

Housestaff Manual

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It is an honor to present the 27th Edition of the **MGH Department of Medicine Housestaff Manual**. We submit this manual, which we view as a great tradition of the Internal Medicine Residency Program, to function as a resource for medical residents and other clinicians at MGH. We hope that it exemplifies the energy, compassion, and spirit of growth with which MGH medical residents approach their training and their profession.

The Housestaff Manual shares lessons from our clinical experiences on the medical services, including our annual review of the literature. Each year, this book reflects the diligent work of the residents, whose contributions join them with past generations of house officers.

We extend our gratitude to those residents who contributed their time and expertise to edit entire sections of this manual. Multiple sections have had significant updates and there are several new articles this year.

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We would like to thank the many faculty, fellows, and administrators who assisted with this book. In addition, we are grateful to the residents in the ENT, General Surgery, Neurology, Ophthalmology, Radiology, and Urology programs who lent their expertise to the relevant sections.

Our work would not be possible without the countless hours of work by the previous editors of the MGH Department of Medicine Housestaff Manual. We hope we have lived up to their example.

1994	Albert Shaw & Ravi Thadhani	2009	David Dudzinski & Elizabeth Guancial
1995	Barry Kitch	2010	Roby Bhattacharya & Paul Cremer
1996	Sam Hahn	2011	Kerry Massman & Vilas Patwardhan
1998	Marc Sabatine	2012	Michelle Long & Mihir Parikh
2000	Sherri-Ann Burnett & Bill Lester	2013	Molly Paras & David Sallman
2001	Jose Florez	2014	Zaven Sargsyan & George Anesi
2003	Andrew Yee	2015	Ang Li & Jehan Alladina
2004	Ishir Bhan	2016	Nino Mihatov & Tessa Steel
2005	Aaron Baggish & Yi-Bin Chen	2017	Michael Abers & C. Charles Jain
2006	Bobby Yeh & Eugene Rhee	2018	Kelsey Lau-Min & Jonathan Salik
2007	Rajeev Malhotra	2019	Melissa Lumish & Shilpa Sharma
2008	Maha Farhat & W. Steve Sigler	2020	Jacqueline Henson & Alexandra Wick

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It has been an incredible honor to edit the Housestaff Manual. We look forward to the contributions of future generations of authors and editors in the years to come.

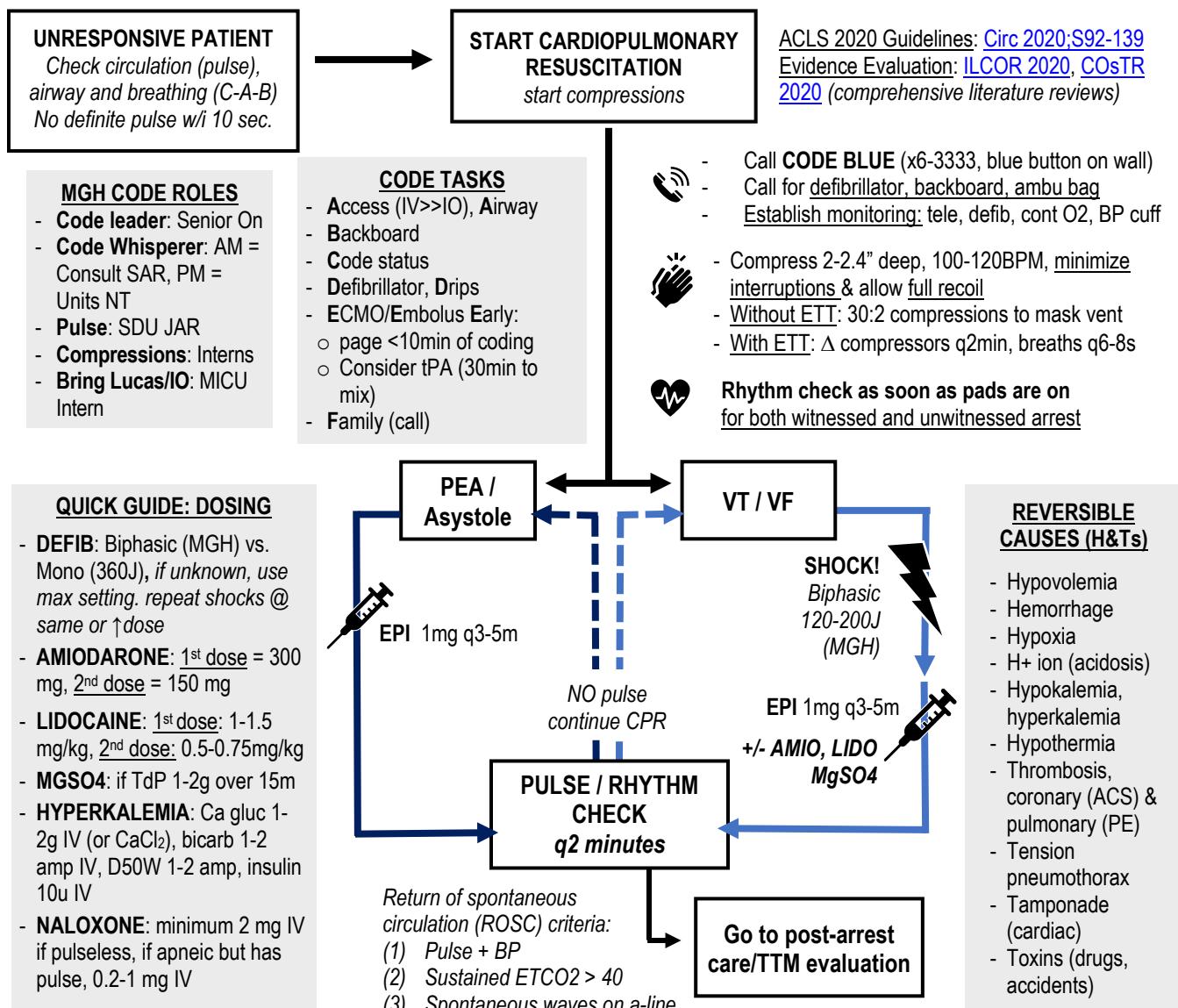
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June 2021

As with any other medical reference, this manual is not intended to provide specific clinical care decisions in any individual case and should not substitute for clinical judgment. Please continue to consult your colleagues and supervisors, as well as the primary literature, whenever possible. We hope to provide guidance in the form of peer education and a forum for future experts to share their knowledge and hone their teaching craft for the benefit of their colleagues. We encourage you to use the manual, not only as a quick reference, but also as a teaching tool, a source of relevant publications, and a jumping-off point for personal exploration. Although we have reviewed every page, errors may exist. Please inform next year's editors [here](#) to ensure these errors are corrected.

MGH Housestaff Manual

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ACLS LOGISTICS & UPDATES

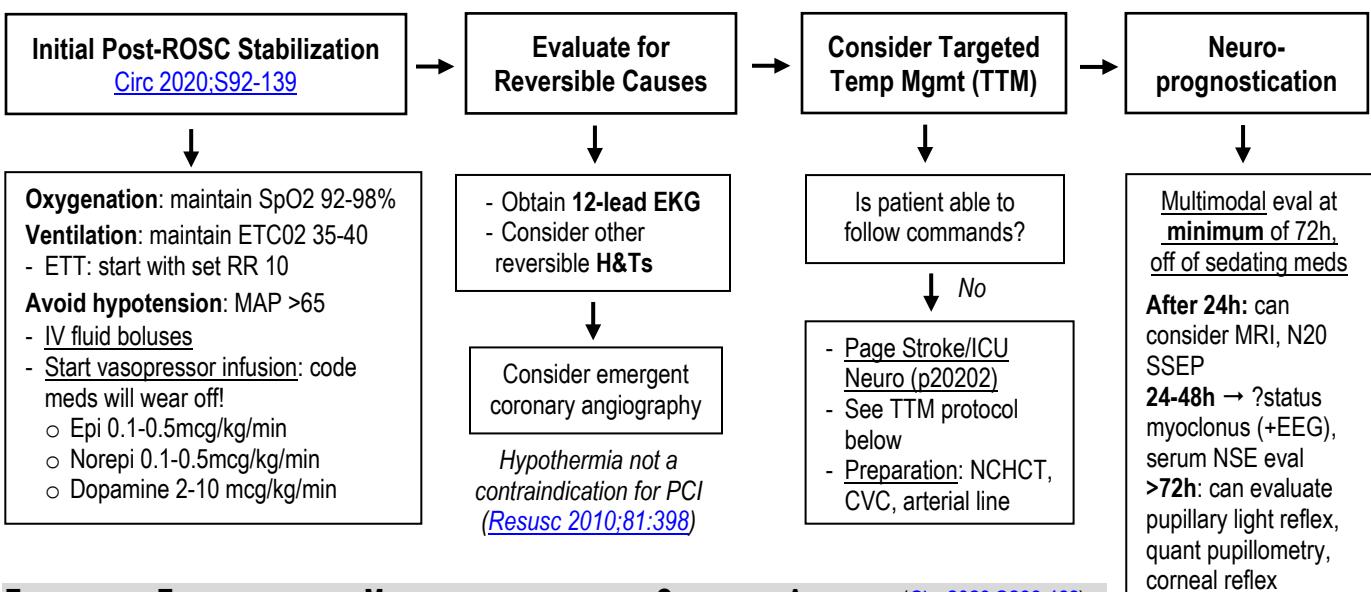
- ACCESS: try IV first, IO if necessary or IV not feasible; c/f reduced drug delivery esp with pre-tibial placement ([AHA 2020 ACLS](#))
- LABS TO ORDER: stat ABG with K & Hgb, CBC, BMP, LFTs, lactate, T&S, coags, fibrinogen, cardiac enzyme
- MONITORING: consider capnography during CPR, keep ETCO₂ at least >10mm H₂O, ideally >20
- PROGNOSTICATION: ETCO₂ <10 mmHg in intubated pts after 20min CPR ~90% sensitive for no ROSC
- PREGNANT WOMEN: new 2020 update: apply continuous left lateral uterine displacement, advise against fetal monitoring during CPR, prep for perimortem delivery early, suggest delivery if no ROSC within 5min, TTM should still be considered with ROSC
- VSE PROTOCOL: vasopressin 20U with first 5 doses of epi + hydrocortisone 200mg x1; not currently used at MGH

Thrombolysis for Known or Suspected PE During Code

- **Alteplase (tPA)**
 - Pulseless: 50mg IV/IO bolus over 2min, may repeat 50mg IV/IO in 15min
 - Pulse present: 100mg infusion over 2h
- **Reteplase:** 10U IV, may repeat 10U in 30min
- **Contraindications (absolute):** prior ICH at any time, ischemic CVA or head trauma within 3mo, known intracranial neoplasm or AVM, suspected aortic dissection or active bleeding
- **Will need anticoagulation after lysis** for compensatory up-regulation of pro-coagulant factors. ASA 325mg + UFH or LMWH. If already on heparin gtt, d/c infusion and restart without bolus after lysis (if PTT<100). If not on heparin, start with bolus
- **Must continue cardiac arrest protocol for at least 15 min** after tPA infusion to give time to work

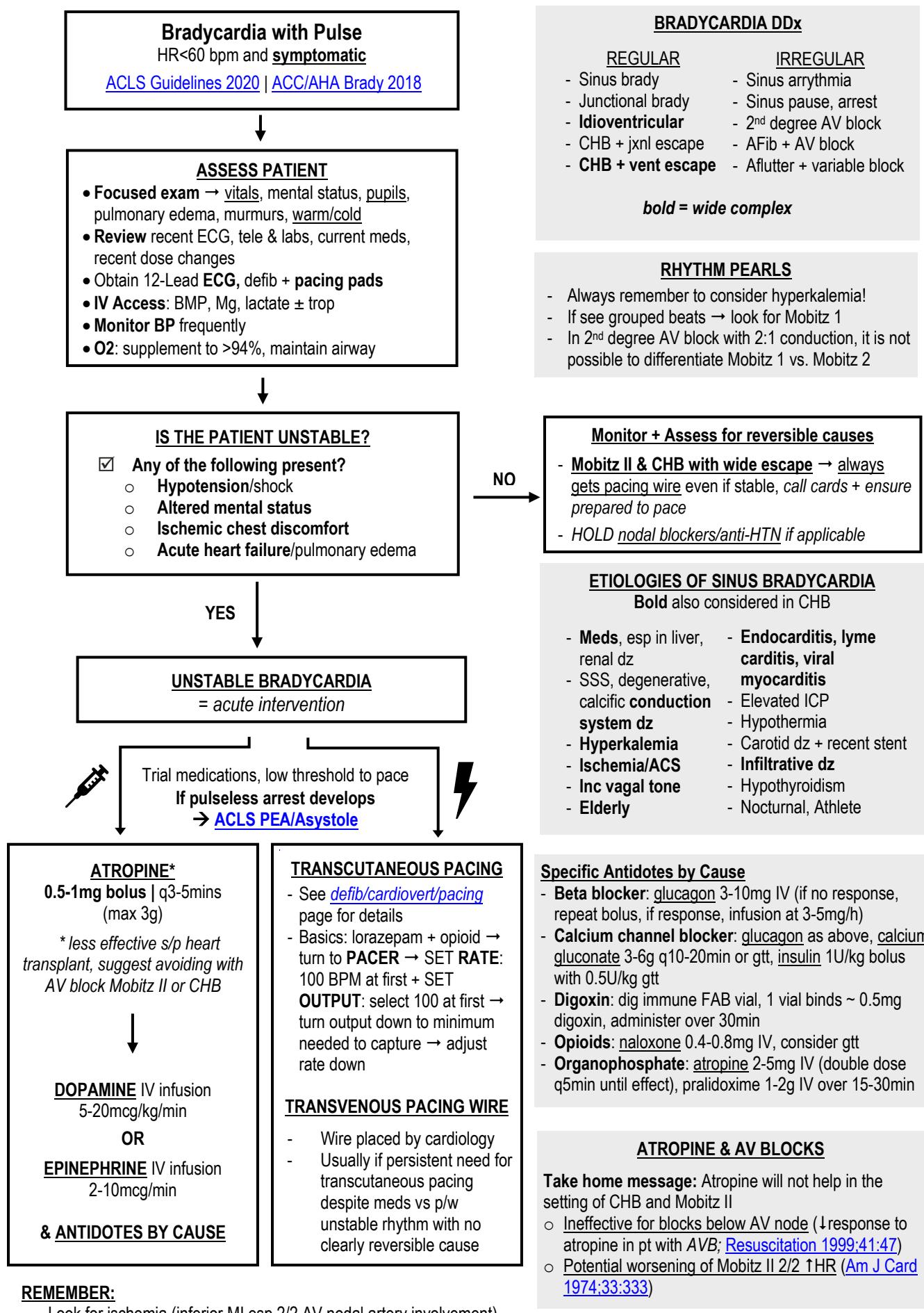
ECMO for Cardiac Arrest

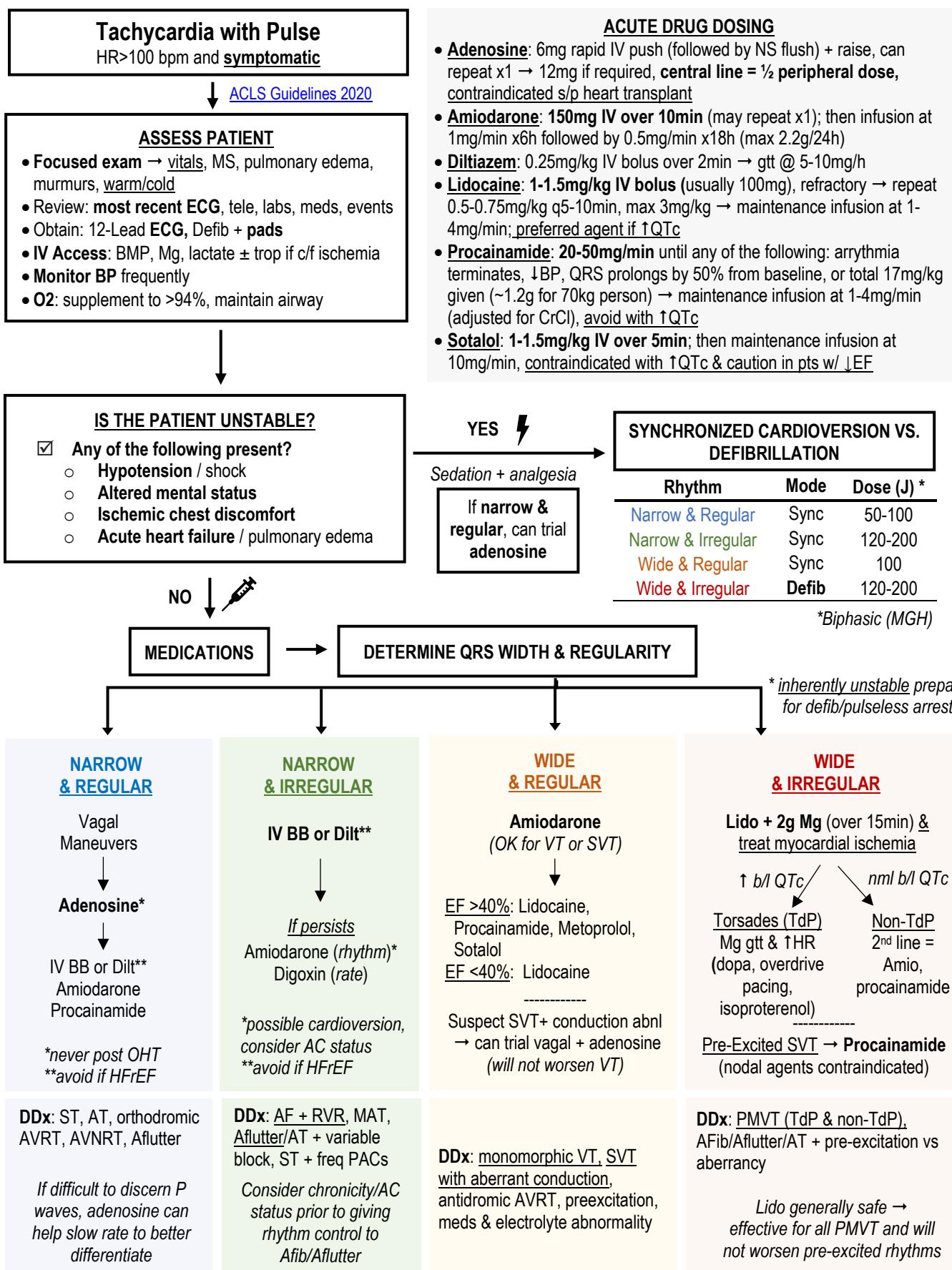
- Consider if possible reversible cause to arrest and ECMO a bridge to definitive treatment
 - At MGH, recommended to contact ECMO team <10 minutes from code initiation. STAT page "ECMO Consult MGH" or use "MGH STAT" app to call consult and for MGH ECMO guidelines
 - No RCTs, all data observational
[Circ 2019;S881-894](#); [Intensive Care Med 2016;42:1922](#)
- ▽ See [ECMO](#)



NEURO - PROGNOSTICATION ([Lancet Neurol 2016;15:597](#); [Circ 2020;S266-468](#)) (also see [Neuroprognostication](#))

- Emphasis on multimodal approach to neuroprognostication, without reliance on any specific modality alone
- Recommended Markers of Poor Neurologic Outcomes
 - Exam:** absence of pupillary light reflexes (>72h post arrest), status myoclonus (72-120h post arrest)
 - Blood markers** (should not be used alone, no cutoff established): high neuron specific enolase (24h, 48h, & 72h post-ROSC)
 - Imaging:** MRI (extensive restriction/diffusion, 2-6d post arrest), CT (reduced gray-white ratio, <2h post arrest if no TTM)
 - Neuro testing:** bilateral N20 SSEP absence (24-72h post arrest), EEG with absence of reactivity, persistent burst suppression, or intractable status epilepticus (72h post arrest)
- In-hospital mortality at 72h post-rewarming (100% if ≥2 criteria present) ([Ann Neurol 2010;67:301](#))
 - unreactive EEG (most helpful)**
 - bilaterally absent SSEP
 - early myoclonus
 - incomplete recovery of brainstem reflexes





Cardiology

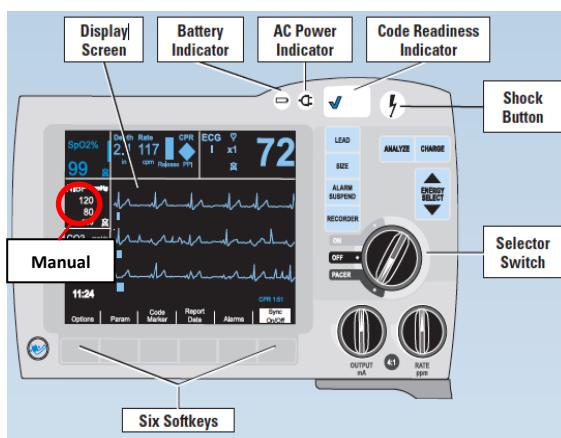
ACLS: Defibrillation/Cardioversion/Pacing

EXTERNAL DEFIBRILLATION/CARDIOVERSION/TRANSCUTANEOUS PACING

- About the device:** the Zoll R Series is on all code carts & ICUs at MGH. This device allows for external defibrillation, cardioversion, and pacing with additional benefits (e.g. display ET-CO₂, CPR quality feedback, & upload rhythm strips into Epic)
- Additional supplies/resources:** Ambu bag, intubation equipment, RICU staff, backboard, suction
- Medications:** use procedural sedation (typically 50mcg fentanyl → 2mg midazolam) when possible, call Cardiac Anesthesia & pharmacy early. Morphine 4mg IV → lorazepam 2mg IV are reasonable alternatives in acute situations (often readily available)

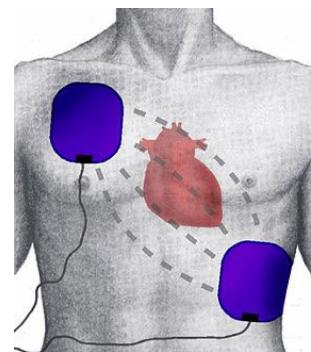
DISPLAY/OPERATION OF ZOLL R SERIES

- Remove all clothing covering the patient's chest. Dry chest if necessary. If the patient has excessive chest hair, shave it to ensure proper adhesion of the electrodes
- Attach hands-free therapy electrodes in anteroapical position (pictured) or anteroposterior position



Pearls:

- CPR ok to perform while pacing, take R-sided pulses (L not reliable)
- Failure to capture? Increase output, ensure pads are in correct location, consider ddx (barrel chest, COPD, tamponade/pericardial effusion, acidosis, hyperK, obesity, MI, cardiac drug tox [dig, anti-arrhythmic])
- Failure to sense? Only happens with synchronous pacing – can switch to asynchronous pacing, reposition pads



Defibrillation	Synchronized Cardioversion	Transcutaneous Pacing
Indications: pulseless VT or VF	Indications: Unstable SVT or VT	Indications: Unstable bradycardia
FIRST turn the Selector Switch to ON . Then press Manual (bottom left soft key) to change to ALS		
<p>1. The default energy selection is 120 J. Use Energy Select (UP) and (DOWN) arrow keys to increase the energy.</p> <p>2. If there is a shockable rhythm on the pulse/rhythm check, press Charge. Continue CPR while charging.</p> <p>3. Once charged, the red shock button illuminates. Shout “Clear!” then <u>press and hold</u> the illuminated Shock button at the top right of the console.</p> <p>4. Resume CPR for 2 minutes before the next pulse/rhythm check</p>	<p>1. Select the desired energy using the up and down arrow keys on the front panel</p> <ul style="list-style-type: none"> <u>Narrow, regular:</u> 50-100 J (atrial flutter often converts with 50 J) <u>Narrow, irregular:</u> 120-200 J (atrial fibrillation typically requires 150 J) <u>Wide, regular:</u> 100 J <u>Wide, irregular:</u> 150-200 J (defib dose) <p>2. Press the Sync On/Off button</p> <ul style="list-style-type: none"> Confirm that a Sync marker (↓) appears on the monitor above each detected R-wave to indicate where discharge will occur If necessary, use the LEAD and SIZE buttons to establish settings that yield the best display <p>3. Press the CHARGE button on the front panel. Ensure patient is “clear”</p> <p>4. <u>Press and hold</u> the illuminated SHOCK button on the front panel. The defibrillator will discharge with the next detected R wave</p> <p>5. If additional shocks are necessary, increase the energy level as needed</p> <ul style="list-style-type: none"> Confirm that a Sync marker (↓) appears above each R-wave; you may need to press Sync between shocks 	<p>1. PACER appears as an option on the Selector Switch. Turn to PACER</p> <p>2. Set the PACER RATE to a value 10-20 bpm higher than the patient's intrinsic heart rate. If unknown or absent intrinsic rate, use 100 bpm</p> <ul style="list-style-type: none"> Observe the pacing stimulus marker on the display and verify that it is well-positioned in diastole <p>3. Increase PACER OUTPUT until the paced beats demonstrate capture (“threshold”); the output mA value is displayed on the screen.</p> <ul style="list-style-type: none"> Capture = widened QRS complex + loss of underlying intrinsic rhythm <p>4. Set the PACER OUTPUT to the lowest setting that maintains consistent capture</p> <ul style="list-style-type: none"> Usually ~10% above threshold (typical threshold: ~40-80 mA) Pressing and holding the 4:1 button temporarily withdraws pacing stimuli, thereby allowing you to observe pt's underlying EKG rhythm & morphology Treat underlying cause and/or pursue transvenous/permanent pacing

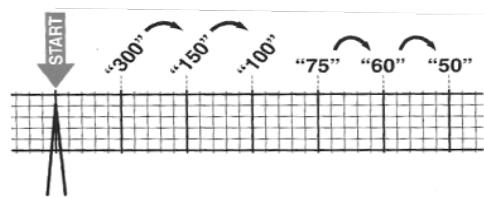
Cardiology

EKG Interpretation

Approach all EKGs systematically. Note rate, rhythm, QRS axis, intervals, complexes, chambers, ischemia/infarction. Compare with prior EKG

RATE (atrial, ventricular)

- If rhythm regular, use the counting method (300 / #large boxes)
- If rhythm irregular, count R waves, multiply by 6 (EKG printout records 10s)
- Normal 60-100 bpm; <60 = bradycardia, >100 = tachycardia

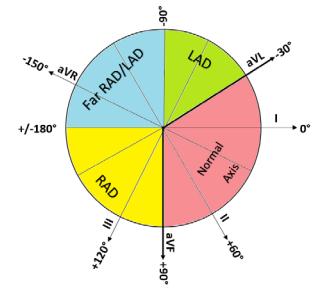


RHYTHM (regular or irregular; sinus vs non-sinus)

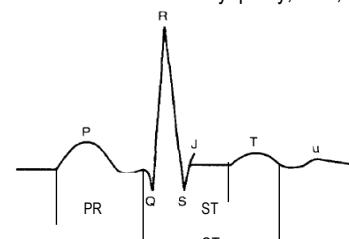
- Sinus rhythm** = P before every QRS and QRS following every P, regular w/ rate 60-100, P wave upright in I, II, aVF, V5-V6
- P waves/morphology**: determine 1) if **P wave** is present (best leads to visualize P wave are II and V1), 2) **atrial rate** (100-180: sinus tachycardia; 140-220: atrial tachycardia, AVNRT, AVRT; 260-320: atrial flutter), and 3) **axis** (e.g. P wave upright in II, biphasic V1)
- QRS morphology**: narrow (<120 ms) = supraventricular rhythm; wide (>120 ms) = aberrant supraventricular conduction or ventricular origin
- P wave/QRS complex association**: if not 1:1, determine if number of P>QRS (AV block) or P<QRS (accelerated junctional or ventricular rhythm). If P precedes QRS, evaluate **PR interval**. If P after QRS, evaluate **RP interval**. Determine if PR or RP interval is fixed or variable
 - AVB**: first degree (PR >200ms); second degree Mobitz I/Wenckebach (PR progressively longer until dropped QRS); second degree Mobitz type II (sudden dropped QRS without PR lengthening); third degree (dissociation of P and QRS)

QRS AXIS (use direction of QRS complex)

Axis Deviation	Lead I	Lead II	Lead aVF	Differential Diagnosis
Normal (-30 to +90°)	⊕	⊕	⊕/-	
Leftward (-30 to -90°)	⊕	-	-	Normal variant, mechanical shifts, LVH, LBBB, LAFB, congenital heart disease, emphysema, hyperK, ventricular ectopic rhythms, WPW, inferior MI
Rightward (+90 to +180°)	-	⊕	⊕	Normal variant, mechanical shifts, RVH, LPFB, dextrocardia, ventricular ectopic rhythms, WPW, lateral MI (RBBB rarely causes RAD)
Extreme/Northwest (180 to -90°)	-	-	-	Lead transposition, ventricular ectopic rhythms, hyperK, artificial pacing, severe RVH



