

# POCKET MEDICINE

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SIXTH EDITION

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Marc S. Sabatine



The Massachusetts General Hospital  
Handbook of Internal Medicine



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# FOREWORD

## *To the 1st Edition*

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

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

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# PREFACE

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

Written by residents, fellows, and attendings, the mandate for *Pocket Medicine* was to provide, in a concise manner as possible, the key information a clinician needs for the initial approach to and management of the most common inpatient medical problems.

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

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

I am grateful for the support of the house officers, fellows, and attendings at the Massachusetts General Hospital. It is a privilege to work with such a knowledgeable, dedicated, and compassionate group of physicians. I always look back on my time there as Chief Resident as one of the best experiences I have ever had. I am grateful to several outstanding clinical mentors, including Hasan Bazari, Larry Friedman, Nesli Basgoz, Eric Isselbacher, Bill Dec, Mike Fifer, and Roman DeSanctis, as well as the late Charlie McCabe, Mort Swartz, and Peter Yurchak.

This edition would not have been possible without the help of Melinda Cuerda, my academic coordinator. She shepherded every aspect of the project from start to finish, with an incredible eye to detail to ensure that each page of this book was the very best it could be.

Lastly, special thanks to my parents for their perpetual encouragement and love and, of course, to my wife, Jennifer Tseng, who, despite being a surgeon, is my closest advisor, my best friend, and the love of my life.

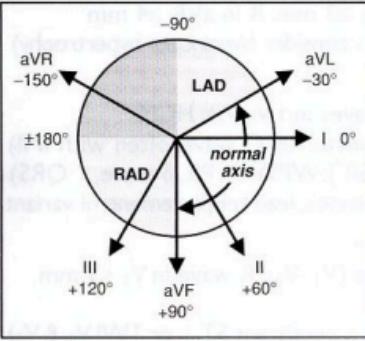
I hope that you find *Pocket Medicine* useful throughout the arduous but incredibly rewarding journey of practicing medicine.

# ELECTROCARDIOGRAPHY

## Approach (a systematic approach is vital)

- Rate (? tachy or brady) and rhythm (? P waves, regularity, P & QRS relationship)
- Intervals (PR, QRS, QT) and axis (? LAD or RAD)
- Chamber abnormality (? LAA and/or RAA, ? LVH and/or RVH)
- QRST changes (? Q waves, poor R-wave progression V<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: LVH, LBBB, inferior MI, WPW
- Left anterior fascicular block (LAFB): 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 (LPFB): 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. 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 (<math>110</math>–<math>119 =</math> IVCD or "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<math>\downarrow</math> or TW<math>\downarrow</math> in R precordial leads</li> </ol>
<b>LBBB</b>		<ol style="list-style-type: none"> <li>1. QRS <math>\geq 120</math> msec (<math>110</math>–<math>119 =</math> IVCD or "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. "Trifascicular block": bifascicular block +  $1^\circ$  AVB.

## Prolonged QT interval (NEJM 2008;358:169; www.torsades.org)

- QT measured from beginning of QRS complex to end of T wave (measure longest QT)
- QT varies w/ HR → corrected w/ Bazett formula:  $QTc = QT/\sqrt{RR}$  (RR in sec), overcorrects at high HR, undercorrects at low HR (nl QTc  $<440$  msec ♂,  $<460$  msec ♀)
- Fridericia's formula preferred at very high or low HR:  $QTc = QT/\sqrt[3]{RR}$
- QT prolongation a/w ↑ risk TdP (espec  $>500$  msec); establish baseline QT and monitor if using QT prolonging meds, no estab guidelines for stopping Rx if QT prolongs
- Etiologies:

**Antiarrhythmics:** class Ia (procainamide, disopyramide), class III (amio, sotalol, dofetilide)

**Psych drugs:** antipsychotics (phenothiazines, haloperidol, atypicals), Li, ? SSRI, TCA

**Antimicrobials:** macrolides, quinolones, azoles, pentamidine, atovaquone, atazanavir

**Other:** antiemetics (droperidol, 5-HT<sub>3</sub> antagonists), alfuzosin, methadone, ranolazine

**Electrolyte disturbances:** hypoCa (nb, hyperCa a/w ↓ QT),  $\pm$  hypoK, ? hypoMg

**Autonomic dysfxn:** ICH (deep TWI), Takotsubo, stroke, CEA, neck dissection

**Congenital** (long QT syndrome): K, Na, & Ca channelopathies (Circ 2013;127:126)

**Misc:** CAD, CMP, bradycardia, high-grade AVB, hypothyroidism, hypothermia, BBB

ECG P-wave Criteria	Left Atrial Abnormality (LAA) 	Right Atrial Abnormality (RAA) 
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## Left ventricular hypertrophy (LVH) (Circ 2009;119:e251)

- Etiologies: HTN, AS/AI, HCM, coarctation of aorta
- Criteria (all w/ Se  $<50\%$ , Sp  $>85\%$ ; accuracy affected by age, sex, race, BMI)

**Romhilt-Estes point-score system** (4 points = probable; 5 points = diagnostic):

↑ volt: limb lead R or S  $\geq 20$  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 pts)

ST displacement opposite to QRS deflection: w/o dig (3 pts); w/ dig (1 pt)

LAA (3 pts); LAD (2 pts); QRS duration  $\geq 90$  msec (1 pt)

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

**Sokolow-Lyon:** S in V<sub>1</sub> + R in V<sub>5</sub> or V<sub>6</sub>  $\geq 35$  mm or R in aVL  $\geq 11$  mm ( $\downarrow$  Se w/  $\uparrow$  BMI)

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

**If LAFB present:** S in III + max (R+S) in any lead  $\geq 30$  mm in men or  $\geq 28$  mm in women

### Right ventricular hypertrophy (RVH) (Circ 2009;119:e251; JACC 2014;63:672)

- Etiologies: cor pulmonale, congenital (tetralogy, TGA, PS, ASD, VSD), MS, TR
- Criteria [all insensitive, but specific (except in COPD); all w/ poor PPV in general population]
  - R > S in V<sub>1</sub>, R in V<sub>1</sub>  $\geq 6$  mm, S in V<sub>5</sub>  $\geq 10$  mm, S in V<sub>6</sub>  $\geq 3$  mm, R in aVR  $\geq 4$  mm
  - RAD  $\geq 110^\circ$  (LVH + RAD or prominent S in V<sub>5</sub> or V<sub>6</sub>  $\rightarrow$  consider 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>); HCM
- Myocardial injury: posterior MI (anterior R wave = posterior Q wave; often with IMI)
- Abnormal depolarization: RBBB (QRS  $> 120$  msec, rSR'); WPW ( $\downarrow$  PR,  $\delta$  wave,  $\uparrow$  QRS)
- Other: dextroversion; counterclockwise rotation; Duchenne's; lead misplacement; nl variant

### Poor R wave progression (PRWP) (Am Heart J 2004;148:80)

- Definition: loss of anterior forces w/o frank Q waves (V<sub>1</sub>-V<sub>3</sub>); R wave in V<sub>3</sub>  $\leq 3$  mm
- Possible etiologies (nonspecific):
  - old anteroseptal MI (usually w/ R wave V<sub>3</sub>  $\leq 1.5$  mm,  $\pm$  persistent ST  $\uparrow$  or TWIV<sub>2</sub> & V<sub>3</sub>)
  - LHV (delayed RWP w/  $\uparrow$  left precordial voltage), RVH, COPD (may also have RAA, RAD, limb lead QRS amplitude  $\leq 5$ , S<sub>1</sub>S<sub>2</sub>S<sub>3</sub> w/ R/S ratio  $< 1$  in those leads)
  - LBBB; WPW; clockwise rotation of the heart; lead misplacement; CMP; PTX

### Pathologic Q waves

- Definition:  $\geq 30$  msec ( $\geq 20$  msec V<sub>2</sub>-V<sub>3</sub>) or  $> 25\%$  height of R wave in that QRS complex
- Small (septal) q waves in I, aVL, V<sub>5</sub> & V<sub>6</sub> are nl, as can be isolated Qw in III, aVR, V<sub>1</sub>
- "Pseudoinfarct" pattern may be seen in LBBB, infiltrative dis., HCM, COPD, PTX, WPW

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

- Acute MI:** upward convexity STE (ie, a "frown")  $\pm$  TWI (or prior MI w/ persistent STE)
- Coronary spasm:** Prinzmetal's angina; transient STE in a coronary distribution
- Pericarditis:** diffuse, upward concavity STE (ie, a "smile"); a/w PR  $\downarrow$ ; Tw usually upright
- HCM, Takotsubo CMP, ventricular aneurysm, cardiac contusion**
- Pulmonary embolism:** occ. STE V<sub>1</sub>-V<sub>3</sub>; classically a/w TWIV<sub>1</sub>-V<sub>4</sub>, RAD, RBBB, S<sub>1</sub>Q<sub>3</sub>T<sub>3</sub>
- Repolarization abnormalities:**
  - LBBB ( $\uparrow$  QRS duration, STE discordant from QRS complex; see "ACS" for dx MI in LBBB)
  - LHV ( $\uparrow$  QRS amplitude); Brugada syndrome (rSR', downsloping STE V<sub>1</sub>-V<sub>2</sub>); pacing Hyperkalemia ( $\uparrow$  QRS duration, tall Ts, no Ps)
- aVR:** STE  $> 1$  mm a/w  $\uparrow$  mortality in STEMIs; STE aVR  $> V_1$  a/w left main disease
- Early repolarization:** most often seen in V<sub>2</sub>-V<sub>5</sub> in young adults (JACC 2015;66:470)
  - 1-4 mm elev of peak of notch or start of slurred downstroke of R wave (ie, J point);  $\pm$  up concavity of ST & large Tw ( $\therefore$  ratio of STE/T wave  $< 25\%$ ; may disappear w/ exercise)
  - ? early repol in inf leads may be a/w  $\uparrow$  risk of VF (NEJM 2009;361:2529; Circ 2011;124:2208)

### ST depression (STD)

- Myocardial ischemia** ( $\pm$  Tw abnl)
- Acute true posterior MI:** posterior STE appearing as anterior STD ( $\pm$   $\uparrow$  R wave) in V<sub>1</sub>-V<sub>3</sub>
  - $\checkmark$  posterior ECG leads; manage as a STEMIs with rapid reperfusion (see "ACS")
- Digitalis effect (downsloping ST  $\pm$  Tw abnl, does not correlate w/ dig levels)
- Hypokalemia ( $\pm$  U wave)
- Repolarization abnl a/w LBBB or LHV (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, symm precordial TWI)  $\rightarrow$  critical prox LAD lesion
- Myopericarditis; CMP (Takotsubo, ARVC, apical HCM); MVP; PE (espec if TWIV<sub>1</sub>-V<sub>4</sub>)
- Repolarization abnl in a/w LHV/RVH ("strain pattern"), BBB
- Posttachycardia or postpacing ("memory" T waves)
- 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  $\ominus$

### Low voltage

- QRS amplitude (R + S)  $< 5$  mm in all limb leads &  $< 10$  mm in all precordial leads
- Etiol: COPD, pericard./pleural effusion, myxedema,  $\uparrow$  BMI, amyloid, diffuse CAD

### Electrolyte abnormalities

- $\uparrow$  K: tented Tw,  $\downarrow$  QT,  $\uparrow$  PR, AVB, wide QRS, STE;  $\downarrow$  K: flattened Tw, U waves,  $\uparrow$  QT

- $\uparrow$  Ca:  $\downarrow$  QT, flattened Tw & Pw, J point elevation;  $\downarrow$  Ca:  $\uparrow$  QT; Tw  $\Delta s$

Disorder	Typical Characteristics & Diagnostic Studies
<b>Cardiac Causes</b>	
<b>ACS</b> (15–25% of chest pain in ED)	Substernal “pressure” ( $\oplus$ LR 1.3) → neck, jaw, arm ( $\oplus$ LR 1.3–2.6) Sharp, pleuritic, positional, or reproducible w/ palp all w/ $\oplus$ LR $\leq$ 0.35 Diaphoresis ( $\oplus$ LR 1.4), dyspnea ( $\oplus$ LR 1.2), a/w exertion ( $\oplus$ LR 1.5–1.8) = prior MI ( $\oplus$ LR 2.2); ↓ w/ NTG/rest (but not reliable; Annals EM 2005;45:581) ± ECG $\Delta$ s: STE, STD, TWI, Qw. $\pm$ ↑ Troponin.
<b>Pericarditis &amp; myo-pericarditis</b>	Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ± Pericardial friction rub. ECG $\Delta$ s (diffuse STE & PR ↓, opposite in aVR) ± pericardial effusion. If myocarditis, same as above + ↑ Tn and ± s/s HF and ↓ EF.
<b>Aortic dissection</b>	Sudden severe tearing pain (absence $\ominus$ LR 0.3). ± Asymm (>20 mmHg) BP or pulse ( $\oplus$ LR 5.7), focal neuro deficit ( $\oplus$ LR >6), AI, widened mediastinum on CXR (absence $\ominus$ LR 0.3); false lumen on imaging. (JAMA 2002;287:2262)
<b>Pulmonary Causes</b>	
<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 $\Delta$ s (sinus tach, RAD, RBBB, S <sub>I</sub> Q <sub>III</sub> T <sub>III</sub> , TWIV <sub>1</sub> –V <sub>4</sub> , occ STE V <sub>1</sub> –V <sub>3</sub> ), $\oplus$ CTA or V/Q, ± ↑ Tn
<b>Pulm HTN</b>	Exertional pressure, DOE. ↓ S <sub>a</sub> O <sub>2</sub> , loud P <sub>2</sub> , RV heave, right S <sub>3</sub> and/or S <sub>4</sub> .
<b>GI Causes</b>	
<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>	Esoph tear precipitated by vomiting. ± Hematemesis. Dx w/ EGD.
<b>Boerhaave</b>	Esoph rupture. Severe pain, ↑ w/ swallow. Mediastinal air palpable & on CT.
<b>PUD</b>	Epigastric pain, relieved by antacids. ± GIB. EGD, ± H. pylori test.
<b>Biliary dis.</b>	RUQ pain, N/V. ↑ by fatty foods. RUQ U/S; ↑ LFTs.
<b>Pancreatitis</b>	Epigastric/back discomfort. ↑ amylase & lipase; abd CT.
<b>Musculoskeletal and Miscellaneous Causes</b>	
<b>Costochond</b>	Localized sharp pain. ↑ w/ movement. Reproduced by palpation.
<b>Zoster</b>	Intense unilateral pain. Pain may precede dermatomal rash.
<b>Anxiety</b>	“Tightness,” dyspnea, palpitations, other somatic symptoms

(Braunwald's Heart Disease, 10<sup>th</sup> ed, 2014; JAMA 2015;314:1955)**Initial approach**

- Focused history:** quality, severity, location, radiation; provoking/palliating factors; intensity at onset; duration, freq & pattern; setting; assoc sx; cardiac hx & risk factors
- Targeted exam:** VS (incl. BP in both arms); gallops, murmurs, rubs; signs of vascular dis. (carotid/femoral bruits, ↓ pulses) or CHF; lung & abd. exam; chest wall for reproducibility
- 12-lead ECG:** obtain w/in 10 min; c/w priors & obtain serial ECGs; consider posterior leads (V<sub>7</sub>–V<sub>9</sub>) to ✓ for posterior STEMII if hx c/w ACS but stdnd ECG unrevealing or ST ↓ V<sub>1</sub>–V<sub>3</sub> (ant ischemia vs. post STEMII) and angina that is hard to relieve or R/S > 1 in V<sub>1</sub>–V<sub>2</sub>
- CXR;** other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing
- Troponin:** ✓ at baseline & 3–6 h after sx onset; repeat 6 h later if clinical or ECG  $\Delta$ s; level >99th %ile w/ rise & fall in appropriate setting is dx of MI; >95% Se, 90% Sp detectable 1–6 h after injury, peaks 24 h, may be elevated for 7–14 d in STEMII high-sens. assays (not yet available in U.S.) offer NPV >99% at 1 h (Lancet 2015;386:2481)  
Causes for ↑ Tn other than plaque rupture (= “type 1 MI”): (1) Supply-demand mismatch not due to  $\Delta$  in CAD (= “type 2 MI”; eg, ↑ HR, shock, HTN crisis, spasm, severe AS), (2) non-ischemic injury (myocarditis/toxic CMP, cardiac contusion) or (3) multifactorial (PE, sepsis, severe HF, renal failure, Takotsubo, infilt dis.) (Circ 2012;126:2020)
- CK-MB:** less Se & Sp than Tn (other sources: skel. muscle, intestine, etc); CK-MB/CK ratio >2.5 → cardiac source. Useful for dx of post-PCI/CABG MI or (re)MI if Tn already high.

**Early noninvasive imaging**

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

# NONINVASIVE EVALUATION OF CAD

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

- Indications:** dx CAD, evaluate Δ in clinical status in Pt w/ known CAD, risk stratify after ACS, evaluate exercise tolerance, localize ischemia (imaging required)
- Contraindications** (Circ 2002;106:1883; & 2012;126:2465)
  - Absolute:** AMI w/in 48 h, high-risk UA, acute PE, severe sx AS, uncontrolled HF, uncontrolled arrhythmias, myopericarditis, acute aortic dissection
  - Relative** (discuss with stress lab): left main CAD, mod valvular stenosis, severe HTN, HCMP, high-degree AVB, severe electrolyte abnl

## Exercise tolerance test (w/ ECG alone)

- Generally preferred if Pt can meaningfully exercise; ECG Δs w/ Se ~65%, Sp ~80%
- Typically via treadmill w/ Bruce protocol (modified Bruce or submax if decond. or recent MI)
- Hold anti-isch. meds (eg, nitrates, βB) if dx'ing CAD but give to assess adequacy of meds

## Pharmacologic stress test (nb, requires imaging as ECG not interpretable)

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

## Imaging for stress test

- Use if uninterpretable ECG (V-paced, LBBB, resting ST ↓ >1 mm, digoxin, LVH, WPW), after indeterminate ECG test, or if pharmacologic test
- Use when need to localize ischemia (often used if prior coronary revasc)
- Radionuclide myocardial perfusion imaging** w/ images obtained at rest & w/ stress **SPECT** (eg, <sup>99m</sup>Tc-sestamibi): Se ~85%, Sp ~80%  
**PET** (rubidium-82): Se ~90%, Sp ~85%; requires pharmacologic stress not exercise ECG-gated imaging allows assessment of regional LV fxn (sign of ischemia/infarction)
- Echo** (exercise or dobuta): Se ~85%, Sp ~85%; no radiation; operator-dependent
- Cardiac MRI (w/ pharmacologic stress) another option with excellent Se & Sp

## Test results

- HR** (must achieve ≥85% of max pred HR [220-age] for exer. test to be dx), **BP response**, peak **double product** ( $HR \times BP$ ; nl >20k), HR recovery ( $HR_{peak} - HR_{1\ min\ later}$ ; nl >12)
- Max exercise capacity** achieved (METS or min); **occurrence of symptoms**
- ECG Δs:** downsloping or horizontal ST ↓ (≥1 mm) 60–80 ms after QRS predictive of CAD (but does not localize ischemic territory); however, STE highly predictive & localizes
- Duke treadmill score = exercise min – (5 × max ST dev) – (4 × angina index) [0 none, 1 nonlimiting, 2 limiting]; score ≥5 → <1% 1-y mort; –10 to +4 → 2–3%; ≤–11 → ≥5%
- Imaging:** radionuclide defects or echocardiographic regional wall motion abnormalities reversible defect = ischemia; fixed defect = infarct; transient isch dilation → ? severe 3VD false ⊕: breast → ant defect; diaphragm → inf defect. False ⊖: balanced (3VD) ischemia.

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

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

## Myocardial viability (Circ 2008;117:103; Eur Heart J 2011;31:2984 & 2011;32:810)

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

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

- In Pts w/ CP, CCTA 100% Se, 54% Sp for ACS, ∴ NPV 100%, PPV 17% (JACC 2009;53:1642). ↓ LOS, but ↑ cath/PCI, radiation vs. fxnal study (NEJM 2012;367:299; JACC 2013;61:880).
- In sx outPt, CCTA vs. fxnal testing → ↑ radiation, cath/PCI, ∼ outcomes (NEJM 2015;372:1291)
- Unlike CCTA, MR does not require iodinated contrast, HR control or radiation. Can assess LV fxn, enhancement (early = microvasc obstr.; late = MI). Grossly ≈ Se/Sp to CCTA.

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

- Quantifies extent of calcium; thus estimates plaque burden (but not % coronary stenosis)
- CAC sensitive (91%) but not specific (49%) for presence of CAD; high NPV to r/o CAD
- May provide incremental value to clinical scores for risk stratification (JAMA 2004;291:210). ACC/AHA guidelines note CAC assessment is reasonable in asx Pts w/ intermed risk (10–20% 10-y Framingham risk; ? value if 6–10% 10-y risk) (Circ 2010;122:e584).

**Indications for coronary angiography in stable CAD or asx Pts**

- CCS class III–IV angina despite med Rx, angina + systolic dysfxn, or unexplained low EF
- High-risk stress test findings (qv) or uncertain dx after noninv testing (& info will  $\Delta$  mgmt)
- Occupational need for definitive dx (eg, pilot) or inability to undergo noninvasive testing
- Survivor of SCD, polymorphic VT, sustained monomorphic VT
- Suspected spasm or nonatherosclerotic cause of ischemia (eg, anomalous coronary)

**Precath checklist & periprocedural pharmacotherapy**

- Document peripheral arterial exam (radial, femoral, DP, PT pulses; bruits). For radial access, ✓ palmar arch intact (eg, w/ pulse oximetry & plethysmography). Ensure can lie flat for several hrs. NPO  $>6$  h. Ensure blood bank sample.
- ✓ CBC, PT, & Cr; IVF (? NaHCO<sub>3</sub>),  $\pm$  acetylcysteine (see "CIAKI"), hold ACEI/ARB
- ASA 325 mg  $\times 1$ . Timing of P2Y<sub>12</sub> inhib debated. ASAP for STEMI. ? preRx NSTEACS if clopi (JAMA 2012;308:2507) or ticag (PLATO), not prasugrel. Cangrelor (IV P2Y<sub>12</sub> inhib)  $\downarrow$  peri-PCI events vs. clopi w/o preload (NEJM 2013;368:1303). ? statin preRx (Circ 2011;123:1622).

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

- Optimal med Rx (**OMT**) should be initial focus if stable, w/o critical anatomy, & w/o  $\downarrow$  EF
- **PCI:**  $\downarrow$  angina more quickly c/w OMT; does *not*  $\downarrow$  D/MI (NEJM 2007;356:1503 & 2015;373:1204); if  $\geq 1$  stenosis w/ FFR (qv)  $\leq 0.8$ ,  $\downarrow$  urg revasc & ? D/MI c/w OMT (NEJM 2014;371:1208); ? noninf to CABG in unprot LM dz. (NEJM 2011;364:1718)
- **CABG** (NEJM 2016;374:1954): in older studies,  $\downarrow$  mort c/w OMT if 3VD, LM, 2VD w/ crit. prox LAD, esp. if  $\downarrow$  EF; recently confirmed if multivessel dis. & EF  $<35\%$  (NEJM 2016;374:1511); in diabetics w/  $\geq 2$ VD,  $\downarrow$  D/MI, but  $\uparrow$  stroke c/w PCI (NEJM 2012;367:2375)
- If revasc deemed necessary, PCI if limited # of discrete lesions, nl EF, no DM, poor operative candidate; CABG if extensive or diffuse disease,  $\downarrow$  EF, DM or valvular disease; if 3VD/LM: CABG  $\downarrow$  D/MI & revasc but trend toward  $\uparrow$  stroke c/w PCI (Lancet 2013;381:629); SYNTAX score II helps identify Pts who benefit most from CABG (Lancet 2013;381:639)

**PCI and peri-PCI interventions**

- **Access:** radial vs femoral, w/ former  $\rightarrow$   $\downarrow$  bleeding and MACE (JACC Intv 2016;9:1419)
- **Fractional flow reserve (FFR):** ratio of max flow (induced by IV or IC adenosine) distal vs. prox to stenosis; help ID lesions that are truly hemodyn. significant
- Balloon angioplasty by itself rare b/c elastic recoil; reserved for lesions too narrow to stent
- **Bare metal stents (BMS):**  $\downarrow$  restenosis & repeat revasc c/w angioplasty alone
- **Drug-eluting stents (DES):**  $\downarrow$  neointimal hyperplasia  $\rightarrow$   $\sim 75\%$   $\downarrow$  restenosis,  $\sim 50\%$   $\downarrow$  repeat revasc (<5% by 1 y), ?  $\uparrow$  late stent thrombosis, no  $\Delta$  D/MI c/w BMS (NEJM 2013;368:254); latest gen. DES w/ very low rates of restenosis, repeat revasc & stent thrombosis
- **Bioresorbable stent:** resorbs over yrs, but ?  $\uparrow$  MACE & stent thromb. (NEJM 2015;373:1905)
- Duration of DAPT: ASA (81 mg) lifelong. If SIHD, P2Y<sub>12</sub> inhib  $\times 4$  wk (BMS) or  $\geq 6$  mo (DES). If ACS, P2Y<sub>12</sub>  $>12$  mo  $\rightarrow$   $\sim 20\%$   $\downarrow$  MACE,  $\uparrow$  bleeding and  $\sim 15\%$   $\downarrow$  CV death (NEJM 2014;371:2155 & 2015;372:1791). If need oral anticoag, consider clopi + NOAC  $\pm$  ASA.

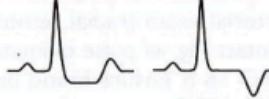
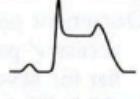
**Post-PCI complications**

- Postprocedure ✓ vascular access site, distal pulses, ECG, CBC, Cr
- **Bleeding**
  - hematoma/overt bleeding: **manual compression**, reverse/stop anticoag
  - retroperitoneal bleed: may p/w  $\downarrow$  Hct  $\pm$  back pain;  $\uparrow$  HR &  $\downarrow$  BP late; Dx w/ abd/pelvic CT (I); Rx: reverse/stop anticoag (d/w interventionalist), IVF/PRBC/plts as required if bleeding uncontrolled, consult performing interventionalist or surgery
- **Vascular damage** (~1% of dx angio, ~5% of transfemoral PCI; Circ 2007;115:2666)
  - pseudoaneurysm: triad of pain, expansile mass, systolic bruit; Dx: U/S; Rx (if pain or  $>2$  cm): manual or U/S-directed compression, thrombin injection or surgical repair
  - AV fistula: continuous bruit; Dx: U/S; Rx: surgical repair if large or sx
  - LE ischemia (emboli, dissection, clot): cool, mottled extremity,  $\downarrow$  distal pulses; Dx: pulse volume recording (PVR), angio; Rx: percutaneous or surgical repair
- **Peri-PCI MI:**  $>5$  ULN of Tn/CK-MB + either sx or ECG/angio  $\Delta$ s; Qw MI in  $<1\%$
- **Contrast-induced acute kidney injury:** manifests w/in 48 h, peaks 3–5 d (see "CIAKI")
- **Cholesterol emboli syndrome** (typically in middle-aged & elderly and w/ Ao atheroma)
  - renal failure (late and progressive,  $\pm$  eos in urine); mesenteric ischemia (abd pain, LGIB, pancreatitis); intact distal pulses but livedo pattern and toe necrosis
- **Stent thrombosis:** mins to yrs after PCI, typically p/w AMI. Due to mech prob. (stent underexpansion or unrecognized dissection, typically presents early) or **d/c of antipt Rx** (espec if d/c both ASA & P2Y<sub>12</sub> inhib; JAMA 2005;293:2126).
- **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

## Spectrum of Acute Coronary Syndromes

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

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

#### • Nonatherosclerotic coronary artery disease

Spasm: Prinzmetal's variant, cocaine-induced (6% of chest pain + cocaine use r/i for MI)

Dissection: spontaneous (vasculitis, CTD, pregnancy), aortic dissection with retrograde extension (usually involving RCA → IMI) or mechanical (PCI, surgery, trauma)

Embolism (Circ 2015;132:241): AF, thrombus/myxoma, endocard., prosthetic valve thrombosis

Vasculitis: Kawasaki syndrome, Takayasu arteritis, PAN, Churg-Strauss, SLE, RA

Congenital: anomalous origin from aorta or PA, myocardial bridge (intramural segment)

#### • Ischemia w/o plaque rupture ("type 2" MI): ↑ demand (eg, ↑ HR), ↓ supply (eg, HoTN)

#### • Direct myocardial injury: myocarditis; Takotsubo/stress CMP; toxic CMP; cardiac contusion

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

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

### Physical exam

- Signs of ischemia: S<sub>4</sub>, new MR murmur 2° pap. muscle dysfxn, paradoxical S<sub>2</sub>, diaphoresis
- Signs of heart failure: ↑ JVP, crackles in lung fields, ⊕ S<sub>3</sub>, HoTN, cool extremities
- Signs of other vascular disease: asymmetric BP, carotid or femoral bruits, ↓ distal pulses

### Diagnostic studies

- **ECG:** ST ↓↑, TWI, new LBBB, hyperacute Tw; Qw/PRWP may suggest prior MI & ∴ CAD
  - ✓ ECG w/in 10 min of presentation, with any Δ in sx & at 6–12 h; compare w/ baseline STEMI dx if old LBBB: ≥1 mm STE concordant w/ QRS (Se 73%, Sp 92%), STD ≥1 mm V<sub>1</sub>–V<sub>3</sub> (Se 25%, Sp 96%), STE ≥5 mm discordant w/ QRS (Se 31%, Sp 92%)

### Localization of MI

Anatomic area	ECG leads w/ STE	Coronary artery
Septal	V <sub>1</sub> –V <sub>2</sub> ± aVR	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> (= STE V <sub>7</sub> –V <sub>9</sub> , posterior leads, ✓ if clinical suspicion)	RCA or LCx

If ECG non-dx & suspicion high, ✓ leads V<sub>7</sub>–V<sub>9</sub> to assess distal LCx/RCA territory. ✓ R-sided precordial leads in 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. STE in aVR suggests LM or prox LAD occlusion or diffuse ischemia.

- **Cardiac biomarkers:** ✓ Tn (preferred over CK-MB) at presentation & 3–6 h after sx onset; repeat 6 h later if clinical or ECG Δs; rise to >99th %ile in appropriate clinical setting dx of MI (see "Chest Pain"); rise in Tn in CKD still portends poor prognosis (NEJM 2002;346:2047)
- If low prob, **stress test, CT angiogram** to r/o CAD; new wall motion abnl on TTE suggests ACS
- **Coronary angiogram** gold standard for CAD

### Prinzmetal's (variant) angina

- Coronary spasm → transient STE usually w/o MI (but MI, AVB, VT can occur)
- Pts usually young, smokers, ± other vasospastic disorders (eg, migraines, Raynaud's)
- Angiography: nonobstructive CAD (spasm can be provoked during cath but rarely done)
- Treatment: high-dose CCB & standing nitrates (+SL prn); ? α-blockers/statins; d/c smoking; avoid high-dose ASA (can inhibit prostacyclin and worsen spasm), nonselect βB, triptans
- Cocaine-induced vasospasm: CCB, nitrates, ASA; ? avoid βB, but labetalol appears safe

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

Feature	High (any of below)	Intermediate (no high features, any of below)	Low (no high/inter. features, may have below)
<b>History</b>	Chest or L arm pain like prior angina, h/o CAD (incl MI)	Chest or arm pain, age >70 y, male, diabetes	Atypical sx (eg, pleuritic, sharp or positional pain)
<b>Exam</b>	HoTN, diaphoresis, HF, transient MR	PAD or cerebrovascular disease	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>	+ Tn or CK-MB	Normal	Normal

**Approach to triage**

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

**Acute Anti-Ischemic and Analgesic Treatment**

<b>Nitrates (SL or IV)</b> 0.3–0.4 mg SL q5min $\times 3$ , then consider IV if still sx	Use for relief of sx, Rx for HTN or HF. No clear $\downarrow$ in mortality. Caution if preload-sensitive (eg, HoTN, AS, sx RV infarct); contraindicated if recent PDE5 inhibitor use.
<b><math>\beta</math>-blockers</b> eg, metop 25–50 mg PO q6h titrate slowly to HR 50–60 IV only if HTN and no HF	$\downarrow$ ischemia & progression of UA to MI (JAMA 1988;260:2259) STEMI: $\downarrow$ arrhythmic death & reMI, but $\uparrow$ cardiogenic shock early (espec if signs of HF) (Lancet 2005;366:1622). IV $\beta$ B prior to 1° PCI $\downarrow$ infarct size and $\uparrow$ EF (Circ 2013;128:1495). Contraindic. PR >0.24 sec, HR <60, 2°/3° AVB, severe bronchospasm, s/s HF or low output, risk factors for shock (eg, >70 y, HR >110, SBP <120, late presentation STEMI)
<b>CCB (nondihydropyridines)</b>	If cannot tolerate $\beta$ B b/c bronchospasm
<b>Morphine</b>	Relieves pain/anxiety; venodilation $\downarrow$ preload. Do not mask refractory sx. May delay antipl. effects of P2Y <sub>12</sub> inhib.
<b>Oxygen</b>	Use prn for resp distress or to keep $S_aO_2 > 90\%$ ? $\uparrow$ infarct size in STEMI w/o hypoxia (Circ 2015;131:2143)

**Other early adjunctive therapy**

- High-intensity statin therapy** (eg, atorva 80 mg qd; PROVE-IT TIMI 22 NEJM 2004;350:1495)
  - $\downarrow$  ischemic events w/ benefit emerging w/in wks (JAMA 2001;285:1711 & JACC 2005;46:1405)
  - $\downarrow$  peri-PCI MI (JACC 2010;56:1099);  $\downarrow$  contrast-induced nephropathy (JACC 2014;63:71)
- ACEI/ARB:** start once hemodynamics and renal function stable
  - Strong indication for ACEI if heart failure, EF <40%, HTN, DM, CKD; ~10%  $\downarrow$  mortality, greatest benefit in ant. STEMI or prior MI (Lancet 1994;343:1115 & 1995;345:669)
  - ARB appear  $\approx$  ACEI (NEJM 2003;349:20); give if contraindic to ACEI
- Ezetimibe, aldosterone blockade, and ranolazine discussed later (long-term Rx)
- IABP: can be used for refractory angina when PCI not available

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

Key issues are antithrombotic regimen and invasive vs. conservative strategy

**Antiplatelet Therapy**

<b>Aspirin</b> 162–325 mg $\times 1$ , then 81 mg qd (non-enteric-coated, chewable)	50–70% $\downarrow$ D/MI (NEJM 1988;319:1105) Low dose (~81 mg) pref long term (NEJM 2010;363:930) If allergy, use clopi and/or desensitize to ASA
<b>P2Y<sub>12</sub> (ADP receptor) inhibitor</b> (choose one of the following in addition to ASA). Timing remains controversial. European guidelines recommend P2Y <sub>12</sub> inhibitor as soon as possible (except prasugrel; EHJ 2011;32:2999). See below for specific recommendations.	
<b>Ticagrelor</b> (preferred over clopi) 180 mg $\times 1 \rightarrow$ 90 mg bid Reversible, but wait 3–5 d prior to surg Use only with ASA <100 mg qd	More rapid and potent plt inhib c/w clopi 16% $\downarrow$ CVD/MI/stroke & 21% $\downarrow$ CV death c/w clopi; $\uparrow$ non-CABG bleeding (NEJM 2009;361:1045) Given upstream or at time of PCI Dyspnea (but $S_aO_2$ & PFTs nl) & ventricular pauses

• <b>Prasugrel</b> (preferred over clopi) 60 mg × 1 at PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery	More rapid and potent plt inhib c/w clopi 19% ↓ CVD/MI/stroke in ACS w/ planned PCI vs. clopi, but ↑ bleeding (NEJM 2007;359:2001), incl fatal bleeds Not sup to clopi if med mgmt w/o PCI (NEJM 2012;367:1297) In NSTEMI-ACS, should be given at time of PCI and not upstream due to ↑ bleeding (NEJM 2013;369:999) Contraindic. if h/o TIA/CVA; ? avoid if >75 y
• <b>Clopidogrel*</b> 300–600 mg × 1 → 75 mg qd Requires ~6 h to steady state	ASA+clopi → 20% ↓ CVD/MI/stroke vs. ASA alone ↑ benefit if given hrs prior to PCI (JAMA 2012;308:2507), but if require CABG, need to wait >5 d after d/c clopi
• <b>Cangrelor</b> Only IV P2Y <sub>12</sub> inhibitor Rapid onset/offset; t <sub>1/2</sub> 3–5 min	22% ↓ CV events (mostly peri-PCI MI and stent thrombosis) vs. clopi 300 mg at time of PCI; no significant ↑ bleeding (NEJM 2013;368:1303) Unclear benefit if upstream clopi administered (NEJM 2009;361:2318) and no data vs. prasugrel or ticagrelor
<b>GP IIb/IIIa inhibitors (GPI)</b> abciximab; eptifibatide; tirofiban Infusions given ≤24 h peri & post PCI; shorter (~2 h) as effective w/ ↓ bleeding (JACC 2009;53:837)	No clear benefit for routinely starting prior to PCI and ↑ bleeding (NEJM 2009;360:2176) Consider if refractory ischemia despite optimal Rx while awaiting angio or in high-risk Pts (eg, large clot burden) at time of PCI, espec if using clopi and no preRx.

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

### Anticoagulant Therapy (choose one)

<b>UFH:</b> 60 U/kg IVB (max 4000 U) then 12 U/kg/h (max 1000 U/h initially) × 48 h or until end of PCI	24% ↓ D/MI (JAMA 1996;276:811) Titrate to aPTT 1.5–2× control (~50–70 sec) Hold until INR <2 if already on warfarin
<b>Enoxaparin</b> (low-molec-wt heparin) 1 mg/kg SC bid (± 30 mg IVB) (qd if CrCl <30) × 2–8 d or until PCI	~10% ↓ D/MI vs. UFH (JAMA 2004;292:45,89). Can perform PCI on enox (Circ 2001;103:658), but ↑ bleeding if switch b/w enox and UFH.
<b>Bivalirudin</b> (direct thrombin inhibitor) 0.75 mg/kg IVB at PCI → 1.75 mg/kg/h	↓ bleeding (espec vs. UFH + GPI), ± ↑ early MI (Lancet 2014;384:599). Use instead of UFH if HIT.
<b>Fondaparinux</b> (Xa inhibitor) 2.5 mg SC qd × 2–8 d	C/w enox, 17% ↓ death & 38% ↓ bleeding (NEJM 2006;354:1464). However, ↑ risk of catheter thrombosis; ∴ must supplement w/ UFH if PCI.

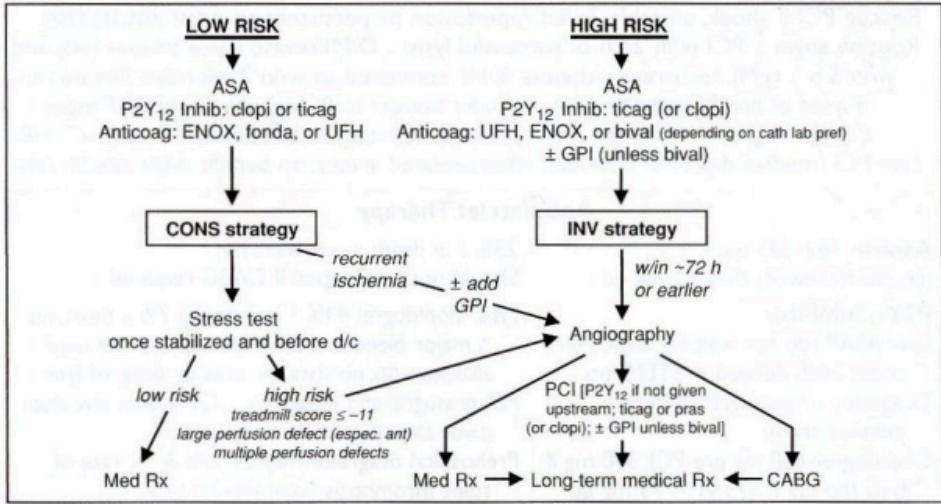
### Coronary angiography (Circ 2014;130:e344)

- **Immediate/urgent coronary angiography** (w/in 2 h) if refractory/recurrent angina or hemodynamic or electrical instability
- **Invasive (INV) strategy** = routine angiography w/in 72 h
  - Early (w/in 24 h) if: ⊕ Tn, ST Δ, GRACE risk score ([www.outcomes.umassmed.org/grace](http://www.outcomes.umassmed.org/grace)) >140 (NEJM 2009;360:2165)
  - Delayed (ie, w/in 72 h) acceptable if w/o above features but w/: diabetes, EF <40%, GFR <60, post-MI angina, TRS ≥3, GRACE score 109–140, PCI w/in 6 mo, prior CABG
  - 32% ↓ rehosp for ACS, nonsignif 16% ↓ MI, no Δ in mortality c/w cons. (JAMA 2008;300:71)
  - ↑ peri-PCI MI counterbalanced by ↓↓ in spont. MI mortality benefit seen in some studies, likely only if cons. strategy w/ low rate of angio
- **Conservative (CONS) strategy** = selective angio. Med Rx w/ pre-d/c stress test; angio only if recurrent ischemia or strongly ⊕ ETT. Indicated for: low TIMI Risk Score, Pt or physician pref in absence of high-risk features, or low-risk women (JAMA 2008;300:71).

### TIMI Risk Score (TRS) for UA/NSTEMI (JAMA 2000;284:835)

Calculation of Risk Score		Application of Risk Score	
Characteristic	Point	Score	D/MI/UR by 14 d
Historical		0–1	5%
Age ≥65 y	1	2	8%
≥3 Risk factors for CAD	1	3	13%
Known CAD (stenosis ≥50%)	1	4	20%
ASA use in past 7 d	1	5	26%
Presentation		6–7	41%
Severe angina (≥2 episodes w/in 24 h)	1	Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH, GP IIb/IIIa inhibitors and early angiography (JACC 2003;41:895)	
ST deviation ≥0.5 mm	1		
⊕ cardiac marker (troponin, CK-MB)	1		
<b>RISK SCORE = Total points</b>	<b>(0–7)</b>		

Figure 1-2 Approach to UA/NSTEMI



## STEMI

### Requisite STE (at J point)

- ≥ 2 contiguous leads w/  $\geq 1$  mm (except for V<sub>2</sub>–V<sub>3</sub>:  $\geq 2$  mm in ♂ and  $\geq 1.5$  mm in ♀), or
- New or presumed new LBBB w/ compelling H&P, or
- True posterior MI: ST depression V<sub>1</sub>–V<sub>3</sub> ± tall Rw w/ STE on posterior leads (V<sub>7</sub>–V<sub>9</sub>)

### Reperfusion ("time is muscle")

- Immediate reperfusion (ie, opening occluded culprit coronary artery) is critical
- In PCI-capable hospital, goal should be **primary PCI w/in 90 min** of 1<sup>st</sup> medical contact
- In non-PCI-capable hospital, consider *transfer* to PCI-capable hospital (see below), o/w **fibrinolytic therapy** w/in 30 min of hospital presentation
- Do not let decision regarding method of reperfusion delay time to reperfusion

### Primary PCI (NEJM 2007;356:47; JACC 2013;61:e78 & 2016;67:1235)

- Definition: immediate PCI upon arrival to hospital or transfer for immediate PCI
- Indic: STE + sx onset w/in <12 h; ongoing ischemia 12–24 h after sx onset; shock
- Superior to lysis: 27% ↓ death, 65% ↓ reMI, 54% ↓ stroke, 95% ↓ ICH (Lancet 2003;361:13)
- Transfer to center for 1<sup>o</sup> PCI superior to lysis (NEJM 2003;349:733), see below
- Routine thrombus aspiration: no benefit, ↑ stroke (Lancet 2015;387:127; 2015;372:1389)
- Complete revasc: ↓ MACE vs. culprit artery alone (NEJM 2013; 369:1115; JACC 2015;65:963); alternatively, assess ischemia due to residual lesions w/ imaging stress (Circ 2011;124:e574)

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

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

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

### Fibrinolysis

- Indic: STE/LBBB + sx <12 h (& >120 min before PCI can be done); benefit if sx >12 h less clear; reasonable if persist. sx & STE or hemodynamic instability or large territory at risk
- Mortality ↓ ~20% in anterior MI or LBBB and ~10% in IMI c/w Ø reperfusion Rx
- Prehospital lysis (ie, ambulance): further 17% ↓ in mortality (JAMA 2000;283:2686)
- ~1% risk of ICH; high risk incl elderly (~2% if >75 y), ♀, low wt. ∴ PCI more attractive

### Contraindications to Fibrinolysis

Absolute contraindications	Relative contraindications
<ul style="list-style-type: none"> <li>Any prior ICH</li> <li>Intracranial neoplasm, aneurysm, AVM</li> <li>Ischemic stroke or closed head trauma w/in 3 mo; head/spinal surg. w/in 2 mo</li> <li>Active internal bleeding or known bleeding diathesis</li> <li>Suspected aortic dissection</li> <li>Severe uncontrollable HTN</li> <li>For SK, SK Rx w/in 6 mo</li> </ul>	<ul style="list-style-type: none"> <li>H/o severe HTN, SBP &gt;180 or DBP &gt;110 on presentation (? absolute if low-risk MI)</li> <li>Ischemic stroke &gt;3 mo prior</li> <li>CPR &gt;10 min; trauma/major surg. w/in 3 wk</li> <li>Internal bleed w/in 2–4 wk; active PUD</li> <li>Noncompressible vascular punctures</li> <li>Pregnancy</li> <li>Current use of anticoagulants</li> <li>For SK, prior SK exposure</li> </ul>

**Nonprimary PCI**

- Rescue PCI if shock, unstable, failed reperfusion or persistent sx (NEJM 2005;353:2758)
- Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/revasc (Lancet 2004;364:1045) and w/in 6 h ↓ reMI, recurrent ischemia, & HF compared to w/in 2 wk (NEJM 2009;360:2705); ∴ if lysed at non-PCI-capable hosp., consider transfer to PCI-capable hosp. ASAP espec if hi-risk (eg, ant. MI, IMI w/ ↓ EF or RV infarct, extensive STE/LBBB, HF, ↓ BP or ↑ HR)
- Late PCI (median day 8) of occluded infarct-related artery: no benefit (NEJM 2006;355:2395)

**Antiplatelet Therapy**

<b>Aspirin</b> 162–325 mg × 1 (crushed/chewed) then 81 mg qd	23% ↓ in death (Lancet 1988;ii:349) Should not be stopped if CABG required
<b>P2Y<sub>12</sub> inhibitor</b> Give ASAP (do not wait for angio) b/c onset inhib delayed in STEMI pts	Lysis: clopidogrel 41% ↑ in patency, 7% ↓ mort, no Δ major bleed or ICH (NEJM 2005;352:1179; Lancet 2005;366:1607); no data for pras or ticag w/ lytic
Ticagrelor or prasugrel (if PCI) as detailed above	PCI: prasugrel and ticagrelor ↓ CV events c/w clopi (Lancet 2009;373:723 & Circ 2010;122:2131)
Clopidogrel: 600 mg pre-PCI; 300 mg if lysis (no LD if >75 y) → 75 mg qd	Prehospital ticagrelor may be safe & ? ↓ rate of stent thrombosis (NEJM 2014;371:1016)
<b>GP IIb/IIIa inhibitors</b> abciximab, eptifibatide, tirofiban	Lysis: no indication (Lancet 2001;357:1905) Peri-PCI: 60% ↓ D/MI/UR (NEJM 2001;344:1895)

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

**Anticoagulant Therapy (choose one)**

<b>UFH</b> 60 U/kg IVB (max 4000 U) 12 U/kg/h (max 1000 U/h initially)	No demonstrated mortality benefit ↑ patency with fibrin-specific lytics Titrate to aPTT 1.5–2× control (~50–70 sec)
<b>Enoxaparin</b> Lysis: 30 mg IVB → 1 mg/kg SC bid (adjust for age >75 & CrCl) PCI: 0.5 mg/kg IVB	Lysis: 17% ↓ D/MI w/ ENOX × 7 d vs. UFH × 2 d (NEJM 2006;354:1477) PCI: ↓ D/MI/revasc and ≈ bleeding vs. UFH (Lancet 2011;378:693)
<b>Bivalirudin</b> 0.75 mg/kg IVB → 1.75 mg/kg/hr IV	PCI: ↓ bleeding (espec vs. UFH + GP IIb/IIIa inhib), ± ↑ MI, ↑ stent thromb, ? ↓ mortality (Lancet 2014;384:599; JAMA 2015;313:1336; NEJM 2015;373:997)

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

**Intraaortic Balloon Pump (IABP) Counterpulsation**

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

**LV failure (~25%)**

- Diurese to achieve PCWP ~14 → ↓ 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 HF 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, mech circulatory support to keep CI >2; pressors to keep MAP >60;  
if not done already, coronary revasc (NEJM 1999;341:625)

**IMI complications** (Circ 1990;81:401; NEJM 1994;330:1211; JACC 2003;41:1273)

- Heart block:** ~20%, occurs in part because RCA typically supplies AV node 40% on present, 20% w/in 24 h, rest by 72 h; high-grade AVB can develop abruptly Rx: atropine, epi, aminophylline (100 mg/min × 2.5 min), temp pacing wire
- RV infarct** (proximal RCA occlusion → compromised flow to RV marginal branch) Angiographically present in 30–50%, but only ½ of those clinically signif.  
HoTN; ↑ JVP, + Kussmaul's; ≥1 mm STE in V<sub>4R</sub>; RA/PCWP ≥0.8; RV dysfxn on TTE Rx: optimize preload (RA goal 10–14; BHJ 1990;63:98); ↑ contractility (dobutamine); maintain AV synchrony (pacing as necessary); reperfusion (NEJM 1998;338:933); mechanical support (IABP or RVAD); pulmonary vasodilators (eg, inhaled NO)

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

- Free wall rupture:** ↑ risk w/ lysis, large MI, ↑ age, ♀, HTN; p/w PEA or hypoTN, pericardial sx, tamponade; Rx: volume resusc., ? pericardiocentesis, inotropes, **surgery**
- VSD:** large MI in elderly; AMI → apical VSD, IMI → basal septum; 90% w/ harsh murmur ± thrill (NEJM 2002;347:1426); Rx: diuretics, vasodil., inotropes, IABP, **surgery**, perc. closure
- Papillary muscle rupture:** more common after IMI (PM pap m. supplied by PDA alone) than AMI (AL supplied by OMIs & diags); 50% w/ new murmur; ↑ v wave in PCWP tracing

**Arrhythmias post-MI** (treat all per ACLS protocols if unstable or symptomatic)

- AF** (10–16% incidence): βB or amio, ± digoxin (particularly if HF), heparin
- VT/VF**: lido or amio  $\times$  6–24 h, then reassess; ↑ βB as tol., replete K & Mg, r/o ischemia; monomorphic VT  $<$ 48 h post-MI does not worsen prognosis;  $>$ 48 h, consider ICD (? wearable; see below)
- Accelerated idioventricular rhythm (AIVR): slow VT ( $<$ 100 bpm), often seen after successful reperfusion; typically asx, self-terminates, and does not require treatment
- May consider **backup transcutaneous pacing** (TP) if: 2° AVB type I, BBB
- Backup TP or initiate transvenous pacing** if: 2° AVB type II; BBB + AVB
- Transvenous pacing** (TV) if: 3° AVB; new BBB + 2° AVB type II; alternating LBBB/RBBB (can bridge w/ TP until TV, which is best accomplished with fluoroscopic guidance)

**Other Post-MI Complications**

Complication	Clinical features	Treatment
<b>LV thrombus</b>	~30% incid. (espec lg antero-apical MI)	Anticoagulate $\times$ 3–6 mo
<b>Ventricular aneurysm</b>	Noncontractile outpouching of LV; 8–15% incid. (espec ant); persist STE	Surgery or perc repair if HF, thromboemboli, arrhythmia
<b>Ventricular pseudoaneurysm</b>	Rupture (narrow neck) $\rightarrow$ sealed by thrombus and pericardium (esp in inf).	Urgent surgery (or percutaneous repair)
<b>Pericarditis</b>	10–20% incid.; 1–4 d post-MI $\pm$ pericardial rub; ECG Δs rare	High-dose ASA, colchicine, narcotics; minimize anticoag
<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
- TIMI Risk Score for STEMI (includes age, time to Rx, anterior MI or LBBB, Killip class, tachycardia, HoTN) defines 30-d mortality after STEMI (JAMA 2001;286:1356)

**Checklist and Long-Term Post-ACS Management****Risk stratification**

- Stress test if anatomy undefined; consider stress if signif residual CAD post-PCI of culprit
- Assess LVEF prior to d/c; EF  $\uparrow$  ~6% in STEMI over 6 mo (JACC 2007;50:149)

**Medications (barring contraindications)**

- Aspirin:** 81 mg daily (no clear benefit to higher doses)
- P2Y<sub>12</sub> inhib:** ticagrelor or prasugrel preferred over clopi; treat for at least 12 mo Prolonged Rx  $>$ 12 mo  $\rightarrow$  ↓ MACE & CV death,  $\uparrow$  in bleeding, but no  $\uparrow$  ICH. Beyond 1<sup>st</sup> 12 mo, ticag 60 bid preferred to 90, as better tolerability (NEJM 2015;372:1791; EHJ 2016;37:390). PPIs  $\downarrow$  GI complic; some PPIs  $\downarrow$  antiplt effect, but no clear  $\uparrow$  in CV risk (NEJM 2010;363:1909)
- β-blocker:** 23%  $\downarrow$  mortality after MI
- Statin:** high-intensity lipid-lowering (eg, atorva 80 mg, PROVE-IT TIMI 22, NEJM 2004;350:1495)
- Ezetimibe:**  $\downarrow$  CV events when added to statin (IMPROVE-IT, NEJM 2015;372:1500)
- ACEI:** lifelong if HF,  $\downarrow$  EF, HTN, DM; 4–6 wk or at least until hosp. d/c in all STEMI ? long-term benefit in CAD w/o HF (NEJM 2000;342:145 & 2004;351:2058; Lancet 2003;362:782)
- Aldosterone antag:** 15%  $\downarrow$  mort if EF  $<$ 40% & either s/s of HF or DM (NEJM 2003;348:1309)
- Nitrates: standing if symptomatic; SL NTG prn for all
- Ranolazine:  $\downarrow$  recurrent ischemia, no impact on CVD/MI (JAMA 2007;297:1775)
- Oral anticoag: if needed (eg, AF or LV thrombus), warfarin w/ target INR 2–2.5 or NOAC. Clopi (not ticag or pras) and ? stop ASA if at high bleeding risk (Lancet 2013;381:1107). Not FDA approved: low-dose rivaroxaban (2.5 mg bid) in addition to ASA & clopi in patients without an indication for anticoag  $\rightarrow$  16%  $\downarrow$  D/MI/stroke and 32%  $\downarrow$  all-cause death, but  $\uparrow$  major bleeding and ICH (NEJM 2012;366:9).

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

- If sust. VT/VF  $>$ 2 d post-MI not due to reversible ischemia; consider wearable defib
- Indicated in 1° prevention of SCD if post-MI w/ EF  $\le$ 30–40% (NYHA II–III) or  $\le$ 30–35% (NYHA I); need to wait  $\ge$ 40 d after MI (NEJM 2004;351:2481 & 2009;361:1427)

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

- Low chol. (<200 mg/d) & fat (<7% saturated) diet; ? Ω-3 FA
- Traditional LDL-C goal  $<$ 70 mg/dL; current recs w/o target; given IMPROVE-IT, ? mid 50s
- BP  $<$ 140/90 & ? 120–130/80 mmHg (HTN 2015;65:1372; NEJM 2015;373:2103); quit smoking
- If diabetic, tailor HbA1c goal based on Pt (avoid TZDs if HF); in Pts w/ CAD, empagliflozin (NEJM 2015; 373:2117) and liraglutide (NEJM 2016;375:311)  $\downarrow$  cardiovascular events
- Exercise (30–60 min 5–7/wk); cardiac rehab; BMI goal 18.5–24.9 kg/m<sup>2</sup>
- Influenza & S. pneumo vaccines (Circ 2006;114:1549; JAMA 2013;310:1711); ✓ for depression

**Rationale**

- Cardiac output (CO) = SV × HR; optimize SV (and thereby CO) by manipulating preload/LVEDV (w/ IVF, diuretics), contractility (w/ inotropes), & afterload (w/ vasodilators)
- Balloon at catheter tip inflated → floats into “wedge” position. Column of blood extends from tip of catheter, through pulm venous circulation to a point just prox to LA. Under conditions of no flow, PCWP ≈ LA pressure ≈ LVEDP, which is proportional to LVEDV.
- Situations in which these basic assumptions fail:
  - (1) Catheter tip not in West lung zone 3 (and ∴ PCWP = alveolar pressure ≠ LA pressure); clues include lack of *a* & *v* waves and if PA diastolic pressure < PCWP
  - (2) PCWP > LA pressure (eg, mediastinal fibrosis, pulmonary VOD, PV stenosis)
  - (3) Mean LA pressure > LVEDP (eg, MR, MS)
  - (4) Δ LVEDP-LVEDV relationship (ie, abnl compliance, ∴ “nl” LVEDP may not be optimal)

**Indications** (*Circ* 2009;119:e391; *NEJM* 2013;369:e35)**Diagnosis and evaluation**

Ddx of shock (cardiogenic vs. distributive; espec if trial of IVF failed or is high risk) and of pulmonary edema (cardiogenic vs. not; espec if trial of diuretic failed or is high risk)

Evaluation of CO, intracardiac shunt, pulm HTN, MR, tamponade, cardiorenal syndrome

Evaluation of unexplained dyspnea (PAC during provocation w/ exercise, vasodilator)

**Therapeutics** (*Circ* 2006;113:1020)

Tailored therapy to optimize PCWP, SV,  $S_{MV}O_2$ , RAP, PVR in heart failure or shock

Guide to vasodilator therapy (eg, inhaled NO, nifedipine) in PHT, RV infarction

Guide periop mgmt in some high-risk Pts, candidacy for mech circ support & transplant

**Contraindications**

**Absolute:** right-sided endocarditis, thrombus/mass or mechanical valve; proximal PE

**Relative:** coagulopathy (reverse), recent PPM or ICD (place under fluoroscopy), LBBB (~5% risk of RBBB → CHB, place under fluoro), bioprosthetic R-sided valve

**Efficacy concerns** (*NEJM* 2006;354:2213; *JAMA* 2005;294:1664)

- No benefit to routine PAC use in high-risk surgery, sepsis, ARDS
- No benefit in decompensated HF (*JAMA* 2005;294:1625); untested in cardiogenic shock
- But: ~1/2 of clinical CO & PCWP estimates incorrect; CVP & PCWP not well correl; ∴ use PAC to (a) answer hemodynamic ? and then remove, or (b) manage cardiogenic shock

**Placement** (*NEJM* 2013;369:e35)

- Insertion site: **R internal jugular** or **L subclavian veins** for “anatomic” flotation into PA
- Inflate** balloon (max 1.5 mL) when **advancing** and to **measure PCWP**
- Use resistance to inflation and pressure tracing to avoid overinflation & risk of PA rupture
- Deflate** the balloon when **withdrawing** and at all other times
- CXR should be obtained after placement to assess for catheter position and PTX
- If catheter cannot be floated (i.e., severe TR, RV dilatation), consider fluoroscopic guidance

**Complications**

- Central venous access:** pneumo/hemothorax (~1%), arterial puncture (if inadvertent cannulation w/ dilation → surgical/endovasc eval), air embolism, thoracic duct injury
- Advancement:** atrial or ventricular arrhythmias (3% VT; 20% NSVT and >50% PVC), RBBB (5%), catheter knotting, cardiac perforation/tamponade, PA rupture
- Maintenance:** infection (espec if catheter >3 d old), thrombus, pulm infarction (≤1%), valve/chordae damage, PA rupture/pseudoaneurysm (espec w/ PHT), balloon rupture

**Intracardiac pressures**

- Transmural pressure (~ preload) = measured intracardiac pressure – intrathoracic pressure
- Intrathoracic pressure (usually slightly  $\ominus$ ) 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 ~1/2 PEEP ( $\times \frac{3}{4}$  to convert cm H<sub>2</sub>O to mmHg).
- PCWP: LV preload best estimated at *a* wave; risk of pulmonary edema from avg PCWP

**Cardiac output**

- Thermodilution:** saline injected in RA or prox thermal filament.  $\Delta$  in temp over time measured at thermistor (in PA) used to calc CO. Inaccurate if ↓ CO, sev TR, or shunt.
- Fick method:**  $O_2$  consumption ( $V\dot{O}_2$ )(L/min) = CO (L/min)  $\times$   $\Delta$  arteriovenous  $O_2$  content  
 $\therefore CO = \dot{V}O_2 / C(a-v)O_2$

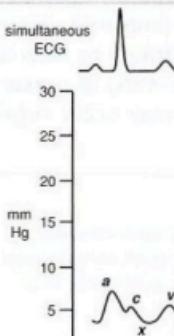
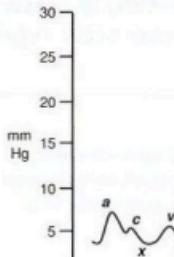
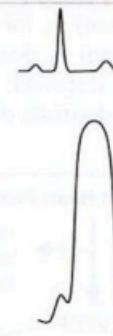
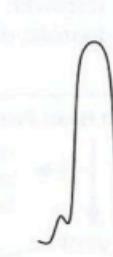
$\dot{V}O_2$  ideally measured (esp. if ↑ metab demands), but freq estimated (125 mL/min/m<sup>2</sup>)

$C(a-v)O_2 = [10 \times 1.36 \text{ mL } O_2/\text{g of Hb} \times \text{Hb g/dL} \times (S_aO_2 - S_{MV}O_2)]$ .  $S_{MV}O_2$  is key variable that  $\Delta s$ .

If  $S_{MV}O_2 > 80\%$ , consider if the PAC is “wedged” (ie, pulm vein sat), L → R shunt,

impaired  $O_2$  utilization (severe sepsis, cyanide, carbon monoxide), ↑↑ FiO<sub>2</sub>.

## PA Catheter Waveforms

Location	RA	RV	PA	PCWP
Distance	~20 cm	~30 cm	~40 cm	~50 cm
Normal Pressure (mmHg)	mean ≤ 6	syst 15–30 diast 1–8	syst 15–30 mean 9–18 diast 6–12	mean ≤ 12
Waves	 	 	 	 
Comment	<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 ≥ 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).      PA diastolic = PCWP unless ↑ trans-pulm gradient (eg, ↑ PVR).</p>	<p>Similar to RA except damped and delayed. a wave after QRS, ± 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 (NEJM 2013;369:1726)

Type of shock	RA	PCWP	CO	SVR
Hypovolemic	↓	↓	↓	↑
Cardiogenic	nl or ↑	↑	↓	↑
RV infarct/massive PE	↑	nl or ↓	↓	↑
Tamponade	↑	↑	↓	↑
Distributive	variable	variable	usually ↑ (can be ↓ in sepsis)	↓

Surrogates: RA ≈ JVP (1 mmHg = 1.36 cm H<sub>2</sub>O); pulmonary edema on CXR implies ↑ PCWP; UOP ∝ CO (barring AKI); delayed capillary refill (ie, >2–3 sec) implies ↑ SVR

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

- **Goals:** optimize both MAP and CO while ↓ risk of pulmonary edema  
 MAP = CO × SVR; CO = HR × SV (which depends on preload, afterload and contractility)  
 pulmonary edema when PCWP >20–25 (↑ levels may be tolerated in chronic HF)  
 hepatic and renal congestion when CVP/RAP >15 mmHg
- **Optimize preload** = LVEDV ≈ LVEDP ≈ LAP ≈ PCWP (NEJM 1973;289:1263)  
 goal **PCWP ~14–18 in acute MI, ≤14 in acute decompensated HF**  
 optimize in individual Pt by measuring SV w/ different PCWP to create Starling curve  
 ↑ by giving NS (albumin w/o clinical benefit over NS; PRBC if significant anemia)  
 ↓ by diuresis (qv), ultrafiltration or dialysis if refractory to diuretics
- **Optimize afterload** = wall stress during LV ejection =  $[(-\text{SBP} \times \text{radius}) / (2 \times \text{wall thick.})]$  and ∴ ∝ MAP and ∝ SVR = (MAP – CVP / CO); goals: **MAP >60, SVR 800–1200**  
 MAP >60 & SVR ↑: vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or wean pressors  
 MAP <60 & SVR ↑ (& ∴ CO ↓): temporize w/ pressors until can ↑ CO (see below)  
 MAP <60 & SVR low/nl (& ∴ inappropriate vasoplegia): vasopressors (eg, norepinephrine [α, β], dopamine [D, α, β], phenylephrine [α] or vasopressin [V<sub>1</sub>] if refractory); better outcomes w/ norepi than dopa even in cardiogenic shock (NEJM 2010;362:779)
- **Optimize contractility** ∝ CO for given preload & afterload; goal **CI = (CO / BSA) >2.2**  
 if too low despite optimal preload & vasodilators (as MAP permits):  
 + inotropes: eg, dobutamine (mod inotrope & mild vasodilator) or milrinone (strong inotrope & vasodilator, incl pulm), both proarrhythmic, or epi (strong inotrope & pressor)  
 mech circulatory support (L/min): IABP (0.5), Impella (2–5), TandemHeart (5), VAD (L-sided, R-sided or both; temp or perm; 10) or ECMO (6) (JACC 2015;65:e7 & 2542)

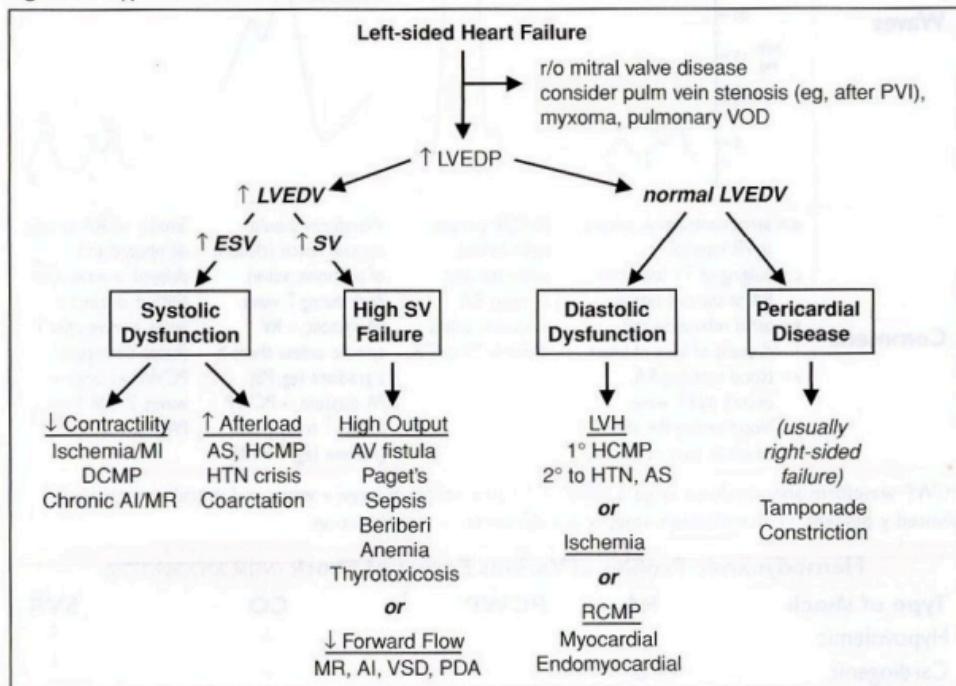
# HEART FAILURE

HF 1-14

## Definitions (Braunwald's Heart Disease, 10th ed., 2014)

- Failure of heart to pump blood forward at rate sufficient to meet metabolic demands of peripheral tissues, or ability to do so only at abnormally high cardiac filling pressures
- Low output ( $\downarrow$  cardiac output) vs. high output ( $\uparrow$  stroke volume  $\pm$   $\uparrow$  cardiac output)
- Left-sided (pulmonary edema) vs. right-sided ( $\uparrow$  JVP, hepatomegaly, peripheral edema)
- Backward ( $\uparrow$  filling pressures, congestion) vs. forward (impaired systemic perfusion)
- Systolic (inability to expel sufficient blood) vs. diastolic (failure to relax and fill normally)
- Reduced (HFrEF, EF <40%), mid-range (HFmrEF, EF 40–49%), & preserved (HFpEF, EF >50%); combination of systolic and diastolic dysfxn may occur regardless of EF

Figure 1-3 Approach to left-sided heart failure



## History

- Low output: fatigue, weakness, exercise intolerance,  $\Delta$  MS, anorexia
- Congestive: left-sided  $\rightarrow$  dyspnea, orthopnea, paroxysmal nocturnal dyspnea  
right-sided  $\rightarrow$  peripheral edema, RUQ discomfort, bloating, satiety

## Functional classification (New York Heart Association class)

- Class I: no sx w/ ordinary activity; class II: sx w/ ordinary activity;  
class III: sx w/ minimal activity; class IV: sx at rest

## Physical exam ("2-minute" hemodynamic profile; JAMA 1996;275:630 & 2002;287:628)

- Congestion ("dry" vs. "wet"):**  $\uparrow$  JVP (~80% of the time JVP  $>10 \rightarrow$  PCWP  $>22$ )
  - ⊕ hepatojugular reflux:  $\geq 4$  cm  $\uparrow$  in JVP for  $\geq 15$  sec w/ abdominal pressure  
Se/Sp 73/87% for RA  $>8$  and Se/Sp 55/83% for PCWP  $>15$  (AJC 1990;66:1002)
  - Abnl Valsalva response: square wave ( $\uparrow$  SBP w/ strain), no overshoot (no  $\uparrow$  BP after strain)
  - S<sub>3</sub> (in Pts w/ HF  $\rightarrow$  ~40%  $\uparrow$  risk of HF hosp. or pump failure death; NEJM 2001;345:574)  
rales, dullness at base 2° pleural effus. (often absent in chronic HF due to lymphatic compensation)  $\pm$  hepatomegaly, ascites and jaundice, peripheral edema
- Perfusion ("warm" vs. "cold")**
  - narrow pulse pressure (<25% of SBP)  $\rightarrow$  CI  $<2.2$  (91% Se, 83% Sp; JAMA 1989;261:884); soft S<sub>1</sub> ( $\downarrow$  dP/dt), pulsus alternans, cool & pale extremities,  $\downarrow$  UOP, muscle atrophy
  - $\pm$  Other: Cheyne-Stokes resp., abnl PMI (diffuse, sustained or lifting depending on cause of HF), S<sub>4</sub> (diast. dysfxn), murmur (valvular dis.,  $\uparrow$  MV annulus, displaced papillary muscles)

## Evaluation for the presence of heart failure

- CXR (see Radiology insert): pulm edema, pleural effusions  $\pm$  cardiomegaly, cephalization, Kerley B-lines; lung U/S better than CXR (PPV & NPV 92% vs. 77%; Chest 2015;148:202)
- BNP/NT-proBNP can help exclude HF; levels  $\uparrow$  w/ age, renal dysfxn, AF;  $\downarrow$  w/ obesity  
Se  $\geq 95\%$ , Sp: ~50%, PPV ~65%, NPV  $\geq 94\%$  for HF in Pts p/w SOB (BMJ 2015;350:h910)
- Evidence of  $\downarrow$  organ perfusion:  $\uparrow$  Cr,  $\downarrow$  Na, abnl LFTs
- Echo (see inserts):  $\downarrow$  EF &  $\uparrow$  chamber size  $\rightarrow$  systolic dysfxn; hypertrophy, abnl MV inflow, abnl tissue Doppler  $\rightarrow$  ? diastolic dysfxn; abnl valves or pericardium;  $\uparrow$  estimated RVSP
- PA catheterization:  $\uparrow$  PCWP,  $\downarrow$  CO, and  $\uparrow$  SVR (in low-output failure)

## Evaluation for the potential causes of heart failure

- ECG:** evidence for CAD, LVH, LAE, heart block or low voltage (? infiltrative CMP/DCMP)
- TTE:** LV & RV size & fxn, valve abnl (cause or consequence?), infiltrative or pericardial dis.
- Cardiac MRI:** distinguishes ischemic vs. nonischemic and can help determine etiol. of latter
- Coronary angio** (or noninvasive imaging, eg, CT angio); if no CAD, w/u for NICM

## Precipitants of acute heart failure

- Dietary indiscretion or medical nonadherence** (~40% of cases)
- Myocardial ischemia or infarction** (~10–15% of cases); myocarditis
- Renal failure** (acute, progression of CKD, or insufficient dialysis) → ↑ preload
- Hypertensive crisis (incl. from RAS), worsening AS** → ↑ left-sided afterload
- Drugs** ( $\beta$ B, CCB, NSAIDs, TZDs), **chemo** (anthracyclines, trastuzumab), or **Toxins** (EtOH)
- Arrhythmias; acute valvular dysfxn** (eg, endocarditis), espec mitral or aortic regurgitation
- COPD/PE** → ↑ right-sided afterload; extreme stress, anemia, systemic infxn, thyroid dis.

