>	common bile duct
<b>angio</b>	angiogram	<b>CCl<sub>4</sub></b>	calcium channel blocker
<b>AoD</b>	aortic dissection	<b>CCS</b>	carbon tetrachloride
<b>AoV</b>	aortic valve	<b>CCY</b>	cyclic citrullinated peptide
<b>APC</b>	activated protein C	<b>CD</b>	Canadian Cardiovascular Society
<b>APL</b>	acute promyelocytic leukemia	<b>CEA</b>	cholecystectomy
<b>APLA</b>	antiphospholipid antibody	<b>ceph.</b>	Crohn's disease
<b>APS</b>	antiphospholipid antibody syndrome	<b>CF</b>	carcinoembryonic antigen
<b>ARB</b>	angiotensin receptor blocker	<b>Cftx</b>	carotid endarterectomy
<b>ARDS</b>	acute respiratory distress syndrome	<b>CFU</b>	cephalosporin
		<b>CHB</b>	cystic fibrosis
<b>ARV</b>	antiretroviral	<b>Cfx</b>	ceftriaxone
<b>ARVC</b>	arrhythmogenic RV cardiomyopathy	<b>CFU</b>	colony forming units
<b>AS</b>	aortic stenosis	<b>CHB</b>	complete heart block
<b>ASA</b>	aspirin	<b>CHD</b>	congenital heart disease
<b>ASD</b>	atrial septal defect	<b>CHF</b>	congestive heart failure

<b>CI</b>	cardiac index	<b>diff.</b>	differential
<b>CIAKI</b>	contrast-induced acute kidney injury	<b>DIP</b>	desquamative interstitial pneumonitis
<b>CIDP</b>	chronic inflammatory demyelinating polyneuropathy	<b>DKA</b>	distal interphalangeal (joint)
<b>CK</b>	creatine kinase	<b>DL<sub>co</sub></b>	diabetic ketoacidosis
<b>CKD</b>	chronic kidney disease	<b>DLE</b>	diffusion capacity of the lung
<b>CLL</b>	chronic lymphocytic leukemia	<b>DM</b>	drug induced lupus
<b>CMC</b>	carpalmetacarpal (joint)	<b>DMARD</b>	dermatomyositis
<b>CML</b>	chronic myelogenous leukemia		diabetes mellitus
<b>CMMI</b>	chronic myelomonocytic leukemia		disease-modifying anti-rheumatic drug
<b>CMP</b>	cardiomyopathy	<b>DOE</b>	dyspnea on exertion
<b>CMV</b>	cytomegalovirus	<b>DRE</b>	digital rectal exam
<b>CN</b>	cranial nerve	<b>DSE</b>	dobutamine stress echo
<b>CO</b>	carbon monoxide	<b>DTRs</b>	deep tendon reflexes
<b>COP</b>	cardiac output	<b>DU</b>	duodenal ulcer
<b>COPD</b>	cryptogenic organizing pneumonia	<b>DVT</b>	deep vein thrombosis
		<b>dx</b>	diagnosis
<b>COX</b>	chronic obstructive pulmonary disease	<b>EAD</b>	extreme axis deviation
<b>CP</b>	cyclooxygenase	<b>EAV</b>	effective arterial volume
<b>CPAP</b>	chest pain	<b>EBV</b>	Epstein-Barr virus
	continuous positive airway pressure	<b>ECG</b>	electrocardiogram
<b>CPP</b>	cerebral perfusion pressure	<b>echo</b>	echocardiogram
<b>CPPD</b>	calcium pyrophosphate dihydrate	<b>ECMO</b>	extracorporeal membrane oxygenation
<b>Cr</b>	creatinine	<b>ED</b>	emergency department
<b>CRC</b>	colorectal cancer	<b>EDP</b>	end-diastolic pressure
<b>CrCl</b>	creatinine clearance	<b>EDV</b>	end-diastolic volume
<b>CRP</b>	C-reactive protein	<b>EEG</b>	electroencephalogram
<b>CRT</b>	cardiac resynchronization therapy	<b>EF</b>	ejection fraction
<b>CsA</b>	cyclosporine A	<b>EGD</b>	esophagogastrroduodenoscopy
<b>CSF</b>	cerebrospinal fluid	<b>EGFR</b>	epidermal growth factor receptor
<b>CSM</b>	carotid sinus massage	<b>EI</b>	entry inhibitor
<b>CT</b>	computed tomogram	<b>EIA</b>	enzyme-linked immunoassay
<b>CTA</b>	CT angiogram	<b>ELISA</b>	enzyme-linked immunosorbent assay
<b>CTD</b>	connective tissue disease	<b>EM</b>	electron microscopy
<b>CV</b>	cardiovascular	<b>EMB</b>	ethambutol
<b>CVA</b>	cerebrovascular accident	<b>ENT</b>	ears, nose, & throat
<b>CVD</b>	cerebrovascular disease	<b>EOM</b>	extraocular movement/muscles
<b>CVID</b>	collagen vascular disease	<b>EP</b>	electrophysiology
	common variable immunodeficiency	<b>Epo</b>	erythropoietin
<b>CVP</b>	central venous pressure	<b>EPS</b>	electrophysiology study
<b>CVVH</b>	continuous veno-venous hemofiltration	<b>ERCP</b>	endoscopic retrograde cholangiopancreatography
<b>CW</b>	chest wall	<b>ERV</b>	expiratory reserve volume
<b>cx</b>	culture	<b>ESP</b>	end-systolic pressure
<b>CXR</b>	chest radiograph	<b>ESR</b>	erythrocyte sedimentation rate
<b>d</b>	day	<b>ESRD</b>	end-stage renal disease
<b>D</b>	death	<b>ESV</b>	end-systolic volume
<b>d/c</b>	discharge	<b>ET</b>	endotracheal tube
<b>ΔMS</b>	discontinue		essential thrombocythemia
<b>DA</b>	change in mental status	<b>EtOH</b>	alcohol
<b>DAD</b>	dopamine	<b>ETT</b>	endotracheal tube
<b>DAH</b>	diffuse alveolar damage	<b>EUS</b>	exercise tolerance test
<b>DAT</b>	diffuse alveolar hemorrhage	<b>EVAR</b>	endoscopic ultrasound
<b>DBP</b>	direct antiglobulin test		endovascular aneurysm repair
<b>DCIS</b>	diastolic blood pressure	<b>FDP</b>	fibrin degradation product
<b>DCMP</b>	ductal carcinoma <i>in situ</i>	<b>FEV<sub>1</sub></b>	forced expiratory volume in 1 second
<b>Ddx</b>	dilated cardiomyopathy	<b>FFP</b>	fresh frozen plasma
<b>DES</b>	differential diagnosis	<b>FHx</b>	family history
<b>DFA</b>	drug-eluting stent	<b>FI</b>	fusion inhibitor
	direct fluorescent antigen detection	<b>FMD</b>	fibromuscular dysplasia
<b>DI</b>	diabetes insipidus	<b>FMF</b>	familial Mediterranean fever
<b>DIC</b>	disseminated intravascular coagulation	<b>FNA</b>	fine needle aspiration
		<b>FOB</b>	fecal occult blood
		<b>FOBT</b>	fecal occult blood testing
		<b>FQ</b>	fluoroquinolone