- Clockwise/counterclockwise rotation ("R wave progression")**: R wave amplitude typically increases from V1 to V5, with transition of R>S in amplitude at V3 or V4. **CCW**: transition occurs prior to V3 due to RVH, WPW, LAFB, posterior MI. **CW**: transition occurs after V4 due to cardiomyopathy, LVH, LBBB, anterior MI. Both rotations are nonspecific and can be normal ([Am Heart J 2004;148:80](#))
- Low voltage**: average QRS amplitude <5 mm in I, II, III **and** <10 mm in precordial leads
 - DDx**: obesity, pericardial effusion, pneumothorax, COPD, restrictive or infiltrative CM (particularly amyloidosis), severe hypothyroidism, or anasarca



COMPLEXES AND INTERVALS ([Circ 2009;119:e241](#))

- P wave**: right and left atrial depolarization. Normal duration <120ms
- PR interval**: atrial depolarization, AV node and His-Purkinje conduction. Normally 140-200ms, changes with rate (shortened at faster rates, longer at lower rates d/t autonomic effects on AV nodal conduction)
- QRS**: ventricular depolarization. Normal duration 60-110ms, not influenced by HR. QRS 100-120ms = incomplete BBB or intraventricular conduction delay (IVCD). QRS >120ms = BBB, ventricular activation (PVC, VT, fusion beats, WPW, paced beats), hyperK, Na channel poisoning, aberrancy, hypothermia

LAFB: left axis deviation, QRS <120, qR in I, aVL and rS in II, III, aVF. Common, nonspecific
LPFB: right axis deviation, QRS <120, rS in I, aVL and qR in II, III, aVF. No alternate reason (RVH, emphysema, lateral MI, PE). Rare to see in isolation, usually occurs with RBBB
Bifascicular block: RBBB with either LAFB or LPFB

RBBB: QRS >120, rSR' in V1, wide qRS in V6, shallow broad S in I



LBBB: QRS >120, wide negative QS in V1, wide tall R in V6



- ST segment**: represents a time of electrical silence. See below
- T wave**: ventricular repolarization, with a slow upstroke and a rapid return to the isoelectric line after peaking. Usually asymmetric and in the same direction as the QRS. Should have smooth contours (bumps in T are usually buried P waves)
- U wave**: occurs in the same direction as the T wave, rate-dependent (shorter at faster rates); **DDx**: bradycardia, hypoK/Mg/Ca, hypothermia
- QT interval**: ventricular depolarization and repolarization. Excludes U wave unless fused with T wave. Rate-dependent (shortened at faster rates). Normal <440ms (M) and <460ms (F). Reassuring if QT is less than half R-R interval with normal HR

CHAMBER ENLARGEMENT ([Circ 2009;119:e251](#)) All have low Sn and Sp

- LVH**: Sokolow-Lyon criteria: S in V1 + R in V5 or V6 ≥35mm **OR** R in aVL ≥11mm. Cornell criteria: S in V3 + R in aVL >28mm (M) or >20mm (F). For non-voltage based criteria consider [Romhilt-Estes score](#)
- RVH**: R>S or R ≥7mm in V1, S ≥7mm in V5 or V6
- LAE**: negative P wave in V1 >1mm wide and deep, total P wave duration >110ms
- RAE**: P wave >2.5mm in II

ISCHEMIA/INFARCTION (JACC 2009;53:1003)

- Analyze abnormalities along the vectors of ventricular depolarization and repolarization (QRS-ST-T)
- T wave abnormalities:** hyperacute, symmetric T waves can be found within minutes, followed by T wave inversions ($\geq 1\text{mm}$ in 2 contiguous leads). TWI not abnormal if only in aVR, V1 or III. Isolated TWI in aVL may indicate mid-LAD lesion vs inferior MI (J Emerg Med 2014;46:165)
 - TWI DDx:** myocardial ischemia (symmetric), prior MI, acute PE (RV strain pattern: TWI V1-V4, II, III, aVF, RBBB, S1Q3T3), intracranial pathology ("cerebral T waves", asymmetric), myocarditis, pericarditis, BBB pattern, V-paced, LVH with "strain", normal variant, digoxin effect
 - De Winter's T waves: 2% of STEMIs present with tall, symmetric T waves + $>1\text{mm}$ STD at J point in precordial leads + 0.5-1mm STE in aVR c/w acute LAD occlusion (NEJM 2008;359:2071)
- ST depression:** suggests subendocardial injury, $\geq 0.5\text{mm}$ below the baseline (PR segment), measured 80ms after the J point in 2 contiguous leads
 - Downsloping or horizontal = more ominous. STD do not localize to territories (Circ Res 1998;82:957)
 - Always look for STE to rule out reciprocal STD. STD in V1-V3 can be posterior MI (check posterior leads)
- ST elevation:** suggests transmural ischemia, $\geq 0.1\text{mV}$, except for leads V2-V3 ($\geq 2\text{mm}$ in M $\geq 40\text{y}$ and $\geq 1.5\text{mm}$ in F), use PR segment (isoelectric interval), measured at the J point
 - Differential Diagnosis** (NEJM 2003;349:2128; Annals 2004;141:858; NEJM 2004;351:2195)

Diagnosis	Characteristic ECG Findings
Acute STEMI	STE in ≥ 2 contiguous leads in coronary distribution (see table), reciprocal STD
LVH	Concave STE in V1-V3 with STD and TWI in I, aVL, V5-V6, voltage criteria as above
LBBB	Concave STE in V1-V3, discordant with negative QRS
Acute pericarditis	Diffuse STE (usually $<5\text{mm}$), PR depression, amplitude of STE:T wave (in mm) >0.26 is specific
Printzmetal's angina/vasospasm	Transient STE in coronary distribution as in STEMI but are transient
Acute PE	STE in inferior and anteroseptal leads, mimics acute MI, complete or incomplete RBBB
Stress-induced cardiomyopathy (Takotsubo's)	Diffuse STE in precordial leads w/o reciprocal inferior STD, STE followed by deep TWI
Ventricular aneurysm	Persistent STE after MI, often with abnormal Q waves
Early repolarization	J point elevation $\geq 1\text{mm}$ in 2 contiguous leads (esp V4), slurred/notched, reciprocal STD in aVR
Brugada syndrome	rSR' and downsloping STE in V1-V2 (see below)
Male pattern	1-3mm concave STE, often highest in V2
Normal variant	STE in V3-V5, TWI, short QT, high QRS voltage
Hyperkalemia	STE in V1-V2, wide QRS, tall/peaked T waves
Cardioversion	Marked (often $>10\text{mm}$) and transient following DCCV

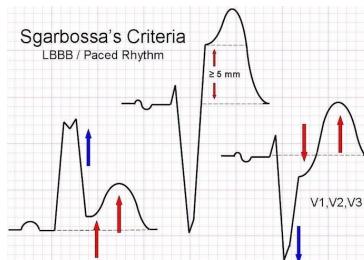
○ Coronary Distribution

EKG Lead	Territory	Coronary Vessel
V1-V2	Anteroseptal	Proximal-mid LAD
V5-V6	Apical	Distal LAD, Distal LCx, RCA
I, aVL	Lateral	LCx (proximal)
II, III, aVF	Inferior	RCA (85%), LCx
V7-V9	Posterior	LCx > RCA
V4R	RV	RCA, LCx
aVR		L main or 3vD

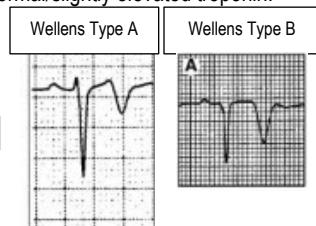
Modified Sgarbossa Criteria:

To diagnose acute MI w/ LBBB (does not apply to pacers). Below = traditional version (need 3pts)

- Concordant STE $>1\text{mm}$ in any lead = 5 points
- Discordant STE $>5\text{mm}$ in any lead = 2 points
- STD $>1\text{mm}$ in V1-V3 = 3 points

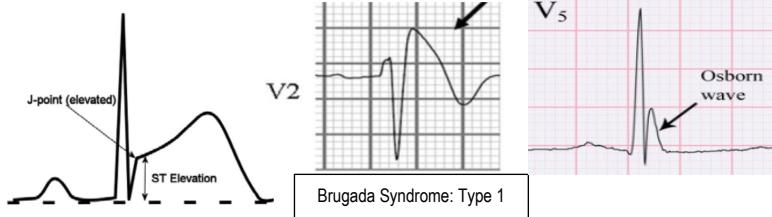


- Q wave:** usually a marker of scar, pathologic Q waves must be deep ($>1\text{mm}$), 25% height of QRS, and 40ms long. More likely 2/2 prior MI if inverted T wave in same lead. Small "septal" Q physiologic in V5, V6, I, aVL
- Wellen's Syndrome:** sign of critical proximal LM or LAD lesion, 75% MI in $<2\text{w}$. Often pain free with h/o angina. Normal/slightly elevated troponin. Type A: 25% biphasic (up then downsloping morphology) T waves in V2 and V3. Type B: 75% symmetric, deeply inverted precordial T waves. Isoelectric or minimally elevated ($<1\text{mm}$) ST segment. No precordial Q waves (Am Emerg Med 2002;20:7; Am Heart J 1982;103:730)



OTHER

- J-Point Elevation Syndromes:** J point is when QRS transitions to ST segment
 - Early repolarization pattern:** benign STE in absence of chest pain, terminal QRS slur, or terminal QRS notch
 - Suspicious features: FH of sudden cardiac arrest or early unexplained death, eval and workup suggestive of channelopathy, h/o unheralded syncope suggestive of arrhythmogenic pathogenesis (Circ 2016;133:1520)
 - Brugada Syndrome:** autosomal dominant SCN5A loss of function mutation in 10-30%, M>F, more common to have nocturnal cardiac arrest, p/w VT/VF or sudden cardiac death (Circ Arrhythm Electrophys 2012;5:606)
 - Osborn wave:** hypothermia T $<93^{\circ}\text{F}$, elevation of J point height ~ proportional to degree of hypothermia
 - Epsilon wave:** found in ARVC, most Sp in V1 (30% with ARVC), low frequency, positive terminal deflection in V1-V3



Electrolyte Abnormalities

Electrolyte Derangement	Characteristic ECG Findings
Hypokalemia	Prolonged QT, ST depression, flattened T wave, prominent U wave
Hyperkalemia	Peaked, symmetric T wave, prolonged PR, flattened P and widened QRS (severe)
Hypocalcemia	Prolonged QT, unchanged T wave
Hypercalcemia	Shortened QT

Cardiology

Narrow Complex Tachycardia

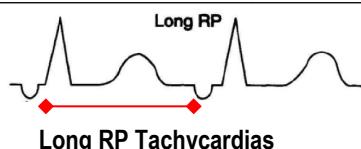
NARROW COMPLEX TACHYCARDIA (QRS <120ms)

(NEJM 2012;367:1438; Mayo Clin Proc 1995;70:371)

Diagnostic approach & general principles:

- Determine if regular or irregular rhythm
- Assess P-wave characteristics
- Compare to baseline ECG
- Treatment (See [ACLS: Tachycardia](#) and [Atrial Fibrillation/Flutter](#))
 - If unstable → synchronized cardioversion
 - If stable → vagal maneuvers/carotid massage/adenosine can resolve diagnostic dilemmas and treat AVNRT and AVRT
 - Acute treatment for all others is BB, CCB or amiodarone (consider risk of pharmacologic cardioversion if pt is not anticoagulated)

Rhythm	
Regular	Irregular
P-waves Characteristics	
Normal P	= Sinus
Abnormal P	= AT
Retrograde P (or not visible)	= AVRT, AVNTR, JT
Flutter waves	= AFL w/ variable block
Flutter waves	= AFL



Sinus Tachycardia (rate >100, 220-age)

- Gradual in onset
- Most important to determine **underlying cause**: hypovolemia, hemorrhage, withdrawal (EtOH, BZD, opiate, BB), intoxication, fever/infection, pain, hypoxemia, PE, anemia, tamponade, dissection, endo (hyperthyroidism, adrenal insufficiency, pheo)

Atrial Tachycardia (AT) (atrial rate 100-180)

- Single P morphology, non-sinus P wave axis
- Arises from increased automaticity at single atrial focus
- Classic digoxin toxicity is AT w/ variable AVB

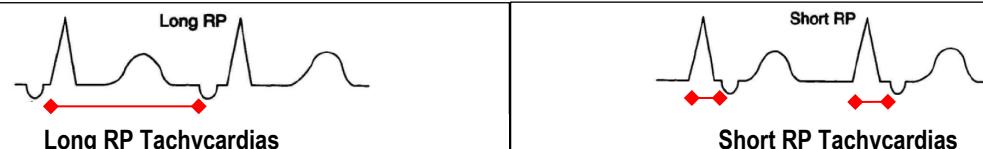
Multifocal Atrial Tachycardia (MAT) (rate ~100-150)

- ≥3 P wave morphologies
- Irregular d/t varying PP, PR, and RR intervals
- Seen in COPD, pHTN, CAD, electrolyte disarray, theophylline

Flutter wave (see [Afib/Aflutter](#))

Atrial Flutter (AFL) (multiples of 300)

- Arises from true (isthmus-dependent, typical) or functional (isthmus-independent, atypical) re-entry in R atrium
- PP interval constant but RR may vary (variable AV block)
- Counterclockwise: negative flutter waves in II, III, aVF
- Clockwise: positive flutter waves in II, III, aVF
- Signature: no isoelectric baseline, atrial rate ~300, always >250, usually with 1:2 conduction



Short RP Tachycardias

Junctional Tachycardia (rates 70-120)

- Arises from increased automaticity in the AV junction
- Usually short RP, can be no RP
- If P waves present, must be negative in aVF

Atrioventricular Re-entrant Tachycardia (AVRT) (rates usually 140-250)

- Arises from true re-entry via bypass tract
- Usually short RP, uncommonly long RP
- Ventricular activation via AV node (orthodromic, narrow QRS) more common than accessory tract (antidromic, wide QRS)

Atrioventricular Nodal Re-entrant Tachycardia (AVNRT) (rates 120–200)

- Arises from functional re-entry within AV node
- Short RP (when conducting fast-slow), however more commonly no RP (when conducting slow-fast)
- Trigger PAC (slow-fast) > PVC (fast-slow)
- Young adults, F>M

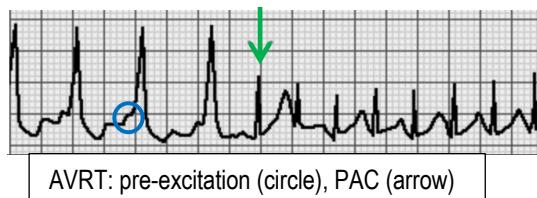
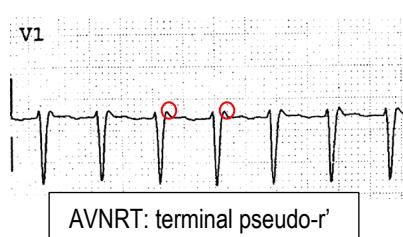
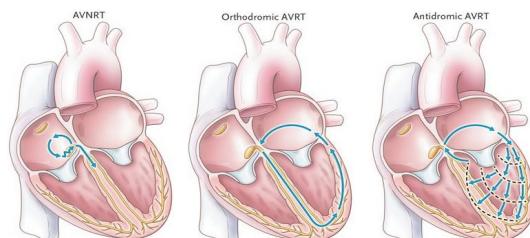
No RP Interval

Atrial Fibrillation (AF)

- No coordinated atrial activity (P wave absent), irregular
- Arises from numerous re-entrant tracts in atria or pulmonary veins

AVNRT vs AVRT

- Both are regular, paroxysmal, re-entrant NCTs w/ variable RPs that terminate w/ adenosine/vagal/AV block
- Use baseline ECG, trigger, terminal activity to help distinguish
 - AVNRT: look for terminal pseudo-r' in V1-2 (below) during tachycardia that is absent on baseline ECG
 - AVRT: look for pre-excitation on baseline ECG (short PR or delta wave/WPW), followed by a PAC which triggers NCT (QRS often narrower than baseline)



Cardiology

Wide Complex Tachycardia

WIDE COMPLEX TACHYCARDIA (QRS ≥ 120 ms)

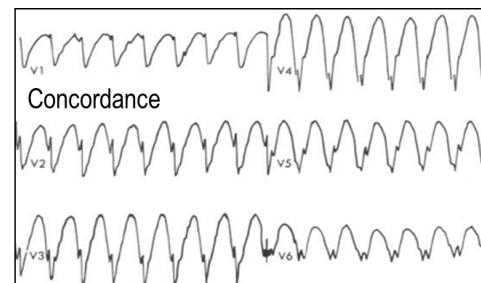
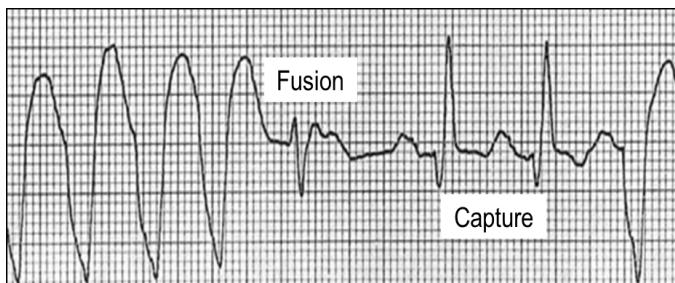
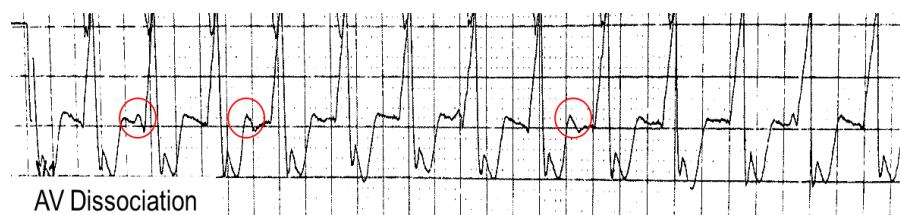
Etiology

- Ddx: VT (90%), SVT with aberrant conduction, pacemaker-mediated tachycardia

ECG Factors that Favor VT	ECG Factors that Favor SVT with Aberrancy
<ul style="list-style-type: none"> Very broad QRS (>160 ms) Superior axis (II, III, aVF neg) or northwest axis (I, aVF neg) AV dissociation (often V rate $>$ A rate) → diagnostic of VT Concordance: all QRS across precordium completely positive or completely negative - Partial (fusion beat) or complete (capture beat) depolarization of ventricle by underlying supraventricular rhythm - Brugada criteria (Circ 1991;83:1649) (only applicable if rhythm is regular); R-wave peak time criteria (Heart Rhythm 2010;7:922) 	<ul style="list-style-type: none"> Pre-existing BBB → functional/rate-dependent BBB d/t encroachment on bundle refractory period; RBBB $>$ LBBB - QRS with sharp initial deflection followed by broad terminal deflection - Pre-excitation on baseline ECG → antidromic AVRT

Other important considerations:

- Hyperkalemia, antiarrhythmic drugs (digoxin, class IA or IC, amiodarone), TCA overdose
- Pacemaker-mediated/endless loop tachycardia: retrograde VA conduction of V-paced beat misidentified as native A-beat → V-pacing. ECG shows V pacing at upper rate limit
- Sensor induced tachycardia: inappropriate sensing of nonphysiologic stimuli (vibrations, electrocautery, etc.) and pacing.



MANAGEMENT OF VT (also see [ACLS: Tachycardia](#))

- Often no way to confidently distinguish VT or SVT with aberrancy. If there is any doubt, treat like VT
- Underlying processes**: active ischemia, CAD with scar, electrolyte derangement (low K, low Mg), indwelling lines
- Check and replete lytes (**K>4, Mg>2**), think about **ischemia**

Monomorphic VT

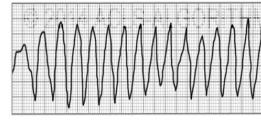
DDx: ischemia, structural heart disease, idiopathic



- Non-sustained VT** (>3 complexes, <30 secs)
 - Asymptomatic → monitor, treat underlying cardiac comorbidities (e.g. CAD, HF)
 - Symptomatic → nodal blockade (BB>CCB), then AADs
- Stable and sustained** (>30 seconds) → antiarrhythmic agent (e.g. amiodarone)
- Unstable** → synchronized cardioversion (100J) if pulseless

Polymorphic VT

DDx: ischemia (acute, CAD, ICM) vs. prolonged QTc



- Evaluate for **ischemia** & need for revascularization
- Stable** → magnesium 2-4g, ↑HR (dopa, epi, iso, overdrive pacing), ↓QTc (lido), avoid bradycardia (amio, CCB/BB)
- Unstable** → defibrillation

Torsades de Pointes



Polymorphic VT that occurs with underlying prolonged QTc (congenital or acquired). Can be prompted by PVC falling on T wave of previous beat (R on T phenomenon)

VT Storm: multiple sustained episodes of unstable VT within 24 hours

- Reduction of autonomic tone: **intubation** and **sedation**
- Treatment of underlying ischemia: **revascularization**, **IABP** to improve coronary perfusion, reduce cardiac afterload
- Anti-tachycardia **pacing** (ATP): over-drive pacing at a faster rate than VT
- Amiodarone** 150mg IV + gtt, co-administer propranolol 60mg q6h (superior to metoprolol [JACC 2018;71:1897](#))
- VANISH trial** ([NEJM 2016;375:111](#)): in patients with ischemic CM and ICD w/ persistent VT, ablation superior to escalation of antiarrhythmic drugs (lower rate of death, VT storm and ICD shocks)

Cardiology

Atrial Fibrillation & Flutter

ATRIAL FIBRILLATION

Epidemiology ([Heart Rhythm 2012;9:632](#))

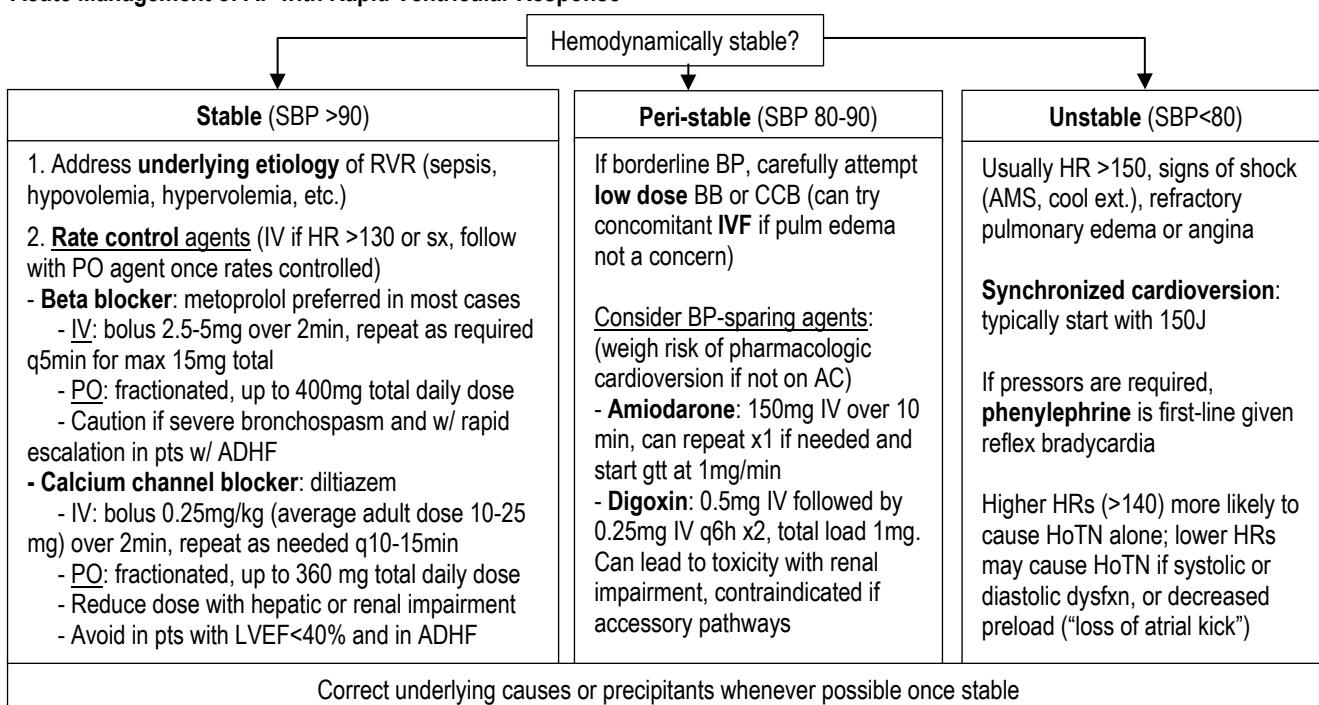
- RF: age, obesity, HTN, smoking, EtOH, DM, previous MI, HF, OSA
- Recurrent in majority of cases due to secondary precipitant (surgery, infection, MI, thyrotoxicosis, acute alcohol, PE)
- Often co-exists with atrial flutter ([Circ Arrhythmia EP 2009;2:393](#))

Clinical Evaluation of New-Onset AF

- H&P:** presence & timing of sx, HTN, DM, valve dz, CHF, angina, congenital heart disease, OSA, FH of AF, acute precipitants (e.g. EtOH, thyrotoxicosis, sympathomimetic drugs, surgery, MI, myocarditis, PE, acute pulmonary disease, infection)
- ECG:** absence of discernible p waves, irregularly irregular R-R intervals (if regularized, may represent escape rhythm and CHB)
- TTE:** LV function, LA/RA size, valve function, pulmonary HTN, LA thrombus (better visualized with TEE)
- CXR:** evaluate for pulmonary parenchymal processes, pulmonary vasculature/edema
- Labs:** TFTs, LFTs, BUN/Cr, CBC, NT-proBNP
- May also need longer term rhythm monitoring (Holter, Zio patch)

Classification of Atrial Fibrillation	
Paroxysmal	Self-termination within 7 days (includes if cardioverted within 7 days)
Persistent	Continuous AF lasting >7 days
Long-standing persistent	Continuous AF lasting >12 mos
Permanent	Term used when decision is made to stop further attempts to restore and/or maintain sinus rhythm

Acute Management of AF with Rapid Ventricular Response



Cardioversion (ALWAYS consider high risk of embolic stroke if any breaks in AC for one month prior)

- Indications:** Urgent: ischemia, end-organ hypoperfusion, symptomatic hypotension, severe pulmonary edema; Elective: new-onset AF or unacceptable symptoms from persistent AF
- Synchronized Electrical Cardioversion (DCCV):** start with 150J (biphasic), increase energy stepwise if sinus rhythm not achieved
 - Use procedural sedation if possible (consult cardiac anesthesia). If elective, should be performed in ICU or EP lab
 - Consider anti-arrhythmic drugs as adjunct (e.g. amiodarone)
- Chemical Cardioversion:** success rate significantly higher for acute (<7d) compared with longer duration AF
 - Pill-in-pocket (flecainide, propafenone), dofetilide, ibutilide
 - Amiodarone (IV infusion weakly effective for cardioversion, PO load over 3-4w 27% rate of cardioversion)
- Anticoagulation** (applies to BOTH chemical and electrical)
 - Pre-procedure: if definitive new onset <48h: may proceed *without anticoagulation*. If onset >48h: must anticoagulate for 3w prior to DCCV *or* obtain TEE immediately prior to DCCV ([NEJM 2001;344:1411](#))
 - Post-procedure: anticoagulate for at least **4 weeks after DCCV** (due to myocardial stunning)

Antithrombotic Therapy ([Stroke 2010;41:2731](#))

- Tx recommended for **all pts except** CHA₂DS₂-VASc 0 or contraindications to tx (AHA/ACC/HRS: [Circ 2019;140:e125](#))
- LA appendage (LAA) is the source of at least 90% of thrombi in pts with CVA and AF
- Subclinical AF still associated with increased stroke/systemic embolism ([ASSERT](#))
- Pts at low risk for thromboembolism may be maintained on ASA alone (see below), no reliable data to guide between 81 vs 325mg

Risk Assessment

- **CHA₂DS₂-VASC:** 1pt for CHF, HTN, Age 65-74, DM, female Sex, Vascular disease; 2pt for Age≥75, Stroke/TIA. CHA₂DS₂-VASC > CHADS₂ in “truly low risk” subjects ([Thromb Haemostasis 2012;107:1172](#))
 - Score 0 = no AC or ASA; Score 1 = no AC vs ASA vs oral AC based on clinical judgment → how high is risk from specified risk factor? (e.g. HTN, DM, age bring greater risk compared to female sex, vascular dz); Score ≥2 = oral AC
 - NOT used to guide decision making for HOCM or mitral stenosis (MS)
- **HAS-BLED:** risk stratification of bleeding risk w/ oral AC. HTN (SBP>160); abnl renal function (CrCl<50); liver disease (cirrhosis or Bili 2x ULN or AST/ALT/AkPhos 3x ULN); stroke; bleeding history; labile INR (<60% in Rx range); elderly (>65y); antiplatelet meds (ASA, NSAID); alcohol (>8 drinks/w) or other drug use. Score ≥3 suggests caution and regular follow-up
- <http://www.sparctool.com/> can aid in risk assessment and choice of anticoagulation

Choice of Antithrombotic Agent (AHA/ACC/HRS: [Circ 2019;140:e125](#))