## Treatment of acute decompensated heart failure

- Assess degree of congestion & adequacy of perfusion
- For congestion: "LMNOP"**
  - Lasix IV; total daily dose  $2.5 \times$  usual daily PO dose → ↑ UOP, but transient ↑ in Cr vs. 1x usual dose; Ø clear diff between contin. gtt vs. q12h (NEJM 2011;364:797)
  - Morphine ( $\downarrow$  sx, venodilator,  $\downarrow$  afterload)
  - Nitrates (venodilator)
    - Oxygen ± noninvasive vent ( $\downarrow$  sx,  $\uparrow P_aO_2$ ; no  $\Delta$  mortality; see "Mechanical Ventilation")
    - Position (sitting up & legs dangling over side of bed →  $\downarrow$  preload)
- For low perfusion**, see below
- Adjustment of oral meds
  - ACEI/ARB: hold if HoTN, consider  $\Delta$  to hydralazine & nitrates if renal decompensation
  - $\beta$ B: reduce dose by at least  $\frac{1}{2}$  if mod HF, d/c if severe HF and/or need inotropes

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

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

- Consider PAC if not resp to Rx, unsure re: vol status, HoTN, ↑ Cr, need inotropes
- Tailored Rx w/ PAC (qv); goals of MAP  $>60$ , CI  $>2.2$  ( $MVO_2 >60\%$ ), SVR  $<800$ , PCWP  $<18$
- IV vasodilators:** NTG, nitroprusside (risk of coronary steal if CAD; prolonged use → cyanide/thiocyanate toxicity); nesiritide (rBNP) not rec for routine use (NEJM 2011;365:32)
- Inotropes** (properties in addition to ↑ inotropy listed below)
  - dobutamine: vasodilation at doses  $\leq 5 \mu\text{g}/\text{kg}/\text{min}$ ; mild  $\downarrow$  PVR; desensitization over time
  - dopamine: splanchnic vasodil. →  $\uparrow$  GFR & natriuresis; vasoconstrictor at  $\geq 5 \mu\text{g}/\text{kg}/\text{min}$
  - milrinone: prominent systemic & pulmonary vasodilation;  $\downarrow$  dose by 50% in renal failure
- Ultrafiltration:** similar wt loss to aggressive diuresis, but  $\uparrow$  renal failure (NEJM 2012;367:2296)
- Mechanical circulatory support** (also see "Tailored Therapy;" JACC 2015;65:e7 & 2542)
  - Temporary:** bridge to recovery, transplant, or durable MCS; periprocedural support
    - Intra-aortic balloon pump (IABP): inflates in diastole & deflates in systole to  $\downarrow$  impedance to LV ejection,  $\downarrow$  myocardial O<sub>2</sub> demand &  $\uparrow$  coronary perfusion.  $\sim 0.5 \text{ L}/\text{min}$  CO
    - Axial flow pumps (eg, Impella): Archimedes screw principle in LV;  $+2.5\text{--}5 \text{ L}/\text{min}$
    - Extracorporeal centrifugal pumps: TandemHeart ( $+5 \text{ L}/\text{min}$ , percutaneous) & CentriMag ( $10 \text{ L}/\text{min}$ , surgical).
  - Extracorporeal membrane oxygenation (ECMO):  $6 \text{ L}/\text{min}$  (Circ 2015;131:676)
  - Durable:** surgically placed LVAD ± RVAD as bridge to recovery (NEJM 2006;355:1873) or transplant (HeartMate II or HeartWare LVAD or Total Artificial Heart if BiV failure), or as destination Rx ( $>50\% \downarrow$  1-y mort vs. med Rx; NEJM 2001;345:1435 & 2009;361:2241).
- Cardiac transplantation:  $\sim 2500/\text{yr}$  in U.S. 10% mort. in 1<sup>st</sup> y, median survival  $\sim 10$  y

## Recommended Chronic Therapy by HF Stage (Circ 2009;119:e391)

Stage (not NYHA Class)	Therapy
<b>A</b>	At risk for HF (eg HTN, FHx CMP); but asx & w/o struct. heart dis.
	Rx HTN, lipids, DM. Stop smoking, EtOH. $\uparrow$ exercise. ACEI/ARB if HTN/DM/CAD/PAD
<b>B</b>	⊕ Struct. heart dis. (eg CMP, LVH), but asx
	As per stage A + ACEI/ARB & $\beta$ B if MI/CAD or $\downarrow$ EF? ICD.
<b>C</b>	⊕ Struct. heart dis. ⊕ Any h/o Sx of HF
	As per stage A + diuretics, $\downarrow$ Na. If $\downarrow$ EF: ACEI, ARB or ARNI; $\beta$ B; aldo antag; ICD; ? CRT; nitrate/hydral; dig.
<b>D</b>	Refractory HF requiring specialized interventions
	All measures for stages A–C. Consider IV inotropes, VAD, transplant, end-of-life care (4-y mortality $>50\%$ )

- Utility of BNP-guided Rx remains debated (*Eur Heart J* 2014;35:16)
- Implantable PA pressure sensor in NYHA III → ~33% ↓ risk of hosp (*Lancet* 2016;387:453)

### Treatment of Chronic Heart Failure with Reduced Ejection Fraction

Diet, exercise	Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
<b>ACEI</b>	↓ mortality: 40% in NYHA IV, 16% in NYHA II/III, 20–30% in asx but ↓ EF ( <i>NEJM</i> 1992;327:685 & <i>Lancet</i> 2000;355:1575) High-dose more effic. than low. Watch for ↑ Cr, ↑ K (ameliorate by low-K diet, diuretics, K binders), cough, angioedema.
<b>ATII receptor blockers (ARBs)</b>	Consider as alternative if cannot tolerate ACEI (eg, b/c cough) Noninferior to ACEI ( <i>Lancet</i> 2000;355:1582 & 2003;362:772) As with ACEI, higher doses more efficacious ( <i>Lancet</i> 2009;374:1840) Adding to ACEI → ↑ risk of ↑ K and ↑ Cr ( <i>BMJ</i> 2013;346:f360)
<b>ARNi (ARB + neprilysin inhib)</b> (do not use w/ ACEI, allow 36-h washout)	Alternative to ACEI/ARB, espec if sx despite ACEI/ARB. Neutral endopeptidase (NEP, aka neprilysin) degrades natriuretic peptides, bradykinin & angiotensins. Valsartan + sacubitril (NEPi) ↓ CV mort & HF hosp c/w ACEi; ↑ HoTN, AKI, ? angioedema ( <i>NEJM</i> 2014;371:993).
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 (A-HEFT, <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 metop in 1 trial ( <i>Lancet</i> 2003;362:7), but meta-analysis suggests no diff between βB ( <i>BMJ</i> 2013;346:f55).
<b>Aldosterone antagonists</b>	Consider if adeq. renal fxn and w/o hyperkalemia; watch for ↑ K 25–30% ↓ mort. in NYHA II–IV & EF ≤35% ( <i>NEJM</i> 2011;364:11) 15% ↓ mort. in HF post-MI, EF ≤40% (EPHESUS, <i>NEJM</i> 2003;348:1309)
<b>Cardiac resynch therapy (CRT, qv)</b>	Consider if EF ≤35%, LBBB (QRS >130 ms) and symptomatic HF 36% ↓ mort. & ↑ EF in NYHA III–IV ( <i>CARE-HF, NEJM</i> 2005;352:1539) 41% ↓ mort. if EF ≤30%, LBBB and NYHA I/II ( <i>NEJM</i> 2014;370:1694)
<b>ICD</b> (see "Cardiac Rhythm Mgmt Devices")	For 1° prevention if EF ≤30–35% or 2° prevention; not if NYHA IV ↓ mort. in ischemic & non-isch CMP; no Δ mort. early post-MI ( <i>NEJM</i> 2004;351:2481 & 2009;361:1427), ∴ wait ≥40 d
Diuretics	Loop ± thiazides diuretics (sx relief; no mortality benefit)
Digoxin	23% ↓ HF hosp., no Δ mort ( <i>NEJM</i> 1997;336:525); ? ↑ mort w/ ↑ levels ( <i>NEJM</i> 2002;347:1403); optimal 0.5–0.8 ng/mL ( <i>JAMA</i> 2003;289:871)
Ivabradine (I <sub>f</sub> blocker w/o ⊖ ino)	Consider if EF ≤35%, NYHA II or III, HR ≥70, NSR on max βB. 18% ↓ CV mort or HF hosp ( <i>Lancet</i> 2010;376:875)
Iron supplementation	? if NYHA II/III, EF ≤40%, Fe-defic (ferritin <100 or ferritin 100–200 & TSAT <20%). ↓ Sx, ↑ 6MWD, independent of Hct ( <i>NEJM</i> 2009;361:2436).
Anticoagulation	If AF,VTE, LV thrombus, ± if large akinetic LV segments In SR w/ EF <35%, ↓ isch stroke, but ↑ bleed ( <i>NEJM</i> 2012;366:1859)
Heart rhythm	Catheter ablation of AF → ↑ in EF, ↓ sx ( <i>NEJM</i> 2004;351:2373) No mortality benefit to AF rhythm vs. rate cntl ( <i>NEJM</i> 2008;358:2667) Pulm vein isolation ↓ sx c/w AVN ablation & CRT ( <i>NEJM</i> 2008;359:1778)
Meds to avoid	NSAIDs, nondihydropyridine CCB, TZDs
Experimental	Serelaxin ± ↓ dyspnea & ? ↓ mortality ( <i>Lancet</i> 2013;381:29) Empagliflozin (SGLT2i) ↓ death/HF hosp in DM ( <i>NEJM</i> 2015;373:2117) Interatrial shunting ↓ PCWP & sx ( <i>Lancet</i> 2016;387:1290)

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

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

- Epidemiology: ~½ of Pts w/ HF have normal or only min. impaired systolic fxn (EF ≥40%); risk factors for HFpEF incl ↑ age, ♀, DM, AF. Mortality = to those w/ systolic dysfxn.
- Etiologies (impaired relaxation and/or ↑ passive stiffness): ischemia, prior MI, LVH, HCMP, infiltrative CMP, RCMP, aging, hypothyroidism
- Precipitants of pulmonary edema: volume overload (poor compliance of LV → sensitive to even modest ↑ in volume); ischemia (↓ relaxation); tachycardia (↓ filling time in diastole), AF (loss of atrial boost to LV filling); HTN (↑ afterload → ↓ stroke volume)
- Dx w/ clinical s/s of HF w/ preserved systolic fxn. Dx supported by evidence of diast dysfxn:
  - echo: abnl MV inflow (E/A reversal and Δs in E wave deceleration time) & ↓ myocardial relax. (↑ isovol relax. time & ↓ early diastole tissue Doppler vel)
  - exercise-induced ↑ PCWP (± ↓ response chronotropic & vasodilator reserve)
- Treatment: diuresis for vol overload, BP control, prevention of tachycardia and ischemia; no benefit to: ACEI/ARB (*NEJM* 2008;359:2456) or PDE5 inhib (*JAMA* 2013;309:1268) spironolactone ? ↓ CV death & HF hosp (at least in Americas) (*NEJM* 2014;370:1383) ARNi (*Lancet* 2012;380:1387) and serelaxin (*Lancet* 2013;381:29) under study

Diseases with mechanical and/or electrical dysfunction of the myocardium

## DILATED CARDIOMYOPATHY (DCM)

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

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

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

- **Familial** (~35%): Pt & ≥2 closely related family members w/ otherwise unexplained DCM; ~30 genes identified to date, encoding structural & nuclear proteins
- **Idiopathic** (<20%): ? undiagnosed infectious, alcoholic or genetic cause
- **Infectious myocarditis** (10–15%; Lancet 2012;379:738; JACC 2012;59:779)
  - Viruses (parvoB19 & HHV6 > Coxsackie, adeno, echo, CMV, HCV): from subacute (dilated LV, mild-mod dysfxn) to fulminant (nondil., thick, edematous LV, sev dysfxn)
  - Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB)
  - HIV: ~8% of asx HIV +; due to HIV, other virus or antiretrovirals; also premature CAD
  - Chagas: apical aneurysm ± thrombus, RBBB, megaesophagus/colon (NEJM 2015;373:456)
- **Toxic**: alcohol (~20%) typ. 7–8 drinks/d × >5 y, but variable; cocaine; XRT (usu RCMP); anthracyclines (risk ↑ >550 mg/m<sup>2</sup>, may manifest late), cyclophosphamide, trastuzumab
- **Infiltrative** (5%): often mix of DCMP + RCMP (qv) with thickened wall amyloidosis, sarcoidosis, hemochromatosis, tumor
- **Autoimmune**: collagen vasc. dis. (3%): PM, SLE, scleroderma, PAN, RA, Wegener's; peripartum (last month → 5 mo postpartum; EHJ 2015;36:1090): ~1:3000 preg. ↑ risk w/ multiparity, ↑ age, Afr Am; stdn HF Rx (if preg, no ACEi or spironolactone); ? bromocriptine to ↓ prolactin; 72% normalize EF (JACC 2015;66:905); ~30% recur w/ next preg
- Idiopathic giant cell myocarditis (GCM): avg age 42, fulminant, AVB/VT (Circ HF 2013;6:15)
- Eosinophilic (variable peripheral eos): hypersensitivity (mild HF but at risk for SCD) or acute necrotizing eosinophilic myocarditis (ANEM; STE, effusion, severe HF)
- **Stress-induced** (Takotsubo = apical ballooning): Typically postmenopausal ♀; mimics MI (chest pain, ± STE & ↑ Tn; deep TWI & ↑ QT); mid/apex dyskinesis; ? Rx w/ βB, ACEi; usu. improves over wks (JAMA 2011;306:277). In-hosp morb/mort similar to ACS (NEJM 2015;373:929).
- **Arrhythmogenic right ventricular cardiomyopathy** (ACM/ARVC): fibrofatty replacement of RV → dilation (dx w/ MRI); ECG: ± RBBB, TWI V<sub>1</sub>–V<sub>3</sub>, ε wave; risk VT (Lancet 2009;373:1289)
- **Tachycardia**: likelihood ∝ rate/duration; often resolves w/ rate cntl (Circ 2005;112:1092)
- **LV noncompaction** (JACC 2015;66:578): prominent trabeculae, arrhythmias, cardioemboli
- **Metab/other**: hypothyroid, acromegaly, pheo, OSA, Vit B<sub>1</sub>, selenium or carnitine defic.

### Clinical manifestations

- **Heart failure**: both congestive & poor forward flow sx; signs of L- & R-sided HF diffuse, laterally displaced PMI, S<sub>3</sub>, ± MR or TR (annular dilat, displaced pap. muscle)
- Embolic events (~10%), supraventricular/ventricular arrhythmias, & palpitations
- Chest pain can be seen w/ some etiologies (eg. myocarditis)

### Diagnostic studies and workup (JACC 2016;67:2996)

- CXR: moderate to marked cardiomegaly, ± pulmonary edema & pleural effusions
- ECG: may see PRWP, Q waves or BBB; low-voltage; AF (20%); may be normal
- Echocardiogram: LV dilatation, ↓ EF, regional or global LV HK ± RV HK, ± mural thrombi
- Cardiac MRI: up to 76% Se, 96% Sp for myocarditis or infiltrative dis. (JACC Imaging 2014;7:254); extent of midwall fibrosis correlated w/ mortality in NICMP (JAMA 2013;309:896)
- Labs: TFTs, Fe panel, HIV, SPEP, ANA; viral sero not recommended; others per suspicion
- Family hx (20–35% w/ familial dis.), genetic counseling ± genetic testing (JAMA 2009;302:2471)
- Stress test: useful to r/o ischemia (low false – rate), high false + rate, even w/ imaging
- Coronary angiography to r/o CAD if risk factors, h/o angina, Qw MI on ECG, equivocal ETT; consider CT angiography (JACC 2007;49:2044)
- ? Endomyocardial biopsy (JACC 2007;50:1914): yield 10%; of these, 75% myocarditis (for which no proven Rx) & 25% systemic disease; 40% false – rate (patchy dis.) & false + (necrosis → inflammation); ∴ biopsy if: acute & hemodyn compromise (r/o GCM, ANEM); arrhythmia or RCMP features (r/o infiltrative); or suspect toxic, allergic, tumor

### Treatment (see "Heart Failure" for standard HF Rx)

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

# HYPERTROPHIC CARDIOMYOPATHY (HCM)

## Definition and epidemiology

- LV (usually  $\geq 15$  mm) and/or RV hypertrophy disproportionate to hemodynamic load
- Prevalence: 1/500; 50% sporadic, 50% familial, most asymptomatic
- Ddx: LVH 2° to HTN, AS, elite athletes (wall usually  $<13$  mm & symmetric and nl/↑ rates of tissue Doppler diastolic relaxation; *Circ* 2011;123:2723), Fabry dis. ( $\uparrow$  Cr, skin findings)

## Pathology

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

## Pathophysiology

- Subaortic outflow obstruction: narrowed tract 2° hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (may be fixed, variable or nonexistent) and papillary muscle displacement. Gradient ( $\nabla$ ) worse w/  $\uparrow$  contractility (digoxin,  $\beta$ -agonists, exercise, PVCs),  $\downarrow$  preload (eg. Valsalva maneuver) or  $\downarrow$  afterload.
- Mitral regurgitation: due to SAM (mid-to-late, post.-directed regurg. jet) and/or abnl mitral leaflets and papillary muscles (panstolic, 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): palpitations, syncope, sudden cardiac death

## Physical exam

- Sustained PMI,  $S_2$  paradoxically split if severe outflow obstruction,  $\oplus S_4$  (occ. palpable)
- **Systolic murmur:** crescendo-decrescendo; LLSB;  $\uparrow$  w/ **Valsalva** & standing ( $\downarrow$  preload)
- $\pm$  mid-to-late or holosystolic murmur of MR at apex
- Bifid carotid pulse (brisk rise, decline, then 2<sup>nd</sup> rise); JVP w/ prominent  $a$  wave
- Contrast to AS, which has murmur that  $\downarrow$  w/ Valsalva and  $\downarrow$  carotid pulses

## Diagnostic studies (*EJH* 2014;35:2733)

- CXR: cardiomegaly (LV and LA)
- ECG: LVH, anterolateral TWI and inferior pseudo-Qw,  $\pm$  apical giant TWI (apical variant)
- **Echo:** any LV wall segment  $\geq 15$  mm (or ? even  $\geq 13$  if  $\oplus$  Hx), often but not necessarily involving septum; other findings include dynamic outflow obstruction, SAM, MR
- MRI: hypertrophy + patchy delayed enhancement (useful for dx & prog) (*Circ* 2015;132:292)
- Cardiac cath: subaortic pressure  $\nabla$ ; *Brockenbrough sign* =  $\downarrow$  pulse pressure post-PVC (in contrast to AS, in which pulse pressure  $\uparrow$  post-PVC)
- ? Genotyping for family screening, but pathogenic mutation ID'd in  $<1/2$  (*Circ* 2011;124:2761)

## Treatment (*Circ* 2011;124:e783 & 2012;125:1432; *Lancet* 2013;381:242)

- Heart failure
  - ⊖ **inotropes/chronotropes:**  $\beta$ -blockers, CCB (verapamil), disopyramide  
Careful use of diuretics, as may further  $\downarrow$  preload. Vasodilators only if systolic dysfxn.  
Avoid digoxin.  
If sx refractory to drug Rx + obstructive physiology ( $\nabla > 50$  mmHg):  
(a) Surgical myectomy: long-term  $\downarrow$  symptoms in 90% (*Circ* 2014;130:1617)  
(b) Alcohol septal ablation (*JCHF* 2015;3:896): gradient  $\downarrow$  by ~80%, only 5–20% remain w/ NYHA III–IV sx; 14% require repeat ablation or myectomy. Good alternative for older Pts, multiple comorbidities. Complic: transient (& occ. delayed) 3° AVB w/ 10–20% req. PPM; VT due to scar formation.  
No clear benefit of dual-chamber pacing (*JACC* 1997;29:435; *Circ* 1999;99:2927)  
If refractory to drug therapy and there is nonobstructive pathophysiology: transplant
- Acute HF: can be precip. by dehydration or tachycardia; Rx w/ fluids,  $\beta$ B, phenylephrine
- AF: rate control w/  $\beta$ B, maintain SR w/ disopyramide or amio; low threshold to anticoag
- SCD: ICD (*JACC* 2003;42:1687). Risk factors: h/o VT/VF,  $\oplus$  FHx SCD, unexplained syncope, NSVT,  $\downarrow$  SBP or rel HoTN ( $\uparrow$  SBP  $< 20$  mmHg) w/ exercise, LV wall  $\geq 30$  mm, ? extensive MRI delayed enhancement. EPS not useful. Risk 4%/y if high-risk (*JAMA* 2007;298:405).
- Counsel to avoid dehydration, extreme exertion
- Endocarditis prophylaxis not recommended (*Circ* 2007;16:1736)
- 1<sup>st</sup>-degree relatives: periodic screening w/ echo, ECG (as timing of HCMP onset variable). Genetic testing if known mutation.

# RESTRICTIVE CARDIOMYOPATHY (RCM)

CMR 1-19

## Definition (Circ 2006;113:1807)

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

## Etiology (JACC 2010;55:1769)

### • Myocardial processes

Autoimmune (scleroderma, polymyositis-dermatomyositis)

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

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

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

ECG: ↓ QRS amplitude (50%), pseudoinfarction pattern (Qw), AVB (10–20%), hemiblock (20%), BBB (5–20%)

Echo: biventricular wall thickening (yet w/ low voltage on ECG), granular sparkling texture (30%), biatrial enlargement (40%), thickened atrial septum, valve thickening (65%), diastolic dysfxn, small effusions

NI voltage/septal thickness has NPV ~90%

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

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

**Sarcoidosis** (can also be DCM): presents at age ~30 y; ↑d in blacks, N. Europe, ♀ 5% w/ systemic sarcoid have overt cardiac involvement; cardiac w/o systemic in 10% ECG: AVB (75%), RBBB (20–60%), VT; PET: ↑ FDG uptake in affected area

Echo: regional WMA (particularly basal septum) w/ thinning or mild hypertrophy

Gallium or FDG uptake at areas of inflam.; sestaMIBI w/ non-cor. perfusion defects

Cardiac MRI: T2 early gad (edema); fibrosis/scar in basal septum; LGE prognostic

Cardiac bx low yield b/c patchy

**Hemochromatosis:** in middle-aged men (espec N. European); 15% p/w cardiac sx

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

### • Endomyocardial processes

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

Toxins: radiation (also p/w constrictive pericarditis, valvular dis, ostial CAD), anthracyclines

Serotonin: carcinoid, serotonin agonists, ergot alkaloids. Metastatic cancer.

## Pathology & pathophysiology

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

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

- Right-sided > left-sided heart failure with peripheral edema > pulmonary edema
- Diuretic "refractoriness"; thromboembolic events
- Poorly tolerated tachyarrhythmias; VT → syncope/sudden cardiac death

## Physical exam

- ↑ JVP, ± Kussmaul's sign (JVP not ↓ w/ inspir., classically seen in constrict. pericarditis)
- Cardiac: ± S<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, biatrial enlarge., ± mural thrombi, ± cavity oblit. w/ diast dysfxn; ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio, ↓ decel. time
- Cardiac MRI/PET: may reveal inflammation or evidence of infiltration (but nonspecific)
- Cardiac catheterization

Atria: **M's** or **W's** (prominent x and y descents)

Ventricles: **dip & plateau** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)

**Concordance** of LV & RV pressure peaks during respiratory cycle (vs. discordance in constrictive pericarditis; Circ 1996;93:2007)

- Endomyocardial biopsy if suspect infiltrative process; fat pad bx for amyloid
- Restrictive cardiomyopathy vs. constrictive pericarditis: see "Pericardial Disease"

## Treatment (in addition to Rx'ing underlying disease)

- Gentle diuresis. May not tolerate CCB or other vasodilators.
- Control HR (but can ↓ CO); maintain SR (helps filling). Digoxin ↑ arrhythmias in amyloid.
- Anticoagulation (particularly with AF or low CO)
- Transplantation for refractory cases

# VALVULAR HEART DISEASE

## AORTIC STENOSIS (AS)

### Etiology

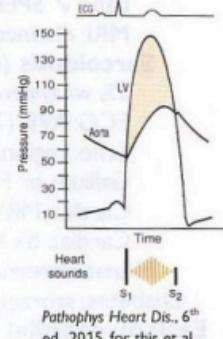
- Calcific:** predominant cause in Pts >70 y; risk factors include HTN, ↑ chol., ESRD
- Congenital** (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- Rheumatic heart disease** (AS usually accompanied by AR and MV disease)
- AS mimickers:** subvalvular (HCMP, subAo membrane)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

### Clinical manifestations (usually indicates AVA < 1 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 obstruct + diastolic dysfxn → pulm. edema, esp. if ↑ HR/AF (↓ LV fill)
- Acquired vWF disease (~20% of sev. AS): destruction of vWF; GI angiodysplasia
- Natural hx: usually slowly progressive (AVA ↓ ~0.1 cm<sup>2</sup>/y, but varies; Circ 1997;95:2262), until sx develop; mean survival based on sx: angina = 5 y; syncope = 3 y; CHF = 2 y

### Physical exam

- Midsystolic crescendo-decrescendo murmur at RUSB,** harsh, high-pitched, radiates to carotids, apex (holosystolic = Gallavardin effect), ↑ w/ passive leg raise, ↓ w/ standing & Valsalva. Dynamic outflow obstruction (HCM) is the reverse.
- Ejection click after S<sub>1</sub> 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: may see LVH, LAE, LBBB, AF (in late disease)
- CXR: cardiomegaly, AoV calcification, poststenotic dilation of ascending Ao, pulmonary congestion
- Echo:** valve morphology, jet velocity, estim pressure gradient (Δ) & calculate AVA, LVEF
- Cardiac cath:** usually to r/o CAD (in ~1/2 of calcific AS); for hemodyn. if disparity between exam & echo: ✓ pressure gradient (Δ) across AoV, calc AVA (underestim. if mod/sev AR)
- Dobutamine challenge** (echo or cath): if low EF and mean Δ <30, use 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)

Classification of Aortic Stenosis (Circ 2014;129:e521)

Stage	Sx	Severity	Max Jet Vel (m/s)	Mean Grad (mmHg)	AVA (cm <sup>2</sup> ) <sup>a</sup>	LVEF
n/a	N	Normal	1	0	3–4	nl
A	N	At risk	<2	<10	3–4	nl
B	N	Mild	2–2.9	<20	>1.5	nl
C1	N	Moderate	3–3.9	20–39	1–1.5	nl
		Severe	≥4	≥40	≤1.0	nl
C2	N	Very severe	≥5	≥60	≤0.8	nl
		Severe + ↓ EF	≥4	≥40	≤1.0	↓
D1		Severe	≥4	≥40	≤1.0	nl
D2	Y	Severe + low flow/Δ + ↓ EF <sup>b</sup>	<4	<40	≤1.0	↓
D3		Severe + low flow/Δ + nl EF <sup>c</sup>	<4	<40	≤1.0	nl

<sup>a</sup>AVA indexed to BSA <0.6 cm<sup>2</sup>/m<sup>2</sup> also severe; <sup>b</sup>DSE → max jet vel ≥4 & AVA ≤1.0; <sup>c</sup>small LV w/ ↓ stroke vol.

### Treatment (Circ 2014;129:e521; NEJM 2014;371:744; Lancet 2016;387:1312)

- Based on symptoms: once they develop, AVR needed. If asx, HTN can be cautiously Rx'd.
- AVR:** indicated in sx (stage D1); **asx severe + EF <50%** (stage C2); or asx severe (stage C1) and undergoing other cardiac surgery  
Reasonable if:
  - Asx severe** (stage C1) but either sx or ↓ BP w/ exercise (can carefully exercise asx AS to uncover sx, do not exercise sx AS) or **very severe**.
  - Sx severe w/ low flow/Δ w/ low EF** & response to dobuta (stage D2) or normal EF but AS felt to be cause of sx (stage D3)
  - Asx moderate AS (stage B) and undergoing cardiac surgery
- Transcatheter AoV replacement (TAVR, see below) indicated if surgical risk prohibitive or as reasonable alternative to surgery if medium (STS predicted 30-d mortality ~4–8%) or high (mortality 8–15%) operative risk

- Medical (if not AVR candidate or to temporize): careful diuresis prn, control HTN, maintain SR; digoxin if ↓ EF & HF or if AF; avoid venodilators (nitrates) & ⊖ inotropes ( $\beta$ B/CCB) if severe AS; avoid vigorous physical exertion once AS mod-severe; ? nitroprusside in HF w/ sev. AS, EF <35%, CI <2.2, & MAP >60 (NEJM 2003;348:1756) or if low flow w/ ↓ EF and HTN (Circ 2013;128:1349)
- IABP: stabilization, bridge to surgery
- Balloon AoV valvotomy (BAV): 50% ↑ AVA & ↓ peak  $\nabla$ , but 50% restenosis by 6–12 mo & ↑ risk of peri-PAV stroke/AR (NEJM 1988;319:125), ∴ bridge to AVR or palliation

### TAVR (transcatheter AoV replacement)

- Valves: balloon-expandable (Edwards SAPIEN) or self-expanding (Medtronic CoreValve)
- Approaches: most commonly retrograde via perc. transfemoral access; also retrograde via axillary art. or ascend.Ao (via small sternotomy & aortotomy). Alternatively antegrade transapical via small thoracotomy & LV puncture (if narrow iliofem art. or calcified Ao).
- Peri- & postprocedural complic.: low CO; annular rupture or coronary occlusion (both rare); local vascular; paravalvular leaks; CHB.
- Lifelong ASA + ? clopidogrel (or OAC) × 6 mo; ? subclinical valve thrombus in ~20%, ↓ w/ anticoag (NEJM 2015;373:2015)
- Outcomes w/ TAVR. In nonoperative Pts (ie, vs. med Rx): 44% ↓ mortality but still ~20% annual mortality in TAVR group (NEJM 2012;366:1696; JACC 2014;63:1972).  
In high-risk Pts vs. surg AVR (NEJM 2012;366:1686 & 2014;370:1790): mortality = (balloon-expand) or 26% ↓ (self-expand); ↑ vasc complic; ↑ early risk of stroke/TIA w/ balloon-expand; PPM required for CHB in ~20% w/ self-expand; paravalvular leaks in ~7%.  
In medium-risk Pts (NEJM 2016;374:1609): death/stroke ≈, ↑ vasc complic but ↓ bleeding, AKI, AF. If transfemoral 21%, ↓ death/stroke, whereas tended to be 21% ↑ if transapical.

## AORTIC REGURGITATION (AR)

### Etiology (Circ 2006;114:422)

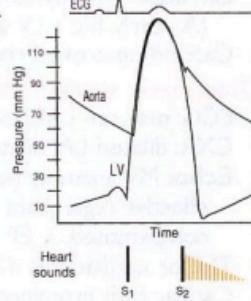
- Valve disease (43%): **rheumatic heart disease** (usually mixed AS/AR + MV disease); **bicuspid AoV** (natural hx:  $1/3$  → normal,  $1/3$  → AS,  $1/6$  → AR,  $1/6$  → endocarditis → AR); **infective endocarditis**; valvulitis (RA, SLE, certain anorectics & serotonergics, XRT)
- Root disease (57%): **HTN**, aortic aneurysm/dissection, annuloaortic ectasia (ie, Marfan), **aortic inflammation** (GCA, Takayasu's, ankylosing spond., reactive arthritis, syphilis)

### Clinical manifestations

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

### Physical exam

- Early diastolic decrescendo murmur at LUSB** (RUSB if dilated Ao root); ↑ w/ sitting forward, expir, handgrip; severity of AR ∝ duration of murmur (except in acute and severe late); **Austin Flint murmur**: mid-to-late diastolic rumble at apex (AR jet interfering w/ mitral inflow)
- Wide pulse pressure** due to ↑ stroke volume, hyperdynamic pulse; pulse pressure narrows in late AR with ↓ LV fxn; bisferiens (twice-beating) arterial pulse
- PMI diffuse and laterally displaced; soft  $S_1$  (early closure of MV); ±  $S_3$  (≠ ↓ EF but rather just volume overload in AR)



### Classic Eponymous Signs in Chronic AR (South Med J 1981;74:459)

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

### Diagnostic studies

- ECG: can see LVH, LAD, abnl repol; CXR: cardiomegaly ± ascending Ao dilatation

- Echo:** severity of AR (severe = regurg jet width  $\geq 65\%$  LVOT, regurg fraction  $\geq 50\%$ , regurg orifice  $\geq 0.3 \text{ cm}^2$ , flow reversal in descend. Ao; moderate = jet width 25–64%, regurg fraction 30–49%, regurg orifice 0.1–0.29  $\text{cm}^2$ ); LV size & fxn

### Treatment (Circ 2014;129:e521; Lancet 2016;387:1312)

- Acute decompensation (consider endocarditis as possible acute precipitant): surgery usually urgently needed for acute severe AR, which is poorly tolerated by LV IV afterload reduction (nitroprusside) and inotropic support (dobutamine)  $\pm$  chronotropic support ( $\uparrow$  HR  $\rightarrow$   $\downarrow$  diastole  $\rightarrow$   $\downarrow$  time for regurgitation) pure vasoconstrictors and IABP contraindicated
- In chronic AR, management decisions based on LV size and fxn (and before sx occur)
- Surgery** (AVR, replacement or repair if possible):
  - severe** and **sx** (if equivocal, consider stress test) **asx** and either **EF  $\leq 50\%$**  or **LV dilation** (LVESD  $> 50 \text{ mm}$ ) or undergoing cardiac surg
- Transcatheter AoV replacement (TAVR) being explored (JACC 2013;61:1577 & 2015;66:169)
- Medical therapy: **vasodilators** (nifedipine, ACEI/ARB, hydralazine) if severe AR w/ sx or LV dysfxn & not operative candidate or to improve hemodynamics before AVR; no clear benefit in asx severe AR w/ mild LV dilation & nl LV fxn (NEJM 2005;353:1342)

## MITRAL REGURGITATION (MR)

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

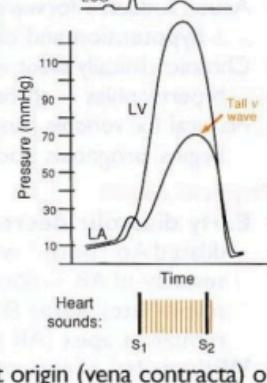
- Primary** (degeneration of valve apparatus)
  - leaflet abnl: myxomatous (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs (phen-fen), XRT
  - chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma
  - papillary muscle dysfxn b/c of ischemia or *rupture* during MI [usu. posteromedial papillary m. (supplied predominantly by PDA) vs. anterolateral (suppl. by diags & OMs)]
- Secondary (functional):** inferoapical papillary muscle displacement due to ischemic LV remodeling or DCM; HCM (JACC 2015;65:1231)

### Clinical manifestations

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

### Physical exam

- High-pitched, blowing, holosystolic murmur at apex;** radiates to axilla;  $\pm$  thrill;  $\uparrow$  w/ handgrip (Se 68%, Sp 92%),  $\downarrow$  w/ Valsalva (Se 93%) (NEJM 1988;318:1572)
- ant. leaflet abnl  $\rightarrow$  post. jet heard at spine
- post. leaflet abnl  $\rightarrow$  ant. jet heard at sternum
- $\pm$  diastolic rumble b/c  $\uparrow$  flow across valve
- Lat. displ. hyperdynamic PMI, obscured S<sub>1</sub>, widely split S<sub>2</sub> (A<sub>2</sub> early b/c  $\downarrow$  LV afterload, P<sub>2</sub> late if PHT);  $\pm$  S<sub>3</sub>
- Carotid upstroke brisk (vs. diminished and delayed in AS)



### Diagnostic studies (NEJM 2005;352:875)

- ECG: may see LAE, LVH,  $\pm$  atrial fibrillation
- CXR: dilated LA, dilated LV,  $\pm$  pulmonary congestion
- Echo:** MV anatomy (ie, etiol); MR severity: jet area, jet width at origin (vena contracta) or effective regurgitant orifice (ERO; predicts survival); LV fxn (EF should be supranormal if compensated,  $\therefore$  EF  $< 60\%$  w/ sev. MR = LV dysfxn)
- TEE or cardiac MR if TTE not sufficiently informative
- Cardiac cath: prominent PCWP c-v waves (not spec. for MR), LVgram for MR severity & EF

### Classification of Primary Mitral Regurgitation

Severity	Regurg. fraction	Jet area (% of LA)	Jet width (cm)	ERO ( $\text{cm}^2$ )	Angio*
Mild	<30%	<20	<0.3	<0.2	1+
Moderate	30–49%	20–40	0.3–0.69	0.2–0.39	2+
Severe†	$\geq 50\%$	>40	$\geq 0.70$	$\geq 0.40$	3/4+

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

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

### Treatment (Circ 2014;129:e521; Lancet 2016;387:1324)

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

- Chronic severe primary MR: surgery** (repair [preferred if feasible] vs. replacement indicated if sx & EF >30% or if asx & either EF 30–60% or LV sys. diam.  $\geq 40$  mm MV repair reasonable if asx & either EF >60% + LVESD <40 mm or new AF or PHT if AF, concomitant surgical ablation ↓ AF recurrence,  $\emptyset$  Δ stroke; consider for sx cntl or if planning no anticoag (NEJM 2015;372:1399)
- Severe secondary MR: consider surgery if NYHA III-IV; replacement results in more durable correction & ↓ HF & ↓ CV admissions than repair (NEJM 2016;374:344)
- In Pts undergoing CABG w/ moderate fxnal MR, annuloplasty ↓ MR but longer surgery, ↑ neurologic events, & no impact on fxnal status or mortality (NEJM 2016;374:1932)
- Percut. MV repair (Circ 2014;130:1712): edge-to-edge clip less effective than surgery but consider for sev. sx nonoperative Pt (NEJM 2011;364:1395); percut valve under study (JACC 2014;64:1814)
- If sx & EF <60% but not operative candidate: HF Rx ( $\beta$ B, ACEI,  $\pm$  aldo antag); ↓ preload w/ diuretics, NTG (espec. if ischemic MR) for sx relief  $\pm$  ↓ ERO; maintain SR
- Asymptomatic:  $\emptyset$  proven benefit of medical therapy;  $\beta$ B ↑ LV fxn (JACC 2012;60:833).

## MITRAL VALVE PROLAPSE (MVP)

### Definition and Etiology

- Billing of MV leaflet  $\geq 2$  mm above mitral annulus in parasternal long axis echo view
- Primary: sporadic or familial myxomatous proliferation of spongiosa of MV apparatus
- Secondary: trauma, endocarditis, congenital, CTD (eg, Marfan's, OI, Ehlers-Danlos)

### Clinical manifestations (usually asymptomatic)

- MR (MVP most common cause), endocarditis, embolic events, arrhythmias (rarely SCD)
- High-pitched, midsystolic click (earlier w/ ↓ preload)  $\pm$  mid-to-late systolic murmur
- No Rx per se [endocarditis Ppx no longer rec. (Circ 2007;116:1736)]; Rx MR as above

## MITRAL STENOSIS (MS)

### Etiology (Lancet 2012;379:953)

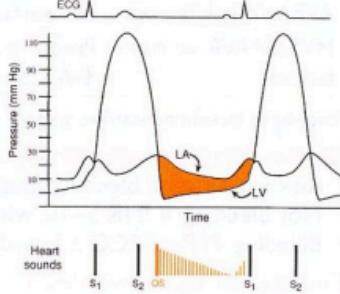
- Rheumatic heart disease (RHD):** fusion of commissures → “fish-mouth” valve from autoimmune rxn to  $\beta$  strep infxn; seen largely in developing world today
- Mitral annular calcification:** encroachment upon leaflets → fxnal MS; espec in ESRD
- Congenital, infectious endocarditis w/ large lesion, myxoma near MV, thrombus
- Valvulitis (eg, SLE, amyloid, carcinoid) or infiltration (eg, mucopolysaccharidoses)

### Clinical manifestations (Lancet 2009;374:1271)

- Dyspnea and pulmonary edema** (if due to RHD, sx usually begin in 30s) precipitants: exercise, fever, anemia, volume overload (incl. pregnancy), tachycardia, AF
- Atrial fibrillation:** onset often precipitates heart failure in Pts w/ MS
- Emolic events:** commonly cerebral, espec in AF or endocarditis
- Pulmonary: hemoptysis, frequent bronchitis (due to congestion), PHT, RV failure
- Ortner's syndrome: hoarseness from LA compression of recurrent laryngeal nerve

### Physical exam

- Low-pitched mid-diastolic rumble at apex w/ presystolic accentuation** (if not in AF); best heard in L lat decubitus position during expiration, ↑ w/ exercise; severity proportional to duration (not intensity) of murmur; loud S<sub>1</sub>
- 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 and immobile)



### Diagnostic studies

- ECG: **LAE** (“P mitrale”),  $\pm$  AF,  $\pm$  RVH
- CXR: **dilated LA** (flat L heart border, R double density, displaced L mainstem bronchus)
- Echo:** estimate pressure gradient (Δ), RVSP, valve area, valve echo score (0–16, based on leaflet mobility & thick, subvalvular thick., Ca<sup>++</sup>); exer. TTE (to assess Δ RVSP and Δ if sx & severity of MS at rest discrepant); TEE to assess for LA thrombus before PMBC
- Cardiac cath:** Δ, calculated MVA; LA tall a wave & blunted y descent; ↑ PA pressures

### Classification of Mitral Stenosis

Stage	Mean Δ (mmHg)	Pressure ½ time	MVA (cm <sup>2</sup> )	PA sys (mmHg)
Normal	0		4–6	<25
Mild-Mod	<5	100–149	1.6–2	<30
Severe	5–9	150–219	1.1–1.5	30–50
Very severe	≥10	≥220	≤1	>50

**Treatment** (Circ 2014;129:e521; Lancet 2016;387:1324)

- Medical: Na restriction, cautious diuresis, βB, AF control, sx-limited physical stress
- Antibiotic Ppx recommended if h/o RHD w/ valvular disease for 10 y or until age 40
- Anticoag: AF; prior embolism; LA clot; ? LA >55 mm or Large LA w/ spont contrast
- Mechanical intervention indicated if **heart failure sx w/ MVA ≤1.5**; reasonable if asx but very severe (MVA ≤1) and morphology favorable for PMBC; may consider PMBC if MVA >1.5 but hemodyn signif w/ exercise, or if asx but MVA ≤1.5 and new-onset AF
- Percutaneous mitral balloon commissurotomy (PMBC)**: preferred Rx if RHD; MVA doubles,  $\nabla \downarrow$  by 50%; ≈ MVR if valve score <8, Ø if mod-severe MR or LA clot
- Surgical (MV repair if possible, o/w replacement): consider in sx Pts w/ MVA ≤1.5 if PMBC unavailable/failed/contraindicated or valve morphology unsuitable
- Pregnancy: if NYHA class III/IV → PMBC, o/w medical Rx w/ low-dose diuretic & βB

**TRICUSPID REGURGITATION**

- 1° etiol: rheumatic, CTD, XRT, IE, Ebstein's, carcinoid, tumors, pacemaker leads
- Fxn etiol (most common): RV and/or PHT (may be 2° to L-sided dis.), RV dilation ± MI
- Holosystolic murmur, 3<sup>rd</sup>/4<sup>th</sup> ICS, ↑ w/ insp (Carvallo's sign); S<sub>3</sub>; prominent cv wave in JVP
- Consider repair, annuloplasty or replacement for sx and severe TR (eg, ERO ≥0.40 cm<sup>2</sup>); transcatheter system (provides surface for coaptation) under study (JACC 2015;66:2475)

**PROSTHETIC HEART VALVES****Mechanical (60%)**

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

**Bioprosthetic (40%)**

- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft
- Less durable, but min. thrombogenic; consider if >~70 y, lifespan <20 y, or Ø anticoag
- If 50–69 y, 2x reop but ½ bleeding or stroke vs. mech (JAMA 2014;312:1323 & 2015;313:1435)

**Physical exam**

- Crisp sounds ± soft murmur during forward flow (normal to have small  $\nabla$ )

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

- High-risk features: prior thromboembolism, AF, EF <30–35%, hypercoagulable
- Warfarin (Ø NOACs)**: mech MVR or high-risk mech AVR: INR 2.5–3.5. Low-risk mech AVR or high-risk bio MVR/AVR: INR 2–3. Consider in low-risk bio MVR/AVR for 1<sup>st</sup> 3 mo.
- + **ASA** (≤100 mg): all prosth. valves unless h/o GIB, uncontrolled HTN, erratic INR, or >80 y
- If thrombosis, ↑ intensity (eg, INR 2–3 → 2.5–3.5; 2.5–3.5 → 3.5–4.5; add ASA if not on)

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

AVR w/o risk factors	d/c warfarin 2–4 d before surg; restart 12–24 h after surg
MVR or AVR w/ risk factors	Preop: d/c warfarin, start UFH (preferred to LMWH) when INR <2 4–6 h preop: d/c UFH; postop: restart UFH & warfarin ASAP

Procedures include noncardiac surgery, invasive procedures, and major dental work

**Correction of overanticoagulation** (Circ 2014;129:e521)

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

**Endocarditis prophylaxis: for all prosthetic valves (see “Endocarditis”)****Complications**

- Structural failure (r/o endocarditis); mechanical valves: rare except for Bjork-Shiley; bioprost: up to 30% rate w/in 10–15 y, mitral > aortic; consider TAVR (JAMA 2014;312:162)
- Paravalvular leak (r/o endocarditis); small central jet of regurg is normal in mech. valves
- Obstruction from thrombosis (JACC 2013;62:1731) or pannus: ✓ TTE, TEE, CTA, or fluoro significantly symptomatic pannus ingrowth: remove w/ surgery
- thrombosis: surgery if L-sided valve & either severe sx or Ig (? ≥0.8 cm) thrombus; lytic successful in ~70% of L-sided thrombosis, but w/ 14% risk of stroke; consider UFH ± lytic (? low-dose tPA via slow infusion; JACC CV Imaging 2013;6:206) if mild sx & small clot burden or poor surg candidate; lytic reasonable for R-sided
- Infective endocarditis ± valvular abscess and conduction system dis. (see “Endocarditis”)
- Embolization (r/o endocarditis); risk highest 1<sup>st</sup> 90 d, ~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 (espec w/ caged-ball valves or paravalvular leak)

## GENERAL PRINCIPLES

## Anatomy

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

## Disease states

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

## PERICARDITIS AND PERICARDIAL EFFUSION

## Etiologies of Acute Pericarditis (JAMA 2015;314:1498)

<b>Idiopathic</b> (>80%)	Most presumed to be undiagnosed viral etiologies
<b>Infectious</b> (<5% can be confirmed infectious)	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); TB Fungal: Histo, Coccidio, Candida; Parasitic: Entamoeba, Echino
<b>Neoplastic</b> (<10%)	Common: metastatic (lung, breast, lymphoma, leukemia, RCC) Rare: primary cardiac & serosal tumors (mesothelioma)
<b>Autoimmune</b>	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, eosin GPA (Churg-Strauss), GPA (Wegener's) Drug-induced: procainamide, hydralazine, INH, CsA
<b>Uremia</b>	~5–13% of Pts prior to HD; ~20% occurrence in chronic HD Pts
<b>Cardiovascular</b>	STEMI, late post-MI (Dressler's syndrome); ascending AoD; chest trauma; postpericardiectomy; procedural complic. (ie, PCI, PPM)
<b>Radiation</b>	>40 Gy to mediastinum; acute or delayed; may be transudative
<b>Effusion w/o pericarditis</b>	CHF, cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis. Transudative.

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

- Pericarditis:** retrosternal CP, pleuritic, positional (often ↓ by sitting forward), → trapezius; may be absent in TB, neoplastic, XRT, or uremic; ± fever; ± s/s of systemic etiologies
- Effusion:** present in ~2/3 of Pts w/ pericarditis; ranges from axs to tamponade

## Physical exam

- Pericarditis:** multiphasic **friction rub** best heard at LLSB w/ diaphragm of stethoscope. Notoriously variable and evanescent leathery sound w/ up to 3 components: atrial contraction, ventricular contraction, ventricular relaxation (NEJM 2012;367:e20).
- Effusion:** distant heart sounds, dullness over left posterior lung field due to compressive atelectasis from pericardial effusion (Ewart's sign)

## Diagnostic studies (JAMA 2015;314:1498; EHJ 2015;36:2921)

- Need ≥2 of the following: chest pain (as noted above), friction rub, ECG findings, effusion
- ECG:** may show diffuse STE (concave up) & PR depression (except in aVR: ST ↓ & PR ↑), TWI; classically and in contrast to STEMI, TWI do not occur until STs normalize  
Stages: (I) STE & PR ↓; (II) ST & PR normalize; (III) diffuse TWI; (IV) Tw normalize  
ECG may show evidence of large effusion w/ low voltage & electrical alternans (beat-to-beat Δ in QRS amplitude and/or axis due to swinging heart)
- CXR: if lg effusion (>250 mL) → ↑ cardiac silhouette w/ "water-bottle" heart & epicardial halo
- Echocardiogram:** presence, size, & location of effusion; presence of tamponade physiology; pericarditis itself w/o spec. abnl (∴ echo can be nl), although can see pericardial stranding (fibrin or tumor); can also detect LV/RV dysfxn (myocarditis?)
- CT: will reveal pericardial effusions, but they often appear larger by CT than by echo.
- MRI:** may reveal pericardial thickening/inflammation, as well as myocardial involvement
- CK-MB or troponin (+ in ~30%; JACC 2003;42:2144) if myopericarditis. Consider CRP/ESR.

## Workup for effusion

- r/o infxn: usually apparent from Hx & CXR; ? value of ✓ acute and convalescent serologies
- r/o noninfectious etiologies: BUN, Cr, ANA, RF, HIV, relevant malignancy evaluation
- Pericardiocentesis if suspect infxn or malignancy or large effusion (>2 cm) or recurrent ✓ cell counts, TP, LDH, glc, Gram stain & Cx, AFB, cytology  
ADA, PCR for MTb, and specific tumor markers as indicated by clinical suspicion  
"exudate": TP >3 g/dL, TP<sub>eff</sub>/TP<sub>serum</sub> >0.5, LDH<sub>eff</sub>/LDH<sub>serum</sub> >0.6 or glc <60 mg/dL;  
high Se (~90%) but very low Sp (~20%); overall low utility (Chest 1997;111:1213)
- Pericardial bx if suspicion remains for malignancy or TB

**Treatment of pericarditis (JAMA 2015;314:1498; EHJ 2015;36:2921)**

- High-dose **NSAID** (eg, ibuprofen 600–800 mg tid) or ASA (eg, 650–1000 mg tid)  $\times$  7–14 d then taper over wks; ASA preferred over NSAID in acute MI; consider PPI to  $\downarrow$  risk of GIB
- Add colchicine** 0.5 mg bid (qd if  $\leq 70$  kg)  $\times$  3 mo;  $\downarrow$  risk of refractory or recurrent pericarditis by 50% (NEJM 2013;369:1522)
- Avoid steroids except for systemic autoimmune disorder, uremic, preg., NSAIDs contraindicated, or refractory idiopathic dis. Appear to  $\uparrow$  rate of pericarditis recurrence (Circ 2008;118:667). If due to TB, steroids  $\downarrow$  risk of constriction (NEJM 2014;371:1121).
- Avoid anticoagulants (although no convincing data that  $\uparrow$  risk of hemorrhage/tamponade)
- Infectious effusion  $\rightarrow$  pericardial drainage (preferably surgically) + systemic antibiotics
- Acute idiopathic pericarditis self-limited in 70–90% of cases
- Recurrent pericarditis (Circ 2007;115:2739)  
risk factors: subacute, Ig effusion/tamponade, T  $>38^{\circ}\text{C}$ , lack of NSAID response after 7 d treatment: colchicine 0.5 mg bid  $\times$  6 mo (Annals 2011;155:409 & Lancet 2014;383:2232)
- Recurrent effusions: consider pericardial window (percutaneous vs. surgical)

**PERICARDIAL TAMPOONADE****Etiology**

- Any cause of pericarditis but espec, **malignancy**, **infectious**, uremia, ascending AoD, myocardial rupture, periprocedural complication, trauma, post-cardiotomy
- Rapidly accumulating effusions most likely to cause tamponade as no time for pericardium to stretch (eg, to  $\uparrow$  compliance) and accommodate  $\uparrow$  intrapericardial fluid volume

**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 physio)  
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 & pulse 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 (EHJ 2014;35:2279)**

- Beck's triad** (present in minority of cases): **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  $\geq 10$  mmHg during inspiration  
 $\oplus$  LR 3.3 (5.9 if pulsus  $>12$ ),  $\ominus$  LR 0.03  
Ddx = PE, hypovolemia, severe COPD, constriction ( $-1/3$ ), RV infarct  
? absent if pre-existing  $\uparrow$  LVEDP, irregular rhythm, severe AI, ASD, regional tamponade
- Distant heart sounds (28%),  $\pm$  pericardial friction rub (30%)
- Tachypnea and orthopnea but clear lungs

**Diagnostic studies**

- ECG:  $\uparrow$  HR,  $\downarrow$  voltage (seen in 42%), electrical alternans (20%),  $\pm$  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 (constriction from visceral pericardium; NEJM 2004;350:469) or myocardial dysfxn (eg, from concomitant myocarditis)

**Treatment (EHJ 2014;35:2279)**

- Volume (but be careful as overfilling can worsen tamponade) and  $\oplus$  inotropes (avoid BB)
- Avoid vasoconstrictors as will  $\downarrow$  stroke volume & potentially  $\downarrow$  HR
- Avoid positive pressure ventilation as it can further impair cardiac filling (Circ 2006;113:1622)
- Pericardiocentesis** (except if due to aortic/myocardial rupture for which emergent surgery treatment of choice; if too unstable, consider small pericardiocentesis to prevent PEA)
- Surgical drainage considered if fluid rapidly reaccumulates, loculated, or hemorrhagic

**Etiology** (Circ 2011;124:1270)

- Any cause of pericarditis (~1–2% incidence overall after acute pericarditis)
- Highest risk w/ **TB, bacterial, neoplastic, XRT**, connective tissue, postcardiac surgery
- Viral/idiopathic**, as most common cause of pericarditis, also account for signif proportion

**Pathophysiology**

- Adhesion of visceral and parietal pericardial layers → rigid pericardium that limits diastolic filling of ventricles → ↑ systemic venous pressures
- Venous return is limited only after early rapid filling phase; ∴ rapid ↓ in RA pressure with atrial relaxation and opening of tricuspid valve and **prominent x and y descents**
- Kussmaul sign: JVP does not decrease with inspiration (↑ venous return with inspiration, but negative intrathoracic pressure not transmitted to heart because of rigid pericardium)

**Clinical manifestations** (NEJM 2011;364:1350)

- Right-sided > left-sided heart failure (systemic congestion > pulmonary congestion)

**Physical exam**

- ↑ **JVP with prominent y descent**,  $\oplus$  **Kussmaul sign** [Ddx: tricuspid stenosis, acute cor pulmonale, RV dysfxn (CMP, RV MI), SVC syndrome]
- Hepatosplenomegaly, ascites, peripheral edema. Consider in Ddx of idiopathic cirrhosis.
- PMI usually not palpable, **pericardial knock**, usually no pulsus paradoxus

**Diagnostic studies**

- ECG: nonspecific, AF common (up to 33%) in advanced cases
- CXR: calcification (MTb most common), espec in lateral view (although not specific)
- Echocardiogram:  $\pm$  thickened pericardium, "**septal bounce**" = abrupt displacement of septum during rapid filling in early diastole
- Cardiac catheterization: atria w/ **Ms or Ws** (prominent x and y descents) ventricles: **dip-and-plateau** or **square-root sign** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)  
discordance between LV & RV pressure peaks during respiratory cycle (Circ 1996;93:2007)
- CT or MRI: thickened pericardium ( $>4$  mm; Se ~80%) w/ tethering (Circ 2011;123:e418)

**Treatment**

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

**Constrictive Pericarditis vs Restrictive Cardiomyopathy**

Evaluation	Constrictive pericarditis	Restrictive cardiomyopathy
Physical exam	$\oplus$ Kussmaul sign Absent PMI $\oplus$ Pericardial knock	$\pm$ Kussmaul sign Powerful PMI, $\pm$ S <sub>3</sub> and S <sub>4</sub> $\pm$ Murmurs of MR, TR
ECG	$\pm$ Low voltage	Low voltage if infiltrative myopathy $\pm$ Conduction abnormalities
Echocardiogram	<b>Respirophasic variation</b> (25–40%): inspir. → ↑ flow across TV and ↓ flow across MV E' (tissue velocity) nl/↑ ( $>12$ cm/sec)  <b>Expir.</b> hepatic vein flow reversal <b>Septal bounce in early diastole</b> Normal wall thickness	<10% respirophasic variation Slower peak filling rate Longer time to peak filling rate E' ↓ ( $<8$ cm/sec) (Se 95%, Sp 96%; HF Rev 2013;18:255)  <b>Inspir.</b> hepatic vein flow reversal <b>Batrial enlargement</b> $\pm$ ↑ wall thickness
CT/MRI	Usually w/ <b>thickened pericardium</b>	Normal pericardium
NT-proBNP	Variable	Typically ↑/↑↑ (JACC 2005;45:1900)
	Prominent x and y descents (more so in constriction)  Dip-and-plateau sign (more so in constriction)	
Cardiac catheterization	LVEDP = RVEDP RVSP $<55$ mmHg (Se 90%, Sp 29%) RVEDP $>1/3$ RVSP (Se 93%, Sp 46%) <b>Discordance</b> of LV & RV pressure peaks during respiratory cycle <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> (esp. 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> (fibrosis, infiltration, hypertrophy)

# HYPERTENSION

## JNC 8 Classification

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

## Ambulatory Thresholds

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

(Circ 2005;111:697)

BP in mmHg. Average  $\geq 2$  measurements  $> 1\text{--}2$  min apart. Confirm stage 1 w/in 1–4 wk; can Rx stage 2 immediately (J Clin HTN 2014;16:14)

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

- Prevalence  $\sim 30\%$  in U.S. adults,  $\geq 44\%$  in African-Americans; M = F
- Of those with HTN,  $\sim 3/4$  were treated,  $\sim 1/2$  achieve target BP,  $\sim 1/6$  were unaware of dx
- **Etiologies**
  - **Essential** (95%): onset 25–55 y;  $\oplus$  FHx. Unclear mechanism but ? additive microvascular renal injury over time w/ contribution of hyperactive sympathetics (NEJM 2002;346:913). ↑ Age → ↓ art compliance → HTN. Genetics + environment involved (Nature 2011;478:103).
  - **Secondary:** Consider if Pt <30 y or if sudden onset, severe, refractory HTN

## Secondary Causes of Hypertension

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

## Standard workup

- Goals: (1) identify CV risk factors; (2) seek 2° causes; (3) assess for target-organ damage
- History: CAD, HF, TIA/CVA, PAD, DM, renal insufficiency, sleep apnea, preeclampsia;  $\oplus$  FHx for HTN; diet, Na intake, smoking, alcohol, prescription and OTC meds, OCP
- Physical exam: ✓ **BP in both arms**; funduscopic exam, BMI, cardiac (LVH, murmurs), vascular (bruits, radial-femoral delay), abdominal (masses or bruits), neuro exam
- Testing: K, BUN, Cr, Ca, glucose, Hct, U/A, lipids, TSH, urinary albumin:creatinine (if ↑ Cr, DM, peripheral edema), ? renin, ECG (for LVH), CXR, TTE (eval for valve abnl, LVH)
- Ambulatory BP monitoring (ABPM): consider for episodic, resistant, or white coat HTN

## Complications of HTN

- Neurologic: **TIA/CVA**, ruptured aneurysms, vascular dementia
- Retinopathy: stage I = arteriolar narrowing; II = copper-wiring, AV nicking; III = hemorrhages and exudates; IV = papilledema
- Cardiac: **CAD, LVH, HF, AF**
- Vascular: aortic dissection, aortic aneurysm (HTN = key risk factor for aneurysms)
- Renal: proteinuria, **renal failure**

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

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

- Lifestyle modifications** (each may ↓ SBP ~5 mmHg)
  - weight loss: goal BMI 18.5–24.9; aerobic exercise: ≥30 min exercise/d, ≥5 d/wk
  - diet: rich in fruits & vegetables, low in saturated & total fat (DASH, NEJM 2001;344:3)
  - limit Na: ≤2.4 g/d (ideally ≤1.5 g/d); maintain K intake (NEJM 2007;356:1966 & 2010;362:2102)
  - limit alcohol: ≤2 drinks/d in men; ≤1 drink/d in women & lighter-wt Pts; avoid NSAIDs

### • Pharmacologic options

**Pre-HTN:** ARB prevents onset of HTN, no ↓ in clinical events (NEJM 2006;354:1685)

**HTN:** choice of therapy controversial, concomitant disease and stage may help guide Rx

**uncomplicated:** CCB, ARB/ACEI, or thiazide (chlorthalidone preferred) are 1<sup>st</sup> line (NEJM 2009;361:2153). βB not 1<sup>st</sup> line (Lancet 2005;366:1545).

For non-black Pts <60 y: reasonable to start w/ ARB or ACEI, then add CCB or thiazide if needed, and then add remaining class if still needed

For black, elderly, and ? obese Pts (all of whom more likely to be salt sensitive): reasonable to start with CCB or thiazide, then add either the other 1<sup>st</sup> choice class or ARB or ACEI if needed, and then all 3 classes if still needed

**+CAD** (Circ 2015;131:e435): ACEI or ARB (NEJM 2008;358:1547); ACEI+CCB superior to ACEI+thiazide (NEJM 2008;359:2417) or βB+diuretic (Lancet 2005;366:895); may require βB and/or nitrates for anginal relief; if h/o MI, βB ± ACEI/ARB ± aldo antag (see "ACS")

**+HF:** ACEI/ARB/ARNi, βB, diuretics, aldosterone antagonist (see "Heart Failure")

**+2<sup>o</sup> stroke prevention:** ACEI ± thiazide (Lancet 2001;358:1033)

**+diabetes mellitus:** consider ACEI or ARB; can also consider thiazide or CCB

**+chronic kidney disease:** ACEI or ARB (NEJM 1993;329:1456 & 2001;345:851 & 861)

- Tailoring therapy: if stage 1, start w/ monoRx; if stage 2, consider starting w/ combo (eg, ACEI + CCB; NEJM 2008;359:2417); start at ½ max dose; after 2–3 wk, uptitrate or add drug

- Pregnancy:** methyldopa, labetalol, & nifedipine pref. Hydral OK; avoid diuretics; Ø ACEI/ARB. Targeting DBP 85 vs. 105 safe and ↓ severe HTN (NEJM 2015;372:407).

### Resistant HTN (BP > goal on ≥3 drugs incl diuretic; JAMA 2014;311:2216)

- Exclude: 2<sup>o</sup> causes (see table) and pseudoresistance: inaccurate measure (cuff size), diet noncomp (↑ Na), poor Rx compliance/dosing, white coat HTN (✓ ABPM)
- Ensure effective diuresis dosing (chlorthalidone > HCTZ, loop > thiazide if eGFR <30)
- Can add aldosterone antagonist (Lancet 2015;386:2059), β-blocker (particularly vasodilators like labetalol, carvedilol, or nebivolol), α-blocker, or direct vasodilator

## HYPERTENSIVE CRISES

- Hypertensive emergency:** ↑ BP → acute target-organ ischemia and damage
  - neurologic damage: encephalopathy, hemorrhagic or ischemic stroke, papilledema
  - cardiac damage: ACS, HF/pulmonary edema, aortic dissection
  - renal damage: proteinuria, hematuria, acute renal failure; scleroderma renal crisis
  - microangiopathic hemolytic anemia; preeclampsia-eclampsia
- Hypertensive urgency:** SBP >180 or DBP >120 (?110) w/ min. or Ø target-organ damage

### Precipitants

- Progression of essential HTN ± medical noncompliance (espc clonidine) or Δ in diet
- Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia
- Endocrine: pheochromocytoma, Cushing's
- Sympathomimetics: cocaine, amphetamines, MAO inhibitors + foods rich in tyramine

### Treatment (Chest 2007;131:1949)

- Tailor goals to clinical context. Treat Ao dissection aggressively. Do not treat HTN in acute ischemic stroke unless lysis planned or extreme BP (>220/120).
- Emergency: ↓ MAP by ~25% in mins to 2 h w/ IV agents (may need arterial line for monitoring); goal DBP <110 w/in 2–6 h, as tolerated
- Urgency: ↓ BP to ≤160/100 in hrs using PO agents; goal normal BP in ~1–2 d
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

### Drugs for Hypertensive Crises

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

\*Metabolized to cyanide → Δ MS, lactic acidosis, death. Limit use of very high doses (8–10 µg/kg/min) to <10 min.

Monitor thiocyanate levels. Hydroxocobalamin or sodium thiosulfate infusion for treatment of cyanide toxicity.

# AORTIC ANEURYSMS

## Definitions

- **True aneurysm** ( $\geq 50\%$  dilation of all 3 layers of aorta) vs. **false** (rupture within adventitia)
- **Location:** root (annuloaortic ectasia), thoracic aortic aneurysm (TAA), thoracoabdominal aortic aneurysm (TAAA), abdominal aortic aneurysm (AAA)
- **Type:** fusiform (circumferential dilation) vs. saccular (localized dilation of aortic wall)

## Epidemiology (Circ 2010;121:e266, 2011;124:2020; Nat Rev Cardiol 2011;8:92)

- **TAA:** ♂:♀ 2:1; ~60% root/ascending; 40% desc.
- **AAA:** ~4–8% prev in those >60y; 5x more common in ♂; mostly infrarenal

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

- Medial degen and/or ↑ wall stress; wall stress  $\propto [(\Delta P \times r) / (\text{wall thickness})]$  (Laplace's law)
- **TAA:** medial degeneration (muscle apoptosis, elastin fiber weakening); a/w CTD, aortitis
- **AAA:** long-standing HTN + athero/inflammation → medial weakening
- Classic **clinical risk factors:** HTN, atherosclerosis, smoking, age, ♂
- **CTD** (Marfan, Ehlers-Danlos type IV, Loeys-Dietz); **congenital** (bicuspid AoV, Turner's aortitis (Takayasu's GCA, spondyloarthritis, IgG4, syphilis); trauma

## Screening (Circ 2010;121:e266 & 2011;124:2020; Annals 2014;161:281; JAMA 2015;313:1156)

- **TAA:** if bicuspid AoV or 1° relative w/: (a) TAA or bicuspid AoV, (b) CTD as above
- **AAA:** ✓ for pulsatile abd mass; U/S ♂ >60 y w/ FHx of AAA & ♂ 65–75 y w/ prior tobacco

## Diagnostic studies (Circ 2010;121:e266 & 2011;124:2020)

- **Contrast CT:** quick, noninvasive, high Se & Sp for all aortic aneurysms
- **TTE/TEE:** TTE most useful for root and proximal Ao; TEE can visualize other sites of TAA
- **MRI:** favored over CT for AoRoot imaging; useful in AAA but time-consuming; noncontrast "black blood" MR to assess aortic wall
- **Abdominal U/S:** screening/surveillance test of choice for infrarenal AAA

## Treatment (Circ 2006;113:e463; 2008;117:1883; 2010;121:e266; NEJM 2014;371:2101)

- Goal is to prevent rupture (50% mortality prior to hospital) by modifying risk factors
- **Risk factor modification:** smoking cessation; LDL-C <70 mg/dL
- **BP control:** βB ( $\downarrow dP/dt$ )  $\downarrow$  aneurysm growth (NEJM 1994;330:1335); **ACEI** a/w  $\downarrow$  rupture risk (Lancet 2006;368:659); **ARB** may  $\downarrow$  rate of aortic root growth in Marfan (NEJM 2008;358:2787)
- Mod CV exercise OK, no burst activity requiring Valsalva maneuvers (eg, heavy lifting)
- **Indications for surgery** (individualized based on FHx, body size, gender, anatomy)
  - **TAA:** sxs, ascending Ao  $>5.5$  cm (4–5 cm if Marfan, bi-AoV, L-D, vascular EDS); size may not predict repair benefit; descending Ao  $>6$  cm;  $\geq 4.5$  cm and planned AoV surgery
  - **AAA:** sx; infrarenal  $>5.5$  cm; consider  $\geq 5.0$  cm in ♀;  $\uparrow >0.5$  cm/y; inflam/infxn

## Endovascular repair (EVAR) (NEJM 2008;358:494; Circ 2011;124:2020 & 2015;313:1291)

- Requires favorable aortic anatomy
- **TEVAR** (thoracic EVAR) for descending TAA  $\geq 5.5$  cm may  $\downarrow$  periop morbidity and possibly mortality (Circ 2010;121:2780; JACC 2010;55:986; J Thorac CV Surg 2010;140:1001 & 2012;144:604)
- **AAA:** guidelines support open repair or EVAR for infrarenal AAA in good surg candidates  $\downarrow$  short-term mort, bleeding, LOS; but long-term graft complic. (3–4%/y; endoleak, need for reintervention, rupture) necessitate periodic surveillance, with no proven  $\Delta$  in overall mortality in trials, except ? in those <70 y (NEJM 2010;362:1863, 1881 & 2012;367:1988)  
In observ. data, EVAR a/w  $\uparrow$  early survival but  $\uparrow$  long-term rupture (NEJM 2015;373:328)  
In Pts unfit for surgery or high periop risks:  $\downarrow$  aneurysm-related mortality but no  $\Delta$  in overall mortality over med Rx (NEJM 2010;362:1872). EVAR noninferior (? superior) to open repair in ruptured AAA w/ favorable anatomy (Ann Surg 2009;250:818).