<b>FRC</b>	functional residual capacity	<b>HSM</b>	hepatosplenomegaly
<b>FSGS</b>	focal segmental glomerulosclerosis	<b>HSP</b>	Henoch-Schönlein purpura
<b>FSH</b>	follicle stimulating hormone	<b>HSV</b>	herpes simplex virus
<b>FTI</b>	free thyroxine index	<b>HTN</b>	hypertension
<b>FUO</b>	fever of unknown origin	<b>HUS</b>	hemolytic uremic syndrome
<b>FVC</b>	forced vital capacity		
<b>G6PD</b>	glucose-6-phosphate dehydrogenase	<b>I&amp;D</b>	incision & drainage
<b>GB</b>	gallbladder	<b>IABP</b>	intraaortic balloon pump
<b>GBM</b>	glomerular basement membrane	<b>IBD</b>	inflammatory bowel disease
<b>GBS</b>	Guillain-Barré syndrome	<b>IC</b>	inspiratory capacity
<b>GCA</b>	giant cell arteritis	<b>ICa</b>	ionized calcium
<b>GCS</b>	Glasgow coma scale	<b>ICD</b>	implantable cardiac defibrillator
<b>G-CSF</b>	granulocyte colony stimulating factor	<b>ICH</b>	intracranial hemorrhage
<b>GE</b>	gastroesophageal	<b>ICP</b>	intracranial pressure
<b>gen.</b>	generation	<b>ICU</b>	intensive care unit
<b>GERD</b>	gastroesophageal reflux disease	<b>IE</b>	infective endocarditis
<b>GFR</b>	glomerular filtration rate	<b>IGF</b>	insulin-like growth factor
<b>GGT</b>	$\gamma$ -glutamyl transpeptidase	<b>IGRA</b>	interferon- $\gamma$ release assay
<b>GH</b>	growth hormone	<b>II</b>	integrase inhibitor
<b>GIB</b>	gastrointestinal bleed	<b>IIP</b>	idiopathic interstitial pneumonia
<b>GIST</b>	gastrointestinal stromal tumor	<b>ILD</b>	interstitial lung disease
<b>glc</b>	glucose	<b>IMI</b>	inferior myocardial infarction
<b>GN</b>	glomerulonephritis	<b>infxn</b>	infection
<b>GNR</b>	gram-negative rods	<b>inh</b>	inhaled
<b>GnRH</b>	gonadotropin-releasing hormone	<b>INH</b>	isoniazid
<b>GPC</b>	gram-positive cocci	<b>INR</b>	international normalized ratio
<b>GPI</b>	glycoprotein IIb/IIIa inhibitor	<b>IPF</b>	idiopathic pulmonary fibrosis
<b>GRA</b>	glucocorticoid-remediable aldosteronism	<b>ITP</b>	idiopathic thrombocytopenic purpura
<b>GU</b>	gastric ulcer	<b>IVB</b>	intravenous bolus
<b>GVHD</b>	graft-versus-host disease	<b>IVC</b>	inferior vena cava
<b>h</b>	hour	<b>IVDU</b>	intravenous drug use(r)
<b>H2RA</b>	H <sub>2</sub> -receptor antagonist	<b>IVF</b>	intravenous fluids
<b>h/o</b>	history of	<b>IVIg</b>	intravenous immunoglobulin
<b>HA</b>	headache		
<b>HAV</b>	hepatitis A virus	<b>JVD</b>	jugular venous distention
<b>Hb</b>	hemoglobin	<b>JVP</b>	jugular venous pulse
<b>HBIG</b>	hepatitis B immunoglobulin		
<b>HBV</b>	hepatitis B virus	<b>LA</b>	left atrium
<b>HCC</b>	hepatocellular carcinoma		long-acting
<b>HCMP</b>	hypertrophic cardiomyopathy	<b>LABA</b>	lupus anticoagulant
<b>Hct</b>	hematocrit	<b>LAD</b>	long-acting $\beta_2$ -agonist
<b>HCV</b>	hepatitis C virus		left anterior descending
<b>HCW</b>	health care worker	<b>LAE</b>	coronary artery
<b>HD</b>	hemodialysis	<b>LAN</b>	left axis deviation
<b>HDL</b>	high-density lipoprotein	<b>LAP</b>	left atrial enlargement
<b>HDV</b>	hepatitis D virus	<b>LAP</b>	lymphadenopathy
<b>HELLP</b>	hemolysis, abnormal LFTs, low platelets	<b>LBBB</b>	leukocyte alkaline phosphatase
<b>HEV</b>	hepatitis E virus	<b>LCA</b>	left atrial pressure
<b>HF</b>	heart failure	<b>LCIS</b>	left bundle branch block
<b>HGPRT</b>	hypoxanthine-guanine phosphoribosyl transferase	<b>LCx</b>	left coronary artery
<b>HHS</b>	hyperosmolar hyperglycemic state	<b>LDH</b>	lobular carcinoma <i>in situ</i>
<b>HIT</b>	heparin-induced thrombocytopenia	<b>LDL</b>	left circumflex coronary artery
<b>HK</b>	hypokinesis	<b>LE</b>	lactate dehydrogenase
<b>HL</b>	Hodgkin lymphoma	<b>LES</b>	low-density lipoprotein
<b>HoTN</b>	hypotension	<b>LFTs</b>	lower extremity
<b>hpf</b>	high power field	<b>LGIB</b>	lower esophageal sphincter
<b>HPT</b>	hyperparathyroidism	<b>LH</b>	liver function tests
<b>HR</b>	heart rate	<b>LLQ</b>	lower gastrointestinal bleed
<b>HRT</b>	hormone replacement therapy	<b>LM</b>	lower extremity
<b>HS</b>	hereditary spherocytosis	<b>LMWH</b>	luteinizing hormone
<b>HSCT</b>	hematopoietic stem cell transplantation	<b>LN</b>	left lower quadrant
		<b>LOC</b>	left main coronary artery
		<b>LOS</b>	low-molecular-weight heparin
		<b>LP</b>	lymph node
		<b>lpf</b>	loss of consciousness
		<b>LR</b>	length of stay
		<b>LQTS</b>	lumbar puncture
		<b>LUSB</b>	low power field
			lactated Ringer's
			long QT syndrome
			left upper sternal border

<b>LV</b>	left ventricle	<b>NMJ</b>	neuromuscular junction
<b>LVAD</b>	LV assist device	<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitor
<b>LVEDP</b>	LV end-diastolic pressure	<b>NNT</b>	number needed to treat
<b>LVEDV</b>	LV end-diastolic volume	<b>NO</b>	nitric oxide
<b>LVH</b>	left ventricular hypertrophy	<b>NPJT</b>	nonparoxysmal junctional tachycardia
<b>LVOT</b>	left ventricular outflow tract	<b>NPO</b>	nothing by mouth
<b>LVSD</b>	LV systolic dimension	<b>NPV</b>	negative predictive value
<b>MAC</b>	mitral annular calcification	<b>NS</b>	normal saline
<b>MAHA</b>	<i>Mycobacterium avium</i> complex	<b>NSAID</b>	nonsteroidal anti-inflammatory drug
	microangiopathic hemolytic anemia	<b>NSCLC</b>	non-small cell lung cancer
<b>MAO</b>	monoamine oxidase	<b>NYHA</b>	New York Heart Association
<b>MAP</b>	mean arterial pressure	<b>NPPV</b>	noninvasive positive pressure
<b>MAT</b>	multifocal atrial tachycardia	<b>NRTI</b>	ventilation nucleoside reverse transcriptase inhibitor
<b>MCD</b>	minimal change disease	<b>NSF</b>	nephrogenic systemic fibrosis
<b>MCP</b>	metacarpal phalangeal (joint)	<b>NTG</b>	nitroglycerin
<b>MCTD</b>	mixed connective tissue disease	<b>NUD</b>	nonulcer dyspepsia
<b>MCV</b>	mean corpuscular volume	<b>NVE</b>	native valve endocarditis
<b>MDI</b>	metered dose inhaler		
<b>MDMA</b>	3,4-methylenedioxymethamphetamine (Ecstasy)	<b>O/D</b>	overdose
<b>MDS</b>	myelodysplastic syndrome	<b>o/w</b>	otherwise
<b>MEN</b>	multiple endocrine neoplasia	<b>OA</b>	osteoarthritis
<b>MG</b>	myasthenia gravis	<b>OCP</b>	oral contraceptive pill
<b>MGUS</b>	monoclonal gammopathy of uncertain significance	<b>OG</b>	osmolal gap
<b>MI</b>	myocardial infarction	<b>OGT</b>	orogastric tube
<b>min</b>	minute	<b>OGTT</b>	oral glucose tolerance test
<b>min.</b>	minimal	<b>OI</b>	opportunistic infection
<b>MM</b>	multiple myeloma	<b>OM</b>	obtuse marginal coronary artery
<b>MMEFR</b>	maximal mid-expiratory flow rate	<b>OSA</b>	obstructive sleep apnea
<b>MMF</b>	mycophenolate mofetil	<b>OTC</b>	over-the-counter
<b>MN</b>	membranous nephropathy		
<b>MNZ</b>	metronidazole	<b>p/w</b>	present(s) with
<b>mod.</b>	moderate	<b>PA</b>	pulmonary artery
<b>MODS</b>	multiple organ dysfunction syndrome	<b>PAC</b>	pulmonary artery catheter
<b>mos</b>	months	<b>PAD</b>	peripheral arterial disease
<b>MPN</b>	myeloproliferative neoplasm	<b>PAN</b>	polyarteritis nodosa
<b>MPGN</b>	membranoproliferative glomerulonephritis	<b>PASP</b>	pulmonary artery systolic pressure
<b>MR</b>	magnetic resonance	<b>PAV</b>	percutaneous aortic valvoplasty
<b>MRA</b>	mitral regurgitation	<b>pb</b>	problem
<b>MRCP</b>	magnetic resonance angiography	<b>PBC</b>	primary biliary cirrhosis
	magnetic resonance cholangio-pancreatography	<b>PCI</b>	percutaneous coronary intervention
<b>MRI</b>	magnetic resonance imaging	<b>PCN</b>	penicillin
<b>MRSA</b>	methicillin-resistant <i>S. aureus</i>	<b>PCP</b>	<i>Pneumocystis jiroveci</i> pneumonia
<b>MS</b>	mitral stenosis	<b>PCR</b>	polymerase chain reaction
<b>MTb</b>	<i>Mycobacterium tuberculosis</i>	<b>PCT</b>	porphyria cutanea tarda
<b>MTP</b>	metatarsal phalangeal (joint)	<b>PCWP</b>	pulmonary capillary wedge pressure
<b>MTX</b>	methotrexate	<b>PD</b>	Parkinson's disease
<b>MV</b>	mitral valve	<b>PDA</b>	peritoneal dialysis
<b>MVA</b>	mitral valve area		patent ductus arteriosus
<b>MVP</b>	mitral valve prolapse	<b>PE</b>	posterior descending coronary artery
<b>MVR</b>	mitral valve replacement	<b>PEA</b>	pulmonary embolism
<b>Mφ</b>	macrophage	<b>PEEP</b>	pulseless electrical activity
<b>N/V</b>	nausea and/or vomiting	<b>PEF</b>	positive end-expiratory pressure
<b>NAC</b>	N-acetylcysteine	<b>PET</b>	peak expiratory flow
<b>NAFLD</b>	non-alcoholic fatty liver disease		positron emission tomography
<b>NASH</b>	non-alcoholic steatohepatitis	<b>PEx</b>	physical examination
<b>NG</b>	nasogastric	<b>PFO</b>	patent foramen ovale
<b>NGT</b>	nasogastric tube	<b>PFT</b>	pulmonary function test
<b>NHL</b>	Non-Hodgkin lymphoma	<b>PGA</b>	polyglandular autoimmune syndrome
<b>NIF</b>	negative inspiratory force	<b>PHT</b>	pulmonary hypertension
<b>NJ</b>	nasogastric	<b>PI</b>	protease inhibitor
<b>nl</b>	normal		
<b>NM</b>	neuromuscular		