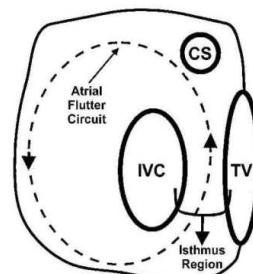
- **DOACs vs warfarin:** DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) recommended > warfarin in all except w/ mod-severe mitral stenosis, HOCM, or mechanical valve. DOACs: ↓ risk of stroke, mortality, & ICH, ↑ risk of GIB ([Lancet 2014;383:955](#)).
- **Dosing:** see [Anticoagulation Agents](#) for dosing. Dose-reduce apixaban to 2.5mg BID if if 2/3: Cr ≥1.5, Wt ≤60kg, age ≥80
- **Renal impairment:** for pts w/ CrCl<15 or on dialysis, can use either warfarin or apixaban
- **Bridging AC:** see [Anticoagulation Management](#)
- **LAA closure (Watchman device):** in non-valvular AF, device placement → comparable stroke prevention to warfarin with ↓ bleeding risk & improved mortality ([JACC 2017;70:2964](#)). AC can be discontinued 6w after LAA closure per MGH protocol

Long-Term Rate vs Rhythm Control

- Rate control noninferior to rhythm control for AF sx, CV mortality, & stroke risk ([AFFIRM, RACE, PIAF, STAF, HOT CAFÉ, AF-CHF](#))
- **Rhythm control** (antiarrhythmics and AF ablation) superior to usual care (rate control) for patients with recently diagnosed AF (within 1 year) and concomitant CV conditions in decreasing CV mortality, stroke, and hospitalization for HF or ACS ([EAST-AFNET 4](#))
 - Also consider **rhythm control** if persistent AF sx impairing quality of life, age <65, or comorbid HF (esp if systolic dysfxn). Restoration of NSR may lead to increased quality of life & exercise performance ([NEJM 2005;352:1861](#); [JACC 2004;43:241](#))
- **Rate Control**
 - BB more successful than CCB in achieving rate control (70% vs 54%), either alone or in combination with digoxin
 - Digoxin alone is moderately effective in controlling V-rate at rest, ineffective during exertion or high adrenergic tone
 - Long-term digoxin a/w increased mortality in AF patients ([JACC 2018;71:1063](#))
 - **Targets:** lenient rate control (resting HR <110) non-inferior to strict (HR <80) w/ similar outcomes in CV death, stroke, bleeding, arrhythmia, & hospitalization for HF ([RACE II](#)). Strict HR (or rhythm) control may be beneficial in younger pts or pts w/ HF
 - **Contraindications/Warnings:** evidence of pre-excitation on ECG (in these patients, IV procainamide is 1st line), cautious use in high-degree AVB. CCB should not be used in pts with LVEF <40% given negative inotropy
- **Rhythm Control** ([Circ 2012;125:381](#))
 - **Choice of Agents:**
 - No structural heart disease: “pill-in-pocket” (flecainide/propafenone), dofetilide, dronedarone, sotalol, amiodarone
 - Structural heart disease: CAD: dofetilide, dronedarone, sotalol, amiodarone; **HF or LVH:** amio, dofetilide
 - **“Pill-in-Pocket”:** for pts with recent pAF and infrequent and well-tolerated episodes, ppx may have risk>benefit. PRN flecainide or propafenone at sx onset is safe and effective ([NEJM 2004;351:2384](#))
 - **Catheter ablation** (pulmonary vein isolation [PVI]): ↓ long-term AF recurrence rate vs AADs in both pAF ([MANTRA-PAF, RAAFT-2](#)) & persistent AF ([EHJ 2014;35:501](#)). Ablation in pts w/ HF ↓ morbidity/mortality ([CASTLE-AF](#)). Ablation more effective than antiarrhythmic for maintaining sinus rhythm for pts w/ pAF. Cryoablation not yet established 1st line ([STOP-AF, EARLY-AF](#))
 - **AV nodal ablation with PPM:** indicated when pharm rate/rhythm control not achievable ([JACC 2014;64:2246](#))

ATRIAL FLUTTER (less prevalent but often coexists with or precedes AF)

- **ECG:** “Sawtooth” P waves (F waves), atrial rate typically 300bpm w/ 2:1 conduction (~V-rate 150), though can be variable block, 3:1, or 4:1. 1:1 conduction can briefly precede VT/VF
 - **Type 1 (typical):** reentrant loop in RA via cavo-tricuspid isthmus
 - Counterclockwise: more common, inverted flutter waves in II, III, aVF + upright flutter waves in V1
 - Clockwise: less common, upright flutter waves in II, III, aVF + inverted flutter waves in V1
 - **Type 2 (atypical):** does not meet criteria for Type 1; is typically faster and often refractory to ablation
- **Anticoagulation:** risk of thromboembolism lower than AF ([J Stroke Cerebrovasc 2018;27:839](#)) but management is similar to AF ([Chest 2012;141:e531S](#))
- **Rate control:** similar strategies (BB, CCB) to AF, but more difficult to successfully rate-control
- **Rhythm control:** cavo-tricuspid isthmus (CTI) ablation for typical flutter >90% effective at 1y ([Circ Arrhythmia EP 2009;2:393](#))

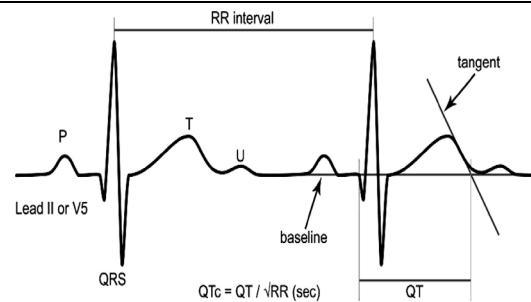


Cardiology

QTc Prolongation

DEFINITION

- QT interval correlates with repolarization time of ventricles
- Prolonged QTc >440ms (M) or >460ms (F)
- Measure from beginning of QRS to end of T wave in a lead with T wave > 2mm (best in II, V5), define end point using tangent from peak of steepest slope to isoelectric line
- QTc is QT corrected for HR
 - Bazett = QT/\sqrt{RR} ; overcorrects at high HR and under corrects at low HR
 - Fridericia = $QT^{3/2}/\sqrt{RR}$; more accurate at high or low HR ([Am J Cardiol 1993;26:72:17B](#))
 - Hodges = $QT + 0.00175 * (60/RR - 60)$



ASSESSMENT OF QT WITH UNDERLYING BBB ([Heart Rhythm 2014;11:2273](#))

- Bundle branch blocks lengthen QT interval. Can obtain rough estimate using QT – (QRS-120)
 - JT Interval = $JT (\text{HR} + 100)/518$, with a $JTI \geq 112$ identifying repolarization prolongation in all ventricular conduction defects
 - Modified QT = $QT_b - (0.485 \times QRS_b)$, where QT_b = measured QT and QRS_b = measured QRS

CONGENITAL LONG-QT SYNDROMES

- Majority of pts are asymptomatic and syndrome often discovered d/t findings on ECG
- Sx: include presyncope/syncope, hemodynamic compromise, sudden cardiac death. Triggered by exercise, stress
- Tx: beta blockers, ICD if previous cardiac arrest and expected survival >1y ([Circ 2006;114:e385](#))

DRUG-INDUCED PROLONGED QT INTERVAL ([Heart 2003;89:1363](#))

- Drugs inhibit I_{Kr} causing prolonged ventricular repolarization & exaggerate heterogeneity in repolarization times in different layers of myocardium leading to reentry and tachyarrhythmia

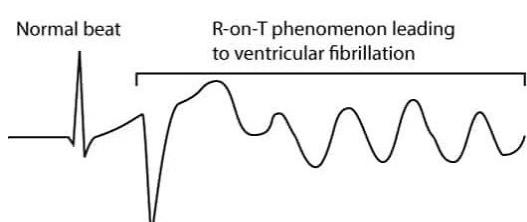
Danger of prolonged QT = increased risk of Torsades de Pointes (TdP), which can degenerate into VF
Longer QT increases risk for "R on T" phenomenon and development of TdP (higher risk if PVCs)

Risk factors for TdP in Hospitalized Patients (Circ 2010;121:1047)	
Demographics	Elderly, female, congenital LQTS, anorexia/starvation, hypothermia
Comorbidities	Renal failure, hepatic dysfunction (or drug-drug interactions impairing liver metabolism), HF, MI, LVH
Rhythm-related	QTc >500ms, bradycardia (sinus, AV block, ectopy causing pauses), PVCs
Electrolytes	Hypomagnesemia, hypokalemia, hypocalcemia
Medication-related	QT-prolonging drugs (esp. IV infusions, use of >1 concurrently), diuretic use, beta blocker use

Class of Drug	QT-Prolonging Drugs (NEJM 2004;350:1013 ; Br J Clin Pharm 2010;70:16)
Antiarrhythmics	- Class IA: quinidine, disopyramide, procainamide - <u>Class III</u> : sotalol , dofetilide , ibutilide, amiodarone (rarely a/w TdP d/t uniform delay in repol across myocardium)
Antimicrobials	- Macrolides (clarithromycin, erythromycin, azithro) - Fluoroquinolones (moxifloxacin > levo, cipro) - Anti-fungals (fluconazole , voriconazole) - Anti-malarials (quinine, chloroquine, hydroxychloroquine)
Antipsychotics	- Haloperidol , thioridazine, chlorpromazine, ziprasidone, quetiapine , risperidone increase QTc 15-30ms at usual doses and have risk of TdP - Olanzapine , aripiprazole carry less risk of QTc prolongation and TdP
Antidepressants	TCA s > SSRI s (citalopram, escitalopram, fluoxetine)
Anti-emetics	Droperidol, ondansetron , metoclopramide (lower risk)
Others	Methadone , propofol, hydroxyzine, donepezil

MONITORING FOR QT/QTc PROLONGATION

- QTc can be calculated with an ECG or by using the caliper function on a telemetry console
- Check QTc before and 12h after initiation/increased dose of QT-prolonging drug. Continue monitoring if prolongation is seen
 - Check QTc 2h post loading-dose of sotalol or dofetilide
- Class I indications for QTc monitoring with ECG ([Circ 2004;110:2721](#))
 - Initiation of QT-prolonging medication and dose changes q8-12h
 - Overdose of proarrhythmic drug
 - New bradycardia
 - Severe hypokalemia or hypomagnesemia



MANAGEMENT OF ACQUIRED LQTS

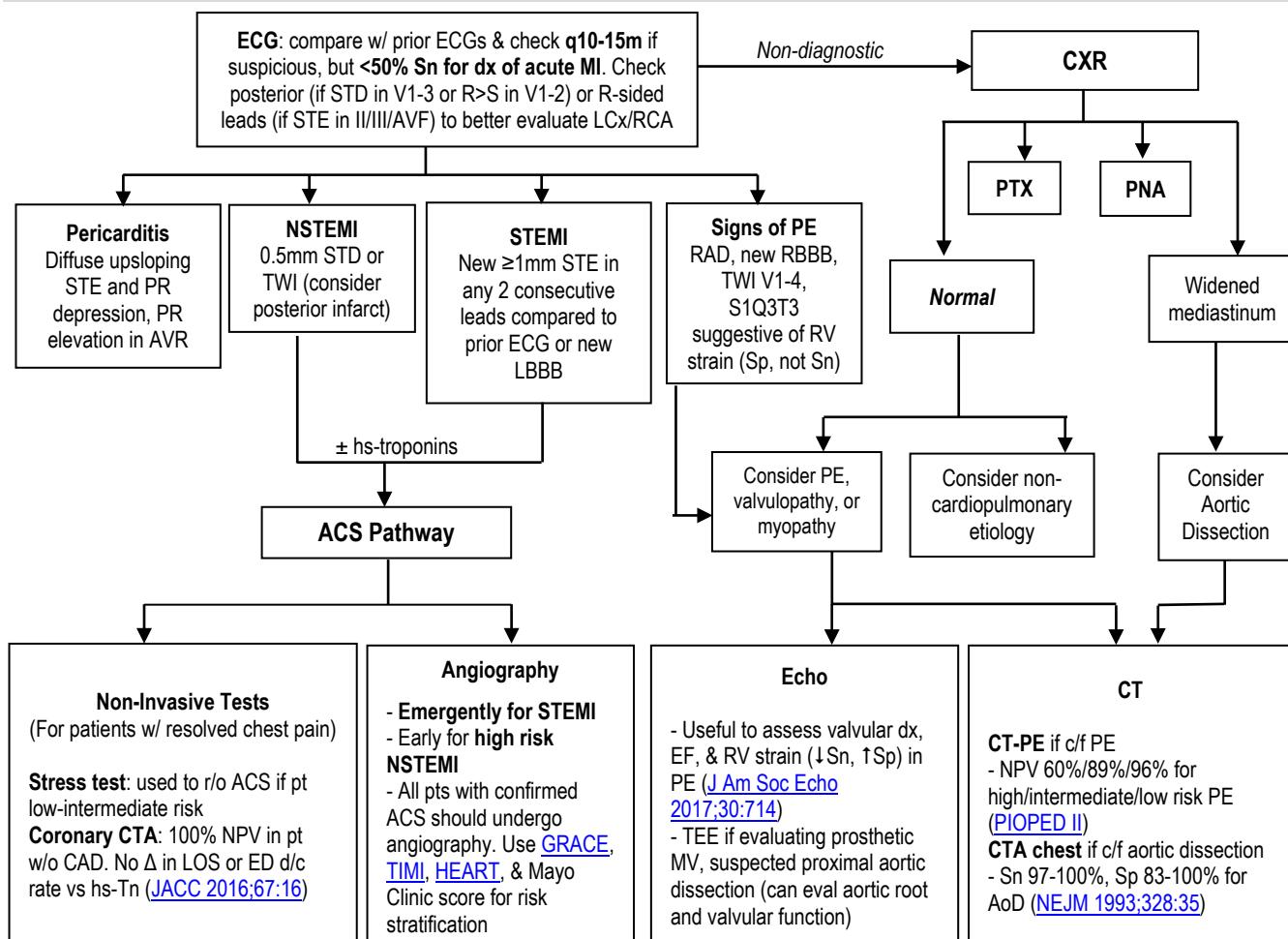
- **Stop offending drug** if QTc >500ms or increase in QTc of >60ms
- ECG should be checked for bradyarrhythmias & signs of impending TdP (R on T). Stop drugs causing bradycardia
- Check electrolytes checked & replete (K >4, Mg >2.4). Supratherapeutic repletion of K to 4.5-5.0 can be used in pts on QT-prolonging drugs who have had TdP

Cardiology

Chest Pain

	HISTORY	PHYSICAL EXAM																		
Stable Angina/ACS	<p>CVD risk: use Framingham or ASCVD Risk Estimator to predict 10y risk of first ASCVD event. Age, h/o CAD, and male sex most predictive of ACS (NEJM 2000;342:1187). Women, elderly, DM may have atypical presentations</p> <p>Angina (NEJM 1979;300:1350): (1) substernal chest pain (2) brought on by stress/exertion (3) relieved by rest or TNG 3/3 = typical, 2/3 = atypical, 1/3 = noncardiac</p> <p>Antianginals: nitrates; avoid if preload sens. (HoTN, AS, recent PDEI); BB (avoid in ADHF, long PR, 2°/3° AV block); CCB if BB intolerant</p> <table border="1"> <thead> <tr> <th colspan="2">Likelihood Ratios for ACS (JAMA 2015;314:1955)</th> </tr> </thead> <tbody> <tr> <td colspan="2">Low Risk</td> </tr> <tr> <td>Pleuritic (0.3)</td> <td>Syncope (0.5)</td> </tr> <tr> <td colspan="2">Intermediate Risk</td> </tr> <tr> <td>Radiation to left arm, neck, or jaw (1.3-1.5)</td> <td>Diaphoresis (1.4): exertional (1.5)</td> </tr> <tr> <td>Pressure / typical (1.9)</td> <td>Pattern change / 24h (2.0)</td> </tr> <tr> <td colspan="2">High Risk</td> </tr> <tr> <td>Similar to prior ischemia (2.2)</td> <td>Pain radiating to both arms (2.6)</td> </tr> <tr> <td>PAD (2.7)</td> <td>Abnormal prior stress test (3.1)</td> </tr> </tbody> </table>	Likelihood Ratios for ACS (JAMA 2015;314:1955)		Low Risk		Pleuritic (0.3)	Syncope (0.5)	Intermediate Risk		Radiation to left arm, neck, or jaw (1.3-1.5)	Diaphoresis (1.4): exertional (1.5)	Pressure / typical (1.9)	Pattern change / 24h (2.0)	High Risk		Similar to prior ischemia (2.2)	Pain radiating to both arms (2.6)	PAD (2.7)	Abnormal prior stress test (3.1)	<ul style="list-style-type: none"> New S4, MR (ischemia) CHF (crackles, +S3, ↑JVP, pedal edema) Carotid, subclavian, & abdominal bruit (indicates vascular disease) Bilateral femoral and radial pulses (<i>document pre-cath</i>) <u>Frank's sign:</u> bilateral diagonal earlobe crease (slight ↑ in likelihood of CAD in adults <60yrs) <u>Less likely ACS:</u> pleuritic, positional, reproducible by palpation (LR 0.28)
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Acute Aortic Syndromes	Abrupt onset of tearing/sharp thoracic or abdominal pain RF: known aneurysm, Marfan syndrome, HTN, M:F 2:1, 60-80y, cocaine use, high-intensity exertion (weightlifting)	BP variation >20mmHg between arms, pulse deficits, new diastolic murmur, focal neurologic changes																		
Acute Pericarditis	Pleuritic, sharp, improves upon leaning forward May have URI prodrome; consider bacterial pericarditis if high fevers	Friction rub (<i>breath hold to distinguish from pleural rub</i>); tamponade (pulsus >10)																		
PE	Sudden onset, dyspnea/hypoxemia, pleuritic RF: hx of cancer/recent surgery/immobility, hemoptysis, calf/thigh pain/swelling	Tachycardia, tachypnea, hypoxemia, calf/thigh erythema, swelling, tenderness																		
Pneumothorax	Sudden onset dyspnea; RF: 20-40y (more likely if tall), FH or personal history, smoker, known emphysema, M > F, recent chest procedures/lines	Ipsilateral absence of breath sounds, contralateral deviation of trachea																		
Pneumonia, Pneumonitis	Sharp, pleuritic CP associated with fever leukocytosis, productive cough, recent radiation, autoimmune (SLE, RA, drug-induced lupus, collagen vascular diseases)	Bronchial breath sounds, crackles, dullness																		
Other	Cardiac: HOCM, AS, vasospasm (Prinzmetal's angina, drug/toxin), Takotsubo CM; MSK: costochondritis, Zoster; GI: GERD, esophageal spasm (may be relieved by TNG), Boerhaave's, PUD, biliary colic, pancreatitis; Psych: panic attack																			

BASIC CHEST PAIN ALGORITHM



Cardiology

Acute Coronary Syndrome

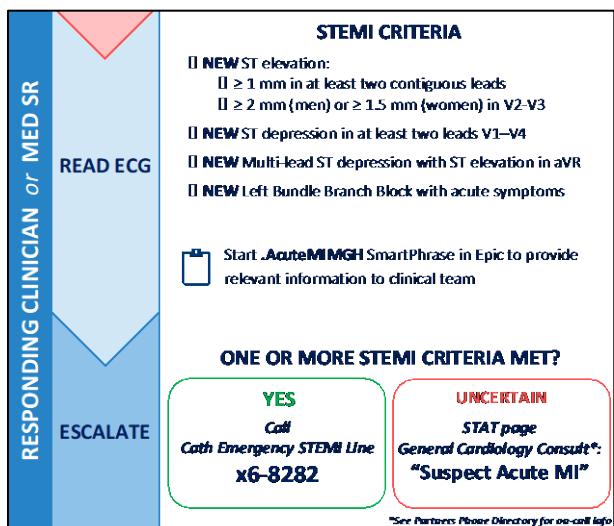
DEFINITIONS AND EVALUATION

Myocardial infarction: myocardial necrosis (trop >99th percentile + Δ) w/ ischemia (4th universal def. of MI: [JACC 2018;72:2231](#))

- **Type 1 MI:** spontaneous plaque rupture, ulceration, fissure, erosion, dissection → intraluminal thrombus
- **Type 2 MI:** supply-demand mismatch – supply may be compromised by dynamic obstruction (e.g. vasospasm), microvascular ischemia (e.g. Takotsubo), non-plaque thromboembolism (e.g. infectious, via PFO), coronary dissection, vasculitis, vascular steal
 - Must have a **clear** precipitating factor. If not, treat as a type 1 MI until further evaluation
 - 50-70% have obstructive CAD – reasonable to initiate ASA, BB, and high-intensity statin

Myocardial injury: defined as any patient with an increased troponin without evidence of myocardial ischemia (sx of ischemia, new ischemic ECG changes, new wall-motion abnormalities, and/or acute coronary thrombus on angio). NOT the same as T2MI

Evaluation of CP with hsTnT		
Emergency Department – CP onset ≥3h PTA	Inpatient or Emergency – CP onset < 3h	
Check hsTNT immediately and at 1h	Check hsTNT immediately and at 3h	
Rule in: hsTnT ≥52 OR Δ ≥5 from baseline → consider ACS	Rule in: hsTnT ≥10 (F) or ≥15 (M) AND Δ ≥7 from baseline AND sx or ECG changes or concerning imaging (CCTA, cath) → consider ACS	
Rule out: hsTNT <10(F) or <12(M) AND Δ <3 from baseline → unlikely ACS	Rule out: no significant Δ in 3h → unlikely ACS	
Intermediate: calculate HEART score , repeat hsTnT in 3h and apply inpatient criteria (right)		
STEMI	NSTEMI	Unstable Angina
1mm STE in two contiguous leads (if V2-V3: >2.5mm in M<40, 2mm in M>40, 1.5mm in F) OR new LBBB AND \oplus biomarkers	\oplus ECG or hx, \oplus biomarkers	\oplus ECG or hx, \ominus biomarkers



Clinical Evaluation & Risk Stratification:

- Consider pt's baseline CAD risk. Review prior stress test and cath data. ↑ risk of MI w/ resp infxn (esp flu) ([NEJM 2018;378:345](#))
- Treat secondary causes of myocardial demand

ECG: ([NEJM 2003;348:993](#))

- Obtain serial tracings (q15-30min) if initial ECG non-diagnostic in pts with compelling hx & sx
- Non-STE ischemic EKG changes: ≥0.5mm STD (horizontal, downsloping), new TWI ≥1mm or normalization ("pseudonormalization") of prior TWI in s/o sx

Cardiac Biomarkers:

- hsTnT 99th %ile among normal subjects: M 15ng/L, F 10ng/L
- 75% of healthy individuals will have measurable hsTnT

REVASCULARIZATION

- **PCI Indications:** recommended over fibrinolysis at a PCI-capable center
 - **STEMI:** PCI if <12h sx onset, goal to PCI ideally <60min at PCI centers. PCI regardless of time from onset for cardiogenic shock, malignant arrhythmia (recurrent sustained VT, VF), persistent STE and/or CP. Late PCI (>48h post-event) generally not indicated in stable pts ([NEJM 2006;355:2395](#)) and delayed PCI (>120min from first medical contact) associated with worse outcomes -- consider fibrinolysis in these cases ([Eur Heart J 2020;4:858](#))
 - **NSTEMI/UA:** see "Risk Stratification" above
- **PCI Strategies:**
 - In pts with STEMI and no cardiogenic shock, complete revascularization strategy (culprit + non-culprit) has a ↓ risk of CV death and MI at 3y (COMPLETE, [NEJM 2019;381:1411](#))
 - In pts with **cardiogenic** shock, culprit-lesion only PCI has a ↓ risk of death/RRT (CULPRIT-SHOCK, [NEJM 2018;379:1699](#))
 - **Access:** radial > fem | Stent: DES > BMS ([NEJM 2016;375:1242](#))
- **CABG:** preferred for 3VD ([NEJM 2009;360:961](#); [NEJM 2008;358:331](#)), left main disease ([Lancet 2016;388:2743](#); [NEJM 2016;375:2223](#)), 2VD with prox LAD stenosis or EF <50%, large area of viable myocardium or high risk. Consider if DM + 2VD ([NEJM 2012;367:2375](#))

Cardiology

Acute Coronary Syndrome

RISK STRATIFICATION FOR PCI TIMING IN NSTEMI/UA

- Multiple risk models incl [GRACE](#), [TIMI](#), PURSUIT. GRACE score is based on predictors of 6mo mortality (age, HR, SBP, Cr, cardiac arrest at admission, ST deviation, elevated troponin) ([BMJ 2006;333:1091](#))
- Four subgroups for urgency to revascularization ([JACC 2014;64:e139](#))
 - Very high risk** ("immediate invasive," within 2h): **refractory/recurrent angina, hemodynamic, or electrical instability**
 - High risk** ("early invasive," within 24h): temporal change in troponin, EKG changes (STD, TWI), high risk pt (GRACE>140)
 - Conflicting results between TIMAC ([NEJM 2009;360:2165](#)) and VERDICT ([Circ 2018;138:2741](#)) trials about outcome benefit of early cath. However, both show improved outcomes with early cath in patients with GRACE >140
 - Intermediate risk** ("delayed invasive," within 72h): none of above but risk factors at baseline (e.g. EF <40%, GFR <60)
 - Low risk** ("ischemia guided," no cath): no risk factors, GRACE <109, TIMI 0-1

ADJUNCTS TO REVASCULARIZATION

- ASA:** established mortality benefit, give to all pts in an immediate load/maintenance strategy (325mg/81mg) ([Lancet 1988;2:8607](#))
- P2Y12 Inhibitors:** (pre-cath load not done at MGH, controversial if beneficial and may delay CABG by 5-7 days)
 - Ticagrelor:** ↓ mortality compared to clopidogrel w/o increasing major bleeding. Reversible with platelet transfusion. Side effect: dyspnea (14-21%, often mild-moderate & transient, but can be severe enough to warrant discontinuation). Avoid in liver disease, prior CVA, oral AC (PLATO, [NEJM 2009;361:1045](#))
 - Prasugrel:** ↓ death, MI, CVA compared to ticag ([NEJM 2019;381:1524](#)). Contraindicated if prior TIA/CVA, wt <60kg, or >75y
 - Clopidogrel:** ↓ death, repeat MI when load/maintenance with PCI ([Lancet 2001;358:5271](#)). Prodrug, metabolized by CYP219, less effective in those with LOF allele ([NEJM 2009;360:354](#)). No apparent cardiovascular interaction between clopidogrel & omeprazole, and co-administration reduced rates of UGIB ([NEJM 2010;363:1909](#))
 - Cangrelor:** IV reversible inhibitor with immediate onset and return of platelet function in 1h. Used in pts with recent PCI who are unable to take PO or are periprocedure
- Nitrates:** TNG SL (0.3-0.6mg) x3, transition to gtt (start 5-10mcg/min) if refractory CP. Nitropaste (7.5mg/0.5inch) and gtt have shorter half-life than SL if c/f HoTN. No mortality benefit. Caution in inferior MI/RVMI, SBP<100, or PDEi use in last 48h. If CP despite ↑ dose of TNG, indication for earlier cath
- Anticoagulation:**
 - UFH:** usually stopped after 48h if ECG changes improving and concern for ongoing ischemia resolved ([BMJ 1996;313:652](#)). Start gtt w/ bolus and use **low intensity PTT goal** (63-83). No bolus if giving lytics or if on warfarin and INR<2
 - LMWH:** possible reduction in death w/ minimal evidence for ↑ major bleeding, trials vs UFH largely null ([BMJ 2012;344:e553](#))
 - Fondaparinux:** preferred to UFH/LMWH if medically managed. Contraindicated in PCI 2/2 ↑ catheter thrombosis/complications ([JAMA 2006;295:1519](#))
 - IIb/IIa Inhibitors:** eptifibatide (Integrilin) used at MGH. Initiated in cath lab if PCI high-risk (extensive thrombus)
 - Bivalirudin:** direct thrombin inhibitor, preferred for patients w/ HIT, otherwise cost does not outweigh benefit
- Beta Blockers:** start within 24h (1b), mortality benefit. Consider early initiation if ischemic arrhythmias present
 - Caution in decompensated HF, ↑ risk for cardiogenic shock (>70y, SBP <120, HR >110 or <60)
 - Contraindications: cocaine-induced MI, PR>240ms, 2nd or 3rd degree AVB, severe bronchospasm ([Lancet 2005;366:1622](#))
- ACEi or ARB:** start within 24h if BP/renal function normal
 - Mortality benefit maximal if EF <40%, pulm edema, or anterior MI ([Lancet 1995;345:669](#))
- Statins:** atorvastatin 80mg daily regardless of baseline LDL ([NEJM 2004;350:1495](#))
 - Early high-dose statin within 24-96h may reduce death/adverse cardiac events if given pre-PCI ([JACC 2009;54:2157](#); [JAMA 2018;319:1331](#)). Early inflammatory effect may stabilize plaque ([JAMA 2001;285:1711](#); [JAMA 2004;291:1071](#))
- Morphine:** consider only if unacceptable level of pain refractory to TNG, careful if suspicious for inferior MI/RVMI
- Discontinue NSAIDs:** ↑ risk of mortality, re-infarction, CHF, and myocardial rupture after ACS