## Complications (Circ 2010;121:e266; Nat Rev Cardiol 2011;8:92)

- **Pain:** gnawing chest, back or abdominal pain; new or worse pain may signal rupture
- **Rupture:** risk  $\uparrow$  w/ diameter, ♀, current smoking, HTN
  - **TAA:** ~2.5%/y if <6 cm vs. 7%/y if >6 cm
  - **AAA:** ~1%/y if <5 cm vs. 6.5%/y if 5–5.9 cm; ~80% mortality at 24 h
- **Aortic insufficiency (TAA), CHF, acute aortic syndromes** (qv)
- **Thromboembolic ischemic events** (eg, to CNS, viscera, extremities)
- **Compression of adjacent structures** (eg, SVC, trachea, esophagus, laryngeal nerve)

## Follow-up (Circ 2010;121:e266; Nat Rev Cardiol 2011;8:92; JAMA 2013;309:806)

- Expansion rate ~0.1 cm/y for TAA, ~0.3–0.4 cm/y for AAA
- AAA: <4 cm q2–3 y; 4–5.4 cm q6–12 mos; more often if rate of expansion >0.5 cm in 6 mo
- TAA: 6 mo after dx to ensure stable, and if stable, then annually (Circ 2005;111:816)
- Screen for CAD, PAD and aneurysms elsewhere, espec popliteal. About 25% of Pts w/ TAA will also have AAA, and 25% of AAA Pts will have a TAA; consider pan-Ao imaging.

# ACUTE AORTIC SYNDROMES

AORTA 1-31

**Definitions** (Circ 2010;121:e266; Eur Heart J 2012;33:26)

- Aortic dissection:** intimal tear → blood extravasates into Ao media (creates false lumen)
- Intramural hematoma (IMH):** vasa vasorum rupture → medial hemorrhage that does not communicate with aortic lumen; 6% of aortic syndromes; clinically managed as AoD
- Penetrating ulcer:** atherosclerotic plaque penetrates elastic lamina → medial hemorrhage

**Classification (proximal twice as common as distal)**

- Proximal:** involves ascending Ao, regardless of origin (= Stanford A, DeBakey I & II)
- Distal:** involves descending Ao only, distal to L subclavian art. (= Stanford B, DeBakey III)

**Risk factors** (Lancet 2015;385:800)

- Classic** (in older Pts): **HTN** (h/o HTN in >70% of dissections); **age** (60s–70s), **sex** (~65% ♂); **smoking**; ↑ lipids. **Acute ↑ BP:** cocaine, Valsalva (eg, weightlifting).
- Genetic or acquired predisposition:** **CTD** (Marfan, Loeys-Dietz, Ehlers-Danlos type IV); **congenital anomaly** (bicuspid AoV, coarct [eg, Turner's syndrome], PCKD); **aortitis** (Takayasu's, GCA, Behcet's, syphilis, TB); **pregnancy** (typically 3<sup>rd</sup> trimester)
- Trauma:** blunt, decel. injury (eg, MVA); IABP, cardiac or aortic surgery, cardiac cath

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

Feature	Proximal	Distal
<b>"Aortic" pain</b> (abrupt, severe, tearing or ripping quality, maximal at onset [vs. crescendo for ACS])	94% (chest, back)	98% (back, chest, abd)
<b>Syncope</b> (often due to tamponade)	13%	4%
<b>HF</b> (usually due to acute AI)	9%	3%
<b>CVA</b>	6%	2%
<b>HTN</b>	36%	70%
<b>HoTN or shock</b> (tamponade, AI, MI, rupture)	25%	4%
<b>Pulse deficit</b> (if involves carotid, subclavian, fem)	19%	9%
<b>AI murmur</b>	44%	12%

\*S/S correlate w/ affected branch vessels &amp; distal organs; may Δ as dissection progresses

**Initial evaluation & diagnostic studies** (Circ 2010;121:e266; JACC CV Img 2014;7:406)

- H&P, incl. bilat BP & radial pulses for symmetry; ECG w/ STE if propagates to cor
- CXR: abnl in 60–90% [↑ mediast. (absence ⊖ LR 0.3), L pl effusion] but cannot r/o AoD
- CT:** quick and available, Se ≥93%, Sp 98%; facilitates "triple rule-out" ACS vs. PE vs. AoD
- MRI:** Se & Sp >98%, but time-consuming test & not readily available
- TEE:** Se >95% prox, 80% for distal; can assess cors/peri/AI; "blind spot" behind trachea
- ⊖ Initial imaging but high clinical suspicion → further studies ( $\frac{2}{3}$  w/ AoD have ≥2 studies)
- D-dimer:** Se/NPV ~97%, Sp ~47%; ? <500 ng/mL to r/o dissec (Circ 2009;119:2702) but not in Pts at high clinical risk (Annals EM 2015;66:368); does not r/o IMH

**Treatment** (Circ 2010;121:1544; JACC 2013;61:1661; Lancet 2015;385:800)

- ↓ dP/dt targeting HR <60 & central BP <120 (or lowest that preserves perfusion; r/o pseudohypotension, eg, arm BP ↓ due to subclavian dissection; use highest BP reading)
- First IV βB** (eg, esmolol, labetalol) to blunt reflex ↑ HR & inotropy in response to vaso-dilators; verap/dilt if βB contraindic; **then ↓ SBP w/ IV vasodilators** (eg, nitroprusside)
- If HoTN:** urgent surgical consult, IVF to achieve euvoolemia, pressors to keep (MAP 70 mmHg); r/o complication (eg, tamponade, contained rupture, severe AI)
- Proximal:** surgery considered in **all acute** and in chronic if c/b progression, AI or aneurysm
- Distal:** med Rx unless complication (see below), however pre-emptive endovascular intervention may ↓ late complications, mort (JACC 2013;61:1661; Circ Cardiovasc Int 2013;6:407)

**Complications (occur in ~20%;** Circ 2010;121:e266; Lancet 2015;385:800)

- Freq assess (sx, BP, UOP), pulses, labs (Cr, Hb, lactic acid), imaging (~7 d or sooner if Δs)
- Uncontrolled BP or persistent pain** may indicate complication/extension
- Progression:** propagation of dissection, ↑ aneurysm size, ↑ false lumen size
- Rupture:** pericardial sac → tamponade (avoid pericardiocentesis unless PEA); blood in pleural space, mediast., retroperitoneum; ↑ in hematoma on imaging portends rupture
- Malperfusion** (partial or complete obstruction of branch artery)
  - coronary → MI (usually RCA → IMI, since dissection often along outer Ao curvature); innominate/carotid → CVA, Horner; intercostal/lumbar → spinal cord ischemia/paraplegia; innominate/subclavian → upper extremity ischemia; iliac → lower extremity ischemia; celiac/mesenteric → bowel ischemia; renal → AKI or gradually ↑ Cr, refractory HTN
- AI:** due to annular dilatation or disruption or displacement of leaflet by false lumen
- Mortality: historically ~1%/h × 48 h for acute prox AoD w/ 10–35% at 30 d
- Long-term serial imaging** (CT or MRI; latter may be preferred due to lower cumulative radiation exposure) at 1, 3, and 6 mo, and then annually (18 mo, 30 mo, etc.)

# ARRHYTHMIAS

## BRADYCARDIAS, AV BLOCK AND AV DISSOCIATION

### Sinus bradycardia (SB) (NEJM 2000;342:703)

- Etiologies: **meds** (incl βB, CCB, amio, Li, dig), ↑ **vagal tone** (incl. athletes, sleep, IMI), **metabolic** (hypoxia, sepsis, myxedema, hypothermia, ↓ glc), OSA, ↑ ICP
- Treatment: if no sx, none; atropine, β<sub>1</sub> agonists (short-term) or pacing if symptomatic
- Most common cause of sinus pause is *blocked premature atrial beat*

### Sick sinus syndrome (SSS)

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

## AV Block

Type	Features
1°	Prolonged PR (>200 ms), all atrial impulses conducted (1:1).
2° Mobitz I (Wenckebach)	Progressive ↑ PR until impulse not conducted (→ "grouped beating"). Due to <b>AV node abnl</b> : ischemia (IMI), inflammation (myocarditis, endocarditis, MV surgery), high vagal tone (athletes), drug induced. Classically (~50%), absolute ↑ in PR decreases over time (→ ↓ RR intervals, duration of pause <2x preceding RR interval); nl QRS. AVB usually worsens w/ carotid sinus massage, improves w/ atropine. Often paroxysmal/nocturnal/asx, no Rx required.
2° Mobitz II	Blocked impulses w/ consistent PR interval, often prolonged QRS. Due to <b>His-Purkinje abnl</b> : ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation/AoV surgery/TAVR. AVB may improve w/ carotid sinus massage, may worsen w/ atropine. May progress to 3° AVB. Pacing pads; transven. pacing often required.
3° (complete)	No AV conduction. Escape, if present, narrow (jxnal) or wide (vent.)

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

### AV dissociation

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

### Temporary pacing wires

- Consider w/ bradycardia with hemodyn instability or unstable escape rhythm when perm pacer not readily available. Risks: infxn, RV perf, VT, PTX, CHB if existing LBBB, etc.
- Consider instead of PPM for sx brady from reversible cause (βB/CCB O/D, Lyme, SBE, myocarditis, s/p cardiac surgery/trauma/TAVR), TdP, acute MI (sx brady/high-grade AVB)

## SUPRAVENTRICULAR TACHYCARDIAS (SVTs)

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

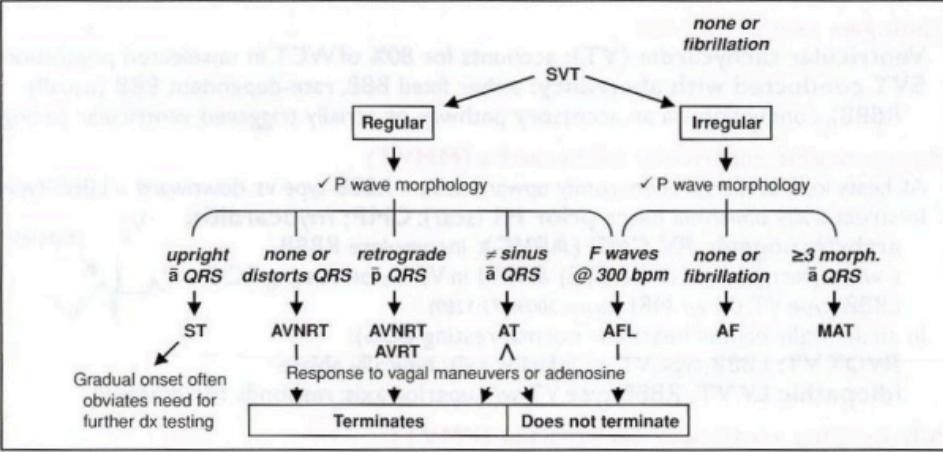
### Common Etiologies of SVT (NEJM 2012;367:1438)

Type	Features
Atrial	Sinus tachycardia (ST) Caused by pain, fever, hypovolemia, hypoxia, PE, anemia, anxiety, withdrawal, β-agonists, etc.
	Atrial tachycardia (AT) Originate at site in atria other than SA node. Seen w/ CAD, COPD, ↑ catechols, EtOH, dig.
	Multifocal atrial tachycardia (MAT) ↑ automaticity at multiple sites in the atria; seen with underlying pulmonary disease
	Atrial flutter (AFL) Clockwise or counterclockwise macroreentry, usually w/in right atrium
	Atrial fibrillation (AF) Chaotic atrial activation with rapid, irregular AVN bombardment; often from pulmonary veins
AV Jxn	AV nodal reentrant tach (AVNRT) Reentrant circuit using dual pathways w/in AVN
	Atrioventricular reciprocating tachycardia (AVRT) Reentry using AVN & access. path. May show preexcitation (WPW) or not (concealed access. path.). Can be ortho or antidromic (see below).
	Nonparoxysmal junctional tachycardia (NPJT) ↑ jxnal automaticity. May see retro. P, AV dissoc. A/w myo/endocarditis, cardiac surg, IMI, dig.

## Diagnosis of SVT Type (NEJM 2012;367:1438)

<b>Onset</b>	Abrupt on/off argues against sinus tachycardia
<b>Rate</b>	Not dx as most can range from 140–250 bpm, but: ST usually <150; AFL often conducts 2:1 → vent. rate 150; AVNRT & AVRT usually >150
<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 QRS (RP interval >100 ms favors AVRT vs. AVNRT) NPJT: either no P wave or retrograde P wave similar to AVNRT Fibrillation or no P waves → AF Saw-toothed "F" waves (best seen in inferior leads & V <sub>1</sub> ) → AFL
<b>Response to vagal stim. or adenosine</b>	Slowing of HR often seen with ST, AF, AFL, AT, whereas re-entrant rhythms (AVNRT, AVRT) may abruptly terminate (classically w/ P wave after last QRS) or no response. Occ AT may terminate. In AFL & AF, ↑ AV block may unmask "F" waves or fibrillation

Figure 1-4 Approach to SVT (adapted from NEJM 2012;367:1438)



## Treatment of SVT (Circ 2016;133:e506)

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

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

- **Catheter ablation:** high overall success rate (AFL/AVNRT ~95%, AVRT ~90%, AF ~80%) complications: stroke, MI, bleeding, perforation, conduction block (JAMA 2007;290:2768)

## ACCESSORY PATHWAYS (WOLFF-PARKINSON-WHITE)

## Definitions

- **Accessory pathway** (bypass tract) of conducting myocardium connecting atria & ventricles, allowing impulses to bypass normal AVN delay
- **Preexcitation (WPW) pattern:** ↓ PR interval, ↑ QRS width w/ δ wave (slurred onset, can be subtle). ST & Tw abnl (can mimic old IMI).  
only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde, then ECG will be normal during SR; "concealed" bypass tract)  
PAC can exacerbate pre-excitation if AV node conduction slowed
- **WPW syndrome:** WPW accessory pathway + paroxysmal tachycardia



**Classic tachycardias of WPW accessory pathways**

- Orthodromic AVRT:** narrow-complex SVT (typically), conducting ↓ AVN & ↑ accessory pathway; requires retrograde conduction and ∴ can occur w/ concealed bypass tracts
- Antidromic AVRT** (rare): wide-complex SVT, conducting ↓ accessory pathway & ↑ AVN; requires antegrade conduction and ∴ should see pre-excitation pattern during SR
- AF w/ rapid conduction down accessory pathway;** ∴ wide-complex irregular SVT; requires antegrade conduction; ∴ should see pre-excitation in SR. Rarely can degenerate into VF.

**Treatment** (*Heart Rhythm* 2012;9:1006; *Circ* 2016;133:e506)

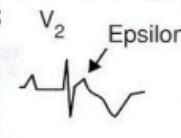
- AVRT** (orthodromic): vagal, βB, CCB; care w/ adenosine (can precip AF); have defib ready
- AF/AFL** w/ conduction down accessory pathway: need to Rx arrhythmia and ↑ pathway refractoriness. Use **procainamide**, **ibutilide**, or **DCCV**; **avoid** CCB, βB, amio, dig, & adenosine, as can ↓ refractoriness of pathway → ↑ vent. rate → VF (*Circ* 2016;133:e506).
- Long term:** RFA if sx; if not candidate for RFA, then antiarrhythmics (IA, III) or CCB/βB; consider RFA if asx but AVRT or AF inducible on EPS (*NEJM* 2003;349:1803) or if rapid conduction possible (✓ w/ EPS if pre-excitation persists during exercise testing) risk of SCD related to how short RR interval is in AF (eg, ≤250ms) and if SVT inducible

**WIDE-COMPLEX TACHYCARDIAS (WCTs)****Etiologies** (*Lancet* 2012;380:1520)

- Ventricular tachycardia (VT):** accounts for 80% of WCT in unselected population
- SVT conducted with aberrancy:** either fixed BBB, rate-dependent BBB (usually RBBB), conduction via an accessory pathway or atrially triggered ventricular pacing

**Monomorphic ventricular tachycardia (MMVT)**

- All beats look similar; predominantly upward in V<sub>1</sub> = RBBB-type vs. downward = LBBB-type
- In structurally *abnormal* heart: **prior MI** (scar); **CMP; myocarditis; arrhythmogenic RV CMP (ARVC):** incomplete RBBB, ε wave (terminal notch in QRS) & TWI in V<sub>1</sub>–V<sub>3</sub> on resting ECG, LBBB-type VT, dx w/ MRI (*Lancet* 2009;373:1289)
- In structurally *normal* heart (w/ normal resting ECG):
  - RVOT VT:** LBBB-type VT w/ inferior axis; typically ablate
  - idiopathic LV VT:** RBBB-type VT w/ superior axis; responds to verapamil

**Polymorphic ventricular tachycardia (PMVT)**

- QRS morphology changes from beat to beat
- Etiologies: **ischemia; CMP; catecholaminergic; torsades de pointes** (TdP = "twisting of the points," PMVT + ↑ QT); ↑ QT **acquired** (meds, lytes, stroke, see "ECG") w/ risk ↑ w/ ↓ HR, freq PVCs (pause dependent) **or congenital** (K/Na channelopathies) w/ resting Tw abnl & TdP triggered by sympathetic stimulation (eg, exercise, emotion, sudden loud noises) (*Lancet* 2008;372:750).

**Brugada syndrome** (Na channelopathy): ♂ > ♀; pseudo-RBBB w/ STE in V<sub>1</sub>–V<sub>3</sub> (provoked w/ class IA or IC) on resting ECG

**Diagnostic clues that favor VT (assume until proven o/w)**

- Prior MI, CHF or LV dysfunction** best predictors that WCT is VT (*Am J Med* 1998;84:53)
- Hemodynamics and rate do *not* reliably distinguish VT from SVT
- MMVT is regular, but initially it may be slightly irregular, mimicking AF w/ aberrancy; grossly irregularly irregular rhythm suggests AF w/ aberrancy or pre-excitation
- ECG features that favor VT (*Circ* 1991;83:1649)
  - AV dissociation** (independent P waves, capture or fusion beats) proves VT
  - very wide QRS (>140 ms in RBBB-type or >160 in LBBB-type); extreme axis deviation
  - QRS morphology atypical for BBB**
    - RBBB-type: absence of tall R' (or presence of monophasic R) in V<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; *EHJ* 2015;36:2793; *Circ* 2016;133:1715)

- Workup: **echo** to ✓ LV fxn, **cath** or **stress test** to r/o ischemia, ? MRI and/or RV bx to look for infiltrative CMP or ARVC, ? **EP study** to assess inducibility
- ICD:** 2° prevention after documented VT/VF arrest (unless due to reversible cause). 1° prev. if high risk, eg, EF <30–35%, ARVC, Brugada, certain LQTS, severe HCMP. See "Cardiac Rhythm Mgmt Devices." Wearable vest if reversible etiology or waiting for ICD? Antitachycardia pacing (ATP = burst pacing faster than VT) can terminate VT w/o shock
- Meds:** βB, verapamil if idiopathic LV VT, or AAD (eg, amio, mexiletine) to suppress VT
- If med a/w TdP → QT >500 ± VPBs: d/c med, replete K, give Mg, ± pacing (*JACC* 2010;55:934)
- RFA** if isolated VT focus or if recurrent VT triggering ICD firing (↓ VT storm by 34%; *NEJM* 2016;375:111); ablation before ICD implantation ↓ discharge rate by 40% (*Lancet* 2010;375:31)

# ATRIAL FIBRILLATION

AF 1-3

## Classification (Circ 2014;130:e199)

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

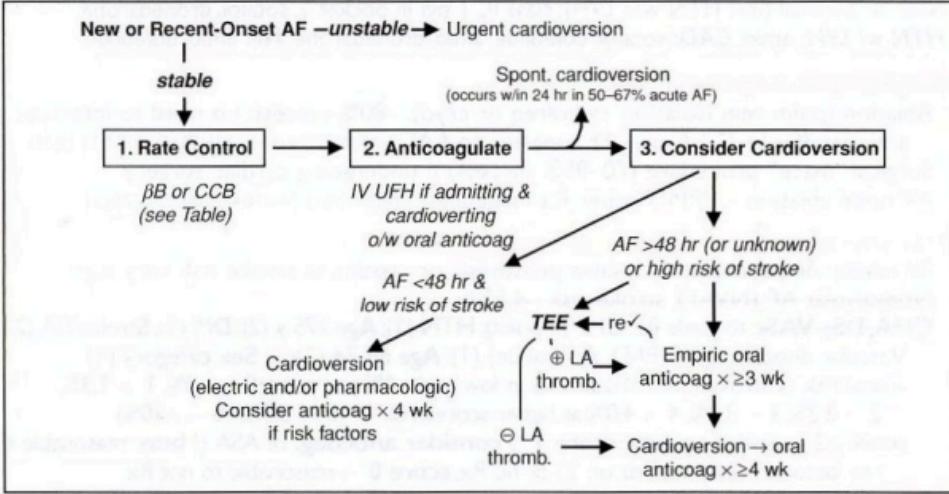
## Epidemiology and etiologies (Circ 2011;124:1982)

- 1–2% of pop. has AF (10% of those age ≥80); M > F; lifetime risk ~25%
- Acute (up to 50% w/o identifiable cause)
  - Cardiac:** HF, new CMP, myo/pericarditis, ischemia/MI, HTN crisis, valve dis., cardiac surg
  - Pulmonary:** acute pulmonary disease or hypoxemia (eg, COPD flare, PNA), PE, OSA
  - Metabolic:** high catecholamine states (stress, infection, postop, pheo), thyrotoxicosis
  - Drugs:** alcohol ("holiday heart"), cocaine, amphetamines, theophylline, caffeine, smoking
  - Neurogenic:** subarachnoid hemorrhage, ischemic stroke
- Chronic: ↑ age, HTN, ischemia, valve dis. (MV, TV, AoV), CMP, hyperthyroidism, obesity

## Evaluation

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

Figure 1-5 Approach to acute AF (Adapted from Circ 2014;130:e199)



Rate Control (if sx, goal HR <80; if asx & EF >40%, goal HR <110; Lancet 2016;388:818)

Agent	Acute (IV)	Maint. (PO)	Comments
CCB	Verapamil	5–10 mg over 2' may repeat in 30'	↓ BP (Rx w/ Ca gluc) Can worsen HF
	Diltiazem	0.25 mg/kg over 2' may repeat after 15' 5–15 mg/h infusion	Preferred if severe COPD Can ↑ dig levels
βB	Metoprolol	2.5–5 mg over 2' may repeat q5' × 3	↓ BP (Rx w/ glucagon) Preferred if CAD Risks: HF & bronchospas.
	Digoxin* (onset >30 min)	0.25 mg q2h up to 1.5 mg/24 h	Consider in HF or low BP Poor exertional HR ctrl
	Amiodarone	300 mg over 1 h → then 10–50 mg/h × 24 h	

Circ 2014;130:e199. IV βB, CCB & dig **contraindicated** if evidence of WPW (ie, pre-excitation or WCT) since may facilitate conduction down accessory pathway leading to VF; ∴ use procainamide, ibutilide or amio.

\*Many meds incl. amio, verapamil, quinidine, propafenone, macrolides & azole antifungals ↑ digoxin levels.

## Cardioversion

- Consider if: 1<sup>st</sup> AF, sx, tachycardia-mediated CMP, or difficult to rate control
  - if AF >48 h 2–5% risk stroke w/ cardioversion (**pharmacologic or electric**)
    - ∴ either TEE to r/o thrombus or ensure therapeutic anticoagulation for ≥3 wk prior if needs to cardiovert urgently, often anticoagulate acutely (eg, IV UFH)
- Likelihood of success ∝ AF duration & atrial size; control precipitants (eg, vol status, thyroid)
- Before electrical cardiovert, consider pre-Rx w/ AAD (eg, ibutilide), esp. if 1<sup>st</sup> cardiovert failed
- For pharmacologic cardioversion, class III and IC drugs have best proven efficacy
- If SR returns (spont. or w/ Rx), atria may be mech. stunned; also, high risk of recurrent AF over next 3 mo. ∴ **Anticoag postcardioversion ≥4 wk** (? unless AF <48 h and low risk).

**Rhythm control** (Lancet 2016;388:829)

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

**Antiarrhythmic Drugs (AAD) for AF** (EHJ 2012;33:2719; Circ 2014;130:e199)

Agent	Conversion	Maintenance	Comments
III	Amiodarone over 30–60' → 1 mg/min, 10-g load	200–400 mg qd (most effective AAD for SR)	↑ QT, TdP rare. Often delay to convert. Poss. pulm, liver, thyroid tox. ↑ INR w/ warfarin.
	Dronedarone n/a	400 mg bid	↓ side effects & effic. vs. amio; Ø if perm AF or ↓ EF; liver tox
IC	Ibutilide 1 mg IV over 10' may repeat × 1	n/a	Contraindic. if ↓ K or ↑ QT (3–8% risk of TdP): give w/ IV Mg
	Dofetilide 500 mcg PO bid	500 mcg bid	↑ QT, ↑ risk of TdP; renal adj
IA	Sotalol n/a	80–160 mg bid	✓ for ↓ HR, ↑ QT; renal adj
	Flecainide 300 mg PO × 1	100–150 mg bid	PreRx w/ AVN blocker. Ø if structural/ischemic heart dis.
IA	Propafenone 600 mg PO × 1	150–300 mg tid	
IA	Procainamide 10–15 mg/kg IV over 1 h	n/a	↓ BP; ↑ QT ± PreRx w/ AVN blocker

**Underlying disease & maintenance AAD of choice:**

None or minimal (incl HTN w/o LVH): class IC ("pill in pocket"), sotalol, dronedarone; **HTN w/ LVH:** amio; **CAD:** sotalol, dofetilide, amio, dronedarone; **HF:** amio, dofetilide

**Nonpharmacologic therapy**

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

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

- All valvular AF (ie, rheum MS, valve prosthesis or repair), as stroke risk very high
- Nonvalvular AF (NVAF): stroke risk ~4.5%/y
- CHA<sub>2</sub>DS<sub>2</sub>-VASc** to guide Rx: **CHF** (1 point); **HTN** (1); **Age ≥75 y** (2); **DM** (1), **Stroke/TIA** (2); Vascular disease (eg, MI, PAD, Ao plaque) (1); **Age 65–74** (1); ♀ **Sex category** (1) annual risk of stroke (Lancet 2012;379:648): at low end, ~1% per point: 0 → ~0%, 1 → 1.3%, 2 → 2.2%, 3 → 3.2%, 4 → 4.0%; at higher scores, risk ↑ (5 → 6.7%, ≥6 → ≥10%)  
**score ≥2 → anticoagulate; score 1 → consider anticoag**, or ASA (? latter reasonable if risk factor 65–74 y, vasc dz or ♀) or no Rx; **score 0 → reasonable to not Rx**
- Rx options:** **NOAC** (NVAF only) or warfarin (INR 2–3); if Pt refuses anticoag, ASA + clopi or, even less effective, ASA alone (NEJM 2009;360:2066)
- AF w/ CAD/ PCI: can consider anticoag + clopi, omit ASA (Lancet 2013;381:1107)
- Periop rate of arterial embolization in NVAF <0.5%; no benefit to bridging anticoag w/ LMWH & ↑ bleeding c/w stopping warfarin 5 d preop (NEJM 2015;373:823)

**Non-vit K antag Oral Anticoag (NOACs) for NVAF** (Lancet 2014;383:955)

Anticoag	Dosing	Efficacy & safety vs warfarin
<b>Dabigatran</b> (Direct thromb inhib)	150 mg bid (110 not avail in U.S.) (75 mg bid if CrCl 15–30)	150 mg: ↓ ischemic stroke & ICH, but ↑ GIB 110 mg: ≈ ischemic stroke & ↓ major bleed/ICH Risks: GI side effects, ↑ MI c/w warfarin
<b>Rivaroxaban</b> (FXa inhib)	20 mg qd (15 mg qd if CrCl 15–50) w/ pm meal	≈ ischemic stroke & major bleeds, but ↓ fatal bleed incl ICH
<b>Apixaban</b> (FXa inhib)	5 mg bid (2.5 mg bid if ≥2 of: ≥80 y, ≤60 kg, Cr ≥1.5 mg/dL)	= ischemic stroke & ↓ major bleed incl ICH, 11% ↓ death. In Pts felt not cand for warfarin, apixa 55% ↓ stroke w/o ↑ bleed vs ASA alone.
<b>Edoxaban</b> (Fx inhib)	60 mg qd if CrCl 51–95 (30 mg if CrCl 15–50)	= ischemic stroke & ↓ major bleed incl ICH, 14% ↓ CV death. ↑ ischemic CVA if CrCl >95.

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

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

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

**Atrial flutter**

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

**Definition**

- Symptom of sudden transient loss of consciousness due to global cerebral hypoperfusion
- If CPR or cardioversion required, then SCD and not syncope (different prognosis)
- Presyncope = prodrome of light-headedness without LOC

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

- **Neurocardiogenic** (a.k.a. vasovagal, ~25%; NEJM 2005;352:1004): ↑ sympathetic tone → vigorous contraction of LV → mechanoreceptors in LV trigger ↑ vagal tone (hyperactive Bezold-Jarisch reflex) → ↓ HR (cardioinhibitory) and/or ↓ BP (vasodepressor). Cough, deglutition, defecation, & micturition → ↑ vagal tone and thus can be precipitants. Carotid sinus hypersensitivity (exag vagal resp to carotid massage) is related disorder.
- **Orthostatic hypotension** (~10%)  
hypovolemia/diuretics, deconditioning; vasodilat. (esp. if combined w/ ⊖ chronotropes)  
autonomic neuropathy [1° = Parkinson's, MSA/Shy-Drager, Lewy body dementia, POTS (dysautonomia in the young); 2° = DM, EtOH, amyloidosis, CKD] (NEJM 2008;358:615)
- **Cardiovascular** (~20%, more likely in men than women)
  - Arrhythmia** (15%): challenging to dx as often transient
    - Bradyarrhythmias: SSS, high-grade AV block, ⊖ chronotropes, PPM malfunction
    - Tachyarrhythmias: VT, SVT (syncope rare unless structural heart disease or WPW)
  - Mechanical (5%)
    - Endocardial/Valvular: AS, MS, PS, prosthetic valve thrombosis, myxoma
    - Myocardial: pump dysfxn from MI or outflow obstruction from HCM (but usually VT)
    - Pericardial: tamponade; Vascular: PE, PHT, AoD, ruptured AAA, subclavian steal
- **Neurologic** (~10%): vertebrobasilar insuff, cerebrovasc dissection, SAH, TIA/CVA, migraine
- Misc. causes of LOC (but not syncope): seizure, ↓ glc, hypoxia, narcolepsy, psychogenic

**Workup (etiology cannot be determined in ~40% of cases)**

- H&P incl. orthostatic VS have highest yield and most cost effective (Archives 2009;169:1299)
- **History** (from Pt and witnesses if available)
  - activity and posture before the incident
  - precipitating factors: exertion (AS, HCM, PHT), positional Δ (orthostatic hypotension), stressors such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, N/V, cough/micturition/defecation/swallowing (neurocardiogenic), head turning or shaving (carotid sinus hypersens.); arm exercise (subclavian steal)
  - prodrome (eg, diaphoresis, nausea, blurry vision): cardiac <~5 sec, vasovagal >~5 sec
  - associated sx: chest pain, palp., neurologic, postictal, bowel or bladder incontinence (convulsive activity for <10 sec may occur w/ transient cerebral HoTN & mimic seizure)
- **PMH:** prior syncope, previous cardiac or neurologic dis.; no CV disease at baseline → 5% cardiac, 25% vasovagal; CV disease → 20% cardiac, 10% vasovagal (NEJM 2002;347:878)
- **Medications that may act as precipitants**
  - vasodilators: α-blockers, nitrates, ACEI/ARB, CCB, hydralazine, phenothiazines, antidep. diuretics; ⊖ chronotropes (eg, βB and CCB)
  - proarrhythmic or QT prolonging: class IA, IC or III antiarrhythmics (see "ECG")
  - psychoactive drugs: antipsychotics, TCA, barbiturates, benzodiazepines, EtOH
- **Family history:** CMP, SCD, syncope (vasovagal may have genetic component)
- **Physical exam**
  - VS including orthostatics** (⊕ if supine → standing results in >20 mmHg ↓ SBP, >10 mmHg ↓ DBP, or >10–20 bpm ↑ HR), BP in both arms
  - cardiac: HF (↑ JVP, displ. PMI, S<sub>3</sub>), murmurs, LVH (S<sub>4</sub>, LV heave), PHT (RV heave, ↑ P<sub>2</sub>)
  - vascular: ✓ for asymmetric pulses, carotid/vert/subclavian bruits; carotid sinus massage to ✓ for carotid hypersens (if no bruits): ⊕ if asystole >3 sec or ↓ SBP >50 mmHg
  - neurologic exam: focal findings, evidence of tongue biting; FOBT
- **ECG** (abnormal in ~50%, but only definitively identifies cause of syncope in <10%)
  - Conduction: SB, sinus pauses/sinus arrhythmia, AVB, BBB/IVCD
  - Arrhythmia: ectopy, ↑ or ↓ QT, preexcitation (WPW), Brugada, ε wave (ARVC), SVT/VT
  - Ischemic changes (new or old): atrial or ventricular hypertrophy
- Lab: glc, Hb, preg test (child-bearing age ♀), ? D-dimer, ? troponin (low yield w/o other s/s)

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

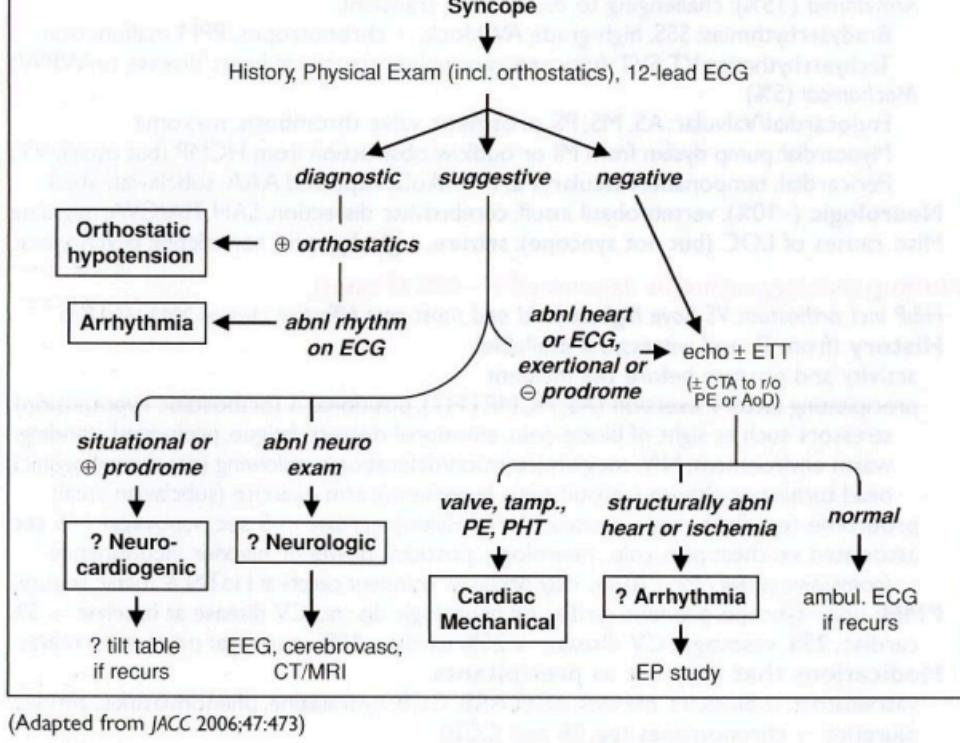
- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope
  - Holter monitoring (continuous ECG 24–48 h): useful if frequent events arrhythmia + sx (4%); asx but signif. arrhythmia (13%); sx but no arrhythmia (17%)
  - Event recorder (activated by Pt to record rhythm strip): limited role in syncope as only useful if established prodrome (because must be Pt activated)

External loop recorders (continuously saves rhythm, .. can be activated after an event): useful for episodes (including w/o prodrome) likely to occur w/in 1 mo; can be coupled w/ mobile cardiac telemetry than can be auto-triggered for specific rhythms

Implantable loop recorders (inserted SC; can record >1 y): useful if episodes <1/mo; dx in 55% of cases (*Circ* 2001;104:46); recommended for recurrent syncope w/o prodrome

- Echo: consider to r/o structural heart disease (eg, CMP [incl HCMP & ARVC], valvular disease [incl AS, MS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- ETT/CCTA/Cath: esp. w/ exertional syncope; r/o ischemia or catechol-induced arrhythmia
- Electrophysiologic studies (EPS): consider in high-risk Pts in whom tachy or brady etiology is strongly suspected, but cannot be confirmed; 50% abnl (inducible VT, conduction abnormalities) if heart disease, but ? significance 3–20% abnl if abnl ECG; <1% abnl if normal heart and normal ECG (*Annals* 1997;127:76)
- ? Tilt table testing: debated utility due to poor Se/Sp/reproducibility; consider only if vasovagal dx suspected but cannot be confirmed by hx
- Cardiac MRI: helpful to dx ARVC if suggestive ECG, echo (RV dysfxn) or + FHx of SCD
- Neurologic studies (cerebrovascular studies, CT, MRI, EEG): if H&P suggestive; low yield

Figure 1-6 Approach to syncope



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

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

- Age >60 y, h/o CAD, HF/CMP, valvular or congenital heart dis., arrhythmias, FHx SCD
- Syncope c/w cardiac cause (lack of prodrome, exertional, resultant trauma) or recurrent
- Complaint of chest pain or dyspnea; abnl VS, cardiac, pulm, or neuro exam
- ECG suggesting conduction abnormality, arrhythmia, or ischemia; Pt w/ PPM/ICD

### Treatment

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

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

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

# CARDIAC RHYTHM MANAGEMENT DEVICES

PM/ICD  
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Pacemaker Code				
	1 <sup>st</sup> letter	2 <sup>nd</sup> letter	3 <sup>rd</sup> letter	4 <sup>th</sup> letter
A, atrial; V, vent; O, none; I, inhibition; D, dual; R, rate-adaptive	Chamber paced	Chamber sensed	Response to sensed beat	Program features

## Common Pacing Modes

VVI	Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia.
DDD	A & V sensing/pacing (RA & RV leads). Native A beat inhib A pacing & triggers V pacing → tracking of intrinsic atrial activity. Maintains AV synchrony, ↓ AF.
Mode Switch	In atrial tachyarrhythmia (eg, AF), PPM Δs from DDD to nontracking mode (eg, VVI). Prevents PPM from pacing at max V rate in response to rapid atrial rate.
Magnet	PPM: fixed rate pacing (VOO/DOO). ICD: no shock, pacing preserved. Indic: ✓ capture; surgery; inapprop PPM inhib/ICD shock, PM-mediated tachy
Leadless intracardiac PPM with emerging indications (NEJM 2015;373:1125 & 2016;374:53)	

## Indications for Permanent Pacing (Circ 2008;117:350 & 2012;126:1784)

AV block	3° or type II 2° AVB a/w sx or w/ either HR <40 or asystole ≥3 sec (≥5 if in AF) while awake; ? asx 3° or type II 2° AVB; bifasc or alter. L & R BBB
Sinus node	SB, pauses (SSS), chronotrop incompet a/w sx or ? if sx w/o clear assoc
Tachy-arrhythmia	AF w/ SSS; sx recurrent SVT term. by pacing after failing drugs/ablation; Sustained pause-dependent VT; ? high-risk congenital long QT
Syncope	Carotid sinus hypersensitivity with asystole >3 sec ? Neurocardiogenic syncope w/ prominent cardioinhib. response ? Syncope with bi- or trifascicular block and not likely 2° to other causes

## Pacemaker Complications

Issue	Manifestation	Description & etiologies
Perforation	Effusion/tamp/pain	Typically acute, consider if HoTN
Failure to pace	Bradycardia	↓ Battery, lead fx/dislodgment, ↑ pacing threshold due to tissue rxn/injury; oversense → inapprop. inhib
Failure to sense	Inapprop. pacing	Lead dislodgment or sensing threshold too high
PM-mediated tachycardia	WCT at device upper rate	Seen w/ DDD.V → A retrograde conduction; sensed by A lead → triggers V pacing → etc.
PM syndrome	Palpit, HF	Seen w/ VVI, due to loss of AV synchrony

## Cardiac resynch therapy (CRT)/Biventricular (BiV) pacing (JACC 2013;61:e6)

- 3-lead pacemaker (RA, RV, coronary sinus to LV); R > S in V<sub>1</sub> suggests approp LV capture
- Synchronize & enhance LV fxn (↑ CO, ↓ adverse remodeling)
- Indications:** LVEF ≤35% + NYHA II–IV despite med Rx + SR + LBBB ≥150 (? ≥120) ms; mort. benefit w/ CRT-D only if LBBB (& QRS ≥130ms) (NEJM 2014;370:1694)  
? benefit in NYHA I–III, EF ≤50% w/ PPM indication for AVB (NEJM 2013;368:1585)  
consider in AF: need rate control or AVN ablation; more pacing → greater CRT effect
- Benefits:** ↓ HF sx, ↓ HF hosp., ↑ survival (NEJM 2005;352:1539 & 2010;363:2385)

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

- RV lead: defib & pacing (± antitachycardia pacing [ATP] = burst pacing >VT rate to stop VT); ± RA lead for dual chamber PPM. Wearable defib & subcut-ICD, but Ø pace/ATP.
- Pt selection** (NEJM 2004;350:2151 & 351:2481; 2005;352:225; 2009;361:1427; Circ 2012;126:1784)
  - 2° prevention: survivors of VF arrest, unstable VT w/o reversible cause; structural heart disease & spontaneous sustained VT (even if asx)
  - 1° prevention: LVEF ≤30% & post-MI or LVEF ≤35% & NYHA II–III (wait: ≥40 d if post-MI, ≥90 d for NICMP) or LVEF ≤40% & inducible VT/VF; life expectancy must be >1 y; consider if unexplained syncope + DCM, or if HCM, ARVC, Brugada, sarcoid, LQTS, Chagas or congenital heart disease if at risk for SCD; ? wearable vest as bridge to ICD
- Risks:** inapprop shock in ~15–20% at 3 y (commonly d/t misclassified SVT); infxn; lead fx
- ICD discharge: ✓ device to see if approp; r/o ischemia; 6-mo driving ban (✓ state law); if recurrent VT, ? drug Rx (eg, amio + βB; JAMA 2006;295:165) or VT ablation (NEJM 2007;357:2657); ablation at time of ICD ↓ risk of VT by 40% (Lancet 2010;375:31)

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

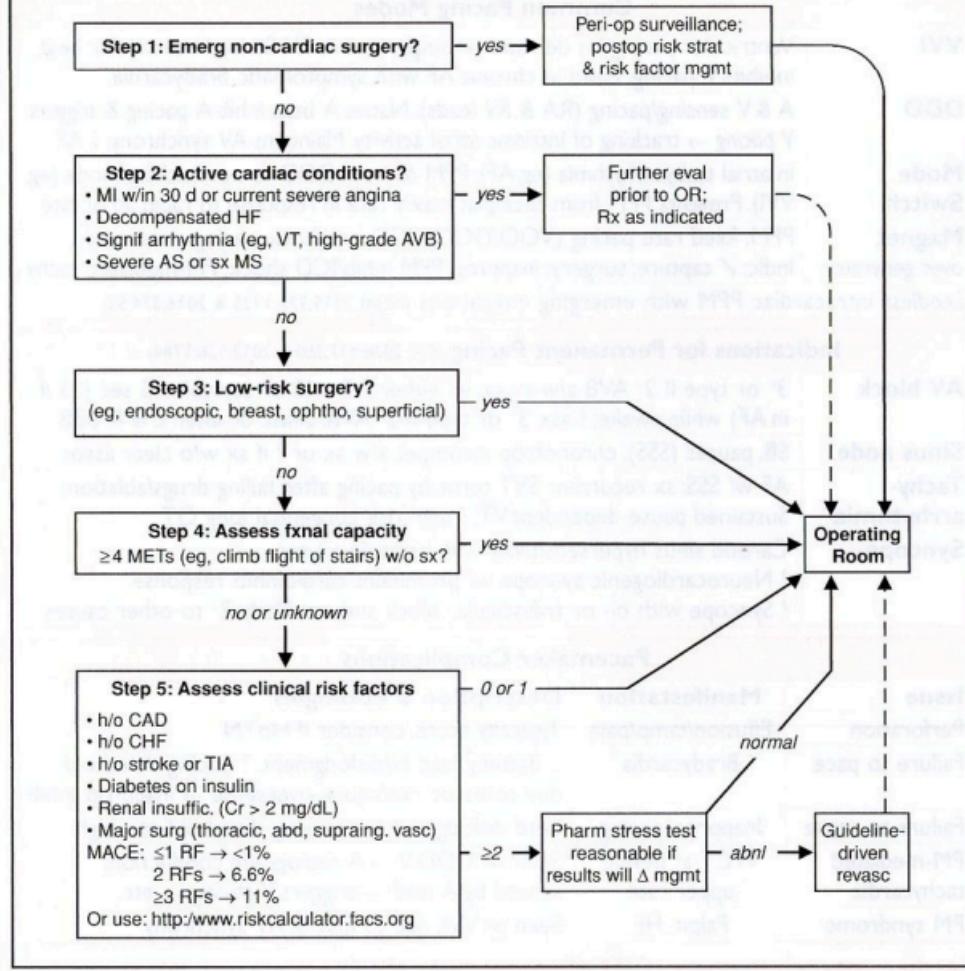
- Presents as pocket infection (warmth, erythema, tenderness) and/or sepsis w/ bacteremia
- Incidence ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%
- TTE/TEE used to help visualize complic. (eg, vegetation), but even Ø TEE does not r/o
- Rx: abx; system removal if pocket infxn or GPC bacteremia; Ø routine abx prior to inv. proc.

## CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

**Goal:** characterize risk of Pt & procedure → appropriate testing (ie, results will Δ management) and interventions (ie, reasonable probability of ↓ risk of MACE)

## Preoperative evaluation (NEJM 2015;373:2258)

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



## Noninvasive Testing Result

High risk	Intermediate risk	Low risk
<b>Ischemia at &lt;4 METs</b> manifested by ≥1 of: <ul style="list-style-type: none"> <li>Horiz/down ST ↓ ≥1 mm or STE</li> <li>≥5 abnl leads or ischemic ECG Δs lasting &gt;3 min after exertion</li> <li>SBP ↓ 10 mmHg or typical angina</li> </ul>	<b>Ischemia at 4–6 METs</b> manifested by ≥1 of: <ul style="list-style-type: none"> <li>Horiz/down ST ↓ ≥1 mm</li> <li>3–4 abnl leads</li> <li>1–3 min after exertion</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>

## Additional preoperative testing (Circ 2014;130:e278)

- ECG if known cardiac disease and possibly reasonable in all, except if low-risk surgery
- TTE if any of following & prior TTE >12 mo ago or prior to Δ in sx: dyspnea of unknown origin; hx of HF w/ ↑ dyspnea; suspect (eg, murmur) or known ≥ moderate valvular dis.

## Coronary artery disease

- If possible, wait ~60 d after MI in the absence of revascularization before elective surgery
- Coronary revasc guided by standard indications. Has not been shown to Δ risk of death or postop MI when done prior to elective vasc. surgery (NEJM 2004;351:2795).

## Heart failure (JACC 2014;64:e77)

- Decompensated HF should be optimally Rx'd prior to elective surgery
- 30-d CV event rate: symptomatic HF > asx HFrEF > asx HFpEF > no HF

## Valvular heart disease

- If meet criteria for valve intervention, do so before elective surgery (postpone if necessary)
- If severe valve disease and surgery urgent, intra- & postoperative hemodynamic monitoring reasonable (espec for AS, since at ↑ risk even if sx not severe; be careful to maintain preload, avoid hypotension, and watch for atrial fibrillation)

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

### Cardiac implantable electronic devices

- Discuss w/ surgical team need for device (eg, complete heart block) & consequences if interference w/ fxn, and likelihood of electromagnetic interference
- Consider reprogramming, magnet use, etc. as needed

### Pre- & perioperative pharmacologic management

- ASA:** continue in Pts w/ existing indication. Initiation prior to surgery does not ↓ 30-d ischemic events and ↑ bleeding (NEJM 2014;370:1494), but Pts w/ recent stents excluded.
- Dual antiplatelet therapy:** delay elective surg 14 d after balloon angioplasty, 30 d after BMS and ideally 6 mos (min 3 mos) after DES implantation (2016 ACC/AHA Update) unless risk of bleeding > risk of stent thrombosis or ACS. If must discontinue P2Y<sub>12</sub> inhibitor, continue ASA and restart P2Y<sub>12</sub> inhibitor ASAP.
- β-blockers** (Circ 2009;120:2123; JAMA 2010;303:551; Am J Med 2012;125:953)
  - Continue βB in Pts on them chronically. Do not stop βB abruptly postop (may cause reflex sympathetic activation). Use IV if Pt unable to take PO.
  - In terms of initiating, conflicting evidence; may depend on how done. Some studies show ↓ death/MI, another ↓ MI, but ↑ death & stroke and ↑ brady/HoTN (Lancet 2008;371:1839).
  - Reasonable to initiate if intermed- or high-risk + stress test, or RCRI ≥3, espec if vasc surgery. Initiate ≥1 wk prior to surgery (*not day of*), use low-dose, short-acting βB, and titrate to achieve HR and BP goal (? HR ~55–65). Avoid bradycardia and HoTN.
- Statins:** ↓ ischemia & CV events in Pts undergoing vascular surg (NEJM 2009;361:980). Consider if risk factors & non-low-risk surgery and in all Pts undergoing vascular surgery.
- ACEI/ARB:** may cause HoTN perioperatively. If held before surgery, restart ASAP.
- Amiodarone:** ↓ incidence of postop AF if started prior to surgery (NEJM 1997;337:1785)

### Postoperative monitoring

- ECG if known CAD or high-risk surgery. Consider if >1 risk factor for CAD.
- Routine troponin prognostic (JAMA 2012;307:2295) but ✓ only if sx/ECG Δs suggestive of ACS

## PERIPHERAL ARTERY DISEASE (PAD)

### Clinical features (NEJM 2016;374:861)

- Prev. ↑ w/ age: <1% if <40 y, ~15% if ≥70 y; risk factors incl. **smoking, DM, HTN, chol**
- Claudication** (dull ache, often in calves) precip by walking and relieved by stopping (vs. spinal stenosis, qv); Leriche synd = claudication, ↓ or Ø femoral pulses, & erectile dysfxn
- Critical limb ischemia (CLI): rest pain** (↑ w/ elevation b/c ↓ perfusion), **ulcer** (typically at pressure foci, often dry; in contrast, venous ulcers are more often at medial malleolus, wet, and with hemosiderin deposition) or **gangrene**, due to PAD, and >2-wk duration (implies chronicity vs. acute limb ischemia; see below)

### Diagnosis

- ↓ peripheral pulses; other signs of chronic PAD: hair loss, skin atrophy, nail hypertrophy
- Ankle-brachial index (ABI): nl 1–1.4; borderline 0.91–0.99; abnl ≤0.90; if >1.4, non-dx possibly due to calcified noncompressible vessel → ✓ PVR. If ABI abnl → segmental ABI w/ PVR to localize disease. If + sx but nl ABI, ✓ for ↓ lower extrem BP after exercise.
- Duplex arterial US; CTA w/ distal run-off; MRA or angio if dx in ? or possible intervention

### Treatment (JACC 2013;61:1555; JAMA 2013;309:453 & 2015;314:1936)

- Risk factor modification. Screen for CAD. Structured exercise program (JAMA 2013;310:57).
- If sx, ASA or clopi to ↓ D/MI/stroke. More intensive Rx (eg, adding ticagrelor or vorapaxar) ↓ both MACE and limb ischemic events (Circ 2013;112:679 & JACC 2016;67:2719).
- Cilostazol (if no HF) & ? ACEI & statins to ↓ sx (Circ 2003;108:1481)
- Endovascular (angioplasty vs. stent) or surgical revasc if limiting/refractory sx or CLI

### Acute limb ischemia (ALI)

- Sudden decrement in limb perfusion that threatens viability; viable (no immed threat of tissue loss): audible art. Doppler signals, sensory, & motor OK threatened (salvage requires prompt Rx): loss of arterial Doppler signal, sensory, or motor
- Etiologies: embolism > acute thrombosis (eg, athero, APS, HITT), trauma to artery
- Clinical manifestations (**6 Ps**): pain (distal to proximal, ↑ in severity), poikilothermia, pallor, pulselessness, paresthesias, paralysis
- Testing: thorough pulse & neuro exam; arterial Doppler; angiography, either CT w/ bilateral run-off through feet or arteriography
- Urgent consultation w/ vascular medicine and/or vascular surgery
- Treatment: immediate anticoagulation ± intra-arterial lytic; angioplasty or surgery

# DYSPNEA

Dysp/PFTs 2-1

Pathophysiology	Etiologies
Airway obstruction (↑ resistance to airflow)	<b>Asthma, COPD, bronchiectasis, cystic fibrosis, tumor, foreign body, anaphylaxis</b>
Alveolar / Parenchymal disease	<b>Pulmonary edema:</b> cardiogenic or noncardiogenic ILD; pneumonia; atelectasis
Vascular (V/Q mismatch)	Large vessel: <b>PE</b> , tumor emboli Small vessel: <b>PHT</b> , vasculitis, ILD, emphysema, PNA
Chest wall (↑ resistance to expansion; weakness of respir. muscles)	<b>Pleural disease:</b> large effusion, fibrosis; pneumothorax <b>Chest wall/diaphragm:</b> kyphoscoliosis, ↑ abd girth <b>Neuromuscular disorders</b> (ALS, GBS, MG) <b>Hyperinflation</b> (COPD, asthma)
Stimulation of receptors	Chemoreceptors: <b>hypoxemia</b> , metabolic acidosis Mechanoreceptors: <b>ILD, pulmonary edema, PHT, PE</b>
↓ O <sub>2</sub> carrying cap. (but nl P <sub>5</sub> O <sub>2</sub> )	<b>Anemia</b> , methemoglobinemia, CO poisoning
Psychological	Anxiety, panic attack, depression, somatization

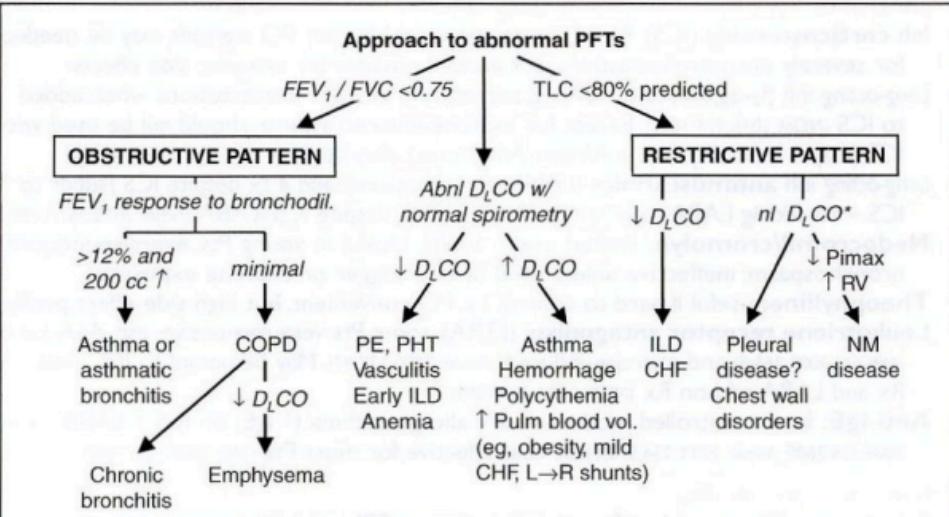
## Evaluation

- History: quality of sensation, tempo, positional dependence, exac./allev. factors, exertion
- Cardiopulmonary exam, S<sub>a</sub>O<sub>2</sub>, CXR (see Appendix & Radiology inserts), ECG, ABG, U/S 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: PFT, chest CT, TTE, cardiopulmonary testing
- BNP & NT-proBNP** ↑ in CHF (also ↑ in AF, RV strain from PE, COPD flare, PHT, ARDS)
  - BNP <100 pg/mL to r/o CHF (90% Se), >400 to r/i (*NEJM* 2002;347:161)
  - NT-proBNP <300 pg/mL to r/o CHF (99% Se); age-related cut points to r/i: >450 pg/mL (<50 y), >900 (50–75 y), >1800 (>75 y) (*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 hyperinflation or 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 (*Lancet* 2013;382:1360)

- Chronic inflam. disorder w/ airway hyperresponsiveness + variable airflow obstruction
- Affects 5–10% population; ~85% of cases by age 40 y

## Clinical manifestations (*NEJM* 2013;369:549)

- Classic triad = **wheezing, cough and dyspnea**; others include chest tightness, sputum; symptoms typically chronic with episodic exacerbation
- Precipitants (**triggers**)
  - respiratory irritants (smoke, perfume, etc.) & allergens (pets, dust mites, pollen, etc.)
  - infections (URI, bronchitis, sinusitis)
  - drugs (eg, ASA & NSAIDs via leukotrienes,  $\beta$ B via bronchospasm, MSO<sub>4</sub> via histamine)
  - emotional stress, cold air, exercise (increase in ventilation dries out airways)

## Physical examination

- Wheezing and prolonged expiratory phase
- Presence of nasal polyps, rhinitis, rash → **allergic component**
- Exacerbation → ↑ RR, ↑ HR, accessory muscle use, diaphoresis, pulsus paradoxus

## Diagnostic studies

- **Peak exp flow (PEF):** ≥60 L/min ↑ after bronchodil or ≥20% diurnal variation c/w asthma. <80% personal best c/w poor control, <50% c/w severe exacerbation.
- **Spirometry:** ↓ FEV<sub>1</sub>, ↓ FEV<sub>1</sub>/FVC, coved flow-volume loop; lung volumes: ± ↑ RV & TLC
  - ⊕ bronchodilator response (↑ FEV<sub>1</sub> ≥12% & ≥200 mL) strongly suggestive of asthma
  - methacholine challenge (↓ FEV<sub>1</sub> ≥20%) if PFTs nl: Se >90% (*AJRCCM* 2000;161:309)
- Allergy suspected → consider ✓ serum IgE, eos, skin testing/RAST

## Ddx ("all that wheezes is not asthma...")

- Hyperventilation & panic attacks
- Upper airway obstruction or inh foreign body; laryngeal/vocal cord dysfxn (eg, 2° to GERD)
- CHF ("cardiac asthma"); COPD, bronchiectasis; ILD (including sarcoidosis); vasculitis; PE

## "Asthma plus" syndromes (*Lancet* 2002;360:1313)

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

## CHRONIC MANAGEMENT

### "Reliever" medications (used prn to quickly relieve sx)

- Short-acting inh  $\beta_2$ -agonists (SABA): albuterol Rx of choice
- Short-acting inh anticholinergics (ipratropium) ↑  $\beta_2$ -agonist delivery → ↑ bronchodilation

### "Controller" meds (taken daily to keep control) (*NEJM* 2009;360:1002)

- Inh corticosteroids (ICS): Rx of choice (*JAMA* 2001;285:2583). PO steroids may be needed for severely uncontrolled asthma, but avoid if possible b/c systemic side effects.
- Long-acting inh  $\beta_2$ -agonists (LABA; eg, salmeterol): safe & ↓ exacerbations when added to ICS (*NEJM* 2016;374:1822). Except for exercise-induced asthma, should not be used w/o ICS (may ↑ mortality, esp. in African-Americans) (*Chest* 2006;129:15; *Annals* 2006;144:904).
- Long-acting inh antimuscarinics (LAMA; eg, tiotropium): add if sx despite ICS (super. to ICS, ≈ to adding LABA; *NEJM* 2010;363:1715) or if sx despite ICS+LABA (*NEJM* 2012;367:1198).
- **Nedocromil/cromolyn:** limited use in adults. Useful in young Pts, exercise-induced bronchospasm; ineffective unless used before trigger or exercise exposure.
- **Theophylline:** useful if hard to control sx; PO convenient, but high side-effect profile
- **Leukotriene receptor antagonists (LTRA):** some Pts very responsive, esp. ASA-sens (*AJRCCM* 2002;165:9) and exercise-induced (*Annals* 2000;132:97). May be noninf to ICS initial Rx and LABA add-on Rx (*NEJM* 2011;364:1695).
- **Anti-IgE:** for uncontrolled mod-to-severe allergic asthma (↑ IgE) on ICS ± LABA (*NEJM* 2006;354:2689; *Annals* 2011;154:573); not cost-effective for most Pts (*JACI* 2007;120:1146)

### Other (*Lancet* 2015;386:1086)

- Behavior modification: identify and avoid triggers; PPI w/o benefit (*NEJM* 2009;360:1487)
- ImmunoRx may be useful if significant allergic component (*JAMA* 2016;315:1715)
- TNF antagonists may be helpful in refractory asthma (*NEJM* 2006;354:697)
- Anti-IL5 (mepolizumab, reslizumab) ↓ exac. in sev asthma (*NEJM* 2014;371:1189 & 1198)
- Anti-IL13 (lebrikizumab) ↑ FEV<sub>1</sub> (*NEJM* 2011;365:1088), not yet FDA approved
- Anti-IL4 (dupilumab): ↓ exac. in sev asthma (*NEJM* 2013;368:2455; *Lancet* 2016;388:31)

- Bronchial thermoplasty (exp'tal): radiofrequency destruction of airway smooth muscle no Δ in FEV<sub>1</sub>, but ↓ in sx and # of exacerbations (NEJM 2007;356:1327)

### Principles of treatment

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

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

Step 1	Step 2	Step 3	Step 4	Step 5
Rapid-acting β <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>	↑ ICS dose (w/ LABA)	Oral steroids (lowest dose)
	LTRA	Low-dose ICS + LAMA	<b>Add LAMA</b>	Anti-IgE Rx
		Med-dose ICS	Add LTRA	
		Low-dose ICS + LTRA	Add Theo	
		Low-dose ICS + Theo		

### EXACERBATION

#### Evaluation

- History: baseline PEF, steroid requirement, ED visits, hospital admissions, prior intubation  
Current exacerbation: duration, severity, potential precipitants, meds used  
Risk factors for life-threatening: prior intubation, h/o near-fatal asthma, ED visit/hosp for asthma w/in 1 y, current/recent PO steroids, not using ICS, overdependent on SABA, Ψ, h/o noncompliance
- Physical exam: VS, pulm, accessory muscle use, pulsus paradoxus, abdominal paradox  
Assess for barotrauma: asymmetric breath sounds, tracheal deviation, subcutaneous air → pneumothorax, precordial (Hamman's) crunch → pneumomediastinum
- Diagnostic studies: **PEF** (used to follow clinical course); **S<sub>a</sub>O<sub>2</sub>**; **CXR** to r/o PNA or PTX ABG if severe: low P<sub>a</sub>CO<sub>2</sub> initially; nl or high P<sub>a</sub>CO<sub>2</sub> may signify tiring

#### Severity of Asthma Exacerbation

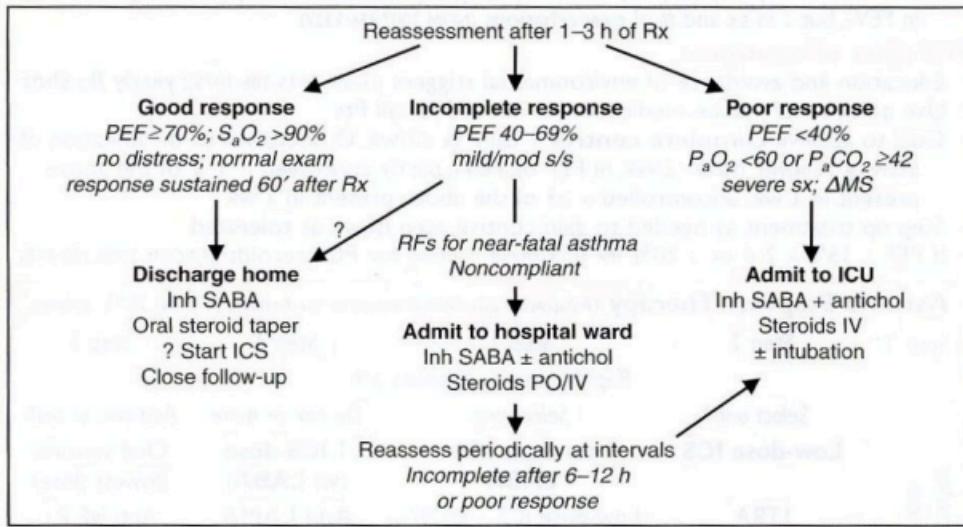
Feature	Mild	Moderate	Severe
Breathless w/...	Walking	Talking	At rest
Talking in ...	Sentences	Phrases	Words
Mental status	± Agitated	Agitated	Agitated
RR	↑	↑	>30
Accessory muscles	Ø	⊕	⊕
Wheeze	Moderate, end-expir	Loud	Usually loud
HR	<100	100–120	>120
Pulsus paradoxus	Normal (<10)	10–25	>25
PEF	>80%	60–80%	<60%
S <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

**Resp arrest imminent:** drowsy, abdominal paradox, wheezes inaudible (b/c Ø air movement), bradycardia, loss of abdominal paradox (respiratory muscle fatigue). Presence of several parameters (not necessarily all) indicates classification (adapted from Chest 2003;123:1018; GINA 2015 update).

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

- Oxygen** to keep S<sub>a</sub>O<sub>2</sub> ≥ 90%
- Inhaled SABA** (eg, albuterol) by MDI (4–8 puffs) or nebulizer (2.5–5 mg) q20min
- Corticosteroids:** prednisone 0.5–1 mg/kg PO; IV if impending resp arrest
- Ipratropium** MDI (4–6 puffs) or nebulizer (0.5 mg) q20min if severe (Chest 2002;121:1977)
- Epinephrine** (0.3–0.5 mL SC of 1:1000 dilution) no advantage over inh SABA
- Montelukast** IV ↑ FEV<sub>1</sub> but did not Δ rate of hosp (J Allergy Clin Immunol 2010;125:374)
- Reassess after 60–90 min of Rx
  - Mild-mod exacerbation: cont SABA q1h
  - Severe exacerbation: SABA & ipratropium q1h or continuously; ± Mg 2 g IV over 20 min (Lancet 2003;361:2114); ± heliox (60–80%)
- Decide disposition within 4 h of presentation and after 1–3 h of Rx

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



### ICU-level care

- **High-dose steroids:** methylprednisolone 125 mg IV q6h (*Archives* 1983;143:1324)
- **Invasive ventilation:**
  - large ET tube,  $P_{plat} < 30 \text{ cm H}_2\text{O}$  (predicts barotrauma better than PIP), max exp time PEEP individualized to Pt physiology
  - paralysis, inhalational anesthetics, bronchoalveolar lavage w/ mucolytic, heliox (60–80% helium) and ECMO have been used with success
- NPPV likely improves obstruction (*Chest* 2003;123:1018), but controversial and rarely used

## ANAPHYLAXIS

### Definition and pathophysiology (*Ann Emerg Med* 2006;47:373)

- Severe, rapid-onset (mins to hrs), potentially life-threatening systemic allergic response
- IgE-mediated mast cell degranulation with release of histamine, tryptase and TNF
- Precipitates systemic reactions (bronchospasm, tissue swelling, fluid shifts, vasodilation)
- Common triggers: penicillins, cephalosporins, shellfish, nuts, insect stings, IV contrast (not truly an IgE-mediated mechanism, but clinically similar)

### Diagnosis: any of the three following criteria

- 1) Acute illness with skin ± mucosal involvement (rash, flushing, hives), AND at least one of
  - Respiratory compromise (wheeze, stridor, dyspnea, hypoxemia)
  - Hypotension or hypoperfusion (syncope, incontinence)
- 2) Two or more of the following after exposure to a **likely** allergen: skin/mucosal involvement, respiratory compromise, ↓ BP or hypoperfusion, GI symptoms
- 3) Hypotension after exposure to **known** allergen for that Pt

### Treatment

- **Epi:** IM/SC 0.3–0.5 mL of 1:1000 dilution q5–20min; if HoTN 1 mg IVB q5min ± gtt
- **Airway:** suppl O<sub>2</sub> ± intubation or cricothyroidotomy (if laryngeal edema); β<sub>2</sub>-agonists
- Fluid resuscitation w/ lg volume of crystalloid (may extravasate up to 35% of blood volume)
- Antihistamines relieve hives & itching, *no effect on airway or hemodynamics* H1RA (diphenhydramine 50 mg IV/IM) ± H2RA (eg, ranitidine 50 mg IV)
- Corticosteroids have no immediate effect but may help prevent relapse: methylprednisolone 125 mg IV q6h if severe or prednisone 50 mg PO
- Avoid unopposed α-adrenergic vasoconstrictors

### Disposition

- Mild rxn limited to urticaria or mild bronchospasm can be observed for ≥ 6 h; admit all others
- Watch for **biphasic reaction**; occurs in 23%, typically w/in 8–10 h but up to 72 h
- At time of d/c: education re: allergen avoidance, instruction and Rx for EpiPen, allergist f/u

### Angioedema (*Ann Allergy Asthma Immunol* 2000;85:521; *J Allergy Clin Immunol* 2013;131:1491)

- Localized swelling of skin/mucosa; involves face, lips, tongue, uvula, larynx, and bowels
- Etiologies: mast cell-mediated (eg, NSAIDs); bradykinin-mediated (eg, ACEi, ARNi, hereditary angioedema, acquired C1 inhibitor deficiency); idiopathic
- Diagnosis: C4 and C1 inhibitor level, tryptase (if suspect anaphylaxis)
- Rx: intubation if risk of airway compromise; allergic angioedema: H1/H2 antihist., steroids if 2° ACEi: d/c ACEi, antihist., **icatibant** (bradykinin-receptor antag; *NEJM* 2015;372:418)
- Hereditary angioedema: synthetic C1 inhibitor cinryze (*NEJM* 2010;363:513)

# CHRONIC OBSTRUCTIVE PULMONARY DISEASE

## Definition and epidemiology (*Lancet* 2014;385:1778)

- Progressive airflow limitation caused by airway and parenchymal inflammation

### Emphysema vs. Chronic Bronchitis

	Emphysema	Chronic Bronchitis
<b>Definition</b>	Dilation/destruction of parenchyma (path definition)	Productive cough >3 mo/y $\times \geq 2$ y (clinical definition)
<b>Pathophysiology</b>	Tissue destruction V/Q: ↑ dead space fraction → hypercarbia, but only mild hypoxemia	Small airways affected V/Q: ↑ shunt fraction → severe hypoxemia, hypercapnia PHT, cor pulmonale
<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 def.: early-onset panacinar emphysema, 1–3% of COPD cases. Suspect if age <45, lower lungs affected, extrathoracic manifestations (liver disease [not if MZ subtype], FMD, pancreatitis]. ✓ serum AAT level (nb, acute phase reactant).
- Low FEV<sub>1</sub> in early adulthood important in genesis of COPD (*NEJM* 2015;373:111)
- Misc: biomass (eg, cooking fuels in enclosed space), chronic asthma (*Lancet* 2009;374:733)

## Clinical manifestations

- Chronic cough, sputum production, dyspnea; later stages → freq exac., a.m. HA, wt loss
- Exacerbation triggers: infxn, other cardiopulmonary disease, incl. PE (*Annals* 2006;144:390)  
Infxn: overt tracheobronchitis/pneumonia from viruses, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* or triggered by changes in strain of colonizers (*NEJM* 2008;359:2355)
- Physical exam: ↑ AP diameter of chest ("barrel-chest"), hyperresonance, ↓ diaphragmatic excursion, ↓ breath sounds, ↑ expiratory phase, rhonchi, wheezes during exacerbation: tachypnea, accessory muscle use, pulsus paradoxus, cyanosis
- Asthma-COPD overlap syndrome (ACOS; *NEJM* 2015;373:1241): features of both present.  
For example: reversibility of airway obstruction w/ bronchodilator in COPD; neutrophilic inflammation in asthma (more classic in COPD); eos in COPD.