<b>PID</b>	pelvic inflammatory disease	<b>r/i</b>	rule in
<b>PIF</b>	prolactin inhibitory factor	<b>r/o</b>	rule out
<b>PIP</b>	peak inspiratory pressure proximal interphalangeal (joint)	<b>RA</b>	refractory anemia rheumatoid arthritis
<b>PKD</b>	polycystic kidney disease	<b>RAD</b>	right atrium
<b>PM</b>	polymyositis	<b>RAE</b>	right axis deviation
<b>PMF</b>	primary myelofibrosis	<b>RAI</b>	right atrial enlargement
<b>PMHx</b>	past medical history	<b>RAIU</b>	radioactive iodine
<b>PMI</b>	point of maximal impulse	<b>RAS</b>	radioactive iodine uptake
<b>PML</b>	progressive multifocal leukoencephalopathy	<b>RBBB</b>	renal artery stenosis
<b>PMN</b>	polymorphonuclear leukocyte	<b>RBC</b>	right bundle branch block
<b>PMV</b>	percutaneous mitral valvuloplasty	<b>RBF</b>	red blood cell
<b>PMVT</b>	polymorphic ventricular tachycardia	<b>RCA</b>	renal blood flow
<b>PNA</b>	pneumonia	<b>RCMP</b>	right coronary artery
<b>PND</b>	paroxysmal nocturnal dyspnea	<b>RCT</b>	restrictive cardiomyopathy
<b>PNH</b>	paroxysmal nocturnal hemoglobinuria	<b>RDW</b>	randomized controlled trial
<b>PMR</b>	polymyalgia rheumatica	<b>RE</b>	red cell distribution width
<b>PO</b>	oral intake	<b>RF</b>	reticuloendothelial
<b>POBA</b>	plain old balloon angioplasty	<b>RHD</b>	rheumatoid factor
<b>POTS</b>	postural orthostatic tachycardia syndrome	<b>RI</b>	rheumatic heart disease
<b>PPD</b>	purified protein derivative	<b>RIBA</b>	reticulocyte index
<b>PPH</b>	primary pulmonary hypertension	<b>RMSF</b>	recombinant immunoblot assay
<b>PPI</b>	proton pump inhibitors	<b>ROS</b>	Rocky Mountain spotted fever
<b>P<sub>plat</sub></b>	plateau pressure	<b>RPGN</b>	review of systems
<b>PPM</b>	permanent pacemaker	<b>RR</b>	rapidly progressive
<b>PPV</b>	positive predictive value	<b>RRT</b>	glomerulonephritis
<b>Ppx</b>	prophylaxis	<b>RT</b>	respiratory rate
<b>PR</b>	PR segment on ECG	<b>RTA</b>	renal replacement therapy
<b>PRBCs</b>	pulmonary regurgitation	<b>RUQ</b>	radiation therapy
<b>PRL</b>	packed red blood cells	<b>RUSB</b>	renal tubular acidosis
<b>PRPP</b>	prolactin	<b>RV</b>	right upper quadrant
<b>PRWP</b>	phosphoribosyl-1- pyrophosphate	<b>RVAD</b>	right upper sternal border
<b>PS</b>	poor R wave progression	<b>RVH</b>	residual volume
<b>PSA</b>	pressure support	<b>RVOT</b>	right ventricle
<b>PSC</b>	pulmonic stenosis	<b>RVSP</b>	RV assist device
<b>PSGN</b>	poor streptococcal glomerulonephritis	<b>Rx</b>	right ventricular hypertrophy
<b>PSHx</b>	past surgical history		RV outflow tract
<b>PSV</b>	pressure support ventilation		RV systolic pressure
<b>Pt</b>	patient		therapy
<b>PT</b>	prothrombin time	<b>s/e</b>	side effect
<b>PTA</b>	percutaneous transluminal angioplasty	<b>s/p</b>	status post
<b>PTH</b>	parathyroid hormone	<b>s/s</b>	signs and symptoms
<b>PTH-rP</b>	parathyroid hormone-related peptide	<b>SA</b>	sinoatrial
<b>PTT</b>	partial thromboplastin time	<b>SAAG</b>	serum-ascites albumin gradient
<b>PTU</b>	propylthiouracil	<b>SAH</b>	subarachnoid hemorrhage
<b>PTX</b>	pneumothorax	<b>SAS</b>	sulfasalazine
<b>PUD</b>	peptic ulcer disease	<b>SBE</b>	subacute bacterial endocarditis
<b>PUVA</b>	psoralen + ultraviolet A	<b>SBP</b>	spontaneous bacterial peritonitis
<b>PV</b>	polycythemia vera	<b>SBT</b>	systolic blood pressure
	portal vein	<b>SC</b>	spontaneous breathing trial
<b>PVD</b>	peripheral vascular disease	<b>SCD</b>	subcutaneous
<b>PVE</b>	prosthetic valve endocarditis	<b>SCID</b>	sudden cardiac death
<b>PVR</b>	pulmonary vascular resistance		severe combined immunodeficiency
<b>PZA</b>	pyrazinamide	<b>SCLC</b>	small cell lung cancer
<b>qac</b>	before every meal	<b>Se</b>	sensitivity
<b>qhs</b>	every bedtime	<b>sec</b>	second
<b>QoL</b>	quality of life	<b>SERM</b>	selective estrogen receptor modulator
<b>Qw</b>	Q wave	<b>sev.</b>	severe
		<b>SIADH</b>	syndrome of inappropriate antidiuretic hormone
		<b>SIEP</b>	serum immunoelectrophoresis
		<b>SIMV</b>	synchronized intermittent mandatory ventilation
		<b>SLE</b>	systemic lupus erythematosus
		<b>SMA</b>	superior mesenteric artery
		<b>SMV</b>	superior mesenteric vein