SECONDARY PREVENTION

- Aspirin:** 81mg w/o enteric coating indefinitely ([NEJM 2010;363:930](#))
- Dual antiplatelet therapy (DAPT):** recommend 6-12mo DAPT after DES ([Circ 2016;134:e123](#)). Use **DAPT score** to help risk stratify. Recent trials explore the evidence for **shortening DAPT duration**, with goal to reduce bleeding risk while preserving ischemic outcomes (TWILIGHT [NEJM 2019;381:2032](#); TICO [JAMA 2020;323:2407](#); STOPDAPT-2 [JAMA 2019;321:2414](#); SMART CHOICE [JAMA 2019;321:2428](#)). Bottom line: single agent P2Y12 inhibitor after 1-3 months (vs. longer duration DAPT) reduces bleeding risk and non-inferior in reduction of cardiovascular events.
- Beta blockers:** start in all pts (1b) w/o contraindication indefinitely
- ACEi or ARB:** start in all pts (2b) but stronger recommendation (1a) in anterior STEMI, EF <40%, stable CKD, HTN, or DM
- Statins:** high intensity statin (atorvastatin 40-80mg or rosuvastatin 20-40mg qd) indefinitely for pts ≤75y, moderate intensity in >75y
 - If very high risk clinical ASCVD w/ LDL>70 mg/dL, add **ezetimibe** and consider PCSK9i ([JACC 2019;73:3168](#))
- Triple therapy:** P2Y12 inhibitor + DOAC > triple therapy in pts with AF + PCI. ↓ bleeding and non-inferior for ischemic events (AUGUSTUS [NEJM 2019;380:1509](#); RE-DUAL PCI [NEJM 2017;377:1513](#); [NEJM 2016; 375:2423](#)). Reference [ACC Consensus Pathway for Anticoagulant and Antiplatelet Therapy in Patients with AF or VTE with CAD or undergoing PCI](#). See [Anticoagulation Management](#)
- Lifestyle:** smoking cessation, BP <130/80 (start treatment if >140/90), cardiac rehab (1c), depression screening (1b)

Cardiology

Acute Coronary Syndrome

MGH P2Y₁₂ SWITCHING GUIDELINES (does not apply to patients on triple therapy)

Acute Setting – within 30 days of index event

		Agent switching TO/STARTING			
Agent switching FROM/STOPPING	Clopidogrel ¹	Ticagrelor	Prasugrel	Cangrelor ^{2,3}	
	Clopidogrel	180 mg when decision is made to switch (no delay time needed), then 90 mg BID	60 mg when decision is made to switch (no delay time needed), then 10 mg daily	Start 0.75 mcg/kg/min 48 hours after discontinuation	
	Ticagrelor	600 mg 24 hours after last dose of ticagrelor, then 75 mg daily	60 mg 24 hours after last dose of ticagrelor, then 10 mg daily	Start 0.75 mcg/kg/min 48 hours after discontinuation	
	Prasugrel	600 mg 24 hours after last dose of prasugrel, then 75 mg daily	180 mg 24 hours after last dose of prasugrel, then 90 mg BID	Start 0.75 mcg/kg/min 96 hours after discontinuation	
	Cangrelor	600 mg at time of drip discontinuation, then 75 mg daily	180 mg dose 0 to 120 minutes before drip discontinuation, then 90 mg BID	60 mg dose 0 to 30 minutes before drip discontinuation, then 10 mg daily	

¹If a patient has active bleeding or is very high-risk for bleeding, consider clopidogrel half load (300 mg) or maintenance dose (75 mg), in lieu of full 600mg loading dose

²If there is concern for lack of absorption of initial LOADING DOSE of oral P2Y12i at time of cangrelor initiation and patient is not at high bleeding risk, could bolus with 30 mcg/kg before starting infusion

³Dose of cangrelor recommended here is for **bridging**. This is different than the dose used in the catheterization lab

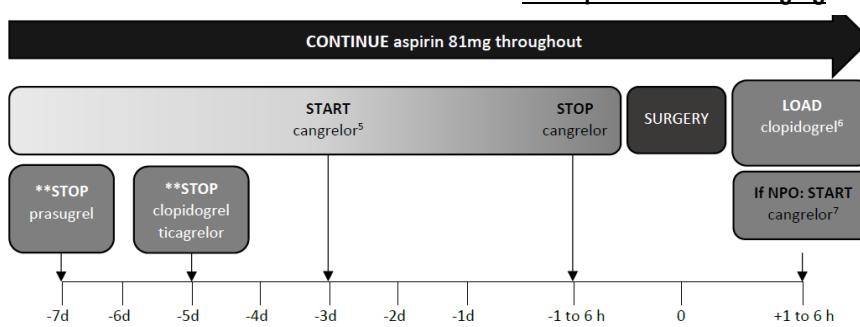
Chronic/Maintenance Setting – >30 days after index event

		Agent switching TO/STARTING			
Agent switching FROM/STOPPING	Clopidogrel	Ticagrelor	Prasugrel	Cangrelor	
	Clopidogrel	90 mg BID 24 hours after last dose of clopidogrel	10 mg daily 24 hours after last dose of clopidogrel	Start 0.75 mcg/kg/min 48 hours after discontinuation	
	Ticagrelor	600 mg 24 hours after last dose of ticagrelor ⁴ , then 75 mg daily	60 mg 24 hours after last dose of ticagrelor, then 10 mg daily	Start 0.75 mcg/kg/min 48 hours after discontinuation	
	Prasugrel	75 mg daily 24 hours after last dose of prasugrel ⁴	90 mg BID 24 hours after last dose of ticagrelor	Start 0.75 mcg/kg/min 96 hours after discontinuation	
	Cangrelor	600 mg at time of drip discontinuation, then 75 mg daily	180 mg at the time of drip discontinuation, then 90 mg BID	60 mg at time of drip discontinuation, then 10 mg daily	

⁴If switch is for high risk of bleeding/active bleeding, could consider starting clopidogrel 75 mg 24 hours after last dose of ticagrelor or prasugrel.

*Consider concomitant PPI therapy if patient on triple therapy or high-risk for GI bleeding

Peri-operative P2Y₁₂ Bridging



⁵Initiate at a dose of 0.75 mcg/kg/min (NO bolus) for a minimum of 48 hours and a maximum of 7 days

⁶ 600 mg loading dose of clopidogrel as soon as oral administration is possible and when surgical bleeding risk is acceptable; use of prasugrel or ticagrelor is discouraged. If a patient is at very high-risk for bleeding, consider clopidogrel half load (300 mg) or maintenance dose (75 mg), in lieu of the full 600mg loading dose.

⁷ONLY resume cangrelor if oral administration is NOT possible (patient NPO or not absorbing oral medications)

Cardiology

MI Complications

MECHANICAL COMPLICATIONS ([JACC 2013;61:e78](#); [JACC Cardiovasc Interv 2019;12:1825](#))

Complication	Prevalence / Risk Factors	Timing / Clinical Signs	Evaluation	Treatment
Early Complications (Hours – Days)				
Cardiogenic Shock (see Inpatient HF)	<ul style="list-style-type: none"> STEMI ~6% NSTEMI ~3% Anterior MI, LBBB, prior MI, 3VD, age, HTN, DM, mechanical complications 50% of post-MI death 	<ul style="list-style-type: none"> STEMI: 50% develop shock w/in 6h of MI, 75% w/in 24h NSTEMI: 72-96h after MI New CP, cold/wet physiology, HoTN, tachycardia, dyspnea, JVD, rales, new murmur 	<ul style="list-style-type: none"> TTE PAC (CI<2.2, PCWP>18) End organ hypoperfusion (lactic acidosis, AKI) 	<ul style="list-style-type: none"> Inotropes/pressors Emergent PCI/CABG (<75y + STEMI + shock w/in 36h of MI). SHOCK trial (NEJM 1999;341:625) IABP and other MCS
Myocardial Free Wall Rupture (Pseudoaneurysm: LV defect contained by only pericardium, scar, more prone to rupture than true aneurysm)	<ul style="list-style-type: none"> 0.01% STEMIs & NSTEMIs Transmural MI, 1-vessel MI, 1st MI (poor collaterals), anterior & lateral MI, HTN, late thrombolysis (>14h), fibrinolysis>>PCI, NSAIDs, female, age >70 10% post-MI death 	<ul style="list-style-type: none"> 40% w/in 24h, 85% w/in 1w Tamponade in 85% Electromechanical dissociation, aberrant T wave evolution, abrupt episodes of ↓HR/BP 	<ul style="list-style-type: none"> TTE (pericardial effusion w/ high acoustic echoes indicating clot) STAT cardiac surgery consult 	<ul style="list-style-type: none"> Emergency surgery for resection of ruptured myocardium w/ primary reconstruction
Interventricular Septal Rupture (VSD)	<ul style="list-style-type: none"> 0.21% STEMIs, 0.04% NSTEMIs 1st MI, 1-vessel MI (esp. LAD), CKD, anterior infarct w/ inferior STE due to wrap-around LAD, older age, female 5% of post-MI death 	<ul style="list-style-type: none"> Bimodal: 24h & 3-5d to up to 2w from event New, harsh holosystolic murmur (50% w/ thrill), S3, loud P2, hypotension, BiV failure (R>L) 	<ul style="list-style-type: none"> TTE w/ doppler (L to R shunt, RV overload) RHC: increase in O2 sat from RA to PA >5, large V waves 	<ul style="list-style-type: none"> Emergency surgery or transcatheter closure device Vasodilators (use cautiously) to decrease L to R shunt (nitroprusside or nitroglycerin) IABP
Papillary Muscle Rupture (leading to acute MR)	<ul style="list-style-type: none"> 0.05% STEMIs, 0.01% NSTEMIs Postero medial (supplied by PDA, with inf. or post. MI) >> anterolateral (dual blood supply by LAD and LCx) 5% of post-MI death 	<ul style="list-style-type: none"> No reperfusion: 2-7d With reperfusion: median 13h Abrupt dyspnea, pulmonary edema, hypotension Hyperdynamic LV, holosystolic murmur at apex (radiates to LSB w/ posterior pap muscle rupture), murmur may be absent in torrential MR or severe HF 	<ul style="list-style-type: none"> TTE (MR) CXR: edema (can be asymmetric to RUL if MR jet directed at right pulmonary veins) Tall c-v wave in PCWP tracing 	<ul style="list-style-type: none"> Aggressive afterload reduction (nitroprusside or nitroglycerin) IABP Emergency surgery
Late Complications (Weeks – Months)				
LV Aneurysm (discrete, dyskinetic area of LV with broad neck, rarely ruptures)	<ul style="list-style-type: none"> No reperfusion: 10-30% Apical-anterior wall >> inferior posterior Steroids, NSAIDs 	<ul style="list-style-type: none"> Days to weeks Acute: diffuse, displaced PMI, S3 and/or S4, MR murmur, CHF Chronic: HF, VT/VF, systemic embolization, may be asymptomatic 	<ul style="list-style-type: none"> ECG w/ persistent STE TTE, other imaging (CMR, CT, ventriculography) 	<ul style="list-style-type: none"> Acute: management of CHF, ACEi, avoid NSAIDs/steroids, start heparin (if EF<35%) Chronic: ACEi, digoxin, diuretics, warfarin (if EF<35%) Surgical repair
LV Thrombus	<ul style="list-style-type: none"> 5% of AMI patients post-PCI Usually in LV apex Large infarct size, severe apical akinesis or dyskinesis, LV aneurysm, anterior MI 	<ul style="list-style-type: none"> Can form 24-72h post MI 90% of thrombi are formed by 2w Embolization risk persists for 6mo but most by 3-4mo; risk 10% if not on warfarin 	<ul style="list-style-type: none"> TTE w/ contrast CMR or CT 	<ul style="list-style-type: none"> Warfarin (INR 2-3) When to stop warfarin unclear, check for resolution of thrombus on TTE at 3-6mo
Pericarditis	<ul style="list-style-type: none"> 5% of pts in the ED w/ CP and no MI, M > F 85-90% idiopathic (viral/post viral), infectious, post-MI, uremic, autoimmune, malignancy, XRT, drugs 	<ul style="list-style-type: none"> 10% at 2-4d post-transmural MI May be focal or diffuse Dressler's syndrome: malaise, fever, leukocytosis, late autoimmune carditis, rare 	<ul style="list-style-type: none"> ECG (diffuse STE, PR depressions) TTE (effusion) CMR and/or cardiac CT (if needed to confirm) 	<ul style="list-style-type: none"> ASA + colchicine Avoid NSAIDs and steroids post MI as can impair infarct healing
Coronary Artery In-Stent Thrombosis	<ul style="list-style-type: none"> Highest risk is absence of P2Y12 inhibitor 1% at 1 year, then ~0.2% per year thereafter 	<ul style="list-style-type: none"> Most cases occur within 30d of PCI irrespective of stent type ACS symptomatology 	<ul style="list-style-type: none"> ECG Biomarkers (troponin/CKMB) 	<ul style="list-style-type: none"> PCI Long term anti-platelet therapy, adherence to therapy

URGENT ASSESSMENT OF POST-MI COMPLICATION (page Cardiology)

- Assess VS for hemodynamic instability, perform focused physical exam (new murmur, pericardial friction rub, elevated JVP, crackles)
- Stat labs (troponin, PT/INR, PTT, T&S, BMP, lactate), ensure adequate vascular access (≥2 PIVs)
- Run telemetry, repeat EKG, urgent TTE, consider STAT CTA if concern for RP bleed/aortic dissection

Cardiology

MI Complications

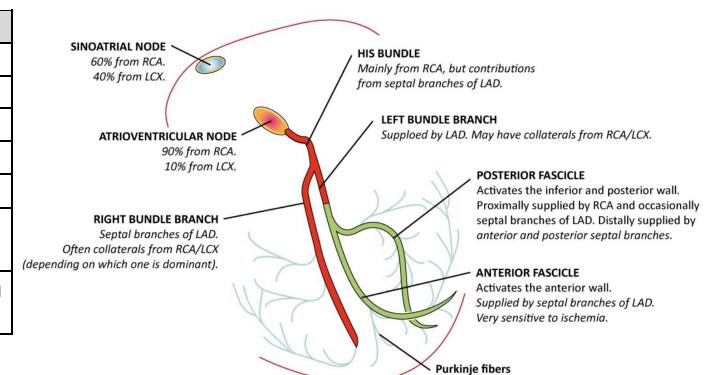
ELECTRICAL COMPLICATIONS

Overview

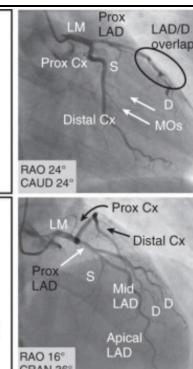
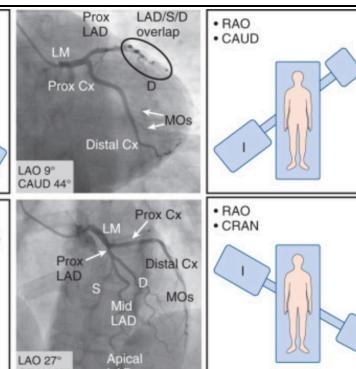
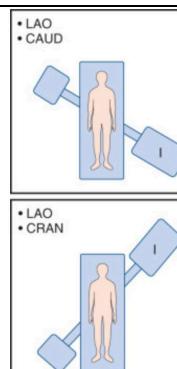
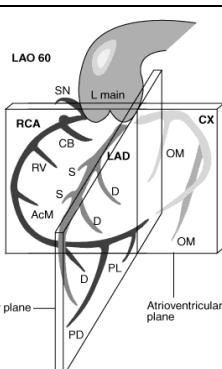
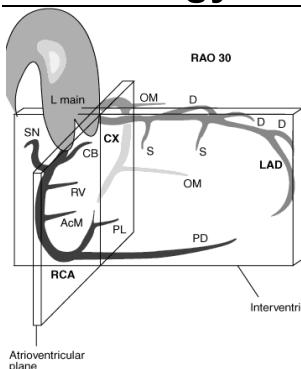
- Bradyarrhythmia/conduction block: may be due to coronary artery occlusion (see below) or baroreceptor reflexes ([Anes 2003;98:1250](#))
- Tachyarrhythmia: related to creation of re-entrant circuit from scar formation and/or ↑automaticity from adrenergic surge

	Arrhythmia	Location/Mechanism	Incidence/Timing	Treatment/Outcome
Bradycardia	Sinus bradycardia	<ul style="list-style-type: none"> Inferior and posterior MI Beneficial: ↓ myocardial O₂ demand 	<ul style="list-style-type: none"> Up to 40% of acute MI Occurs early in STEMI 	<ul style="list-style-type: none"> Atropine, pacing if unstable, dopa/epi if HoTN
	First degree AV block	<ul style="list-style-type: none"> <u>Inferior</u>: ↑ vagal tone or AV node ischemia (RCA), narrow QRS <u>Anterior</u>: septal necrosis below AV node, RBBB, wide QRS 	More common in inferior MI	<ul style="list-style-type: none"> If due to inferior MI, transient (vagal) Continue CCB or BB unless PR interval >240ms
	Second degree AV block: Mobitz Type I	Usually inferoposterior MI (↑ vagal tone, narrow QRS) or AV node ischemia	Usually within first 24h of MI	<ul style="list-style-type: none"> Usually transient; observe Atropine if symptoms or HR <45
	Second degree AV block: Mobitz Type II	Usually anterior MI with infranodal conduction injury, wide QRS, HR often <30, 33% progress to CHB	Usually within first 24h of MI	<ul style="list-style-type: none"> Consider temporary pacing In infranodal block, <i>atropine may paradoxically worsen AV block</i>
	Third degree AV block	<ul style="list-style-type: none"> If <u>inferior MI</u>: intra-nodal lesion; narrower QRS escape If <u>anterior MI</u>: infra-nodal lesion; wide, unstable escape rhythm 	<ul style="list-style-type: none"> 3-7% acute MI <u>Inferior</u>: gradual, stable <u>Anterior</u>: sudden, 12-24h after MI 	<ul style="list-style-type: none"> Recovery 3-7d; temp pacing required <u>Inferior</u>: transient, resolves on own <u>Anterior</u>: carries high mortality rate (80%) and indicates extensive necrosis
Intraventricular Conduction Blocks		<ul style="list-style-type: none"> 50% already present on first ECG, may represent antecedent disease of conduction syndrome Suggests more extensive infarct 	2-5% of MI	<ul style="list-style-type: none"> Patients w/ BBB are more likely to have comorbid conditions, less likely to have received therapies, have larger area infarcts, and have high mortality
Supraventricular Arrhythmias	Sinus tachycardia	<ul style="list-style-type: none"> May be compensatory for LV dysfunction, common in anterior MI Pain, anxiety, pericarditis, fever 	25% of acute MI	<ul style="list-style-type: none"> Undesirable as ↑ myocardial oxygen demand, ↓ diastole time causes ↓ coronary perfusion time Treat underlying cause
	Atrial fibrillation, Atrial flutter	<ul style="list-style-type: none"> <u>Early</u>: may be transient due to ↑ sympathetic; atrial ischemia <u>Late</u>: due to atrial stretch/HF 	6-8%, may be >30% of acute MI	<ul style="list-style-type: none"> A/w mortality, particularly if late (>30d) AF (Circ 2011;123:2094) If unstable, cardioversion; consider BB, amiodarone, digoxin, anticoagulation
Ventricular Tachyarrhythmias	Premature Ventricular Contraction	Due to electrical instability and increased sympathetic tone	Variable	<ul style="list-style-type: none"> Correct electrolyte deficits, BB. Do NOT treat with anti-arrhythmics as can ↑ mortality (NEJM 1991;324:781)
	Accelerated Idioventricular Rhythm (AIVR)	50-110bpm, higher V- vs A-rate; in 40%, considered a reperfusion rhythm	<ul style="list-style-type: none"> Up to 20% of STEMI Usually within 12-48h, can occur after reperfusion 	<ul style="list-style-type: none"> Do not treat unless symptomatic or hemodynamically unstable, usually short duration & does not affect prognosis
	Ventricular Tachycardia	<ul style="list-style-type: none"> Monomorphic VT <170bpm is unusual early after STEMI, suggests pre-existing arrhythmogenic scar; recurrent ischemia usually polymorphic VT 	<ul style="list-style-type: none"> NSVT 1-7%, sustained VT (2-3% of STEMI, <1% NSTEMI) Usually 48h post STEMI, late VT (>48h) has very poor prognosis 	<ul style="list-style-type: none"> Antiarrhythmic agents (amio, lidocaine) Urgent resusc if due to ischemia Cardioversion/defibrillation to prevent VF and restore hemodynamic stability Correct underlying abnormalities (pH, K, Mg, hypoxemia)
	Ventricular Fibrillation	<ul style="list-style-type: none"> <u>Risk factors</u>: Tage, prior MI (scar), anterior MI, cardiogenic shock, ↓ LVEF, CKD VF >48h post-MI may indicate LV dysfunction 	<ul style="list-style-type: none"> 5% of STEMI 1% of NSTEMI 	<ul style="list-style-type: none"> See: ACLS: Defibrillation Anti-arrhythmic infusion (24-48h amiodarone post-defibrillation) Maintain K>4, Mg>2.2

Circuit	Coronary Vessel Supply
SA Node	60% from RCA, 40% from LCx
AV Node	90% from distal RCA, 10% from distal LCx
Bundle of His	AV nodal artery (RCA), LAD septal perforators
RBB	LAD septal perforators, collaterals from RCA/LCx
LBB	LAD, collaterals from RCA/LCx
LAFB	LAD septal perforators (single supply, sensitive to ischemia)
LPFB	AV nodal arteries proximally, distally dual supply from LAD/PDA septal perforators



Cardiology



Cardiac Catheterization

ANATOMY

- LCA and RCA & their branches create two rings around the heart: RCA + LCX in AV groove; LAD + PDA in IV groove
- 80% of PDA arises from RCA (right dominant), thus inferior MI more likely due to RCA lesion; 10% from LCx; 10% co-dominant

PREPARATION FOR CATHETERIZATION

- NPOPMN; INR<2; monitor Cr closely, no ppx abx. Continue ASA, statin, BB, UFH gtt (hold when on call) or LMWH (hold 24h prior to cath; see [Peri-Procedural AC](#)). Hold metformin (usually 1d pre-, 2d post-proc), may need to hold/delay starting ACEi
- Document b/l radial, femoral, popliteal, DP pulses, & Allen's test. Check for bruits. Note history of HIT, PVD, Ao aneurysm/dissection
- Contrast allergy:** pre-tx w/ steroids & benadryl if patient has documented allergy. See [Contrast Allergy](#) for MGH protocols. Consult Allergy for expedited protocol if the cath is required emergently
- Respiratory distress:** patient will need to lie flat; consider intubation if prohibitive hypoxemia/pulmonary edema
- Pre-hydration** w/ crystalloids and NAC/bicarb have not been shown to prevent CIN in most patients with moderate CKD ([Lancet 2017;389:1312](#); [NEJM 2018;378:603](#)); [CIN risk calculator](#); diagnostic cath = 25cc contrast (CT-PE = 80-100cc). See [Contrast](#)

PERCUTANEOUS CORONARY INTERVENTION CONSIDERATIONS

- Access:** fewer bleeding/vascular complications if **radial** (vs femoral), possible ↓ death in ACS ([JACC 2018;71:1167](#)); due to radial vasospasm, CCB or nitroglycerin is administered along with UFH to prevent arterial occlusion
- BMS vs DES:** ↓ in-stent thrombosis with **DES** leading to subsequent ↓ revascularization; however, ↑ risk of late stent restenosis so requires longer duration of DAPT
- Contraindications to stents:** predicted DAPT non-adherence, anticipated major surgery within treatment time, elevated bleeding risk
- Antiplatelet:** 81mg ASA indefinitely ([Circ 2016;134:e123](#)). P2Y12 inhibitor added after cath (prasugrel, ticagrelor or clopidogrel)
 - Not high bleeding risk:** ACS, 12mo DAPT (DES/BMS); stable ischemic heart disease, ≥6mo DAPT if DES or ≥1mo if BMS
 - High bleeding risk:** ACS, 6mo DAPT (DES/BMS); stable ischemic heart disease, ≥3mo DAPT if DES or ≥1mo if BMS
 - Triple therapy: see [ACS](#)

POST-PROCEDURE CARE

- Groin access:** 4-6h bedrest after procedure. Closure devices decrease time needed for bedrest
 - Groin checks immediately, 6h, 8h post-procedure: **check b/l pulses, palpate for pulsatile masses, auscultate for bruits**
 - Sheaths: during pass-off, ask interventional fellow about timing of arterial removal; **only cardiology fellows remove sheaths**
- Radial access:** TR band for 4-6h

POST-CATHERIZATION COMPLICATIONS

- Access site complications:** always inform the interventional fellow who performed the procedure, **diagnose by exam and US**
 - Hematoma:** mass w/o bruit. Apply compression. If unable to control, may require Fem-Stop device to apply external pressure
 - Pseudoaneurysm:** pulsatile mass with bruit at access site. Tx w/ compression; if <2cm, may require thrombin injection or surgery if >2 cm. Urgent US & Vascular Surgery consult
 - AV fistula:** continuous bruit with no mass. Evaluate w/ US. Surgical repair usually necessary
 - Limb ischemia:** from thrombus, dissection, or malpositioned closure device. Evaluate pulses, limb warmth, & PVR
 - Retroperitoneal bleed:** presents within **hours** post-cath, often with hemodynamic instability ± flank pain ± ecchymoses. **STAT CT A/P if stable.** Transfuse, IV fluids, discuss with attending about stopping/reversing anticoagulation
- Other complications:**
 - Infection:** more common in setting of vascular closure devices
 - Atheroembolism:** eosinophilia; livedo reticularis; blue toes; mesenteric ischemia; acute, subacute, or chronic renal dysfunction
 - CIN:** occurs within 24-72h with peak Cr 1-5d post contrast load, risk correlated with contrast load and initial GFR
 - Tamponade:** post-cath **hypotension** from coronary or cardiac perforation. Check pulsus paradoxus ($\Delta >10\text{mmHg}$), **STAT TTE**, alert cath fellow. Consider IVF to temporize
 - MI/CVA:** due to in-stent thrombosis (MI) or distal embolization post-cath (CVA). Discuss all CP/neuro changes with cath fellow
 - Radiation injury:** more common in CTO cases. Occurs days to weeks after PCI. Ranges from erythema to skin ulceration

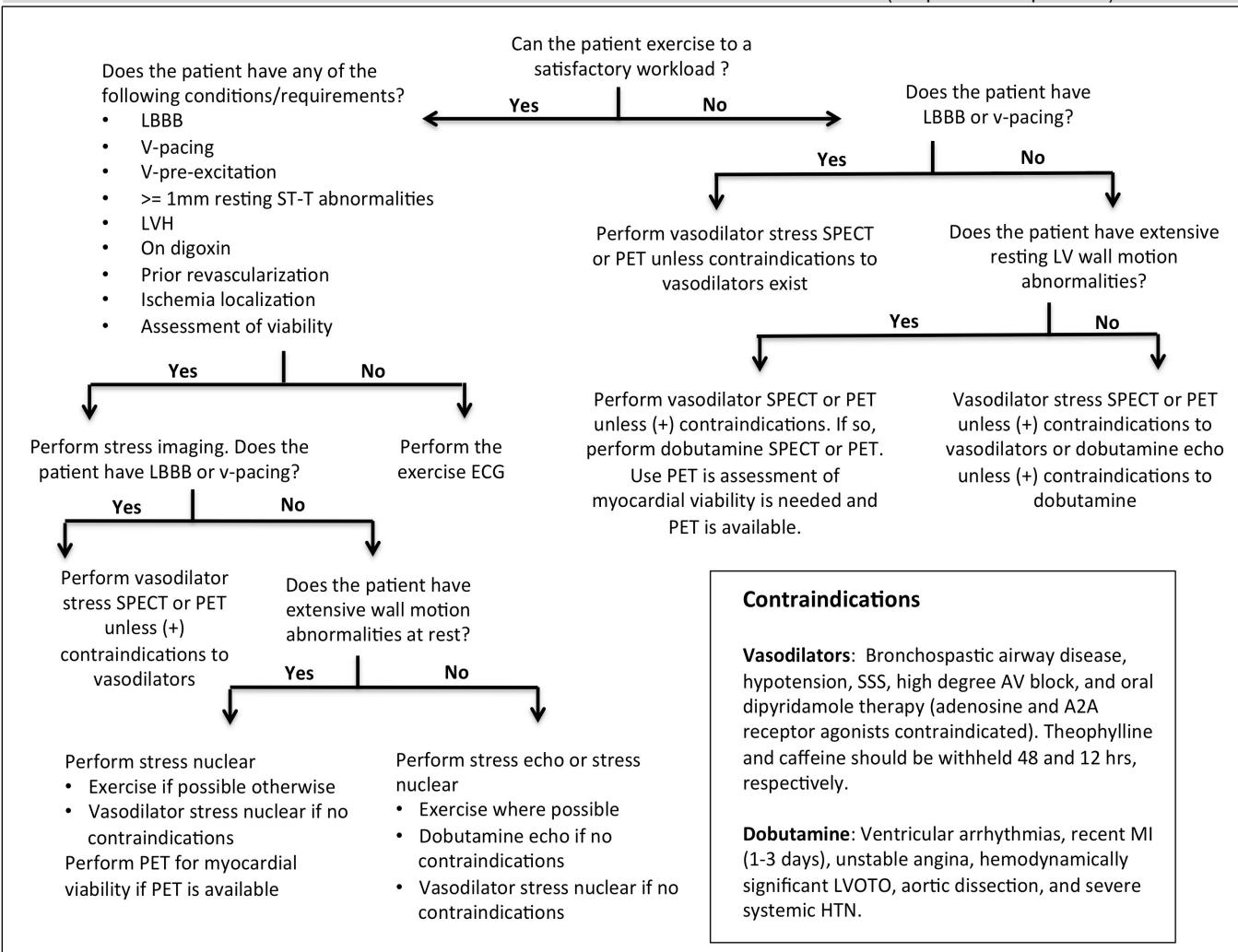
Cardiology

Non-Invasive Cardiac Testing

STRESS TESTING BASICS

- Indications:**
 - Diagnose CAD: sx of stable angina in pts with intermediate-high risk of CAD. Not indicated for low risk or asymptomatic pts
 - Evaluate new or changing sx concerning for ischemia in pts with known CAD
 - Post-revascularization: evaluate pts with angina or asymptomatic pt if incomplete revasc or >2y post-PCI/5y post-CABG
 - Pre-op risk assessment: not routinely indicated (see *Perioperative Medicine*)
 - Newly diagnosed HF or cardiomyopathy likely 2/2 ischemia, functional capacity (for exercise prescription), viability testing, valvular disorders
- Contraindications**: untreated ACS, MI within 2d, high risk or LM CAD, uncontrolled arrhythmia, ADHF, severe AS or HOCM, recent DVT/PE, acute myo-/peri-/endocarditis, aortic dissection, uncontrolled HTN
- Preparation**: NPO 3h prior, longer if imaging or adenosine. Must reverse DNR/DNI for test
 - If the question is “*Does the patient have CAD?*” → **hold BB and nitrates**
 - If the question is “*How well are meds working in known CAD?*” → **continue BB and nitrates**
 - Hold caffeine** >12h for adenosine. Hold BB >24h for dobutamine
- Caveats**:
 - Majority of vulnerable plaques are angiographically insignificant (<70% stenosis) → stress testing unable to identify the presence of these plaques (CTA more sensitive)
 - Angiographically significant (>70% stenosis) 3VD may produce false-negative vasodilator stress test → “**balanced ischemia**”
- Positive test results**: optimize medical tx. Decision re: angiography/revascularization varies by pt (degree of sx, known stenosis, current meds). In ISCHEMIA trial, revascularization did not Δ ischemic CV events for pts w/ stable CAD ([NEJM 2020;382:1395](#))