## Diagnostic studies

- CXR (see Radiology inserts): hyperinflation, flat diaphragms, ± interstitial markings & bullae
- PFTs: **obstruction:** ↓↓ FEV<sub>1</sub>, ↓ FVC, **FEV<sub>1</sub>/FVC <0.7 (no sig Δ post bronchodilator)**, expiratory 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 (*Lancet* 2015;385:1789)

- Bronchodilators (first-line therapy): anticholinergics, β<sub>2</sub>-agonists (BA), theophylline**  
Long-acting (LA) antimuscarinic (LAMA; eg, tiotropium): ↓ exac., ↓ admit, ↓ resp failure (*NEJM* 2008;359:1543), better than ipratropium or LABA as mono Rx (*NEJM* 2011;364:1093)  
LABA: ~11% ↓ in exacerbations, no ↑ in CV events (*Lancet* 2016;387:1817)  
LABA + inh steroid: ? ↓ mort. vs. either alone (*NEJM* 2007;356:775)  
LAMA + LABA: ↑ FEV<sub>1</sub>, ↓ sx vs. either alone (*Chest* 2014;145:981) and superior to LABA + inh steroid (*NEJM* 2016;374:2222)
- Corticosteroids (inhaled, ICS):** ~11% ↓ in exacerb & slow ↓ FEV<sub>1</sub>; no Δ in risk of PNA or in mortality (*Lancet* 2016;387:1817)
- Roflumilast (PDE-4 inhibitor): ↑ FEV<sub>1</sub> & ↓ exacerbations when added to bronchodilator (*Lancet* 2009;374:685, 695 & 2015;385:857)
- Antibiotics: daily azithro ↓ exacerb, but not yet routine (*JAMA* 2014;311:2225)
- Mucolytics: no Δ FEV<sub>1</sub>, but ? ↓ exacerbation rate (*Lancet* 2008;371:2013)
- Oxygen:** if PaO<sub>2</sub> ≤55 mmHg or SaO<sub>2</sub> ≤89% (during rest, exercise, or sleep) to prevent cor pulmonale; only Rx proven to ↓ mortality (*Annals* 1980;93:391; *Lancet* 1981;i:681)
- Prevention:** Flu/Pneumovax; smoking cessation (eg, varenicline, bupropion) → 50% ↓ in lung function decline (*AJRCCM* 2002;166:675) and ↓ long-term mortality (*Annals* 2005;142:223)
- Rehabilitation: ↓ dyspnea and fatigue, ↑ exercise tolerance, ↓ QoL (*NEJM* 2009;360:1329)

- Experimental**
  - Lung volume reduction surgery: ↑ exer. capacity, ↓ mort. if  $\text{FEV}_1 > 20\%$ , upper-lobe, low exer. capacity (*NEJM* 2003;348:2059)
  - Bronchoscopic lung reduction w/ endobronchial valves or coils: ↑ lung fxn but significant complications (PTX, PNA) (*NEJM* 2015;373:2325; *Lancet* 2015;386:1066; *JAMA* 2016;315:175)
  - Nocturnal BiPAP: may improve survival, ? decrease QoL (*Thorax* 2009;64:561)
- Lung transplant: ↑ QoL and ↓ sx (*Lancet* 1998;351:24), ? survival benefit (*Am J Transplant* 2009;9:1640)

### Staging and prognosis

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

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

Smoking cessation & vaccinations in all. Pulm rehab in groups B–D. Consider theophylline as alternative. O<sub>2</sub> as indicated per S<sub>a</sub>O<sub>2</sub>. (Adapted from Global Initiative for Chronic Obstructive Pulmonary Disease, 2016)

### EXACERBATION

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

Agent	Dose	Comments
Ipratropium	MDI 4–8 puffs q1–2h or Nebulizer 0.5 mg q1–2h	First-line therapy ( <i>NEJM</i> 2011; 364:1093)
Albuterol	MDI 4–8 puffs q1–2h or Nebulizer 2.5–5 mg q1–2h	Benefit if component of reversible bronchoconstriction
Corticosteroids	No consensus for optimal dose & duration ( <i>Cochrane</i> 2009;CD001288) Consider: Prednisolone 30–40 mg/d × 10–14 d or even 5 d ( <i>JAMA</i> 2013;309:2223) Methylprednisolone 125 mg IV q6h × 72 h for more severe exacerbations	↓ 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) ? use periph eos >2% to trigger use ( <i>AJRCCM</i> 2012;186:48)
Antibiotics	Amox, TMP-SMX, doxy, clarithro, antipneumococcal FQ, etc., all reasonable (no single abx proven superior). Consider local flora and avoid repeat courses of same abx. ≤5d course likely enough for mild-mod exacerbation ( <i>JAMA</i> 2010;303:2035).	H. flu, M. catarrhalis, S. pneumoniae freq. precipitants. ↑ PEF, ↓ Rx failure, ? ↓ short-term mort, ↓ subseq exacerb ( <i>Chest</i> 2008;133:756 & 2013;143:82) Consider if ↑ sputum purulence or CRP >40 ( <i>Chest</i> 2013;144:1571)
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) <i>but must maintain oxygenation!</i>
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:**  $\sim 600 \text{ mL}/24-48 \text{ h}$ ; gas exchange more important than blood loss
- Massive hemoptysis usually from tortuous or invaded **bronchial arteries**

## Etiologies (Crit Care Med 2000;28:1642)

Infection/ Inflammation	<b>Bronchitis</b> (most common cause of trivial hemoptysis) <b>Bronchiectasis incl. CF</b> (common cause of massive hemoptysis) TB or aspergilloma (can be massive); pneumonia or lung abscess
Neoplasm	Usually primary <b>lung cancer</b> , sometimes metastasis (can be massive)
Cardiovasc.	<b>PE</b> (can be massive), pulmonary artery rupture ( $2^{\circ}$ to instrumentation), CHF, mitral stenosis, trauma/foreign body, bronchovascular fistula
Other	<b>Vasc</b> (GPA, Goodpasture's, Behcet's; can be massive), AVM, anticoag (w/ underlying lung dis), coagulopathy, cocaine, pulm hemosiderosis

## Diagnostic workup

- Localize bleeding site (r/o GI or ENT source by H&P  $\pm$  endo); determine whether **unilateral or bilateral, localized or diffuse, parenchymal or airway** by CXR/ chest CT  $\pm$  bronch
- PT, PTT, CBC to rule out **coagulopathy**
- Sputum culture/stain for bacteria, fungi and AFB; cytology to **r/o malignancy**
- ANCA, anti-GBM, urinalysis to  $\checkmark$  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  $\uparrow$  risk of asphyxiation
- Massive hemoptysis: **put bleeding side dependent**; selectively intubate nl lung if needed  
*Angiography:* Dx & Rx (vascular occlusion balloons or **selective embol of bronchial art**)  
*Rigid bronch:* allows more options (electrocautery, laser) than flex. Surgical resection.

# BRONCHIECTASIS

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

- Obstructive airways disease of bronchi and bronchioles, chronic transmural inflam w/ airway dilatation and thickening, collapsibility, mucus plugging w/ impaired clearance

## Initial workup

- H&P: cough, dyspnea, copious sputum production,  $\pm$  hemoptysis, inspiratory "squeaks"
- CXR: scattered or focal; rings of bronchial cuffing; "tram track" of dilated, thick airways
- PFTs: obstructive; chest CT: airway dilation & thickening  $\pm$  cystic  $\Delta$ s, infiltrates, adenopathy

Etiology	Other Features	Diagnostic Testing
Chronic infxns (eg, MTb, ABPA)	Chronic cough, freq/persist infiltrate, refract asthma (ABPA)	Sputum cx (incl myobact, fungal), $\pm$ bronch/BAL, IgE & eos (ABPA)
1° ciliary dyskin	Sinusitis, infertility, otitis	Dynein mutations
Immunodefici.	Recurrent infxns often as child	IgA, IgG, IgM, IgG subclasses
RA, SLE	Resp sx may precede joint sx	RF, ANA
IBD	Not relieved by bowel resection	Colonoscopy, biopsy
$\alpha_1$ -AT deficiency	Lower lobe emphysema	$\alpha_1$ -AT level
Anatomic	R middle lobe synd. from sharp takeoff, foreign body aspir.	Bronchoscopy

## Treatment

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

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

- Autosomal recessive genetic disorder due to mutations in chloride channel (CFTR gene)
- $\uparrow$  mucus thickness,  $\downarrow$  mucociliary clearance,  $\uparrow$  infections  $\rightarrow$  bronchiectasis
- Clinical: recurrent PNA, weight loss, sinus infxns, infertility, pancreatic insuffic (fatty stools)
- Rx: airway clearance (chest PT, inh hypertonic saline, DNase), abx for exacerb. for drug-resistant org. (eg, *Pseudomonas*, *Burkholderia*), gene targeted with CFTR potentiator (ivakaftror) & corrector (lumakaftor) (NEJM 2011;365:1663 & 2015;372:220), lung transplant

## Non-tuberculous mycobacterium (NTM; ubiquitous hydrophilic bacteria)

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

# SOLITARY PULMONARY NODULE

## Principles

- Definition: single, <3 cm, surrounded by normal lung, no LAN or pleural effusion
- Often "incidentalomas," esp with ↑ CT use, but may still be early, curable malignancy

## Etiologies

Benign (70%)	Malignant (30%)
<b>Granuloma</b> (80%): TB, histo, coccidio	<b>Bronchogenic carcinoma</b> (75%): adeno & large cell (peripheral)
<b>Hamartoma</b> (10%)	squamous & small cell (central)
Bronchogenic cyst, AVM, pulm infarct	<b>Metastatic</b> (20%): breast, head & neck, colon, testicular, renal, sarcoma, melanoma
Echinococcosis, ascariasis, aspergilloma	Carcinoid, primary sarcoma
Wegener's, rheumatoid nodule	
Lipoma, fibroma, amyloidoma, pneumonitis	

## Initial evaluation

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

## Diagnostic studies

- PET:** detects metab. activity of tumors, 97% Se & 78% Sp for malig. (esp. if >8 mm) also useful for surgical staging b/c may detect unsuspected mets (JAMA 2001;285:914) useful in deciding which lesions to bx vs. follow w/ serial CT (J Thor Oncol 2006;1:71)
- Transthoracic needle biopsy (TTNB):** if tech. feasible, 97% will obtain definitive tissue dx (AJR 2005;185:1294); if noninformative or malignant → resect
- Video-assisted thoracoscopic surgery (VATS):** for percutaneously inaccessible lesions; highly sensitive and allows resection; has replaced thoracotomy
- Transbronchial bx (TBB): most lesions too small to reliably sample w/o endobronchial U/S (Chest 2003;123:604); bronch w/ brushings low-yield unless invading bronchus; navigational bronchoscopy w/ 70% yield, ↑ sens w/ larger nodules (Chest 2012;142:385)
- PPD, fungal serologies, ANCA

## Management (for solid SPN >8 mm; if ≤8 mm, serial CT) (Chest 2013;143:840)

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

# SLEEP APNEA

## Definition and pathophysiology

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

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

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

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

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

# INTERSTITIAL LUNG DISEASE

## WORKUP OF ILD (Thorax 2008;63:v1)

ILD  
Z-9

### Broad categories

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

### Rule out mimickers of ILD

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

### History and physical exam

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

### Diagnostic studies (see Appendix & Radiology inserts)

- CXR and **high-resolution chest CT**: reticular, nodular or ground-glass pattern  
Upper lobe-predominant → coal, silica, hypersens, sarcoid, TB, RA  
Lower lobe-predominant → IPF, asbestos, scleroderma  
Adenopathy → sarcoidosis, berylliosis, silicosis, malignancy, fungal infections  
Pleural disease → collagen-vascular diseases, asbestosis, infections, XRT
- PFTs: ↓ DLCO (early sign), restrictive pattern (↓ volumes), ↓ PaO<sub>2</sub> (esp. w/ exercise); if also obstructive, consider sarcoid, LAM, silicosis
- Serologies: ✓ ACE, ANA, RF, ANCA, anti-GBM, HIV, ± myositis panel & other serologies
- Bronchoalveolar lavage: dx infxn, hemorrhage, eosinophilic syndromes, PAP
- Biopsy (transbronch, CT-guided, VATS, open) if no clear precipitant and w/u unrevealing

## SPECIFIC ETIOLOGIES OF ILD

### Sarcoidosis (Lancet 2014;383:1155)

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

### Clinical Manifestations of Sarcoidosis

Organ system	Manifestations
Pulmonary	Hilar LAN; fibrosis; pulm hypertension. Stages: I = bilat hilar LAN; II = LAN + ILD; III = ILD only; IV = diffuse fibrosis.
Cutaneous (~15%)	Waxy skin plaques; lupus pernio (violaceous facial lesions) Erythema nodosum (red tender nodules due to panniculitis, typically on shins). Ddx: idiopathic (34%), infxn (33%, strep, TB), sarcoid (22%), drugs (OCP, PCNs), vasculitis (Behçet's), IBD, lymphoma.
Ocular (10–30%)	Anterior > posterior uveitis; ↑ lacrimal gland
Endo & renal (10%)	Nephrolithiasis, hypercalcemia (10%), hypercalciuria (40%) Due to vitamin D hydroxylation by macrophages
Neuro (10% clin, 25% path)	CN VII palsy, periph neuropathies, CNS lesions, seizures
Cardiac (5% clin, 25% path)	Conduction block, VT, CMP
Liver, spleen, BM	Granulomatous hepatitis (25%), splenic & BM gran. (50%)
Constitutional	Fever, night sweats, anorexia & wt loss (a/w hepatic path)
Musculoskeletal	Arthralgias, periarticular swelling, bone cysts

- **Löfgren's syndrome:** erythema nodosum + hilar adenopathy + arthritis (good prognosis)
- Diagnostic studies: **LN bx** → **noncaseating granulomas** + multinucleated giant cells  
endobronchial ultrasonography superior to conventional bronch (JAMA 2013;309:2457)  
<sup>18</sup>FDG PET can be used to identify extent and potentially targets for dx bx  
↑ **ACE** (Se 60%, 90% w/ active dis., Sp 80%, false + in granulomatous diseases)
- To assess extent: CXR, PFTs, full ophtho exam, ECG, CBC (lymphopenia, ↑ eos), Ca, 24-h urine for Ca, LFTs; ± Holter, echo, cardiac MRI, brain MRI, etc., based on s/s
- Rx: **steroids** if sx or extrathoracic organ dysfxn (eg, prednisone 20–40 mg/d), improves sx, but doesn't Δ long-term course; hydroxychloroquine for extensive skin disease; anti-TNF, MTX, AZA, mycophenolate or cyclophosphamide for chronic/refractory disease
- Prognosis: ~<sup>2</sup>/<sub>3</sub> spontaneously remit w/in 10 y (60–80% of stage I, 50–60% stage II, 30% stage III), w/ relapses uncommon; ~<sup>1</sup>/<sub>3</sub> have progressive disease

### Exposure

- **Drugs/iatrogenic**

**Amio** (dose & duration depend.): chronic interstitial PNA ↔ ARDS; Rx: d/c amio; steroids

Other drugs: nitrofurantoin, sulfonamides, thiazides, INH, hydralazine, gold

Chemo: **bleomycin** (triggered by hyperoxia), busulfan, cyclophosphamide, MTX, etc.

**XRT:** COP/BOOP w/ sharply linear, nonanatomic boundaries; DAH

- **Pneumoconioses** (inorganic dusts) (NEJM 2000;342:406; Clin Chest Med 2004:467)

Coal worker's: upper lobe coal macules; may progress to massive fibrosis

Silicosis: upper lobe opacities ± eggshell calcification of lymph nodes; ↑ risk of TB

Asbestosis: lower lobe fibrosis, calcified pleural plaques, DOE, dry cough, rales on exam. Asbestos exposure also → pleural plaques, benign pleural effusion, diffuse pleural thickening, rounded atelectasis, mesothelioma, lung Ca (esp. in smokers).

Berylliosis: multisystemic granulomatous disease that mimics sarcoidosis

- **Hypersensitivity pneumonitis** (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)

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

#### • Rheumatologic disease

Scleroderma: fibrosis in ~67%; PHT seen in ~10% of CREST Pts

PM-DM: ILD & weakness of respiratory muscles; MCTD: PHT & fibrosis

SLE & RA: pleuritis and pleural effusions more often than ILD; SLE can cause DAH

#### • Vasculitis (can p/w DAH)

GPA (Wegener's granulomatosis) (+ c-ANCA) w/ necrotizing granulomas

EGPA (Churg-Strauss) (+ c- or p-ANCA) w/ eosinophilia & necrotizing granulomas

Microscopic polyangiitis (+ p-ANCA) w/o granulomas

#### • Goodpasture's syndrome = DAH + RPGN; typically in smokers; (+ anti-GBM in 90%)

#### • Lymphangioleiomyomatosis (LAM): cystic, ↑ in ♀, Rx w/ sirolimus (NEJM 2011;364:1595)

### Idiopathic interstitial pneumonias (IIPs) (AJRCCM 2013;188:733; NEJM 2014;370:1820)

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

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

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

- Rx for UIP/IPF: suppl O<sub>2</sub>, pulm rehab, Rx for GERD, lung transplant referral
- **Pirfenidone** (antifibrotic) or **nintedanib** (tyrosine kin. inhib mediating fibrogenic growth factors) ↓ rate of FVC decline (NEJM 2014;370:2071 & 2083; AJRCCM 2015;192:3)  
High-dose steroids may be used for acute exacerbations
- Steroids for other IIPs: NSIP (esp. cellular type) and COP (AJRCCM 2000;162:571); ? benefit for AIP and DIP/RB-ILD (for which Pts should stop smoking)

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

#### • Allergic bronchopulmonary aspergillosis (ABPA)

- Löffler's syndrome: parasites/drugs → transient pulm infilt + cough, fever, dyspnea, eos
- Acute eosinophilic PNA (AEP): acute hypox febrile illness; Rx: steroids, tobacco cessation
- Chronic eosinophilic pneumonia (CEP): "photonegative" of CHF, typically in women

### Miscellaneous

- Pulm alveolar proteinosis (PAP): accum of surfactant-like phospholipids; ♂ smokers; white & gummy sputum; BAL milky fluid (NEJM 2003;349:2527); Rx w/ lung lavage & GMCSF
- Langerhans cell granulomatosis (LCG): young ♂ smokers; apical cysts; PTX (25%)
- Lymphocytic interstitial PNA: polyclonal B-cell infiltration (? lymphoma); Rx: steroids

# PLEURAL EFFUSION

## Pathophysiology

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

## Transudates

- **Congestive heart failure (40%):** 80% bilateral, ± cardiomegaly on CXR occasionally exudative (esp. after aggressive diuresis or if chronic), but ~75% of exudative effusions in CHF Pts found to have non-CHF cause (Chest 2002;122:1518)
- **Constrictive pericarditis** (knock on exam, calcification or thickening on imaging)
- **Cirrhosis ("hepatic hydrothorax"):** diaphragmatic pores allow passage of ascitic fluid often right-sided ( $\frac{2}{3}$ ) & 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 (esp. breast, lymphoma, etc.), mesothelioma (✓ serum osteopontin levels; NEJM 2005;353:15)

- **Pulmonary embolism (10%):** effusions in ~40% of PEs; exudate (75%) > transudate (25%); hemorrhagic—must have high suspicion b/c presentation highly variable

- **Collagen vascular disease:** RA (large), SLE (small), Wegener's, Churg-Strauss

- **Gastrointestinal diseases:** pancreatitis, esophageal rupture, abdominal abscess

- **Hemothorax (Hct<sub>eff</sub>/Hct<sub>blood</sub> >50%):** trauma, PE, malignancy, coagulopathy, leaking aortic aneurysm, aortic dissection, pulmonary vascular malformation

- **Chylothorax (triglycerides >110):** thoracic duct damage due to trauma, malignancy, LAM

- Other:

post-CABG: left-sided; initially bloody, clears after several wks

Dressler's syndrome (pericarditis & pleuritis post-MI), uremia, postradiation therapy

Asbestos exposure: benign;  $\oplus$  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)

↓ PTX w/ U/S and experienced supervisor; even with INR ~1.9, risk of bleed low w/ U/S & experienced operator (Chest 2009;135:1315 & 2013;144:456; Archives 2010;170:332)

- **Transudate vs. exudate (JAMA 2014;311:2422)**

**Light's criteria:** exudate =  $TP_{eff}/TP_{serum} > 0.5$  or  $LDH_{eff}/LDH_{serum} > 0.6$  or  $LDH_{eff} > \frac{2}{3} ULN$  of  $LDH_{serum}$ ; 97% Se, 85% Sp; best Se of all methods; however, will misidentify 25% of transudates as exudates; .. if clinically suspect transudate but meets criterion for exudate, confirm w/ test w/ higher Sp

exudative criteria w/ better Sp:  $chol_{eff} > 55 \text{ mg/dL}$  (95–99% Sp);  $chol_{eff} > 45 \text{ mg/dL}$  and  $LDH_{eff} > 200$  (98% Sp);  $chol_{eff}/chol_{serum} > 0.3$  (94% Sp); serum-effusion alb gradient  $\leq 1.2$  (92% Sp); serum-effusion TP gradient  $\leq 3.1$  (91% Sp)

CHF effusions: TP may ↑ with diuresis or chronicity → "pseudoexudate"; alb gradient  $\leq 1.2$ ,  $chol_{eff} > 60 \text{ mg/dL}$  (Se 54%, Sp 92%) or clin judgment to 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  $\geq 1500$  pg/mL has 91% Se & 93% Sp for CHF (Am J Med 2004;116:417)
  - WBC & diff.: exudates tend to have ↑ WBC vs. transudates but nonspecific neutrophils → parapneumonic, PE, pancreatitis
  - lymphocytes ( $>50\%$ ) → cancer, TB, rheumatologic
  - eos ( $>10\%$ ) → blood, air, drug rxn, asbestos, paragonimiasis, Churg-Strauss, PE
  - RBC: Hct<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>1</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
  - fibulin-3: ↑ plasma and/or effusion levels → mesothelioma (NEJM 2012;367:1417)
- Chest CT; pleural biopsy; VATS
- Undiagnosed persistent pleural effusions (Clin Chest Med 2006;27:309)
  - Transudative: most commonly CHF or hepatic hydrothorax. ✓ s/s CHF or cirrhosis, NT-proBNP<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- $\gamma$  release assay; consider thoracoscopy

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

Etiology	Appear	WBC diff	RBC	pH	Glc	Comments
<b>CHF</b>	clear, straw	<1000 lymphs	<5000	normal	≈ serum	bilateral, cardiomegaly
<b>Cirrhosis</b>	clear, straw	<1000	<5000	normal	≈ serum	right-sided
<b>Uncomplicated parapneumonic</b>	turbid	5–40,000 polys	<5000	normal to ↓	≈ serum ( $>40$ )	
<b>Complicated parapneumonic</b>	turbid to purulent	5–40,000 polys	<5000	↓↓	↓↓ (<40)	need drainage
<b>Empyema</b>	purulent	25–100,000 polys	<5000	↓↓↓	↓↓	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	<1000	↓	RA ↓↓↓ SLE nl	↑ RF, ↓ C <sub>1</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	<5000 >50,000	<10,000	↓↓↓	↓↓	left-sided, ↑ amylase

### Treatment

- Symptomatic effusion: therapeutic thoracentesis, treat underlying disease process
- Parapneumonic effusion (Chest 2000;118:1158)
  - uncomplicated → antibiotics for pneumonia
  - >½ hemithorax or complicated or empyema → tube thoracostomy**  
(otherwise risk of organization and subsequent need for surgical decortication)
  - loculated → tube thoracostomy or VATS; intrapleural t-PA + DNase ↓ need for surgical referral (NEJM 2011;365:518)
- Malignant effusion: serial thoracenteses vs. tube thoracostomy + pleurodesis (success rate ~80–90%) vs. indwelling pleural catheter (JAMA 2012;307:2383); systemic steroids & pH  $<7.2$  a/w ↑ pleurodesis failure rate
- TB effusions: effusion will often resolve spontaneously; however, treat Pt for active TB
- Hepatic hydrothorax
  - Rx: Δ pressure gradient (ie, ↓ ascitic fluid volume, NIPPV)  
avoid chest tubes; prn thoracenteses, pleurodesis, TIPS or VATS closure of diaphragmatic defects if medical Rx fails; NIPPV for acute short-term management
  - spontaneous bacterial empyema (SBEM) can occur (even w/o SBP being present), ∴ thoracentesis if suspect infection
  - transplant is definitive treatment and workup should begin immediately

# VENOUS THROMBOEMBOLISM (VTE)

VTE  
2-13

## Definitions

- Superficial thrombophlebitis: pain, tenderness, erythema along superficial vein
- Deep venous thrombosis (DVT): **Proximal** = thrombosis of iliac, femoral, or popliteal veins (nb, "superficial" femoral vein part of deep venous system). **Distal** = calf veins below knee; lower risk of PE/death than proximal (*Thromb Haem* 2009;102:493).
- Pulmonary embolism (PE): thrombosis originating in venous system and embolizing to pulmonary arterial circulation; 1 case/1000 person y; 250,000/y (*Archives* 2003;163:1711)

## Risk factors

- Virchow's triad for thrombogenesis
  - stasis:** bed rest, inactivity, CHF, CVA w/in 3 mo, air travel >6 h (*NEJM* 2001:779)
  - injury to endothelium:** trauma, surgery, prior DVT, inflamm., central catheter
  - thrombophilia:** genetic disorders (qv), HIT, OCP, HRT, tamoxifen, raloxifene
- Malignancy (12% of "idiopathic" DVT/PE; *Circ* 2013;128:2614)
- History of thrombosis (greater risk of recurrent VTE than genetic thrombophilia)
- Obesity, smoking, acute infection, postpartum (*JAMA* 1997;277:642; *Circ* 2012;125:2092)

## Thromboprophylaxis (*Chest* 2012;141:e195S, 227S, 278S)

Patient & situation	Prophylaxis
Low-risk med; same-day surg & <40 y	Early, aggressive ambulation
Minor surgery in mobile Pt	Mechanical Ppx
High-risk med (immobile, h/o VTE, thrombophilia or cancer) & most surgery Pts	<b>UFH</b> 5000 U SC bid or tid, or <b>LMWH</b> , or fonda (if HIT $\oplus$ ), or mech Ppx (esp. if high bleed risk); ? extended Ppx w/ <b>NOAC</b> ( <i>NEJM</i> 2016;375:534)
High-risk surg (trauma, stroke, spinal cord injury, h/o VTE/thrombophilia)	[LMWH or UFH SC] + mech Ppx
Orthopedic surgery	LMWH [or fonda, direct oral anticoag (qv) or warfarin (INR 2–3)] + mech Ppx NOACs overall appear favorable vs LMWH

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

## Clinical manifestations—DVT

- Calf pain, swelling (>3 cm c/w unaffected side), venous distention, erythema, warmth, tenderness, palpable cord,  $\oplus$  Homan's sign (calf pain on dorsiflexion, seen in <5%)
- **Phlegmasia cerulea dolens:** massive prox DVT w/ edema, cyanosis, pain, compart. synd.
- 50% of Pts with sx DVT have asx PE
- Popliteal (Baker's) cyst: may lead to DVT due to compression of popliteal vein

## "Simplified Wells" Pretest Probability Scoring of DVT (*JAMA* 2006;295:199)

- +1 point each for: active cancer (Rx ongoing or w/in 6 mo or palliative); paralysis, paresis, or recent immobilization of lower extremities; recently bedridden for  $\geq 3$  d or major surgery w/in 12 wk; localized tenderness along distribution of deep venous system; entire leg swelling; calf  $\geq 3$  cm larger than asx calf (at 10 cm below tibial tuberosity); pitting edema confined to sx leg; collateral superficial veins (nonvaricose); previous DVT  
-2 points if alternative dx at least as likely as DVT

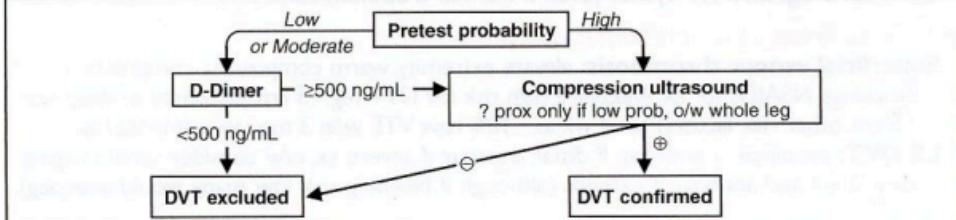
## Pretest Probability Assessment (useful if outPt, less so if inPt; *JAMA IM* 2015;175:1112)

- | Score $\leq 0$       | Score 1 or 2               | Score $\geq 3$         |
|----------------------|----------------------------|------------------------|
| Low probability (5%) | Moderate probability (17%) | High probability (53%) |
- For UE DVT, +1 point each for venous cath, local pain, & unilateral edema, -1 if alternative dx.  $\leq 1$  = unlikely;  $\geq 2$  = likely. U/S if likely or if unlikely but abnl D-dimer

## Diagnostic studies—DVT

- D-dimer: <500 helps r/o; ? use 1000 as threshold if low risk (*Annals* 2013;158:93)
- Compression U/S >95% Se & Sp for sx DVT (lower if asx); survey whole leg if  $\geq$ mod prob

Figure 2-3 Approach to suspected DVT (*Chest* 2012;141:e351S)



**Clinical manifestations—PE**

- Dyspnea (~50%), pleuritic chest pain (~40%), cough (~23%), hemoptysis (~8%)
- ↑ RR (>70%), crackles (51%), ↑ HR (30%), fever, cyanosis, pleural friction rub, loud P<sub>2</sub>
- Massive: syncope, HoTN, PEA; ↑ JVP, R-sided S<sub>3</sub>, Graham Steell (PR) murmur

**Simplified Wells Pretest Probability Scoring for PE** (*Annals* 2011;154:709)

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>Prior PE or DVT</li> <li>Active cancer</li> <li>Immobilization (bed rest ≥3 d) or surgery w/in 4 wk</li> <li>Alternative dx less likely than PE</li> </ul> | <ul style="list-style-type: none"> <li>Clinical signs of DVT</li> <li>HR &gt;100 bpm</li> <li>Hemoptysis</li> </ul> |
|---|---|

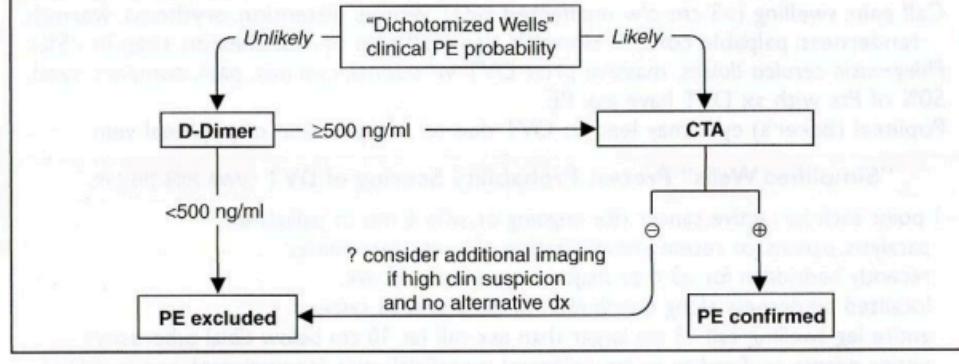
**Dichotomized Wells Probability Assessment**

≤1 Variable = “Unlikely” (13% probability)      ≥2 Variables = “Likely” (39% probability)

**Diagnostic studies—PE** (*EJH* 2014;35:3033)

- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, ↑ hemidiaphragm, Hampton hump (wedge-shaped density abutting pleura); Westermark sign (avascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, S<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 mmHg, 6% w/ nl A-a gradient (*Chest* 1991;100:598)
- D-dimer (*JAMA* 2015;313:1668): high Se, poor Sp (~25%); ⊖ ELISA has >99% NPV  
∴ use to r/o PE if “unlikely” pretest prob. (*JAMA* 2006;295:172)  
consider age-specific cut point: 500 if <50 y, 10x age if ≥50 y (*JAMA* 2014;311:1117)
- Echocardiography: useful for risk stratification (RV dysfxn), but not dx (Se <50%)
- V/Q scan: high Se (~98%), low Sp (~10%). Sp improves to 97% for high prob VQ.  
Use if pretest prob of PE high and CT not available or contraindicated. Can also exclude PE if low pretest prob, low prob VQ, but 4% false ⊖ (*JAMA* 1990;263:2753).
- CT angiography** (CTA; see Radiology inserts; *JAMA* 2015;314:74): Se ~90% & Sp ~95%; PPV & NPV >95% if imaging concordant w/ clinical suspicion, ≤80% if discordant (∴ need to consider both); ~1/4 of single & subseg may be false ⊕; CT may also provide other dx
- Lower extremity compression U/S shows DVT in ~9%, sparing CTA, but when added to CTA, does not Δ outcomes (*Lancet* 2008;371:1343)

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

**Workup for idiopathic VTE** (*NEJM* 2015;373:697)

- Thrombophilia workup:** ✓ if ⊕ FH, may be helpful but consider timing as thrombus, heparin and warfarin Δ results. Not helpful for Pt if will not Δ management (eg, plan for long-term anticoagulation regardless), although could be of use to relatives.
- Malignancy workup:** 12% Pts w/ “idiopathic” DVT/PE will have malignancy; age-appropriate screening adequate; avoid extensive w/u

**Risk stratification for Pts with PE**

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

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

- Superficial venous thrombosis:** elevate extremity, warm compresses, compression stockings, NSAIDs for sx. Anticoag if high risk for DVT (eg, ≥5 cm, proximity to deep vein ≤5 cm, other risk factors) for 4 wk as ~10% have VTE w/in 3 mo (*Annals* 2010;152:218)
- LE DVT:** proximal → anticoag. If distal: anticoag if severe sx; o/w consider serial imaging over 2 wk and anticoag if extends (although if bleeding risk low, many would anticoag).

- **UE DVT:** anticoagulate (same guidelines as LE; NEJM 2011;364:861). If catheter-associated, need not remove if catheter functional and ongoing need for catheter.
- **PE:** anticoagulate

### Anticoagulation options (Chest 2012;141:e419S & 2016;149:315; JAMA 2014;311:717)

- Initiate parenteral Rx immediately if high or intermed suspicion while dx testing underway
- **Non-vitamin K antag oral anticoag** (NEJM 2010;363:2499; 2012;366:1287; 2013;369:799 & 1406)
  - Preferred b/c as good/better than warfarin in preventing recurrent VTE w/ less bleeding
  - Can give as sole anticoag w/ initial loading dose (riva or apixa) or initiate after  $\geq 5$  d of parenteral anticoag (edox or dabi; 1<sup>st</sup> dose when d/c IV UFH or w/in 2 h before next LMWH dose would have been due)
- **LMWH** (eg, enoxaparin 1 mg/kg SC bid or dalteparin 200 IU/kg SC qd)
  - Preferred over UFH (espec in cancer) except: renal failure ( $\text{CrCl} < 25$ ), extreme obesity, hemodynamic instability or bleed risk (Cochrane 2004;CD001100)
  - Can use as outpatient bridge to long-term oral anticoagulation
- If cancer, LMWH  $\downarrow$  recurrence and mortality c/w UFH & warfarin (NEJM 2003;349:146; Lancet Oncol 2008;9:577); ✓ head CT for brain mets if melanoma, renal cell, thyroid, chorioCA
- **Fondaparinux:** 5–10 mg SC qd (NEJM 2003;349:1695); use if HIT  $\oplus$ ; avoid if renal failure
- **IV UFH:** 80 U/kg bolus  $\rightarrow$  18 U/kg/h  $\rightarrow$  titrate to PTT 1.5–2.3  $\times$  cntl (eg, 60–85 sec); preferred option when contemplating thrombolysis or catheter-based Rx (qv)
- IV Direct thrombin inhibitors (eg, argatroban, lepirudin) used in HIT  $\oplus$  Pts
- **Warfarin** (goal INR 2–3): start same day as parenteral anticoag unless instability and ? need for lytic, catheter-based Rx or surgery; overlap  $\geq 5$  d w/ parenteral anticoag & until INR  $\geq 2 \times \geq 24$  h

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

- Typically TPA 100 mg over 2 h or wt-adjusted TNK bolus; risk of ICH ~1.5%,  $\uparrow$  w/ age
- **Massive PE** (hemodynamic compromise):  $\downarrow$  death and recurrent PE each by ~50% (JAMA 2014;311:2414; EHJ 2015;36:605) & lower PVR long term (JACC 1990;15:65)
- **Submassive PE** (hemodyn. stable but RV dysfxn on echo or enlargement on CTA, or ? marked dyspnea or severe hypoxemia):  $\downarrow$  hemodyn. decompensation,  $\uparrow$  ICH,  $\downarrow$  mortality; consider if  $< 75$  y and/or low bleed risk (NEJM 2014;370:1402; JAMA 2014;311:2414). Some centers prefer catheter-directed therapy.
- **Moderate PE w/ large clot burden** ( $\geq 2$  lobar arteries or main artery on CT or high-prob VQ w/  $\geq 2$  lobes w/ mismatch): low-dose lytic (50 mg if  $\geq 50$  kg or 0.5 mg/kg if  $< 50$  kg; for both 10-mg bolus  $\rightarrow$  remainder over 2 h)  $\downarrow$  pulm HTN w/  $\sim$  bleeding vs. heparin alone
- **DVT:** consider if (a) acute ( $< 14$  d) & extensive (eg, iliofemoral), (b) severe sx swelling or ischemia, (c) catheter-directed Rx not available, and (d) low bleed risk

### Mechanical intervention

- **Catheter-directed** (fibrinolytic & thrombus fragmentation/aspiration; Circ 2012;126:1917)
  - Consider if extensive DVT (see above) and to  $\downarrow$  postthrombotic synd (Lancet 2012;379:31)
  - Consider if PE w/ hemodyn. compromise or high risk & not candidate for systemic lysis or surgical thrombectomy (Circ 2011;124:2139). Preferred to systemic lytic by some centers.
  - U/S-assisted improves hemodynamics & RV fxn vs. anticoag alone (EHJ 2015;36:597)
- **Thrombectomy:** if large, proximal PE + hemodynamic compromise + contra. to lysis; consider in experienced ctr if large prox. PE + RV dysfxn (J Thorac CV Surg 2005;129:1018)
- **IVC filter:** use instead of anticoagulation if latter contraindicated
  - No benefit to adding to anticoag (including in submassive) (JAMA 2015;313:1627)
  - Consider removable filter for temporary indications
  - Complications: migration, acute DVT,  $\uparrow$  risk of recurrent DVT & IVC obstruction (5–18%)

### Duration of full-intensity anticoagulation

- Superficial venous thrombosis: 4 wk
- 1<sup>st</sup> prox DVT or PE 2° reversible/time-limited risk factor or distal DVT: 3–6 mo
- 1<sup>st</sup> unprovoked prox DVT/PE:  $\geq 3$  mo, then reassess; benefit to prolonged Rx
  - Consider clot, bleed risk, Pt preference, and intensity of Rx when crafting strategy: full-dose NOAC: 80–90%  $\downarrow$  recurrent VTE, 2–5 $\times$  bleeding, but no signif excess in major bleeding (NEJM 2010;363:2499; 2013;368:699 & 709)
  - $\frac{1}{2}$  dose apixa (2.5 mg bid): 80%  $\downarrow$  recur. VTE, w/o signif  $\uparrow$  bleeding (NEJM 2013;368:699)
  - warfarin, either regular (JAMA 2015;314:31) or low-intensity (NEJM 2003;348:1425)
  - aspirin: 32%  $\downarrow$  recurrent VTE (NEJM 2012;366:1959 & 367:1979)
- 2<sup>nd</sup> VTE event or cancer: indefinite (or until cancer cured) (NEJM 2003;348:1425)

### Complications & prognosis

- Postthrombotic syndrome (23–60%): pain, edema, venous ulcers
- Recurrent VTE: 1%/y (after 1<sup>st</sup> VTE) to 5%/y (after recurrent VTE)
- Chronic thromboembolic PHT after acute PE ~3.8%, consider thromboendarterectomy
- Mortality: ~10% for DVT and ~10–15% for PE at 3–6 mo (Circ 2008;117:1711)

# PULMONARY HYPERTENSION (PHT)

PHT defined as PA mean pressure  $\geq 25$  mmHg at rest

PA mean =  $CO \times PVR + PA$  wedge pressure. Trans pulm gradient = PA mean - PA wedge.

## Etiologies (Revised WHO Classification) (Circ 2009;119:2250)

<b>Primary Pulmonary arterial HTN (PAH)</b> (group 1) Precapillary PHT $PCWP \leq 15$ mmHg $\uparrow$ transpulm grad $\uparrow$ PVR	<ul style="list-style-type: none"> <li>Idiopathic (IPAH): yearly incidence 1–2 per million; mean age of onset 36 y (<math>\delta</math> older than <math>\varphi</math>); <math>\delta:\varphi = \sim 2:1</math>, usually mild <math>\uparrow</math> in PAP</li> <li>Familial (FPAH)</li> <li>Associated conditions (APAH)           <ul style="list-style-type: none"> <li>Connective tissue dis.: CREST, SLE, MCTD, RA, PM, Sjögren</li> <li>Congenital L <math>\rightarrow</math> R shunts: ASD, VSD, PDA</li> <li>Portopulmonary HTN (? <math>2^{\circ}</math> vasoactive substances not filtered in ESLD; <math>\neq</math> hepatopulmonary syndrome)</li> <li>HIV; drugs &amp; toxins: anorexic agents, L-tryptophan</li> </ul> </li> <li>Pulmonary veno-occlusive disease: ? <math>2^{\circ}</math> chemo, BMT; orthopnea, pl eff, <math>CHF</math>, nl PCWP; art vasodil. worsen CHF (AJRCCM 2000;162:1964)</li> <li>Pulmonary capillary hemangiomatosis</li> </ul>
<b>Left heart disease</b> (group 2). $\uparrow$ PCWP	<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>
<b>Lung diseases and/or chronic hypoxemia</b> (group 3)	<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>
<b>Chronic thromboembolic dis</b> (group 4)	<ul style="list-style-type: none"> <li>Prox or distal PEs; <math>\sim 1/2</math> w/o clinical h/o PE (NEJM 2011;364:351)</li> <li>Nonthrombotic emboli (tumor, foreign body, parasites)</li> </ul>
<b>Miscellaneous</b> (group 5)	<ul style="list-style-type: none"> <li>Sarcoidosis, histiocytosis X, LAM, schistosomiasis, ESRD</li> <li>Compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis, histoplasmosis, XRT)</li> <li>Other: thyroid dis., glycogen storage dis., Gaucher dis., HHT, sickle cell etc, chronic myeloprolif d/o, splenectomy</li> </ul>

## Clinical manifestations

- Dyspnea, exertional syncope (hypoxia,  $\downarrow$  CO), exertional chest pain (RV ischemia)
- Symptoms of R-sided CHF (eg, peripheral edema, RUQ fullness, abdominal distention)
- WHO class: I = asx w/ ordinary activity; II = sx w/ ord. activ; III = sx w/ min activ; IV = sx at rest

## Physical exam

- PHT: prominent P<sub>2</sub>, R-sided S<sub>4</sub>, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- $\pm$  RV failure:  $\uparrow$  JVP, hepatomegaly, peripheral edema

## Diagnostic studies & workup (JACC 2013;62:D40; Circ 2014;130:1820)

- High-res chest CT: dil. & pruning of pulm arteries,  $\uparrow$  RA & RV; r/o parenchymal lung dis.
- ECG: RAD, RBBB, RAE ("P pulmonale"), RVH (Se 55%, Sp 70%)
- PFTs: disproportionate  $\downarrow$  D<sub>L</sub>co, mild restrictive pattern; r/o obstructive & restrict. lung dis.
- ABG & polysomnography:  $\downarrow$  PaO<sub>2</sub> and SaO<sub>2</sub> (espec w/ exertion),  $\downarrow$  PaCO<sub>2</sub>,  $\uparrow$  A-a gradient; r/o hypoventilation and OSA
- TTE:  $\uparrow$  RVSP (but estimate over/under by  $\geq 10$  mmHg in  $\frac{1}{2}$  of PHT Pts; Chest 2011;139:988)
  - $\uparrow$  RA, RV, & PA;  $\uparrow$  pressure  $\rightarrow$  interventricular septum systolic flattening ("D" shape)
  - $\downarrow$  RV systolic fxn (TAPSE  $< 1.6$  cm); TR, PR; r/o LV dysfxn, MV, AoV, congenital disease
- RHC:  $\uparrow$  RA, RV, & PA pressures;  $\checkmark$  L-sided pressures and for shunt
  - if PAH: nl PCWP,  $\uparrow$  transpulm gradient (mean PAP-PCWP  $> 12-15$ ),  $\uparrow$  PVR,  $\pm$   $\downarrow$  CO
  - if  $2^{\circ}$  to L-heart disease: PCWP (or LVEDP)  $> 15$ ; if PVR nl  $\rightarrow$  "passive PHT"; PVR  $> 240$  suggests mixed picture: if  $\downarrow$  PCWP  $\rightarrow$   $\downarrow$  PVR, then "reactive" PHT; if no  $\Delta$ , then "fixed"
- CTA (large/med vessel), V/Q scan (small vessel to r/o CTEPH),  $\pm$  pulm angio if still concern
- Vasculitis labs: ANA (~40%  $\oplus$  in PAH), RF, anti-Scl-70, anticitromere, ESR
- LFTs & HIV: r/o portopulmonary and HIV-associated PAH
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

## Treatment (JACC 2013;62:255 & 2015;65:1976; EHJ 2016;37:67)

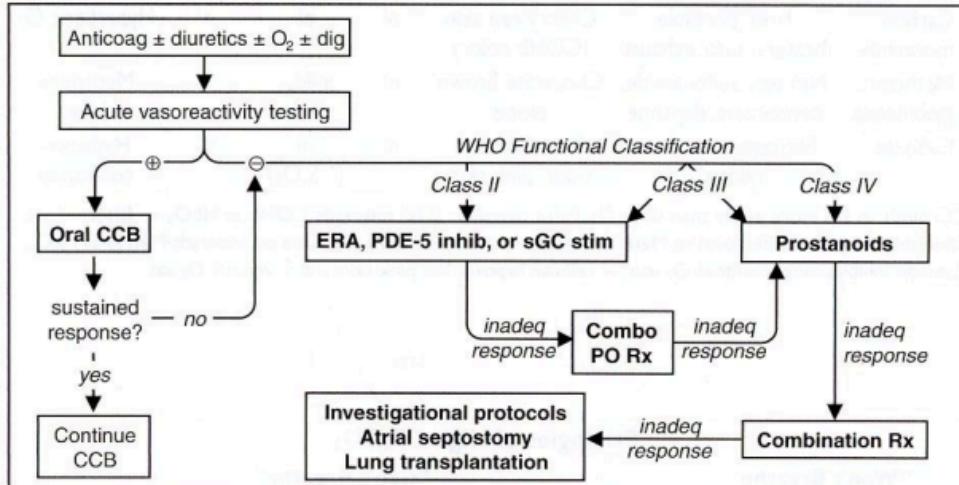
- Principles: 1) prevent & reverse vasoactive substance imbalance and vascular remodeling
- 2) prevent RV failure:  $\downarrow$  wall stress ( $\downarrow$  PVR, PAP, RV diam); ensure adeq. systemic DBP
- Supportive**
  - Oxygen: maintain SaO<sub>2</sub>  $> 90-92\%$  (reduces vasoconstriction)
  - Diuretics:  $\downarrow$  RV wall stress and relieve RHF sx; gentle b/c RV is preload dependent
  - Digoxin: control AF, ? counteract neg. inotropic effects CCB
  - Dobutamine and inhaled NO or prostacyclin for decompensated PHT
  - Anticoag: not routinely used;  $\downarrow$  VTE risk of RHF; ? prevention of *in situ* microthrombi; ? mort. benefit even if in NSR, no RCTs (Circ 1984;70:580; Chest 2006;130:545)
  - Supervised exercise training; aggressive apnea/hypoventilatory Rx w/ CPAP/BiPAP

- Vasodilators** (ideally right heart catheterization prior to initiation; NEJM 2004;351:1425)
  - acute vasoreactivity test: use inh NO, adenosine or prostacyclin to identify Pts likely to have long-term response to CCB ( $\oplus$  response =  $\downarrow$  PAP  $\geq 10$  mmHg to  $<40$  mmHg w/  $\uparrow$  or stable CO); ~10% Pts acute responders; no response  $\rightarrow$  still candidate for other vasodil.

Vasoactive agents	Comments (data primarily in Group 1; little evidence in 2° PHT)
<b>PDE-5 Inhibitor</b> Sildenafil, tadalafil, vardenafil	$\uparrow$ cGMP $\rightarrow$ vasodilation, $\downarrow$ smooth muscle proliferation, $\downarrow$ sx, $\uparrow$ 6MWT, no data on clinical outcomes. Often first-line b/c minimal side-effect profile: HA, vision $\Delta$ 's, sinus congestion (NEJM 2009;361:1864).
<b>Endothelin receptor antagonists (ERAs)</b> Bosentan, ambrisentan, macitentan	$\downarrow$ Smooth muscle remodeling, vasodilation, $\downarrow$ fibrosis, $\downarrow$ sx, $\uparrow$ 6MWT, $\downarrow$ worsening PAH or need for prostanoids w/ trend for $\downarrow$ PAH mort. (w/ macitentan). Side effects: $\uparrow$ LFTs, HA, anemia, edema, teratogen (NEJM 2002;346:896; Circ 2008;117:3010; NEJM 2013;369:809).
<b>IV Prostacyclin</b> Epoprostenol (Flolan)	Vasodilation, $\downarrow$ plt agg, $\downarrow$ smooth muscle proliferation; benefits $\uparrow$ w/ time (? vascular remodeling). $\uparrow$ 6MWT, $\uparrow$ QoL, $\downarrow$ mortality. Side effects: HA, flushing, jaw/leg pain, abd cramps, nausea, diarrhea, catheter infxn (NEJM 1996;334:296 & 1998;338:273; Annals 2000;132:425).
<b>Prostacyclin analogues [Iloprost (inh) Treprostinil (IV, inh, SC)] &amp; receptor agonist selexipag (PO)</b>	Same mechanism as prostacyclin IV but easier to take, $\downarrow$ side effects, and w/o risk of catheter infxn, $\downarrow$ sx, $\uparrow$ 6MWT; trend to $\downarrow$ clinical events w/ iloprost but not treprostinil. Iinh Rx with improved V/Q matching. Selexipag $\downarrow$ disease prog & hosp by ~40% (NEJM 2015;373:2522).
<b>Soluble guanylate cyclase (sGC) stim.</b> Riociguat	NO-independent $\uparrow$ cGMP $\rightarrow$ vasodilation, $\downarrow$ smooth muscle proliferation, $\downarrow$ sx, $\uparrow$ 6MWT in PAH; $\downarrow$ sx, $\downarrow$ PVR, $\uparrow$ 6MWT in CTEPH (NEJM 2013;369:319 & 330)
<b>Oral CCB</b> Nifedipine, diltiazem	Consider if $\oplus$ acute vasoreactive response; $<1/2$ long-term responder (NYHA I/II & near-nl hemodynamics) & have $\downarrow$ mortality. Not 1 <sup>st</sup> line b/c side effects: HoTN, lower limb edema (Circ 2005;111:3105).

- Upfront combination Rx (tadalafil + ambrisentan vs. monotherapy):  $\downarrow$  sx,  $\downarrow$  NT-BNP,  $\uparrow$  6MWT,  $\downarrow$  hospitalizations (NEJM 2015;373:834)
- Treat underlying causes of 2° PHT; can use vasodilators, although little evidence
- CTEPH: Rx as above. Pulm endarterectomy potentially curative (AJRCCM 2011;183:1605).
- Refractory PHT:
  - balloon atrial septostomy: R  $\rightarrow$  L shunt causes  $\uparrow$  CO,  $\downarrow$  S<sub>a</sub>O<sub>2</sub>, net  $\uparrow$  tissue O<sub>2</sub> delivery
  - lung transplant (single or bilateral); heart-lung needed if Eisenmenger physiology

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



### Management of ICU patient

- Avoid tachyarrhythmias & overly aggressive volume resuscitation
- Caution w/ vasodilators if any L-sided dysfxn. *Intubation can cause hemodynamic collapse.*
- May benefit from inotropes/chronotropes
- Consider fibrinolysis if acute, refractory decompensation (eg, TPA 100 mg over 2 h)

### Prognosis

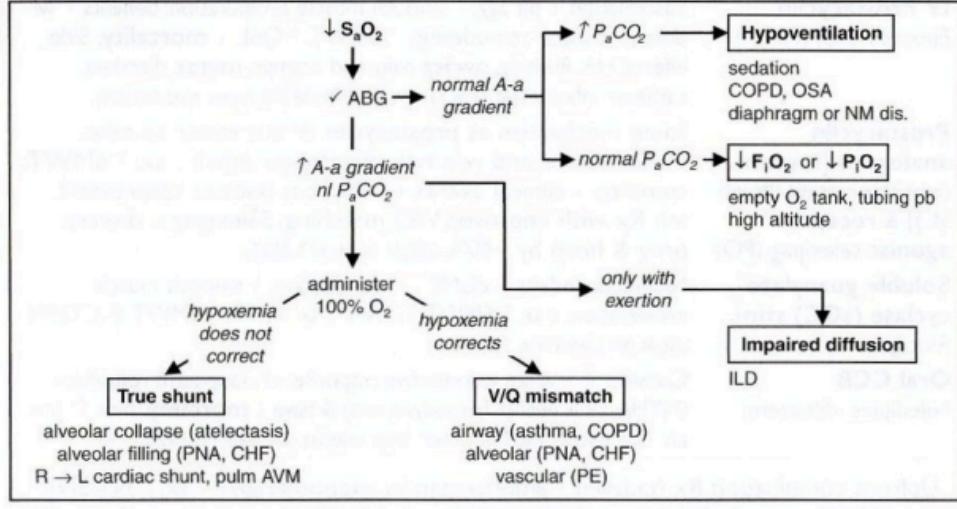
- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (Chest 2004;126:78-S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO (modified NYHA) class IV, 6MWT  $<300$  m, peak VO<sub>2</sub>  $<10.4$  mL/kg/min,  $\uparrow$  RA or RV or RV dysfxn,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

# RESPIRATORY FAILURE

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

- A-a gradient** =  $P_aO_2 - P_aCO_2$ : normal (on room air) = "4 + age/4" or "2.5 + (0.2 × age)"
- Hypoxemia + nl A-a gradient: problem is ↓  $P_iO_2/F_iO_2$  or ↑  $P_aCO_2$  (ie, hypoventilation)
- Hypoxemia + ↑ A-a gradient: problem is either
  - R → L shunt, anatomic (congen. heart dis.) or severe pathophys. (alveoli filled w/ fluid; eg, PNA, pulm edema); cannot overcome w/ 100% O<sub>2</sub> b/c of sigmoidal Hb-O<sub>2</sub> curve
  - V/Q mismatch where "shunt-like" areas (↓ V & nl Q) cause unoxygenated blood to mix with oxygenated blood; can be overcome w/ ↑ O<sub>2</sub> delivery
- Diffusion limitation: generally seen with exercise/↑ CO

Figure 2-6 Workup of acute hypoxemia



- Cyanosis:** seen when >4 g/dL of reduced Hb in blood vessels of skin/mucous membranes
  - central: ↓  $S_aO_2$  (pulm disease, shunt); abnl Hb [metHb, sulfHb, COHb (not true cyanosis)]
  - peripheral: ↓ blood flow → ↑ O<sub>2</sub> extraction (eg, ↓ CO, cold, arterial or venous obstruction)

## Chemical Causes of Cellular Hypoxia

Condition	Causes	Classic features	$P_aO_2$	Pulse Ox sat	CO-Ox sat	Treatment (+ 100% O <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 (↑ $S_vO_2$ )	nl	Hydroxy-cobalamin

CO binds to Hb more avidly than does O<sub>2</sub>. Pulse oximeter (Ox) misreads COHb as HbO<sub>2</sub> → falsely nl sat. Oxidizing drugs Δ Hb (ferrous) to MetHb (ferric), which cannot carry O<sub>2</sub>. Pulse ox misreads MetHb 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.

$$\text{Hypercapnia} \rightarrow P_aCO_2 = k \times \frac{\dot{V}CO_2}{RR \times V_T \times \left(1 - \frac{V_D}{V_T}\right)}$$

## Etiologies of High ↑ $P_aCO_2$

"Won't Breathe"	"Can't Breathe"		
↓ RR	↓ $V_T$	↑ $V_D$ and/or ↓ $V_T$	
Respiratory Drive	NM System ↓ $P_{lmax}$ ↓ $P_{Emax}$	CW/Pleura Abnl PEx Abnl CT	Lung/Airways Abnl PFTs ↓ End Tidal CO <sub>2</sub>
Metabolic alkalosis 1° neurologic: brainstem stroke, tumor, 1° alveolar hypovent	Neuropathies: cervical spine, phrenic nerve, GBS, ALS, polio NMJ: MG, LE	Chest wall: obesity, kyphosis, scoliosis	Lung parench.: emphysema, ILD/fibrosis, CHF, PNA
2° neurologic: sedatives, CNS infxn, hypothyroidism	Myopathies: diaphragm PM/DM; ↓ PO <sub>4</sub> musc dystrophies	Pleura: fibrosis effusion	Airways: asthma, COPD, OSA, bronchiect., CF

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

# MECHANICAL VENTILATION

## Indications

- Improve gas exchange: ↑ oxygenation, ↑ alveolar vent. and/or reverse acute resp. acidosis
- Relieve respiratory distress: ↓ work of breathing (can account for up to 50% of total O<sub>2</sub> consumption), ↓ respiratory muscle fatigue
- Apnea, airway protection, pulmonary toilet

## SUPPORTIVE STRATEGIES PRIOR TO INTUB. OR AFTER EXTUB.

### Oxygen Delivery Systems (*Lancet* 2016;387:1867)

System or Device	O <sub>2</sub> Flow <sup>a</sup>	F <sub>i</sub> O <sub>2</sub> range & Comments
Low-flow nasal cannula	1–6	24–40%, 1L adds approx 3% F <sub>i</sub> O <sub>2</sub>
Standard face mask	5–10	35–50%, minimum 5 L/min
Partial rebreather mask	>10	40–70%
Nonrebreather mask	>10	60–80% (not 100% b/c air leaks)
Air-entrainment mask (Venturi or Venti mask)	10–15 <sup>b</sup>	24–50%, F <sub>i</sub> O <sub>2</sub> stays constant
High-flow nasal O <sub>2</sub> (NEJM 2015;372:2185 JAMA 2015;313:2331 & 2016;315:1354)	≤40	21–100%. In nonhypercapnic acute hypoxic resp failure, ± ↓ intub. (espec if P <sub>a</sub> O <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> ≤200) & ↓ 90-d mort vs. stdnd O <sub>2</sub> or NPPV. Routine use after extub. ↓ need for reintub.

<sup>a</sup>L/min. <sup>b</sup>Total airflow >60L/min. (Adapted from Marino P. *The ICU Book*, 4th ed, Philadelphia: LWW, 2014:431)

### Noninvasive Positive Pressure Ventilation (NPPV) (NEJM 2015;372:e30)

<b>Indications</b> <i>Lancet</i> 2009;374:250	Clinical: mod-severe dyspnea, RR >24–30, signs of ↑ work of breathing, accessory muscle use, abd paradox Gas exchange: P <sub>a</sub> CO <sub>2</sub> >45 mmHg (& significantly worse than baseline), hypoxemia, P <sub>a</sub> O <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> <200
<b>Contraindications</b> <i>Crit Care Med</i> 2007;35:2402	Claustrophobia, poor mask fit, <b>ΔMS</b> , vomiting, <b>cannot protect airway</b> , extrapulm organ failure, HD instab, sev UGIB, ↑ secretions
<b>Continuous positive airway pressure (CPAP)</b>	≈ PEEP. Pt breathes spont. at own rate while vent maintains constant positive airway pressure throughout respiratory cycle. 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 hypoxemia (eg, CHF)
<b>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 hypoventilation; F <sub>i</sub> O <sub>2</sub> delivery limited
<b>Mask ventilation</b> (? helmet better; <i>JAMA</i> 2016;315:2435)	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
<b>Conditions w/ strong evidence</b> <i>Lancet</i> 2000;355:1931 <i>AJRCCM</i> 2006;173:164	<b>Cardiogenic pulmonary edema:</b> may ↓ intub. & mortality ( <i>JAMA</i> 2005;294:3124; <i>Lancet</i> 2006;367:1155) although recent trial (w/ high crossover) did not show any mortality benefit (NEJM 2008;359:142) <b>COPD exac.</b> w/ ↑ P <sub>a</sub> CO <sub>2</sub> : ↓ intub. & mort, but if pH <7.3 → intubate High-risk extub. (age >65, CHF, APACHE II >12): NPPV × 24 h directly after extub. → ↓ reintub. and, if P <sub>a</sub> CO <sub>2</sub> >45 mmHg during SBT, ↓ mortality Hypoxemic resp failure after abdominal surgery: ↓ reintubation <b>Immunosupp.</b> w/ infiltrates: ↓ complications & mortality

## VENTILATOR MANAGEMENT

### Ventilator Modes and Principles (NEJM 2001;344:1986, CHEST 2015;148:340–355)

<b>Cont. mandatory ventilation (CMV), aka Assist control (AC)</b>	Vent delivers a minimum number of supported breaths Additional Pt-initiated breaths trigger <b>fully assisted</b> vent breaths ∴ Vent-triggered breaths identical to Pt-triggered breaths Tachypnea → ? resp. alkalosis, breath-stacking, & auto-PEEP May be pressure targeted or volume targeted (qv)
<b>Pressure support vent (PSV)</b>	Support Pt-initiated breaths w/ a set inspiratory pressure & PEEP A mode of <b>partial</b> vent support because no set rate
<b>Other</b>	Synch intermittent mand. vent: deliver min. # supported breaths; V <sub>T</sub> of additional Pt-initiated breaths determined by Pt's effort Proportional assist ventilation (PAV): delivers variable pressure to achieve targeted % of work of breathing

**Volume or Pressure Targeted**

<b>Volume targeted</b>	Vent delivers a set $V_T$ ; pressures depend on airway resist. & lung/CW compl. <b>Benefit:</b> ↑ control over ventilation (ideal initial ventilator setting); benefit in ALI/ARDS; easy to measure mechanics (PIP, $P_{plat}$ , airway resist., compl.) Volume control (VC) ⊕: vent delivers variable pressure (depending on real-time lung compliance) to achieve set $V_T$ .
<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>General principles</b>	<b>Institutional/practitioner preference</b> and <b>patient comfort</b> usually dictate ventilator strategy; no strategy has proven superior <b>Alarms</b> can be set for ↑ volumes and ↑ airway pressures in pressure-targeted and volume-targeted strategies, respectively <b>Risks:</b> volutrauma (ie, overdistention, if set volume too high; <i>NEJM</i> 2013;369:2126), barotrauma [can happen w/ relatively high set volumes (espec if stiff lungs) or if pressure target set too high; key is to monitor transpulmonary pressure (difference between $P_{plat}$ and esophageal ≈ intrapleural), not just airway pressure]; can result in PTX, pneumomediastinum <b>Hypo-/hyperventilation:</b> need to ✓ minute vent & pH/ $P_aCO_2$

**Variables on the Ventilator**

<b>F<sub>i</sub>O<sub>2</sub></b>	Fraction of inspired air that is oxygen
<b>V<sub>T</sub> (tidal vol)</b>	Volume of breath delivered; Lung protective ventilation: goal ≤ 6 cc/kg IBW
<b>f (resp. rate)</b>	Rate set by ventilator, f may be lower than RR if Pt triggering breaths. Adjust to achieve desired $P_aCO_2$ .
<b>Positive end-expiratory pressure (PEEP)</b>	Positive pressure applied during exhalation via resistor in exhalation port Benefits: prevents alveolar collapse, ↓ shunt, ↑ O <sub>2</sub> via alveolar recruitment and improved compliance, allows severely obstructed Pt to initiate breath Cardiac effects: ↓ preload by ↑ intrathoracic pressure → ↓ venous return; ↓ afterload by ↓ cardiac transmural pressure; may ↑ or ↓ CO and may ↑ or ↓ oxygen delivery based on the above Auto-PEEP or intrinsic PEEP: inadequate exhalation time → lungs unable to completely empty before the next breath (ie, "breath stacking"); if flow at end-expiration, there must be pressure = auto-PEEP Will ↓ preload and may ↓ CO, espec if hypovolemic Will ↑ work of breathing as must be overcome by Pt to trigger breaths; can prevent Pt from triggering ventilator, extrinsic PEEP helps Can be detected if end-expiratory flow ≠ 0 before next breath Can measure by occluding expiratory port of vent at end-expiration Can ↓ by: ↑ exp time, ↓ RR, ↓ $V_T$ , Rx bronchospasm and secretions
<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>	Dynamic measurement during inspiration; set in pressure-targeted mode Determined by airway resistance and lung/chest wall compliance ↑ PIP w/o ↑ $P_{plat}$ → ↑ airway resist (eg, bronchospasm, plugging) ↓ PIP → ↓ airway resistance or air leak in the system
<b>Plateau pressure (<math>P_{plat}</math>)</b>	Static measurement at the end of inspiration when there is no flow Determined by resp system compliance (resist. not a factor since Ø flow) ↑ $P_{plat}$ → ↓ lung or chest wall compliance (eg, PTX, pulmonary edema, pneumonia, atelectasis), ↑ PEEP or auto-PEEP $P_{plat} < 30 \text{ cm H}_2\text{O}$ ↓ barotrauma (↓ $V_T$ , ↓ PEEP or ↑ compl [eg, by diuresis])

**Tailoring the ventilator settings**

- To improve oxygenation: options include ↑ F<sub>i</sub>O<sub>2</sub>, ↑ PEEP  
 $S_aO_2$  88–92% acceptable (*AJRCCM* 2016;193:43)  
First, ↑ F<sub>i</sub>O<sub>2</sub>. If >0.6 and oxygenation remains suboptimal, then try ↑ PEEP:  
If ↑  $P_aO_2/F_iO_2$  and  $P_{plat}$  stable, suggests recruitable lung (ie, atelectasis). Continue to ↑ PEEP until either can ↓ F<sub>i</sub>O<sub>2</sub> to <0.6 or  $P_{plat} \geq 30 \text{ cm H}_2\text{O}$ . If PEEP 20 & F<sub>i</sub>O<sub>2</sub> 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see "ARDS").

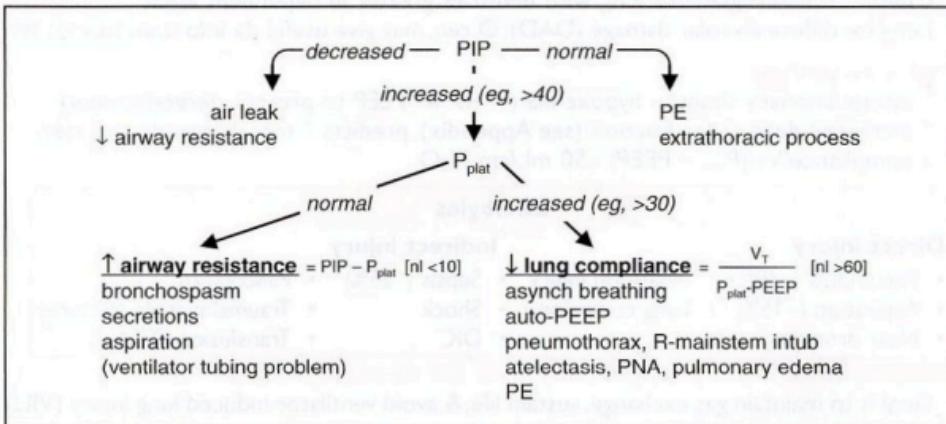
If  $\uparrow$  PEEP yields no  $\Delta$  or  $\downarrow$   $P_aO_2/F_iO_2$  or  $\uparrow$   $P_aCO_2$ , suggests additional lung not recruitable and instead overdistending lung  $\rightarrow$   $\uparrow$  shunt & dead space;  $\therefore \downarrow$  PEEP

- To improve ventilation:  $\uparrow V_T$  or inspiratory pressure,  $\uparrow RR$  (may need to  $\downarrow I$  time). Nb, tolerate  $\uparrow P_aCO_2$  (permissive hypercapnia) in ALI/ARDS (qv) as long as pH  $>7.15$ .