SOS	sinusoidal obstructive syndrome	TV	tricuspid valve
Sp	specificity	Tw	T wave
SPEP	serum protein electrophoresis	TWF	T-wave flattening
SR	sinus rhythm	TWI	T-wave inversion
SSCY	<i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i>	Tx	transplant
SSRI	selective serotonin reuptake inhibitor	TZD	thiazolidinediones
SSS	sick sinus syndrome	U/A	urinalysis
ST	sinus tachycardia	U/S	ultrasound
STD	sexually transmitted disease	UA	unstable angina
STE	ST-segment depression	UAG	urine anion gap
SV	ST-segment elevation	UC	ulcerative colitis
SVC	stroke volume	UCx	urine culture
SVR	superior vena cava	UES	upper esophageal sphincter
SVT	systemic vascular resistance	UFH	unfractionated heparin
sx	supraventricular tachycardia	UGIB	upper gastrointestinal bleed
	symptom(s) or symptomatic	UIP	usual interstitial pneumonitis
T1D	type 1 diabetes mellitus	ULN	upper limit of normal
T2D	type 2 diabetes mellitus	UOP	urine output
T <sub>3</sub> RU	T <sub>3</sub> resin uptake	UPEP	urine protein electrophoresis
TA	thoracic aortic aneurysm	UR	urgent revascularization
TB	tuberculosis	URI	upper respiratory tract infection
TBG	thyroid binding globulin	UTI	urinary tract infection
TCA	tricyclic antidepressant	V/Q	ventilation-perfusion
TCD	transcranial Doppler	VAD	ventricular assist device
TCN	tetracycline	VAP	ventilator-associated pneumonia
TdP	torsades de pointes	VATS	video-assisted thoracoscopic surgery
TdT	terminal deoxynucleotidyl transferase	VBI	vertebrobasilar insufficiency
TEE	transesophageal echo	VC	vital capacity
TFTs	thyroid function tests	VD	vessel disease
TG	triglycerides	VDRL	venereal disease research laboratory (test for syphilis)
TGA	transposition of the great arteries	VEGF	vascular endothelial growth factor
TIA	transient ischemic attack	VF	ventricular fibrillation
TIBC	total iron binding capacity	VLDL	very-low-density lipoproteins
TINU	tubulointerstitial nephritis and uveitis	VOD	veno-occlusive disease
TIPS	transjugular intrahepatic portosystemic shunt	VSD	ventricular septal defect
TLC	total lung capacity	V <sub>T</sub>	tidal volume
Tn	troponin	VT	ventricular tachycardia
TP	total protein	VTE	venous thromboembolus
TPN	total parenteral nutrition	vWD	von Willebrand's disease
Tpo	thrombopoietin	vWF	von Willebrand's factor
TPO	thyroid peroxidase	VZV	varicella zoster virus
TR	tricuspid regurgitation	w/	with
TRALI	transfusion-related acute lung injury	w/o	without
TRH	thyrotropin releasing hormone	w/u	workup
TRS	TIMI risk score	WBC	white blood cell (count)
TRUS	transrectal ultrasound	WCT	wide-complex tachycardia
TS	tricuspid stenosis	WHO	World Health Organization
TSH	thyroid stimulating hormone	wk	week
TSI	thyroid-stimulating immunoglobulin	WM	Waldenström's macroglobulinemia
TSS	toxic shock syndrome	WMA	wall motion abnormality
TTE	transsphenoidal surgery	WPW	Wolff-Parkinson-White syndrome
TTKG	transthoracic echo	XRT	radiation therapy
TPP	transtubular potassium gradient		
	thrombotic thrombocy-topenic purpura		

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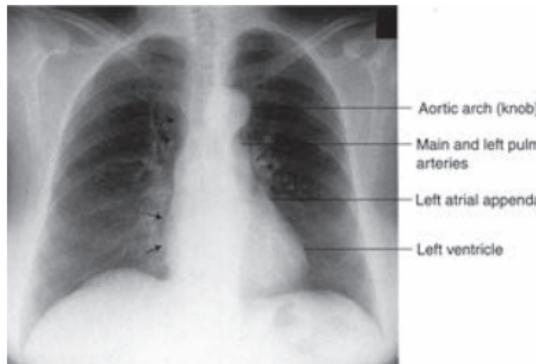
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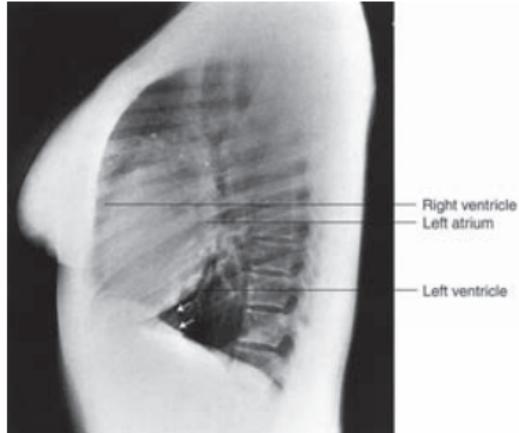
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## NOTES

# 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.)



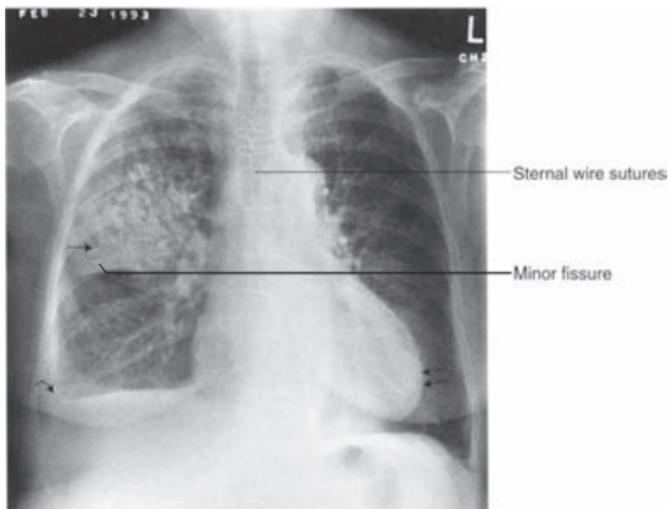
**3 COPD:** with hyperlucent, overinflated lungs and flat diaphragms. (*Radiology 101*, 3rd ed, 2009.)



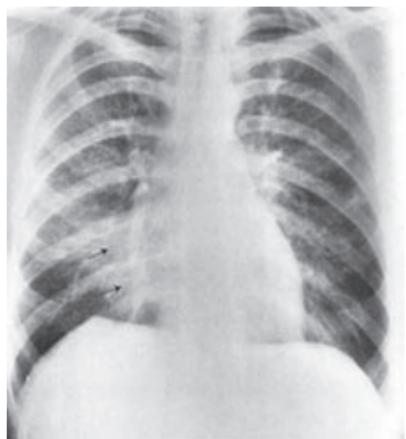
**4 Interstitial pulmonary edema:** with Kerley A, B, and C lines and cephalization of the vascular markings. (*Fund. Diag. Radiology* 3rd ed, 2006.)



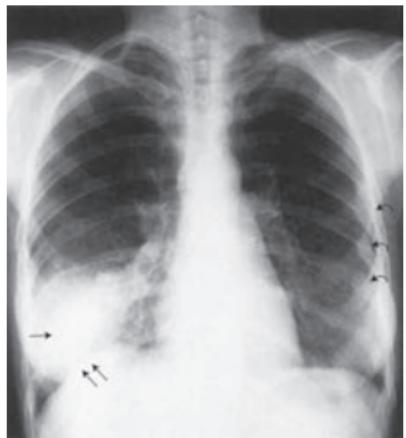
**5 Alveolar pulmonary edema.** (*Fund. Diag. Radiology* 3rd ed, 2006.)



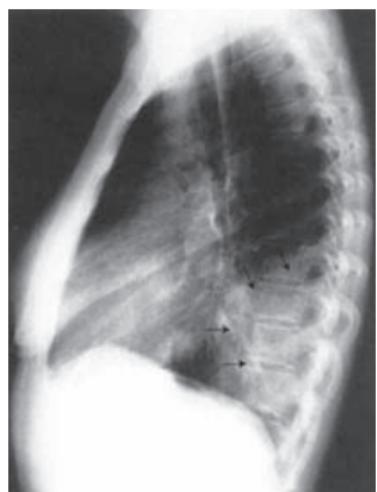
**6 Right upper lobe pneumonia.** (*Radiology 101*, 3rd ed, 2009.)



**7 Right middle lobe pneumonia.** (*Radiology 101*, 3rd ed, 2009.)



**8 Right lower lobe pneumonia (PA).** (*Radiology 101*, 3rd ed, 2009.)



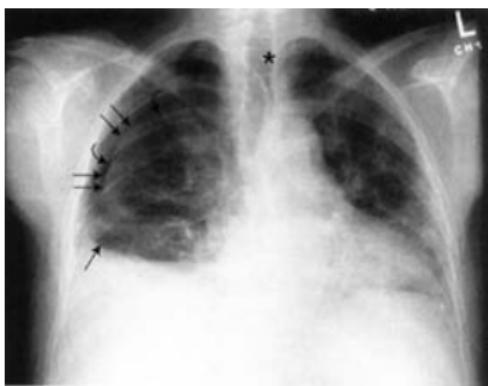
**9 Right lower lobe pneumonia (lateral).** (*Radiology 101*, 3rd ed, 2009.)