SCHEMATIC APPROACH TO NONINVASIVE CARDIAC TESTING (adapted from UpToDate)



Stress Modality	Imaging Modality
Exercise (treadmill)	EKG, TTE, SPECT
Vasodilator (adenosine, regadenoson)	TTE, SPECT, PET, MRI
Inotropy (dobutamine)	

Cardiology

Non-Invasive Cardiac Testing

STRESS TESTS

Exercise Tolerance Test (ETT) → ECG or imaging (TTE, SPECT)

- ETT preferred over pharmacologic testing if pt is able to reach goal exertion
- Assesses exercise duration, METs, BP/HR response, HR recovery, double product (HR x SBP), [Duke Treadmill Score](#) (estimates risk of CAD in pts w/ chest pain undergoing exercise stress testing, [Circ 1998;98:1622](#))
- **Protocols:** Bruce (large changes in workload between stages), modified Bruce (for less fit pts → adds stages of lower workload)
- **Diagnostic** if >85% max-predict HR (220-age), peak double product ($HR \times BP$) >20k, HR recovery ($HR_{peak} - HR_{1\text{min post-exercise}}$) >12
- **Increased probability of ischemia:** ↑ # of leads with STD, ↑ degree of max STD, ↓ METs when EKG changes occur, ventricular ectopy during recovery, increased time to recovery of EKG, failure of SBP to rise with exercise

Pharmacologic Stress Test → imaging only (TTE, SPECT, PET, MRI)

- **Choosing an agent:**
 - **Adenosine/Regadenoson:** detects ischemia by coronary steal (vasodilation via cAMP). Stenosed coronary arteries are unable to further dilate to adenosine → limited flow reserve to distal areas and relative perfusion deficit
 - Side effects: **wheezing, bradycardia, HoTN.** Caution if ACTIVE bronchospasm, high grade AVB, SSS, severe AS
 - **Regadenoson:** decreased respiratory/conduction side effects, more cost-effective in obese pts. Caution if seizure hx (reversal agent aminophylline ↑seizure risk)
 - **False negative** can occur in 3VD: no relative perfusion deficit when all 3 vessels affected equally ("balanced ischemia")
 - **Dobutamine:** workload induced by positive inotropy and chronotropy via β-1 receptor agonism
 - **Extremely high dose** of dobutamine is given, dose titrated up to 40mcg/kg/min
 - Side effects: tachyarrhythmias. Caution if MI <48h, hx of malignant arrhythmia, severe AS, HOCM, severe HTN, severe PAH, aortic dissection
- **Choosing an imaging modality:**
 - **TTE:** preferred if primary objective is to exclude CAD (76% Sn, 88% Sp). Can give info regarding hemodynamics/valve disorders
 - *Do not use* in pts with LBBB, V-pacing or extensive wall motion abnormalities at rest
 - **Nuclear imaging:** utilizes a radioactive tracer to detect areas of ↓perfusion between rest and stress states. More expensive than TTE & high amount of radiation (SPECT > PET)
 - **PET** is more Sn & Sp than SPECT with faster image acquisition. Less widely available & most expensive. Additional uses for imaging in rheumatologic (i.e. cardiac sarcoid) and oncologic contexts (i.e. cardiac myxoma, metastases)

VIABILITY TESTING

- Indication: determine viability of ischemic myocardial tissue ("hibernating myocardium")
- Imaging modalities: SPECT (thallium or sestamibi), PET, TTE, MRI
 - SPECT is performed using exercise or pharmacologic stress. PET/TTE/MI performed using pharmacologic stress only

REST IMAGING

Coronary CTA: used to evaluate for presence and extent of CAD ([JACC 2010;55:2663](#))

- Requires cardiac gating (goal HR 60-70, may need to give BB) and respiratory gating (breath hold for 5+ sec)
- Indications:
 - Should NOT be used to screen asymptomatic pts
 - **Low risk pts:** has high NPV (99%) for CAD rule-out ([JACC 2008;52:1724](#))
 - Moderate risk pts: reasonable to further risk stratify pts at intermediate risk of CAD or pts with equivocal stress test results
- Findings: 2y ACS risk significantly elevated if high-risk plaque (16%) and/or stenotic disease (6%) ([JACC 2015;28:337](#))
 - Higher Sn & Sp for coronary stenosis compared to cMRI ([Annals 2010;152:167](#))
- Less useful in pts with extensive calcifications or stented vessels due to "blooming" artifact (cannot evaluate patency)

Coronary Artery Calcium (CAC) Scans: CT modality that provides risk assessment score (CAC or "Agatston" Score) for CAD. Either performed alone or concurrently with coronary CTA. Non-gated, **non-contrast chest CT** scans can be used to provide a **qualitative** estimation of CAC score

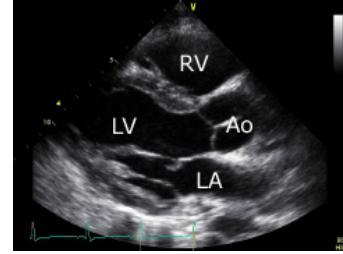
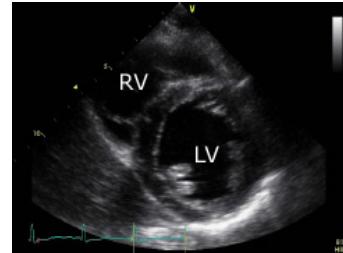
- Indications: to guide decision making for primary prevention for asymptomatic adults ≥ 40 y at intermediate risk (7.5-19.9% 10y ASCVD risk) if statin therapy decision remains uncertain. Do NOT use as a stand-alone test in evaluation of symptoms of myocardial ischemia. Do NOT use in high risk patients, including those with familial hypercholesterolemia
- Findings:
 - If CAC (Agatston) scores ≥ 100 or $> 75\%$ ile for age & gender independent of ASCVD risk, recommend aggressive therapeutic lifestyle changes, ASCVD RF modification (BP, smoking cessation, diabetes treatment), & statin therapy ([JACC 2019;73:285](#))
 - For those with calcium score of 0, reasonable to defer statin therapy for up to 5 years ([Circ 2019;140:496](#))

Cardiac MRI:

- Modality of choice for assessment of functional & tissue properties of the heart that cannot be adequately assessed w/ echocardiography or CCTA (inflammation, infiltration, cardiac tumors, pericardial disease)
- Preferred for post-CABG vessel imaging, evaluation of suspected or known congenital or acquired coronary abnormalities

Cardiology

Echocardiography

View/Description	Position	View*
PARASTERNAL LONG AXIS <ul style="list-style-type: none"> • LV size, function, wall thickness (septum/posterior wall) • MV/AoV function/flow (w/ Doppler) • LVOT diameter, aortic root size 	Patient: lying on left side, with left arm under head Probe: 2-3 inches left of sternum at 3 rd -4 th intercostal space, indicator at 10 o'clock (facing R shoulder) 	
PARASTERNAL SHORT AXIS <ul style="list-style-type: none"> • Cross-sectional views of the heart from base to apex, at level of AoV, MV and mid-ventricle/papillary muscles 	Patient: same as above Probe: from long axis view, turn probe clockwise until indicator at 2 o'clock (facing L shoulder) 	
APICAL 4 CHAMBER <ul style="list-style-type: none"> • RV/LV size, function, thrombus • TV/MV function/flow (w/ Doppler) • Septal size/motion • Pericardial effusion • In 5-chamber view, can see AoV and proximal ascending aorta 	Patient: lying flat on back Probe: at PMI w/ probe indicator at 3 o'clock (to the pt's L). For 5-chamber view, tilt probe upward 	
SUBXIPHOID <ul style="list-style-type: none"> • RV/LV size, function • Pericardial effusion 	Patient: laying flat on back, can slightly bend legs Probe: below xyphoid process, indicator to pts R 	
INFERIOR VENA CAVA <ul style="list-style-type: none"> • IVC diameter and respiratory variation gives estimate of volume status and RA pressure 	Patient: same as above Probe: rotate probe 90°, indicator should point towards the patient's head	

*Images from <https://echobasics.de/tte-en.html>

REVIEWING THE MGH REPORT: for questions or clarification of findings, call Echo Lab (x6-8871) or page on-call Echo Fellow

- Valvulopathy: stenosis/regurgitation (valve area, gradients, severity), leaflet numbers/motion, vegetations
- Structure/chamber dimensions: aorta, LVIDd & LVIDs (LV internal diameter in diastole & systole), IVS (septum), PWT (posterior wall thickness, ↑ in LVH, diastolic dysfunction)
- EF: “preserved” EF ≥50%, “borderline” EF 40-50%, “reduced” EF <40%
- WMA: territory correlates w/ coronary vessels (anterior + septal = LAD, inferior = RCA, lateral = LCx). If global WMA, r/o diffuse ischemia vs non-ischemic insult (sepsis, stress)
- RVSP: RVSP=4v² + RAP. **RAP assumed to be 10 mmHg** and v = TR jet velocity. Can suggest pHTN if >35 (not gold standard for dx)

Indications for STAT TTE:

- Eval hemodynamic instability of suspected cardiac etiology
- Eval for early MI complication
- Suspected MI w/ non-diagnostic biomarkers and EKG
- Identify potential cause of cardiac arrest

CLINICAL QUESTIONS AND ASSOCIATED TTE FINDINGS

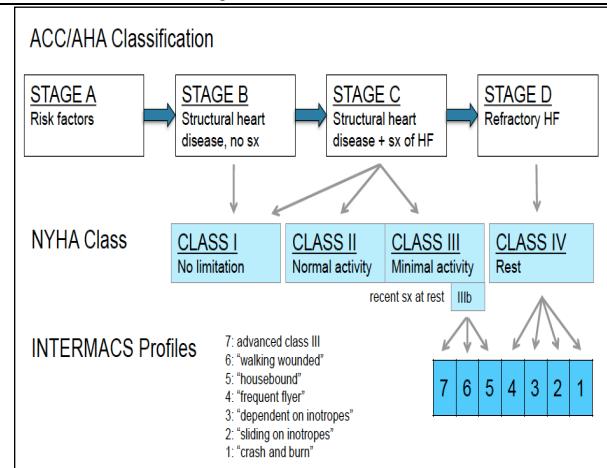
- Right heart strain in acute PE: RV WMA or hypokinesis, RV dilation (RV:LV ratio >1), interventricular septal bowing, IVC collapse, “D-sign”: septal flattening, “McConnell’s sign”: RV free wall akinesia w/ normal RV apex motion (77% Sn, 94% Sp for acute PE)
- Tamponade: large effusion, swinging heart, R-sided chamber collapse, interventricular septal bowing, dilated IVC (no ↓ w/ inspiration)
- ACS/mechanical complications of ACS: regional WMA, septal/free wall rupture, acute MR, LV thrombus
- Stress (Takotsubo) cardiomyopathy: LV apical ballooning and akinesis/hypokinesis
- Heart failure: depressed EF, RV/LV hypertrophy and/or dilation, regional WMA
- Constrictive pericarditis: thickened or hyperechoic pericardium, abnormal septal motion, respiratory variation in ventricular size, dilated IVC

Cardiology

Inpatient Heart Failure

INITIAL WORKUP - NEW HEART FAILURE DIAGNOSIS

- Echocardiography:** TTE for all new presentations; obtain thereafter only if concern for clinical/functional change
 - **HFrEF** (EF ≤40%), **HFmrEF** ("mid-range" EF 41-49%), **HFpEF** (EF ≥50%)
- Ischemic workup:** FHx, EKG, TnT, stress test, cor. angio. vs CCTA
- Non-ischemic workup:** FHx, CBC, BMP, LFTs, lipid panel, TSH, A1c, urine hCG, iron studies, HIV, SPEP/SFLC w/ UFC
 - Consider: ANA, *T. cruzi* serologies, viral panel, antimyosin Ab, tox screen, thiamine, genetic testing, cardiac MRI, endomyocardial bx (if serologic testing neg, new onset <6mo unexplained HF, major arrhythmias) to r/o myocarditis, ARVC, sarcoid, cardiac masses
- Consider high-output etiologies:** anemia, thyroid dysfxn, liver failure, Paget's, systemic infection, AV shunts



Dilated Cardiomyopathy

Etiologies: **Ischemic** (most common cause, 50-75%), HTN/LVH, valvular (e.g. MR), myocarditis, stress-induced (Takotsubo), tachyarrhythmia, infiltrative (as below) CTD, ARVC, LVNC, HIV, cocaine/methamphetamines, EtOH, chemotherapy, nutritional deficiency, cirrhosis, sepsis, peripartum, idiopathic/genetic

Condition	Etiology and Management
Alcohol-induced	Mechanism: associated with >80g/d EtOH (6 standard drinks) over >5y (toxic to myocytes via O ₂ free radicals + defects in protein synthesis) Tx: abstinence + HF therapy Prognosis: better/equivalent to idiopathic CM if <20g/d (<2 drinks) or abstinence, worse w/ continued EtOH use
Stress-induced (Takotsubo)	Mechanisms: catecholamine surge from physical/emotional stress, coronary artery spasm, microvascular ACS Presentation: may present like ACS with CP (most common), SOB, shock, syncope. If in shock, urgent TTE to assess for LVOT obstruction Dx (need all 4): 1) transient dysfxn of LV mid-segments, WMAs extending beyond a single coronary distribution; 2) rule out ACS/obstructive CAD (via cath); 3) new EKG Δ (STE or TWI) OR ↑TnT; 4) absence of pheo or myocarditis Tx/Prognosis: Remove stressor, ACEi (may improve survival), BB; most recover LV function in 1-4w

Hypertrophic Cardiomyopathy (HCM) (JACC 2020;76:e159)

Characteristics: LV and/or RV hypertrophy of various morphologies ± LVOT dynamic obstruction (**HOCM**), diastolic dysfxn, ischemia, MR; **risk of arrhythmia/SCD**

Exam: SEM at LLSB/apex that augments with Valsalva or on standing (due to ↓ preload); S2 paradox split, S4

Dx: **EKG** (prominent voltages w/ depolarization abnormalities, large abnormal Q waves in inferior/lateral leads, LAD, giant negative T waves in V2-V4 (apical HCM variant→ "Yamaguchi's syndrome"), **TTE** (unexplained LVH >15mm, SAM of MV, outflow tract gradient), **cMRI** (late gadolinium enhancement [LGE] = fibrosis)

Tx: **avoid volume depletion** or high dose vasodilators (may worsen obstruction). **Phenylephrine is pressor of choice** if no response to IVF bolus for HoTN (↑ afterload, stents open LVOT). Activity restriction, meds (BB > verapamil), septal ablation or surgical myectomy for medically refractory sx, ICD (for high SCD risk)

Clinical **genetic testing** (mutation in ~70%) helpful for family screening; not useful for dx or risk stratification

Risk factors for **SCD/VT**: prior VT/SCD/unexplained syncope; FHx of SCD in 1° relative; massive LVH (>30mm); NSVT on Holter; abnormal BP response to exercise; burden of LGE on cMRI

Restrictive Cardiomyopathy (JACC 2010;55:1769) – conditions below may also manifest as Dilated CM

Etiologies: in addition to below, Löffler's, radiation, metabolic storage disease, carcinoid

Tx: treat underlying disease and HF as below. For **amyloidosis**: tafamidis (↓ TTR deposition) (NEJM 2018;379:1007)

Condition	Presentation	EKG	Echo	cMRI
Amyloidosis (AL, TTR)	- HF w/ other findings of amyloid (renal, neurologic, hepatic dz)	- ↓ voltage , pseudoинфаркт pattern in inferolateral leads	- Symmetric LV/RV ↑ wall thickness , speckled myocardium	- LGE in subendocardium
Hemochromatosis	- If hereditary: M >30yo; F >40yo - If 2°: any age - Abnl LFTs , arthralgias, DM , hyperpigmented skin	- SVT (ventricular conduction abnormalities rare)	- Dilated LV with global systolic dysfunction	- Iron overload with T2 protocol
Sarcoidosis	- Young adult w/ HF (more commonly as DCM)	- Infrahisian block , atypical infarct pattern	- Variable wall thickness, focal/global hypokinesis, LV aneurysm	- Patchy enhancement of basal and LV walls

INPATIENT ACUTE DECOMPENSATED HEART FAILURE (ADHF)

- Admission orders: tele, 2g Na restricted diet, daily standing weights, strict I/Os, DVT ppx
- Avoid:** CCB (esp. non-dihydropyridines), NSAIDs, flecainide
- Check NT-proBNP (& weight) on admission and at discharge
 - ADHF unlikely if NT-proBNP <300 (NPV 98%), likely if >450 (>900 if age >50) ([Am J Cardiol 2005;95:948](#))
 - Difficult to interpret in CKD/dialysis. May be falsely low in **obesity**, HFrEF
- Screen for & treat **iron deficiency** in all HF pts independent of Hgb ([JACC HF 2019;7:36](#))
 - Dx: ferritin <100 or ferritin <300 + TSat <20% ([JACC 2017;70:776](#)); though some evidence that TSat ≤19.8% or serum iron ≤13 μmol/L most predictive & ferritin may be less useful ([Circ Heart Fail 2018;11:e004519](#))
 - Tx: replete with IV iron ([JACC 2018;71:782](#)) to ↓sx, ↑functional capacity, ↑QOL (FAIR-HF, [NEJM 2009;361:2436](#)); PO ineffective in HF ([JAMA 2017;317:1958](#))

ADHF MANAGEMENT – FLOOR/SDU

- Identify **hemodynamic profile & triage** accordingly ([JACC 2019;74:1966](#))
 - Warm vs Cold: adequate vs inadequate tissue perfusion (AMS, lactate, cool extremities, narrow PP)
 - Dry vs Wet: presence vs absence of congestion (JVD, crackles, pleural effusions, ascites, LE edema, interstitial/alveolar edema on CXR)
 - Evaluate for signs of **pulmonary congestion on exam**. Pulm edema may be **absent on CXR** in chronic HF due to lymphatic compensation ([Chest 2004;125:669](#))
 - ~80% of decomp HFrEF and nearly all decomp HFpEF pts will be warm and wet

		Congestion at Rest	
		NO	YES
Low Perfusion at Rest	NO	Warm and Dry Outpatient mgmt	Warm and Wet Diuresis ± Vasodilators
		Cold and Dry Inotropes (ICU)	Cold and Wet Tailored Therapy (ICU)

- Identify precipitants**: dietary/med non-adherence (~40%), **new ischemia/infarction**, uncontrolled HTN, arrhythmia, inadequate diuretic dose, meds (NSAIDs, steroids, CCB, TZDs, anthracyclines), acute infection (URI, PNA, UTI), AKI, PE, toxins (EtOH, cocaine), new/worsening valve disease, myocarditis
- Early/Acute Management**:
 - Diuresis**: ↓CVP, PCWP to optimize Starling curve mechanics & relieve sx ([NEJM 2017;377:1964](#); [JACC 2020;75:1178](#))
 - Initial tx: IV loop diuretics (furosemide, bumetanide, torsemide), start with 2x home dose (IV/PO). No difference between continuous gtt vs bolus dosing (DOSE, [NEJM 2011;364:797](#)). See [Advanced Diuresis](#) for conversions
 - Refractory diuresis: metolazone 2.5-5mg (or chlorothiazide 500mg IV) administered 30min before loop diuretic. May need RHC to clarify hemodynamics or inotropes to augment diuresis. Step-up pharmacologic therapy superior to RRT in the setting of cardiorenal syndrome ([NEJM 2012;367:2296](#))
 - Worsening renal function: occurs in ~23% of pts treated for ADHF. Mild-mod “Cr bumps” are likely benign hemodynamic changes, should not necessarily preclude further diuresis if pt still congested ([Circ 2018;137:2016](#))
 - Endpoints: target resolution of signs/symptoms of congestion. Daily weights & hemoconcentration are useful adjuncts
 - If acute pulmonary edema, **NIPPV** may improve mortality and need for intubation ([Annals 2010;152:590](#))
 - Vasodilators**: arterial/venous dilation can relieve symptoms by ↓afterload, ↓PCWP and ↑SV. Can accelerate early sx relief. Consider esp. in severe HTN, acute MR, acute AR
 - Floor: isosorbide dinitrate, hydralazine, nitropaste, captopril; SDU/CCU: TNG, nitroprusside
 - Guideline-Directed Medical Therapy (GDMT)**: if not in cardiogenic shock, continue ACEi/ARB and βB during ADHF (but do not newly initiate βB) ([EHJ 2009;30:2186](#))

- Pre-Discharge Optimization**: document **d/c weight & NT-proBNP**, appt in HF Transitions Clinic if pt has MGH cardiologist

- HFrEF (EF ≤40%) GDMT**:
 - Beta blockers**: initiate, uptitrate evidence-based βB (carvedilol, metoprolol succ., bisoprolol) ([COPERNICUS](#); [MERIT-HF](#)). Caution if recently weaned from inotropes
 - RAAS inhibitors**: if renal fxn stable, initiate/titrate ACEi/ARB ([CONSENSUS](#); [CHARM](#)) or ARNI (sacubitril/valsartan) ([PARADIGM-HF](#); [PIONEER-HF](#)). Switch to ARNI from ACEi/ARB if tolerating and NYHA II-III, needs 36h washout period
 - Guidance for GDMT in advanced CKD: [JACC HF 2019;7:371](#)
 - Mineralocorticoid receptor antagonist**: initiate spironolactone or eplerenone if CrCl >30 ([EMPHASIS-HF](#); [RALES](#)). Watch for rebound hyperK after de-escalation of diuretics (check K, Cr within 72h of discharge)
 - Hydralazine/isosorbide dinitrate**: consider if contraindication to ACEi/ARB (unstable renal fxn) or in African Americans w/ persistent NYHA III-IV sx despite BB and ACE/ARB ([A-HeFT](#))
 - SGLT2i (dapagliflozin, empagliflozin)**: further reduce CV deaths & HF admissions regardless of DM hx ([DAPA-HF](#); [EMPEROR-Reduced](#); [Lancet 2020;396:819](#)) (see [Outpatient Type 2 Diabetes](#))
- Diuretic plan**: determine maintenance diuretic dose and provide specific instructions for taking additional rescue doses. Observe on maintenance dose and decide if needs K replacement
- HFmrEF (EF 40-49%)**: treat with diuretics & consider adding GDMT agents for HFrEF ([Curr Heart Fail Rep 2020;17:1](#))
- HFpEF (EF ≥50%)**: prevent volume overload, treat with diuretics, treat comorbidities (DM, HTN, AF)
 - Consider **spironolactone** if normal renal fxn/K, ↓CV death/admits in N/S Am. sites in TOPCAT ([Circ 2015;131:34](#))
 - No proven benefit to BB ([EHJ 2018;39:26](#)), ACEi ([PEP-CHF](#)), ARNi ([PARAGON-HF](#)), ARB ([CHARM-Preserved](#); [I-PRESERVE](#))
- ICD indicated** if: ischemic CM w/ EF ≤30 or ≤35% w/ NYHA II-III; CRT if: EF ≤35% & prolonged QRS ± LBBB & some w/ EF ≤50% (see [Cardiac Devices: PPM/ICD](#) & guidelines for specifics: [JACC 2013;61:e6](#); [EHJ 2016;37:2129](#))

CARDIOGENIC SHOCK – CCU

- Definition: HoTN (SBP<90 for 30min or pressor req) + **hypoperfusion** (cold extremities, oliguria, lactate) + hemodynamics (CI <2.2, PCWP >15, [EJH 2019;40:2671](#))
- Etiology: acute MI ± mechanical complications, end-stage heart failure, acute myocarditis, acute MR/AR, myocardial contusion
- Evaluation: EKG, troponin to r/o acute MI. TTE to exclude tamponade/mechanical lesions/contraindications to MCS
- Monitoring: A-line, consider **PA catheter** for inotropes/pressors and MVO₂ monitoring

Immediate Management:

- If c/f **acute MI**, activate cath lab for immediate revascularization (only intervention proven to definitely improve outcomes in cardiogenic shock) ([NEJM 1999;341:625](#))
- Consider early **SHOCK consult** (p11511). Escalating inotropes/pressors exacerbate myocardial supply/demand imbalance and are associated with poor outcomes. Emerging evidence supports early initiation of MCS ([Cath Cardio Interv 2019;93:1173](#))
- Stabilize MAP with **norepinephrine** PRN prior to obtaining PA catheter to guide tailored therapy

Tailored Therapy:

 uses invasive hemodynamic monitoring (i.e. PAC) to guide medical therapy

- **Goals:** tissue perfusion (↑CO, MAP), decongestion (↓CVP, PCWP), ventricular unloading (minimize myocardial O₂ demand)
 - **Preload:** LVEDV ∝ LVEDP ≈ PCWP; goal **PCWP 14-18, PAD 16-20, CVP 8-12**
 - Diuresis, UF with RRT, TNG
 - **Afterload:** wall stress ∝ MAP (Laplace's law); SVR = (MAP - CVP)/CO; goal **MAP >60, SVR <800-1200**
 - **Vasodilators:** captopril, hydralazine, nitroprusside, TNG
 - **Vasopressors:** ↑afterload, sometimes needed to ↑MAP in mixed shock or to counteract vasodilatory effect of inodilators
 - **IABP:** (see [Mechanical Circulatory Support](#))
 - **Contractility:** ∝ CO for given preload/afterload; goal **CO>4, CI >2.0-2.2, MVO₂ >65**
 - **Dobutamine (inodilator):** β1>β2 agonist (↑production of cAMP); initial dose 0.5-1 mcg/kg/min
 - Watch for tachycardia, ↑ventricular response to AF, arrhythmias, ischemia, HoTN, tachyphylaxis in infusions >24-48h
 - **Milrinone (inodilator):** PDE-3 inhibitor (↓breakdown of cAMP); initial dose 0.125 mcg/kg/min
 - Watch for tachycardia, arrhythmias, ischemia, HoTN. Compared to dobutamine, milrinone has longer half-life, greater pulmonary vasodilatation, slightly less chronotropy, fewer arrhythmic events
 - Preferred in patients on βB and w/ RV failure. Is renally cleared. Often choice for home inotrope for palliative therapy
 - Epinephrine, norepinephrine, dopamine (inopressors): use if severe HoTN, unable to tolerate inodilators
 - Watch for tachycardia, arrhythmias, end-organ hypoperfusion
 - **Advanced:** consideration of need for mechanical circulatory support or transplant
 - Goal of mechanical circulatory support: improve systemic perfusion while reducing myocardial oxygen demand (in contrast to inotropes which ↑CO at the expense of increased oxygen demand)
 - Types of MCS at MGH: IABP, Impella, VAD, VA-ECMO (see [MCS](#)) – if considering, obtain SHOCK c/s (p11511)
- **Limitations:**
 - CO measured via thermodilution or calculated using Fick equation: CO = VO₂/(13.4 × Hgb × [SpO₂-MVO₂]); CI = CO/BSA; VO₂ estimate = 125 × BSA
 - Thermodilution: uses temp gradient between two points on PAC. Less reliable if shunt/valvular insufficiency (e.g. TR)
 - Fick equation: assumes a VO₂ (oxygen consumption) that in reality varies depending on physiologic state (e.g. infxn)