### Acute ventilatory deterioration (usually $\uparrow$ PIP)

- Response to  $\uparrow$  PIP: disconnect Pt from vent., bag, auscultate, suction,  $\checkmark$  CXR & ABG

Figure 2-7 Approach to acute ventilatory deterioration



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

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

- Perform daily assessment of readiness for spontaneous breathing trial (SBT)
- Clinical screening criteria: VS stable, minimal secretions, adequate cough, cause of respiratory failure or previously failed SBT reversed
- Vent parameters:  $P_aO_2/F_iO_2 > 200$ , PEEP  $\leq 5$ ,  $f/V_T < 105$ ,  $V_E < 12$  L/min,  $VC > 10$  mL/kg; rapid shallow breathing index ( $f/V_T$ )  $> 105$  predicts failure, NPV 0.95 (NEJM 1991;324:1445)
- Daily awakening trial (d/c all sedation; Lancet 2008;371:126): open eyes & w/o: agitation, RR  $> 35$ ,  $S_aO_2 < 88\%$ , resp distress or arrhythmias (if fail, restart sedation at  $\frac{1}{2}$  prior dose).
- SBT = CPAP or T piece  $\times 30$ –120 min  
failure if: deteriorating ABGs,  $\uparrow$  RR,  $\uparrow$  or  $\downarrow$  HR,  $\uparrow$  or  $\downarrow$  BP, diaphoresis, anxiety
- Tolerate SBT  $\rightarrow$  extubation. Fail SBT  $\rightarrow$  ? cause  $\rightarrow$  work to correct  $\rightarrow$  retry SBT qd
- ? acetazolamide in Pts w/ COPD & metabolic alkalosis (JAMA 2016;315:480)

### Complications

- Oxygen toxicity (theoretical); proportional to duration + degree of  $\uparrow$  oxygen ( $F_iO_2 > 0.6$ )
- Ventilator-induced lung injury (see "ARDS")
- Ventilator-associated pneumonia (~1%/day, mortality rate ~30%)  
typical pathogens: MRSA, *Pseudomonas*, *Acinetobacter* and *Enterobacter* species  
preventive strategies (AJRCCM 2005;171:388): wash hands, HOB elevated, non-nasal intub., enteral nutrition rather than TPN, routine suction of subglottic secretions, avoid unnecessary abx & transfusions, routine oral antiseptic, stress-ulcer prophylaxis w/ ? sucralfate ( $\downarrow$  VAP,  $\uparrow$  GIB) vs.  $H_2RA/PPGI$ , ? silver-coated tubes (JAMA 2008;300:805)
- Laryngeal edema: for Pts vent  $> 36$  h; ? predicted by  $\oplus$  cuff leak test. Methylprednisolone 20 mg IV q4h starting 12 h pre-extub.  $\rightarrow \downarrow$  edema and 50%  $\downarrow$  in reintubation (Lancet 2007;369:1003). ulceration: consider tracheostomy for patients in whom expect  $> 14$  d of mech vent  $\rightarrow$   $\downarrow$  duration mech vent,  $\downarrow$  # ICU days (BMJ 2005;330:1243); no benefit to performing at  $\sim 1$  wk vs. waiting until  $\sim 2$  wk (JAMA 2010;303:1483)
- Malnutrition (for all critically ill Pts): enteral nutrition initiated early is safe but not necessary (JAMA 2012;307:795), but bolus may  $\uparrow$  risk of VAP & *C diff.* (JPEN 2002;26:174); no clear benefit to  $\checkmark$ ing gastric residuals (JAMA 2013;309:249); permissive enteral underfeeding ( $\sim \frac{1}{2}$  of calculated caloric req) & standard enteral feeding w/ similar outcomes (NEJM 2015;372:2398); parenteral nutrition should be delayed until after day 8 to  $\downarrow$  risk of infections, cholestasis, RRT, ventilator days (NEJM 2011;365:506)
- Oversedation/delirium: BDZs and polypharmacy are risk factors  
propofol: HoTN in ~25%; propofol infusion syndrome (PRIS) ? espec w/ high ( $> 5$  mg/kg/h) & prolonged ( $> 48$  h) infusions & concom vasopressors  $\rightarrow$   $\uparrow$  AG, cardiac dysfxn, rhabdomyolysis,  $\uparrow$  triglycerides, & renal failure (Crit Care 2009;13:R169)  
dexmedetomidine:  $\uparrow$  vent-free days, but brady & HoTN c/w BDZ (JAMA 2012;307:1151 & 2016;315:1460)

# ACUTE RESPIRATORY DISTRESS SYNDROME

Berlin definition (JAMA 2012;307:2526)

- Acute onset within 1 wk of clinical insult or worsening respiratory status
- Bilateral infiltrates without alternative explanation (eg, effusion, atelectasis, nodules)
- Edema not fully explained by fluid overload or congestive heart failure
- Hypoxemia:  $P_aO_2/F_iO_2$  determined with 5 cm H<sub>2</sub>O of PEEP  
 $P_aO_2/F_iO_2 \geq 200$  = mild ARDS (may be on NPPV),  $100-200$  = mod,  $<100$  = severe
- Chest CT: heterogeneous lung with densities greater in dependent areas
- Lung bx: diffuse alveolar damage (DAD); Ø req. may give useful dx info (Chest 2004;125:197)

## Pathophysiology

- ↑ intrapulmonary shunt → hypoxemia (∴ Rx w/ PEEP to prevent derecruitment)
- ↑ increased dead space fraction (see Appendix), predicts ↑ mort. (NEJM 2002;346:1281)
- ↓ compliance:  $V_T/(P_{plat} - PEEP) < 50 \text{ mL/cm H}_2\text{O}$

## Etiologies

### Direct injury

- Pneumonia (~40%)
- Inhalation injury
- Aspiration (~15%)
- Lung contusion
- Near drowning

### Indirect injury

- Sepsis (~25%)
- Pancreatitis
- Shock
- Trauma/multiple fractures
- DIC
- Transfusion (TRALI)

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

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

Mechanisms of VILI	Ventilator Strategies (see ARDSnet.org)
<b>Barotrauma/volutrauma:</b> alveolar dist → mech 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)
<b>Biotrauma</b> → SIRS	Low $V_T$ , open lung strategy w/ high PEEP
<b>Atelectrauma:</b> repetitive alveoli recruit & decruit	<b>Titrate PEEP to prevent tidal alveolar collapse</b> See below for options
<b>Hyperoxia:</b> ? injury; worsened V/Q matching	↑ <b>PEEP</b> rather than $F_iO_2$ (keep <0.60) $O_2$ -induced injury only theoretical in humans

## PEEP titration methods (best method unclear)

- No benefit at given  $V_T$  if titrated to  $P_aO_2$  alone (NEJM 2004;351:327; JAMA 2008;299:637)
- Best PEEP trial: incremental PEEP titration using compliance,  $O_2$ , hemodynamics  
 If able to ↑ PEEP w/o ↑  $P_{plat}$ , suggests "recruitability"  
 ∴ ↑ PEEP if → ↑  $S_aO_2$  (target ≥ 88–90%) &  $P_{plat} \leq 30 \text{ cm H}_2\text{O} \rightarrow$  ↓ time on vent, better lung mechanics (JAMA 2008;299:646), ↓ mortality (JAMA 2010;303:865)
- ARDSnet "high" PEEP table for optimal  $F_iO_2/PEEP$  combo for goal  $S_aO_2$  (ARDSnet.org)
- Esophageal balloon: used to determine true transpulmonary pressure, adjust PEEP according to esoph pressure (=pleural pressure) to maintain positive transpulm pressure and optimal PEEP; improves oxygenation and lung compliance but no effect on mortality (NEJM 2008;359:2095); helpful in obese Pts or w/ ↑ abdominal pressure

## Other treatment considerations

- **Fluid balance:** target CVP 4–6 cm H<sub>2</sub>O (if nonoliguric & normotensive) → ↑ vent/ICU-free days, but no Δ mortality (NEJM 2006;354:2564); PA catheter unproven (NEJM 2006;354:2213); consider using BNP >200 to trigger diuresis (UOP goal 4.5–9 mL/kg/h × 3 h)
- **Steroids:** debate continues. Adverse effects include neuromuscular weakness, poor glucose control, ? infection. Benefit may vary by time since ARDS onset:  
 <72 h: older studies w/o benefit (NEJM 1987;317:1565); ↓ mortality, ↑ vent/ICU-free days in more recent, controversial study (Chest 2007;131:954)  
 7–13 d: ? benefit → ↑ vent/ICU-free days, no mortality difference (NEJM 2006;354:1671)  
 ≥14 d: ↑ mortality (NEJM 2006;354:1671)
- **Paralysis:** if  $P_aO_2/F_iO_2 < 150$ , cisatracurium × 48 h ↓ mortality by 32% (NEJM 2010;363:1107)
- **Proning:** if  $P_aO_2/F_iO_2 < 150$ , prone-positioning ≥ 16 h ↓ mort. by ~50% (NEJM 2013;368:2159)
- **Experimental** (JAMA 2010;304:2521)
  - Inhaled NO or prostacyclins: ↑  $P_aO_2/F_iO_2$ , no ↓ mort. or vent-free days (BMJ 2007;334:779)
  - Lung recruitment: apply CPAP 40–45 cm H<sub>2</sub>O × 2 min to recruit lung and then ↑ PEEP to maintain; sicker Pts had ↑ recruitable lung (NEJM 2006;354:1775 & 1839)
  - Driving pressure ( $\Delta P = P_{plateau} - PEEP$ ): ↓  $\Delta P$  a/w ↑ survival; target < 15 (NEJM 2015;372:747)
  - V-V ECMO: may be useful in refractory ARDS, but no good trial data (NEJM 2011;365:1905)

## Prognosis (JAMA 2016;315:788)

- Mortality ~40% overall in clinical trials; 9–15% resp. causes, 85–91% extrapulm (MODS)
- Survivors: PFTs ~normal, ↓  $D_lCO$ , muscle wasting, weakness persists (NEJM 2003;348:683)  
 ↓ exercise tolerance, ↓ QoL, ↑ psych morbidity (NEJM 2011;364:1293)

# SEPSIS AND SHOCK

SEPSIS  
2-23

## Definitions (JAMA 2016;315:801)

<b>Systemic inflammatory response synd. (SIRS)</b>	≥2 of the following: (1) Temp >38 or <36°C; (2) HR >90; (3) RR >20 or $P_{a}CO_2 <32$ ; (4) WBC >12k or <4k or >10% bands
<b>Sepsis</b>	Life-threatening organ dysfxn (SOFA Δ ≥2) due to infxn qSOFA ≥2 useful in triage of potentially septic pts
<b>Septic shock</b>	Sepsis-induced circulatory abnl: pressor required for MAP ≥65 and lactate >2 despite adequate fluid resuscitation

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

Points	0	1	2	3	4
<b>Resp:</b> $P_{a}O_2/F_iO_2$	≥400	<400	<300	<200 <sup>a</sup>	<100 <sup>a</sup>
<b>Coag:</b> plt ( $10^3/\mu L$ )	≥150	<150	<100	<50	<20
<b>Liver:</b> bili (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12
<b>CV:</b> MAP <sup>b</sup>	≥70	<70	dopa ≤5 or any DBA	dopa 5.1-15 or norepi/epi ≤0.1	dopa >15 or norepi/epi >0.1
<b>Neuro:</b> GCG	15	13-14	10-12	6-9	<6
<b>Renal:</b> Cr or UOP	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 <500	>5 <200

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

<sup>a</sup>w/ respiratory support; <sup>b</sup>catechols (in  $\mu g/kg/min$ ) for ≥1 h (JAMA 2016;315:762;775; & 801)

## Shock (see "PA Catheter & Tailored Therapy" for subtypes; NEJM 2013;369:1726)

- Tissue hypoxia due to ↓ tissue perfusion and hence ↓ tissue O<sub>2</sub> delivery and/or ↑ O<sub>2</sub> consumption or inadequate O<sub>2</sub> utilization
- Typical signs include HoTN (SBP <90 mmHg or drop in SBP >40 mmHg), tachycardia, oliguria (UOP <0.5 cc/kg/h), Δ mentation, metabolic acidosis ± ↑ lactate
- Hard to dx as ↑ SVR can maintain SBP, but tissue perfusion poor; shock index (HR/SBP) >0.9 and pulse pressure [(SBP - DBP)/SBP] <25% clues to significant shock

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

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

## Pressors (also see "ICU Medications")

- MAP target 65-70 mmHg as good as 80-85 and ↓ AF (NEJM 2014;370:1583)
- Norepinephrine: ↓ arrhythmia & mortality c/w dopamine (NEJM 2010;362:779; Crit Care Med 2012;40:725) and ∴ is pressor of choice in septic shock
- Vasopressin: added to low-dose norepi not superior to high-dose norepi but ? benefit in less severe shock (norepi 5-14) (NEJM 2008;358:877); consider if HoTN catechol refractory

## Antibiotics

- Start empiric IV abx w/in 1 h of recognition of severe sepsis or septic shock; every hour delay in abx admin a/w 8% ↑ in mortality (Crit Care Med 2006;34:1589)
- If possible, obtain 2 sets of BCx before urgently starting abx (but do not delay abx)
- Broad gram-positive (incl MRSA) & gram-neg (incl highly resistant) coverage, ± anaerobes

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

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

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

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

Drug/toxin	Signs/Sx and Diagnostics	Management options
<b>Acetaminophen</b>	Vomiting, ↑ AG & nl OG metabolic acidosis, hepatitis & hepatic failure, renal failure	N-acetylcysteine (NAC) infusion Hemodialysis if massive O/D See "Acute liver failure"
<b>Salicylates</b>	Tinnitus, hyperventilation, abd. pain, vomiting, ΔMS, mixed ↑ AG & nl OG metabolic acidosis + respiratory alkalosis	IVF resuscitation Alkalization w/ NaHCO <sub>3</sub> Maintain respiratory alkalemia Consider hemodialysis
<b>Opioids</b>	↓ mentation, ↓ RR, miosis	IV naloxone
<b>Benzodiazepines</b>	↓ mentation, ataxia, ↓ RR	Flumazenil <i>not</i> rec (can precipitate withdrawal/seizures)
<b>Calcium channel blockers</b>	Bradycardia, AV block, hypotension, HF, hyperglycemia	IVF, vasopressors, Ca infusion, hyperinsulinemic euglycemia, ? intralipid emulsion, pacing
<b>Beta-blockers</b>	Bradycardia, AV block, hypotension, HF, hypoglycemia	Glucagon, vasopressors, pacing
<b>Digoxin</b>	N/V, bradycardia, AV block, delirium, xanthopsia. ✓ serum dig level (but may be inaccurate if <6 h since last dose), renal function	Correct hypokalemia Digibind if hyperkalemia, life-threatening dysrhythmia Consider hemodialysis Lidocaine for arrhythmias
<b>Tricyclic antidepressants</b>	Hypotension, seizures, arrhythmia, ↑ QRS, ↑ QT	IVF resuscitation, IV sodium bicarbonate, vasopressors
<b>Lithium</b>	N/V/D, tremor, hyperreflexia, clonus, drowsiness, seizure, ↑ QT, AV block, bradycardia	IVF (NS), maintain UOP Consider hemodialysis
<b>Ethylene glycol</b>	CNS depression, ↑ AG & OG metabolic acidosis	Ethanol or fomepizole, NaHCO <sub>3</sub> Consider hemodialysis
<b>Methanol</b>	CNS depression, blindness ↑ AG & OG met. acidosis	Ethanol or fomepizole, NaHCO <sub>3</sub> Consider hemodialysis
<b>Isopropanol</b>	CNS depression, gastritis	Supportive care
<b>Carbon monoxide</b>	HA, dizziness, nausea, ΔMS carboxyHb level, CO-oximetry (pulse ox. invalid)	100% normobaric oxygen, hyperbaric O <sub>2</sub> in severe cases
<b>Organophosphate</b>	Salivation, lacrimation, diaphoresis, miosis, emesis, bronchospasm, ΔMS	Endotracheal intubation for respiratory failure, atropine, pralidoxime, benzodiazepines
<b>Cyanide</b>	Coma, seizure, metabolic acidosis, hypotension	IV Na nitrite and Na thiosulfate IV hydroxocobalamin

(Chest 2011;140:1072)

## LUNG TRANSPLANT

### Overview

- Indications: end stage, progressive decline despite max medical Rx, <2-y life expectancy; COPD, ILD (IPF), pulmonary HTN, cystic fibrosis, alpha 1-antitrypsin
- Contraindic: age >65 (relative), uncontrolled/unRx'd infxn, malig in prior 2 y, severe non-pulm dis., BMI ≥35, active smoking, drug dependence, med noncompliance, psychosocial

### Posttransplant care

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

### Complications

- Anastomotic: vascular (stenosis, thrombosis) and airway (infection, necrosis, dehiscence, granulation tissue, tracheobronchomalacia, stenosis, fistula)
- Acute rejection: ↓ lung fxn, cough, SOB, fever. Dx w/ trans-bronch bx. Rx immunosupp.
- Chronic rejection: bronchiolitis obliterans w/ obstruction. Dx w/ PFTs, trans-bronch bx. Rx limited (azithromycin, montelukast, Δ immunosuppressives).
- Infection: ↑ bacterial, fungal, viral pneumonia, systemic infections, CMV, OI
- Malignancy: 2x ↑ risk overall. 5.5x ↑ risk lung cancer. PTLD (assoc w/ EBV) common.
- Misc: GVHD, CKD, DM, CAD, CHF, stroke, encephalopathy, drug toxicity

# ESOPHAGEAL AND GASTRIC DISORDERS

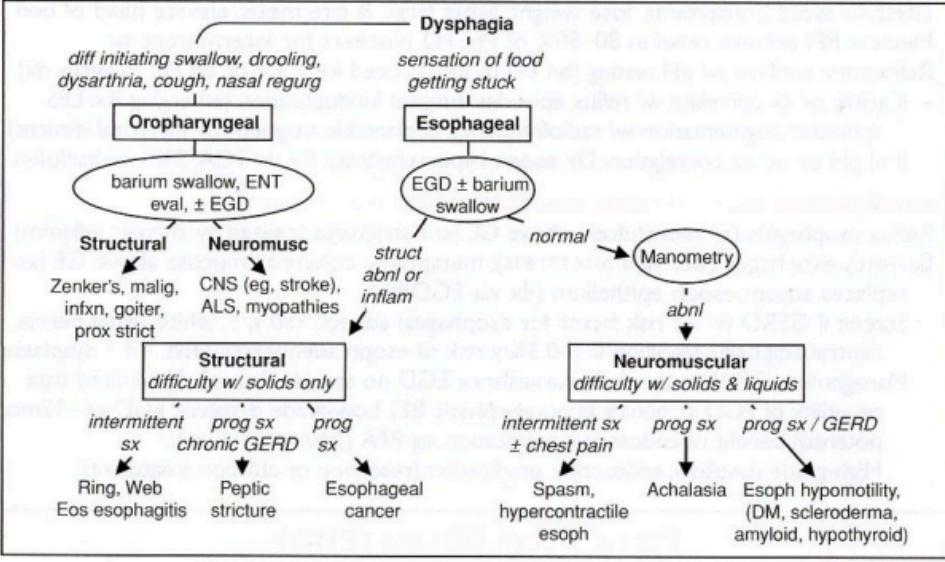
## DYSPHAGIA

ESOPHAGEAL  
3-1

### Definitions

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

Figure 3-1 Etiologies of and approach to dysphagia (NCP Gastrohep 2008;5:393; Neurogastro 2012;24:57)



### Structural dysphagia (JAMA 2015;313:18; Gastro 2014;147:1238)

- Caused by inflammatory or malignant changes in oropharynx/esophagus; **solids > liquids**
- Oropharyngeal**
  - Zenker's diverticulum (post pharyngeal pouch): in elderly, a/w aspiration, dx w/ video fluoroscopy, Rx w/ endo/surg
  - malignancy, radiation injury, infection, goiter, osteophytes, proximal strictures/rings/webs
- Esophageal**
  - rings (concentric obstructing tissue, eg, Schatzki ring): near GE jxn, a/w food impaction, linked to GERD; Rx w/ PPI, dilation
  - webs (nonconcentric): usually prox, can be a/w Fe defic. (Plummer-Vinson synd.)
  - peptic or XRT strictures, foreign body, tumor, vascular compression (dysphagia lusoria)
- Infxn esophagitis: odynophagia > dysphagia; often immunosupp w/ *Candida*, HSV, CMV
- Pill esophagitis: odynophagia > dysphagia; NSAID, KCl, bisphosp., doxy & tetracycline
- Eosinophilic esophagitis: predominantly young or middle-aged ♂. Dx: >15 eos/hpf on bx, esoph dysfxn (ie, dysphagia, food impaction) & exclude GERD (empiric PPI trial). Rx: 3Ds: 1<sup>st</sup> modify Diet (Ø milk, soy, eggs, wheat, nuts, fish); if no Δ, Rx w/ Drugs (swallow inh steroids); if ongoing sx & stricturing, Dilation.

### Neuromuscular dysphagia

- Caused by aberrant motility or innervation of oropharynx/esophagus; **solids & liquids**
- Oropharyngeal:** consider CNS disorders (eg, stroke, ALS, myopathies, CNS tumors)
- Esophageal:** motility disorder a/w dysphagia, CP, GERD; dx via manometry or high-res esophageal pressure topography. Entities include:

**Distal spasm:** uncoordinated peristalsis w/ simultaneous contractions

**Hypercontractile:** high amp contractions; Rx w/PPI, nitrates/CCB/PDEi, TCA/SSRI

**Hypomotility:** ↓ amp of distal esoph contractions; seen in scleroderma, DM, hypothyroidism; Rx w/ PPI & Rx underlying disorder

**Achalasia:** simult. ↓ amp contractions & ↓ LES relaxation; barium swallow w/ dilated esophagus & distal "bird's beak" narrowing; mostly idiopathic, although can be a/w Chagas; Rx: pneumatic dilation as effective as Heller myotomy (NEJM 2011;364:1868); per oral endoscopic myotomy; CCB/nitrates/PDEi; Botox inj if not candidate for surgery

## GASTROESOPHAGEAL REFLUX DISEASE (GERD)

### Pathophysiology

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

**Clinical manifestations**

- Esophageal: **heartburn**, atypical chest pain, regurgitation, water brash, dysphagia
- Extraesophageal: **cough**, asthma (often poorly controlled), laryngitis, dental erosions

**Diagnosis** (*Annals* 2015;163:ITC1)

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

**Treatment** (*Lancet* 2013;381:1933)

- Lifestyle: avoid precipitants, lose weight, avoid large & late meals, elevate head of bed
- Medical: PPI achieve relief in 80–90% of Pts; H2 blockers for intermittent sx
- Refractory: confirm w/ pH testing (on PPI to assess need for ↑ Rx, or off PPI to verify dx).
  - If acidic or sx correlate w/ reflux episodes: surgical fundoplication (emerging Rx: LES sphincter augmentation w/ radiofrequency, implantable magnetic or electrical devices)
  - If nl pH or no sx correlation: Dx esoph hypersensitivity. Rx w/ TCA, SSRI or baclofen.

**Complications** (*NEJM* 2014;371:836; *Gastro* 2011;140:1084.e18 & 2015;149:1599)

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

**PEPTIC ULCER DISEASE (PUD)****Definition & etiologies** (*Lancet* 2009;374:1449)

- Ulcers (break in mucosal lining >5 mm) & erosions (<5 mm) in stomach and duodenum
- Principal risk factors: *H. pylori* infection > NSAID/ASA use
- ***H. pylori* infection**: causes ~80% of duodenal ulcers (DU) & ~60% of gastric ulcers (GU). ~50% of world colonized w/ *H. pylori*, but only 5–10% will develop PUD.
- **ASA & NSAIDs**: damage to mucosa caused by ↓ prostaglandin synthesis. Cause majority of non-*H. pylori*-related DU & GU. Regular use a/w 5–6x ↑ odds of GIB.
- Other: smoking, stress, excessive EtOH, gastric cancer/lymphoma, Crohn's, viral infxn (eg, CMVHSV in immunosupp), bisphosphonates, steroids (in combo w/ NSAIDs, but not risk factor alone); rarely gastrinoma (Zollinger-Ellison synd.), mastocytosis, idiopathic
- Stress ulcer: risk factors = ICU & coagulopathic, mech vent, h/o GIB, steroid use; Rx w/ PPI

**Clinical manifestations**

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

**Diagnostic studies**

- Testing for *H. pylori*: stool antigen or EGD + rapid urease test. False Ø if on abx, bismuth, PPI, so stop prior to testing if possible. Serology: ↓ utility, useful only to exclude infection in low prevalence areas (most of U.S.).
- EGD (definitive dx): if fail empiric Rx or alarm features (see above); bx GU to r/o malig & *H. pylori*; relook in 6–12 wk if >2 cm, malig features, risk factors for gastric cancer (ie, + FHx + *H. pylori*, atrophic gastritis, dysplasia/ metaplasia on bx, > 50 y.o.), or sx persist

**Treatment** (*NEJM* 2010;362:1597; *Gut* 2012;61:646; *BMJ* 2013;347:f4587)

- If *H. pylori* +, eradicate ("test and treat") (*Gastro* 2016;151:51):
  - Triple Rx: clarith + [amox, MNZ or levoflox] + PPI bid × 10–14 d (if clarith resist rate <20%)
  - Quadruple Rx: MNZ + TCN + bismuth + PPI (if clarith resist rate >15% or amox allergy)
    - erad vs. triple 93 vs. 70%, clarith sens 95 vs. 85%, resist 91 vs. 8% (*Lancet* 2011;377:905)
    - Sequential Rx: PPI + amox × 7 d → PPI + clarith + MNZ × 7 d (*Lancet* 2013;381:205)
    - Besides PUD, test & Rx if: gastric MALT lymphoma, atrophic gastritis, FHx gastric ca
- If *H. pylori* Ø: gastric acid suppression w/ PPI
- Lifestyle changes: d/c smoking and probably EtOH; diet does not seem to play a role
- Surgery: if refractory to med Rx (1<sup>st</sup> r/o NSAID use) or for complications (see above)

**Prophylaxis if ASA/NSAID required** (*JACC* 2016;67:1661; *Aliment PharmRx* 2016;43:1262)

- PPI if (a) h/o PUD/UGIB; (b) also on clopidogrel (although ? ↓ antipt effect); (c) ≥2 of the following: age >60, steroids or dyspepsia; prior to start test & Rx *H. pylori*
- Consider misoprostol; consider H2RA if ASA monotherapy (*Lancet* 2009;374:119)
- Consider Δ to COX-2 inhibit (↓ PUD & UGIB but ↑ CV events) if low CV risk & not on ASA

# GASTROINTESTINAL BLEEDING

## Definition

- Intraluminal blood loss anywhere from the oropharynx to the anus
- Classification: **upper** = above the ligament of Treitz; **lower** = below the ligament of Treitz
- "Severe" GIB: defined as having associated shock, orthostatic hypotension, ↓ Hct by 6% (or ↓ Hb by 2 g/dL), or requiring transfusion  $\geq 2U$  PRBCs. Requires hospitalization.

## Clinical manifestations

- **Hematemesis** = blood in vomitus (UGIB)
- **Coffee-ground emesis** = blood exposed to gastric acid (UGIB)
- **Melena** = black, tarry stools from digested blood (usually UGIB, but can be from R colon)
- **Hematochezia** = bloody or maroon-colored stools (LGIB or rapid UGIB)

## Initial management

- **Assess severity:** VS including orthostatic Δs, JVP. Tachycardia (can be masked by βB use) suggests 10% volume loss, orthostatic hypotension 20% loss, shock >30% loss
- **History:** prior GIB, tempo of current bleed, specific bleeding manifestations (see above), other GI s/s (eg, abd pain, Δ in bowel habits, weight loss, N/V), NSAID/ASA or EtOH use, anticoag/antiplt drugs, h/o or risk factors for cirrhosis, radiation, prior GI or aortic surgery.
- **Physical exam:** localizable abd tenderness, peritoneal signs, masses, LAN, prior surgery signs of liver disease (hepatosplenomegaly, ascites, jaundice, telangiectasias)  
rectal exam: masses, hemorrhoids, anal fissures, stool appearance, color, occult blood
- **Resuscitation:** placement of 2 large-bore (18-gauge or larger) intravenous lines  
Volume replacement: NS or LR to achieve normal VS, UOP, & mental status
- **Lab studies:** Hct (may be normal in first 24 h of acute GIB before equilibration)  
2–3% → 500 mL blood loss; low MCV → Fe deficient and chronic blood loss; plt, PT, PTT; BUN/Cr (ratio >36 in UGIB b/c GI resorption of blood ± prerenal azotemia); LFTs
- **Transfuse:** BB sample for type & cross; use O-neg if emerg; for UGIB (esp. w/ portal HTN) transfuse w/ more restrictive Hb goal (eg, 7 g/dL) or >8 g/dL if CAD (NEJM 2013;368:11)
- **Reverse coagulopathy:** FFP & vit K to normalize PT; plts to keep count >50,000
- **Triage:** alert endoscopist. Consider ICU if unstable VS or poor end organ perfusion.  
Intubation for emergent EGD, if ongoing hematemesis, shock, poor resp status, Δ MS?  
OutPt management if SBP  $\geq 110$ , HR <100, Hb  $\geq 13$  (♂) or  $\geq 12$  (♀), BUN <18, Ø melena, syncope, heart failure, liver disease (Lancet 2009;373:42)

## Diagnostic studies

- **Nasogastric tube** can aid localization: fresh blood or coffee grounds → active or recent UGIB; nonbloody → does not exclude UGIB (~15% missed). ⊕ occult blood test no value.
- **UGIB: EGD** w/in 24 h. If severe bleed, ↑ Dx/Rx yield by gastric lavage and **erythro 250 mg IV 30 min prior to endoscopy** to clear stomach contents (Am J Gastro 2006;101:1211).
- **LGIB: colonoscopy** (identifies cause in >70%); if severe, colo w/in 12 h → consider rapid purge w/ PEG solution (6–8 L over 4–6 h). If hematochezia a/w orthostasis, concern for brisk UGIB → exclude UGIB w/ EGD first. Push enteroscopy, anoscopy, capsule endoscopy in combo w/ urgent colo results in dx >95% of cases (GI Endo 2015;81:889).
- **Imaging:** if too unstable for endo or recurrent bleeding, can then → IR procedure or surgery
- **tagged RBC scan:** can identify general luminal location if bleeding rate  $\geq 0.04$  mL/min
- **arteriography:** can localize exact vessel if bleeding rates  $\geq 0.5$  mL/min, allows for IR Rx
- Emergent exploratory laparotomy (last resort) if no localization and life-threatening bleed

Etiology UGIB	Comment & Treatment
<b>PUD (20–67%)</b> (NEJM 2016;374:2367) See "PUD"	Treatment: <b>PPI:</b> 80 mg IV bolus + 8 mg/h drip ≈ 40 mg IV BID boluses <b>Endoscopic therapy:</b> epi inj + bipolar cautery or hemoclip. Biopsies for ? <i>H. pylori</i> and treat if ⊕. High-risk (for rebleeding) ulcer: arterial spurting, adherent clot, visible vessel. Endo Rx, IV PPI × 72 h post EGD, then Δ to high-dose oral PPI. Arteriography w/ embolization; surgery (last resort). Intermediate-risk ulcer: oozing, in o/w stable Pt. Endo Rx, can Δ to oral PPI after EGD and observe 24–48 h. Low-risk ulcer: clean-based or flat. Oral PPI and ? discharge. Hold anticoag & antiplatelet Rx until hemostasis; can resume after hemostasis & PPI on board (BMJ 2012;344:e3412).
<b>Erosive gastropathy (4–31%)</b>	Precipitants: NSAIDs, ASA, EtOH, cocaine, gut ischemia, XRT Stress-related mucosal injury in ICU Pts. Risk factors include severe coagulopathy, mech vent >48 h, high dose glucocorticoids Treatment: high-dose PPI
<b>Erosive esophagitis (5–18%)</b>	Risk factors: cirrhosis, anticoagulation, critical illness. Rx offending cause + high dose PPI; repeat EGD later to r/o underlying Barrett's.

**Esophageal or gastric varices**  
(4–20%)  
(Hep 2007;46:922;  
NEJM 2010;362:823)  
See "Cirrhosis"

2° to portal HTN. If isolated gastric → r/o splenic vein thrombosis.

#### Pharmacologic

**Octreotide** 50 µg IV bolus → 50 µg/h infusion (84% success).

Usually × 5 d, but most benefit w/in 24–48 h.

Abx: 20% cirrhotics p/w GIB have infxn, & ~50% develop infxn during hospitalization; Ppx w/ IV CTX, cipro, or levoflox × 7 d

#### Nonpharmacologic

**Endoscopic band ligation** (>90% success) or sclerotherapy

Arteriography w/ coiling, or if available, endoscopic injection of cyanoacrylate (glue) for gastric varices

Covered esophageal stent placement or balloon tamponade used for bleeding refractory to ligation as bridge to TIPS (consider early if persistent bleed on EGD or Child-Pugh C; NEJM 2010;362:2370)

For persistent gastric variceal bleed: TIPS or balloon-retrograde transvenous obliteration

Portal HTN gastropathy	↑ portal venous pressure → ectatic vessels, hyperemia in prox. gastric body. No endoscopic option; Rx portal HTN (octreotide), BB.
Vascular (2–8%)	Angioectasia AVMs, HHT (see below)
	AVMs congenital. Angioectasia (ectatic submucosal vessels) a/w ↑ age, CKD, cirrhosis, CTD, severe CV dis. Heyde syndrome: GIB d/t angioectasias + aortic stenosis. Endo Rx.
	Dieulafoy's lesion
	Large (1–3 mm) submucosal artery protruding through fundal mucosa → sudden, massive UGIB. Difficult to identify. Endo Rx.
Gastric antral vasc. ectasia (GAVE)	"Watermelon stomach"; ectatic gastric vessels, often a/w cirrhosis, CTD, typically older ♀. Rx w/ thermal hemostasis, repeat q4–8wk to eradicate lesions. TIPS does not improve outcomes.
Aortoenteric fistula	AAA or aortic graft erodes into 3 <sup>rd</sup> portion of duodenum. P/w "herald bleed"; if suspected, diagnose by endoscopy or CT.
Malignancy (2–8%)	Endoscopic hemostasis of mass temporizing measure till cancer Rx
Mallory-Weiss tear (4–12%)	GE jxn lacerations due to vomiting → ↑ intraabd pressure & shearing effect. Can self-resolve w/o endo Rx. Rx w/ antiemetics, PPI.
Cameron's lesions	Linear erosions in hiatal hernia due to mech trauma of diaphragm
Post-sphincterotomy bleeding	Occurs in ~2% of cases, ↑ risk w/ more complicated procedure. Bleeding into duodenum. Rx w/ endo hemostasis.

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

Etiology LGIB	Comment & Treatment (Am J Gastro 2015;110:1265 & 2016;111:755)
Diverticular bleed (30%)	<b>Pathophysiology:</b> Intimal thickening and medial thinning of vasa recta as they course over dome of diverticulum → weakening of vascular wall → arterial rupture. Diverticula more common in left colon; but <i>bleeding diverticula more often in right colon</i> . <b>Clinical:</b> older, ASA/NSAIDs, painless hematochezia, ± abd cramping <b>Treatment:</b> Usually stops spont. (~75%) but may take hrs–days; ~20% recur. Can perform endo hemostasis w/ epi injections ± electrocautery (NEJM 2000;342:78), hemoclip, banding. Intra-arterial vasopressin or embo. Surgery (partial colectomy) last resort.
Polyp/Tumor (20%)	Typically slow ooze, p/w fatigue, weight loss, iron deficiency anemia
Colitis (20%)	Infectious (see "Acute Diarrhea"), IBD, ischemic colitis, XRT
Anorectal disorders (20%)	Internal, external hemorrhoids; anal fissures, rectal ulcers, rectal varices (Rx by ↓ portal venous pressure in cirrhotics), XRT
Vascular (<10%)	Angioectasia & AVMs (see above). <b>Heredity Hemorrhagic Telangiectasia (Weber-Osler-Rendu):</b> diffuse AVMs, telangiectasias throughout GI mucosa (also involve lips, oral mucosa, fingertips).
Meckel's diverticulum	Congenital blind intestinal pouch due to incomplete obliteration of vitelline duct. 2% of pop, w/in 2' of IC valve, 2" long, ♂:♀ 2:1, often present age 2 (but can cause obscure GIB in adults). Dx w/ <sup>99m</sup> Tc-pertechnetate scintigraphy. Rx w/ angioembo, surgical resection.

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

- Definition:** continued bleeding (melena, hematochezia) despite ⊖ EGD & colo; 5% of GIB
- Etiologies:** Dieulafoy's lesion, GAVE, small bowel angiomyolipoma, ulcer or cancer, Crohn's disease, aortoenteric fistula, Meckel's diverticulum, hemobilia
- Diagnosis:** repeat EGD w/ push enteroscopy/colonoscopy when bleeding is active  
If ⊖, video capsule to evaluate small intestine (Gastro 2009;137:1197)  
If still ⊖, consider <sup>99m</sup>Tc-pertechnetate scan ("Meckel's scan"), enteroscopy (single-balloon, double-balloon or spiral), tagged RBC scan and arteriography

# DIARRHEA

## ACUTE DIARRHEA (<4 WEEKS' DURATION)

Acute Infectious Etiologies (NEJM 2014;370:1532; JAMA 2015;313:71)

Pathogen		Epidemiology & Clinical Sx
Noninflammatory		Predom. disruption small intestine absorp. & secretion. Voluminous diarrhea, N/V. $\ominus$ fecal WBC & FOB.
Preformed toxin		"Food poisoning," <24 h dur. <i>S. aureus</i> (meats & dairy), <i>B. cereus</i> (fried rice), <i>C. perfringens</i> (rewarmed meats).
Viral	Rotavirus	Outbreak person to person (PTP), daycare; lasts 4–8 d.
	Norovirus	~50% of all diarrhea. Winter outbreaks; PTP & food/water; no immunity. Lasts 1–3 d. Vomiting prominent.
Bacterial	<i>E. coli</i> (toxigenic)	>50% of traveler's diarrhea; cholera-like toxin; <7 d.
	<i>Vibrio cholerae</i> (Lancet 2012;379:2466)	Contam H <sub>2</sub> O, fish, shellfish; 50 cases/y in U.S. Gulf Coast. Severe dehydration & electrolyte depletion.
Parasitic ( $\pm$ malab for mos after Rx)	<i>Giardia</i>	Streams/outdoor sports, travel, outbreaks. Bloating. Acute (profuse, watery) $\rightarrow$ chronic (greasy, malodorous).
	<i>Cryptosporidiosis</i> (NEJM 2002;346:1723)	Water-borne outbreak; typically self-limited, can cause chronic infxn if immunosupp. Abd pain (80%), fever (40%).
	<i>Cyclospora</i>	Contaminated produce
Inflammatory		<b>Predom. colonic invasion. Small vol diarrhea. LLQ cramps, tenesmus, fever, typically <math>\oplus</math> fecal WBC or FOB.</b>
Bacterial	<i>Campylobacter</i>	Undercooked poultry, unpasteurized milk, travel to Asia; carried by puppies & kittens. Prodrome; abd pain $\rightarrow$ "pseudoappendicitis"; c/b GBS, reactive arthritis.
	<i>Salmonella</i> (nontyphoidal)	Eggs, poultry, milk. Bacteremia in 5–10%. 10–33% of bacteremic Pts >50 y may develop aortitis.
	<i>Shigella</i>	Abrupt onset; gross blood & pus in stool; $\uparrow\uparrow$ 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 $\rightarrow$ 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 $\rightarrow$ pea-soup diarrhea, bacteremia.
Parasitic	<i>E. histolytica</i>	Yersinia: undercooked pork; unpasteurized milk, abd pain $\rightarrow$ "pseudoappendicitis" (aka mesenteric adenitis)
	<i>CMV</i>	Aeromonas, <i>Plesiomonas</i> , <i>Listeria</i> (meats & cheeses)

### Evaluation (NEJM 2014;370:1532)

- History:** stool freq, bloody, abd pain, duration of sxs [~1 wk for viral & bacterial (except *C. diff*), >1 wk for parasitic], travel, food, recent abx, immunocompromise
- PEx:** vol depletion (VS, UOP, axillae, skin turgor, MS), fever, abd tenderness, ileus, rash
- Laboratory:**  $\checkmark$  **fecal WBC** (high false  $\oplus$  &  $\ominus$ ) or stool lactoferrin & calprotectin (PMN products; Se/Sp >90%), stool cx, BCx, lytes, *C. diff* (if recent hosp/abx), stool O&P (if >10 d, travel to endemic area, exposure to unpurified H<sub>2</sub>O, community outbreak, daycare, HIV  $\oplus$  or MSM);  $\pm$  stool ELISAs (viruses, *Crypto*, *Giardia*), serologies (*E. histolytica*)
- Imaging/endoscopy** warranted if **warning signs:** fever, signific abd pain, blood or pus in stools, >6 stools/d, severe dehydration, immunosupp, elderly, duration >7 d, hosp-acquired. CT/KUB if ? toxic megacolon; sig/colo if immunosupp or cx  $\ominus$

### Treatment (Am J Gastro 2016;111:602)

- If none of the above warning signs and Pt able to take POs  $\rightarrow$  supportive Rx only: oral hydration, loperamide, bismuth subsalicylate (avoid anticholinergics)
- If moderate dehydration: 50–200 mL/kg/d of oral solution ( $\frac{1}{2}$  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: IV fluids.
- Fluoroquinolone or rifaximin if high suspicion for traveler's diarrhea
- If high suspicion for protozoal infection can consider metronidazole or nitazoxanide
- Empiric abx** for non-hospital-acquired **inflammatory diarrhea** reasonable: FQ  $\times$  5–7 d abx rec for *Shigella*, cholera, *Giardia*, amebiasis, *Salmonella* if Pt >50 y or immunosupp or hospitalized, ? *Campylobacter* (if w/in 4 d of sx onset) avoid abx if suspect *E. coli* O157:H7 as may  $\uparrow$  risk of HUS

# CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA (CDAD)

## Pathogenesis & epidemiology (NEJM 2015;372:825)

- Ingestion of *C. diff* spores → colonization when colonic flora Δd by abx or chemo → release of toxin A/B → colonic mucosal necrosis & inflammation → pseudomembranes
- Most frequently reported nosocomial infxn; community-acquired infxn may account for up to 1/3 of new cases. Associated w/ all abx (esp. β-lactams, clinda, quinolones).
- Additional risk factors: elderly, nursing home residents, IBD, PPI (CID 2011;53:1173)

## Clinical manifestations (a spectrum of disease)

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

## Diagnosis

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

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

- If possible d/c abx ASAP; stop antimotility agents
- Non-severe:** vanco 125 mg PO q6h or MNZ 500 mg PO q8h  $\times$  10–14 d; equal cure rates, but MNZ less well tolerated
- Severe** (any of the following: >12 BM/d, Temp >103°F, WBC >25, HoTN, ICU care required, ileus): vanco 125 mg PO q6h + MNZ 500 mg IV q8h
- If worsening (ileus, ↑ WBC, ↑ lactate, shock, toxic megacolon, peritonitis): abd CT & urgent surgical consult re: subtotal colectomy (? possible role for diverting loop ileostomy or colonic lavage); may also consider vanco PR
- If Pt needs to continue on abx, continue *C. diff* Rx for  $\geq$  7 d post-abx cessation
- Stool carriage may persist 3–6 wk postcessation of sx & should not trigger further Rx (retesting for *C. diff* of limited utility during this time)
- Recurrent infection:** 15–30% risk after d/c of abx, most w/in 2 wk of stopping abx  
1st recurrence: vanco 125 mg PO q6h  $\times$  10–14 d or fidaxomicin 200 mg PO bid  $\times$  10 d  
Subsequent recurrences: vanco PO pulse → taper. Consult ID physician. Consider fecal microbial transplant (NEJM 2013;368:407 & JAMA 2016;315:142) or fidaxomicin (200 mg bid  $\times$  10 d). Pilot data for oral admin of nontoxicigenic *C. diff* strain spores (JAMA 2015;313:1719).
- Probiotics w/o clear benefit (Lancet 2013;382:1249)

# CHRONIC DIARRHEA (>4 wk; JAMA 2016;315:2712)

## General evaluation

- Clinically can be organized into watery, fatty, or inflammatory stools
- Additional hx: timing (freq, relation to meals; nocturnal diarrhea a/w organic causes like IBD rather than IBS), abd pain, wt loss, prior surg, chemo/XRT, diet (incl caffeine or poorly absorbed carbs/sugars), infectious sxs, immunocompromise, travel, laxative use, etc.
- Hx offending meds: PPI, colchicine, abx, H2RA, SSRIs, ARBs, NSAIDs, chemo, caffeine
- PEx: gen appearance (BMI), signs of systemic disease, surgical scars, rectal tone/DRE
- Lab testing: CBC, metabolic profile, alb, TSH, Fe studies, ESR; see under each category
- Imaging/endoscopy: colonoscopy for chronic diarrhea of unknown cause. Abd CT/MRI usually warranted if systemic problem suspected.

## Osmotic (watery; $\ominus$ fecal fat, ↑ osmotic gap, ↓ diarrhea with fasting)

- Caused by ingestion of poorly absorbed cations/anions (Mg, sulfate, phos; found in laxatives) or poorly absorbed sugars (eg, mannitol, sorbitol; found in chewing gum; or lactose if lactose intolerant). *Diarrhea resolves w/ cessation of offending substance.*
- Dx: ↑ stool osmotic gap (see Figure); stool pH <6 if unabsorbed carbohydrates
- Lactose intolerance** (75% nonwhites & 25% whites lactase-deficient): can be acquired after gastroenteritis, med illness, GI surg. Clin: bloating, flatulence, discomfort, diarrhea. Dx: H<sub>2</sub> breath test or empiric lactose-free diet. Rx: lactose-free diet & lactase tablets.

## Secretory (watery; normal osmotic gap, no Δ diarrhea w/ fasting, often nocturnal diarrhea)

- Caused by secretion of anions or K<sup>+</sup> into lumen or inhib of Na absorption → ↑ H<sub>2</sub>O in stool. Most commonly caused by bacterial toxins from **infxn** (see above). Other causes:
- Endocrine:** Addison's, VIPoma, carcinoid, Zollinger-Ellison, mastocytosis, hyperthyroid ( $\uparrow$  motility). ✓ serum peptide levels (eg, gastrin, calcitonin, VIP) & urinary histamine.
- GI neoplasm:** carcinoma, lymphoma, villous adenoma

**Microscopic colitis:** common cause of chronic diarrhea w/ obscure origin. Often seen in middle-aged women w/ autoimmune disorders. NSAIDs, SSRIs, PPIs notable triggers. Grossly nl on colo but bx shows lymphocytic & plasmacytic infiltration of mucosa ± thickened submucosal collagen. Rx: antidiarrheals, cholestyramine, bismuth, budesonide; consider anti-TNFs if refractory.

**Bile acid-induced diarrhea:** ileal resection or disease (eg Crohn's), etc. → bile acids in colon → electrolyte & H<sub>2</sub>O secretion. Rx w/ empiric bile-acid binders (eg, cholestyramine).

**Fxnal/IBS** (watery; normal osmotic gap, ↓ diarrhea with fasting): see **Dysmotility**

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

- Defective mucosal absorption of nutrients b/c Δs in: mucosal surface (surgical resection) or gen. mucosal dis. (celiac, IBD). Bloating, foul-smelling, floating stools (steatorrhea).

**Celiac disease** (NEJM 2012;367:2419; Gastro 2015;148:1175)

Immune rxn in genetically predisposed Pts (~1% pop) to gliadin, a component of gluten (wheat protein) → small bowel inflammatory infiltrate → impaired absorption

Other s/s: Fe/folate defic anemia; osteoporosis; dermatitis herpetiformis; ↑ AST/ALT

Dx: IgA anti-tissue transglutaminase Ab (most Se), IgA anti-deamidated gliadin peptide Ab; IgA α-endomysial Ab. Duodenal bx to confirm dx (blunted villi, crypt hyperplasia, inflamm infiltrate) but may not be necessary if serology + and Pt sx. HLA-DQ2/Q8 testing useful for high - predictive value if - serologies already on gluten-free diet.

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

Complic: ~5% refractory sx, risk of T-cell lymphoma and small bowel adenocarcinoma

**Whipple's disease:** infxn w/ *T. whipplei* (NEJM 2007;365:55)

Other s/s: fever, LAN, edema, arthritis, CNS Δs, gray-brown skin pigmentation, AI & MS, oculomasticatory myorhythmia (eye oscillations + mastication muscle contract)

Rx: (PCN + streptomycin) or 3<sup>rd</sup>-gen ceph × 10–14 d → Bactrim for ≥1 y

**Small intestinal bacterial overgrowth** (SIBO): colonic bacteria in SI → steatorrhea,

B12/Fe defic, protein-losing enteropathy. A/w dysmotility (DM neuropathy, scleroderma), Δd anatomy (Crohn's, surgery, fistulae), immune deficiency, celiac, CF. Dx w/ H<sup>+</sup> or <sup>14</sup>C-xylose breath testing or empiric abx. Rx w/ 7–10 d abx (eg, rifaximin, MNZ, FQ).

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

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

- Defective intraluminal hydrolysis of nutrients, typ. 2/2 pancreatic/hepatobiliary pathology

**Pancreatic insufficiency:** most commonly from chronic pancreatitis or pancreatic cancer. Test w/ stool elastase, chymotrypsin levels, or empiric pancreatic enzyme replacement.

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

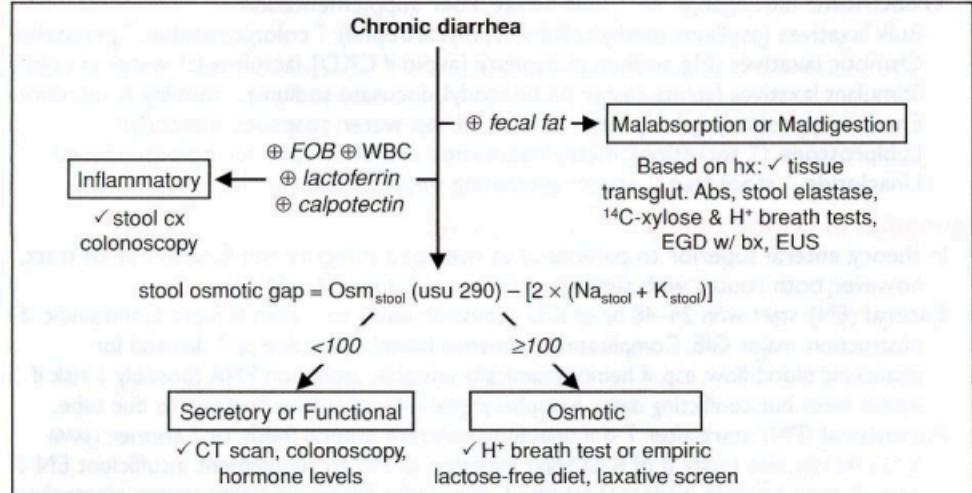
**Inflammatory** (+ fecal WBC or lactoferrin or calprotectin, + FOB, fever, abd pain)

- Infections:** chronic *C. diff*, *Entamoeba histolytica*, *Yersinia*, CMV, TB especially in immunocompromised hosts. *CMV*, *C. diff* notorious for causing exacerbations of IBD.

- Inflammatory bowel disease** (Crohn's, UC)

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

Figure 3-2 Workup of chronic diarrhea



# DYSMOTILITY & NUTRITION

## Functional GI Disease

- Recurrent GI sx caused by abnl gut-brain interactions rather than structural cause
- >20 types of FGIDs per Rome III criteria; now Rome IV (Gastro 2016;150:1257)
- Irritable Bowel Syndrome (IBS)** (JAMA 2015;313:949)
  - Abd discomfort a/w ≥2 of following: improve w/ defecation, Δ stool frequency, Δ stool form
  - IBS-C** (constipation predominant) vs. **IBS-D** (diarrhea predominant) vs. IBS-M (mixed) vs. IBS-U (unclassified). Sx may be related to stress, diet, lifestyle, possibly microbiome.
- Treatment:** exercise, cognitive behavioral Rx, Δ diet, probiotics, ? peppermint oil  
IBS-C: laxatives (eg, lubiprostone, linaclotide, PEG), biofeedback  
IBS-D: rifaximin or loperamide; eluxadoline,  $\mu$  &  $\kappa$  agonist,  $\delta$  antag (NEJM 2016;374:242)
- Cyclical Vomiting Syndrome:** stereotypic episodes of acute recurrent vomiting; a/w marijuana use, family hx of migraine  
acute Rx: antiemetics, IVF, sumatriptan, BZDs; prevention: TCAs/AEDs; avoid marijuana

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

- Delayed gastric emptying w/o obstruction, typically p/w nausea (>90%), vomiting (>80%), early satiety (60%), postprandial fullness/pain
- Etiol: DM, post-surg, thyroid disease, critical illness, Parkinson's, opiates, CCB, anti-cholin
- Dx: gastric emptying scintigraphy
- Treatment:** prokinetic agents (metoclopramide or erythromycin), antiemetics for sx; feeding tube if refractory; intrapyloric botox & gastric stimulator experimental

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

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

## Constipation (Annals 2015;162:ITC1)

- Defined as dissatisfaction w/ defecation or (per Rome III): ≥2 of following during last 3 mo  
≥25% of the time: straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction, manual maneuvers to facilitate defecation, stool frequency <3/wk
- Secondary etiologies (4 M's)**
  - Mech obstruction: malignancy, compression, rectocele, strictures
  - Meds: opioids, TCAs, anticholinergics, CCB, NSAIDs, diuretics,  $\text{Ca}^{2+}$ , Fe
  - Metabolic/endo: DM, hypothyroid, uremia, preg, panhypopit, porphyria, ↑ Ca, ↓ K, ↓ Mg
  - Myopathy/Neuro: Parkinson's, Hirschsprung's, amyloid, MS, spinal injury, dysautonomia
- Dx:** H&P w/ DRE. Labs: consider CBC, electrolytes w/ Ca, TSH. Colonoscopy if alarm sx. Anorectal manometry/balloon expulsion test; colonic transit study; defecography.
- Treatment:** diet change w/ ↑ fluid intake, fiber supplementation
  - Bulk laxatives (psyllium, 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 ( $\uparrow$  secretion); methylnaltrexone and alvimopan for opioid-induced Linaclotide  $\uparrow$  stool freq, ↓ straining/bloating (NEJM 2011;365:6:527)

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

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

## DIVERTICULOSIS

Definition & pathophysiology (*Lancet* 2004;363:631)

- Acquired herniations of colonic mucosa & submucosa in areas where vasa recta penetrate
- Thought to occur in setting of abnormal motility and ↑ intraluminal pressure

## Epidemiology

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

## Clinical manifestations

- Usually asx, but 5–15% develop diverticular hemorrhage (see "GIB") and <5% diverticulitis
- For asx diverticulosis, limited data for ↑ fiber diet or avoiding nuts/seeds (*JAMA* 2008;300:907)

## DIVERTICULITIS

Pathophysiology (*NEJM* 2007;357:2057; *Gastroenterol* 2015;147:1944)

- Retention of undigested food and bacteria in diverticulum → fecalith formation → obstruction → compromise of diverticulum's blood supply, infection, perforation
- Uncomplicated:** microperforation → localized infection
- Complicated** (15%): macroperf → abscess, peritonitis, fistula (65% w/ bladder), obstrxn

## Clinical manifestations

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

## Diagnostic studies

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

Treatment (*JAMA* 2014;311:287; *Dis Colon Rectum* 2014;57:284)

- Mild: outPt Rx indicated if Pt has few comorbidities and can tolerate POs  
PO abx: (MNZ + FQ) or amox/clav for 7–10 d; liquid diet until clinical improvement  
Possible that abx not be needed for uncomplicated diverticulitis (*Cochrane CD009092*)
- Severe: inPt Rx if cannot take POs, narcotics needed for pain, or complications  
NPO, IVF, NGT (if ileus)  
IV abx (GNR & anaerobic coverage; eg, CTX/MNZ or pip-tazo)
- Abscesses >4 cm should be drained percutaneously or surgically
- Surgery: if progression despite med Rx, undrainable abscess, free perforation  
Resection superior to laparoscopic lavage (*JAMA* 2015;314:1364)  
After source control, 4 d abx may be sufficient (*NEJM* 2015;372:1996)  
Resection for recurrent bouts of diverticulitis on a case by case basis  
Consider lower threshold for urgent & elective surgery for immunocompromised Pts

## Prevention

- Mesalamine ± rifaximin may provide sx relief in chronic/recurrent dis. (*Dig Dis Sci* 2007;52:2934)
- Risk of recurrence 10–30% w/in 10 y of 1<sup>st</sup> episode; more likely 2<sup>nd</sup> episode complicated

## POLYPS &amp; ADENOMAS

Pathophysiology & Epidemiology (*NEJM* 2016;374:1065)

- Accumulation of mutations in colonic epithelial cell DNA affecting oncogenes & tumor suppressor genes → *tumor initiation* (formation of adenoma; APC loss of fxn) → *tumor progression* (adenoma → carcinoma; K-ras gain of fxn, DCC, p53 loss of fxn).
- Risk factors: ↑ age, FHx (sporadic in 1<sup>o</sup> relatives, Lynch, FAP), IBD, ↑ dietary fat, central adiposity, ↑ EtOH, ↓ fiber, ↑ red meat, ? smoking, DM
- Protective factors: ↑ physical activity, ASA/NSAIDs, Ca<sup>2+</sup> intake, HRT, ↓ BMI; possibly ↑ fiber, vitamin D, fish oil, statins, selenium
- Neoplastic polyps: adenomas (tubular, villous, tubulovillous dysplasia), sessile serrated adenomas/polyps (concern for interval CRC), carcinomas.
- Nonneoplastic polyps: hyperplastic, juvenile, Peutz-Jeghers, inflammatory

## Detection

- Colonoscopy is gold standard
- Recommended in all Pts starting at age 50 and then typically q10y unless pathology found
- If + FHx, start age 40, or 10 y before age of dx in youngest family member, repeat q5y

# INFLAMMATORY BOWEL DISEASE

## Definition

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

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

- 1.4 million people in U.S.; prev 1:1000 UC & 1:3000 CD; ↑ incidence in Caucasians, Jews
- Age of onset 15–30 y in UC and CD; CD is bimodal and has second peak at 50–70 y
- Smokers at ↑ risk for CD, whereas nonsmokers & former smokers at ↑ risk for UC
- Genetic predisposition + environmental risk factors → T cell dysregulation → inflammation

## ULCERATIVE COLITIS (NEJM 2011;365:1713; Lancet 2012;380:1606)

### Clinical manifestations

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

### Diagnosis

- **Colonoscopy:** involves rectum (95%) & extends proximally and contiguously within colon
- Classify by location: proctitis (25–55%), left-sided colitis (50–70%) and pancolitis (20%)
- Appearance: granular, friable mucosa with diffuse ulceration; *pseudopolyps*
- Histology: superficial chronic inflammation; crypt abscesses & architectural distortion
- Barium enema with featureless and tubular appearance of colon (*leadpipe appearance*)
- Flares: ↑ ESR & CRP (not Se or Sp); ⊕ fecal calprotectin (Se 77%, Sp 71%)

### Complications

- **Toxic megacolon** (5%): colon dilatation (≥6 cm on KUB), colonic atony, systemic toxicity, & ↑ risk of perf. Rx w/ IV steroids & broad-spectrum abx; surgery if needed.
- Stricture (5%): occurs in rectosigmoid after repeated episodes of inflammation
- CRC and dysplasia (see below)
- For patients s/p surgery w/ ileal pouch, may develop *pouchitis* (inflammation of ileal pouch, up to ½ of pts), Rx w/ abx (MNZ, cipro), probiotics

### Prognosis

- 50% of Pts in remission at any given time; intermittent exacerbations in 90%; continual active disease in ~18%. Rate of colectomy at 10 y is 24%.
- Mortality rate of severe UC flare is <2%, & overall life expectancy in UC = non-UC Pts

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

### Clinical manifestations

- **Abdominal pain,** loose/frequent stools (up to 50% ⊕ FOBT), fever, malaise, wt loss
- Mucus-containing, **nongrossly bloody diarrhea**
- N/V, bloating, obstipation if presence of obstruction; extracolonic manifestations as in UC

### Diagnosis

- **Ileocolonoscopy + bx** is gold standard; **small bowel imaging** (eg MR-enterography – 91% accuracy in identifying Crohn's compared to endoscopy); capsule endoscopy
- Classify by location: small bowel (47%), ileocolonic (21%), colonic (28%); upper tract rare
- Montreal classification: age at dx, disease location & behavior (stricture vs. nonstricture, penetrating vs. nonpenetrating), plus modifiers for upper tract & perianal disease
- Appearance: nonfriable mucosa, cobblestoning, aphthous ulcers, deep & long **fissures**
- Histology: **transmural inflammation** with mononuclear cell infiltrate, **noncaseating granulomas** (seen in <25% of mucosal biopsies), fibrosis, ulcers, fissures
- Track disease severity w/ Crohn's Disease Activity Index (CDAI) questionnaire

### Complications

- **Perianal disease:** fissures, fistulas, skin tags, perirectal abscesses (in 24% of Pts; perianal disease precedes intestinal symptomatology)
- **Stricture:** small bowel, postprandial abd pain; can lead to complete SBO & require surgery
- **Fistulas:** perianal, enteroenteric, rectovaginal, enterovesicular, enterocutaneous
- **Abscess:** fever, tender abd mass, ↑ WBC; steroids mask sx, ∴ need high-level suspicion
- **Malabsorption:** ileal disease/resection: ↓ bile acids abs → gallstones; ↓ fatty acid abs → Ca oxalate kidney stones; ↓ fat soluble vitamin abs → vit D deficiency → osteopenia

### Prognosis

- Variable at 1 y: ~50% in remission, ~20% flare, ~20% low activity, ~10% chronic active

- At 20 y, majority will have required some surgery; overall life expectancy is slightly ↓

**Initial evaluation**

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

**Goals of treatment**

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

**Medical Therapy for IBD (in stepwise sequence)****Ulcerative colitis**

Mild	<b>5-ASA:</b> many formulations (sulfasalazine, mesalamine, olsalazine, balsalazide) depending on disease location. Used to induce remission & for maintenance. Complications: diarrhea, abd pain, pancreatitis.
Mild-Moderate	<b>MMX-budesonide:</b> oral formulation of budesonide released throughout entire colon for flare. 1 <sup>st</sup> pass metab ↓ systemic adverse effects of steroid.
Moderate-Severe	<b>PO prednisone:</b> 40–60 mg w/ taper over several wks to induce remission <b>AZA/6-MP:</b> 0.5–1 mg/kg and uptitrate over several wks for maintenance. Complic: BM suppression, lymphoma, pancreatitis, hepatitis; ✓ TPMT levels prior to dosing to ↓ risk of generation of toxic metabolites. In selected cases can add allopurinol to boost activity in non-responders.
Severe or refractory disease	<b>IV steroids:</b> eg, 100 mg hydrocort q8h or 16–20 mg methylpred q8h to induce remission w/ plan to taper & switch to non-steroid maintenance. <b>Cyclosporine:</b> for severe flares refractory to steroids, 2–4 mg/kg infusion × 7 d w/ goal to Δ to maintenance medication (eg, AZA/6-MP) <b>Anti-TNF</b> (infliximab, adalimumab & golimumab): 15–20% remission rates (Gastro 2012;142:257). For steroid-refractory flares or to maintain remission. Complic: reactivation TB (✓ PPD prior to Rx); exclude viral hepatitis; small ↑'d risk NHL; infusion & lupus-like rxn, psoriasis, MS, CHF. <b>Vedolizumab</b> (see below) Investigational: tofacitinib (janus kinase inhib; NEJM 2012;367:616), fecal transplant (Gastro 2015;149:102)

**Crohn's disease**

Mild	<b>5-ASA:</b> Sulfasalazine 4–6 g/d may be useful in inducing remission <b>Abx:</b> FQ/MNZ or amox/clav for pyogenic complic (fistulas, perineal dis.)
Mild-mod	<b>Budesonide:</b> oral formulation able to reach ileum
Moderate-severe	<b>PO prednisone:</b> same as UC, for inducing remission, not maintenance <b>AZA/6-MP:</b> same as UC, for maintenance <b>MTX:</b> 15–25 mg IM/SC or PO qwk for maintenance; 1–2 mo to take effect
Severe or refractory disease	<b>Anti-TNF:</b> infliximab, adalimumab or certolizumab (pegylated) If flare on infliximab, ✓ trough & presence of anti-inflix Ab. Low & ⊖ Ab → ↑ dose/freq. If ⊕ Ab → Δ to other biologic (Am J Gastro 2011;106:685). <b>Vedolizumab</b> (anti-α4β7 integrin) and <b>ustekinumab</b> (anti-IL 12/23) if refractory to anti-TNFs SMAD7 anti-sense oligonucleotide (NEJM 2015;372:1104) under study

**Surgery**

- UC:** colectomy if sx refractory to or intolerable side effects from meds, CRC, perforation, toxic megacolon, uncontrolled hemorrhage. Often **ileal pouch-anal anastomosis (IPAA)**.
- CD:** resection if refractory disease; endoscopic dilation or surgery for strictures; diverting ileostomy for perineal disease

**Cancer screening (NEJM 2015;372:1441)**

- Colon cancer:** risk in UC ~2% at 10 y, ~8% at 20 y, ~18% at 30 y. Similar for colonic CD, plus risk of small bowel cancer as well. Dysplasia best marker for risk. Other risk factors include: PSC, ⊕ FHx, greater extent of disease, stricture, & pseudopolyps.
- Surveillance:** colonoscopy w/ random bx 8 y after dx to eval for dysplasia, q1–3y thereafter based on risk factors. Chromoendoscopy using dye to stain high-risk lesions for targeted biopsy is emerging technique. If high-grade dysplasia or dysplasia assoc. lesion/mass → colectomy. Chemoprophylaxis: 5-ASA & ursodeoxycholic acid (if PSC) ? beneficial (AJG 2011;106:731; Aliment Pharmacol Ther 2012;35:451).