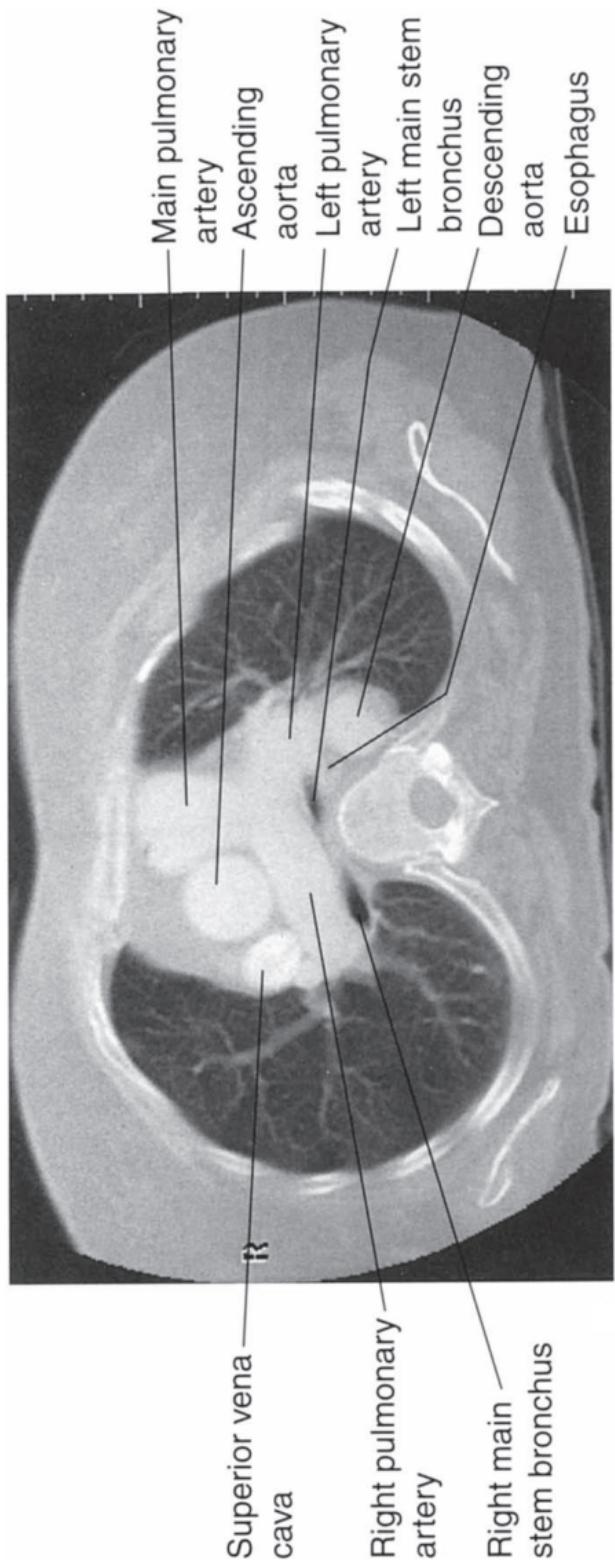
**10 Bilateral pleural effusions** (curved arrows) and enlarged azygous vein (straight arrow) (PA). (*Radiology 101*, 3rd ed, 2009.)



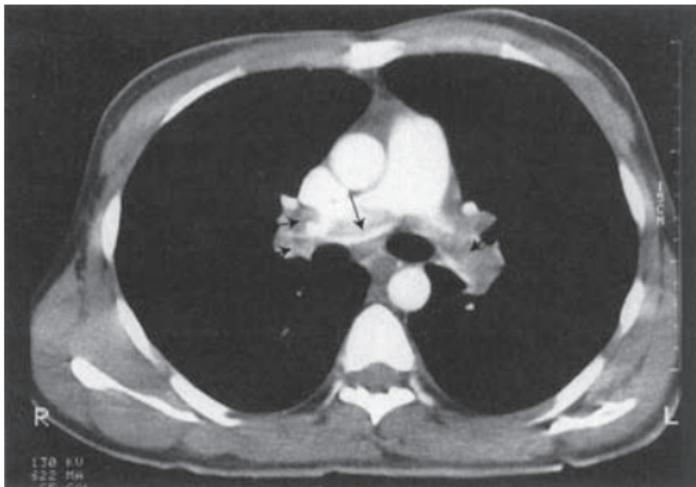
**11 Bilateral pleural effusions** (curved arrows) (lateral). (*Radiology 101*, 3rd ed, 2009.)



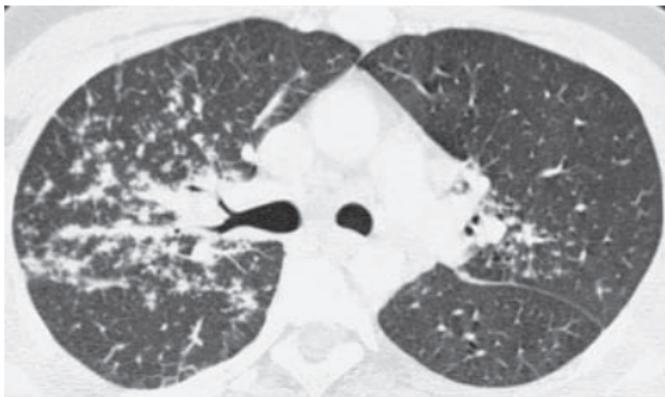
**12 Pneumothorax.** (*Radiology 101*, 3rd ed, 2009.)



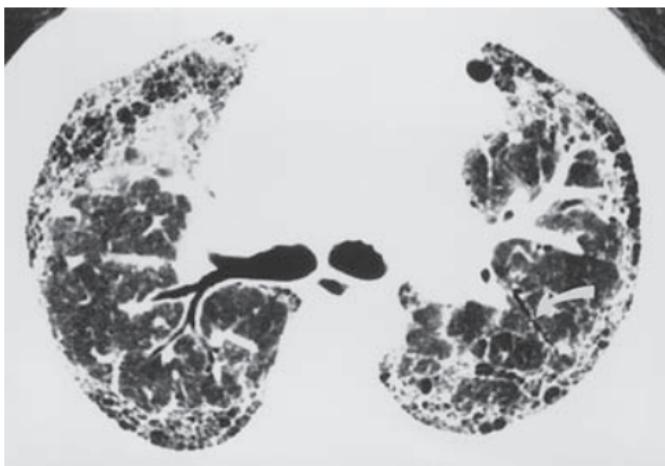
**13 Normal chest CT** at level of pulmonary arteries (parenchymal windows).  
(Radiology 107, 3rd ed, 2009)



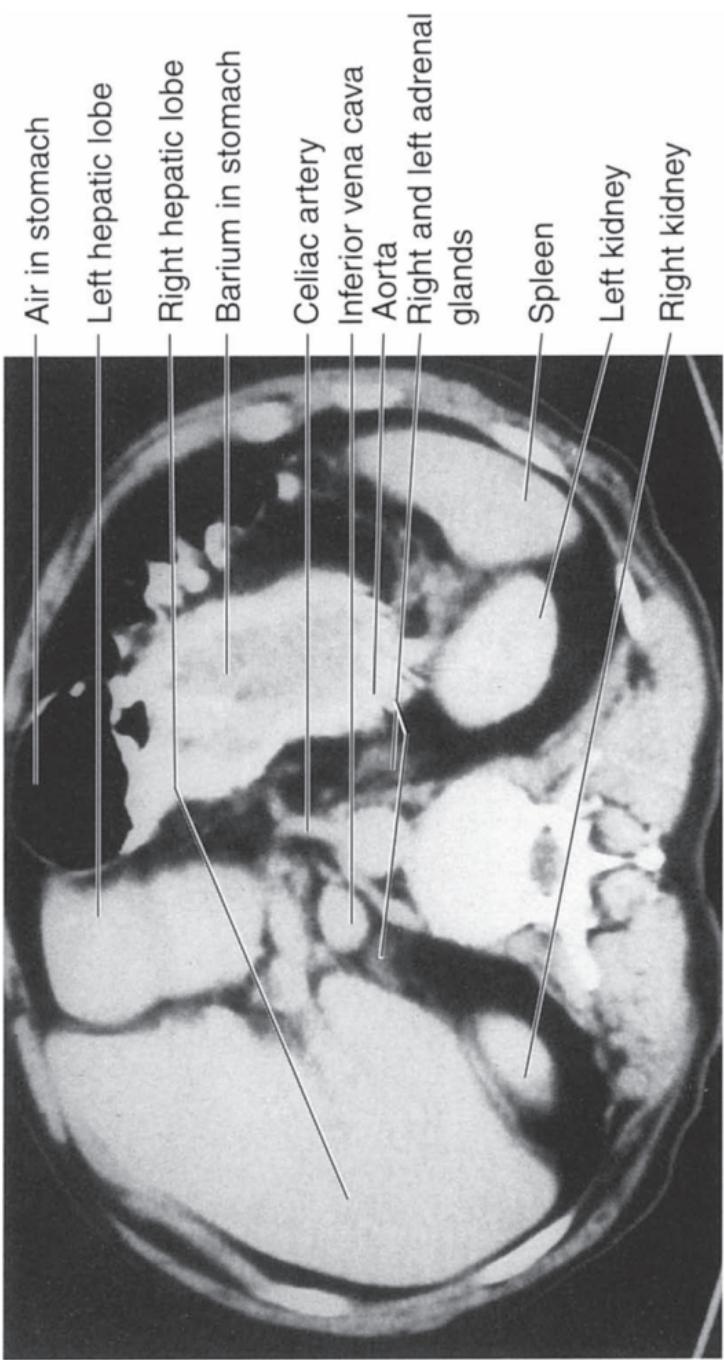
**14 Bilateral PE (mediastinal windows).** (*Radiology 101*, 3rd ed, 2009.)