Cardiology

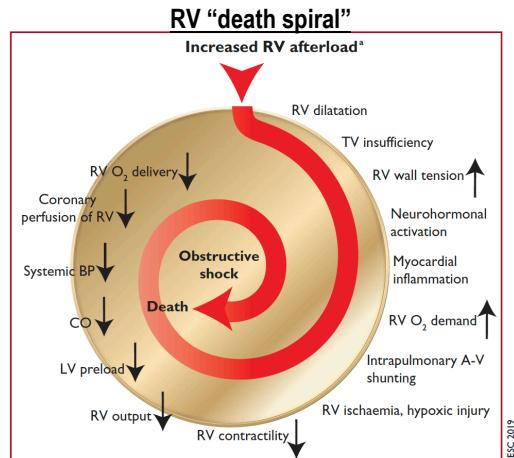
Right Ventricular Failure

PATHOPHYSIOLOGY

- Normal RV function: governed by systemic venous return, PA pressure, pericardial compliance, and native contractility of the RV free wall and interventricular septum. The RV is coupled to the high-compliance, low-resistance pulm circulation → can adapt to changes in volume >> pressure
- Acute RV Failure: RV & LV interdependent → failure of RV → failure of LV via: (1) decreased LV preload because RV output = LV preload & (2) septal bowing into LV, causing diastolic impairment ("Bernheim effect")
 - ↑RV afterload (e.g. PE, hypoxia, acidemia), ↑RV preload (e.g. L→R shunt or TV disease), or ↓RV contractility (e.g. MI, myocarditis) all lead to increased RV wall stress & resultant ischemia
- Chronic RV Failure: gradual ↑RV afterload (from PH, PS, TR) → **RV "death spiral"**

CLINICAL FEATURES AND WORKUP

- Exam: ↑JVP, peripheral edema, RV heave, pulsatile liver, split S2, new TR (loudest at RLSB)
- Imaging: PA/lateral CXR; CT → RV/LV ratio >0.9 suggests RV strain
- Echo: measure RV size/function to elucidate underlying etiology. RVEF based on displacement of base towards apex; TAPSE = tricuspid annular plane systolic excursion
 - RVSP: correlates w/ RHC but can vary up to 10mmHg (esp w/ chronic lung disease, PPV)
- RHC: gold standard for measurement of ventricular filling pressures, CO, PA pressures
 - RV function: CVP/PCWP ratio: normal = 0.5; ↑ is sign of RV failure; PAPI: (PAs – PAd)/CVP <0.9 = RV failure; RV stroke work index: (mPAP – CVP) x (CI/HR) x 0.0136 (normal 8-12 g/m/beat/m²)
- Labs: ↑NT-proBNP, troponin, also ↑Cr and LFTs 2/2 venous congestion



Eur Heart J 2020;41:543

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MANAGEMENT (AHA: [Circ 2018;137:e578](#))

- Treat reversible causes (pericardial disease, RVMI, PE, hypoxemia, infections)
- Preload (CVP goal 8-12mmHg): both hypo- and hypervolemia can ↓CO
 - Acute: judicious IVF (0.5-1L) in acute RVMI or PE in absence of CVP elevation (goal CVP 10-14 in RVMI)
 - Subacute/chronic: IV diuresis to ↓RV filling pressures, ↓functional TR, and improve LV CO
- Afterload:
 - Systemic: if pt hypotensive, start pressors – **do not tolerate HoTN** as propagates RV death spiral (↓CPP); no clinical data regarding pressor of choice, but often choose vasopressin or norepinephrine (vaso affects PVR less than norepi)
 - Pulmonary: remove factors that ↑pulm vasc tone (e.g. hypoxemia, acidemia). Consider pulm vasodilators if evidence of PAH (inhaled>oral to deliver vasodilators to ventilated vascular beds)
 - Types: iNO, prostacyclin agonists (epoprostenol, inhaled or IV), endothelin antagonists (e.g. bosentan, ambrisentan), nitric oxide enhancers (e.g. PDE-5 inhibitors: sildenafil, tadalafil)
- Contractility: dobutamine or milrinone (milrinone: ↑reduction in RV afterload but higher risk of hypotension)
- Devices: if refractory RVF, consider RV MCS and/or pulmonary support (Impella RP, VA-ECMO)

INTUBATION AND MECHANICAL VENTILATION ([Curr Heart Fail Rep 2012;9:228](#))

- Intubation/NIPPV in RV failure precipitate risk for **hemodynamic collapse & cardiac arrest**
 - Drugs commonly used in intubation (BZDs, propofol, muscle relaxants) → tendency towards vasodilation and negative inotropy → decreased venous return → decreased LV preload → systemic hypotension → propagates "death spiral"
 - Consider **RSI** (etomidate >> propofol for induction) & push dose epinephrine (10-20mcg), vasopressin (1-2U), or phenylephrine if emergent intubation **anticipating hypotension**
- Positive pressure ventilation → increased pulmonary pressures and RV afterload → increased RV dilation → "death spiral"
- Vent management: prevent hypoxemia & hypercarbia (↑PVR), consider moderate TV (~8cc/kg), low PEEP (<12 cm H₂O), and moderate plateau pressure goal (<30 mmHg)

RIGHT VENTRICULAR MYOCARDIAL INFARCTION (ACC/AHA: [Circ 2013;127:e362](#))

- EKG: check R-sided EKG leads in pts with inferior STEMI (10-15% have RV involvement)
 - 1mm STE in V4R → 88% Sn, 78% Sp in inferior STEMI; STE III>II suggests RCA > LCx and ∴ RVMI
 - High-grade AV block seen in ~50% of pts with RVMI
- Management: pts with RVMI may initially benefit from fluid bolus; **caution w/ TNG (↓preload) & BB**
 - If CVP >15mmHg & BP not improving w/ IVF, additional IVF may worsen RV failure ([Eur Heart J Acute Cardiovasc Care 2013;2:226](#))

Cardiology

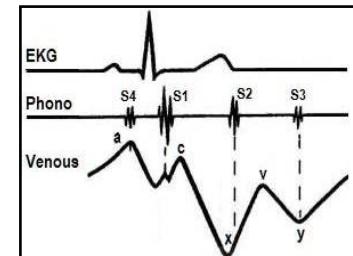
Pulmonary Artery Catheterization

OVERVIEW

- Indications:** tailored therapy; diagnose (1) etiology of shock (e.g. cardiogenic vs. distributive); (2) cardiogenic vs. non-cardiogenic pulm edema; (3) LV vs RV failure; (4) etiology of PH; (5) L→R shunting; (6) valve disease; (7) pericardial disease
- Efficacy:** controversial - ESCAPE trial ([JAMA 2005;294:1625](#)) showed no mortality benefit to PAC use in pts w/ ADHF not on inotropes. PACs are still standard of care and guideline-recommended in cardiogenic/mixed shock or in pts w/ MCS ([JACC 2013;62:e147](#))
- Line course:** central vein (IJ/subclavian/femoral) → SVC/IVC → RA → RV → PA → distal pulmonary arteriole

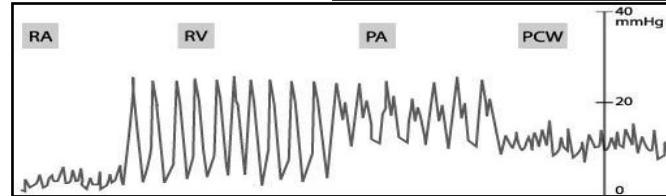
VENOUS WAVEFORMS (CVP/PCWP)

- a wave:** atrial contraction; coincides with QRS complex (on CVP tracing)
- c wave:** bowing of TV/MV into atrium during ventricular contraction; more visible in 1st degree AV block. Often absent on PCWP
- x descent:** atrial relaxation (early x descent), downward mvmt. of TV/MV (late x descent)
- v wave:** passive atrial filling (venous return) when TV/MV closed; coincides with T wave
 - Prominent v waves seen in MR & TR
- y descent:** rapid atrial emptying following opening of the TV/MV (ventricular diastole)
 - Prominent x+y descents seen in pericardial constriction; blunted y descent seen in tamponade



OBTAINING PA LINE NUMBERS ON AM ROUNDS

- Position patient supine with head-of-bed 0-60° elevation
- Check level of transducer with phlebostatic axis (4th intercostal space & mid-axillary line)
- Zero transducer to air & assess waveform for dampness
- Record PA systolic, PA diastolic, PA mean, CVP, & line position
- Open the PA catheter balloon port & remove 1.5cc air
- Inject 1.5cc air slowly until PCWP waveform observed (use minimum air required to reduce risk of PA infarction/rupture) & record PCWP (limit balloon inflation to no more than 8-10 seconds)
- Release safety syringe & allow balloon to deflate passively. Verify balloon deflated by confirmation of PA waveform
- Troubleshooting:** CXR to evaluate position
 - Arrhythmia:** catheter may be in RVOT. Talk to fellow/attending & consider repositioning catheter
 - Dampened waveform:** kinked tubing, air/thrombus, or catheter tip against vessel wall. Flush and/or withdraw catheter
 - No PCWP tracing:** catheter tip is not far enough, balloon has ruptured, or catheter coiled in RV
 - Continuous PCWP:** catheter tip is advanced too far



CALCULATING HEMODYNAMIC PARAMETERS

- Normal:** "rule of 5s" → RA 5, RV 25/5, PA 25/10, PCWP 10, LV 125/10
- Cardiac output:** TD better predicts mortality ([JAMA Cardiol 2017;10:10](#))
 - Fick** = $\dot{V}O_2 / (13.4 * Hgb * [SpO_2 - MvO_2])$ [ml: 4-7 L/min]
 - $\dot{V}O_2 \approx 250 \text{ ml/min OR } 3 \times \text{wt(kg)} \text{ OR } 125 \times \text{BSA}$
 - Thermodilution (TD):** temp change (measured by thermistor in PA) is proportional to LV CO (inaccurate w/ TR/PR, intracardiac shunt)
- Cardiac index** = CO/BSA [normal: 2.6-4.2 L/min/m²]
- SVR** = $(MAP-CVP) / CO \times 80$ [normal: 700-1200 dynes*s*cm⁻⁵]
- PVR** = $(mPAP-PCWP) / CO$ [normal: <2 Woods units]

Subtype	Hemodynamic Profiles of Shock			
	CVP [JVP]	PCWP [CXR]	CO/CI [MvO ₂ , UOP]	SVR [cap. refill]
Hypovolemic	↓	↓ [nl]	↑ [var, ↓]	↑ [delayed]
Cardiogenic	↑	↑ [nl, wet]	↓ [↓, ↓]	↑ [delayed]
Septic	Var	Var [nl, wet]	↑ [↑, ↓]	↓ [normal]
RHF or PE	↑	N [nl, large PA]	Var [var, nl to ↓]	Var [nl to ↓]
Tamponade	↑	↑ [nl, large heart]	↓ [↓, ↓]	↑ [delayed]

HEMODYNAMIC CONSIDERATIONS

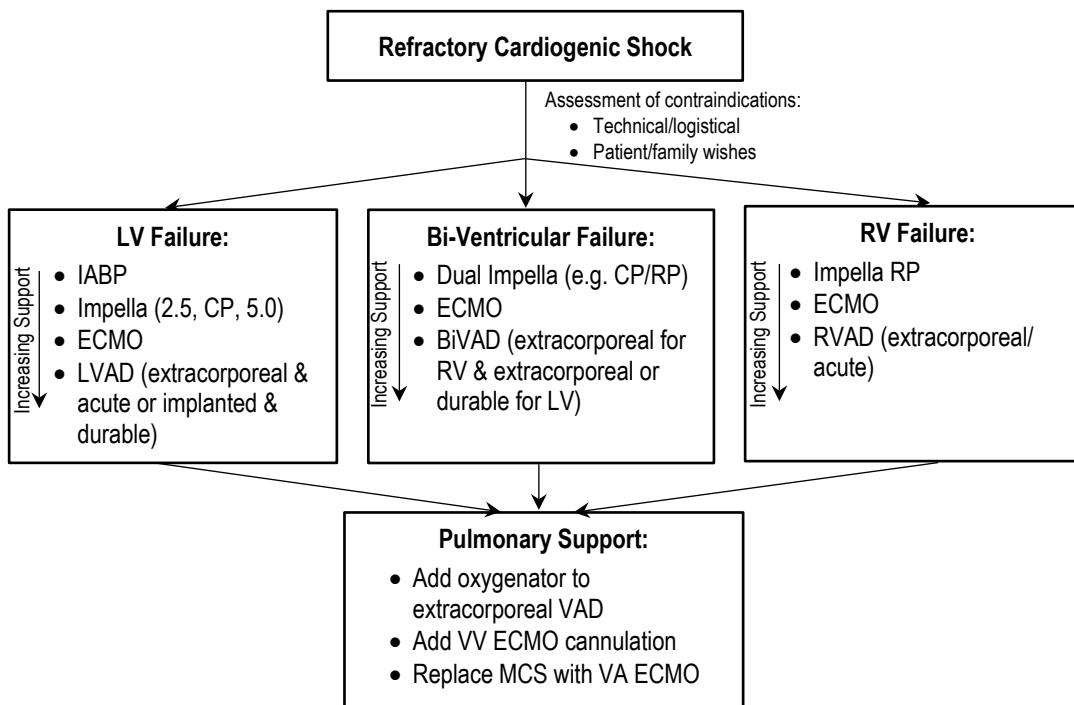
- All quantitative pressure measurements (especially PCWP) should be made at **end-expiration** (when intrathoracic pressure is zero)
 - Spontaneous respiration:** RA & PCWP ↑ with expiration → measure from the higher a waves ("patient = peak")
 - Positive pressure ventilation:** RA & PCWP ↓ with expiration → measure from the lower a waves ("vent = valley")
- Measure RA & PCWP at **end-diastole** (i.e. just before the **c wave**)
- Correlate PCWP with PA diastolic pressure; if well correlated, can trend PAd as proxy for PCWP

CLINICAL CONSIDERATIONS

- Placement:** usually through RIJ Cordis. Advance ONLY with balloon inflated. Deflate balloon when withdrawing and at ALL other times. Must have cardiology or pulmonary fellow present to place/advance at MGH
 - Cath lab if: severe PH (>70mmHg), large RV/RA, LBBB, PPM/ICD <6mo, temp wire, severe TR, prosthetic TV/PV, femoral access
- Contraindications:** absolute – insertion site infection, RVAD; RA/RV mass/thrombosis, mechanical TV/PV, endocarditis (TV/PV)
- Markings on PA catheter:** each thin line=10cm; each thick line=50cm
- Position:** on CXR: should be in middle 1/3 of the chest bilaterally. Ability to wedge more important than CXR position
- Complications:** infection, bleeding, PTX, VT, RBBB, CHB, PA rupture (place patient on side with the catheter "bleeding side down", order STAT CXR, CBC, coags, CT surgery consult), pulm infarct, PE, catheter knotting (difficult removal)
- Duration:** no data defining maximum length of time; at MGH, standard is 7d; others suggest 4-5d

MECHANICAL CIRCULATORY SUPPORT (MCS) – if inotrope-refractory cardiogenic shock, call SHOCK team (p11511)

Selected MCS Modalities					
Device	Indications	Support Provided	Considerations	Management	Complications
IABP (intra-aortic balloon pump)	<ul style="list-style-type: none"> Refractory heart failure (bridge to durable MCS) Cardiogenic shock/massive PE Refractory malignant arrhythmias Support during high-risk procedures: <ul style="list-style-type: none"> Complex PCI Ablation of ventricular arrhythmias Percutaneous valve repair Acute allograft failure 	Minimal hemodynamic support (0.5 L/min), greater in ADHF than acute MI shock (Am J Card 2019;124:1947) <ul style="list-style-type: none"> ↓LV afterload ↑Coronary perfusion Requires native contractility to work 	<ul style="list-style-type: none"> Bedside insertion Does not require AC (when at 1:1) No ↓ mortality in cardiogenic shock (IABP-SHOCK II, NEJM 2012;367:1287) Prevents mobility (if femoral placement) Least costly 	<ul style="list-style-type: none"> ✓CXR daily (tip 1-4cm below aortic knob) ✓ Waveform daily Wean by ↓ ratio (then return to 1:1, stop AC, pull) 	<ul style="list-style-type: none"> Limb ischemia Vascular injury Thromboembolism Bleeding Infection Balloon leak/rupture (STAT vascular surg c/s)
Impella	<ul style="list-style-type: none"> Support during high-risk procedures: <ul style="list-style-type: none"> Complex PCI Ablation of ventricular arrhythmias Percutaneous valve repair Acute allograft failure 	Partial LV support <ul style="list-style-type: none"> <u>Cath lab placement:</u> Impella 2.5 (2.5 L/min), Impella CP (3.5 L/min) <u>OR placement:</u> Impella 5.0 (5 L/min) or 5.5 (6.5 L/min) Partial RV support Impella RP (4 L/min) 	<ul style="list-style-type: none"> Ventricular unloading Requires AC (purge ± systemic) Allows pt mobilization (if axillary placement) Longer-term support (days to weeks) ↑ complications compared to IABP 	<ul style="list-style-type: none"> P1 (lowest) to P9 (highest support) ✓ Urine color (hemolysis), LDH ✓ Suction events (↓preload, RV failure, position) ✓ Ventricular arrhythmias (device migration) 	<ul style="list-style-type: none"> Infection Bleeding Limb ischemia Thromboembolism Thrombocytopenia Vascular injury Position alarm (reposition under fluoro/echo)
VA-ECMO		Full bi-ventricular HD support (4-10 L/min) + oxygenation & CO₂ clearance	<ul style="list-style-type: none"> Bedside and urgent insertion possible Short-term support (days/weeks) Often requires additional device for LV venting, i.e. Impella 	See ECMO	
Durable VAD	<ul style="list-style-type: none"> Bridge to transplant Destination therapy (DT) “Bridge to decision” (on transplant or DT) Bridge to recovery (LV unloading can be therapeutic) 	Full LV support (10 L/min) <ul style="list-style-type: none"> HeartMate II HeartMate 3 HeartWare HVAD 	<ul style="list-style-type: none"> Mobility Long-term support (years) 	<ul style="list-style-type: none"> BP via manual cuff w/ doppler (goal MAP 70-80) If hypotensive, place A-line If unconscious, w/o hum, and MAP<50: chest compressions TTE if any concern 	<ul style="list-style-type: none"> Acquired vWF defic. Hemolysis (possible pump thrombosis) Ventricular arrhythmias Thromboembolism RV failure AR Driveline infections



Cardiology

Cardiac Devices: PPM, ICD, & CRT

PERMANENT PACEMAKERS (PPM), IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS (ICD), & CARDIAC RESYNCHRONIZATION THERAPY (CRT)

- Types: single chamber (RA or RV lead), dual chamber (RA + RV leads), biventricular (RV + coronary sinus ± RA leads)
- PPM: sense/pace the RA & RV to treat bradyarrhythmias (see tables for nomenclature and common modes)
- ICD: device with an RV lead capable of terminating re-entrant ventricular tachyarrhythmias via pacing, cardioversion, or defibrillation
- CRT: provides simultaneous RV + LV pacing in HFrEF pts w/ wide QRS to ↓ dyssynchrony → LV reverse remodeling & ↑ LVEF
 - **CRT-P** = BiV ± RA pacing; **CRT-D** = CRT-P w/ ICD function

HARDWARE OVERVIEW

- System consists of pulse generator + leads. Usually implanted SQ in upper chest (L>R) >> abdominal
- Types: **traditional** (SQ pulse generator + intracardiac leads), **leadless** (pulse generator directly implanted into RV; no pocket complications; when battery dies, device retrieval is rare), **SQ ICD** (no IV hardware; low risk for infection but NO pacing capabilities)
- Placement: RA lead → RA appendage; RV lead → RV apex; LV lead → coronary sinus → branches of great cardiac vein
- Interrogation: page EP Technician ([p16939](#)) during normal business hours; EP fellow on call if after-hours/weekend
- MRI compatibility: not all devices are MRI compatible, however even non-MRI compatible devices may be safe to scan after re-programming ([NEJM 2017;376:755](#)). Determined on case-by-case basis by radiology. Need to know device model
- Magnet response: PPM - asynchronous pacing (DOO or VOO); ICD - suspends detection & treatment of tachyarrhythmias (pacing function unaffected)

NASPE/BPEG Codes for Pacing Operating Modes			
Position I	Position II	Position III	Position IV
Chamber(s) Paced	Chamber(s) Sensed	Response to Sensing	Rate Modulation
O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T = Triggered	R = Rate Modulation
V = Ventricle	V = Ventricle	I = Inhibited	
D = Dual (A+V)	D = Dual (A+V)	D = Dual (A+V)	

Code	Action	Use
Single Chamber Modes		
AAI	Atrial Demand; A-paced, A-sensed, atrial activity inhibits PM	Isolated SN dysfxn, intact AV node
VVI	Ventricular Demand; V-paced, V-sensed, ventricular activity inhibits PM	High-grade AVB, bradycardia; does not track atrial activity (i.e. chronic AF)
AOO / VOO	Asynchronous; A- or V-paced, no sensing	Obsolete (AOO), Temp wire pacing (VOO)
Dual Chamber Modes		
Tracking Modes		
DDD	Synchronous; paces & senses in atrium & ventricle; <i>atrial activity is tracked/triggers ventricular activity</i>	Allows coordination of A- & V-pacing; most closely mimics intrinsic conduction system
VDD	Atrial Synchrony Possible; V-paced, A- & V-sensed	Rarely used; high-grade AVB
Non-Tracking Modes		
DDI	AV Sequential; paces & senses in atrium & ventricle; <i>atrial activity not tracked; atrial tachyarrhythmia does not trigger RVR</i>	SSS or sinus brady with intermittent atrial tachycardias
DOO	Asynchronous Fixed Rate; paces atrium & ventricle, no sensing	Avoid sensing electrocautery or electromagnetic interference

PPM INDICATIONS (CLASS I) ([JACC 2019;74:e51](#))

Sinus Node Dysfunction:

- **Symptomatic sinus bradycardia** (± sinus pauses) or chronotropic incompetence
- Symptomatic medication-induced bradycardia *if* there is no accepted alternative medication

AV Block (AVB)/Conduction Disease:

- **3°AVB with or without symptoms**
- **Symptomatic 2° AVB Mobitz I or II**
- Permanent 2° AVB Mobitz II or intermittent 3° AVB (regardless of symptoms)
- Alternating bundle branch block

Neurocardiogenic:

- Only if syncope associated with marked cardioinhibitory or bradycardic event

ICD INDICATIONS (CLASS I)

- Primary prevention indicated for pts with heart failure only if already on **optimized medical therapy** (OMT). All pts must have a reasonable **expectation of 1-year survival** ([JACC 2018;72:e91](#))

Primary Prevention	Secondary Prevention
Ischemic CM: NYHA Class I: EF ≤30% at least 40d s/p MI & 90d s/p revascularization NYHA Class II/III: EF ≤35% at least 40d s/p MI & 90d s/p revascularization Other: EF ≤40% at least 40d s/p MI + NSVT + inducible VT/VF on EP study	- Prior episode of cardiac arrest (VF/pulseless VT) or sustained unstable VT if no reversible cause found (includes HCM, long or short QT syndrome, ARVC, cardiac sarcoidosis, catecholaminergic VT, type 1 Brugada pattern, ACHD after ablation if needed) - Structural heart disease with spontaneous sustained VT (stable or unstable)
Non-ischemic CM* : EF ≤35% + NYHA Class II/III Other: unexplained syncope w/ hemodynamically significant inducible VT/VF on EP study, cardiac sarcoidosis w/ LVEF ≤35%, LQTS refractory to βB. ARVC w/ LV or RV EF ≤35%	

*DANISH ([NEJM 2016;375:1221](#)): in pts with non-ischemic CM, ICD reduced risk of sudden cardiac death, but did **not** provide a mortality benefit

CRT INDICATIONS (CLASS I): ↓mortality compared to OMT ([JACC 2013;61:e6](#))

	NYHA I	NYHA II	NYHA III/IV
Class I	None	LVEF ≤35%, QRS ≥150ms, LBBB, & sinus rhythm	LVEF ≤35%, QRS ≥150ms, LBBB, & sinus rhythm

Cardiology

Valvular Heart Disease

AORTIC STENOSIS

- **Etiology:** senile calcific (most common cause >70yo; a/w metabolic syndrome, CAD, CKD), bicuspid valve (most common cause <70yo), rheumatic heart disease (leaflets fuse, often with concurrent MV disease)
- **Clinical Manifestations:** most important determinant of prognosis → 50% mortality at 5y for angina, 3y for syncope, 2y for HF
 - Angina: ↑afterload → ↑LV pressures → LVH → ↑O₂ demand → supply-demand mismatch w/ exertion or tachycardia
 - Syncope: exercise-induced vasodilation → inability to augment CO due to obstruction → hypotension
 - Heart failure (dyspnea): LVH → diastolic dysfunction (*systolic dysfunction is a late finding*)
 - Acquired vWF def: 20% of severe AS, can expose bleeding from GI AVMs "Heyde's syndrome" ([NEJM 2012;367:1954](#))
- **Diagnosis:**
 - Physical exam: harsh, mid-systolic crescendo-decrescendo murmur at RUSB radiating to carotids. **If more severe:** murmur late-peaking, delayed carotid upstroke (pulsus parvus et tardus), soft S2 ([Am Heart J 1999;137:298](#))
 - TTE: measure mean (not peak) gradient, valve area, & jet velocity; also important to assess EF (gradient can be underestimated with **reduced EF → low flow, low gradient AS**)
- **Severe AS:** peak AV velocity ≥4m/s, **mean AV pressure gradient ≥40mmHg**, or **AV area (AVA) ≤1cm²** (AHA/ACC: [Circ 2021;143:e35](#))
 - EKG: LVH, LAE, LAFB, LBBB
 - Exercise stress testing: recommended in asymptomatic severe AS to assess for symptoms; do **not** perform in pts w/ sx
- **Natural History:** highly variable, but on average, AVA ↓ ~0.1 cm²/y & mean gradient ↑8mmHg/y ([JACC 1989;13:545](#)). Patients with bicuspid valves, advanced age, & those with severe leaflet calcification are at risk for more rapid progression
- **Aortic Valve Replacement (AVR)** ([J Am Soc Echo 2018;31:117](#)): determining indication for valve replacement is based on evaluating:
 - (1) presence of **symptoms**, (2) **severity** by TTE criteria, (3) LV function (EF)
 - Symptomatic, severe AS (Stage D): AVR indicated
 - Asymptomatic, severe (Stage C): AVR appropriate if LVEF<50% or undergoing other cardiac surgery; for patients with asymptomatic very severe AS (AVA ≤0.75cm²) early surgery may have mortality benefit ([NEJM 2020;382:111](#))
 - If suspect low-flow (LVEF <50%) & low-gradient (<40mmHg) w/ AVA <1cm²: **dobutamine stress TTE (DSE)** to distinguish between low-flow, low-gradient AS versus "pseudosevere AS" ([Circ 2011;124:e739](#))
 - Low-flow, low-gradient severe AS: if DSE results in V_{max} >4m/s or mean gradient >40mmHg while AVA remains <1cm², then AVR is indicated
 - Pseudosevere AS: if DSE results in AVA >1cm², then AVR not indicated
 - **SAVR vs TAVR:** depends on surgical risk ([STS-PROM score](#)) and/or concomitant heart/vascular disease that is amenable to surgery. TAVR is recommended for those at extreme surgical risk (compared to medical therapy, [PARTNER](#)). TAVR is noninferior to SAVR in those at high ([NEJM 2011;364:2187](#)), intermediate ([PARTNER2](#)), & low surgical risk ([PARTNER3](#)). Valve-in-valve TAVR may additionally be beneficial in pts with surgical bioprosthetic AV failure ([JACC 2017;69:2283](#))
 - **TAVR Evaluation:** c/s **structural cardiology, cardiac surgery.** Obtain **TTE, TAVR-protocol CT, dental clearance (Panorex)**
 - **TAVR Complications:** valve embolization, valvular/paravalvular regurgitation, cardiogenic shock, coronary occlusion, annular rupture, ventricular perf, CHB requiring PPM, stroke (ischemic/hemorrhagic), bleeding/hemorrhage, access site complication
- **Medical Management:** AS is a *surgical disease & medical management is only utilized for sx management*
 - Treat HTN: reduce the "double load" on the ventricle. In theory, ACE-I may have beneficial effect on LV fibrosis. However, no optimal regimen exists because anti-hypertensives can lead to hemodynamic issues (diuretics reduce preload which lead to decreased CO, vasodilators can reduce coronary perfusion, BB can reduce contractility). Bottom line: **start low and go slow**
 - Control volume status: operate within a narrow preload range, prone to underfilling (low preload) & overfilling (volume overload)
- **Anticoagulation after Valve Replacement:**
 - DOACs are not approved for valve replacement & may cause harm ([NEJM 2013;369:1206](#))
 - Bridging UFH or LMWH if AC interrupted only in mechanical MV or mechanical AV with RFs (Class I)
 - RFs: AF, LV dysfxn, prior VTE, hypercoag. state, older gen. mech AVR (Star-Edwards valve, disc valve other than Medtronic Hall) ([Circ 2021;143:e35](#))
 - Bleeding risk: mechanical > bioprosthetic (likely AC related). Reoperation risk: bioprosthetic > mechanical
 - TAVR: aspirin monotherapy non-inferior to DAPT for thrombotic events & associated with less bleeding ([NEJM 2020;383:1447](#))