# INTESTINAL ISCHEMIA

## ACUTE MESENTERIC ISCHEMIA

### Definition and Causes

- Reduced or absent blood flow to small intestine, typically caused by arterial (ie, SMA or its branches) occlusion or transient hypoperfusion or less often by venous occlusion
- SMA thrombosis** (~60%): typically due to atherosclerosis at origin of SMA; other risk factors incl. vascular injury from abd trauma, infxn, or mesenteric dissections/aneurysms
- SMA embolism** (~30%): embolic occlusion to SMA (has narrow take-off angle), often in setting of AF, valvular disease incl. endocarditis, atherosclerotic plaque in aorta
- Nonocclusive mesenteric ischemia** (~10%): transient intestinal hypoperfusion due to ↓ CO, athero, sepsis, drugs that ↓ gut perfusion (pressors, cocaine, amphetamines)
- Mesenteric **venous thrombosis** (MVT, ~5%): a/w hypercoag. states, portal hypertension, IBD, malignancy, inflammation (pancreatitis, peritonitis), pregnancy, trauma, surgery
- Focal segmental ischemia of the small bowel** (<5%): vascular occlusion to small segments of the small bowel (vasculitis, atheromatous emboli, strangulated hernias, XRT)

### Clinical manifestations

- Total arterial or venous occlusion: **sudden abd pain out of proportion to abdominal tenderness on exam**, progressing to frank infarction w/ peritoneal signs if untreated
- Nonocclusive: abd distention & pain, N/V, **lower GI bleeding** due to mucosal sloughing; often occurring after episode of hypoperfusion (e.g. cardiac event or shock)

### Physical Exam

- From unremarkable ± abd distention to peritoneal signs (bowel infarction);  $\oplus$  **FOBT ~75%**

### Diagnostic Studies

- Dx relies on high level of suspicion; rapid dx essential to avoid infarction (occurs w/in hrs)
- Mortality 20 to >70% if bowel infarcted; dx prior to infarction strongest predictor of survival
- Laboratory: often nl; ~75% ↑ WBC; ↑ amylase, LDH, PO<sub>4</sub>, D-dimer; ~50% ↑ lactate (late)
- KUB: nl early before infarct; "thumbprinting," ileus, pneumatoasis in later stages
- CT angiography** (arterial phase): noninvasive test of choice; venous phase for dx MVT
- Angiography**: gold standard; potentially therapeutic; indicated if vasc occlusion suspected

### Treatment (NEJM 2016;374:959)

- IVF, NPO, **optimize hemodynamics** (minimize pressors), **broad-spectrum abx**, **anti-coagulation** w/ heparin ± tPA (for occlusive disease), **IV papaverine** (vasodilator; for all)
- If evidence of peritonitis: to OR for surgical endovascular therapies & bowel resection
- SMA thrombosis**: percutaneous (stenting) or surgical revascularization
- SMA embolism**: embolectomy (catheter-based aspiration vs. surgical)
- Nonocclusive**: correct underlying cause (esp. cardiac)
- Mesenteric venous thrombosis**: 3–6 mo. warfarin after initial heparinization. Fibrinolysis or thrombectomy typically reserved for Pts w/ hemodynamic instability or refractory sx.
- Focal segmental ischemia**: typically surgical resection

## CHRONIC MESENTERIC ISCHEMIA

- Definition and causes: ↓ blood flow to gut typically because of mesenteric atherosclerosis
- Sx: "intestinal angina" = **postprandial abd pain**, early satiety, & ↓ wt due to fear of eating. If pain becomes constant → could represent acute thrombosis (see above).
- Dx: angiography (gold std) ≈ gastric tonometry exercise testing + duplex U/S (if available)
- Treatment: surgical revascularization (1<sup>st</sup> line); could also consider angioplasty ± stenting

## ISCHEMIC COLITIS

### Definition & pathophysiology

- Nonocclusive disease 2° to Δs in systemic circulation or anatomic/fxnal Δs in local mesenteric vasculature; often underlying etiology unknown, frequently seen in elderly
- "**Watershed**" areas (splenic flexure & rectosigmoid) most susceptible, 25% involve R side

### Clinical manifestations, diagnosis, & treatment

- Disease spectrum: reversible colopathy (35%), transient colitis (15%), chronic ulcerating colitis (20%), resulting stricture (10%), gangrene (15%), fulminant colitis (<5%)
- Usually p/w **cramping LLQ pain w/ overtly bloody stool**; fever and peritoneal signs should raise clinical suspicion for infarction
- Dx: **flex sig/colonoscopy** or **CT abd/pelvis** to make diagnosis; r/o IBD, infectious colitis
- Treatment: bowel rest, IV fluids, **broad-spectrum abx**, serial abd exams; **surgery** for infarction, fulminant colitis, hemorrhage, failure of med Rx, recurrent sepsis, stricture
- Resolution w/in 48 h w/ conservative measures occurs in >50% of cases

## ACUTE PANCREATITIS (AP)

**Pathogenesis**

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

**Etiologies** (*Lancet* 2015;386:85)

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

**Clinical manifestations**

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

**Diagnostic studies**

- Dx requires 2 of 3:** characteristic abd pain; lipase or amylase >3× ULN; + imaging
- Laboratory (*Am J Gastro* 2013;108:1400)
  - levels of both amylase and lipase do *not* correlate w/ severity of disease
  - ↑ **amylase:** >3× ULN >90% sensitive, >70% specific for acute pancreatitis  
false -: acute on chronic (eg, alcoholic); hypertriglyceridemia (↓ amylase activity)  
false +: other abd or salivary gland process, acidemia, renal failure, macroamylasemia
  - ↑ **lipase:** >3× ULN 99% sensitive, 99% specific for acute pancreatitis  
false +: renal failure, other abd process, diabetic ketoacidosis, HIV, macrolipasemia  
longer half-life than amylase: useful in Pts w/ delayed presentation after onset of sx  
lipase >10,000 has 80% PPV for biliary dx, 99% NPV for EtOH (*Dig Dis Sci* 2011;56: 3376)  
ALT >3× ULN has 95% PPV for gallstone pancreatitis (*Am J Gastro* 1994;89:1863)

- Imaging studies (*Am J Gastro* 2013;108:1400)
  - Abd U/S:** typically not useful to visualize pancreas (obscured by bowel gas) but should be ordered for all pts with AP to r/o biliary etiology (ie, gallstones, BD dilatation)
  - Abd CT:** not rec for initial eval unless dx unclear (local complic. not yet visible & concern for AKI w/ IV contrast). However, if persistent pain and/or clinical deterioration after 48–72 h, CT(+) useful to r/o local complications (necrosis, fluid collections).
  - MRI/MRCP:** Can detect necrosis; also used to assess for stones & ductal disruption
  - Endoscopic U/S (EUS):** limited role; useful for occult biliary disease (microlithiasis)

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

- Severity defined by presence of organ failure (AKI, resp failure, GIB, shock) & local or systemic complic. (panc necrosis, fluid collections, gastric outlet obstrxn, splenic & PVT).
- Mild:** 80% of cases. No organ failure or local/systemic complications, low mortality.
- Moderate:** transient (<48 h) organ failure ± local/systemic complications, high morbidity
- Severe:** persistent (>48 h) organ failure, very high mortality

**Prognosis**

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

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

- Fluid resuscitation:** early aggressive IVF, titrate to UOP  $\geq 0.5$  mL/kg/h, goal to  $\downarrow$  BUN & Hct over first 12–24 h. LR may be superior to NS ( $\downarrow$  SIRS, CRP at 24 h; avoid if  $\uparrow$  Ca)
- Nutrition** (*Clin Gastro Hepatol* 2007;5:946; *Intern Med* 2012;51:523; *Crit Care* 2013;17:R118)
  - Early enteral feeding encouraged (maintains gut barrier,  $\downarrow$  bacterial translocation) though new data suggest may not be superior to oral feeding at 72 h (*NEJM* 2014;317:1983)
  - Mild: Start feeding once pain-free w/o ileus. Low-fat low-residue diet as safe as liquid diet.
  - Severe: early (w/in 48–72 h) enteral nutrition indicated and preferred over TPN b/c  $\downarrow$  infectious complications, organ failure, surgical interventions, and mortality.

Nasogastric feeding shown to be non-inferior to nasojejunal feeding

- Analgesia:** IV opioids (monitor respiratory status, adjust dosing if  $\uparrow$  renal impairment)
- Gallstone pancreatitis:** urgent (w/in 24 h) ERCP w/ sphincterotomy if cholangitis, sepsis, or Tbili  $\geq 5$ . For mild disease, CCY during initial hosp to  $\downarrow$  risk of recurrence (*Lancet* 2015;386:1261); defer surgery if necrotizing AP until improvement in inflam., fluid collections.
- Hypertriglyceridemia:** insulin gtt (activates lipoprotein lipase), fibrates,  $\pm$  apheresis
- No role for ppx abx in absence of infectious complications (*World J Gastroenterol* 2012;18:279)

**Complications**

- Systemic: ARDS, abdominal compartment syndrome, AKI, GIB (pseudoaneurysm), DIC
- Metabolic: hypocalcemia, hyperglycemia, hypertriglyceridemia
- Fluid collections:
  - Acute fluid collection:** seen early, not encapsulated, most resolve w/in 1–2 wk w/o Rx
  - Pseudocyst:**  $\sim 4$  wk after initial attack, encapsulated. No need for Rx if asx (regardless of size/location). If sx  $\rightarrow$  endoscopic (*Gastro* 2013;145:583) vs. perc/surg drainage.
- Pancreatic necrosis: Nonviable pancreatic tissue. CT-guided FNA if infection suspected
  - Sterile necrosis:** if asx, can be managed expectantly, no role for ppx antibiotics
  - Infected necrosis** (5% of all cases, 30% of severe): high mortality. Rx w/ carbapenem or MDZ+FQ. “Step-up” Rx w/ perc drainage and minimally invasive surg debridement or endoscopic necrosectomy superior to open necrosectomy (*NEJM* 2010;362:1491)
- Pancreatic abscess:** circumscribed collection of pus (usually w/o pancreatic tissue), usually seen  $\geq 4$  wk into course. Rx with abx + drainage (CT-guided if possible).

**CHRONIC PANCREATITIS****Pathogenesis & Etiology**

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

**Clinical manifestations**

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

**Diagnostic studies**

- Labs: amylase/lipase  $\uparrow$  early, may be nl later.  $\oplus$  fecal fat,  $\downarrow$  stool elastase & A1AT. ✓ A1c, consider IgG4/ANA & genetic testing (CFTR, SPINK1, PRSS1) if young or  $\oplus$  FHx.
- Imaging: Ca<sup>2+</sup> on KUB/CT. ERCP/MRCP/EUS high Sens for dx: stricture, dilated ducts

**Treatment** (*Lancet* 2016;387:1957)

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

**Complications**

- Pseudocysts, pseudoaneurysms, pancreatic ascites or pleural effusion,  $\uparrow$  risk of panc Ca

**AUTOIMMUNE PANCREATITIS****Pathogenesis**

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

**Clinical Manifestations**

- Abdominal pain**, can p/w obstructive jaundice and panc mass mimicking panc Ca.
- Extrapancreatic: Sjögren's, interstitial nephritis, autoimmune thyroiditis, UC/PSC, RA

**Diagnosis**

- Labs: cholestatic LFTs ( $\uparrow$  A $\phi$   $>$  AST/ALT),  $\uparrow$   $\gamma$ -globulins and IgG4,  $\oplus$  ANA, RF
- HISORt criteria: Histology, Imaging (“sausage pancreas”, bile duct stricture), Serology, other Organ involvement, Response to therapy

**Treatment**

- Corticosteroids 1<sup>st</sup>-line, immunomodulators (AZA, MMF, cyclophosphamide) if relapse

# 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)  
↑ levels seen w/ most types of hepatocellular injury; skeletal musc. injury, MI (AST > ALT)
- Alkaline phosphatase (A $\phi$ ):** enzyme bound in hepatic canalicular membrane.  
↑ levels seen w/ biliary obstrxn or intrahepatic cholestasis  
also found in bone, intestines, kidney, placenta; confirm from liver w/: ↑ GGT (or ↑ 5'-NT).
- Bilirubin:** product of heme metab (unconjugated, "indirect") carried by alb to liver where taken up for conjugation ("direct") to make soluble, then excreted into bile.  
↑ direct hyperbili seen with cholestasis, enzymatic disorders (eg, Dubin-Johnson, Rotor's)  
↑ indirect hyperbili seen with hemolysis, enzymatic disorders (eg, Crigler-Najjar, Gilbert's)  
jaundice seen when bili >2.5 mg/dL (esp. in sclera or under tongue);  
if hyperbili conjugated then ↑ urine bilirubin

## Tests of hepatic function

- Albumin:** marker for liver protein synthesis, ↓ slowly in liver failure ( $t_{1/2} \sim 15-18$  d)
- Prothrombin time (PT):** depends on synthesis of coag factors by liver (except FVIII); b/c  $t_{1/2}$  of some factors (eg, V, VII) is short, ↑ PT can occur w/in hrs of liver dysfxn

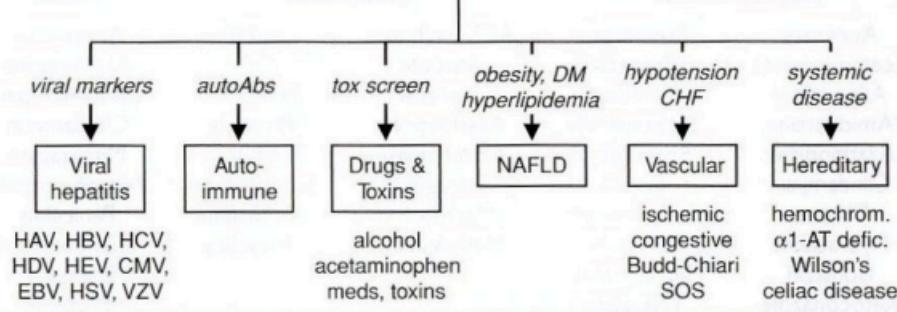
## Patterns of LFTs

Pattern	ALT	AST	A $\phi$	Bilirubin
<b>Hepatocellular</b>	↑↑	↑↑	±↑	±↑ (direct)
Viral hepatitis, NASH	Often ALT > AST		±↑	±↑ (direct)
Alcoholic hepatitis	AST:ALT ≥ 2:1		±↑	±↑ (direct)
Ischemic injury	↑↑↑	↑↑↑	↑↑	↑↑ (direct)
Wilson's disease	↑	↑	A $\phi$ :Tbili < 4	
<b>Cholestatic</b>	±↑	±↑	↑↑	↑↑ (direct)
<b>Infiltrative</b>	near nl	near nl	↑↑	±↑
<b>Nonhepatic</b>				
Skeletal muscle injury	AST >> ALT		nl	nl
Bone disease	nl	nl	↑ (w/ nl GGT)	nl
Hemolysis	nl	nl	nl	↑ (indirect)

- R-value** = ratio of ALT:A $\phi$  normalized to ULN for each = (ALT/ULN) ÷ (A $\phi$ /ULN)  
R >5 suggests hepatocellular injury, <2 suggests cholestatic injury, 2–5 suggests mixed

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

### Hepatocellular injury (predom ↑ AST & ALT, ± ↑ bili and A $\phi$ )



## • Workup for acute enzyme elevation (often symptomatic)

Severe ALT & AST elevation (>1000):

toxins (usu. acetaminophen) → ✓ tox screen, EtOH, acet. levels. Other toxins: INH, disulfiram, pyrazinamide, OTC/herbal, fenofibrate, niacin, amiodarone, MDMA.

ischemia (eg, sepsis, hypotension, Budd Chiari) → ✓ liver U/S w/ Doppler. Etiologies usually lead to ↑ LDH. ∴ usually ratio ALT:LDH <1.5 (vs. >1.5 w/ toxins, viruses).

viruses (Hep A-E; HSV, CMV, VZV) → ✓ viral serologies

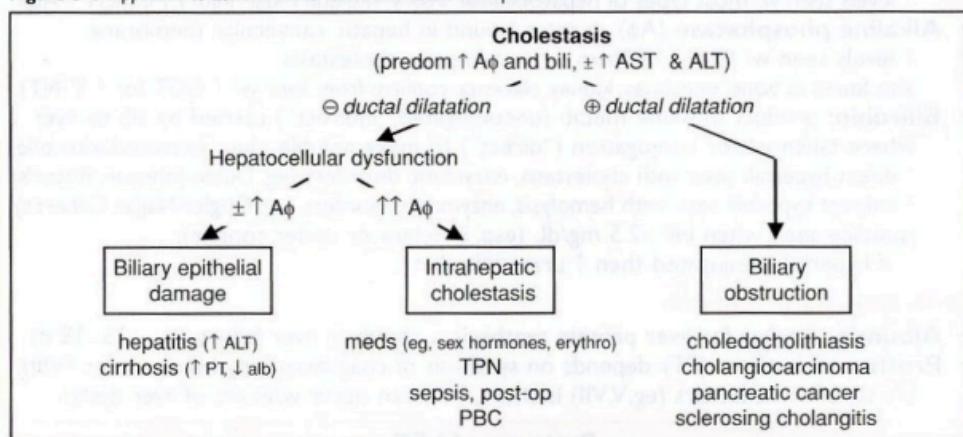
other (AIH, acute Wilson Disease, acute biliary obstrxn) → see ALF & cirrhosis sections  
Acute mild-moderate ALT & AST elevation: as above, think meds/toxins (see list at end of section), viruses, ischemia/vascular issues in hospitalized Pts, obstruction (if mixed picture), systemic disease (see "Workup for chronic enzyme elevation," below)

## • Workup for chronic enzyme elevation (often asymptomatic)

Screen for common causes: hep serologies, EtOH, liver U/S (? NAFLD, cirrhosis), meds

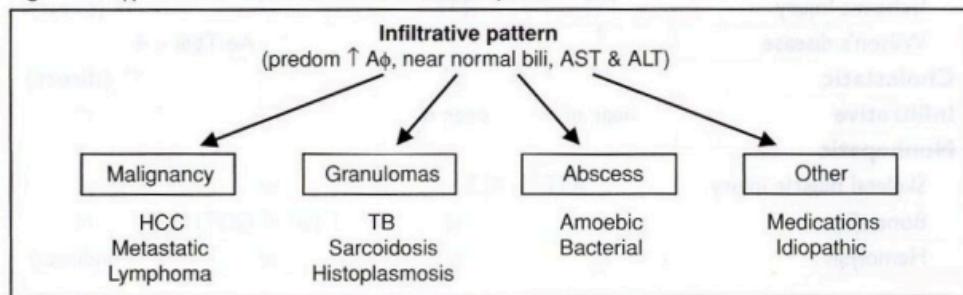
If suspect underlying systemic disease: iron studies (HFE); ANA, ASMA, Ig levels (AIH); ceruloplasmin, urinary copper (Wilson);  $\alpha$ 1-AT (can cause liver dis even w/o lung involvement); celiac screening (rare cause of liver dis); thyroid studies; see "Cirrhosis" If ⊖ evaluation → lifestyle modification (wt loss, DM control) & repeat testing 3–6 mo  
If evidence of chronic liver disease or persistent lab abnl, consider liver bx

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



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

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



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

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

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

## VIRAL

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

- Transmission: fecal-oral route; contaminated food, water, shellfish; daycare center outbreaks
- Incubation: 2–6 wk; no chronic carrier state
- Sx: ↓ appetite, malaise, fever, N/V, RUQ pain, jaundice; rarely fulminant ( $\uparrow$  w/ chronic HCV)
- Diagnosis: acute hepatitis =  $\oplus$  IgM anti-HAV; past exposure =  $\oplus$  IgG anti-HAV ( $\ominus$  IgM)
- Rx for acute HAV: supportive care; refer to liver txplnt center if fulminant hepatitis
- Postexposure ppx: age 1–40 y  $\rightarrow$  vaccine; age <1 y or >40 y, immunosupp, liver dis.  $\rightarrow$  Ig

**Hepatitis B (dsDNA; ~45% of acute viral hepatitis in U.S.; Lancet 2014;384:2053)**

- Transmission: blood (IVDU, transfusion), sexual, perinatal
- Incubation: 6 wk–6 mo (mean 12–14 wk)
- Acute infxn: 70% subclinical, 30% jaundice, <1% fulminant hepatitis (up to 60% mortality)
- Chronic infxn: HBsAg  $\oplus$  >6 mo in <5% of adult-acquired ( $\uparrow$  if immunosupp), >90% of perinatal; ~40% chronic HBV  $\rightarrow$  cirrhosis ( $\uparrow$  risk w/ HCV, HDV, or HIV coinfxn, EtOH)
- HCC:  $\uparrow$  risk if cirrhotic,  $\oplus$  FHx HCC, African >20 y old, Asian ♂ >40 y old or ♀ >50 y old, or >40 y old w/  $\uparrow$  ALT  $\pm$  HBV DNA >2000. Screen w/ AFP & U/S q6mo.
- Extrahepatic syndromes: PAN (<1%), membranous nephropathy, MPGN, arthritis
- Serologic and virologic tests (see Annals 2014;161:58 for screening guidelines)

HBsAg: appears before sx; used to screen blood donors; persists >6 mo = chronic HBV

HBeAg: evidence of viral replication and  $\uparrow$  infectivity

IgM anti-HBc: 1<sup>st</sup> Ab to appear; indicates acute infection

window period = HBsAg becomes  $\ominus$ , anti-HBs not yet  $\oplus$ , anti-HBc only clue to infxn

IgG anti-HBc: indicates previous (HBsAg  $\ominus$ ) or ongoing (HBsAg  $\oplus$ ) HBV infection

anti-HBe: indicates waning viral replication,  $\downarrow$  infectivity

anti-HBs: indicates resolution of acute disease & immunity (sole marker after vaccination)

HBV DNA: presence in serum correlates w/ active viral replication in liver

Diagnosis	HbsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV DNA
Acute hepatitis	$\oplus$	$\ominus$	IgM	$\oplus$	$\ominus$	$\oplus$
Window period	$\ominus$	$\ominus$	IgM	$\pm$	$\pm$	$\oplus$
Recovery	$\ominus$	$\oplus$	IgG	$\ominus$	$\pm$	$\ominus$
Immunization	$\ominus$	$\oplus$	$\ominus$	$\ominus$	$\ominus$	$\ominus$
Chronic hepatitis HBeAg $\oplus$	$\oplus$	$\ominus$	IgG	$\oplus$	$\ominus$	$\oplus$
Chronic hepatitis HBeAg $\ominus$	$\oplus$	$\ominus$	IgG	$\ominus$	$\oplus$	$\pm^*$

\*Precore mutant: HBeAg not made, but anti-HBe can develop due to x-reactivity w/ HBcAg; a/w  $\uparrow$  HBV DNA

- Rx for acute HBV: supportive; hospitalize for  $\Delta$  MS or  $\uparrow$  INR (liver transplant center); consider antiviral therapy if severe

## Phases of Chronic HBV

Phase	ALT (ULN*)	HBV DNA (IU/mL)	HBeAg	Liver Histology (inflammation/fibrosis)	Progression to cirrhosis
Immune-tolerant	NI	$\geq 10^6$	$\oplus$	Minimal	<0.5%/y
Immune-active HBeAg $\oplus$	$\geq 2\times$	$\geq 20k$	$\oplus$	Moderate-to-severe	2–5.5%/y
Inactive	NI	$\leq 2k$	$\ominus$	Min necroinflam.; variable fibrosis	0.05%/y
Immune Reactivation; HBeAg $\ominus$ precore mutant	$\geq 2\times$	$\geq 2k$	$\ominus$	Moderate-to-severe	8–10%/y

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

- Rx of chronic HBV: Rx in immune-active or immune reactivation phases or cirrhotics w/ elevated HBV DNA or decomp. Consider liver bx if ALT 1–2 $\times$  ULN or in immune-tolerant phase if age >40 y; Rx if mod-to-severe inflammation or fibrosis on bx.
- Entecavir or tenofovir:** nucleo(s/t)ide analogs, well tolerated, low resistance; at 5 y, HBeAg seroconversion is 30–40% & loss of HBsAg is 5–10% (Gastro 2012;142:1360; Lancet 2013;381:468). Tenofovir preferred if h/o lamivudine resistance.
- PEG IFN- $\alpha$ 2a:** At 2 y, HBeAg seroconversion is 27%; contraindicated if autoimmune disease, uncontrolled psych disorder, seizures, decompensated cirrhosis

- Rx duration: (1) HBeAg  $\oplus$  immune-active w/o cirrhosis: if seroconversion (HBeAg  $\ominus$ , anti-HBe  $\oplus$ ), can stop after 1 y if ALT nl & HBV DNA suppressed or until HBsAg clears; (2) HBeAg  $\ominus$  immune reactivation: indefinite; (3) cirrhotic: indefinite
- If undergo liver transplant: HBIG + nucleos(t)ide analogue effective in preventing reinfection
- HIV/HBV coinfection: Rx w/ 2 drugs active against both HBV & HIV (NEJM 2007;356:1445)
- Immunosuppression: prior to initiating chemoRx, anti-TNF, steroids ( $>20$  mg/d  $> 1$  mo), screen Pts for HBV; Rx if moderate to high risk of reactivation (Gastro 2015;148:215)
- Postexposure (risk infxn ~30%) ppx: HBIG  $\rightarrow$  vaccine (if unvac or known nonresponder)

### Hepatitis C (ssRNA; ~10% of acute viral hepatitis in U.S.; Lancet 2015;385:1124)

- Transmission: blood (IVDU, transfusion rare cause)  $>$  sexual; 20–30% w/o clear precipitant
- Incubation: 1–5 mo; mean 6–7 wk
- Acute infxn: 80% subclinical; 10–20% sx hepatitis w/ jaundice; fulminant hepatitis rare; prob of spont clearance a/w IL28B & HLA class II genotypes (Annals 2013;158:235)
- Chronic: up to 85%  $\rightarrow$  chronic hepatitis, 20–30% of whom develop cirrhosis (after ~20 y ↑ risk of cirrhosis in men, EtOH, HIV; HCC in 1–4% of cirrhotics/)
- Extrahepatic syndromes: mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, leukocytoclastic vasculitis, thyroiditis, MPGN, IPF, NHL and monoclonal gammopathies
- Serologic, virologic, & genetic tests  
anti-HCV (ELISA):  $\oplus$  in 6 wk, does not = recovery or immunity; can be  $\ominus$  after recovery  
HCV RNA:  $\oplus$  w/in 2 wk, marker of active infection  
HCV genotype (1–6): guides duration & predicts response to Rx; geno. 3 a/w ↑ risk HCC
- Dx: acute hepatitis =  $\oplus$  HCV RNA,  $\pm$  anti-HCV; resolved =  $\ominus$  HCV RNA,  $\pm$  anti-HCV; chronic =  $\oplus$  HCV RNA,  $\oplus$  anti-HCV
- Treatment indications (www.hcvguidelines.org)
  - Acute: if no spont. clearance at 12–16 wk, can Rx w/ same regimens for chronic HCV
  - Chronic: Rx recommended for all except those with ↓ life expectancy
- Rx: NS3/4A protease inhibitors ("...previr"; PI), NS5a inhibitors ("...asvir"; NS5ai), RNA polymerase inhibitors ("...buvir"; RNAPi), ribavirin (RBV), pegylated-interferon (PEG-IFN)

#### Approved HCV Regimens for Treatment-Naïve Patients

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

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

- Monitoring on Rx: CBC, INR, LFTs, GFR, HCV VL, and TSH (if IFN is used) prior to starting Rx. PIs contraind. if decomp. liver dx (ascites, encephalopathy) or CTP score  $\geq 7$ . D/c Rx if jaundice, N/V, weakness, 10x ↑ in ALT, or significant ↑ in bili, A $\phi$ , INR after 4 wk.
- Goal is sustained virologic response (SVR) =  $\emptyset$  viremia 12 wk after completion of Rx. Success depends on genotype but SVR rates  $>90\%$  with current regimens
- Special populations (HCV/HIV coinfection, decompensated cirrhosis, s/p liver transplant, renal impairment): www.hcvguidelines.com for updated recs on mgmt
- Vaccinate all chronic HCV patients against HBV and HAV if not immune
- Postexposure (needlestick risk ~3%) ppx: none; if HCV RNA  $\rightarrow$   $\oplus$ , consider Rx w/in 3 mo

### Hepatitis D (RNA)

- Transmission: blood or sexual; endemic in Africa & E. Europe. Generally requires host to already have HBV infxn in order to cause co-infection or superinfection; in rare cases (immunosupp s/p liver txplt) can replicate autonomously.
- Natural hx: acute HBV-HDV coinfection resolves in >80% of cases; however acute HDV superinfection leads to chronic HBV-HDV in most cases ( $\uparrow$  progression to cirrhosis, HCC)

### Hepatitis E (ssRNA; NEJM 2012;367:1237; Lancet 2012;379:2477)

- Most common cause of acute viral hepatitis in endemic areas
- Transmission: fecal-oral; travelers to central & SE Asia, Africa and Mexico, exp. to swine
- Natural hx: acute hepatitis w/ ↑ mort. (10–20%) if pregnant; rare chronic in transplant Pts
- Dx: IgM anti-HEV (through CDC), HEV RNA
- Extrahepatic sx: arthritis, pancreatitis, anemia, neuro (GBS, meningoencephalitis)

### Other viruses (human pegivirus, CMV, EBV, HSV, VZV)

**Classification** (*J Hep* 2011;55:171; *Hep* 2010;51:2193)

- Type 1: antismooth muscle Ab (ASMA), ANA; antisoluble liver antigen (anti-SLA), a/w more severe disease and relapsing disease
- Type 2: anti-liver/kidney microsome 1 (anti-LKM1); anti-liver cytosol type 1 (ALC-1);
- Overlap syndrome: AIH + PBC (suspect if  $\oplus$  antimitochondrial Ab or  $\oplus$  histology  $\rightarrow$  "autoimmune cholangitis") or PSC (suspect if  $\oplus$  A $\phi$ , IBD, pruritus, or  $\oplus$  radiology/histology)
- Drug-induced: minocycline, nitrofurantoin, infliximab, hydralazine,  $\alpha$ -methyl DOPA, statins

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

- 70% female; 40% present w/ severe AIH (3% fulminant) w/ ALT  $>10 \times$  ULN; 34–45% asx
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs'  $\oplus$  hemolytic anemia
- Dx: scoring system combining serologies,  $\uparrow$  IgG,  $\emptyset$  viral hepatitis, & liver bx (interface hepatitis & lymphoplasmacytic infiltrate) has high Sp & mod Se (*Hep* 2008;48:169)
- Rx: (1) ALT  $10 \times$  ULN; (2) ALT  $5 \times$  ULN & IgG  $2 \times$  ULN; or (3) bridging/multiacinar necrosis
- Induction Rx: (1) prednisone monoRx; (2) prednisone + AZA, or (3) budesonide (if non-cirrhotic) + AZA  $\rightarrow$  65–80% remission (asx, nl LFTs, bili, & IgG, none to minimal interface hepatitis); taper steroids as able; relapse rate of 50–80% (*J Hep* 2015;62:S100)
- Nonresponders or AZA intolerant: cyclosporine, tacrolimus, MMF, rituximab, infliximab
- HCC screening and liver transplant referral for ESLD

**OTHER CAUSES OF HEPATITIS OR HEPATOTOXICITY****Alcoholic hepatitis** (*J Hep* 2012;57:399; *Hep* 2010;51:307)

- Sx: progressive jaundice, tender hepatomegaly, fever, ascites, GIB, encephalopathy
- Labs: ALT usually  $<300$ –500 w/ AST:ALT  $>2:1$ ,  $\downarrow$  plt,  $\uparrow$  Tbili & INR indicate severe hepatitis
- Prognosis: scoring systems include Maddrey's discriminant fxn (MDF), Lille model, MELD MDF ( $4.6 \times [\text{PT} - \text{control}] + \text{Tb}$ )  $>32$  w/ 30–50% 1-mo mortality if un Rx'd (*Gastro* 1996;110:1847)  
Lille model: predicts nonresponse to steroids after 1<sup>st</sup> week of Rx; score  $> 0.45$  predicts poor response to further steroid Rx and a/w  $\downarrow$  in 6-mo survival (*Hep* 2007;45:1348)  
Combination of Lille + MELD scores best predictor of mortality (*Gastro* 2015;149:398)
- Rx: consider if MDF  $>32$ , MELD  $>18$ , or presence of encephalopathy  
Steroids (eg, methylprednisolone 32 mg/d or prednisolone 40 mg/d  $\times$  4 wk  $\rightarrow$  4–6 wk taper)  $\downarrow$  death but  $\uparrow$  rate of infections (*NEJM* 1992;326:507 & 2015;372:1619)  
Contraindications: active GIB, pancreatitis, untreated HBV, uncontrolled infections  
Pentoxifylline of no benefit alone or when added to steroids (*NEJM* 2015;372:1619)  
Addition of NAC to steroids  $\downarrow$  1-mo but not 6-mo mortality (*NEJM* 2011;365:1781)

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

- Pathophysiology: >90% of acetaminophen (N-acetyl-p-aminophenol, APAP) metab into nontoxic metab, but ~5% metab by CYP2E1 into NAPQI, a hepatotoxic metab detoxified by glutathione conjugation; APAP overdose ( $>10$  g) depletes glutathione stores  $\rightarrow$  injury
- CYP2E1 induced by fasting, alcohol, and certain anticonvulsants and anti-TB drugs, resulting in a "therapeutic misadventure" with even low doses (2–6 g) of acetaminophen
- Liver dysfunction may not be apparent for 2–6 d
- Rx: NG lavage, activated charcoal if w/in 4 h. Consider early transfer to transplant ctr.  
**N-acetylcysteine:** administer up to 72 h after ingestion, if time of ingestion unknown or chronic ingestion  $>4$  g/d; low threshold to start NAC w/ low or undetectable APAP levels  
PO NAC (preferred): 140 mg/kg loading dose  $\rightarrow$  70 mg/kg q4h  $\times$  17 additional doses  
IV NAC: 150 mg/kg  $\times$  1 h  $\rightarrow$  50 mg/kg  $\times$  4 h  $\rightarrow$  100 mg/kg  $\times$  16 h; risk of anaphylaxis ( $\downarrow$  w/ 12-h regimen; *Lancet* 2014;383:697); use if unable to tolerate POs, GIB, pregnancy, ALF

**Ischemic hepatitis**

- "Shock liver" w/ AST & ALT  $>1000$  +  $\uparrow\uparrow$  LDH; delayed  $\uparrow\uparrow$  Tbili
- Seen in HoTN & CHF; often requires  $\uparrow$  venous +  $\downarrow$  portal/arterial pressure + hypoxia

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

- Definition: fatty infiltration of liver *and* absence of EtOH or other cause of steatosis  
**NAFL** = steatosis,  $\emptyset$  inflam; **NASH** = steatosis + inflam  $\pm$  fibrosis on bx
- NAFLD: 10–30% of U.S. pop. & over 60% in T2DM & obesity
- NASH: 2–5% of NAFLD & risk of cirrhosis in NASH w/ fibrosis on bx is 30% at 10 y
- Clinical: 80% asx,  $\uparrow$  ALT  $>$  AST, but nl ALT/AST does not exclude poss. of NASH on bx
- Dx: liver bx remains gold standard. NAFLD fibrosis score = clinical variables to predict NASH w/ advanced fibrosis with PPV  $>80\%$  ([www.nafldscore.com](http://www.nafldscore.com)).
- Rx: wt loss (ideally  $\geq 10\%$ , *Gastro* 2015;149:367), exercise, DM control (liraglutide, *Lancet* 2016;387:679 or pioglitazone), statins (*Lancet* 2010;376:1916); vit E  $\downarrow$  steatosis but not fibrosis in Pts w/o DM (*NEJM* 2010;362:1675). HCC is a complication of NAFLD that has progressed to NASH cirrhosis but can occur in absence of advanced liver disease.

# ACUTE LIVER FAILURE (ALF)

## Definition

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

## Etiology (*Lancet* 2010;376:190)

- Drugs/toxins** (nearly 80% of cases in U.S.; *Hepatology* 2010;52:2065)  
Drugs: acetaminophen (most common cause; >40% of all cases in U.S., typically unintentional overdose); anti-TB drugs (INH, rifampin, pyrazinamide); AEDs (phenytoin, valproate, carbamazepine); NSAIDs (idiosyncratic, not dose-related); abx (eg, fluoroquinolones, macrolides); MDMA (ecstasy)  
Toxins: *Amanita phalloides* (mushroom sp. in West Coast), certain herbal preparations
- Viral** (12% of cases in the US): HAV, HBV, HCV (rare), HDV + HBV, HEV (esp. if pregnant). In immunosupp: HSV (50% have skin lesions), EBV, VZV, CMV, HHV6
- Vascular**: Budd-Chiari, ischemic hepatitis, hepatic sinusoidal obstructive syndrome
- Other**: Wilson's disease, pregnancy-related ALF (acute fatty liver, preeclampsia, HELLP), initial presentation of autoimmune hepatitis; idiopathic

## Clinical manifestations

- Initial presentation usually nonspecific: n/v, malaise; then jaundice & multiorgan failure
- Neurologic: **encephalopathy**: grade 1 = attn deficit, tremor; grade 2 = asterixis, lethargy, confusion, ataxia; grade 3 = somnolence, rigidity, clonus, hyporeflexia; grade 4 = coma  
**cerebral edema**: astrocyte swelling likely related to ↑ ammonia levels
- Cardiovascular: **hypotension** with low SVR, shock
- Pulmonary: **respiratory alkalosis**, impaired peripheral O<sub>2</sub> uptake, pulm edema, ARDS
- GI: bleeding (due to bleeding diathesis), pancreatitis (? due to ischemia, drugs, infxn)
- Renal: ATN, **hepatorenal syndrome**, hyponatremia, hypokalemia, hypophosphatemia
- Hematology: thrombocytopenia, ↑ PT/PTT, ↓ fibrinogen, **bleeding diathesis** (↓ synthesis of coag factors balanced by ↓ protein C/S; bleeding mostly due to low platelet count), DIC
- Infection (~90% of Pts): esp. with Staph, Strep, GNRs and fungi (↓ immune fxn, invasive procedures); SBP in 32% of Pts; fever and ↑ WBC may be absent
- Endocrine: **hypoglycemia** (↓ glc synthesis), metabolic acidosis (↑ lactate), adrenal insuf.

## Workup (*Hepatology* 2012;55:965)

- CBC, PT/PTT, LFTs, lytes, BUN/Cr, pH, lactate, NH<sub>3</sub>, acetaminophen level, viral serologies (qv) in all Pts, with additional labs as below if suspected
- Autoimmune hep serologies & IgG levels, ceruloplasmin & serum/urine copper, preg test
- Imaging studies (RUQ U/S or abd CT, Doppler studies of portal and hepatic veins)
- Liver biopsy if underlying etiology remains elusive after initial testing

## Management (*NEJM* 2013;369:2525)

- ICU care at liver transplant center** for hemodynamic & ventilatory support; CVVH for AKI
- Early listing for liver transplantation in selected Pts (see below)
- Cerebral edema: consider ICP monitoring if grade 3/4 enceph; if ↑ ICP → mannitol 0.5–1.0 mg/kg; if arterial NH<sub>3</sub> >150, grade 3/4 enceph, AKI or on vasopressors → prophylactic 3% saline for goal Na 145–155 mEq/L; barbiturates & hypothermia if refractory ↑ ICP
- Encephalopathy: intubate for grade 3 or 4; lactulose is of little benefit
- Coagulopathy: vit K, FFP/plts/cryo if active bleeding or before invasive procedure; PPI ppx
- Infection: low threshold for abx (broad spectrum, eg, vancomycin & 3<sup>rd</sup>-gen ceph.) if suspect infection; anti-fungal coverage in high-risk Pts. Daily blood cultures.
- Rx of specific causes: NAC if acetaminophen-related; antiviral (eg, entecavir) for HBV; plasma exchange can be temporizing measure for Wilson's; IV acyclovir for HSV; PCN-G for *A. phalloides*; delivery of child for pregnancy-related; TIPS, anticoag for Budd-Chiari. Lack of data for use of steroids in autoimmune, but often given (*Hepatology* 2014;59:612).
- NAC may benefit pts w/ non-APAP ALF but data inconclusive (*Gastro* 2009;137:856)
- Liver transplantation** if poor prognosis but could survive surgery

## Prognosis

- Non-acetaminophen ALF mortality ~80%, acetaminophen-induced ALF mortality ~30%
- Predictors of poor outcome (King's College Hospital, UK):  
Acetaminophen-induced: pH <7.25, INR >6.5 or PT >100, Cr >3.4, or grade 3/4 enceph.  
Non-acetamin.-induced: INR >6.5 or PT >100; or ≥3 of the following: unfavorable etiology (seronegative hepatitis or drug reaction); age <10 or >40 y; INR >3.5 or PT >50; Tbili >17.5; duration of jaundice >7 d prior to onset of encephalopathy
- ~25–30% of Pts undergo liver transplantation w/ 5-y survival rate of 70%
- BMI >30, Cr >2, age >50 y, need for pressors/vent support a/w poorer acute transplant outcome

**Definition** (Hep 2011;54:1864 & 2012;56:1983; J Hep 2012;56:S13)

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

**Etiologies**

- **Alcohol** (~60–70%) and other toxins (eg, arsenic)
- **Viral hepatitis** (~10%): chronic HBV, HCV, HDV infection
- **Autoimmune hepatitis:** ♀, ↑ IgG, ⊕ ANA, antismooth muscle Ab, anti-LKM-1, anti-LC1
- **Metabolic diseases** (~5%): hemochromatosis, Wilson's disease,  $\alpha_1$ -AT deficiency
- **Biliary tract diseases** (~5%): primary biliary cholangitis, secondary biliary cirrhosis (calculus, neoplasm, stricture, biliary atresia), primary sclerosing cholangitis
- **Vascular diseases:** Budd-Chiari syndrome, R-sided CHF, constrictive pericarditis, SOS
- **Nonalcoholic fatty liver dis. (NAFLD,** 10–15%) cause of most "cryptogenic cirrhosis"
- **Medications:** amiodarone, methotrexate, vitamin A, valproate acid

**Clinical manifestations**

- Nonspecific sx (anorexia, fatigue) or jaundice, encephalopathy, ascites, variceal bleeding

**Physical exam**

- Liver: *initially* enlarged, palpable (L lobe predom), firm; *eventually* shrunken, nodular
- Signs of liver failure: jaundice (bili >2.5), spider angiomas & 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**

- LFTs:  $\uparrow$  bili,  $\uparrow$  PT/INR (poor correlation w/ bleeding; factor VIII nl as not synthesized by liver),  $\downarrow$  alb,  $\pm$   $\uparrow$  aminotransferases (AST > ALT if late) and  $\uparrow$  A $\phi$  (variable)
- Hematologic tests: anemia (marrow suppress., hypersplenism, Fe  $\pm$  folate defic.), neutropenia (hypersplenism), thrombocytopenia (hypersplenism,  $\downarrow$  Tpo production, EtOH tox)
- Chem:  $\downarrow$  Na ( $\uparrow$  ADH due to  $\downarrow$  EAV);  $\uparrow$  Fe/TIBC,  $\uparrow$  ferritin (released from hepatocytes)
- Lab indices predictive of cirrhosis: AST/plt >2; Lok index; Bonacini score (JAMA 2012;307:832)

**Workup** (Lancet 2014;383:1749)

- Abd U/S w/ Doppler: liver size & echotexture, r/o HCC, ascites, ✓ patency of vasculature
- Determine etiology: hepatitis serologies (HBsAg, anti-HBs, anti-HCV), autoimmune hepatitis studies (IgG, ANA, anti-smooth muscle Ab), Fe and Cu studies,  $\alpha_1$ -AT, AMA
- Assess fibrosis: biomarkers (FibroSURE = panel of 5 markers validated in HCV,  $\uparrow$  score predictive of fibrosis); elastography (U/S or MR-based; measurement of liver stiffness)
- Liver bx (gold standard): percutaneous or transjugular (consider if ascites or coagulopathy), used to confirm presence of cirrhosis and dx etiology.

**Prognosis**

Modified Child-Turcotte-Pugh (CPS) Scoring System			
Points scored			
	1	2	3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (sec > control) 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 tx list & to predict 3-mo survival in Pts w/ cirrhosis and some acute forms of liver disease. Based on Cr, INR, & total bili. Calculator: [www.mayoclinic.org/meld/mayomodel6.html](http://www.mayoclinic.org/meld/mayomodel6.html) (Gastro 2011;14:1952). If MELD <21 additional predictors of mortality include Na <130 (NEJM 2008;359:1018; Clin Gastroenterol Hepatol 2009;7:1236), refractory ascites,  $\uparrow$  HVPG and low QoL.

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

- Due to portal HTN (defined as hepatic venous pressure gradient [HVPG] >5 mmHg)
- Develops in 60% w/in 10 y; ~50% mortality at 5 y

- Treatment: ↓ **Na intake** (1–2 g/d); restrict intake of free water if Na <125  
**Diuretics:** goal diuresis ~1 L/d. Use spironolactone ± furosemide in 5:2 ratio (eg, 100 & 40 mg daily); urine Na/K >1 implies effective natriuresis if Pt compliant w/ low-Na diet  
 Avoid NSAIDs in cirrhotic Pts as interfere w/ diuretic action and are nephrotoxic

- **Refractory ascites:** seen in 5–10% of Pts; 2-y survival 25%

Diuretic-resistant on 2 g Na diet, minimal weight loss on maximal diuretic doses, or diuretic-induced complications (AKI, Na <125, ↑ K, encephalopathy)

Med mgmt: conflicting evid. for d/c'ing βB (*Hep* 2016;63:1968); if limited by HoTN, add midodrine

**Large-volume paracenteses (LVP; >5 L fluid removal):** give 6–8 g albumin per L fluid

removed (above 5 L) as colloid replacement a/w ↓ risk of post-para circulatory dysfxn & possibly ↓ mortality (*Hep* 2012;55:1172). Avoid LVP if SBP present as ↑ risk of AKI.

**Transjugular intrahepatic portosystemic shunt (TIPS)** (*Clin Gas Hep* 2011;9:936)

↓ ascites in 75%; ↑ CrCl, ↑ enceph, survival benefit over LVP remains controversial

Contraindic: grade II enceph, CHF or pulm HTN, active infxn or biliary obstruction

Complications: bleeding, fistula; stent thrombosis (1-y patency w/ coated stents ~80%); infxn ("endotipsitis"); new or ↑ enceph in 20–30%, hemolysis (*Hep* 2010;51:306)

Consider for liver transplant if above fail

- **Hepatic hydrothorax:** 2° diaphragmatic defect; often unilateral, R > L, ± ascites

Treatment: avoid chest tube (↑ complications); Rx same as ascites (TIPS if refractory)

Spontaneous empyema can occur (even w/o SBP) → dx thoracentesis; Rx abx

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

- Develops in ~20%; 20% mortality; risk factors: ascitic TP <1 g/dL, hx of SBP, current GIB
- Can p/w encephalopathy, abd pain, fever, but often (25%) asx; perform paracentesis in all hospitalized cirrhotics w/ ascites
- Micro: GNRs (*E. coli*, *Klebs*) > GPCs (*S. pneumo*, *enterococcus*) (see "Ascites")
- Rx: 3<sup>rd</sup>-gen. ceph or amox/clav × 5 d. If uncomplicated (no encephalopathy or AKI) can use FQ but avoid if already on for ppx or if in ↑ FQ resistance area.  
 IV albumin 1.5 g/kg at time of dx & 1 g/kg on day 3 → ↑ survival (*NEJM* 1999;341:403)  
 If not improving, repeat paracentesis at 48 h: expect 25% ↓ in PMNs if Rx working
- Indefinite Ppx if (1) h/o SBP or (2) ascitic TP <1.5 plus: Na ≤130 or Cr ≥1.2 or BUN ≥25 or [CPS ≥9 + Tbil ≥3] (*Am J Gastro* 2009;4:993) → cipro 500 mg qd or Bactrim DS qd.  
 Short-term Ppx: CTX 1 g IV × 7 d if GIB; cipro 500 mg PO qd × 1 y if ascitic fluid TP <1.5

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

- Presence of varices correlates w/ severity of liver dis (40% of Child A Pts → 85% Child C)
- ↑ varix size, Child B/C, & red wale marks assoc w/ ↑ risk of bleeding
- UGIB 1° prevention: screen at time of dx w/ EGD; data best for Pts w/ med-large varices  
**nonselective β-blockers:** ~50% ↓ risk of bleeding & ↓ mortality if med-large varices.  
 Nadolol or propranolol typically used, titrate to max tolerated dose; carvedilol can be considered in nonresponders or if systemic HTN ( $\alpha_1$  blockade → ↓ intrahepatic vasc resistance, *Gut* 2013;62:1634). EGD not req. to document improvement.

**endoscopic variceal ligation (EVL):** superior to βB in ↓ risk of 1<sup>st</sup> bleed but no diff in mortality (*Ann Hep* 2012;11:369); risk of serious complications (esoph perf, ulcers).

Repeat q1–2wk until varices gone, w/ f/u EGD at 3 mo then q6–12mo

βB vs. EVL: choice based on Pt/physician preference, βB often 1<sup>st</sup> (*Hepatol* 2008;47:1764); using both βB and EVL for primary prevention currently not recommended

- 2° prevention: for all Pts after 1<sup>st</sup> bleed, given ~50% risk of rebleed & ~30% mortality  
 βB + EVL > either alone (*Annals* 2008;149:109); TIPS if refractory, or consider in Child B or C w/in 72 h of admission for esoph variceal bleed (↑ 1-y survival; *NEJM* 2010;362:2370)

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

- Pathogenesis: failure of liver to detoxify NH<sub>3</sub> + other substances (eg, ADMA; *J Hepatol* 2013;58:38) that cause cerebral edema, ↓ O<sub>2</sub> consumption, ↑ ROS → brain dysfxn
- Precipitants: bleeding, infxn, med nonadherence, ↓ K, ↓ Na, dehydration, hypoxia, portosystemic shunt (eg, TIPS), meds (eg, sedatives), acute insult to liver (eg, PVT)
- Stages: see section in "Acute Liver Failure"
- Dx: NH<sub>3</sub> levels have poor Se for dx & monitoring Rx; remains a *clinical dx*
- Rx: identify/correct precipitants; **lactulose** (acidification of colon: NH<sub>3</sub> → NH<sub>4</sub><sup>+</sup>) w/ goal 2–4 stools/d (PEG may be more effective; *JAMA IM* 2014;174:1727); alternatively, **rifaximin** 550 mg bid (↓ gut bacteria → ↓ NH<sub>3</sub> prod; rifaximin + lactulose may be more effective than lactulose alone; *Am J Gastro* 2013;108:1458); acarbose & probiotics may benefit
- 2° prevention: lactulose or rifaximin 550 bid (*Gastro* 2009;137:885; *NEJM* 2010;362:1071)

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

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

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

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

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

- Precipitants: GIB, overdiuresis, infection, serial LVP, drugs (aminoglycosides, NSAIDs)
- Rx: if critically ill  $\rightarrow$  vasopressor (eg, norepinephrine or vasopressin) + albumin (1 g/kg, max 100 g, bolus daily) to  $\uparrow$  MAP 10 mmHg. If not critically ill  $\rightarrow$  octreotide (100–200 mcg SC tid) + midodrine (max 15 mg PO tid) + 1 g/kg (max 100 g) albumin on day of presentation followed by 20–60 g albumin qd to  $\uparrow$  MAP (Hep 2010;51:576).

May need dialysis or TIPS as bridge to liver transplant.

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

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

### Other Complications

- Hepatopulmonary syndrome (HPS)** (Dig Dis Sci 2015;60:1914)
  - Abnl gas exchange (A-a gradient  $\geq$ 15 or  $P_aO_2 < 80$ ) caused by intrapulmonary vascular dilatations leading to intrapulmonary shunting
  - S/S: platypnea-orthodeoxia, clubbing, cyanosis
  - Dx w/ contrast echo showing "late" A-V shunting (contrast in LA 3–6 cycles after RA)
  - Rx:  $O_2$ ; potential embolization if large vessel on CT, ? TIPS, liver tx only definitive Rx
- Portopulmonary hypertension (POPH)** (Expert Rev Gastro Hepatol 2015;9:983)
  - Pulm HTN in Pt w/ portal HTN w/o other cause. ESLD  $\rightarrow$  ↑ endothelin  $\rightarrow$  pulm vasoconst.
  - Rx w/ same therapies as for idiopathic PAH, incl prostacyclin analogs, endothelin receptor antagonists, sildenafil; liver transplant is often curative.
- Cirrhotic cardiomyopathy:** ↓ inotropic & chronotropic response, ↓ systolic and diastolic fxn, prolonged QT, hyperkinetic circulation; ↑ troponin, BNP (JACC 2010;56:539)
- Infxns:** unless already immune, vaccinate for HAV, HBV, PCV13 & PPSV23; flu yearly. Cellulitis in ~20% of Pts hospitalized w/ cirrhosis, often in abd wall or LE a/w skin edema.
- Endocrine: diabetes (15–30%), ↑ frequency of adrenal insufficiency (Hep 2012;55:1282)
- Coagulopathy: balanced defects w/ ↓ synth of coag factors, hyperfibrinolysis, ↓ plt balanced by ↓ synthesis anticoag factors (protein C/S), defic. of profibrinolytic factors, ↑ levels of vWF. No support for routine administration of FFP, plt, cryo unless in DIC.
- Nutrition: monitor and supplement fat soluble vitamins, zinc
- Meds: acetaminophen can be used up to 2 g/d; avoid ASA/NSAIDs; aminoglycosides contraindicated; oral hypoglycemics if compensated but insulin if decompensated

### Liver transplantation

- Undertake evaluation when MELD  $\geq$ 15. Exception points added if HCC as above
- Indic: recurrent/severe enceph, refractory ascites, recurrent variceal bleeding, HRS, HPS, PPH, HCC (if no single lesion is >5 cm or  $\leq$ 3 lesions with largest  $\leq$ 3 cm), acute liver failure
- Contraindic: inadequate social support, active substance abuse (EtOH w/in 6 mo), sepsis, advanced cardiopulm dis., extrahepatic Ca, cholangio Ca, hemangiosarcoma, persistent noncompliance, AIDS, fulminant LF w/ sustained ICP  $>$ 50 mmHg or CPP  $<$ 40 mmHg
- Survival: 1-y up to 90%, 5-y up to 80%, though lower with HCV; autoimmune liver disease, such as AIH/PBC/PSC may recur in 10–30% (or more) of allografts

## OTHER ETIOLOGIES OF CIRRHOSIS

### Hemochromatosis & Iron Overload Syndromes (Lancet 2016;388:706)

- Recessive disorder of iron sensing or transport leading to tissue **iron deposition**
- HFE** mutations (85% of cases): typically C282Y homozyg. (~0.5% of N. Europeans), rarely C282Y/H63D compound heterozyg. C282Y homozygotes: 28% of ♂ & 1% of ♀ develop sx (delayed since menses ↓ Fe load). C282Y/H63D: only 1.5% manifest dis.
- Non-HFE mutations: hemajuvelin, hepcidin, transferrin receptor 2, & ferroportin
- 2° causes of iron overload: iron-loading anemias (eg, thalassemia major, sideroblastic anemia, aplastic anemia), parenteral iron-overload (RBC transfusions, long-term HD), chronic liver disease (due to ETOH, HBV, HCV, NASH, etc), dietary iron overload

- Sx: fatigue & arthralgias, loss of libido in ♂. In advanced disease (rare): bronze skin (melanin + iron), hypogonadism (esp. in juvenile onset), DM, arthropathy (MCP), CHF, infxns (↑ risk Vibrio, Listeria, Yersinia), cirrhosis (↑ risk if EtOH/fatty liver disease; 15% risk of HCC). Disease also a/w ALS (H163D homozygotes) & porphyria.
- Dx: iron sat >45% (iron/TIBC × 100%); ↑ ferritin (acute phase reactant, so poor Sp; often nl in young Pts). If ↑ iron sat. → ✓ HFE to confirm dx, imaging by MRI (black liver). If HFE  $\oplus$  & ferritin >1000 ng/mL or ↑ LFTs → liver bx for quant Fe index & to stage fibrosis
- Treatment: phlebotomy (250 mL = 1 unit, ~250 mg of Fe) qwk until Fe sat <50% & ferritin 50–100  $\mu$ g/L, then q3–4mo; PPI ↓ intestinal Fe absorption & may ↓ need for phlebotomy; avoid vit C & uncooked seafood; deferoxamine if phleb. contraindic.; genetic counseling

### Wilson's disease (J Hep 2012;56:671)

- Recessive disorder of copper transport (mutation in ATP7B) → **copper overload**; primarily affects liver, but also other tissues (brain, eye)
- Epidemiology: 1 in 30,000, majority present b/t 5 & 35 y/o, only 3% of Pts present >40 y/o
- Extrahepatic s/s: neuro ψ disease, parkinsonism & movement disorder (hepatolenticular disease), Kayser-Fleischer rings ( $\oplus$  in 99% w/ neuro ψ but in <50% w/ hepatic disease), Coombs  $\ominus$  hemolytic anemia, renal disease
- Dx: ↑ 24-h urine Cu, ↓ serum ceruloplasmin (Se 90%), rarely penicillamine challenge w/ ↑ urine Cu excretion, liver bx w/ hepatic Cu content. In acute liver failure, A $\phi$ /bili <4 + AST/ALT >2.2 better Se & Sp than urine Cu or ceruloplasmin (Hepatology 2008;4:1167).
- Treatment: **chelation** w/ D-penicillamine (supplement B6 as d-pen inactivates); 2<sup>nd</sup>-line trientine (↓ toxicity w/ = efficacy, but \$\$). **Zinc**: ↓ intestinal Cu transport & can help delay disease; best used in conjunction w/ chelation (must give 4–5 h apart from chelators). Elim. Cu-rich foods. Transplant for fulminant LF or for chronic dis. unresponsive to Rx.

### $\alpha_1$ -antitrypsin deficiency ( $\alpha_1$ -AT) (J Hepatol 2016;65:413)

- Abnl  $\alpha_1$ -AT → polymerization in liver (cirrhosis) & uninhibited protease activity in lung (emphysema). Affects 1/3000 of European ancestry. Varied presentations: neonatal hepatitis; cholestatic jaundice in children; ↑ AST/ALT or cirrhosis in children/adults.
- Extrahepatic disease includes: emphysema, necrotizing panniculitis, ANCA vasculitis
- Dx: serum  $\alpha_1$ -AT level (acute phase reactant), level <50% of nl typically diagnostic; gold standard = phenotyping of protease inhibitor (Pi). Alleles most a/w hepatic dis.: Z (63% of ZZ adults found to have chronic liver dis.) & M (malton) (Am J Respir Crit Care Med 2013;137:502). Liver bx shows characteristic PAS  $\oplus$  cytoplasmic inclusion bodies.
- Treatment: standard Rx for cirrhosis/chronic liver dis., including liver transplantation

### Primary biliary cholangitis (PBC) (Lancet 2015;386:1565)

- Autoimmune destruction of intrahepatic bile ducts (previously "primary biliary cirrhosis")
- Epi: ♀ 40–60 y/o; a/w Sjögren's, Raynaud's, scleroderma, celiac & thyroid disease; may be triggered by certain infxns or toxins; a/w X monosomy, variants in IL12 $\alpha$  & IL12R genes
- Sx (late): fatigue/sleep disturbance, pruritus, steatorrhea, xanthelasma, jaundice, cirrhosis
- Ddx: PSC, AIH, hepatic sarcoidosis, meds, idiopathic adult ductopenia, biliary stricture/Ca
- Dx: ↑ A $\phi$ , ↑ bili, ↑ IgM, ↑ chol,  $\oplus$  antimitochondrial Ab (AMA) in 95%. If  $\oplus$  AMA, liver bx not needed due to high Se & Sp. 0.5% gen pop  $\oplus$  AMA & nl LFTs → 10% develop PBC at 6 y. If AMA  $\ominus$ , liver bx (Pts often  $\oplus$  ANA, smooth muscle Ab; same prognosis as  $\oplus$  AMA).
- Rx: **ursodeoxycholic acid** (13–15 mg/kg/d) regardless of stage  
~25% complete response, ↑ survival & ↓ histologic change & complications (eg, varices) (Gastro 2005;128:297). Budesonide may benefit in short term.

Pruritus: cholestyramine (give 2–4 h after UDCA); if refractory sx: naltrexone, rifampin  
Fat-soluble vitamins; screen/Rx osteoporosis (risk independent of vit D deficiency)  
If ESLD: liver tx: ~20% recur but no impact on long-term survival

### Primary sclerosing cholangitis (PSC) (Lancet 2013;382:1587; World J Hepatol 2016;8:265)

- Diffuse inflammation of intrahepatic and extrahepatic bile ducts leading to fibrosis & stricturing of biliary system. A/w HLA-B8 and -DR3 or -DR4, frequent  $\oplus$  autoantibodies.
- Epi: ♂ > ♀ (20–50y) ~70% Pts w/ PSC have IBD (usually UC); only 1–4% w/ UC have PSC.
- Clinical: fatigue, pruritus, jaundice, fevers, RUQ pain, concomitant IBD, ESLD
- Ddx: extrahepatic obstruction, PBC, may also have overlap w/ AIH and similar presentation to IgG4 autoimmune cholangitis (steroid responsive) (Gastro 2008;134:706)
- Dx: MRCP ± ERCP → multifocal beaded bile duct strictures, but may miss dx if confined to small intrahepatic ducts (~2% "small duct PSC": better prognosis, ? different disease). Liver bx may show "onion-skin" fibrosis around bile ducts but not necessary for dx.
- Treatment: supportive care, fat-soluble vitamins; no meds have improved survival  
Ursodeoxycholic acid may ↓ colon CA risk in Pts w/ UC & improve LFTs in Pts w/o UC  
Dominant stricture: endoscopic dilation, short-term stenting or surgical resection  
Cholangiocarcinoma (20%): ? biannual surveillance w/ MRCP/RUQ U/S and CA19-9  
Liver transplantation: ~30% recurrence, though if UC, colectomy may ↓ recurrence

# HEPATIC VASCULAR DISEASE

## Portal vein thrombosis (PVT) (*Hepatology* 2009;49:1729 & 2015;61:660)

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

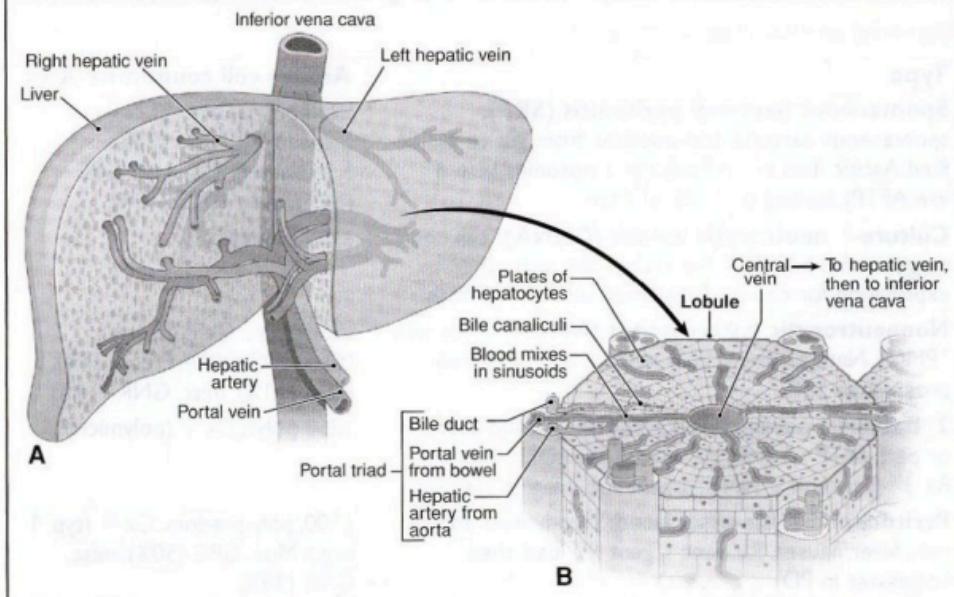
## Budd-Chiari syndrome (*Hepatology* 2009;49:1729)

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

## Sinusoidal obstruction syndrome (SOS) (*Hepatology* 2009;49:1729)

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

Figure 3-6 Hepatic vasculature



**Pathophysiology**

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

**Etiologies****Portal HTN related (SAAG ≥ 1.1)**

- Presinusoidal obstruction  
portal or splenic vein thrombosis, schistosomiasis, sarcoidosis
- Sinusoidal obstruction:  
**cirrhosis** (81%), including SBP, acute hepatitis, malignancy (HCC or mets)
- Postsinusoidal obstruction  
right-sided CHF incl constriction & TR  
Budd-Chiari syndrome, SOS

**Non-portal HTN related (SAAG < 1.1)**

- Malig:** peritoneal carcinomatosis; chylous ascites from malignant lymphoma;  
**Meigs' syndrome** (ovarian tumor)
- Infection:** TB, chlamydia/gonorrhea (ie, Fitz-Hugh-Curtis syndrome)
- Inflam: pancreatitis, ruptured pancreatic/biliary/lymph duct; bowel obstrxn
- Hypoalbuminemic states: **nephrotic syndrome**, protein-losing enteropathy

**Symptoms**

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

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

- Physical exam: flank dullness (NPV ~90%; >1500 mL needed), shifting dullness (Se ~83%)
- Radiologic: **U/S** detects >100 mL; MRI/CT (also help with Ddx)
- **Paracentesis** (Hep 2013;57:1651): perform in all Pts w/ new ascites, consider in all hosp. cirrhotics w/ ascites. Low complic. rate (~1% hematoma formation). Prophylactic FFP or plts does not ↓ bleeding complic. Most useful tests: cell count, alb, total protein, culture.
- **Serum-ascites albumin gradient (SAAG):** serum alb (g/dL) – ascites alb (in g/dL)  
If  $\geq 1.1$  g/dL → cause of ascites likely portal HTN (~95% accuracy; Annals 1992;117:215)  
If  $< 1.1$  g/dL → non-portal hypertension related  
If portal HTN + another cause (seen in ~5% of cases) SAAG still  $\geq 1.1$
- Ascites fluid total protein (**AFTP**): useful when SAAG  $\geq 1.1$  to distinguish cirrhosis (AFTP  $< 2.5$  g/dL) from cardiac ascites (AFTP  $\geq 2.5$  g/dL). Low AFTP ( $< 1$  g/dL) assoc. w/ ↑ risk of SBP (see "Cirrhosis" for guidelines on SBP Ppx based on AFTP).
- **Cell count:** normal limit of PMNs in ascitic fluid up to 250 PMNs/mm<sup>3</sup>. Bloody tap (typically from traumatic para) can skew cell count; subtract 1 PMN for every 250 RBCs to correct PMN count. Ascitic PMNs  $\geq 250$  suggest infection (see below).
- Other tests: amylase (pancreatitis, gut perforation); bilirubin (test in dark brown fluid, suggests bile leak or proximal intestinal perf); TG (chylous ascites); BNP (HF); cytology (peritoneal carcinomatosis, ~95% Se w/ 3 samples). SBP a/w ↓ glc & ↑ LDH is fluid.

**Treatment (see "Cirrhosis" for details)**

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

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

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

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

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

**Types of gallstones**

- Cholesterol (90%):** 2 subtypes
  - mixed: contain >50% cholesterol; typically smaller, multiple stones
  - pure: 100% cholesterol; larger, yellow, white appearance
- Pigment (10%):**
  - Black:** unconjugated bili & calcium; seen w/ chronic hemolysis, cirrhosis, CF, Gilbert synd
  - Brown:** stasis & infection in bile ducts → bacteria deconjugate bilirubin → precipitates w/ calcium; seen w/ duodenal diverticula, biliary strictures, parasites

**Clinical manifestations**

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

**Diagnostic studies**

- RUQ U/S: Se & Sp >95% for stones >5 mm; can show complications (cholecystitis); should be performed only after fasting ≥8 h to ensure distended, bile-filled gallbladder

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

- Cholecystectomy (CCY), usually laparoscopic, if symptomatic
- CCY in asx Pts w/ GB calcification (~7% risk of ca) (*Surgery* 2001;129:699), GB polyps >10 mm, Native American, stones >3 cm or bariatric surgery or cardiac transplant candidates
- Ursodeoxycholic acid (rare) for cholesterol stones w/ uncomplicated biliary pain or if poor surgical candidate; also reduces risk of gallstone formation with rapid wt loss
- Biliary pain: NSAIDs (eg, diclofenac 50 mg IM) drug of choice, efficacy = opiates & ↓ complications (*Aliment Pharmacol Ther* 2012;35:1370)

**Complications**

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

**CHOLECYSTITIS** (*NEJM* 2008;358:2804)**Pathogenesis**

- Acute cholecystitis: stone impaction in cystic duct → inflammation behind obstruction → GB swelling ± secondary infection (50%) of biliary fluid
- Acalculous cholecystitis: gallbladder stasis and ischemia → inflammatory response; occurs mainly in critically ill, hosp. Pts (postop major surgery, TPN, sepsis, trauma, burns, opiates, immunosuppression, infxn [eg, CMV, Crypto, *Campylobacter*, typhoid fever])

**Clinical manifestations**

- History: RUQ/epigastric pain ± radiation to R shoulder/back, nausea, vomiting, fever
- Physical exam: **RUQ tenderness, Murphy's sign** = ↑ RUQ pain and inspiratory arrest with deep breath during palpation of R subcostal region, ± palpable gallbladder
- Laboratory evaluation: ↑ WBC, ± mild ↑ bilirubin, AΦ, ALT/AST and amylase; AST/ALT >500 U/L, bili >4 mg/dL or amylase >1000 U/L → choledocholithiasis

**Diagnostic studies**

- RUQ U/S:** high Se & Sp for stones, but need specific signs of cholecystitis: GB wall thickening >4 mm, pericholecystic fluid and a sonographic Murphy's sign

- **HIDA scan:** most Se test (80–90%) for acute cholecystitis. IV inj of HIDA (selectively secreted into biliary tree). In acute cholecystitis, HIDA enters BD but not GB. 10–20% false + (cystic duct obstructed from chronic cholecystitis, lengthy fasting, liver disease).

### Treatment

- NPO, IV fluids, nasogastric tube if intractable vomiting, analgesia
- **Antibiotics** (*E. coli*, *Klebsiella* and *Enterobacter* sp. are usual pathogens) ([2<sup>nd</sup>- or 3<sup>rd</sup>-generation cephalosporin or FQ] + MNZ) or piperacillin-tazobactam
- **CCY** (typically laparoscopic) w/in 24 h ↓ morbidity vs. waiting 7–45 d (*Ann Surg* 2013;258:385)
- If unstable for surgery, EUS-guided transmural, ERCP-guided transcystic duct drainage, or percutaneous cholecystotomy (if w/o ascites or coagulopathy) are alternatives to CCY (*NEJM* 2015;373:357)
- Intraoperative cholangiogram or ERCP to r/o choledocholithiasis in Pts w/ jaundice, cholangitis or stone in BD on U/S

### Complications

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

## CHOLEDOCHOLITHIASIS

### Definition

- Gallstone lodged in common bile duct (CBD)

### Epidemiology

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

### Clinical manifestations

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

### Diagnostic studies

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

### Treatment

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

### Complications

- Cholangitis, cholecystitis, pancreatitis, stricture

## CHOLANGITIS

### Definition & etiologies

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

### Clinical manifestations

- Charcot's triad: RUQ pain, jaundice, fever/chills; present in ~70% of Pts
- Reynolds' pentad: Charcot's triad + shock and Δ MS; present in ~15% of Pts

### Diagnostic studies

- RUQ U/S
- Labs: ↑ WBC, bilirubin, Aϕ, amylase; + BCx
- ERCP; percutaneous transhepatic cholangiogram if ERCP unsuccessful

### Treatment

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

# ACID-BASE DISTURBANCES

## GENERAL

### Definitions

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

### Consequences of Severe Acid-Base Disturbances (NEJM 1998;338:26 & 107)

Organ system	Acidemia (pH < 7.20)	Alkalemia (pH > 7.60)
Cardiovascular	↓ contractility, arteriolar vasodilation ↓ MAP & CO; ↓ response to catecholamines ↑ risk of arrhythmias	Arteriolar vasoconstriction ↓ coronary blood flow ↑ risk of arrhythmias
Respiratory	Hyperventilation, ↓ resp. muscle strength	Hypoventilation
Metabolic	↑ K (resp. > metab.), insulin resistance	↓ K, ICa, Mg, PO <sub>4</sub>
Neurologic	Δ MS	Δ MS, seizures, tetany

### Workup (NEJM 2014;371:1434)

- **Traditional or physiologic approach** (Brønsted-Lowry definition of acids & bases)
  - Determine **primary disorder**: ✓ pH,  $P_aCO_2$ ,  $HCO_3$
  - Determine if **degree of compensation** is appropriate

### Primary Disorders

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

### Compensation for Acid/Base Disorders (JASN 2010;21:920)

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

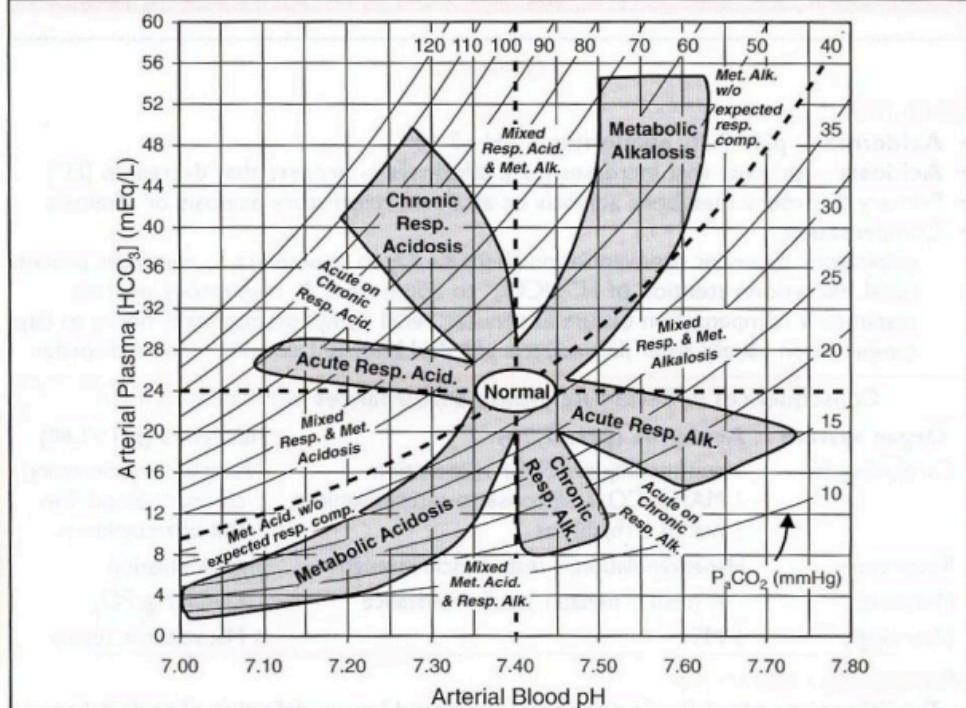
### Alternative approaches

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

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

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

Figure 4-1 Acid-base nomogram



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

- ABG vs. VBG:** concordant for pH (~0.04), HCO<sub>3</sub> (~2 mEq) but **not PCO<sub>2</sub>** (~8±17 mmHg). VBG can be used to screen for hypercarbia w/ PCO<sub>2</sub> cutoff ≥45 mmHg (100% Se), **but** may not accurately assess degree of hypercarbia (Am J Emerg Med 2012;30:896).