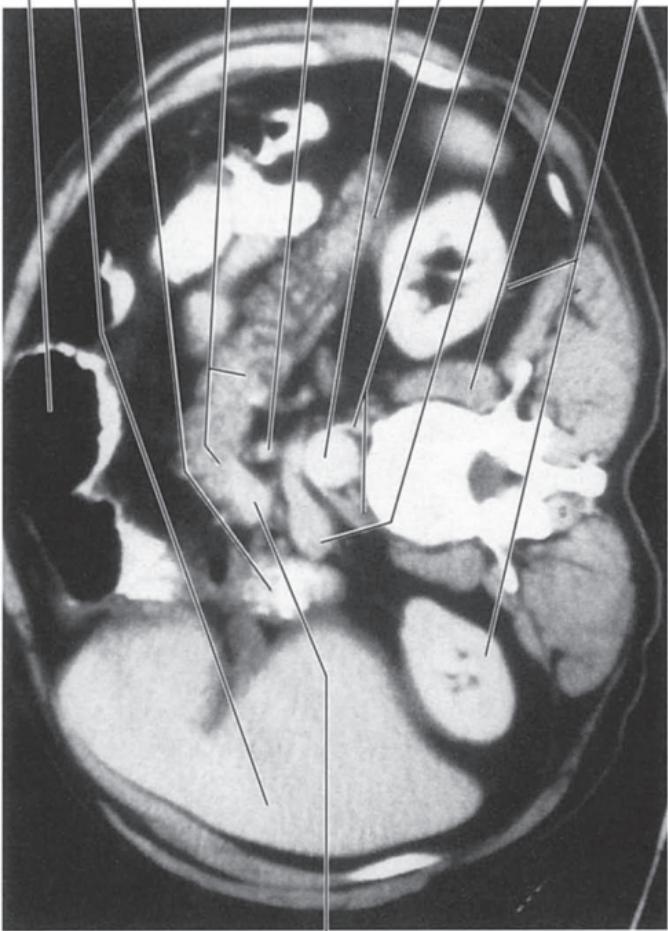
**15 Sarcoidosis with perilymphatic nodules.** (*Fund. Diag. Radiology* 3rd ed, 2006.)



**16 Idiopathic pulmonary fibrosis.** (*Fund. Diag. Radiology* 3rd ed, 2006.)

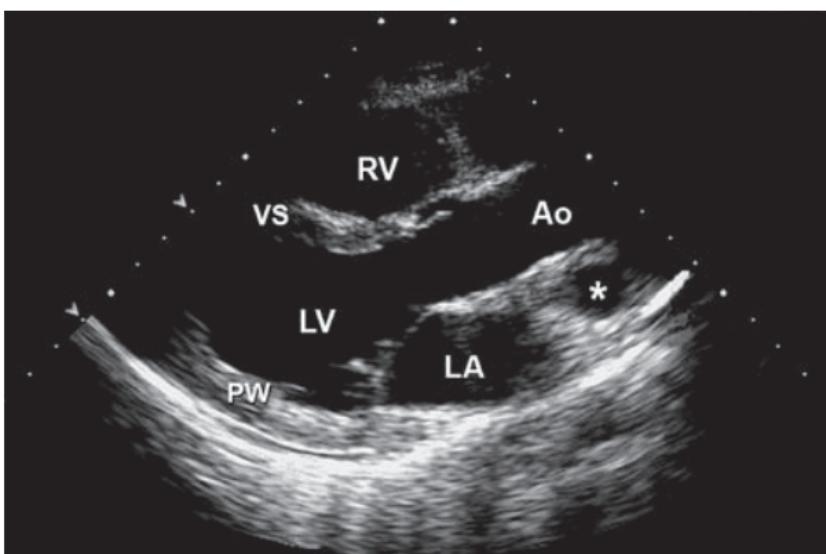
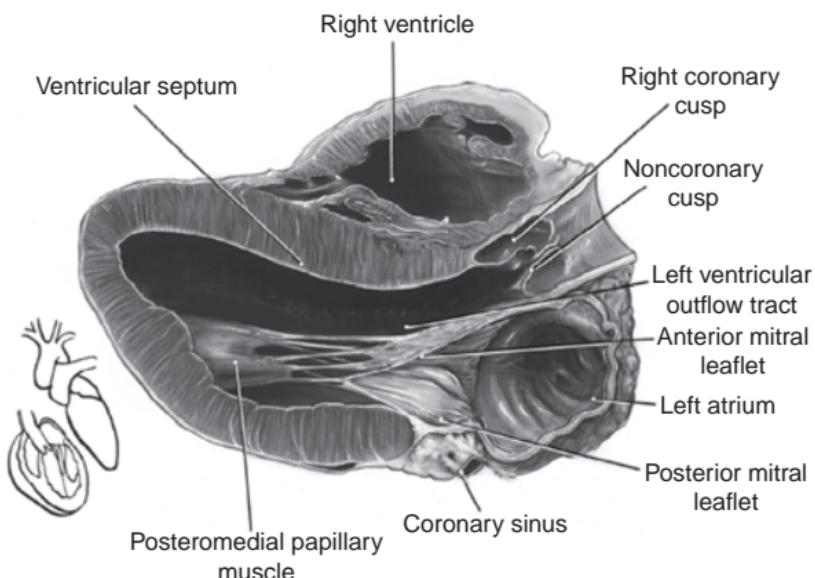


17 Normal abdomen CT at level of liver & spleen. (Radiology 101, 3rd ed, 2009.)

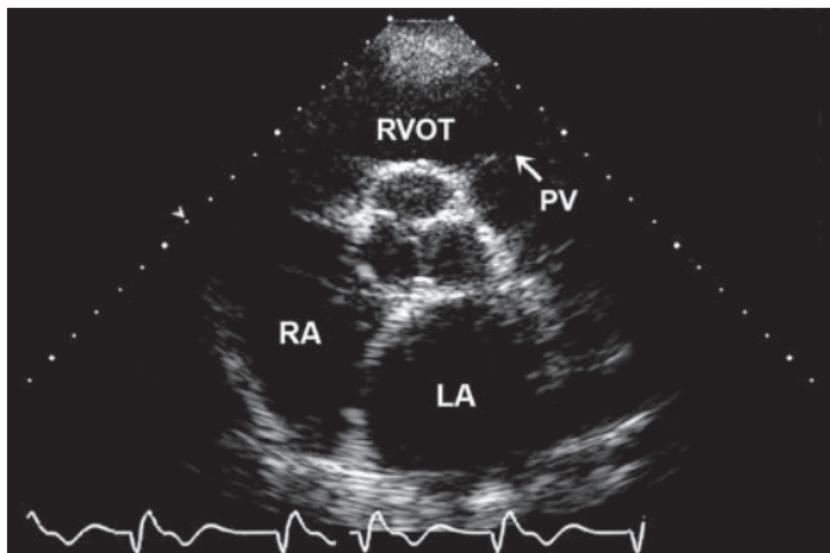
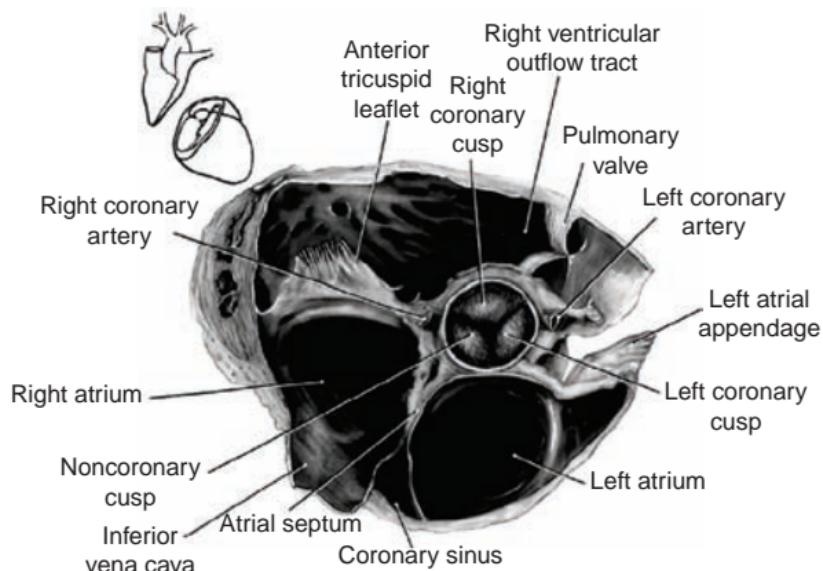