Prosthesis	Location	Timing and Risk Factors	INR	Class
Mechanical	Mitral	Indefinitely	2.5-3.5 (+ ASA 81)	I
	Aortic	Indefinitely, (+) risk factors	2.5-3.5 (+ ASA 81)	I
		Indefinitely, (-) risk factors	2.0-3.0 (+ ASA 81)	I
Bioprosthetic	Mitral	First 3 months after placement, regardless of RFs	2.0-3.0 (+ ASA 81)	IIa
		>3 months after placement	ASA 81	IIa
	Aortic	First 3 months after placement, regardless of RFs	2.0-3.0 (+ ASA 81)	IIb
		>3 months after placement	ASA 81	IIa
TAVR	Aortic	No AC; indefinite antiplatelet monotherapy	ASA 81 or Clopidogrel 75	IIb

Cardiology

Valvular Heart Disease

OTHER VALVULAR DISEASES (Circ 2021;143:e35)

	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation	Tricuspid Regurgitation
Etiology	<p>Acute: aortic dissection, valve perforation (usually due to MI or endocarditis), traumatic valve leaflet rupture</p> <p>Chronic: leaflet abnormalities (bicuspid valve, endocarditis, RHD) or root dilation (HTN, CTD, dissection, syphilis)</p>	- 80% due to RHD (only 50-70% report h/o rheumatic fever), endocarditis, annular calcification (rarely significant), congenital, autoimmune valvulitis (SLE), carcinoid, endomyocardial fibroelastosis, XRT (10-20y after Hodgkin's)	- Dilated annulus ("functional MR"), MVP, ischemic papillary muscle dysfunction, ruptured chordae, endocarditis, RHD, CTD	- Dilated annulus, pulmonary hypertension ("functional TR"), direct valve injury, endocarditis, RHD, carcinoid, ischemic pap muscle dysfxn, CTD, drug-induced
Pathophys.	<p>Acute: diastolic regurgitant flow → sudden ↑LVEDP (w/o remodeling time) → ↓CO → pulm edema</p> <p>Chronic: diastolic regurgitant flow → ↑LVEDV → initial maintenance of SV/CO → progressive dilatation, failure</p>	<ul style="list-style-type: none"> - Elevated LAP → pulmonary HTN, AF (47%) - Demand for ↑CO precipitates symptoms - Valve narrows ~0.1cm²/y 	<ul style="list-style-type: none"> - LA/LV volume overload → LV dysfunction, progressive enlargement of LV → dilated mitral annulus → worsening MR 	<ul style="list-style-type: none"> - Similar to MR
Clinical	<ul style="list-style-type: none"> - Cardiogenic shock (acute), angina, left-sided HF - 31 eponyms for signs in chronic AI, most due to large initial SV (Int J Car 2006;107:421) 	<ul style="list-style-type: none"> - Dyspnea (most common symptom), pulmonary edema, hemoptysis, thromboembolism even w/o AF (Annals 1998;128:885), RV failure 	<p>Acute: flash pulmonary edema, HTN, shock</p> <p>Chronic: DOE, orthopnea, PND, edema, AF</p>	<ul style="list-style-type: none"> - <u>Right-sided HF:</u> hepatosplenomegaly, ascites, edema
Exam	<ul style="list-style-type: none"> - ↑pulse pressure (bounding pulses, bouncing head/uvula, nail bed capillary pulse) - High-pitched, blowing diastolic decrescendo murmur along LSB - Longer = more severe/chronic - May hear low-pitched diastolic murmur at apex 2/2 regurgitant jet displacing anterior leaflet 	<ul style="list-style-type: none"> - Loud S1, high-pitched opening snap (earlier more severe, indicating higher LAP) - Low-pitched diastolic rumble heard best at apex at end-expiration 	<ul style="list-style-type: none"> - Holosystolic murmur at apex radiating to axilla, S3, displaced PMI - Early diastolic rumble and S3 may be the only signs in acute MR 	<ul style="list-style-type: none"> - Holosystolic murmur at left mid or lower sternal border that increases with inspiration, S3, large V wave in JVP, pulsatile liver, substernal pulsations
Treatment	<p>Acute: usually needs urgent surgery. <u>Nitroprusside</u> to ↓afterload; ino- and chronotropes to ↓diastole time</p> <p>- <u>Do not use vasoconstrictors or IABP</u> (worsens regurg) or beta-blockers (blocks compensation, ↑diastolic regurgitant time)</p> <p>Chronic: ACE-I, CCB, or hydralazine/nitrates (to reduce LV afterload)</p> <p>- <u>Proceed to AVR if:</u> symptomatic, LV systolic dysfunction (EF <50%), LV end-systolic dimension >50mm, need for CABG or other valve surgery</p>	<p>Medical: warfarin if LA thrombus, AF, prior embolism (Class I) or LA > 55mm (Class IIb)</p> <ul style="list-style-type: none"> - βB if tachycardic or dyspneic - Diuresis if pulm vasc congestion - If hx of rheumatic fever: 2° prevention for recurrence with penicillin, sulfadiazine or macrolide for 10y or until 40yo (whichever longer) <p>Intervention: need to have severe MS + symptoms to be considered for surgery (unless noted below)</p> <ul style="list-style-type: none"> - Tx is <u>percutaneous balloon mitral commissurotomy</u> (PBMC) if pt has favorable valve morphology (Wilkins Score based on TTE) - <u>Proceed to MVR</u> if not PBMC candidate, PBMC fails, or undergoing another cardiac surgery (even if asymptomatic) 	<p>Acute: ↓afterload (e.g. nitroprusside), inotropes (dobutamine), diuresis</p> <ul style="list-style-type: none"> - If hemodynamically unstable (esp. post-MI or endocarditis), consider IABP and/or urgent surgical repair (NEJM 2012;366:2466) - If ischemic, consider revascularization <p>Chronic: MVR if primary symptomatic severe MR <u>OR</u> asymptomatic severe MR with EF ≤60% or LVEDD ≥40mm (Circ 2021;143:e35)</p> <ul style="list-style-type: none"> - If excessive surgical risk, percutaneous MV clip/repair or CRT also options (EVEREST II) - If severe functional MR, repair equivalent to chord-sparing replacement (NEJM 2014;370:23) - Benefit of percutaneous clip if HF and secondary symptomatic failing GDMT including CRT (COAPT) 	<p>Medical: diuresis, management of underlying cause</p> <p>Intervention: TVR if severe symptomatic primary TR <u>OR</u> asymptomatic w/ RV dilation/dysfunction</p> <ul style="list-style-type: none"> - For secondary severe TR, consider TVR if undergoing left-sided valve surgery <u>OR</u> if tricuspid annular dilation >4cm and/or s/sx of RHF (Circ 2021;143:e35) - Isolated TV surgery a/w high mortality, although may be recommended for severe TR refractory to medical therapy - Numerous transcatheter therapies are potential options but still lack long-term clinical outcome & performance data (JACC 2018;71:2935)

Cardiology

Pericardial Disease

CARDIAC TAMPONADE

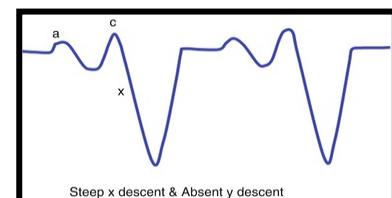
- **Definition:** hemodynamic insufficiency caused by impaired cardiac filling due to ↑ pericardial pressure due to effusion, leading to ↑ intracardiac chamber pressures & eventually equalization of diastolic pressure in all 4 heart chambers
- **Etiologies of pericardial effusion:** idiopathic (20%), iatrogenic (16%), malignant (13%), uremic, HF, autoimmune ([Am J Med 2000;109:95](#)). Tamponade more likely in malignant, post-viral, uremic, iatrogenic (i.e. post-cath) etiologies. Also seen with prox. aortic dissection & myocardial wall rupture

Clinical Manifestation and Diagnosis:

- **Beck's Triad:** ↓BP, ↑JVP, muffled heart sounds
- **Pulsus paradoxus (PP):** exaggeration of normal decrease in SBP during inspiration (If $>10\text{ mmHg}$, $\oplus\text{LR}=3.3$. If $\leq 10\text{ mmHg}$, $\oplus\text{LR}=0.03$)
 - [How to measure PP](#)
 1. Slowly deflate cuff → note pressure when systolic Korotkoff sounds only heard w/ during expiration (will sound irregular) (a) → continue slowly deflating cuff until heard throughout (b). $\text{PP} = a - b$
 2. Via A-line tracing ($\text{PP} = \text{height exp.} - \text{height insp. systolic waveform}$)
 - **False-negative PP conditions:** pre-existing disease w/ ↑LVEDP (e.g. chronic HTN), regional tamponade, pericardial adhesion, acute MI, arrhythmia, ASD/VSD, severe AI, hypotension/shock, RVH
 - **PP DDx:** severe COPD/asthma, massive PE, hypovolemic shock, RVMI, constrictive physiology, tense ascites
- **ECG:** sinus tach, low QRS voltage (50%; limb $\leq 5\text{ mm}$, precordial $\leq 10\text{ mm}$), electrical alternans (20%; precordial leads)
- **TTE:** inspiratory leftward septal shift, diastolic collapse of cardiac chambers (R > L-sided), respirophasic changes in transvalvular velocities, IVC plethora. **SIZE** of effusion does NOT predict tamponade – **RATE** of accumulation is more important

5 Clinical Features Associated with Tamponade (JAMA 2007;297:1810)		
Sign/Sx	Sensitivity	95% CI
Dyspnea	87-88%	n/a
Tachycardia	77%	69-85%
Pulsus paradoxus	82%	72-92%
Elevated JVP	76%	62-90%
Cardiomegaly on CXR	89%	73-100%

CVP tracing in tamponade



Treatment:

- **Fluid resuscitation:** administer volume urgently to increase intracardiac pressures (monitor closely as overfilling can worsen tamponade), starting w/ 250-500cc bolus
- **Inotropes:** administer if IVF insufficient. Unclear benefit b/c endogenous catecholamines already at max level. **Avoid BB**
- **PPV:** avoid if possible as ↑ positive intrathoracic pressure will further impede ventricular filling
- **Pericardial effusion removal:** catheter **pericardiocentesis**, surgical pericardectomy (if aortic/myocardial rupture), or HD (if uremic)
 - **Analysis of pericardial fluid:** cell count, total protein, LDH, gram stain/cx, viral markers/cx (Coxsackie, HSV, CMV, EBV, HIV), AFB smear/cx, ADA/IFN-gamma/lysozyme (if concerned for TB pericarditis), cytology/tumor markers
 - **Removal of drain:** when output $<50\text{cc/d}$, otherwise consider **pericardial window** (pleural>abdominal). See [Pericardial Drain](#)

PERICARDITIS

- **Classification:** acute (<6w), subacute (6w to 6mo), chronic (>6mo)
- **Epidemiology:** 5% of pts in ED w/ CP and no MI, M > F
- **Etiology:** 85-90% idiopathic (usually viral/post-viral), bacterial, fungal, post-MI, uremic, mycobacterial (TB), autoimmune (CTD, vasculitis), malignancy (e.g. lung, breast), XRT, drugs (procainamide, hydral, INH)

ECG Evolution in Pericarditis



Clinical Manifestations and Diagnosis:

- **Symptoms:** sudden onset, pleuritic, retrosternal **CP relieved w/ sitting up & leaning forward** (may radiate to trapezius muscles), ± viral prodrome if infectious etiology. Uremic or CTD pericarditis: CP may be absent
- **Exam:** pericardial **friction rub** (~30% cases), best heard at LLSB w/ diaphragm of stethoscope at end-expiration w/ pt leaning forward
- **ECG:** 4 stages: (1) **diffuse ↑ST & ↓PR** ($\uparrow\text{PR}$ & $\downarrow\text{ST}$ in aVR/V1); (2) ST & PR normalize; (3) diffuse TWI; (4) TW normalize. May see continual low-voltage or electrical alternans if effusion present. **Uremic pericarditis:** ECG can be normal b/c epicardium not inflamed
- **Diagnosis:** ≥2 of the following: (1) characteristic CP, (2) friction rub, (3) suggestive ECG changes, (4) pericardial **effusion**
 - **Workup:** infectious w/u, BUN/Cr, ANA/RF/CCP, HIV, IgRA, ESR/CRP, troponin (elevated in ~30%, indicative of myopericarditis)
 - **TTE:** assess for presence/size/location of co-existent effusion and/or tamponade physiology
 - **Pericardiocentesis/Surgical Drainage:** if (1) suspect **malignancy** or **bacterial** etiology (2) large effusion ($>2\text{cm}$) (3) tamponade
 - **Cardiac MRI:** adjuvant test if dx uncertain or c/f myocardial involvement; +LGE has 94% Sn for pericarditis ([JACC 2020;75:76](#))

Treatment: self-limited (days-weeks) in 70-90% of cases

- **Hospitalize if:** fever, ↑WBC, large effusion ($>2\text{cm}$), immunocompromised, anticoagulated, trauma, ↑troponin, unstable/signs of tamponade, failure to respond to NSAIDs after 7d. Also consider hospitalization if subacute presentation
- **1st-line treatment:** **NSAIDs** (e.g. ibuprofen 600-800mg TID; ASA 650-1000mg TID) ± **colchicine** 0.6mg BID (qd if pt $<70\text{kg}$)
 - **Colchicine** ↓sx at 72h, improves 1w remission and 18mo recurrence in acute idiopathic pericarditis ([Circ 2005;112:2012](#); [NEJM 2013;369:1522](#)). No benefit w/ malignant or uremic cases
 - **ASA:** preferred over NSAIDs if: post-MI, CAD, concomitant anti-platelet/anticoagulant therapy
- **Glucocorticoids** (prednisone 0.2-0.5mg/kg/d): preferred over NSAIDs if: sx refractory to 7d of NSAID treatment, recurrent (>2 episodes), uremic pericarditis, CTD pericarditis, or contraindication to NSAIDs
- **Duration:** NSAIDs: until sx resolve (1-2w), then taper (total 3-4w). **Colchicine:** 3mo. **Glucocorticoids:** 2w, then taper (3mo total)

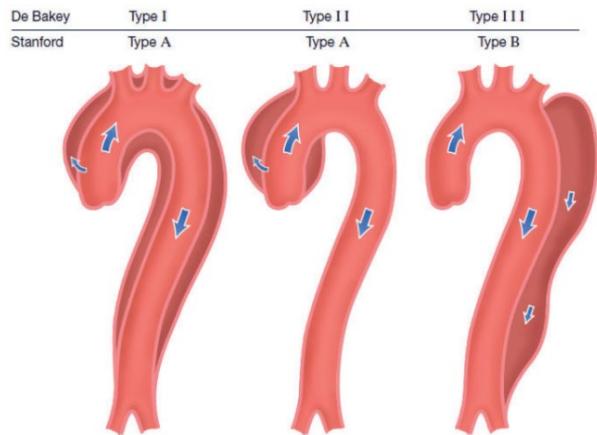
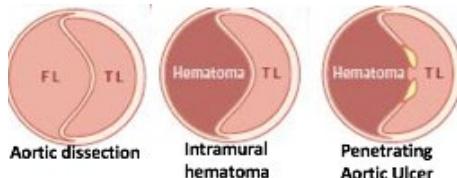
Cardiology

Aortic Disease

ACUTE AORTIC SYNDROMES (AAS) ([Nat Rev Cardiol 2015;12:103](#))

Definitions: three distinct processes with risk of rupture

- **Aortic dissection (AD):** intimal tear resulting in a false lumen
- **Intramural hematoma (IMH):** rupture of vasa vasorum causing hematoma within aortic wall without tear
- **Penetrating aortic ulcer (PAU):** ulceration of atherosclerotic plaque that penetrates into intima of aortic wall



Classification:

- **DeBakey:** type I (ascending + descending aorta); type II (ascending aorta only); type III (descending aorta only)
- **Stanford:** type A (ascending ± descending); type B (descending only)

Epidemiology:

- **Prevalence:** aortic dissection most common (62-88%), followed by IMH (10-30%) & PAU (2-8%)
- **Risk factors:** male, HTN, age 60-70 (if <40yo, think Marfan syndrome, CTD, or bicuspid valve), atherosclerosis, prior cardiac surgery, aortic aneurysm, FHx of AAS, aortitis, trauma, pregnancy
- **Aortic dissection prognosis:**
 - Type A: mortality at 3y among patients discharged alive: *Medical*: 31%, *Surgical*: 10% ([Circ 2006;114:I350](#))
 - Type B: *Medical*: 9% in-hospital mortality, 16% 1y, 20% 5y
- IMH will progress to complete dissection in 28-47%. PAU will progress to aortic rupture in 42%

Diagnosis:

- **Clinical features:** AD, IMH, & PAU cannot be distinguished by presentation alone
 - **Signs:** AI murmur, pulse deficit, upper extremity BP differential (>20mmHg), CHF
 - **Sx:** chest or back pain (radiates to neck/jaw if ascending; back/abdomen if descending; may be migratory pain)
- **Complications:** syncope, shock, tamponade, branch artery occlusion (MI, CVA, paraplegia, cold extremity, renal failure)
- **Labs:** D-dimer <500ng/mL (96% NPV), **troponin** (can be + if dissection extends into coronaries)
- **Imaging:**

CXR	- 50% with AAS have normal CXR; only 1/3 will have widened mediastinum
CT	- Sn 95%, Sp 87-100%; first-line modality in pts w/ high clinical probability of AAS - Combined I+/-I- (assess for IMH, mediastinum hemorrhage, or hemopericardium)
TTE	- Sn 73-100%, Sp 71-91%, least accurate of diagnostic imaging modalities - Useful for identifying AV dysfunction, prox dissections extending to Ao root/pericardium
TEE	- Sn 99%, Sp 90-100%. Often used intra-op to confirm dx prior to surgery - Invasive nature limits use; cannot detect pathology below the diaphragm

Management:

- **Goal:** "impulse control" → minimize aortic wall stress by ↓ LV ejection force (dP/dT): HR <60, SBP 100-120mmHg
- **Agents:** **IV beta blockade** (esmolol, labetalol). If additional BP control required, consider IV nitroprusside, TNG, nicardipine. **NEVER** use vasodilators without concomitant beta blockade → will increase wall stress via reflex tachycardia, thereby increasing dP/dT
- **Aortic Dissection:**
 - **Type A:** immediate open surgical repair 26% mortality vs >50% with medical management ([JAMA 2000;283:897](#))
 - **Type B:** *uncomplicated*: medical therapy (80% survival at 5y); *complicated* (compromise of renal/mesenteric vessels): TEVAR preferred to open surgery (which has 25-50% in-hospital mortality)
- **IMH & PAU:**
 - **Type A:** urgent (i.e. within days) open surgical repair
 - **Type B:** medical management or TEVAR (endovascular repair generally reserved for those with higher risk features such as persistent pain, growth over time, aortic expansion or rupture, compromise of renal/mesenteric vessels)

Cardiology

AORTIC ANEURYSMS ([JACC 2016;68:1054](#))

Aortic Disease

	AAA	TAA
Epidemiology	<ul style="list-style-type: none"> M>F, >65yo, mostly infrarenal 	<ul style="list-style-type: none"> M>F, mostly 50-70yo, 50% ascending Ao, 40% descending Ao, 10% arch
Etiology	<ul style="list-style-type: none"> Usually due to atherosclerotic disease RFs: smoking, male sex, age, pre-existing atherosclerosis, obesity, HLD, HTN, FHx 	<ul style="list-style-type: none"> Atherosclerotic: majority of cases. Mostly in descending Ao. RFs: smoking, HLD, HTN Structural/genetic: mostly root & ascending aorta. Causes: CTD (Marfan, Ehlers-Danlos, Loeys-Dietz), Turner, bicuspid AoV, trauma Infectious: 3° syphilis, mycotic aneurysm (most common org: <i>Staph</i> spp., <i>Salmonella</i> spp.) Inflammatory: GCA (~10% have TAA), Takayasu, RA, psoriasis, Behcet's, Wegener's, IgG4
Screening / Surveillance	<ul style="list-style-type: none"> ACC/AHA: one-time abdominal US in all men >60 w/ FHx of AAA & all men 65-75 who have ever smoked Surveillance (J Vasc Surg 2018;67:2): interval depends on size 	<ul style="list-style-type: none"> General population: not recommended Indications: at time of dx of Marfan, Turner, Loeys-Dietz, Takayasu or GCA. 1° relatives of pt w/ TAA, dissection, bicuspid valve Surveillance (JACC 2010;55:e27): interval depends on presence of aneurysm vs dissection & size by CT/MRI
Imaging Modalities	<ul style="list-style-type: none"> Abdominal US: screening and surveillance of infrarenal AAAs. High Sn/Sp (>90%), operator-dependent CT w/ contrast: high Sn/Sp, better than US for suprarenal AAAs MRI/MRA: good Sn/Sp, preferred for aortic root imaging & for imaging tortuous aortas CXR: "enlarged aorta" nonspecific (tortuous aorta vs aneurysm) TTE: useful for root & proximal thoracic aorta; TEE: will visualize entire thoracic aorta but rarely used 	
Treatment	<p>Medical</p> <ul style="list-style-type: none"> Smoking cessation (slows growth by 25%) Reduce BP per ACC/AHA guidelines Meds: statins (reduce all-cause mortality in pts s/p surgery); BBs (may slow expansion); ACEi (controversial); low dose ASA (may slow growth) <p>Surgical</p> <ul style="list-style-type: none"> Men: >5.5cm OR growing >0.5cm/6mo or >1.0cm/y OR sx Women: >4.5-5cm (controversial) Open repair vs EVAR 	<p>Medical</p> <ul style="list-style-type: none"> Reduce BP (<140/90 or <130/80 if DM or CKD) Meds: BBs (decrease TAA growth in Marfan pts), ARBs (slows expansion in Marfan pts), statins (goal LDL<70) Smoking cessation, avoid straining Stress test used to guide BP management <p>Surgical</p> <ul style="list-style-type: none"> Root/ascending TAAs: ± concomitant AVR Arch/descending TAAs: mostly open graft (EVAR)
Complications	<ul style="list-style-type: none"> Rupture: devastating mortality. Risk factors: size, rate of expansion, female gender. Sx: triad of abd/back pain + pulsatile abd mass + HoTN → immediate OR Dissection: pain (chest/abdomen/back), occlusion of aortic vessels, thromboembolism Post-repair: EVAR: endoleak, graft failure, thrombosis. Open: MI, embolization, AKI, ischemic colitis 	

OVERVIEW

- Definition: transient (self-limited) loss of consciousness due to cerebral hypoperfusion that is associated with loss of postural tone, followed by complete spontaneous recovery; excludes metabolic causes (e.g. hypoglycemia, hypoxia, intoxication)
- Risk assessment and need for hospitalization:
 - High-risk symptoms: preceding **palpitations**, **exertional** syncope, bleeding, syncope while supine, **lack of prodrome**, trauma
 - High-risk features: angina, CHF, mod-severe valvular or structural heart disease, ECG features of ischemia/arrhythmia, FHx of SCD, preexcitation syndromes, high-risk occupation (e.g. airline pilot)
 - Risk calculators have high NPV (>95%) but do NOT replace clinical judgment
 - [San Francisco Syncope Rule \(SFSR\)](#): admit pt if ≥1: EKG changes or non-sinus rhythm, dyspnea, Hct<30, SBP<90, HF
- Ddx: seizure, metabolic causes (hypoglycemia, hypoxia), intoxication, vertebrobasilar TIA, fall, psychiatric

Etiology and Diagnosis: (AHA/ACC/HRS: [JACC 2017;70:e39](#))

Etiology	Historical Features	Diagnosis	Treatment
Reflex (60%) • Vasovagal • Situational • Carotid sinus syncope	<u>Vasovagal</u> : prodrome of dizziness, nausea, warmth, diaphoresis, pallor; a/w intense emotion, pain, or stress <u>Situational</u> : cough, sneeze, laugh, micturition, defecation <u>CSS</u> : neck turning/surgery/irradiation	<ul style="list-style-type: none"> • <u>Vasovagal</u>: can dx w/ tilt table test, not necessary if clear dx by history (JACC 1996;28:263) • <u>Carotid sinus syncope</u>: diagnose via carotid sinus massage (if no underlying bruits or CVA history) 	<ul style="list-style-type: none"> • Avoid provocative stimuli • Isometric counterpressure maneuvers of the limbs (e.g. leg crossing, hand grip, Valsalva, squatting) • Meds for select cases (i.e. midodrine, fludrocortisone, βB) (NEJM 2005;352:1004)
Orthostasis (15%) • Autonomic failure (1° or 2°) • Drug-induced • Volume depletion	Prodrome of dizziness, nausea, warmth, diaphoresis, pallor <u>Risk factors for autonomic failure</u> : - 1°: PD, Lewy body, Shy-Drager - 2°: DM, amyloid, spinal cord injury, chronic EtOH, Lyme, syphilis, B12 deficiency, meds (vasodilators, diuretics, BB, TCAs, PD meds, opiates, α-blockers)	<ul style="list-style-type: none"> • <u>Orthostatic vital signs</u> (systolic ↓20mmHg or diastolic ↓10mmHg w/in 3min of standing) - ↑HR is NOT part of definition • <u>Consider</u>: Hct, A1C, SPEP if c/f amyloid, RPR, B12 	<ul style="list-style-type: none"> • <u>Primary</u>: fludrocortisone (0.1-0.2mg QD), midodrine (5-20mg TID), pyridostigmine, droxidopa (for PD-associated orthostasis) • <u>Secondary</u>: treat underlying etiology, replete volume, d/c culprit meds
Cardiac (15%) • Arrhythmia • Structural (AS, LVOT obs.) • Obstruction (e.g.,PE, tamponade) • Dissection	<u>No prodrome</u> , syncope while in sitting or supine position, palpitations, FHx or personal history of heart disease	<ul style="list-style-type: none"> • Causes of cardiac syncope in young people (+ ECG signs): <ol style="list-style-type: none"> 1. WPW (delta wave) 2. HOCM (LVH, apical TWI) 3. Brugada (pseudo-RBBB with coved/saddleback pattern in V1-V2) 4. Long QTc syndrome (QTc >500ms) 5. ARVC (Epsilon wave) • <u>Consider cardiac monitoring</u> on basis of frequency and nature of syncpe events (inpatient telemetry, Holter, Zio patch, implantable cardiac monitor) • <u>TTE only if H&P suggestive</u> of cardiac cause (<u><1% yield if no underlying heart disease and normal ECG</u>) <ul style="list-style-type: none"> ○ ROMEO criteria: Sn 99.5%, Sp 15.4% (JHM 2018;13:823) • <u>Consider PE</u> if no other apparent cause → identified in 17.3% hospitalized w/ 1st syncpe (& 25.4% w/ no other apparent cause for syncpe) (NEJM 2016;375:1524) 	<ul style="list-style-type: none"> • Based on etiology, follow guideline-directed management and therapy
Neurologic (<10%) • Seizure • Stroke/TIA • Subclavian steal	<u>Seizure</u> : lateral tongue biting (Sn 20-33%, Sp 96-100%), urinary/fecal incontinence (Sn 38%, Sp 57%), aura, postictal confusion <u>Focal deficits</u> : stroke, TIA <u>Steal</u> : syncope after arm exercise	<ul style="list-style-type: none"> • <u>Seizure</u>: EEG • <u>Stroke</u>: CT, MRI/MRA • <u>Steal</u>: UENI w/ Dopplers (specify for subclavian steal) • Carotid dopplers are of <u>low clinical utility</u> (changes management in <2% of patients) (JAHA 2014;3:e001063) 	<ul style="list-style-type: none"> • Based on etiology, consider neurology consult and follow guideline-directed management & therapy

Cardiology

Hypertensive “Urgency” & Emergency

DEFINITIONS, TRIAGE, AND MANAGEMENT: see [Outpatient CV Health](#) for workup ([NEJM 2019;381:1843](#); [HTN 2018;71:1269](#))

- Hypertensive “urgency” = **severe asymptomatic HTN**: BP $\geq 180/120$ w/o evidence of end-organ damage (may have **mild headache**)
 - **Assess adherence** to prior Rx before aggressively uptitrating regimen to avoid overcorrection of BPs & hypotension
 - **Assess cause** prior to treating BP. Commonly due to pain, anxiety, urinary retention, medication SE (e.g. steroids), etc.
- **Hypertensive emergency:** BP $\geq 180/120$ w/ evidence of acute end-organ damage (rate of BP rise may be more impt. than actual BP)
 - **End-organ damage:** Neuro: HTN encephalopathy (severe HA, seizure, AMS), PRES, TIA, CVA (SAH, ICH); Retinopathy: papilledema, hemorrhage; Resp/CV: pulm edema, MI, +TnT, angina, Ao dissection; **Heme:** MAHA; **Renal:** AKI, hematuria