## METABOLIC ACIDOSIS

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

- ✓ **anion gap (AG)** =  $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$  = unmeasured anions – unmeasured cations  
if ↑ glc, use measured *not* corrected Na  
expected AG is [albumin] × 2.5 (ie, 10 if albumin is 4 g/dL, 7.5 if albumin is 3 g/dL)  
↑ AG → ↑ unmeasured anions such as organic acids, phosphates, sulfates  
↓ AG → ↓ alb or ↑ unmeasured cations (Ca, Mg, K, Li, bromide, iodide, immunoglobulin)
- If ↑ AG, ✓ **delta-delta** ( $\Delta\Delta = \Delta\text{AG}/\Delta\text{HCO}_3$ ) 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 (NEJM 2014;372:546)
Lactic acidosis (NEJM 2014; 371:2309)	<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. ↓ clearance (eg, hepatic dysfxn) or ↑ generation [eg, malig, EtOH, thiamine def., meds (metformin, NRTIs, salicylates, propylene glycol, propofol, isoniazid, linezolid)] <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. <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, and phenobarbital; antifreeze): lactic acidosis
Ingestions	<b>Salicylates:</b> metabolic acidosis (from lactate, ketones) + respiratory alkalosis due to stimulation of CNS respiratory center <b>Glutathione depletion:</b> acetaminophen → ↑ endogenous organic acid 5-oxoproline in susceptible hosts (malnourished, female, renal failure)

**Workup for AG metabolic acidosis**

- ✓ for **ketonuria** (dipstick acetoacetate) or plasma  $\beta$ -hydroxybutyrate ( $\beta$ BOHB)
    - nb, urine acetoacetate often not present in early ketoacidosis due to shunting to  $\beta$ BOHB; ∴ 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
    - 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)
- OG > 10 → suggests ingestion (see below) but lacks specificity (can be elevated in lactic acidosis, DKA, and alcoholic ketoacidosis)
- for methanol/ethylene glycol: early on, OG precedes AG; later OG may be nl with  $\oplus$  AG

Ingestions			
AG	OG	Ingestion	Other manifestations
↑	nl	Acetaminophen	Hepatitis
		Salicylates	Fever, tachycardia, tinnitus; met. acid. + resp. alkalosis
↑	↑	Ethanol	Alcoholic fetor, $\Delta$ MS, hepatitis; keto + lactic acidosis $\pm$ met. alk. (vomiting)
		Methanol	$\Delta$ MS, blurred vision, pupillary dilation, papilledema
		Ethylene glycol	$\Delta$ MS, cardiopulm. failure, hypoCa. <b>Ca oxalate crystals</b> → AKI. Urine fluoresces under UV light.
		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 IV fluids
Posthypocapnia	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 (JASN 2012;7:671)**

- Evaluate history for causes (see above)
- ✓ **urine anion gap (UAG)** =  $(\text{U}_{\text{Na}} + \text{U}_{\text{K}}) - \text{U}_{\text{Cl}}$ 
  - UAG = unmeasured anions – unmeasured cations; as  $\text{NH}_4^+$  is primary unmeasured cation, UAG is indirect assay for renal  $\text{H}^+$  excretion as  $\text{NH}_4^+$  (NEJM 1988;318:594)
- $\ominus$  UAG → ↑ renal  $\text{NH}_4^+$  excretion → appropriate renal response to acidemia
  - Ddx: GI causes, proximal RTA, ingestions or dilutional
- $\oplus$  UAG → failure of kidneys to generate  $\text{NH}_4^+$ 
  - Ddx: distal or hypoaldo RTA, early renal failure
    - nb, plasma K usually ↓ in distal and ↑ in hypoaldo RTA
- UAG evaluation assumes Pt volume replete ( $\text{U}_{\text{Na}} > 25$ ),  $\text{U}_{\text{pH}} < 6.5$  & no AG met. acidosis (which causes  $\oplus$  UAG due to excretion of organic anions)

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

- Proximal** (Type II): ↓ proximal reabsorption of  $\text{HCO}_3^-$ 
  - 1° (Fanconi's syndrome) = ↓ proximal reabsorption of  $\text{HCO}_3^-$ ,  $\text{PO}_4^{2-}$ , 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°, 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° adrenal disorders, ACEI, ARBs, heparin
  - ↓ response to aldosterone
    - meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors
    - tubulointerstitial disease: sickle cell, SLE, amyloid, diabetes
- Combined** (Type III): rarely discussed or clinically relevant, also called juvenile RTA, has distal & proximal features, can be due to carbonic anhydrase II deficiency

## Renal Tubular Acidosis

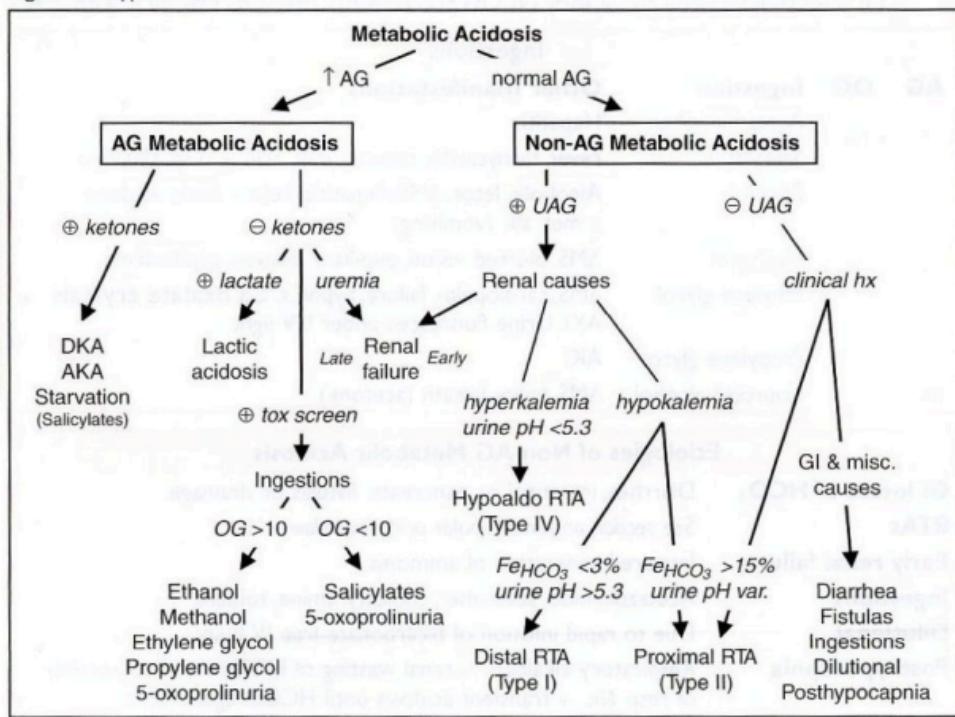
Location	Type	Acidosis	UAG	UpH	$\text{Fe}_{\text{HCO}_3}$ , <sup>b</sup>	Serum K
Proximal	II	Moderate	±	<5.3 <sup>a</sup>	>15%	↓
Distal	I	Severe	⊕	>5.3	<3%	↓ <sup>c</sup>
Hypoaldo	IV	Mild	⊕	<5.3	<3%	↑

<sup>a</sup>Urine pH will rise above 5.3 in the setting of  $\text{HCO}_3$  load

<sup>b</sup> $\text{Fe}_{\text{HCO}_3}$  should be checked after an  $\text{HCO}_3$  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) (Nat Rev Nephrol 2012;8:589)

- DKA: insulin & IVF; AKA: dextrose, IVF, replete K, Mg,  $\text{PO}_4$  as needed
- Lactic acidosis: treat underlying condition, avoid vasoconstrictors, avoid "Type B" meds
- Renal failure: hemodialysis
- Methanol & ethylene glycol: early fomepizole, vit. B<sub>6</sub> (for ethylene glycol), folate (for methanol), hemodialysis (esp. if late presentation) (NEJM 2009;360:2216)
- Alkali therapy:  $\text{NaHCO}_3$  (eg, three 50-mmol amps in 1 L D<sub>5</sub>W) to get serum  $\text{HCO}_3$  > 8 and pH > 7.2 (estimate mmol of  $\text{HCO}_3$  needed as  $8 - [\text{HCO}_3]_{\text{serum}} \times \text{wt} \times 0.5$ ) side effects: ↑ volume, ↑ Na, ↓ ICa, ↑  $\text{P}_a\text{CO}_2$  (& ∴ intracellular acidosis), overshoot No proven benefit in lactic acidosis or DKA (Annals 1986;105:836 & 1990;112:492)
- THAM in Pts w/ ↑  $\text{P}_a\text{CO}_2$  (proton acceptor that generates  $\text{HCO}_3^-$  and consumes  $\text{CO}_2$ )

## METABOLIC ALKALOSIS

### Pathophysiology

- Saline-responsive etiologies require *initiating event* and *maintenance phase*
- *Initiating event*: gain of  $\text{HCO}_3$  or loss of acid  
**loss of H<sup>+</sup>** from GI tract or kidneys  
**exogenous alkali**: iatrogenic  $\text{HCO}_3$  administration, milk alkali syndrome  
**contraction alkalosis**: diuresis → excretion of  $\text{HCO}_3$ -poor fluid → extracellular fluid "contracts" around fixed amount of  $\text{HCO}_3$  → ↑  $\text{HCO}_3$  concentration  
**posthypercapnia**: respiratory acidosis → renal compensation with  $\text{HCO}_3$  retention; rapid correction of respiratory disorder (eg, with intubation) → transient excess  $\text{HCO}_3$
- *Maintenance phase*
  - volume depletion** → ↑ proximal reabsorption of  $\text{NaHCO}_3$  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  $\text{HCO}_3$  retention)
  - hypokalemia** → transcellular K<sup>+</sup>/H<sup>+</sup> exchange; intracellular acidosis in renal proximal tubular cells promotes bicarbonate reabsorption and ammonogenesis

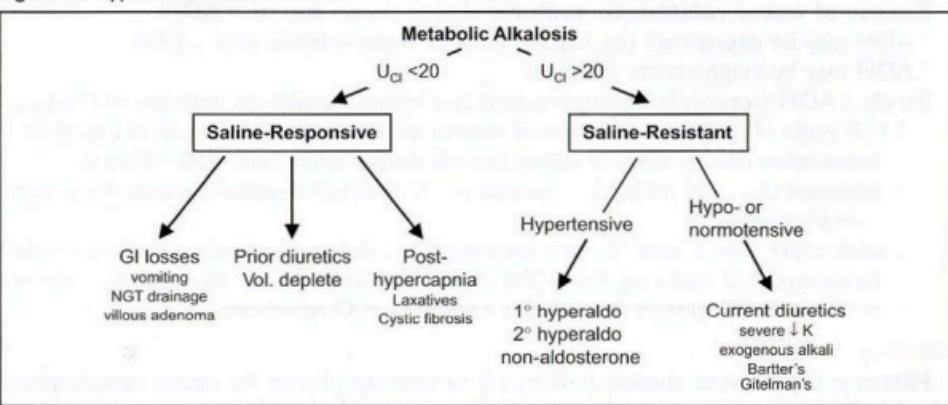
## Etiologies of Metabolic Alkalosis

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

### Workup

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

Figure 4-3 Approach to metabolic alkalosis



### Treatment of severe metabolic alkalosis ( $pH > 7.6$ )

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

## RESPIRATORY ACIDOSIS

### Etiologies (also see "Hypercapnia")

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

## RESPIRATORY ALKALOSIS

### Etiologies (NEJM 2002;347:43)

- **Hypoxia → hyperventilation:** pneumonia, pulm. edema, PE, restrictive lung disease
- **Primary hyperventilation**
  - CNS stimulation, pain, anxiety, fever, trauma, stroke, voluntary drugs: salicylates, progesterone, methylxanthines, nicotine
  - pregnancy, sepsis, hepatic failure, fever
- **Pseudorespiratory alkalosis:** ↓ perfusion w/ preserved ventilation (eg, CPR, severe HoTN) → ↓ delivery of  $CO_2$  to lungs for excretion; low  $P_aCO_2$  but ↑ tissue  $CO_2$

# SODIUM AND WATER HOMEOSTASIS

## OVERVIEW

### General (NEJM 2015;372:55 & 373:1350)

- Disorders of serum sodium are generally due to  $\Delta s$  in total body water, not sodium
- Hyper- or hypo-osmolality  $\rightarrow$  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), angiotensin II
  - 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

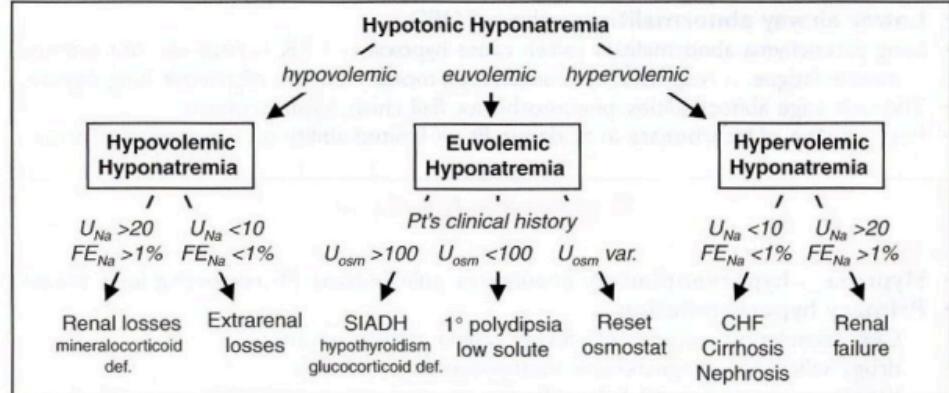
### Pathophysiology (NEJM 2015;372:1349)

- 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  $[Na]_{serum}$ 
  - $\uparrow H_2O$  intake ( $^1$  polydipsia): ingestion of massive quantities (usually  $>12$  L/d) of free  $H_2O$  overwhelms diluting ability of kidney (normal dietary solute load ~750 mOsm/d, minimum  $U_{osm} = 60$  mOsm/L  $\rightarrow$  excrete in ~12 L; if  $H_2O$  ingestion exceeds this amount  $\rightarrow H_2O$  retention)
  - $\downarrow$  solute intake ("tea & toast" & "beer potomania"):  $\downarrow\downarrow$  daily solute load  $\rightarrow$  insufficient solute to excrete  $H_2O$  intake (eg, if only 250 mOsm/d, minimum  $U_{osm} = 60$  mOsm/L  $\rightarrow$  excrete in ~4 L; if  $H_2O$  ingestion exceeds this amount  $\rightarrow H_2O$  retention)

### Workup (JASN 2012;23:1140; Crit Care 2013;17:206; NEJM 2015;372:55)

- History:** (1) acute vs. chronic (>48 h); (2) sx severity; (3) risk for neuro complications (alcoholism, malnourished, cirrhosis, older females on thiazides, hypoxia, hypoK)
- Measure plasma osmolality**
  - Hypotonic hyponatremia most common scenario; true excess of free  $H_2O$  relative to Na
  - Isotonic hyponatremia: rare lab artifact from hyperlipidemia or hyperproteinemia
  - Hypertonic hyponatremia: excess of another effective osmole (eg, glucose, mannitol) that draws  $H_2O$  intravascularly; each 100 mg/dL  $\uparrow$  glc  $>100$  mg/dL  $\rightarrow \downarrow [Na]$  by 2.4 mEq/L
- 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  $\uparrow H_2O$  intake or  $\downarrow$  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** ( $U_{Na} > 20 \text{ mEq/L}$ ,  $FE_{Na} > 1\%$ ): diuretics (esp. thiazides, as loop diuretics) ↓ tonicity of medullary interstitium and impair urine concentrating ability), salt-wasting nephropathy, cerebral salt wasting, mineralocorticoid deficiency
- Extrarenal losses** ( $U_{Na} < 10 \text{ mEq/L}$ ,  $FE_{Na} < 1\%$ ): hemorrhage, GI loss (diarrhea), third-spacing (pancreatitis), ↓ PO intake, insensible losses

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

- SIADH** (euvolemia or mild hypervolemia, **inappropriately ↑  $U_{osm}$** , approp.  $U_{Na}$ , ↓ BUN & UA)
  - malignancy:** lung, brain, GI, GU, lymphoma, leukemia, thymoma, mesothelioma
  - pulmonary:** pneumonia, TB, aspergillosis, asthma, COPD, PTX, + pressure ventilation
  - intracranial:** trauma, stroke, SAH, seizure, infxn, hydrocephalus, Guillain-Barré synd.
  - drugs:** antipsychotics, antidepressants (esp. SSRIs), chemotherapy, AVP, MDMA, NSAIDs
  - miscellaneous:** pain, nausea, postoperative state
- Endocrinopathies:** ↑ ADH activity seen in glucocorticoid deficiency (co-secretion of ADH & CRH) and severe **hypothyroidism/myxedema coma** (↓ CO & ↓ GFR)
- Psychogenic polydipsia** ( $U_{osm} < 100$ , ↓ uric acid): usually requires intake > 12 L/d
- Low solute** (↓  $U_{Na}$ , ↓  $U_{osm}$ ) "tea & toast"; "beer potomania"
- Reset osmostat: chronic malnutrition (↓ intracellular osmoles) or pregnancy (hormonal effects) → ADH physiology reset to regulate a lower  $[Na]_{serum}$

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

- ↓ EAV → activation of RAAS → ↑ aldosterone and ↑↑ ADH
- CHF** (↓ CO & renal venous congestion → ↓ EAV;  $U_{Na} < 10 \text{ mEq/L}$ ,  $FE_{Na} < 1\%$ )
- Cirrhosis** (splanchnic arterial vasodilation + ascites → ↓ EAV;  $U_{Na} < 10 \text{ mEq/L}$ ,  $FE_{Na} < 1\%$ )
- Nephrotic syndrome** (hypoalbuminemia → edema → ↓ EAV;  $U_{Na} < 10 \text{ mEq/L}$ ,  $FE_{Na} < 1\%$ )
- Advanced renal failure** (diminished ability to excrete free  $H_2O$ ;  $U_{Na} > 20 \text{ mEq/L}$ )

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

- Approach:** depends on volume status, acuity of hyponatremia, and if **symptomatic**
  - Acute sx: initial rapid correction of  $[Na]_{serum}$  (2 mEq/L/h for the first 2–3 h) until sx resolve
  - Asx or chronic symptomatic: correct  $[Na]_{serum}$  at rate of ≤ 0.5 mEq/L/h
  - Rate of ↑ Na should not exceed 6 (chronic) to 8 (acute) mEq/L/d to avoid central pontine myelinolysis/osmotic demyelination syn. (CPM/ODS: paraplegia, dysarthria, dysphagia)
  - If severe (<120) or neuro sx: consider 3% NaCl + dDAVP (to prevent rapid overcorrection) in consultation w/ nephrology (AJKD 2013;61:571)
- Frequent lab draws and IVF rate adjustments** are cornerstones of treatment
- Overly rapid correction:** can lead to CPM/ODS. Should be emergently reversed w/ dDAVP ± D5W; partial neurologic recovery possible (CJASN 2014;9:229)
- Effect of IV fluids** (<http://www.medcalc.com/sodium.html>)

$$\text{initial } \Delta [Na]_{serum} \text{ per L infusate} = \frac{[Na]_{infusate} - [Na]_{serum}}{TBW + 1} \quad \begin{array}{l} TBW = \text{wt (kg)} \times 0.6(\delta) \text{ or } 0.5(\%) \\ \text{if elderly use } 0.5(\delta) \text{ or } 0.45(%) \end{array}$$

If  $[Na]_s = 110 \text{ mEq/L}$  in 70 kg male:

IVF type	$[Na]_{content}$	$1 \text{ L IVF } \uparrow [Na]_s$	Rate to $\uparrow [Na]_s$ by 0.5 mEq/L/h
5% NaCl	856 mEq/L	17.3 mEq/L	~25 mL/h
3% NaCl	513 mEq/L	9.4 mEq/L	~50 mL/h
0.9% NaCl	154 mEq/L	1 mEq/L	~500 mL/h
LR	130 mEq/L	0.5 mEq/L	~1000 mL/h

however, above assumes entire infusate retained without any output of Na or  $H_2O$

if Pt euvolemic, as in SIADH, infused Na will be excreted

e.g. 1 L NS (154 mEq of Na or 308 mOsm of solute in 1 L free  $H_2O$ ) given to Pt with SIADH with  $U_{osm} = 616 \rightarrow 308 \text{ mOsm}$  solute excreted in 0.5 L  $H_2O \rightarrow$  net gain 0.5 L  $H_2O \rightarrow \downarrow [Na]_{serum}$

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

- Hypovolemic hyponatremia:** volume repletion with normal saline at a **slow rate**. Once volume replete → stimulus for ADH removed (w/ very short ADH t<sub>1/2</sub>) → kidneys excrete free  $H_2O \rightarrow$  serum Na will correct rapidly (D5W ± ddAVP if overcorrection)
- SIADH** (NEJM 2007;356:2064; AJKD 2015;65:435): **free water restrict** + treat underlying cause
  - hypertonic saline** (± loop diuretic) if sx or Na fails to ↑ w/ free  $H_2O$  restriction
    - 1 L hypertonic saline (3% NaCl) will raise  $[Na]_{serum}$  by ~10 mEq (see above)
    - ~50 mL/h will ↑ [Na] by ~0.5 mEq/L/h; 100–200 mL/h will ↑ [Na] by ~1–2 mEq/L/h
    - formula only provides estimate; ∴ recheck serum Na frequently (at least q2h)

NaCl tabs: particularly if chronic and no CHF

aquareesis: ? vaptans (vasopressin receptor antag) for refractory SIADH (NEJM 2015;372:23)

demeclocycline: causes nephrogenic DI, ↓  $U_{osm}$  (rarely used)

## • Hypervolemic hyponatremia: free water restrict

mobilize excess Na & H<sub>2</sub>O (use loop diuretics; avoid thiazides) & ↑ EAV (vasodilators to ↑ CO in CHF, colloid infusion in cirrhosis)

aquaresis: raptans sometimes used; however, no proven mortality benefit, hypoNa recurs after stopping drug, risk of overcorrection, contraindicated in cirrhosis, and expensive (NEJM 2015;372:2207)

## HYPERNATREMIA

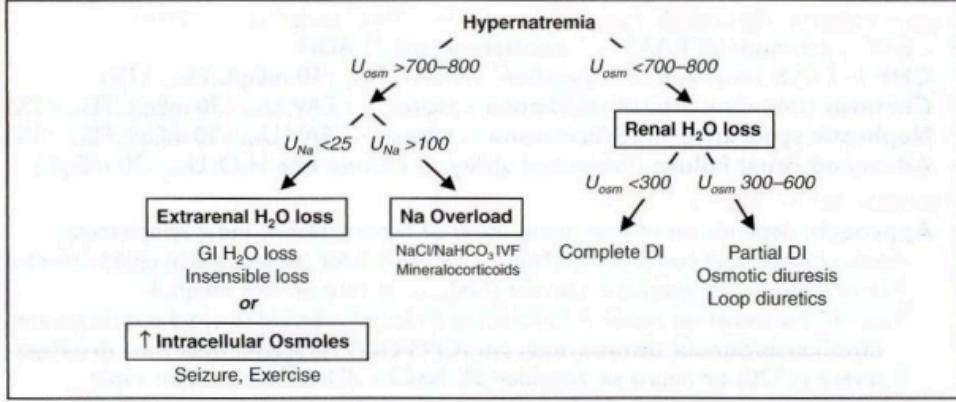
### Pathophysiology (Crit Care 2013;17:206; NEJM 2015;372:55)

- Deficit of water relative to sodium; by definition, all hypernatremic Pts are hypertonic
- Usually loss of hypotonic fluid (ie, "dehydration"); occasionally infusion of hypertonic fluid
- And impaired access to free water** (eg, intubation, Δ MS, elderly): hypernatremia is a powerful thirst stimulus, ∴ usually only develops in Pts w/o access to H<sub>2</sub>O

### Workup

- ✓ U<sub>osm</sub>, U<sub>Na</sub>, volume status (vital signs, orthostatics, JVP, skin turgor, BUN, Cr)

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 (glucose, mannitol, urea), loop diuretics
- Diabetes insipidus** (*J Clin Endocrinol Metab* 2012;97:3426)

Central: hypothalamic or posterior pituitary disease (congenital, trauma/surgery, tumors, infiltrative/IgG4); also idiopathic, hypoxic encephalopathy, anorexia, EtOH

#### Nephrogenic (*Annals* 2006;144:186)

congenital (ADH receptor V2 mutation, aquaporin-2 mutation; *Ped Nephrol* 2012;27:2183)

drugs: lithium, amphotericin, demeclocycline, foscarnet, cidofovir

metabolic: hypercalcemia, severe hypokalemia, protein malnutrition, congenital tubulointerstitial: postobstruction, recovery phase of ATN, PKD, sickle cell, Sjögren's, amyloid, pregnancy (placental vasopressinase)

DI usually presents as severe polyuria and mild hypernatremia

### Other (U<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):

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

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

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

eg, 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

nb, do not forget to correct Na if hyperglycemia also present

- Rate of ↓ of Na should not exceed 0.5 mEq/L/h** to avoid cerebral edema  
shortcut: in 70-kg man, 125 mL/h of free H<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 + 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<sub>osm</sub>
- 24-h osmole excretion rate = 24-h UOP (actual or estimate) × U<sub>osm</sub>  
>1000 mOsm/d → osmotic diuresis  
<800 mOsm/d → water diuresis

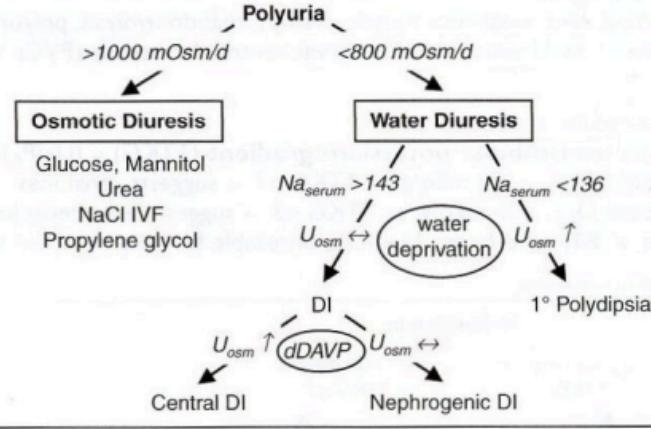
### Osmotic diuresis

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

### Water diuresis

- Etiologies: **diabetes insipidus (DI)** (Na<sub>serum</sub> >143) or **1° polydipsia** (Na<sub>serum</sub> <136) see “Hypernatremia” above for list of causes of central and nephrogenic DI
- Workup of DI: U<sub>osm</sub> <300 (complete) or 300–600 (partial)
  - water deprivation test** (start in a.m., ✓ Na<sub>serum</sub>, P<sub>osm</sub>, U<sub>osm</sub>, UOP q1–2h)  
Deprive until P<sub>osm</sub> >295, then ✓ U<sub>osm</sub>. If U<sub>osm</sub> <300, then administer vasopressin (5 U SC) or dDAVP (10 µg intranasal), then check U<sub>osm</sub> in 1–2 h:  
U<sub>osm</sub> ↑ by >50% = central DI  
U<sub>osm</sub> 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 dysfunctional diluting segment of kidney), consider amiloride for lithium-induced DI (*Kid Int* 2009;76:44)
  - pregnancy-induced DI: due to vasopressinase from placenta, ∴ Rx w/ dDAVP

# POTASSIUM HOMEOSTASIS

## Overview (NEJM 2015;373:60)

- Renal: potassium excretion regulated at **distal nephron** (collecting tubule)
  - distal Na delivery & urine flow: Na absorption → lumen electronegative → K secretion
  - metabolic alkalemia and aldosterone: increase Na absorption and K secretion
  - nb, diurnal urinary K excretion (day > night), ∴ 24-h sample preferred over spot
- Transcellular shifts: most common cause of acute Δ in serum K (98% intracellular)
  - Acid-base disturbance:  $K^+/H^+$  exchange across cell membranes
  - Insulin → stimulates Na-K ATPase → hypokalemia (mitigates postprandial ↑ K)
  - Catecholamines → stimulate Na-K ATPase → hypokalemia; reversed by β-blockers
  - Massive necrosis (eg, tumor lysis, rhabdo, ischemic bowel) → release of intracellular K
  - Hypo- or hyperkalemic periodic paralysis: rare disorders due to channel mutations
- Diet: alone rarely causes ↑ or ↓ K (total body store ~3500 mEq, daily intake ~100 mEq)

## HYPOKALEMIA

### Transcellular shifts ( $U_{K,Cr} < 20 \text{ mEq/g}$ )

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

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

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

### Renal potassium losses ( $U_K > 30 \text{ mEq/d}$ , ? $U_{K,Cr} > 20 \text{ mEq/g}$ , TTKG > 7)

- Hypotensive or normotensive
  - acidosis: DKA, RTA [proximal RTA (type II) and some distal RTAs (type I)]
  - alkalosis: diuretics, vomiting/NGT drainage (via 2° hyperaldosteronism)
    - Bartter's syndrome (loop of Henle dysfxn → furosemide-like effect; NEJM 1999;340:1177)
    - Gitelman's syndrome (distal convoluted tubule dysfxn → thiazide-like effect)
    - ↓ Mg: ? release Mg-mediated inhib. of ROMK channel ∴ ↑ K secretion (JASN 2007;18:2649)
- Hypertensive: mineralocorticoid excess
  - 1° hyperaldosteronism (eg, Conn's syndrome, glucocorticoid-remediable aldosteronism)
  - 2° hyperaldosteronism (eg, renovascular disease, renin-secreting tumor)
  - nonaldosterone mineralocorticoid (eg, Cushing's, Liddle's, exogenous mineralocort., licorice, congenital adrenal hyperplasia)

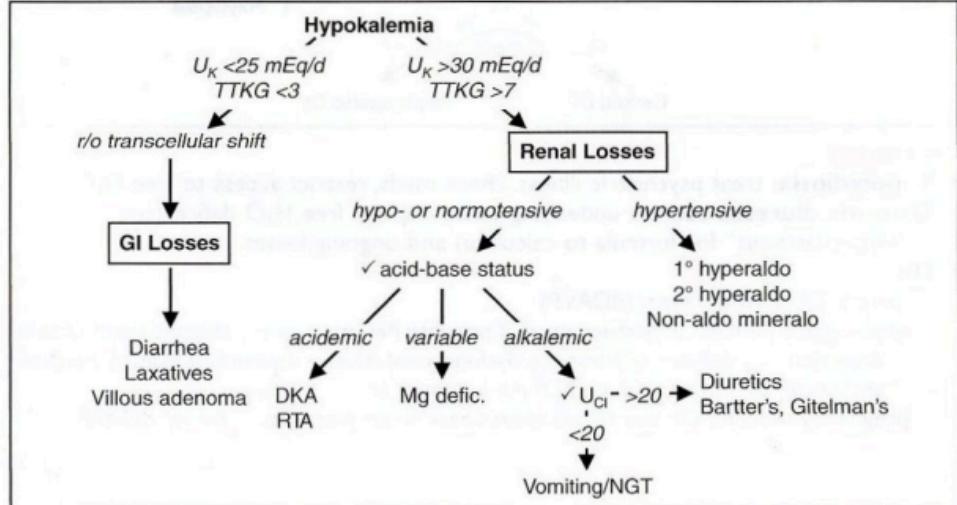
### Clinical manifestations

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

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

- Rule out transcellular shifts
- ✓ 24-h  $U_K$  and **transtubular potassium gradient (TTKG) =  $(U_K/P_K)/(U_{osm}/P_{osm})$** 
  - $U_K > 30 \text{ mEq/d}$ , ?  $U_{K,Cr} > 20 \text{ mEq/g}$ , or TTKG > 7 → suggests renal loss
  - $U_K < 25 \text{ mEq/d}$ ,  $U_{K,Cr} < 20 \text{ mEq/g}$ , or TTKG < 3 → suggests 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** ( $\downarrow 1 \text{ mEq/L} \approx 200 \text{ mEq total body loss}$ )
  - 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 low Mg: IV Mg-SO<sub>4</sub> 1-2 g q2h (oral Mg-oxide poorly tolerated b/c diarrhea)
  - Causes of low Mg: GI loss (diarrhea, bypass, pancreatitis, malnutrition, PPI); renal loss (diuretics, nephrotoxic drugs, EtOH,  $\uparrow$  Ca, 1° wasting syndromes, volume expansion)

**HYPERKALEMIA****Transcellular shifts** (BMJ 2009;339:1019)

- Acidemia, insulin defic. (DM),  $\beta$ -blockers, dig intox. (blocks Na-K ATPase), massive cellular release (tumor lysis, rhabdo, ischemic bowel, hemolysis, transfusions, resorbing hematomas, hyperthermia, rewarming), hyperkalemic periodic paralysis, succinylcholine

**Decreased GFR**

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

**Normal GFR but with  $\downarrow$  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
  - ureterojejunostomy (absorption of urinary K in jejunum)
- 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, then consider  $\downarrow$  distal Na delivery and urine flow. ✓ transtubular K gradient (TTKG) =  $(U_k/P_k)/(U_{osm}/P_{osm}) < 6$  c/w hypoaldo (JASN 2008;19:424).

**Treatment of Hyperkalemia**

Intervention	Dose	Onset	Comment
Ca gluconate Ca chloride <sup>a</sup>	1-2 amps IV	<3 min	transient effect (30-60 min) stabilizes cell membrane
Insulin	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
Bicarbonate (esp. if acidemic)	1-2 amps IV	15-30 min	transient effect (60 min) exchange K for H <sup>+</sup> in cells
$\beta$ 2 agonists	albuterol 10-20 mg inh. or 0.5 mg IV	30-90 min	transient effect (~2 h) drives K into cells
K-binding resins	Kayexalate <sup>b</sup> 30-90g PO/PR ? Na zirconium 1.25-10 g/tid PO Patiromer 8.4-25.2 g/d PO	hrs hrs hrs-d	exchange K for cations in gut (Na, Ca, H); $\downarrow$ total body K; (NEJM 2015;372:211 & 222)
Diuretics	furosemide $\geq 40$ mg IV	30 min	$\downarrow$ total body K
Hemodialysis			$\downarrow$ 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>? rare a/w intestinal necrosis esp. with postoperative ileus or obstructive bowel disease (AJKD 2012;60:409)

- Rate of onset important to note when establishing a treatment plan
- Calcium helps prevent/treat cardiac complications;  $\therefore$  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 Rxs will wear off with time;
  - Kayexalate or Na zirconium  $\pm$  diuretics may be effective in many cases, but emergent hemodialysis should be considered in life-threatening situations
- Patient information for diet education: <http://www.kidney.org/atoz/content/potassium.cfm>

# RENAL FAILURE

## ACUTE KIDNEY INJURY (AKI)

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

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

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

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

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

	Etiologies	U/A, Sediment, Indices
Prerenal	↓ Effective arterial volume (NEJM 2007;357:797) Hypovolemia, ↓ cardiac contractility (eg, CHF), systemic vasodilatation (eg, sepsis)	Bland Transparent hyaline casts FE <sub>Na</sub> <1%
	Renal vasoconstriction: NSAIDs, ACEI/ARB, contrast, calcineurin inhib., HRS, hyperCa	BUN/Cr >20
	Large vessel: RAS (bilateral + ACEI), vasculitis, dissection, abd compartment synd., renal venous congestion, VTE	U <sub>Na</sub> <20 U <sub>osm</sub> >500
Intrinsic	Acute tubular necrosis (ATN) Ischemia: progression of prerenal disease Toxins	Pigmented granular muddy brown casts in ~75% (± in CIAKI) ± RBCs & protein from tubular damage FE <sub>Na</sub> >2%, BUN/Cr <20, U <sub>Na</sub> >20 (except pigment, CIAKI) U <sub>osm</sub> <350
	Drugs: AG, amphotericin, cisplatin, HES (starch) Pigments: Hb, myoglobin (NEJM 2009;361:62) Monoclonal: Ig light chains (Blood 2010;116:1397) Crystals: UA, ACV, MTX, indinavir, oral NaPO <sub>4</sub> Contrast-induced AKI (CIAKI): ↓ RBF + toxin	WBCs, WBC casts, ± RBCs w/ neg UCx ⊕ urine eos in abx ⊕ lymphs in NSAIDs
	Acute interstitial nephritis (AIN) Allergic: β-lactams, sulfa drugs, NSAIDs, PPIs Infection: pyelonephritis, legionella, TB, leptospirosis Infiltrative: sarcoid, lymphoma, leukemia Autoimmune: Sjögren's, TINU syndrome, IgG4, SLE	± RBCs ⊕ urine eos in chol emboli
	Small-med vessel: chol emboli, PAN, TMAs (TTP, HUS, atypical HUS, DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)	Dysmorphic RBCs, RBC casts
Post	Glomerulonephritis (see "Glomerular Disease")	Bland
	Bladder neck: BPH, prostate cancer, neurogenic bladder, anticholinergic meds	± nondysmorphic RBCs
	Ureteral (bilateral or unilateral in single kidney): malig, LAN, retroperitoneal fibrosis, nephrolithiasis	FE <sub>Na</sub> variable

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

- Prerenal: isotonic IVF = alb (NEJM 2004;350:22), HES (starch) nephrotoxic (NEJM 2012;367:124)
- Avoid nephrotoxic insults; review dosing of renally cleared drugs
- Optimize hemodynamics (both MAP & CO)
- No benefit to dopamine (Annals 2005;142:510), diuretics (JAMA 2002;288:2547), or mannitol

### Managing complications

- May take 1–3 wk to recover from ATN; anticipate volume overload, ↑ K, ↑ PO<sub>4</sub>, acidosis
- Episodes of AKI ↑ risk of CKD progression, even after recovery (NEJM 2014;371:58)
- Indications for urgent dialysis (when condition refractory to conventional therapy)
  - Acid-base disturbance: refractory acidemia
  - Electrolyte disorder: generally hyperkalemia; occasionally hypercalcemia, tumor lysis

Intoxications (<http://www.extrip-workgroup.org/>): contact Poison Control (1-800-222-1222)

Indicated for: methanol, ethylene glycol, metformin, Li, valproic acid, salicylates, barbiturates, theophylline, thallium

Also consider for: carbamazepine, acetaminophen, dig (also give Digibind), dabigatran (also give idarucizumab)

**Overload of volume (CHF)**

**Uremia:** pericarditis, encephalopathy, bleeding

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

## DISEASE-SPECIFIC MANAGEMENT

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

- Multifactorial pathophys including: 1) ↓ CO, 2) ↑ renal venous congestion, 3) ↑ RAAS
- Bidirectionality: acute CHF → AKI, and oliguric AKI can worsen CHF (*JACC* 2008;52:1527)
- Treatment: **IV loop diuretics** (bypass potential gut edema; see below for dosing); no diff. between high vs. low dose and bolus vs. gtt (*NEJM* 2011;364:797). No clinical benefit with vaptans (ADH receptor antag; *JAMA* 2007;297:1319), dopamine or nesiritide (*NEJM* 2011;365:32; *JAMA* 2013;310:2533), or ultrafiltration (*NEJM* 2012;367:2296).
- Prognosis: 7% ↑ mortality a/w each 10 mL/min ↓ eGFR in ADHF (*JACC* 2006;47:1987)

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

- Risk factors: CKD, DM, CHF, age, hypotension, ↑ contrast volume (*JACC* 2004;44:1393)
- Clinical: AKI w/in 48 h of contrast exposure, peaks in 3–5 d, resolves in 7–10 d (if does not resolve, consider cholesterol emboli or other etiology)
- Prevention: consider when eGFR <60 or diabetes (*CJASN* 2013;8:1618)

**Isotonic IV fluids** (unless contraindic, eg, CHF)

Outpatients: 3 mL/kg/h × 1 h before, 1–1.5 mL/kg/h × 6 h after (*JAMA* 2004;291:2328)

Inpatients: 1 mL/kg/h × 6–12 h before, during, and 6–12 h after;

if undergoing cardiac cath, consider rate of IVF based on LVEDP:

5, 3, or 1.5 mL/kg/h if LVEDP <13, 13–18, or >18 mmHg (*Lancet* 2014;383:1814)

NaHCO<sub>3</sub> similar to NaCl (*CJASN* 2015;10:1519).

Hold ACEI/ARB (*AJKD* 2012;60:576), NSAIDs, diuretics. ? high-dose statin (*Circ* 2012;126:3008)

Minimize contrast volume and use iso-osmolar contrast (*JACC* 2006;48:692)

N-acetylcysteine 600–1200 mg PO bid on day prior to & day of contrast; benefit in some but not all studies (*Annals* 2016;164:406); as safe, reasonable to consider in high-risk Pts

No proven benefit to Ppx RRT in addition to above, may be harmful (*Am J Med* 2012;125:66)

- Gadolinium: can cause AKI in stage IV CKD (*Neph Dial Trans* 2006;21:697), no effective Ppx  
Nephrogenic systemic fibrosis: fibrosis of skin, joints, eyes, and internal organs ~2–4 wk post exposure in Pts w/ mod-severe CKD (*JACC* 2009;53:1621). Postgado HD encouraged albeit no data. Physical therapy. Can be irreversible.

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

- Albumin + either octreotide & midodrine or IV vasopressors

**Rhabdomyolysis (NEJM 2009;361:62)**

- Multifactorial pathophys: myoglobin-induced oxidant injury, vasoconstriction, myoglobin precipitation & pre-renal (extravasation). Can lead to ↓ Ca, ↑ K, and ↑ PO<sub>4</sub>.
- Diagnosis: UA ⊕ for heme but 0 RBCs (ie, myoglobinuria)
- Generally low risk of AKI when CK <5000, but correlation imperfect. Rhabdo & risk of AKI/death calculator: <http://www.brighamandwomens.org/research/rhabdo/default.aspx>
- Aggressive IVF resuscitation and augmenting UOP (tailor IVF to target UOP ~3 mL/kg and ensure ↓ CK). If urine pH <6.5, can consider NaHCO<sub>3</sub> solutions and watching pH.  
✓ K & Ca frequently. Monitor for compartment syndrome.

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

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

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

**Obstructive diseases**

- Dx: imaging w/ renal U/S if undifferentiated or abd/pelvic CT (↑) if suspect nephrolithiasis
- Treatment: Foley catheter vs. percutaneous nephrostomy for decompression
- Following decompression, at risk of:  
Hypotonic diuresis (2° buildup of BUN, tubular damage); Rx w/ IVF (eg, 1/2 NS)  
Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly

## CHRONIC KIDNEY DISEASE (CKD)

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

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

- Cr poor estimate of GFR, use equation ([www.kidney.org/professionals/KDOQI/gfr\\_calculator.cfm](http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm))  
CKD-EPI preferred over MDRD as less likely to underestimate at normal GFRs  
cystatin-C-based formulae perform better than Cr-based (*NEJM* 2012;367:20)
- Etiologies: DM (45%), HTN/RAS (27%), glomerular (10%), interstitial (5%), PKD (2%) (*NEJM* 2008;359:1477), congenital, drugs, myeloma, progression of AKI (*JAMA* 2009;302:1179)
- Presence and degree of albuminuria a/w worse outcomes independent of GFR
- Rates of all-cause mortality and CV events increase with each stage of CKD & albuminuria and are greater than rate of progression to kidney failure (*NEJM* 2004;351:1296)

### Stages of CKD (*Kid Int* 2013;3[Suppl]:5)

GFR Stage	GFR mL/min/1.73 m <sup>2</sup>	Goals
1 (nl or ↑ GFR)	>90	Dx/Rx of underlying condition & comorbidities, slow progression; cardiovascular risk reduction
2 (mild)	60–89	Estimate progression
3a (mild-mod)	45–59	Evaluate and treat complications
3b (mod-severe)	30–44	Evaluate and treat complications
4 (severe)	15–29	Prepare for renal replacement therapy (RRT)
5 (kidney failure)	<15 or dialysis	Dialysis if uremic

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

### Signs and Symptoms of Uremia (*NEJM* 2007;357:1316)

General	Nausea, anorexia, malaise, fetor ureemicus, metallic taste, susceptibility to drug O/D, decreased temperature
Skin	Uremic frost (white crystals in & on skin), pruritus, calciphylaxis, NSF
Neurologic	Encephalopathy (Δ MS, ↓ memory & attention), seizures, neuropathy, impaired sleep, restless leg syndrome
Cardiovascular	Pericarditis, accelerated atherosclerosis, hypertension, hyperlipidemia, volume overload, CHF, cardiomyopathy (esp. LVH)
Hematologic	Anemia, bleeding (due to platelet dysfunction and Epo deficiency)
Metabolic	↑ K, ↑ PO <sub>4</sub> , acidosis, ↓ Ca, 2° hyperparathyroidism, osteodystrophy

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

- General:** nephrology referral when GFR <30 and access planning (avoid subclavian lines; preserve an arm for access by avoiding blood draws, BP measurements, IVs); Rx CV risk factors (eg, smoking, LDL-C; *Lancet* 2011;377:2181), vaccines (flu, PNA, HBV)
- Dietary restrictions:** Na (if HTN), K (if oliguric or hyperkalemic), PO<sub>4</sub>, ? moderate protein restriction, strict glucose control in DM, avoid herbal and unknown OTCs
- BP Control:** goal <130/80, ? <120/80 if tolerated (*NEJM* 2015;373:2103); start w/ ACEI (or ARB), effective in DM & nondiabetic CKD (*NEJM* 2004;351:1952); no benefit of ACEI + ARB combined and a/w adverse outcomes (*NEJM* 2013;369:1892). For outPts, ✓ Cr & K in 1–2 wk, d/c if Cr ↑ 30% or K >5.4 (after dietary Δ & loop diuretic).
- Metabolic acidosis:** sodium bicarbonate or sodium citrate if low HCO<sub>3</sub> (*JASN* 2015;26:515)
- Hyperkalemia** (qv)
- Anemia:** goal Hb ~10 g/dL, worse outcomes if target higher (*NEJM* 2009;361:2019) erythropoietin (start 80–120 U/kg SC, divided 3x/wk) or darbepoietin (0.45 μg/kg q wk) iron supplementation to keep transferrin sat >20% (often given IV in HD Pts)
- Uremic bleeding:** desmopressin (dDAVP) 0.3 μg/kg IV or 3 μg/kg intranasally
- 2° HyperPTH:** ↑ PO<sub>4</sub>, ↓ Ca, ↓ calcitriol, ↑ FGF-23 → ↑ PTH → renal osteodystrophy

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

phosphorus binders (take with meals!) (*NEJM* 2010;362:1312)

if ↑ PO<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)  
non-Ca-based binders a/w ↓ mort. compared to Ca-based (*Lancet* 2013;382:1268)  
if PTH above goal then start vit. D (if 25-(OH)D <30) before adding 1,25-(OH)D analogue (paricalcitol); stop if ↑ Ca (*AJKD* 2009;53:408)  
cinacalcet (parathyroid calcium-sensing receptor agonist) if ↑ PTH despite phosphorus binders ± vit. D analogue (*CJASN* 2016;11:161); consider parathyroidectomy

- Calciphylaxis** (calcific uremic arteriopathy):
  - Pathophys: calcification of media of small- to med-sized blood vessels of dermis & SC fat → ischemia and skin necrosis w/ painful lesions (*NEJM* 2007;356:1049)
  - Risk Factors: uremia in ESRD (↑ PO<sub>4</sub>, ↑ Ca, ↑ PTH), ♀>♂, DM, obesity, warfarin
  - Diagnosis: skin bx gold standard; bone scan used in support of dx

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

## • Transplant evaluation

### DIURESES

#### General considerations

- Increases Na excretion for treatment of HTN or edema in CHF, renal failure, and cirrhosis
- Daily wt most effective method of documenting successful diuresis

#### Loop diuretics (NEJM 1998;339:387)

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

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

- Drugs:** hydrochlorothiazide (HCTZ), chlorothiazide (Diuril), metolazone (Zaroxolyn)
- Mech:** inhibit Na-Cl cotransporter in the distal convoluted tubule (DCT); 5% Na reabsorp. synergistic with loop diuretic, esp. if chronic loop use  
↓ effect when GFR <30, except metolazone which is still effective in renal insufficiency
- Dosing:** give prior to loop diuretic, typically ~30 min before

#### K-sparing diuretics

- Drugs:** spironolactone (Aldactone), amiloride, triamterene, eplerenone
- Mech:** ↓ Na reabsorption (~1%) in collecting duct (amiloride/triamterene inhibit principal cell Na channel [ENaC]; spironolactone/eplerenone inhibit mineralocorticoid receptor). Relatively weak natriuretic activity, useful in combination with thiazide or in cirrhosis.

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

Step	Action
1	<b>Loop diuretic PO:</b> ✓ response at 3 h, redose at 2x prior dose if needed
2	<b>Add thiazide diuretic PO</b> (potentiates response to loop diuretic)
3	<b>Loop diuretic IV:</b> bolus bid-qid ± thiazide (may start here if inPt) ↑ dose needed w/ ↑ Cr; initial effective IV Lasix dose ≈ 30 × Cr (ie, if Cr = 4 → 120 mg IV lasix)
4	<b>Loop diuretic infusion:</b> bolus + continuous IV infusion ± thiazide (PO or IV)
5	<b>RRT:</b> 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 2–3x normal dose
- Cirrhosis: spironolactone (blocks 2° hyperaldosteronism) + Lasix in 2.5:1 ratio
- Severe metabolic alkalosis: acetazolamide & treat underlying cause

#### Adverse effects

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

### RENAL REPLACEMENT AND DIALYSIS

#### General

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

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

- Physiology: blood flows along one side of semipermeable membrane, dialysate along other  
Fluid removal (ie, Na + H<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
- 6x vs. 3x/wk improved HTN, LV mass, QoL, but ↑ vasc issues (NEJM 2010;363:2287); w/ 3x/wk HD, ↑ adverse outcomes after 2-d interval (NEJM 2011;365:1099)
- Complications: HoTN, arrhythmia, access issues (clot, stenosis, infxn, recirculation), disequilibrium syndrome (sx of cerebral edema due to H<sub>2</sub>O shifts after removal of plasma urea during dialysis, esp. in new HD Pts w/ ↑ BUN), high-output HF
- Fever w/ catheter: empiric abx (vanc + GNR coverage qHD). GPC > GNR > mixed/fungal. Catheter removal, replacement, or “lock” abx. Consider metastatic infxn w/u (AJKD 2004;44:779; JASN 2014;25:2927).

### Vascular Access

	Advantages	Disadvantages
<b>AV fistula</b>	Highest patency Lowest risk of bacteremia Lowest mortality (JASN 2013;24:465)	Long maturation time (2–6 mo) Primary nonfunction (20%)
<b>AV graft</b>	Easier to create than AVF Maturation time (2–3 wk)	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 2012;367:26)

- Physiology: hemofiltration rather than dialysis. Blood under pressure passes down one side of highly permeable membrane allowing H<sub>2</sub>O and solutes to pass across membrane via TMP gradient (convective clearance). Filtrate discarded. Replacement fluid infused (solute concentrations similar to plasma, except no urea, Cr, PO<sub>4</sub>). Fluid balance precisely controlled by adjusting filtrate/replacement fluid.
- Access: double-lumen central venous catheter
- Typical orders: volume goals, replacement fluid buffer: **HCO<sub>3</sub>** (requires heparin to prevent machine from clotting, although can be run heparin-free) **vs. citrate** [hepatically metabolized (∴ cannot be given in cirrhosis/liver failure) to HCO<sub>3</sub>; provides anticoagulation w/in machine via Ca chelation]
- 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 met acidosis)
- Potential advantages over HD: less hypotension, better volume control, removal of inflammatory mediators; however, no survival advantage (Lancet 2006;368:379)
- No advantage for high-intensity CVVH over standard intensity (NEJM 2008;359:7)

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

- Physiology: peritoneum acts as membrane. Fluid balance controlled by choosing dialysate [glucose] (higher concentrations pull more fluid into peritoneum); longer dwell times pulls first more and then less fluid as glc equilibrates across peritoneum
- Access: permanent catheter inserted in OR
- Typical orders for CAPD (continuous ambulatory peritoneal dialysis): PD fluid = dextrose (1.5%, 2.5%, or 4.25%), buffer (lactate), Na<sup>+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup> infuse 10 min, dwell 90 min–5.5 h, drain 20 min
- Can use overnight cycler device that infuses & drains more rapidly, with shorter dwells, while Pt sleeps. Called automated or continuous cycling peritoneal dialysis (APD, CCPD).
- Complications: hypoalbuminemia; right-sided pleural effusion  
Peritonitis: abd pain, tenderness, cloudy drainage (WBC >100 and >50% PMNs) spectrum: 60–70% GPC, 15–20% GNR, remainder no bacteria or fungal Rx: abx IV or in PD, catheter removal for certain pathogens (eg, yeast, *Pseudomonas*)  
Hyperglycemia: exacerbated by inflammation, long dwell times, and higher [glucose]

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

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

# GLOMERULAR DISEASE

## GLOMERULONEPHRITIS (GN)

### Definition (*Lancet* 2016;387:2036)

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

### ANCA $\oplus$ Vasculitis (pauci-immune, minimal staining) ~40–45% of total

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

Disease	Gran	Renal	Pulm	Asthma	ANCA Type <sup>a</sup>	ANCA $\oplus$
Granulomatosis with polyangiitis <sup>b</sup>	$\oplus$	80%	90% (+ ENT)	—	anti-PR3 (c-ANCA)	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO (p-ANCA)	70%
Eosinophilic gran with polyangiitis <sup>b</sup>	$\oplus$	45%	70%	$\oplus$	anti-MPO (p-ANCA)	50%

<sup>a</sup>Predominant ANCA type; either p- or c-ANCA can be seen in all three diseases (*NEJM* 2012;367:214)

<sup>b</sup>GPA is formerly Wegener's granulomatosis and EGPA is formerly Churg-Strauss

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

Disease	Glomerulonephritis	Pulm hemorrhage	Anti-GBM
Goodpasture's	$\oplus$	$\oplus$	$\oplus$
Anti-GBM disease	$\oplus$	—	$\oplus$

### Immune Complex (IC) Disease (granular staining) ~40–45% of total

Renal-limited diseases	Systemic diseases
Infection-related GN (Staph & Strep; $\downarrow$ C3, $\pm$ ASLO)	SLE ( $\oplus$ ANA, $\oplus$ anti-dsDNA, $\downarrow$ C3, $\downarrow$ C4)
Membranoproliferative GN (MPGN) ( $\downarrow$ C3)	Cryoglobulinemia ( $\oplus$ cryocrit, $\oplus$ RF, $\oplus$ HCV, SPEP, $\downarrow$ C3, $\downarrow$ C4)
Fibrillary and Immunotactoid GN (normal C3)	Endocarditis (fever, $\oplus$ BCx, valvular disease, $\downarrow$ C3)
IgA nephropathy (normal C3) ( <i>NEJM</i> 2013;368:2402)	Henoch-Schönlein purpura (IgA nephropathy + systemic vasculitis w/ IgA deposits, nl C3)

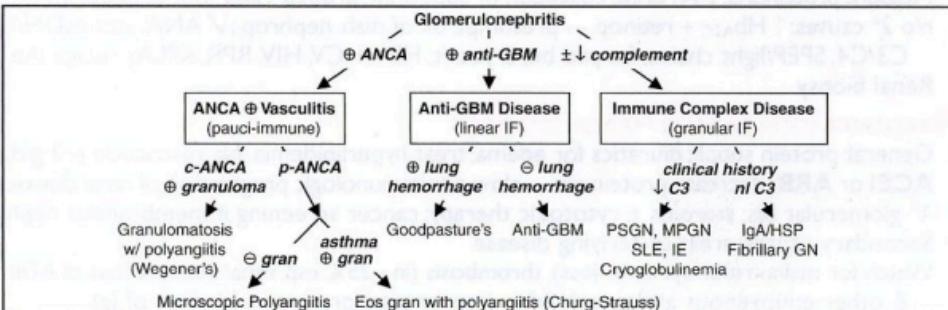
### Oncology-related glomerulopathy (*Kid Int* 2013;84:34; *CJASN* 2012;7:1701)

- Associations between malig (solid tumors & heme) and/or their Rx (HSCT & chemotherapeutics) and GN, nephrotic syndrome, and thrombotic microangiopathies (TMA)
- Most common associations: membranous (solid tumors, HSCT), MCD (Hodgkin's, solid tumors), MPGN (CLL, MM), TMA (HSCT, VEGF, anti-EGFR, CNIs, TKIs, mTOR)

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

- Acute GN/RPGN  $\pm$  lung hemorrhage is an emergency  $\rightarrow$  requires early Dx and Rx
- $\checkmark$  ANCA (*Lancet* 2006;368:404), anti-GBM, complement levels
- Depending on clinical hx: ANA, ASLO, BCx, cryocrit, hepatitis serologies, skin bx
- Consider GN mimics: thrombotic microangiopathies (qv), myeloma, AIN, cholesterol emboli
- Renal biopsy with immunofluorescence (IF)  $\pm$  electron microscopy (EM)

Figure 4-8 Approach to glomerulonephritis based on immunofluorescence pattern



**Treatment** (Kid Int Sup 2012;2:143; AJKD 2014;63(4):656)

- If acute GN/RPGN suspected, give 500–1000 mg methylpred. IV qd × 3d ASAP while awaiting bx results. Consider plasmapheresis & further Rx based on underlying disease.
- SLE nephritis: induction w/ steroids + cyclophosphamide (CYC) or MMF (JASN 2010;21:2028)
- ANCA + or anti-GBM: pulse steroids + CYC (or rituximab) ± plasma exchange (JASN 2007;18:2180; NEJM 2010;363:221; AJKD 2011;57:566)
- See "Vasculitis" for further disease specific treatment details

**ASYMPTOMATIC GLOMERULAR HEMATURIA****Definition and etiologies**

- Hematuria ± proteinuria of glomerular origin w/o renal insufficiency or systemic disease (nonglomerular hematuria more common; see "Hematuria")
- Ddx: any cause of GN (esp. IgA); also consider Alport's (X-linked, deafness, renal failure), thin basement membrane nephropathy (autosomal dominant, benign; JASN 2006;17:813)

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

- Most common cause of GN; ♂ pred; peak incidence 20–30s; can also be post-infectious
- Wide range of clinical presentations: asx hematuria (30–40%), gross hematuria ~1–3 d after URI (30–40%), chronic GN (10%), nephrotic syndrome (5%), RPGN (<5%)
- Though clinical presentation can be highly suggestive, definitive dx only w/ bx
- Prognosis: 20–40% will reach ESRD w/in 20 y of presentation
- Rx: ACEI/ARB (JASN 1999;10:1772); steroids if proteinuria (JASN 2012;23:1108; NEJM 2015;373:2225); ± cytotoxic Rx for crescentic GN & nephrotic sx, consider for prog. chronic GN

**NEPHROTIC SYNDROME****Definition** (NEJM 1998;338:1202)

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

**Primary glomerular diseases (grouped by pathology)**

- Focal segmental glomerulosclerosis** (40%; NEJM 2011;365:2398): 1° (? ↑ soluble urokinase receptor; Nat Med 2011;17:952), HIV (collapsing variant), NSAIDs, lymphomas, pamidronate, heroin, congenital, ↑ filtration from prior nephron loss, obesity, vesicoureteral reflux, anabolic steroids, ApoL1 mutation in AA (JASN 2015;26:1443)
- Membranous nephropathy** (30%; CJASN 2014;9:609; Lancet 2015;385:1983): idiopathic (auto Ab to phospholipase A<sub>2</sub> or thrombospondin; NEJM 2009;361:11 & 2014;371:2277), infxn (esp. HBV, also HCV, syphilis), autoimmune (eg, SLE), carcinomas, drugs (NSAIDs, penicillamine)
- Minimal change disease** (20%, more common in children; NDT 2003;18:vi52) idiopathic, NSAIDs, Hodgkin's disease, & other lymphoproliferative disorders
- Membranoproliferative GN** (5%, mixed nephrotic/nephritic features; CJASN 2014;9:600) Immune complex-mediated: infection (esp. HCV ± cryos, IE, HBV, "shunt" nephritis, other chronic infxns), SLE, cryos, Sjögren's, lymphomas, dysproteinemia, idiopathic Complement-med (rare); abnl C3 convertase activity, dense deposit dis, C3GN
- Fibrillary-immunotactoid glomerulopathy** (1%; Kid Int 2003;63:1450)
- Mesangial proliferative GN** (? atypical forms of MCD/FSGS, 5%) IgM, C1q nephropathy

**Systemic diseases with secondary glomerular involvement**

- Diabetes mellitus:** nodular glomerulosclerosis (Kimmelstiel-Wilson lesion); large kidneys hyperfiltration → microalbuminuria → dipstick + → nephrotic range (10–15 y) concomitant proliferative retinopathy seen in 90% of type 1 and 60% of type 2
- Amyloidosis:** AL or light chain amyloid or AA amyloid secondary to inflammation
- SLE:** typically with membranous nephropathy (WHO class V)
- Cryoglobulinemia:** typically with membranoproliferative GN

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

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

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

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

# URINALYSIS

## Urine Dipstick

Measurement	Significance and uses
Specific gravity	Estimate $U_{osm}$ : each 0.001 above 1 $\approx$ 30 osm (SG 1.010 $\rightarrow$ $U_{osm} \approx 300$ ) SG and $U_{osm}$ useful in evaluating AKI, dysnatremias, polyuria heavy substances (glucose, contrast) $\uparrow$ SG more than $U_{osm}$
pH	Range: 4.5–8.5; useful in evaluation of stones, RTAs, infection
Protein	Detects albumin (marker for glomerular dysfxn); see "Proteinuria"
Blood	See "Hematuria"; can also be $\oplus$ w/ few RBCs on sediment review in myoglobinuria (rhabdomyolysis) False $\oplus$ : semen, dilute urine ( $\rightarrow$ osmotic cell lysis), $\uparrow$ pH, vaginal blood
WBC	Suggests inflammation (UTI, interstitial nephritis, GN)
Ketones	Detects acetoacetate (ie, ketoacidosis) but not $\beta$ -hydroxybutyrate
Nitrite	Suggests presence of nitrate reductase $\oplus$ bacteria (most enteric GNRs)
Bilirubin	$\uparrow$ in biliary or hepatic disease
Glucose	$\oplus$ in hyperglycemia ( $>180$ mg/dL), pregnancy, Fanconi's syndrome

U/A

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

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

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

## PROTEINURIA

### Etiologies of Proteinuria

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

#### • Urine dipstick

$1+ \approx 30$  mg/dL,  $2+ \approx 100$  mg/dL,  $3+ \approx 300$  mg/dL,  $4+ >2$  g/dL; interpretation depends on SG; eg,  $3+$  in very concentrated urine might not indicate heavy proteinuria  
Insensitive for microalbuminuria and myeloma light chains (Bence-Jones protein)

- **Spot urine:** protein (mg/dL)/creatinine (mg/dL)  $\approx$  g/d of proteinuria (NEJM 1983;309:1543)  
unlike urine dipstick, will accurately measure myeloma light chains  
reliable surrogate for 24-hr urine, esp. 1st morning void (JASN 2009;20:436); inaccurate if AKI depends on Cr production,  $\therefore$  underestimates if muscular, overestimates if cachectic
- **Microalbuminuria** (30–300 mg/24h or mg/L or  $\mu\text{g}/\text{mg}$  of Cr): early sign of glomerular vascular disease; marker for  $\uparrow$  risk of CV adverse outcomes (JAMA 2001;286:421)
- **Orthostatic proteinuria:** typically in adolescents; ~90% of young ♂ with isolated proteinuria have orthostatic proteinuria; typically resolves spontaneously

## Etiologies of Hematuria

Extrarenal (far more common)	Intrarenal
Nephrolithiasis	Nephrolithiasis or crystalluria
Neoplasm: transitional cell, prostate	Neoplasm
Infxn: cystitis, urethritis, prostatitis	Trauma/exercise (? extrarenal component)
Foley trauma	Vascular: renal infarcts, renal vein thromb., sickle cell, ruptured hemangioma
BPH	Glomerular: IgA, thin BM > others; ? loin pain synd.
Schistosoma haematobium	PKD (NEJM 2008;359:1477)

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

## Workup (JAMA 2015;314:1865 &amp; 2016;315:2726; Annals 2016;164:488)

- Urine dipstick:** + if ≥3 RBCs; + dipstick and - sediment → myo- or hemoglobinuria
- Urine sediment:** dysmorphic RBCs or RBC casts → GN → consider renal bx
- If no evidence of glomerulonephritis:  
 r/o UTI and non-GU causes (GI or vaginal bleed)  
 Urine cytology (Se ~70%, Sp ~95%), not adequate substitute for cystoscopy  
 Renal imaging: helical CT ± contrast (r/o nephrolithiasis and neoplasia of upper tract),  
 cystoscopy (r/o bladder neoplasia, esp. ≥35 y), ± MRI, retrograde pyelogram, U/S

## NEPHROLITHIASIS

## Types of stones and risk factors (J Clin Endocrinol Metabol 2012;97:1847)

- Calcium** (Ca oxalate > Ca phosphate): **70–90% of kidney stones**  
 Urine findings: ↑ Ca, ↑ oxalate (Ca-ox only), ↑ pH (Ca-phos only), ↓ citrate, ↓ volume  
 2° hypercalciuria: 1° hyperparathyroidism, distal RTA, sarcoid  
 2° hyperoxaluria: Crohn's, ileal disease w/ intact colon, gastric bypass, pancreatic insuffic.  
 Diet: ↑ animal protein, ↑ sucrose, ↑ Na, ↓ K, ↓ fluid, ↓ fruits/vegetables, ↑ vit. C, ↓ Ca
- Uric acid:** 5–10% of kidney stones, radiolucent on plain film  
 Urine findings: ↑ uric acid, ↓ pH (eg, from chronic diarrhea)
- Magnesium ammonium phosphate** ("struvite" or "triple phosphate")  
 Chronic upper UTI w/ urea-splitting organisms (eg, *Proteus*, *Klebs*) → ↑ urine NH<sub>3</sub>, pH > 7
- Cystine:** inherited defects of tubular amino acid reabsorption

## Clinical manifestations

- Hematuria (absence does not exclude diagnosis), flank pain, N/V, dysuria, frequency
- Ureteral obstruction (stones >5 mm unlikely to pass spont.) → AKI if solitary kidney
- UTI: ↑ risk of infection proximal to stone; urinalysis of distal urine may be normal

## Workup

- Noncontrast helical CT scan** (ureteral dilation w/o stone suggests recent passage) 97% sens. 96% spec. (AJR 2008;191:396); U/S appears comparable (NEJM 2014;371:1100)
- Strain urine for stone to analyze; U/A & UCx; electrolytes, BUN/Cr, Ca, PO<sub>4</sub>, PTH
- 24-h urine × 2 (>6 wk after acute setting) for Ca, PO<sub>4</sub>, oxalate, citrate, Na, Cr, pH, K, vol.