- Stomach air
- Right hepatic lobe
- Duodenum second portion
- Pancreas head and body
- Superior mesenteric artery
- Aorta
- Pancreas tail
- Diaphragm crura
- Inferior vena cava
- Psoas muscle
- Right and left kidneys
- Superior mesenteric vein-portal vein confluence

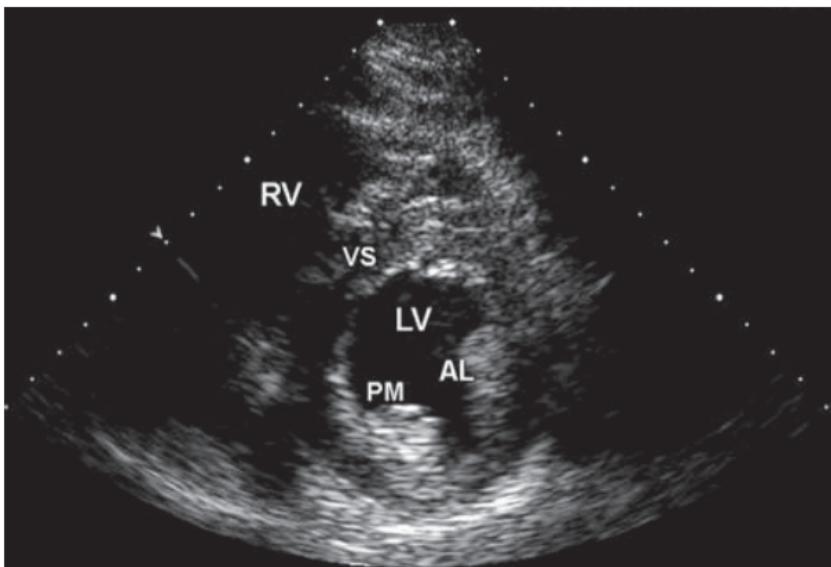
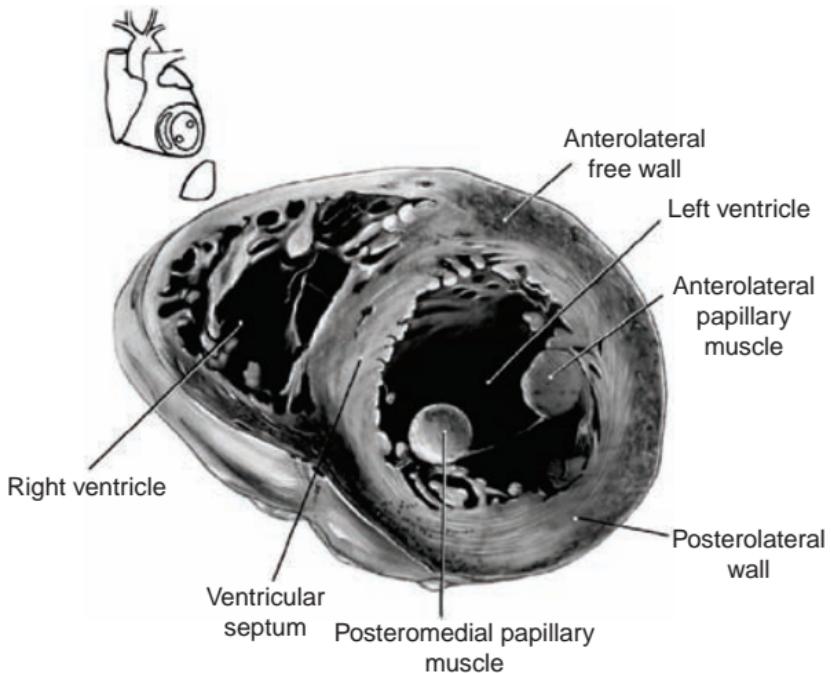
18 Normal abdomen CT at level of pancreas. (*Radiology* 101, 3rd ed, 2009.)

**Echocardiography**

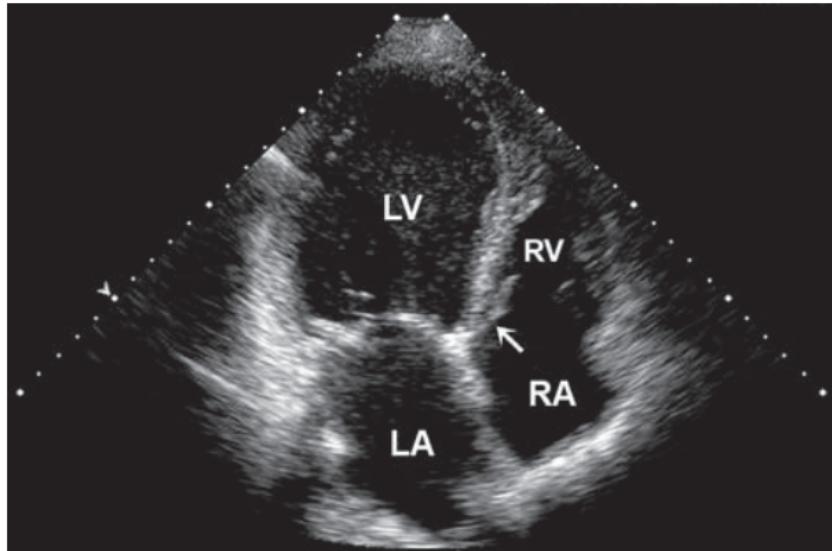
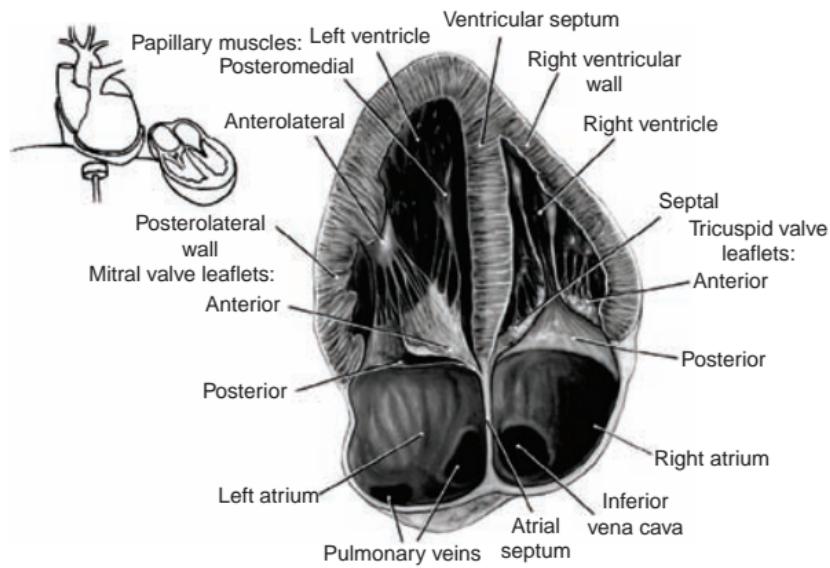
**1 Parasternal long-axis view** allows visualization of the right ventricle (RV), ventricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). \*Pulmonary artery. (Top: From *Mayo Clinic Proceedings*. [Tajik 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.)