## Acute treatment (NEJM 2004;350:684)

- Analgesia (narcotics ± NSAIDs; combination superior, Ann Emerg Med 2006;48:173), ensure adequate fluid repletion, antibiotics if UTI
- Consider alpha blocker > CCB to promote ureteral relaxation (Lancet 2006;368:1171)
- Indications for **immediate urologic eval and/or hosp:** obstruction (esp. solitary or transplant kidney), urosepsis, intractable pain or vomiting, significant AKI
- Urologic Rx: lithotripsy (NEJM 2012;367:50), stent, percutaneous nephrostomy, ureteroscopic removal

## Chronic treatment (J Clin Endocrinol Metabol 2012;97:1847)

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

# ANEMIA

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

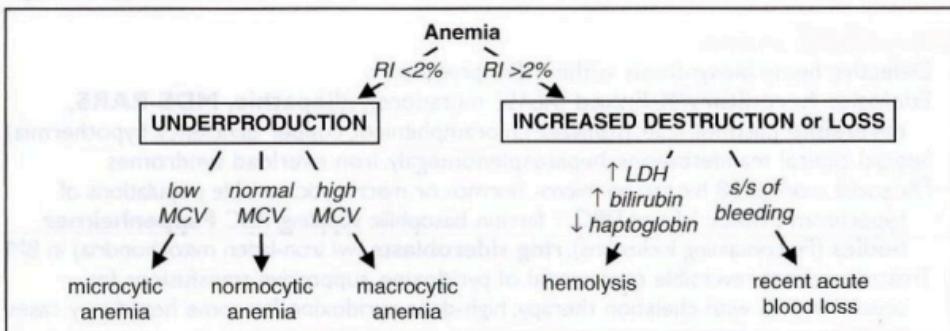
## Clinical manifestations

- Symptoms: ↓ O<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

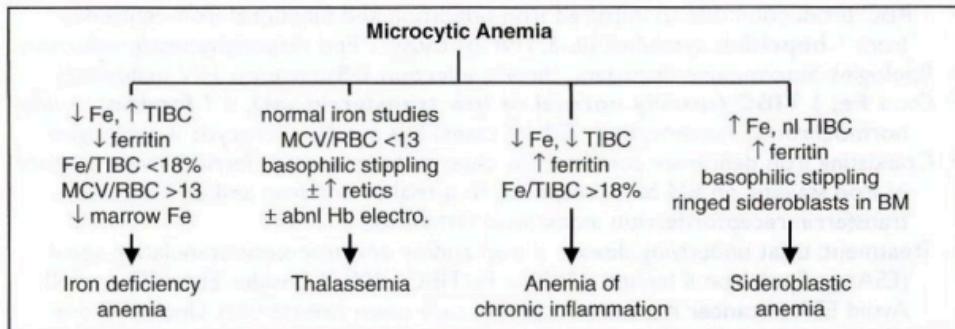
- History: bleeding, systemic illness, drugs, exposures, alcohol, diet (including **pica**), FHx
- CBC w/ diff.; RBC params incl. retics, MCV (nb, mixed disorder can → nl MCV), RDW
- Reticulocyte index (RI)** = [reticulocyte count × (Pt's Hct/nl Hct)]/maturation factor maturation factors for a given 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%, see below), iron/TIBC, ferritin, folate, B<sub>12</sub>, LFTs, BUN & Cr, TFTs, Hb electrophoresis, enzyme/gene mutation screens
- Bone marrow (BM) aspirate and biopsy (bx)** with cytogenetics as indicated

Figure 5-1 Approach to anemia



## MICROCYTIC ANEMIAS

Figure 5-2 Approach to microcytic anemias (NEJM 2014;371:1324)



## Iron deficiency (NEJM 2015;372:1832; Lancet 2016;387:907)

- ↓ marrow iron & depleted body iron stores → ↓ heme synthesis → microcytosis → anemia
- Special clinical manifestations: angular cheilosis, atrophic glossitis, pica (consumption of nonnutritive substances such as ice, clay), koilonychia (nail spooning)  
Plummer-Vinson syndrome (iron deficiency anemia, esophageal web & atrophic glossitis)
- Etiologies: **chronic bleeding** (GI—incl. cancer, menstrual, parasites, NSAIDs, etc.),  
↓ **supply** (malnutrition; ↓ absorp. due to celiac sprue, Crohn's, ↑ gastric pH, subtotal gastrectomy), ↑ **demand** (preg., Epo). Iron-refractory iron-defic. anemia (IRIDA; rare Fe refractory genetic disorder due to hepcidin dysregulation; Nat Genet 2008;40:569).
- Diagnosis (eval ideally before Rx): ↓ Fe, ↑ TIBC, ↓ ferritin (esp. <15), ↓ transferrin sat (Fe/TIBC; esp. <15%), ↑ soluble transferrin receptor; ↑ plt  
Unless hx c/w other etiology, initiate workup for GI bleed, incl. H. pylori serology  
? Celiac sprue labs (**anti-TTG**, antigliadin, antiendomysial Ab)  
Cytogenetics & molecular testing as indicated

- Treatment oral Fe tid (~6 wk to correct anemia; ~6 mo to replete Fe stores; nb, oral Fe does not give  $\oplus$  Hemoccult). In excessive/persistent GI losses or dialysis, cancer, CHF, or prior to Epo Rx, IV iron (Fe-sucrose, -gluconate, -dextrans) should be considered.

### Thalassemias (*Lancet* 2013;379:373)

- $\downarrow$  synthesis of  $\alpha$ - or  $\beta$ -globin chains of Hb  $\rightarrow$   $\neq$  subunits  $\rightarrow$  destruction of RBCs and erythroid precursors;  $\therefore$  anemia from hemolysis and ineffective erythropoiesis
- $\alpha$ -thalassemia** (*NEJM* 2014;371:1908): deletions in  $\alpha$ -globin gene complex (nl 4  $\alpha$  genes), seen w/ Southeast Asian, Mediterranean, African, Middle East ancestry
  - 3  $\alpha$   $\rightarrow$   $\alpha$ -thal-2 trait = silent carrier; 2  $\alpha$   $\rightarrow$   $\alpha$ -thal-1 trait or  $\alpha$ -thal minor = mild anemia
  - 1  $\alpha$   $\rightarrow$  HbH ( $\beta_4$ ) disease = severe anemia, hemolysis and splenomegaly
  - 0  $\alpha$  genes  $\rightarrow$  Hb Barts ( $\gamma_4$ ) = intrauterine hypoxia and hydrops fetalis
- $\beta$ -thalassemia:** mutations in  $\beta$ -globin gene  $\rightarrow$  absent or  $\downarrow$  gene product seen w/ Mediterranean (espec. Greek or Italian), African, or Asian ancestry
  - 1 mutated  $\beta$  gene  $\rightarrow$  thal minor (or trait) = mild anemia (no transfusions)
  - 2 mutated  $\beta$  genes  $\rightarrow$  thal intermedia (occasional transfusions) or thal major (= Cooley's anemia; transfusion dependent) depending on severity of mutations
- Severe clinical manifestations: chipmunk facies, pathologic fractures, hepatosplenomegaly (due to extramedullary hematopoiesis), high-output CHF, bilirubin gallstones, Fe overload
- Diagnosis: MCV <70, **normal Fe, MCV/RBC count <13** [Mentzer Index, 60% Se, 98% Sp; (*Ann Hem* 2007;86:486)],  $\pm \uparrow$  retics, basophilic stippling; **Hb electrophoresis:**  $\uparrow$  HbA<sub>2</sub> ( $\alpha_2\delta_2$ ) in  $\beta$ -thal; **normal** pattern in  $\alpha$ -thal trait,  $\therefore$  PCR or supravital stain for dx
- Treatment: folate; transfusions + Fe chelator [either deferoxamine (IV) or deferasirox (PO)]; ? splenectomy if  $\geq 50\%$   $\uparrow$  in transfusions; consider allo-HSCT in children w/ severe  $\beta$ -thal

### Anemia of chronic inflammation (see below)

#### Sideroblastic anemia

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

## NORMOCYTIC ANEMIAS

### Pancytopenia (see below)

### Anemia of chronic inflammation (ACI; *NEJM* 2012;366:4)

- $\downarrow$  RBC production due to impaired iron utilization and functional iron deficiency from  $\uparrow$  **hepcidin**; cytokines (IL-6, TNF- $\alpha$ ) cause  $\downarrow$  Epo responsiveness/production
- Etiologies: autoimmune disorders, chronic infection, inflammation, HIV, malignancy
- Dx:  **$\downarrow$  Fe,  $\downarrow$  TIBC (usually normal or low transferrin sat),  $\pm \uparrow$  ferritin**; usually normochromic, normocytic (~70% of cases) but can be microcytic if prolonged
- Coexisting iron deficiency common. Dx clues include  $\downarrow$  serum ferritin levels, absence of iron staining on BM bx,  $\oplus$  response to a trial of oral iron and/or  $\uparrow$  soluble transferrin receptor/ferritin index (*Blood* 1997;89:1052).
- Treatment: treat underlying disease  $\pm$  iron and/or erythropoiesis-stimulating agent (ESA; eg, Epo). Iron if ferritin <100 or Fe/TIBC <20%. Consider ESA if Epo <500. Avoid ESA in cancer if treatment goal is cure (*Lancet* 2009;373:1532). Unclear if one should treat highly sx Pts w/ goal Hb 10–12 g/dL; weigh risk of thrombosis.

### Anemias of other chronic disorders

- Anemia of chronic kidney disease:  $\downarrow$  Epo; treat w/ Epo (see "Chronic Kidney Disease")
- Endocrine deficiencies: hypometabolism and  $\downarrow$  O<sub>2</sub> demand with thyroid, pituitary, adrenal, or parathyroid disease  $\rightarrow$   $\downarrow$  Epo; can be normocytic or macrocytic

### Sideroblastic anemia (see above)

#### Pure red cell aplasia

- Destructive antibodies or lymphocytes  $\rightarrow$  ineffective erythropoiesis
- Associated with thymoma, CLL and parvovirus infection, autoimmunity, drugs
- Diagnostic studies: **lack of erythroid precursors on BM bx**, other lines normal
- Treatment: thymectomy if thymus enlarged; IV Ig if parvovirus infection; immunosuppression/chemoRx if CLL or idiopathic; supportive care w/ PRBC transfusions; ? erythropoietin receptor agonist if due to antierythropoietin Ab (*NEJM* 2009;361:1848) consider hematopoietic cell transplantation.

## MACROCYTIC ANEMIAS

includes megaloblastic and nonmegaloblastic causes

ANEMIA  
5-3

### Megaloblastic anemia

- Impaired DNA synthesis → cytoplasm matures faster than nucleus → ineffective erythropoiesis and macrocytosis; due to **folate** or **B<sub>12</sub> deficiency**; also in **MDS**
- ✓ 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; NEJM 2015;373:1649), ↑ 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 (NEJM 2013;368:149)

- 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 (Cochrane Rev CD004655) even w/o IF

### Nonmegaloblastic macrocytic anemias

- Liver disease: often macrocytic, may see target cells, or spur cell anemia w/ hemolysis
- Alcoholism: BM suppression & macrocytosis independent of folate/B<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 syndrome

## PANCYTOPENIA

### Etiologies

- Hypocellular bone marrow (nl cellularity ~100 – age): **aplastic anemia**, hypoplastic MDS
- Cellular bone marrow: **MDS**, aleukemic leukemia, PNH, severe megaloblastic anemia
- Marrow replacement (myelophthisis): **myelofibrosis**, metastatic solid tumors, granulomas
- Systemic diseases: hypersplenism, sepsis, alcohol, toxins

### Clinical manifestations

- Anemia → fatigue
- Neutropenia → recurrent infections
- Thrombocytopenia → mucosal bleeding & easy bruising

### Aplastic anemia = stem cell failure (NEJM 2015;373:35)

- Epidemiology: 2–5 cases/10<sup>6</sup>/y; biphasic (major peak in adolescents, 2<sup>nd</sup> peak in elderly)
- Diagnosis: pancytopenia w/ ↓ retics, BM bx w/ cytogenetics showing hypocellularity
- Etiologies: **idiopathic** (½ – ⅔ of cases)  
**stem cell destruction:** **radiation, chemotherapy, chemicals** (eg, benzene)  
**idiosyncratic med rxn** (eg, chloramphenicol, NSAIDs, sulfa drugs, gold, carbamazepine, antithyroid)  
**viruses** (HHV-6, HIV, EBV, parvovirus B19); **post-viral hepatic failure** (not Hep A/B/C)  
**immune disorders** (SLE, GVHD post-HSCT, thymoma)  
**PNH** (see below); Fanconi's anemia (congenital disorder w/ pancytopenia, macrocytic anemia, ↑ risk of MDS, AML, & SCC of head & neck, and multiple physical anomalies); shortened telomeres: seen w/ telomerase (TERT, TERC) mut. (10% of aplastic anemia), dyskeratosis congenita/DKC1 mut; a/w IPF, cirrhosis (NEJM 2009;361:2353)  
somatic mutations: PNH clones in ~50% of aplastic anemia (Haematologica 2010;95:1075)

- Treatment and prognosis
  - allogeneic HSCT:** for young Pts → ~80% long-term survival and significantly ↓ risk of malignant evolution, but has risk of transplant-related morbidity & mortality; if possible avoid transfusions (and alloimmunization) pretransplant
  - immunosuppression** (CsA/tacrolimus, ATG): 70–80% respond, with 80–90% 5-y survival in responders (96% vs. 76% w/ horse vs. rabbit ATG; NEJM 2011;365:430); 15–20% 10-y incidence of clonal disorders (mostly MDS, AML, PNH)
  - TPO mimetics** (eg, eltrombopag) an option in refractory disease (Blood 2014;123:1818)
  - supportive care:** transfusions, antibiotics, possible utility of G-CSF and Epo (if Epo <500)

### Myelodysplastic syndromes (MDS) (qv)

### Paroxysmal nocturnal hemoglobinuria (PNH) (Blood 2009;113:6522)

- Acquired clonal stem cell disorder = inactivating somatic mutation of *PIG-A* gene → deficiency of GPI-anchor for CD55 & CD59 (inhib of complement) → complement-mediated RBC lysis, plt aggreg., & hypercoagulability
- Clinical: intravascular **hemolytic anemia, hypercoagulability** (venous > arterial; esp. intraabdominal, cerebral), smooth muscle dystonias, **deficient hematopoiesis** (cytopenias); a/w aplastic anemia, MDS and evolution to AML
- Dx: **flow cytometry** (↓ CD55 & CD59) on RBCs and granulocytes; urine hemosiderosis
- Treatment: supportive care (iron, folate, transfusions); consider anticoagulation allogeneic HSCT for hypoplasia or severe thrombosis  
eculizumab (Ab inactivates terminal complement C5s): ↓ hemolysis, improves QoL & stabilizes Hb levels (NEJM 2004;350:552 & 2006;355:1233; Lancet 2009;373:759); effective in pregnancy (NEJM 2015;373:1032); must have meningococcal vaccination

### Myelophthisic anemia (see also "Primary Myelofibrosis")

- Infiltration of bone marrow by cancer, leukemia, infection, fibrosis (primary myelofibrosis), granulomas, lysosomal storage disorders

## HEMOLYTIC ANEMIAS

**Causes of Hemolytic Anemia by Mechanism** (Lancet 2000;355:1169 & 1260)

Location	Mechanism	Examples	Mode
Intrinsic	Enzyme deficiency	G6PD deficiency	Hereditary
	Hemoglobinopathies	Sickle cell anemia, thalassemia	
	Membrane abnormalities	Hereditary spherocytosis PNH, spur cell anemia in liver disease	
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	

### Diagnostic evaluation

- ↑ reticulocyte count (RI >2%), ↑ LDH, ↓ haptoglobin (83% Se, 96% Sp), ↑ indirect bili
- Autoimmune hemolysis: Coombs' test = direct antiglobulin test (DAT) → ⊕ if agglutination occurs when antisera against Ig or C3 are applied to patient RBCs
- Intravascular: ↑↑ LDH, ↓↓ haptoglobin; hemoglobinemia, hemoglobinuria, hemosiderinuria
- Extravascular: splenomegaly
- Family h/o anemia; personal or family h/o cholelithiasis

### Glucose-6-phosphate dehydrogenase (G6PD) deficiency (Lancet 2008;371:64)

- X-linked defect of metabolism (G6PD mutations) w/ ↑ susceptibility to oxidative damage
- Most common in ♂ of African or Mediterranean descent (malaria-endemic areas)
- Hemolysis precipitated by **drugs** (sulfonamides, dapsone, nitrofurantoin, rasburicase, primaquine, doxorubicin, methylene blue), **infection**, **DKA** or **foods** (fava beans)
- Diagnosis: smear may show RBC **Heinz bodies** (oxidized Hb) that result in **bite cells** once removed by spleen; ↓ G6PD levels (*may be normal after acute hemolysis* as older RBCs have already lysed and young RBCs may still have near normal levels)

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

- Recessive β-globin mutation → structurally abnl hemoglobin (HbS). ~8% African Americans heterozygotes ("sickle trait"; usually w/o sx); ~1/400 homozygotes (sickle cell disease).
- ↓ O<sub>2</sub> → HbS polymerizes → RBC sickles, ↓ RBC deformability → **hemolysis** & **microvascular occlusion** due to endothelial activ. & PMN adhesion (Blood 2013;122:3892)
- Anemia:** chronic hemolysis ± acute aplastic (parvo. B19) or splenic sequestration crises

- Vaso-occlusion and infarction:** painful crises, acute chest syndrome, CVA, splenic sequestration, hand-foot syndrome, renal papillary necrosis, aseptic necrosis, priapism
- Infection:** splenic infarction → overwhelming infection by **encapsulated organisms**; infarcted bone → **osteomyelitis** (*Salmonella*, *Staph. aureus*)
- Diagnosis: sickle-shaped RBCs and Howell-Jolly bodies on smear; Hb electrophoresis
- Treatment: **hydroxyurea** causes ↑ HbF → ↓ painful crises, acute chest episodes and may ↓ mortality (NEJM 2008;358:1362); allogeneic HSCT may have a role in young Pts w/ severe disease (Blood 2000;95:1918) and adults (NEJM 2009;361:2309; Blood 2012;120:4285)
- Supportive care: folic acid qd; pneumococcal, meningococcal, *H. flu* & HBV vaccination; pain crises Rx'd w/ **hydration, O<sub>2</sub> & analgesia**; simple or exchange transfusion for TIA or stroke, severe acute chest syndrome, or preop (goal Hb 10 g/dL; Lancet 2013;381:930)

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

- Defect in a cytoskeletal protein of RBC membrane → membrane loss mutations in ankyrin, α- and β-spectrin, band 3, and pallidin have been identified
- Most common in N. European populations (1/5000 births); ⊕ FHx (75% of Pts)
- Anemia, jaundice (mostly neonates), splenomegaly, pigmented gallstones
- Diagnosis: spherocytes on smear; ⊕ osmotic fragility test (~80% Se), ↓ eosin-5-maleimide (EMA) binding (93% Se; 99% Sp; Haemat 2012;97:516), acidified glycerol lysis test (Se 95%)
- Treatment: folate, transfusions, splenectomy for moderate and severe HS (balance w/ ↑ risk of future thrombosis and infection; J Thromb Haemost 2008;6:1289)

### Paroxysmal nocturnal hemoglobinuria (see above)

### Autoimmune hemolytic anemia (AIHA)

- Acquired, antibody-mediated RBC destruction
- Warm AIHA:** IgG Abs opsonize RBCs at body temp → removal by spleen Etiologies: idiopathic, lymphoproliferative (CLL, NHL), autoimmune (SLE), drugs, HIV
- Cold AIHA:** IgM Ab binds to RBCs at temp <37°C → **complement fixation** → intravascular hemolysis and acrocyanosis on exposure to cold Etiologies: idiopathic, lymphoprolif. disorders (eg, Waldenström's; monoclonal), *Mycoplasma pneumoniae* infxn and infectious mononucleosis (polyclonal)
- Diagnosis: spherocytes on smear, ⊕ **Coombs'**; ✓ cold agglutinin titer, splenomegaly
- Treatment: treat underlying disease
  - warm AIHA: corticosteroids ± splenectomy, IVIg, cytotoxic agents, rituximab
  - cold AIHA: avoid cold; steroids ineffective; rituximab (Blood 2004;103:2925)

### Drug-induced hemolytic anemia

- Acquired, antibody-mediated, RBC destruction precipitated by a medication:
  - abx: cephalosporins, sulfa drugs, rifampin, ribavirin
  - CV: methyldopa, procainamide, quinidine, thiazides
  - TCA, phenothiazines, NSAIDs, sulfonylureas, MTX, 5-FU, rasburicase (G6PD defic.)
- Diagnosis: Coombs' usually negative, ↑ LDH
- Treatment: discontinue offending agent

### Microangiopathic hemolytic anemia (MAHA; NEJM 2014;371:654)

- Intra-arteriolar fibrin damages RBCs → acquired intravascular hemolysis
- Etiologies: **hemolytic-uremic syndrome (HUS)**, **thrombotic thrombocytopenic purpura (TTP)**, **disseminated intravascular coagulation (DIC)**, malignancy, malignant HTN, eclampsia/HELLP, mech. cardiac valves, infected vascular prostheses
- Diagnosis: **schistocytes** ± thrombocytopenia ± abnormalities a/w specific disorders (eg, ↑ PT in DIC, ↑ Cr in HUS, ↑ LFTs in HELLP)
- Rx underlying dx; **urgent plasma exchange w/ TTP** (replace low ADAMTS13)

### Hypersplenism

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

#### Causes of Splenomegaly

Etiology	Comments*
RES hyperplasia	Hemolytic anemia, sickle cell disease, <b>thalassemia major</b>
Immune hyperplasia	Infxn [HIV, EBV, CMV, TB, <b>malaria</b> , <b>kala azar</b> ("black water fever" from visceral leishmaniasis), <i>Mycobacterium avium</i> complex], autoimmune disorders (SLE, RA w/ 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>CMM</b> , leukemia, lymphoma ( <b>NHL</b> , <b>HL</b> , <b>hairy cell leukemia</b> , <b>CLL</b> , <b>PLL</b> , <b>WM</b> ), T-LGL, myeloma, amyloid

RES = reticuloendothelial system; \*boldface = causes of massive splenomegaly.

# DISORDERS OF HEMOSTASIS

## Clinical Characteristics of Bleeding Disorders

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

Figure 5-3 Approach to abnormal hemostasis (NEJM 2014;370:847)

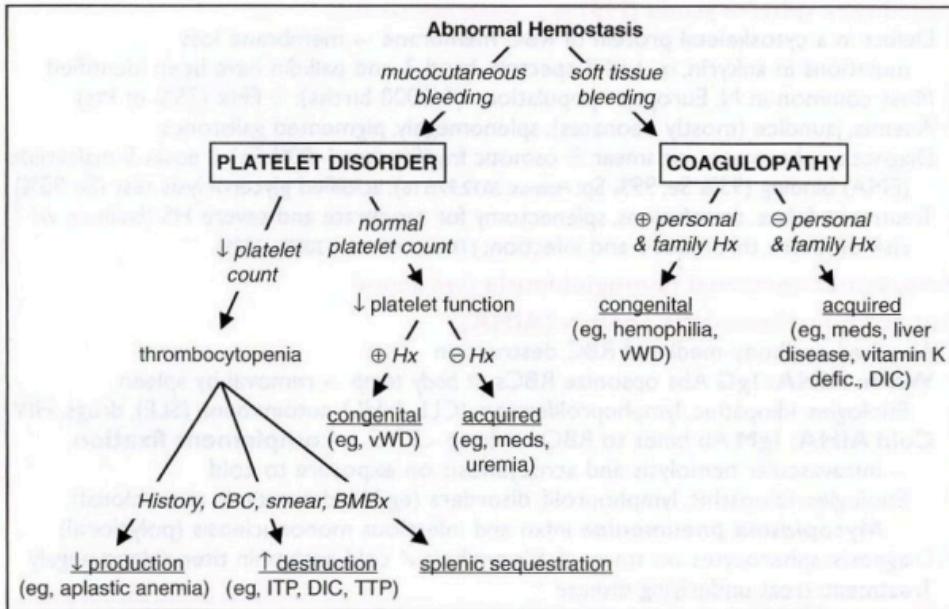
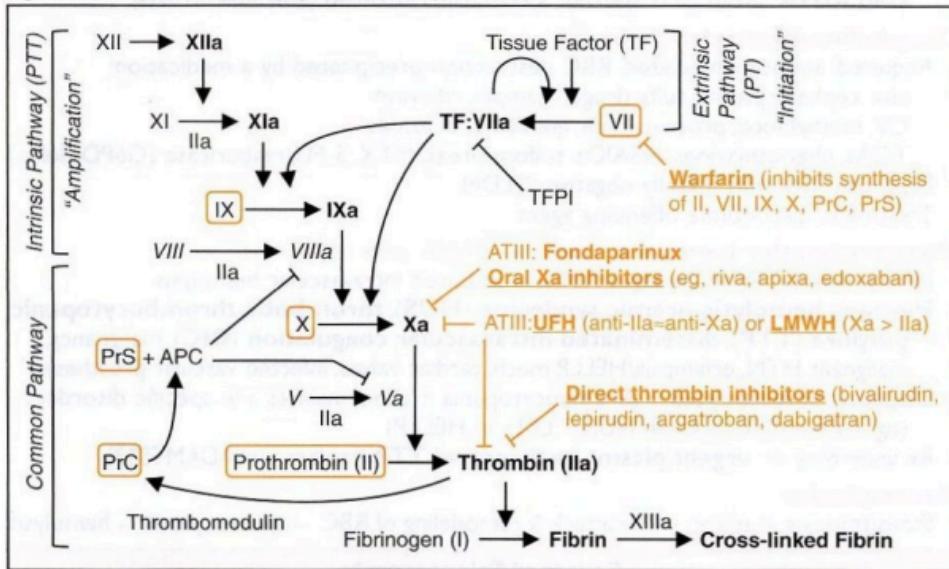


Figure 5-4 Coagulation Cascade (NEJM 2008;359:938)



APC, activated protein C; AT, antithrombin; PrC, protein C; PrS, protein S; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

**Purpura** (nonblanching purple/red lesions due to extravasation of RBCs into dermis)

- **Nonpalpable** (macular; ≤3 mm in diameter = petechiae; >3 mm = ecchymoses)
  - platelet disorder: thrombocytopenia, defect in platelet fxn
  - thromboemboli: DIC, TTP, cholesterol or fat emboli
  - trauma or vascular fragility: amyloidosis, Ehlers-Danlos, scurvy
- **Palpable** (papular); **vasculitis**: leukocytoclastic, HSP, PAN, RMSF;
- **infectious emboli**: meningococcemia, bacterial endocarditis
- **Purpura fulminans** (aka retiform purpura): **purpura + hypotension + DIC**; typically due to infxn/sepsis, protein C or S deficiency or APS (see section on DIC)

# PLATELET DISORDERS

## THROMBOCYTOPENIA (PLT COUNT <150,000/ $\mu$ L)

### Thrombocytopenia and Risk of Bleeding

Platelet count (cells/ $\mu$ L)	Risk
50,000–100,000	Risk with major trauma; can proceed with general surgery
20,000–50,000	Risk with minor trauma or surgery
<20,000	Risk of spontaneous bleeding (less so with ITP)
<10,000	Risk of severe, life-threatening bleeding

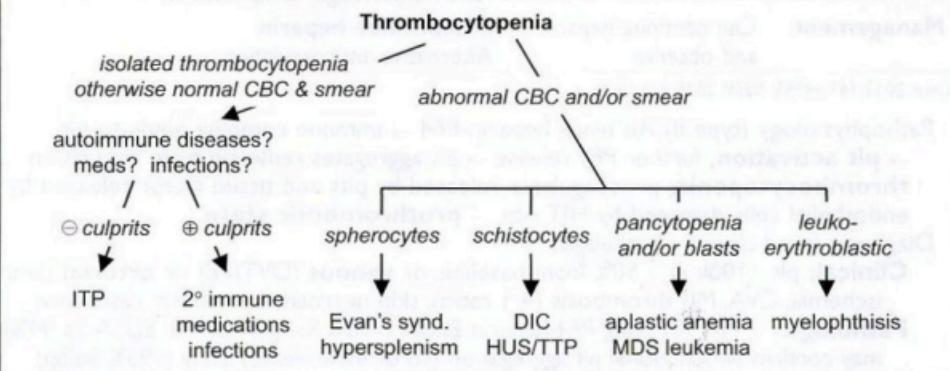
### Etiologies

- ↓ production
  - hypocellular bone marrow:** aplastic anemia (qv), rarely MDS, drugs (eg, thiazides, antibiotics), alcohol, cirrhosis
  - hypercellular bone marrow:** MDS, leukemia, severe megaloblastic anemia
  - marrow replacement:** myelofibrosis, hematologic and solid malignancies, granulomas
- ↑ destruction
  - immune-mediated** (distinguish primary from secondary; *Blood* 2009;113:2386)
    - Primary (idiopathic): immune thrombocytopenic purpura (**ITP**, see below)
    - Secondary: infxn (**HIV**, **HCV**, HSV), collagen vascular diseases (**SLE**, APS, lymphoproliferative (**CLL**, lymphoma), drugs (many, including **heparin**, abciximab, quinidine, sulfonamides, vancomycin), alloimmune (posttransfusion)
  - non-immune-mediated:** **MAHA** (DIC, HUS, TTP), ticlopidine/clopidogrel, vasculitis, preeclampsia/HELLP, cardiopulm bypass, CVVH, IABP, cavernous hemangioma
- **Abnormal distribution or pooling:** splenic sequestration, dilutional, hypothermia
- **Unknown:** ehrlichiosis/anaplasmosis, babesiosis, RMSF

### Diagnostic evaluation

- H&P: meds, infxns, underlying conditions, splenomegaly, lymph nodes, **bleeding hx**
- **CBC with differential:** isolated thrombocytopenia vs. multilineage involvement
- **Peripheral smear**
  - ↑ destruction → look for large plt, **schistocytes** (see “Peripheral Smear” inserts)
  - ↓ production → rarely limited to platelets → look for **blasts**, hypersegmented PMNs, leukoerythroblastmic Δs; can see inclusion bodies (anaplasma), parasites (*Babesia*)
  - r/o **pseudothrombocytopenia** due to platelet clumping (✓ platelet count in non-EDTA-containing tube, eg, citrate or heparin-containing tube)

Figure 5-5 Approach to thrombocytopenia



- Additional laboratory evaluations as indicated (eg, viral titers, flow cytometry, ANA, APLA) if anemia: ✓ reticulocyte count, LDH, haptoglobin, bilirubin to detect hemolysis if hemolytic anemia: ✓ PT, PTT, fibrinogen, D-dimer, Coombs, ANA BM bx for unexplained thrombocytopenia, esp. if associated with splenomegaly

### Primary immune thrombocytopenic purpura (ITP) (*Blood* 2010;115:168)

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

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

### Treatment of Primary ITP in Adults

Approach	Treatment	Notes
First-line	<b>Steroids:</b> prednisone 0.5–2 mg/kg/d PO tapered ~4 wk, or dexamethasone 40 mg PO $\times$ 4 d	$\downarrow$ Mφ FcR & $\downarrow$ anti-plt Ab 70–90% initial response ~20% sustained remission
	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 $\times$ 2–3 d) consider if need rapid $\uparrow$ in plt	Blocks Mφ FcR, $\downarrow$ anti-plt Ab Up to 80% initial response
Second-line	<b>Splenectomy</b> (? for ITP >6 mo)	~65% long-term remission
	<b>Rituximab</b> (anti-CD20) $\pm$ dex	anti-B-cell Ab
	<b>Romiplostim or eltrombopag</b>	TPO-R agonists $\rightarrow$ $\uparrow$ plt prod
	Azathioprine, cyclophosphamide Danazol, vincristine Aminocaproic acid	Immunosuppressants $\downarrow$ plt clearance Inhibits plasmin activation
Bleeding	Methylprednisolone 1g/d IV $\times$ 3 d	See above
	IVIg	See above
	Platelet transfusion	Given w/ IVIg or anti-Rh(D)
Refractory	Romiplostim or eltrombopag	See above
	Autologous HSCT	Limited data, investigational

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

### Overview of Heparin-Induced Thrombocytopenias

Feature	Type I (historic)	HIT (formerly type II)
<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, $\downarrow$ >50%
<b>Sequelae</b>	None	Thrombotic events ( <b>HITT</b> ) in 30–50% Rare hemorrhagic complications
<b>Management</b>	Can continue heparin and observe	<b>Discontinue heparin</b> Alternative anticoagulation

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

- Pathophysiology (type II):** Ab binds heparin-PF4  $\rightarrow$  immune complex binds to plt  $\rightarrow$  **plt activation**, further PF4 release  $\rightarrow$  plt aggregates removed from circulation  $\rightarrow$  **thrombocytopenia**; procoagulants released by plts and tissue factor released by endothelial cells damaged by HIT Abs  $\rightarrow$  **prothrombotic state**
- Diagnosis (need clinical + pathologic)**
  - Clinical:** plt <100k or  $\downarrow$  50% from baseline; or **venous** (DVT/PE) or **arterial** (limb ischemia, CVA, MI) thrombosis (4:1 ratio); skin necrosis; ?  $\uparrow$  heparin resistance
  - Pathologic:**  $\oplus$  HIT Ab using PF4-heparin ELISA ( $\geq$ 90% Se, IgG-specific ELISA Sp 94%), may confirm w/ functional plt aggregation (serotonin-release) assay ( $>$ 95% Se/Sp)
- Clinical context important: HIT Ab (esp. IgM ELISA) may be  $\oplus$  in 10–20% of Pts on UFH/LMWH (Am J Hem 1996;52:90), up to 50% of cardiac bypass Pts (Circ 1997;95:1242)
- Pretest prob w/ "4 T's" criteria (Blood 2012;120:4160):  $\leq$ 3 points  $\rightarrow$  99% NPV, investigate other causes; 4–5 points 22% PPV & 6–8 points 64% PPV,  $\checkmark$  lab test & replace UFH

### Evaluation of Suspected HIT ("4T's")

Factor	2 points	1 point	0 points
<b>Thrombocytopenia</b>	$\downarrow$ >50% and nadir $\geq$ 20k	$\downarrow$ 30–50% or nadir 10–19k	$\downarrow$ <30% or nadir <10k
<b>Timing</b>	5–10 d or $\leq$ 1 d if heparin w/in 30 d	? 5–10 d (but not clear), >10 d or $\leq$ 1 d if hep w/in 30–100 d	$\leq$ 4 d w/o recent hep
<b>Thrombosis</b>	New thromb, skin necrosis, acute rxn after IV UFH	Prog/recurrent thromb, suspect thromb or non-nec skin lesion	None
<b>Other cause</b>	None apparent	Possible	Definite

- Treatment of HIT (type II) (Chest 2012;141:e495S; Blood 2012;119:2209; NEJM 2013;368:737)
  - Discontinue heparin** (incl. flushes, LMWH Ppx, heparin lines). Avoid plt (anecdotal link w/ thrombosis); if given warfarin, give vit K to reverse, prevent warfarin skin necrosis.
  - Nonheparin anticoag** (argatroban, bivalirudin; NEJM 2013;368:737) regardless of thrombosis; start warfarin when plt >150k, overlap ≥5 d (✓ chromogenic Xa to titrate)
  - ⊕ thrombosis (HITT): anticoagulate for ≥3–6 mo
  - ⊖ thrombosis (HIT): screen for DVT; unclear duration of subsequent anticoag (until plt count recovers, often ~2–3 mo if no clot); 25–50% thrombosis rate w/in 30 d
- H/o HIT: if PF4 Ab ⊖ or SRA ⊖ (typically >100 d after dx) → may consider re-exposure to UFH (eg, for surgery); HIT recurrence low but can be seen (Blood 2014;123:2485)

### Thrombotic microangiopathies (NEJM 2014;371:654)

- Includes hemolytic-uremic syndrome (HUS) & thrombotic thrombocytopenic purpura (TTP)
- Definition: vascular occlusive disorders w/ systemic (TTP) or intrarenal (HUS) plt aggreg. → thrombocytopenia & mechanical injury to RBCs (MAHA) (NEJM 2002;347:589)
  - HUS triad** = thrombocytopenia + MAHA + renal failure
  - TTP pentad** (all 5 in only ~5%) = ↓ plts + MAHA (100%) ± Δ MS (65%) ± renal failure (50%, late feature) ± fever (25%)
- Pathophysiology: mechanism in most HUS cases is distinct from TTP (NEJM 1998;339:1578)
  - HUS:** Shiga toxin binds & activates renal endothelial cells & plts → intrarenal thrombi
  - TTP:** ↓ ADAMTS13 protease activity or inhibitor → persistence of large vWF multimers on endothelial surface → adhesion and aggregation of passing platelets → thrombosis
- Clinical manifestations and associations
  - HUS:** usually in children; prodrome of bloody diarrhea due to enterohemorrhagic E. coli
  - TTP (low ADAMTS13):** usually in adults; **idiopathic**, autoimmune dis., familial, preg
  - TTP-like (nl ADAMTS13): drugs** (CsA, tacrolimus, gemcitabine, mitomycin-C, ticlopidine, clopidogrel, quinine), HIV, HSCT, malig
- Dx: unexplained **thrombocytopenia** (typically <20k) + **MAHA** → sufficient for dx
  - ⊕ **schistocytes** (>2–3/hpf), ⊖ Coombs, normal PT/PTT & fibrinogen, ↓↓ ADAMTS13
  - ↑↑ LDH (tissue ischemia + hemolysis), ↑ indirect bili., ↓↓ haptoglobin, ↑ Cr (esp. in HUS)
  - Biopsy: arterioles filled with platelet hyaline thrombi
  - Ddx: DIC, vasculitis, malignant hypertension, preeclampsia/HELLP syndrome
- Rx: **urgent plasma exchange** ± glucocorticoids if ? TTP; FFP if delay to plasma exchange (Blood 2010;116:4060); ? eculizumab in HUS & ? caplacizumab in TTP (NEJM 2013;368:2169 & 2016;374:511); plt transfusions contraindic. → ↑ microvascular thromb (NEJM 2006;354:1927)

**Disseminated intravascular coagulation (DIC):** see "Coagulopathies"

## DISORDERS OF PLATELET FUNCTION

### Mechanisms and Etiologies of Platelet Function Abnormalities

Function	Inherited	Acquired
<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

- Platelet aggregation tests: measure aggregation in response to agonists (eg, ADP)
- von Willebrand's disease (vWD)** (NEJM 2004;351:683 & 2012;367:1954)
- von Willebrand's factor (vWF) function = platelet glue & plasma carrier of factor VIII
  - vWD most common inherited (usually auto dom) bleeding disorder; ~85% (type 1) have partial quantitative defic of vWF, ~15% (type 2) have qualitative defic in vWF
  - Acquired vWD: a/w many disorders (malig, MPN w/ ↑ plt count; autoimmune; hypothyroidism; drugs) and caused by different mechanisms (anti-vWF Abs, ↑ clearance, ↓ synthesis); Heyde's syndrome = vWF destruction by severe AS, a/w GI AVMs/bleed
  - Diagnosis: ↓ **vWF:Ag**, ↓ **vWF activity** (measured by ristocetin cofactor assay), ↓ **factor VIII**, ± ↑ PTT, ± ↓ platelets; confirm with **vWF multimer analysis**
  - Clinical condition, factor VIII levels and ristocetin cofactor assay useful to guide Rx decision
  - Rx: **desmopressin** (dDAVP, IV/IN) → ↑ endothelial cell release of vWF; efficacy depends on type (avoid in type 2), ∴ ✓ response before use w/ subseq. bleeding or procedures; **vWF replacement**: cryoprecipitate, factor VIII concentrates rich in vWF, recomb. vWF

### Uremic bleeding

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

# COAGULOPATHIES

## Screening Test Abnormalities in Inherited and Acquired Coagulopathies

PT	PTT	Factors	Inherited	Acquired
↑	↔	VII	FVII defic.	<b>Vit. K defic.; liver dis.; factor inhib.</b>
↔	↑	VIII or IX	Hemophilias, vWD	<b>Antiphospholipid Ab; factor inhib.</b>
↑	↑	I, II, V or X	Fbgn, FII or FV defic.	<b>DIC; liver dis.; factor inhib.</b>

### Further coagulation tests

- Mixing study: useful if ↑ PT or PTT; mix Pt's plasma 1:1 w/ normal plasma and retest PT/PTT normalizes → **factor deficiency**; PT/PTT remains elevated → **factor inhibitor**
- Coagulation factor levels: useful if mixing study suggests factor deficiency  
DIC → all factors consumed; ∴ ↓ factors V and VIII  
liver disease → ↓ all factors except VIII; ∴ ↓ factor V, normal factor VIII  
vitamin K deficiency → ↓ factors II, VII, IX, X (and protein C, S); ∴ normal V and VIII
- DIC screen:** fibrinogen (consumed), fibrin degradation products (FDPs, + due to intense fibrinolysis), D-dimer (more specific FDP test that detects degradation of X-linked fibrin)

### Hemophilias (*Lancet* 2016;388:187)

- X-linked recessive **factor VIII** (hemophilia A) or **factor IX** (hemophilia B) **deficiency**
- Classification: mild (5–25% normal factor activity), moderate (1–5%) or severe (<1%)
- Clinical manifestations: hematomas, hemarthroses, bruising, bleeding (mucosal, GI, GU)
- Diagnosis: ↑ PTT (normalizes w/mixing study), normal PT & vWF, ↓ factor VIII or IX
- Rx: purified/recomb. factor VIII (*NEJM* 2016;374:2054) or IX; desmopressin (mild dis.); amino-caproic acid; cryo (FVIII); recomb. factor VII or IX-Fc fusion proteins have ↑  $t_{1/2}$ , so 1–2x/wk dosing for Ppx (*NEJM* 2013;369:2313); ? emicizumab (binds FIX & X; *NEJM* 2016;374:2044)

### Coagulation factor inhibitors (most commonly anti-factor VIII)

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

### Disseminated intravascular coagulation (DIC) (*NEJM* 2014;370:847)

- Etiologies: trauma, shock, infection, malignancy (esp. APL), obstetric complications
- Pathogenesis: massive activation of coagulation that overwhelms control mechanisms **thrombosis** in microvasculature → ischemia + microangiopathic hemolytic anemia acute consumption of coagulation factors and platelets → **bleeding**  
chronic DIC → able to compensate by ↑ factors and platelets → **thrombosis**
- Diagnosis: ↑ PT, ↑ PTT, ↓ **fibrinogen** (may be nl b/c acute phase), + FDP/D-dimer, ↓ plt, + schistos, ↑ LDH, ↓ haptoglobin; chronic DIC: + FDP/D-dimer, variable plt, other labs nl
- Treatment: Rx underlying process; support w/ **FFP, cryo** (goal fbgn >100 mg/dL) & plt

### 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 (*Circ* 2016;134:248)

Anticoag.	$t_{1/2}$	Labs	Rx for O/D w/ serious bleeding (+ d/c anticoag)
UFH	60–90', RES	↑ PTT	<b>Protamine</b> IV 1 mg/100 U UFH (max 50 mg). For infusions, dose to reverse 2x UFH given per h.
LMWH	2–7°, K	anti-Xa*	Protamine reverses ~60%
Bivalirudin	25', K	↑ PTT	Dialysis
Argatroban	45', L	↑ PTT	? Dialysis
Fondaparinux	24°, K	anti-Xa*	? Dialysis
Warfarin	36°, L	↑ PT	No bleeding: INR 4.5–10, Ø Rx or <b>vit. K</b> 2.5 mg PO; INR >10 give 5 mg PO (sup to SC, ≈ IV at 24 h) Bleeding: <b>vit. K</b> 10 mg IV + <b>FFP</b> 2–4 U IV q6–8h; PCC (eg, KCentra) faster, ↓ tfn ( <i>Circ</i> 2013;128:360)
Fibrinolytic	20', LK	↓ fbgn	<b>Cryoprecipitate, FFP, ± aminocaproic acid</b>
Dabigatran	~12°, K	↑ PTT*	Idarucizumab ( <i>NEJM</i> 2015;373:511)
Rivaroxaban	8–12°, K > L	↑ PT* anti-Xa*	Anti-fibrinolytic agent; consider PCC; specific reversal agents (eg, andexanet) under development ( <i>NEJM</i> 2015;373:2413; <i>J Thromb Haemost</i> 2015;13:S187)
Apixaban			
Edoxaban			

\*Routine monitoring not performed. Mode of excretion: K, kidney; L, liver; RES, reticuloendothelial system. PCC: prothrombin complex concentrate (FII, VII, IX, X; Protein C & S). Anti-fibrinolitics: tranexamic, aminocaproic acid.

# HYPERCOAGULABLE STATES

Suspect in Pts with venous or arterial thrombosis at young age or unusual locations, recurrent thromboses or pregnancy loss, or  $\oplus$  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 $\rightarrow$ ↑ 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 heparin-resistant

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

## Vascular Beds Affected by Inherited and Acquired Hypercoagulable States

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

### Diagnostic evaluation (not routinely required for initial VTE)

- APC resistance screen; prothrombin PCR test; functional assays for proteins C and S, ATIII; homocysteine level; factor VIII levels; anticardiolipin and lupus anticoagulant Ab. Also consider nephrotic syndrome, PNH (esp. if mesenteric thrombus).
- Consider JAK2 mutation testing if suspect MPN or splanchnic thrombosis
- Proteins C & S and ATIII levels are affected by acute thrombosis and anticoagulation  $\therefore$  levels best assessed  $\geq 2$  wk after completing anticoagulation course
- Age-appropriate malignancy screening (occult cancer in ~4% of initial unprovoked VTE; no benefit of routine abd/pelvis CT; NEJM 2015; 373:697)

### Treatment

- Asx w/ inherited risk factor: consider prophylactic anticoag. if develops acquired risk factor
- Thrombosis w/ inherited risk factor: see "Venous Thromboembolism"

### Antiphospholipid syndrome (APS) (J Thromb Haemost 2006;4:295; NEJM 2013;368:1033)

- Definition: dx requires  $\geq 1$  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),  $\oplus$  lupus anticoagulant (LA), or  $\oplus$   $\beta_2$ -glycoprotein-I ( $\beta_2$ -GP-I) Ab, on  $\geq 2$  occasions, at least 12 wk apart
- Clinical: **DVT/PE/CVA, recurrent fetal loss,  $\downarrow$  plts, hemolytic anemia, livedo reticularis; "catastrophic APS":**  $\geq 3$  organ systems in <1 wk w/  $\oplus$  APLA & tissue microthrombi; 44% mortality (Arth Rheum 2006;54:2568); Rx w/ plasmapheresis, rituximab
- Antiphospholipid antibodies (APLA)**  
✓ if: SLE, age <40 y & arterial thromb, recurrent venous thromb, spontaneous abortion  
ACL: Ab against cardiolipin, a mitochondrial phospholipid; IgG more specific than IgM  
LA: Ab that prolongs phospholipid-dependent coagulation reactions;  $\therefore$   $\uparrow$  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 (uncertain role of Abs in pathogenesis)  
False  $\oplus$  VDRL: nontreponemal test for syphilis in which cardiolipin is part of Ag complex  
Risk of thromboembolic phenomena may increase with titer of APLs
- Etiologies: primary (idiopathic) or secondary due to **autoimmune syndromes** (eg, SLE), **malignancy, infections, drug reactions**
- Treatment: UFH/LMWH  $\rightarrow$  warfarin after thromboembolic event (lifelong for most Pts)  
Intensity of anticoagulation controversial (Nat Rev Rheum 2015;11:586)  
Initial venous thrombosis: INR 2–3 (NEJM 2003;349:1133; J Thromb Haemost 2005;3:848)  
Initial arterial thrombosis: typically INR 2–3 + ASA 81, although some treat to INR 3–4  
Recurrent thrombosis on warfarin: consider INR 3–4 vs. LMWH or fondaparinux (Arth Rheum 2007;57:1487)

Consider ASA prophylaxis for high-risk asx Pt (eg, SLE); no current evidence for NOACs

# DISORDERS OF LEUKOCYTES

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

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

## Neutropenia ( $\text{ANC} <1000/\mu\text{L}$ )

Congenital	Myelokathexis, Shwachman-Diamond-Oski, Chédiak-Higashi, retic dysgen., WHIM syndrome, cyclic neutropenia, monoMAC syndrome ( $\downarrow$ monos, NKs)
Infection	Viral (CMV, EBV, HIV); bacterial (brucella, Rickettsia, TB); malaria
Nutritional	Vit B <sub>12</sub> defic., copper defic.
Drugs and toxins	Chemotherapeutics, clozapine, methimazole, TMP-SMX, NSAIDs, sulfasalazine, phenytoin ( <i>Am J Hem</i> 2009;84:428), alcohol
Neoplasm	MDS, leukemia (AML, ALL, hairy cell, LGL, others)

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

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 (eg, CLL, hairy cell, LGL), lymphoma (eg, mantle cell, folic.)

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

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

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

Infection	Usually parasitic (helminths)
Allergic	Drugs; asthma, hay fever, eczema; ABPA
Collagen vasc dis.	RA, Churg-Strauss syndrome, eosinophilic fasciitis, PAN
Endocrine	Adrenal insufficiency
Neoplasm	HL, CML, mycosis fungoides, carcinomas, systemic mastocytosis
Atheroembolic dis.	Cholesterol emboli syndrome
Hypereosinophilic syndrome	Multiorgan involvement incl. heart & CNS, a/w FIP1L1-PDGFR $\alpha$ fusion ( <i>NEJM</i> 2003;348:1201)

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

Neoplasm	MPN, Hodgkin lymphoma
Alteration in BM or reticuloendothelial compartment	Hemolytic anemia, splenectomy
Inflammation or allergy	IBD, chronic airway inflammation

## Lymphadenopathy

Viral	HIV, EBV, CMV, HSV, VZV, hepatitis, measles, rubella
Bacterial	Generalized (brucellosis, leptospirosis, TB, atypical mycobacteria, syphilis) Localized (streptococci, staphylococci, cat-scratch disease, tularemia)
Fungal and parasitic	Histoplasmosis, coccidioidomycosis, paracoccidioidomycosis Toxoplasmosis
Immunologic	Collagen vascular disease, drug hypersensitivity (eg, phenytoin), serum sickness, histiocytosis X, Castleman's and Kawasaki disease
Neoplasm	Lymphoma, leukemia, amyloidosis, metastatic carcinoma
Other	Sarcoidosis; lipid storage diseases
Factors that favor biopsy	Age ( $>40$ y), size ( $>2$ cm), location (supraclavicular is always abnormal), duration ( $>1$ mo) Consistency (hard vs. rubbery vs. soft) & tenderness are not reliable

**Blood Products and Indications** (*Lancet* 2013;381:1845)

Packed red blood cells (PRBCs) (Annals 2012;157:49)	For acute blood loss or to ↑ O <sub>2</sub> -carrying capacity if end organ ischemia. 1 U PRBC → ↑ Hb by ~1 g/dL. Conservative Hb goal >7 g/dL adequate for UGIB & critically ill Pts ( <i>NEJM</i> 2013;368:11 & 2014;371:1381; <i>BMJ</i> 2015;350:h1354). Controversy remains re: coronary ischemia, although Hb >8 may be adequate ( <i>JAMA Int Med</i> 2013;173:132), but perhaps not peri-cardiac surgery ( <i>NEJM</i> 2015;372:997; <i>Anesth</i> 2016;125:46).
Platelets (plt)	For plt <10k ( <i>NEJM</i> 2010;362:600) or <20k w/ infxn or ↑ bleeding risk or <50k w/ active bleeding or preprocedure. 6 U pooled donor plt ~1 single donor plt apheresis unit (↓ alloimmunization) → ↑ plt ~30–60k. <b>Contraindic:</b> TTP/HUS, HELLP, HIT.
(Annals 2014;162:205)	Refractory if ↑ <5k 30–60' post-plts. Suggests alloimmunization → trial ABO-matched plt. If still refractory ✓ panel reactive Abs to assess utility of HLA-matched plt.
Fresh frozen plasma (FFP)	Contains all coagulation factors. For bleeding due to deficiency of multiple coagulation factors (eg, DIC, TTP/HUS, liver disease, warfarin excess, dilution) or INR >2 preprocedure ( <i>Transfusion</i> 2006;46:1279).
Cryoprecipitate	Enriched for fibrinogen, vWF, VIII and XIII. For bleeding in vWD, factor XIII deficiency or fibrinogen <100 mg/dL.
Irradiated	Prevents donor T-cell proliferation. Use if risk of transfusion-assoc. GVHD (HSCT, heme malignancy, congenital immunodeficiency).
CMV-negative	From CMV-negative donors. For CMV-seronegative pregnant women, transplant candidates/recipients, SCID, AIDS Pts.
Leuko-reduced	WBCs cause HLA alloimmunization and fever (cytokine release) and carry CMV. For chronically transfused Pts, potential transplant recipients, h/o febrile nonhemolytic transfusion reaction, cases in which CMV-negative products are desired but unavailable.
Intravenous immune globulin (IVIg)	Polyvalent IgG from >1000 donors. For postexposure prophylaxis (eg, HAV), certain autoimmune disorders (eg, ITP, Guillain-Barré, MG, ? CIDP), congenital or acquired hypogammaglobulinemia (CVID, CLL).
Therapeutic apheresis	Removes large molec wt subst. (eg, cryoglobulinemia, Goodpasture's, Guillain-Barré, hyperviscosity syndrome, TTP) or cells (eg, leukemia w/ hyperleukocytosis, sx thrombocytosis, sickle cell) from plasma.
Massive transfusion	Large-vol. PRBC → ↓ Ca, ↑ K, ↓ plt, ↑ coags; ratio of PRBC:plt:FFP repletion controversial, follow labs ( <i>J Trauma</i> 2006;60:S91 & 2008;65:272).

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

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

**Transfusion reactions**

- For all reactions (except minor allergic): **stop transfusion**; send remaining blood product and fresh blood sample to blood bank
- Acute hemolytic:** fever, HoTN, flank pain, AKI w/in 24 h. Due to ABO incompatibility → preformed Abs vs. donor RBCs. Rx: IVF, ↑ UOP w/ diuretics, mannitol or dopamine
- Delayed hemolytic:** generally less severe than acute hemolytic; 5–7 d after transfusion. Due to undetected allo-Abs against minor antigens → anamnestic response. Rx: usually no specific therapy required; dx is important for future transfusion
- Febrile nonhemolytic:** fever, rigors 0–6 h post transfusion. Due to Abs vs donor WBCs and cytokines in blood product. Rx: acetaminophen ± meperidine; r/o infection, hemolysis
- Allergic:** urticaria; rarely, **anaphylaxis:** bronchospasm, laryngeal edema, hypotension. Reaction to transfused proteins; anaphylaxis seen in IgA-deficient Pts w/ anti-IgA Abs. Rx: urticaria → diphenhydramine; anaphylaxis → epinephrine ± glucocorticoids
- Transfusion-associated circulatory overload (TACO):** ↑ volume → pulm edema, ↑ BP. Rx: slow transfusion rate, diuretics, O<sub>2</sub>, ± nitrates, ± positive pressure ventilation
- Transfusion-related acute lung injury (TRALI):** noncardiogenic pulmonary edema. Due to donor Abs that bind recipient WBCs, which then aggregate in pulmonary vasculature and release mediators causing ↑ capillary permeability. Rx: see "ARDS."

# MYELODYSPLASTIC SYNDROMES (MDS)

## Myeloid neoplasm overview (Blood 2016;127:2391)

- Categories based on clinical features, morphology, immunophenotyping, and genetics

### WHO 2016 classification of myeloid neoplasms & acute leukemia

Acute myeloid leukemia	Clonal myeloid stem cell (SC) disorder w/ ≥20% blasts
Myelodysplastic syndromes	Dysplastic clonal myeloid SC disorder → cytopenias; <20% blasts, risk of leukemic transformation
Myeloproliferative neoplasms	Nondysplastic multipotent myeloid SC clonal expansion
MDS/MPN neoplasms	Features of MDS & MPN (eg, CMML, atypical CML)
Myeloid/lymphoid malig. w/ eos & rearrangements of PDGFR or FGFR 1 or w/ PCM 1-JAK2	May be responsive to TKI therapy (eg, imatinib) for PDGFR rearrangement
Mastocytosis	Systemic disease, assoc w/ KIT mutations
Myeloid neoplasms w/ germ line predisposition	MDS, MDS/MPN, acute leukemias in background of predisposing germline mutations

## Myelodysplastic syndromes (MDS) overview (Lancet 2014;383:2239)

- Acquired clonal stem cell disorder → ineffective hematopoiesis → **cytopenias, dysmorphic blood cells and precursors**, variable risk of **leukemic transformation**
- Epidemiology: >10,000 cases/y; median age ~70 y; male predominance (1.8x)
- **Idiopathic** or 2° to chemo w/ **alkylating agents**; ↑ risk w/ radiation, benzene
- Clinical manifestations: **anemia** (85%), neutropenia (50%), thrombocytopenia (40–65%)
- Diagnosis: dysplasia (usually multilineage) in peripheral smear (oval macrocytes, **pseudo-Pelger-Hüet anomaly**) and bone marrow (≥10% dysplasia with blasts ± RS)
- Both **cytogenetic** [eg, del(5q), mono 7, del(7q), trisomy 8, del(20q)] and **molecular** abnl (TP53, EZH2, ETV6, RUNX1, ASXL1, SF3B1, DNMT3A) may carry prognostic signif
- Prior to dx MDS: exclude AML (≥20% blasts) and CMML (monos >1 × 10<sup>9</sup>/L); r/o 2° BM Δs (defic. of B<sub>12</sub>, folate, copper); viral infx (eg, HIV); chemo; EtOH; lead, arsenic exposures

### WHO 2016 Classification Systems for MDS (Blood 2016;127:2391)

Classification	WHO 2008	Features
MDS w/ single lineage dysplasia (MDS-SLD)	RCUD (RA/RN/RT)	1 dysplastic lineage, 1–2 cytopenias, <15% RS*, <5% BM/<1% PB blasts, no Auer rods
MDS w/ multilineage dysplasia (MDS-MLD)	RCMD	2–3 dysplastic lineages, 1–3 cytopenias, <15% RS*, <5% BM/<1% PB blasts, no Auer rods
MDS w/ ring sideroblast (MDS-RS)	RARS	≥15% RS or ≥5% RS if SF3B1 mut. is present, <5% BM/<1% PB blasts, no Auer rods
MDS w/ isolated del(5q)	Del(5q)	Del(5q) alone or w/ 1 abnl except -7 or del(7q)
MDS w/ excess blasts (MDS-EB)	RAEB-1 RAEB-2	EB-1: 5–9% BM/2–4% PB blasts, no Auer rods EB-2: 10–19% BM/5–19% PB blasts or Auer rods
MDS, unclassifiable (MDS-U)	MDS-U	w/ 1% PB blasts, single lineage dysplasia & pancytopenia, or defining cytogenetic alteration

Certain cytogenetics [eg, t(15;17), t(8;21), inv16, t(16;16), or MLL rearrangement] classified as AML, regardless of BM blast count. RS, ring sideroblast; BM, bone marrow; PB, peripheral blood. \* <5% RS if SF3B1 mutation.

- Rx (Am J Hematol 2012;87:692): intensity based on IPSS-R (qv), age, performance status (PS)
  - Poor PS, any risk → supportive care (transfusions, G-CSF, Epo, TPO-mimetic, abx prn)
  - Low/intermediate risk → Epo (if Epo level <500); lenalidomide (esp. for 5q syndrome; NEJM 2006;355:1456); DNA hypomethylating agents (azacitidine or decitabine)
  - Intermediate/high risk → DNA hypomethylating agents (survival advantage w/ azacitidine; Lancet Oncol 2009;10:223), combination **chemo** (akin to AML Rx) or **allogeneic HSCT**
  - Hypoplastic MDS (rare) → consider **immunosuppression** (CsA, ATG, pred), HSCT
- Prognosis: IPSS-R correlates with **survival** and **progression to AML**

### Revised International Prognostic Scoring System (IPSS-R) (Blood 2012;120:2454)

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermed	Poor	Very poor
BM blasts (%)	≤2	-	>2 to <5	-	5–10	>10	-
Hb (g/dL)	≥10	-	8 to <10	<8	-	-	-
Plt (k)	≥100	50 to <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-
Total score	≤1.5	>1.5 to 3	>3 to 4.5	>4.5 to 6	>6		
Category	Very low	Low	Intermed	High	Very high		
Median survival (y)	8.8	5.3	3.0	1.6	0.8		

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

- Results from clonal expansion of multipotent hematopoietic stem cell
- Different from MDS in that the cells are not dysplastic (ie, normally developed)
- Categories of MPN: polycythemia vera (PV); essential thrombocythemia (ET); primary myelofibrosis (PM); chronic myelogenous leukemia (CML), BCR-ABL1  $\oplus$ ; chronic neutrophilic leukemia (CNL); chronic eosinophilic leukemia, not otherwise specified; myeloproliferative neoplasms, unclassifiable
- Mutations useful as clonal markers & dx tools:
  - Gain of fxn mutations in **JAK2 V617F** (Janus kinase) frequently present (PV ~95%, ET ~50%, PMF ~50%; NEJM 2005;352:1779)
  - BCR-ABL** fusion in all cases of CML
  - CALR** exon 9 mutation (most MPNs w/o JAK2 or *MPL* mutation, including ~25% of ET, ~35% of myelofibrosis Pts; NEJM 2013;369:2379 & 2391)
  - MPL, TET2, & ASXL 1** mutation w/ lower frequency
  - CSF3R** mutation present in ~60% of CNL

**POLYCYTHEMIA VERA (PV)****Definition**

- $\uparrow$  in RBC mass  $\pm$   $\uparrow$  granulocytes and platelets in the absence of physiologic stimulus

**Etiologies of erythrocytosis**

- Relative  $\uparrow$  RBC ( $\downarrow$  plasma): dehydration; "stress" erythrocytosis (Gaisböck's syndrome)
- Absolute  $\uparrow$  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  $\rightarrow$  often termed "vasomotor symptoms"
  - hyperviscosity** (erythrocytosis): headache, dizziness, tinnitus, blurred vision
  - thrombosis** (hyperviscosity, thrombocytosis): transient visual disturbances (amaurosis, ocular migraine); Budd-Chiari syndrome; erythromelalgia = intense burning, pain and erythema of extremities due to microvascular ischemia;  $\uparrow$  risk of **DVT, MI, stroke**. Risk of thrombosis highly correlated with  $\uparrow$  WBC in PV and ET (see below).
  - bleeding** (abnormal platelet function): easy bruising, epistaxis, GI bleeding  
 $\uparrow$  histamine from basophils  $\rightarrow$  **pruritus**, peptic ulcers;  $\uparrow$  uric acid (cell turnover)  $\rightarrow$  gout
- Signs: **plethora, splenomegaly**, hypertension, engorged retinal veins
- Expression profiling beyond JAK2 may define different phenotypes (NEJM 2014;371:808)

**Diagnostic evaluation**

- Men: Hb  $>16.5$  g/dL or HCT  $>49%$ , women: Hb  $>16$  g/dL or HCT  $>48%$ , or  $\uparrow$  red cell mass
- BM bx  $\rightarrow$  hypercellularity for age, trilineage growth, pleomorphic mature megakaryocytes
- **JAK2 V617F** mutation in ~95% of PV; other Pts typically harbor JAK2 exon 12 mutations
- ✓ Epo to rule out secondary causes of erythrocytosis; if Epo  $\downarrow$ , PV more likely  
If Epo  $\uparrow$ , then ✓ SaO<sub>2</sub> or PaO<sub>2</sub>, carboxyhemoglobin, BM exam
- $\pm$   $\uparrow$  WBC, platelets, basophils;  $\uparrow$  uric acid, leukocyte alkaline phosphatase, vit B<sub>12</sub>
- Peripheral smear  $\rightarrow$  no morphologic abnormalities

**Treatment**

- **Phlebotomy** to goal Hct  $<45\%$  (NEJM 2013;368:22), consider  $<42\%$  in women
- **Low-dose ASA** in all Pts (NEJM 2004;350:114)
- **Hydroxyurea** if high risk of thrombosis (age  $\geq 60$ , prior thrombosis) or symptomatic thrombocytosis (plt  $>1.5 \times 10^9/\mu\text{L}$ ), or if inadequate Hct by phlebotomy alone
- Ruxolitinib (JAK1/2 inhibitor) if poor response, intolerant of hydroxyurea (NEJM 2015;372:426)
- PEG IFN $\alpha$ -2a yields high response rate w/ limited toxicity (Blood 2008;112:3065)
- Supportive: allopurinol (gout), H<sub>2</sub>-blockers/antihistamines (pruritus)

**Prognosis**

- Median survival w/ Rx ~13.5 y (Blood 2014;124:2507);  $\uparrow$  age, WBC, additional acquired somatic mutations  $\rightarrow$  worse prognosis (Haematol 2013;160:251)
- Post-PV myelofibrosis (spent phase) occurs in 10–20% of cases, usually after 10 y
- Risk of transformation into acute leukemia (<2–5%; higher if previous cytoreductive chemo)

**ESSENTIAL THROMBOCYTHEMIA (ET)****Definition**

- Sustained  $\uparrow$  in platelets ( $>450,000/\mu\text{L}$ )  $\pm$   $\uparrow$  RBC and granulocytes

**Etiologies of thrombocytosis**

- 1° = ET or other MPN; myelodysplastic syndromes (5q-syndrome); RARS-T
- 2° = **reactive thrombocytosis**: inflammation (RA, IBD, vasculitis), infection, acute bleeding, iron deficiency, postsplenectomy, neoplasms (eg, Hodgkin lymphoma)
- Of patients with plt >10<sup>6</sup>/μL, <1 in 6 will have ET

**Clinical manifestations (also see "Polycythemia Vera")**

- Thrombosis with erythromelalgia (risk of thrombosis highest in Pts with leukocytosis), bleeding, pruritus; mild splenomegaly; migraine, TIA; early fetal loss

**Diagnostic evaluation**

- Peripheral smear: large hypogranular platelets
- BM bx: megakaryocytic hyperplasia; absence of Philadelphia chromosome and very rarely, minor increase in reticulin fibers; normal iron stores
- **JAK2 V617F** present in ~50% of ET; **MPL** or **CALR** mutations in majority of JAK2 wt
- Patients should not meet WHO criteria for diagnosis of CML, PV, PMF or MDS

**Treatment of ET**

Risk	Features	ASA 81 mg qd	Cytoreduction
<b>Low</b>	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
<b>Int.</b>	Neither low nor high	±	Consider if plt >1.5 × 10 <sup>6</sup> /μL
<b>High</b>	Age ≥60 or h/o thrombosis or plt >1.5 × 10 <sup>6</sup> /μL	⊕ (consider holding if plt >1 × 10 <sup>6</sup> /μL and lab evid. of acquired vWD)	<b>Hydroxyurea.</b> Goal plt <0.4 × 10 <sup>6</sup> /μL or sx free. IFNα if young or pregnant.

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

**Prognosis**

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

**PRIMARY MYELOFIBROSIS (PMF)****Definition**

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

**Etiologies of myelofibrosis**

- Myeloproliferative neoplasm = primary myelofibrosis; post-PV/ET myelofibrosis
- Other hematologic (CML, AML, ALL, MDS) and solid cancers (breast, prostate)
- Autoimmune (SLE and other collagen vascular disorders)
- Toxins (benzene); radiation; granulomas (TB, fungal, sarcoid); deposition dis. (Gaucher's)

**Clinical manifestations (BJH 2012;158:453)**

- Ineffective erythropoiesis → anemia; extramedullary hematopoiesis → **massive splenomegaly** (abdominal pain, early satiety) ± hepatomegaly
- Tumor bulk and ↑ cell turnover → fatigue, weight loss, fever, sweats

**Diagnostic evaluation (JAMA 2010;303:2513; Blood 2016;127:2391)**

- Anemia with variable WBC and platelet counts
- Peripheral smear → "**leukoerythroblastic**" (teardrop cells, nucleated RBCs, immature WBCs); large abnormal platelets
- BM aspirate → "**dry tap**"; BM bx → **severe fibrosis**, replacement by reticulin & collagen
- **JAK2 V617F** in 45–50%; **CALR** mut in 45–50%, **MPL** mut in 7–10%, triple neg in 1–2%
- No BCR-ABL translocation; also does not meet criteria for PV or MDS

**Treatment (Blood 2011;117:3494)**

- In absence of adverse prognostic factors (eg, anemia or sx) → no treatment
- Allogeneic HSCT only potential cure → consider in young Pts with poor prognosis
- Supportive care: **transfusions**; inconsistent benefit from androgens or Epo; ? splenectomy if refractory to transfusions, failed chemoRx, painful splenomegaly
- Hydroxyurea for significant leukocytosis or thrombocytosis
- Ruxolitinib (JAK1/JAK2 inhibitor) ↓ sx, ↓ splenomegaly, ↑ survival (NEJM 2012;366:787 & 799)
- Thalidomide and lenalidomide ± steroids may improve red cell count
- Imetelstat (telomerase inhib) under investigation (NEJM 2015;373:908)

**Complications and prognosis**

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

## ACUTE LEUKEMIA

**Definition**

- Clonal proliferation of hematopoietic progenitor with failed differentiation into mature elements → ↑ blasts in bone marrow and periphery → ↓ RBCs, platelets and neutrophils

**Epidemiology and risk factors**

- Acute myelogenous (AML): ~21k cases/y in U.S.; median age 67 y; >80% of adult acute leukemias
- Acute lymphocytic (ALL): ~6k cases/y in U.S.; median age 14 y but 2<sup>nd</sup> peak in older adults
- Risk factors: **radiation, chemo** (alkylating agents, topo II inhib), benzene, smoking, ? rising from acquired somatic mutations and clonal hematopoiesis (NEJM 2014;371:2477)
- Secondary to acquired hematopoietic dis.: MDS, MPN (esp. CML), aplastic anemia, PNH
- Inherited: Down's, Klinefelter's, Fanconi's anemia, Bloom syndrome, ataxia telangiectasia

**Clinical manifestations**

- Cytopenias → **fatigue** (anemia), **infection** (neutropenia), **bleeding** (thrombocytopenia)
- More common in **AML**

**leukostasis** (more often when blast count >50,000/µL): occluded microcirculation → local hypoxemia and hemorrhage → dyspnea, hypoxia, headache, blurred vision, TIA/CVA; look for **hyperviscosity retinopathy** (vascular engorgement, exudates, hemorrhage)

**DIC** (esp. with APL); leukemic infiltration of skin, gingiva (esp. with monocytic subtypes); chloroma: extramedullary tumor of leukemic cells, virtually any location

- More common in **ALL**:

bony/lumbar pain, lymphadenopathy, hepatosplenomegaly (also in monocytic AML)  
CNS involvement (up to 10%): cranial neuropathies, N/V, headache  
anterior mediastinal mass (esp. in T-cell); tumor lysis syndrome (qv)

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

- Peripheral smear:** anemia, thrombocytopenia, variable WBC + circulating **blasts** (seen in >95%; ⊕ Auer Rods in AML), peripheral flow cytometry for blast origin (ALL vs. AML)
- Bone marrow:** hypercellular with >20% blasts; test for cytogenetics and flow cytometry
- Presence of certain **cytogenetic anomalies**, eg, t(15;17), t(8;21), inv(16) or t(16;16), are sufficient for dx of AML regardless of the **blast count**
- ✓ for tumor lysis syndrome (rapid cell turnover): ↑ UA, ↑ LDH, ↑ K, ↑ PO<sub>4</sub>, ↓ Ca
- Coagulation studies to r/o DIC: PT, PTT, fibrinogen, D-dimer, haptoglobin, bilirubin
- LP (w/ **co-admin of intrathecal chemotherapy** to avoid seeding CSF w/ circulating blasts) for Pts w/ ALL (CNS is sanctuary site) and for Pts w/ AML w/ CNS sx
- TTE if prior cardiac history or before use of anthracyclines
- HLA typing** of Pt, siblings > parents/children for potential allogeneic HSCT candidates

**ACUTE MYELOGENOUS LEUKEMIA (AML)** (NEJM 2015;373:1136)**Classification** (WHO; Blood; 2016;127:2391)

- Features used to confirm myeloid lineage and subclassify AML to guide treatment:  
morphology: **blasts**, ⊕ **granules**, ± **Auer rods** (eosinophilic needle-like inclusions)  
cytochemistry: ⊕ **myeloperoxidase** and/or **nonspecific esterase**
- Immunophenotype: myeloid: CD13, CD33, CD117; monocyte: CD11b, CD64, CD14, CD15
- Cytogenetics: important for prognosis. Intermed. risk = no favorable/unfavorable features.

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

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

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

	Favorable prognosis	Unfavorable prognosis
Karyotype	t(15;17) in APL; t(8;21); inv(16)/t(16;16)	-5; -7; 3q26 aberrations; t(6;9); 11q23 aberrations; complex karyotype
Gene mutations	<i>NPM1</i> +; biallelic <i>CEBPA</i>	<i>FLT3</i> ITD; <i>MLL</i> -PTD; <i>TP53</i> , <i>RUNX1</i>

Recurrent somatic mutations: DNMT3A; TET2; ASXL1; RAS; WT1; IDH1/2; spliceosome