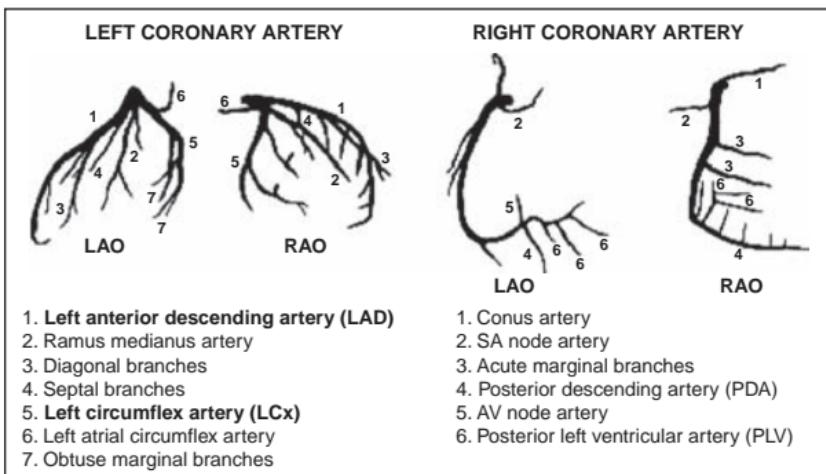


**3 Parasternal short-axis view at the level of the papillary muscles:** AL, anterolateral papillary muscle; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum; LV, left ventricle. (Top: From *Mayo Clinic Proceedings*. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional 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.)



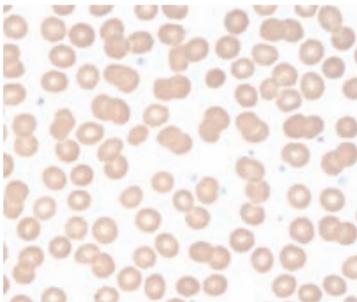
**4 Apical four-chamber view:** Note that at some institutions the image is reversed so that the left side of the heart appears on the right side of the screen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Top: From Mayo Clinic Proceedings. [Tajik AJ, Seward JB, Hagler 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

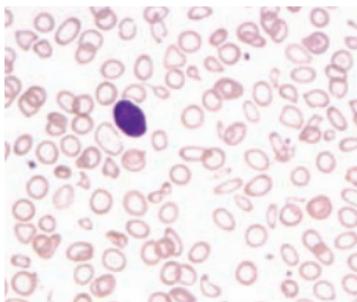


**Coronary arteries.** (From Grossman WG. *Cardiac Catheterization and Angiography*, 4th ed. Philadelphia: Lea & Febiger, 1991, with permission.)

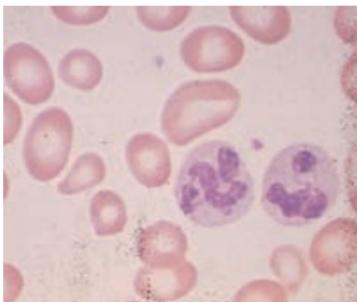
## Peripheral Blood Smears



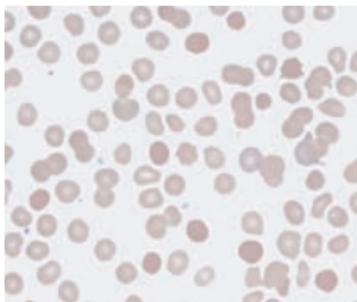
**1** Normal smear.



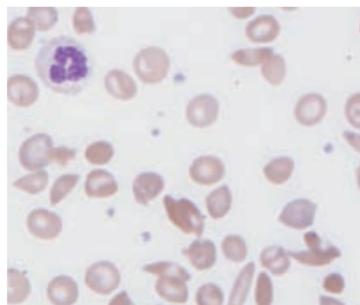
**2** Hypochromic, microcytic anemia due to iron-deficiency.



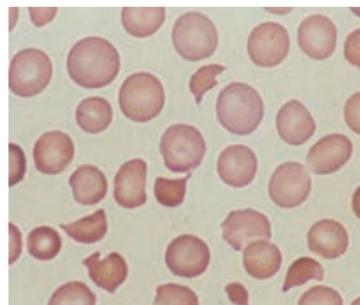
**3** Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



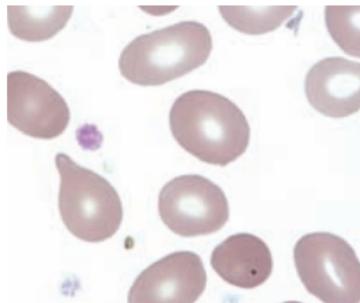
**4** Spherocytes due to autoimmune hemolytic anemia.



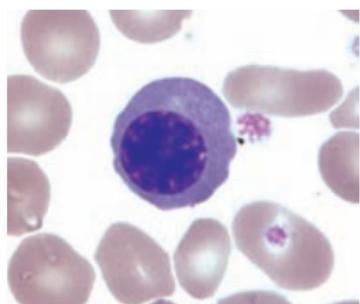
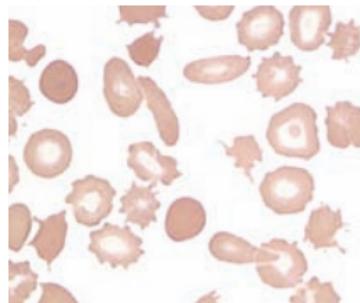
5 Sickle cell anemia.



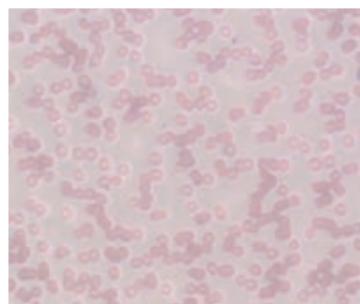
6 Schistocytes.



7 Teardrop shaped RBC (dacrocyte). 8 Acanthocytes.

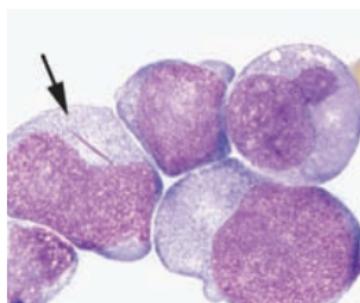


9 Nucleated RBC.

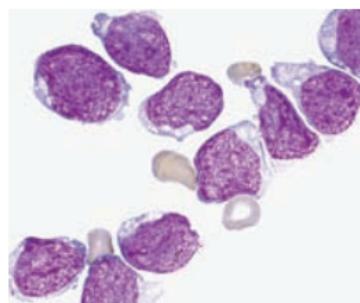


10 Rouleaux.

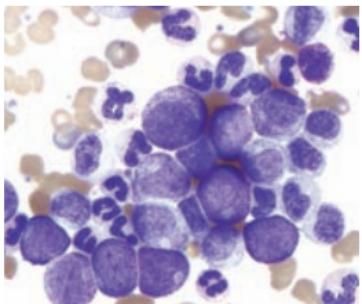
## Leukemias



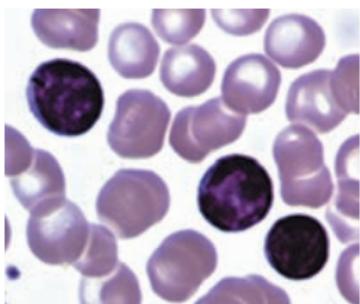
1 AML with Auer rod.



2 ALL.



3 CML.



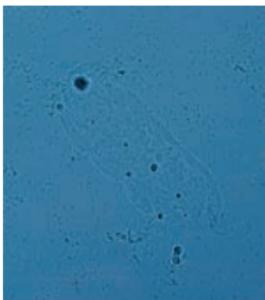
4 CLL.

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. & Pract. of Oncol.* 8th ed, 2008.

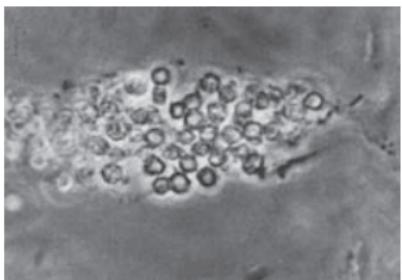
## Urinalysis



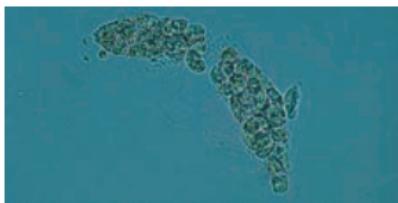
1 Granular cast. (College of Am. Pathologist, with permission.)



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.)