	Hypertensive “Urgency”	Hypertensive Emergency
Triage location	Floor vs outpatient mgmt (with close follow up) (JAMA IM 2016;176:981)	ICU > Floor (ICU if needs arterial line, antihypertensive gtt, or if severe end-organ damage)
Correction time course	Reduce BP to $< 160/100$ over several hrs; then to normal ($< 130/90$) over 1-3d	Reduce no more than 25% within the first hour, and to no lower than 160/100 within 2-5h; reduce to normal range over 1-3d
Route of medication administration	Initial PO short-acting medications; convert to long-acting prior to discharge	Start with short-acting, titratable IV agents; transition to PO agents for floor/discharge
Suggested meds (see below for dosing)	PO: captopril, labetalol >> hydralazine (unpredict., reflex tachy), isosorbide dinitrate	IV: labetalol >> hydralazine Topical: nitro paste (may be used on the floor) Drips: see below

Disease Process-Specific Recommendations for Hypertensive Emergency

	BP Goal	Suggested Medications
ACS	SBP < 140 w/in 1h; keep DBP > 60	TNG, esmolol > labetalol, nicardipine. BBs contraind. if LV failure w/ pulm edema, HR < 60 , SBP < 100 , poor peripheral perfusion, or 2°/3° heart block; TNG contraindicated in RV MI
Acute pulm edema	SBP < 140 w/in 1h	TNG, nitroprusside, clevipidine; BBs contraindicated
Aortic dissection	SBP < 120 & HR < 60 w/in 20min	IV BB first (esmolol, labetalol), followed by vasodilator (nitroprusside)
Ischemic stroke	$< 185/110$ if tPA; $< 220/120$ if no tPA or end-organ damage	Nicardipine, labetalol, clevipidine > nitroprusside

Antihypertensive Dosing – ICU

Agent	Dosing	Onset	Duration	Indications
Esmolol (IV)	500 μ g/kg load + 25-50 μ g/kg/min; then adjust by 25 μ g/kg/min q10-20min up to 300 μ g/kg/min	<1min	10-20min	Ao dissection, CAD
Labetalol (IV)	0.5-2mg/min, adjust to goal; max 10mg/min	<5min	3-6h	Ao dissection
Nitroprusside (IV)	0.25-2 μ g/kg/min (dose limit to avoid cyanide toxicity), temporarily (<10min) can use up to max 10 μ g/kg/min	<1min	<2min	AS/LVSD and HF; CI in CAD (coronary steal)
Nitroglycerin (IV)	Start 10-30 μ g/min, titrate by 10-20 μ g/min q5-10min; max 400 μ g/min (if no response by 200 μ g/min = non-responder)	2-5min	5-10min	ACS, flash pulm edema
Nicardipine (IV)	Start at 5mg/h; ↑ by 2.5mg/h q5-15min; max 15mg/h	<10min	30min	SAH, Ao diss. (w/ BB)
Clevipidine (IV)	Start at 1mg/h; max 21mg/h	2-4min	5-15min	HTN post-CT surg

Antihypertensive Dosing – Floor

Agent	Dosing	Onset	Duration	Specific Indications
Labetalol	IV: 10-80mg q10min until effect seen, then use PO	5-10min	3-6h	Ao dissection, CVA; avoid in ADHF
	PO: Start 100mg q8-q12h (max: 2400mg/d)	20min	8-12h	
Hydralazine	IV: 5-20mg q15-30min until effect seen, then use PO, can have unpredictable response	10-20min	1-4h	Eclampsia
	PO: Start 10mg q6h, inc by 10-25mg/dose q2-5d	20-30min	~8h	
Captopril (PO)	12.5-25mg q8h (NOT TID)	30-90min	6-8h	
Lisinopril (PO)	Initial 2.5-5mg qd. Inc 10mg q2w to max 40mg qd. (Can use ARB if ACEi intolerance)	1h	24h	
Amlodipine (PO)	Initial 2.5-5mg qd. Inc 2.5mg q7d to max 10mg qd. Requires few days to take effect	24-48h	24h	
Nifedipine (PO)	10-30mg TID. Use with caution (may cause pronounced vasodilation, orthostasis)	20min	6-8h	
Hydrochlorothiazide (PO)	Initial 12.5mg qd (max: 50mg qd, doses > 25 mg a/w ↑ electrolyte derangements)	2h	6-12h	
Isosorbide dinitrate (PO)	Initial 5-20mg 2-3 times/d (dose TID not q8h for nitrate holiday). Mononitrate = long-acting	1h	~8h	Anti-anginal, CHF
Nitropaste (topical)	0.5-1.5 inches. Apply to chest. Need 10-12h nitrate holiday to avoid tachyphylaxis	15-30min	~12h	If lacking IV/PO access

PERIPHERAL ARTERY DISEASE

Overview:

- Definition: arterial stenosis or occlusion causing an imbalance of blood flow relative to muscular metabolism
- Epidemiology: smoking, DM, HTN, HLD, age (20% prevalence >70y) ([Lancet 2013;382:1329](#))

Clinical Presentation and Diagnosis:

- Sx: **classic claudication** (10-35%) - reproducible exertional pain distal to occlusion, relieved by rest; **atypical leg pain** (most common, 40-50%); asymptomatic (20-50%) ([Circ 2006;113:e463](#)). **Threatened limb** (1-2%): ischemic rest pain (improved w/ hanging feet off bed or walking), ulcers at pressure points, dry gangrene
- Exam: arterial bruit, ↓**peripheral pulses** (palpation, Doppler), ↓cap refill, pallor on elevation, ulcers, atrophic changes, ↓hair growth
- ABI: Doppler US. Ratio of DP/PT (higher of the two) SBP to brachial SBP. Abnormal: **≤0.9**. ABI ≥1.30 suggests ↓compressibility usually due to ↑calcifications (e.g. elderly, DM, ESRD)
 - If ABI abnormal: obtain segmental ABI w/ pulse volume recordings (**PVR**) to localize disease
- Exercise testing: if high suspicion for PAD & normal resting ABIs
- CTA (w/ distal run off), MRA, or angiography: if considering revascularization

Treatment:

- Optimize cardiac risk factors (e.g. HTN, DM, HLD, weight loss), formal exercise program, high-intensity statin, smoking cessation
- Ischemic ulcers: wound care, may also need revascularization for appropriate healing depending on ABI
- Anti-platelets: if symptomatic, **ASA** 81-325mg qd or **clopidogrel** 75mg qd: ↓MI, CVA, vascular death ([NEJM 2017;376:32](#)). If asymptomatic, can give ASA 81mg. **Avoid DAPT** ([NEJM 2006;354:1706](#)) unless clinically indicated, usually post-revascularization
- Anticoagulation: rivaroxaban 2.5mg BID + ASA: ↓major adverse cardiac & limb events vs ASA alone ([Lancet 2018;391:219](#)). Caution as ↑major bleeding, but no ↑fatal bleeding in pts w/ stable PAD in study
- Cilostazol: 100mg BID. Adjunct agent, ↑exercise capacity ([Am J Cardiol 2002;90:1314](#)). Contraindicated in HF
- Endovascular repair (angioplasty vs stent) if: threatened limb and/or severe symptoms refractory to medical management

Acute Limb Ischemia: ([BMJ 2000;320:764](#))

- Sudden decrease in limb perfusion threatening viability. **Surgical emergency** - consult Vascular Surgery STAT
 - **Viable**: no immediate threat of tissue loss; audible arterial Doppler signal, intact motor/sensory
 - **Threatened**: salvage requires prompt intervention; no audible arterial Doppler signal, motor or sensory deficits
- Etiologies: embolic (e.g. AF, endocarditis, proximal lesion) > thrombosis (e.g. atherosclerosis, APS, HITT), trauma
- Precipitating factors: dehydration, HoTN, abnormal posture (i.e. kneeling), malignancy, hyperviscosity, hypercoagulability
- Presentation: (6Ps) Pain, Poikilothermia, Pallor, Pulselessness, Paresthesia (unable to sense light touch), Paralysis
- Diagnosis: pulse (w/ Doppler) + neuro checks; angiography (CTA w/ run-off or arteriography)
- Treatment: urgent Vascular Surgery consult; anti-coagulation ± IA lytic; endovascular repair
 - After treatment, monitor for reperfusion acidosis, hyper-K, myoglobinemia (ATN), & compartment syndrome

CARDIO-ONCOLOGY ([JACC 2017;70:2536](#); [JACC 2017;70:2552](#))

Overview: toxicities include HF, ischemia, HTN, myocarditis, pericardial disease, thromboembolism, QTc prolongation, arrhythmia
Chemo-induced CM = EF drop ≥10% to <55% w/o sx or decline ≥5% to <55% w/ sx ([Eur Cardiol. 2018;13:64](#))

Risk factors: heart disease, DM, HLD, young or old, female, high-dose chemo

Dx: TTE (compare to baseline), EKG, TnT (↑correlates to adverse cardiac events post-chemo), MRI/PET/bx if suspect ICI myocarditis ([Lancet Onc 2018;19:e447](#))

Prevention:

- Consider BB/ACE-I if EF <50%, EF drop >10% or abnml TnT ([Am J Clin Onc 2018;41:909](#)), ARB > BB protection against LVEF decline in early breast Ca with adjuvant tx ([EJH 2016;37:1671](#))
- Consider pre-emptive vasodilators/serial EKGs in 5-FU + capecitabine

Monitoring:

- **TTE** surveillance schedule depends on therapy & baseline cardiac risk; ranges from q3-6mo with long-term risk >10y
- Monitor weekly BP in first cycle, then q2-3w on therapy, initiate therapy when DBP >20mmHg

Treatment: cessation of chemotherapy is a last resort

- Appropriate risk factor modification, standard HF therapy, ischemia w/u & tx (stress/cath, ASA if PLT >10k, DAPT if PLT >30K)
- HTN management as above
- Stress testing w/in 5-10y after chest radiation
- **ICI myocarditis**: stop therapy, glucocorticoids/other immunosuppressives; re-challenging will depend on type of cardiotoxicity

Common Cardiotoxicities ([Circ Res 2016;118:1008](#))

Anthracyclines (doxorubicin): HF, LV dysfunction (5-23% pts), based on cumulative dosage
HER2 agents (trastuzumab): 2.1% risk of reducing LV function, resolves once stopped, TTE q3mo
TKI (esp. sunitinib): HF, cardiac dysfunction
Angiogenesis inhibitors (bevacizumab, lenalidomide): HTN, 3-fold ↑in arterial thromboembolic (TE) events
Platinum-based (cisplatin): HTN, HL, CAD, TE, in advanced testicular disease
Microtubule inhibitors (paclitaxel): arrhythmias
Anti-metabolites (5-FU, cytarabine): MI, angina, CP, EKG changes, 1-8% pts, early onset
Immune checkpoint inhibitor (ICI) : fulminant lymphocytic myocarditis, HF, cardiac arrest; onset variable, risk factor = combo therapy
Radiation : CAD (up to 85%), pericardial dz (6-30%), CM (up to 10%), valvular abnormalities, PVD, arrhythmias, autonomic dysfunction, can occur 10-15y later, many RF incl dosage, metabolic RF

Cardiology

Outpatient CV Health

EPIDEMILOGY OF CARDIOVASCULAR DISEASE

Overview: leading cause of death in developed countries; CVD includes: CAD, CVA, PAD, aortic disease

Risk Factors:

- Non-modifiable: M 3x > F, age (each decade older confers 2x risk), FHx (1st degree relative <55M or <65F with CVD)
- Modifiable: HTN, HLD, DM, obesity, smoking, alcohol, exercise, diet, psychosocial stress, chronic inflammation, radiation, HIV, CKD

ASPIRIN FOR CVD PREVENTION

- 2019 ACC/AHA 1° prevention guidelines: consider low-dose ASA for 1° prevention in select pts 40-70y at higher ASCVD risk & not at increased bleeding risk. Avoid aspirin for 1° prevention in pts >70y ([Circ 2019;140:e596](#))
- ASCEND ([NEJM 2018;379:1529](#), pts >40y w/ DM), ARRIVE ([Lancet 2018;392:1036](#), moderate CVD risk pts), & ASPREE trials ([NEJM 2018;379:1519](#), pts >70) w/ variable CV benefit for low-dose aspirin, at expense of increased bleeding events

OUTPATIENT BLOOD PRESSURE SCREENING AND MANAGEMENT

2017 ACC/AHA guidelines: HTN = SBP >130 or DBP >80 independent of kidney function or age; US prevalence 46% ([HTN 2018;71:1261](#))

- Method: 2 checks >1w apart, sitting 5min with arm at heart level, cuff bladder 80% length & 40% width of arm circumference
- 24h ambulatory SBPs show greater association w/ all-cause mortality than clinic BPs
- Definition: Normal: <120/(and)<80; Elevated: 120-129/(and)<80; Stage 1 HTN: 130-139/(or)80-89; Stage 2 HTN: >140/(or)>90

Initial Workup: BMP, UA (with protein/Cr ratio), CBC, fasting glucose, TSH, lipids, baseline ECG (consider TTE to assess for LHV)

2° HTN: indications for workup include: ([HTN 2018;72:e53](#))

- Severe HTN (control w/ 4+ agents) or resistant HTN (not controlled on 3+ agents, one of which is a diuretic)
- Acute rise in blood pressure in a previously well-controlled patient, esp. DBP
- Age <30y w/o risk factors (e.g. obesity, FHx)

Secondary Causes of HTN		
Cause	Clinical Clues	Work-up
Medications/Drugs (use or withdrawal)	NSAIDS, OTC decongestants, OCPs, sudden d/c of anti-HTN meds (i.e. clonidine)	Thorough history
OSA	Obesity, snoring, smoking	Sleep study
Renal disease	Elevated Cr, protein/blood on UA	See AKI and CKD
Primary aldosteronism	Hypokalemia, hypernatremia, adrenal incidentaloma, FHx	Plasma aldo:renin activity; ratio >30. MUST measure in the <u>morning</u> (~8AM), after being <u>upright/ambulatory</u> for >3h, with both drawn at the same time
Renal artery stenosis	>50% rise in Cr after ACEi initiation Lateralizing abdominal bruit Atrophic or asymmetric kidneys	If intervention likely to be pursued, begin with Duplex Doppler US (Sn 85%, Sp 92%) → if stenosis (ARAS>50%) or ambiguous results, then angiography
Rare: pheochromocytoma (screen w/ 24h urine fractionated metanephrenes/catecholamines [Sn 98%, Sp 98%], plasma fractionated metanephrenes if high suspicion), Cushing's disease, hyper/hypothyroidism, hyperparathyroidism, aortic coarctation, ADPKD		
Lifestyle Counseling (JACC 2014;63:2960)		
Exercise	40min/d, 3-4x/w, moderate to vigorous intensity	↓5mmHg for aerobic exercise, unclear for resistance
Diet	DASH diet (salt intake <2g/d); ↓ sweets & red meat	↓8-14mmHg (DASH); ↓2-8mmHg (low Na)
Caffeine	Limit to <2cup/d	↓5/2.5mmHg
Alcohol	Limit consumption (<2-3 standard drink/d)	↓2-4mmHg
Medical Management – 2017 ACC/AHA Guidelines (Circ 2018;138:e426)		
When to Treat	Stage II HTN or Stage I if: clinical CVD, DM2, CKD, or ASCVD ≥10%	
Target BP	<130/80	
Choice of Agent	First-line: thiazides (chlorthalidone may not be > HCTZ, ↑SEs (JAMA IM 2020;180:542)), ACEi/ARB, CCB Other: βB, hydralazine, isosorbide, clonidine, α-blockers (e.g. doxazosin), minoxidil (rare)	
Compelling Indications	African-Amer: CCB, thiazide CAD: βB	HF: βB, ACEi/ARB, diuretic, spiro Pregnancy: labetalol, CCB DM2: ACEi/ARB (if proteinuria) CKD: ACEi/ARB
Monitoring	BP check 2-4w after change in medication (home readings vs office) Labs: yearly BMP/Mg if on ACEi/ARB or diuretic	
Important Trials Re: BP goals	SPRINT (NEJM 2015;373:2103): SBP goal <120 vs 135-139 ↓CVD events & all-cause mortality in high-risk pts, but ↑ non-orthostatic hypotension, syncope, electrolyte abnormalities, & AKI ACCORD BP (NEJM 2010;362:1575): no benefit for CV mortality in pts w/ DM of SBP goal <120 vs <140	

OUTPATIENT CHOLESTEROL SCREENING AND MANAGEMENT

2018 ACC/AHA guidelines refine ASCVD risk categories w/ focus on "risk-enhancing" factors to further est. CV risk ([Circ 2019;139:e1082](#))

- Screen adults ≥20y
- Fasting not routinely needed unless evaluating for hyperTG; if non-fasting TG >440, then obtain 12-14h fasting panel
- AHA criteria for FH: LDL-C >190 and either: 1° relative similar or premature CAD or genetic testing for *LDLR*, *APOB*, *PCSK9*
- Assess lipids 4-12w after initiation of med or dose change, repeat 3-12mo as needed

Lifestyle modification: weight loss, exercise, smoking cessation, diet low in sat. fat a/w 15-20mg/dL ↓ in LDL-C, ~50% ↓risk of CAD
Can also refer to ESC Guidelines, overall stricter with absolute goal of LDL <55 in "very high risk" patients ([EHJ 2020;41:111](#))

Cardiology

Outpatient CV Health

Indications for Lipid-Lowering Therapy	
ASCVD Risk Score	
Clinical ASCVD	Maximally-tolerated statin to reduce LDL-C by $\geq 50\%$
LDL-C ≥ 190	High-intensity statin; if LDL-C remains ≥ 100 , sequentially consider adding ezetimibe & PCSK9 inhibitor
Diabetes (age 40-75)	Moderate-intensity statin; consider high-intensity statin for ASCVD risk $> 7.5\%$ to reduce LDL-C by $\geq 50\%$
Age 40-75 w/o above	For low risk $< 5\%$, lifestyle changes; borderline risk $5-7.5\%$, consider mod-intensity statin based on risk-enhancers*; intermediate risk $7.5-19.5\%$, statin to \downarrow LDL-C $\geq 30\%$; high risk $> 20\%$, statin to \downarrow LDL-C $\geq 50\%$

*ASCVD risk enhancers: FHx premature ASCVD, LDL-C ≥ 160 , CKD, premature menopause (age < 40), pre-eclampsia, metabolic syndrome, inflammatory dz (RA, HIV, psoriasis), ethnicity (South Asian), TG ≥ 175 , hs-CRP ≥ 2 , Lp(a) ≥ 50 , apoB ≥ 30 , ABI < 0.9 . Coronary artery calcium (CAC) score 1-99 favors statin therapy; CAC 100+, initiate statin

Common Medications					
Medication	Mechanism	Indication	% \downarrow in LDL-C	Effect on CV outcomes	Adverse effects
Statins*	HMG-CoA reductase inhibitor	1st-line therapy for 1° & 2° prevention	20-60% LDL-C reduction	1° & 2° prevention, \downarrow CV events (ARR 1.1%, NNT 91, HOPE-3)	Myopathy, \uparrow LFTs, memory loss & confusion
Ezetimibe (10mg qd)	\downarrow intestinal cholesterol absorption	- Statin-intolerant - LDL-C > 70 w/ CVD or $< 50\%$ \downarrow LDL-C w/o CVD on max-tolerated statin	Ezetimibe + statin therapy \downarrow LDL-C by $\sim 23\%$	Ezetimibe + statin \downarrow CV events (ARR 2%, NNT 50, IMPROVE-IT)	Mild \uparrow LFTs (usually w/ statin)
PCSK9 inhibitors (alirocumab, evolocumab)	Promotes degradation of LDL-R on hepatocyte surface	High risk pts w/ CVD & LDL-C > 70 on statin + ezetimibe; approved for use in FH	38-72% reduction; $\sim 60\%$ in pts on statin therapy	Evolocumab + statin \downarrow CV events (ARR 1.5%, NNT 67 at 48w, FOURIER); alirocumab + statin \downarrow CV events (ARR 1.6%, ODYSSEY)	Uncommon; mainly injection site reactions Cost: 150k/QALY
O3FAs (e.g. Vascepa [EPA])	Incorporates into phospholipids	Severe hyperTG, CVD prevention	\downarrow TG $\geq 30\%$ with no Δ in LDL	EPA + statin \downarrow CV events (ARR 4.8%, NNT 21, REDUCE-IT)	Interaction (e.g. warfarin), GI sx

Note: if patient has concomitant **severe hypertriglyceridemia** (TG $> 886 \text{ mg/dL}$), then also start **fenofibrate** (many formulations)

Statin Potency	
High-intensity ($\geq 50\% \downarrow$ LDL-C)	atorvastatin 40-80mg rosuvastatin 20-40mg
Moderate-intensity (30-49% \downarrow LDL-C)	atorvastatin 10-20mg, rosuvastatin 5-10mg, simvastatin 20-40mg, pravastatin 40-80mg, lovastatin 40mg
Low-intensity ($< 30\% \downarrow$ LDL-C)	simvastatin 10mg, pravastatin 10-20mg, lovastatin 20mg

*Statin Properties:

Biggest change in LDL: rosuvastatin > atorvastatin > simvastatin

Safest in CKD: atorvastatin, fluvastatin (no renal dose adj. required)

Safest in cirrhosis: pravastatin

Lowest rate of myopathy: pravastatin, fluvastatin

Least DDI: pravastatin, rosuvastatin, fluvastatin (no CYP450 metabol.)

Lower overall side effects: pravastatin, rosuvastatin (hydrophilic)

[ACC Statin Intolerance Tool](#): to assess for muscle side effects

OUTPATIENT OBESITY SCREENING AND MANAGEMENT (also see [Weight & Weight Loss](#))

Definition: Overweight: BMI 25.0-29.9kg/m²; **Obesity:** BMI $\geq 30\text{kg/m}^2$; **Severe Obesity:** BMI $\geq 40\text{kg/m}^2$

Management:

Set goals: target initial weight loss of 5-7% body weight

Diet: diet compliance (\downarrow # calories) more important than macronutrient composition. No data to guide specific diet choice ([JAMA 2014;312:923](#))

- **Mediterranean:** high in monounsaturated fats, fruits, vegetables, legumes, grains; moderate dairy & EtOH; low meat (\downarrow overall & CV mortality; may \downarrow DM incidence independent of wt loss) ([NEJM 2018;21:378](#))
- **DASH:** high in fruits/vegetables, moderate dairy, $< 25\%$ caloric intake from fat (\downarrow SBP/DBP) ([Br J Nutr 2015;14:113](#))

Exercise:

- $> 30\text{min}, 5-7 \text{ days/w}$; combine aerobic + resistance training for optimal health gains ([Arch Intern Med 2009;169:122](#))
- Not sufficient for wt loss; improves glycemic control, BP, & functioning; \downarrow CVD risk, predicts long-term weight mgmt

Medications:

- Consider pharmacotherapy if BMI ≥ 30 or BMI ≥ 27 with ≥ 1 comorbidity
- **Options:** Orlistat, phentermine/topiramate, naltrexone/bupropion, lorcaserin, liraglutide, metformin (if pre-diabetic)
- All have significant short-term weight loss (~5-15lbs), but weight is typically gained back when medication stopped

Bariatric surgery: recommended for: BMI ≥ 40 OR BMI ≥ 35 with comorbid conditions; BMI < 35 has insufficient evidence

Benefits of Weight Loss on Comorbidities (Curr Obes Rep 2017;6:187)	
DM or at risk	2.5-5kg wt loss over $\geq 2\text{y}$: \downarrow risk T2DM 30-60% 2-5% wt loss: \downarrow HbA1c by 0.2-0.3% in 1-4y
HLD	5-8kg weight loss: \downarrow LDL 5mg/dL, \uparrow HDL 2-3mg/dL
HTN	5% weight loss: \downarrow SBP 3mmHg & \downarrow DBP 2mmHg
CVD	MI: HR 1.26 for overweight & HR 1.88 for obesity

Cardiology

Anti-Arrhythmic Medications

Class	Name	Mechanism	Usage	Dosing	Side effects, Contraindications (CI)
IA	Procainamide (IV)	Na ⁺ channel blockade; slows conduction; ↑action potential; Class III action also	VT; AF, especially in accessory bypass tracts (WPW)	VT: 100mg q5min until total 500mg, wait 10min for distribution. Admin to arrhythmia control, HoTN or QRS inc. by 50% WPW: 20mg/min until total 17mg/kg (e.g. ~1h, BP q5min); then 2-6mg/min (in urgent situations, up to 50mg/min may be given to total dose ≤17 mg/kg)	HoTN, PVCs, VT, ↑QT, drug-induced lupus (long term use), agranulocytosis, neg. inotropy. CI: CHB, AVB, SLE, TdP
	Disopyramide (PO)	Na ⁺ channel blockade; anticholinergic effects	HOCM (efficacy relates to negative inotropic effect), VT, AF, A-flutter	VT: if <50kg→load 200mg x1, then 100mg q6h; if >50kg→load 200mg x1, then 150mg q6h AF conversion: 200mg q4-6h AF prevention: 400-750mg, divide q6h (w/ BB/CCB) HOCM: 200mg q12h, CR form is oral	Anticholinergic side effects, neg. inotropy, HoTN, CI: ↑QTc, HFrEF
IB	Lidocaine (IV)*	Na ⁺ channel blockade; no effect on conduction; may ↓action potential	VT, pulseless VT/VF	Load: bolus 1.0-1.5mg/kg. May give additional 0.5-0.75 mg/kg IV push PRN q5-10min; total ≤3 mg/kg Maintenance: 1-4mg/min (30-50mcg/kg/min)	Bradycardia, junctional arrhythmia, HoTN, angina, AMS, tremor, seizure, dysarthria, paresthesias, nausea, dizziness
	Mexiletine (PO)	PO analogue of lidocaine	VT	Load: 400mg x1 Maintenance: 200mg q8h	Tremor, nausea, dizziness, GI. CI: cardio.. shock, 2°/3° AVB
IC	Flecainide (PO)*	Na ⁺ channel blockade	pAF ("pill in the pocket"), rarely ventricular arrhythmia	Pill in the pocket: 200mg (<70kg) or 300mg (>70kg). Max: QD Sinus rhythm maintenance: 50-150mg BID	Ventricular arrhythmia (↑risk if structural heart dz), neg. inotropy, dizziness. CI: HFrEF, IHD, ↑QTc, CrCl<50, liver dz
	Propafenone (PO)	Na ⁺ channel blockade; Some β1 blockade	Same as above	Pill in the pocket: 450mg(<70kg) or 600mg (>70kg). Max: once/24h. Start BB/CCB prior Sinus rhythm maintenance: 225-425 BID ER q12h	Ventricular arrhythmia (↑risk if structural heart dz), GI sx, dizzy. CI: IHD, HFrEF, LVH, ↑QTc
II	Esmolol (IV)	β1 antagonist. t 1/2 = 9min	Acute HR/BP control in Ao dissection, SVT	Load: 0.5-1mg/kg x1min Maintenance: 2-21mg/min IV (25-300mcg/kg/min)	Same as other β-blockers Atenolol is renally cleared
	Atenolol (PO)*	β1 antagonist; 2x as potent as metoprolol	SVT, ACS, post-MI, CAD, HTN, HF	25-50mg QD (max: 100mg QD)	
	Propranolol (IV, PO)*	Non-selective βB	Thyroid storm, AoD, tremor, EV ppx, pheno, anxiety	IV: 0.5-1mg load→1-3mg every several hours PO: 120-320mg/d (based on indication)	Crosses BBB, may cause AMS. Less HoTN than β1 antagonists
	Nadolol (PO)*		Variceal ppx	20-80mg qd (max: 240mg)	Δ in mental status. Less HoTN
III	Amiodarone (IV/PO)	Blocks K ⁺ channels, slows repol. Multiple effects incl class Ia, II, & IV. Class II property (i.e. BB) is fastest effect	SVT, VT, pulseless VT/VF, (off-label) AF	Pulseless VT/VF: 300mg IV push, may repeat 150 mg IV push every 3-5min as needed WCT: - IV: 150mg x1 (repeat q10 min prn)→1mg/min x6h (360mg)→0.5mg/min x18h (540mg) - PO: total 8-10g over days (200-400mg, BID-TID) - Maintenance: 100-200mg PO QD-BID AF: PO 8-10g over 2-4w	HoTN (IV), bradycardia, ↑QT. Long t _{1/2} (58d). Systemic SEs w/ long-term use (check baseline PFTs, LFTs, TFTs). Do NOT use for TdP, pre-excitation. CI: ↑QTc, SSS, 2°/3° AVB, sx bradycardia, cardiogenic shock
	Sotalol (IV, PO)*	Nonselective β1/β2 antagonist, K ⁺ channel blockade	AF, VT	IV: 75mg q12h, may ↑dose by 37.5mg q3d (max: 300mg/d) PO: 80mg q12h, may ↑dose by 40mg q3d (max: 320mg/d). Adjust dosing interval in renal impairment	↑QT, typical effects of β-blockade; CI: CrCl <40, LVH, HFrEF, ↑QTc, hypoK
	Ibutilide (IV)	Blocks K+, prolongs action potential	AF, AFlutter	>60kg: 1mg over 10min; can repeat x1 in 10min; <60kg: same except dose is 0.01mg/kg	↑QT, TdP, HA
	Dofetilide (PO)*		AF, AFlutter, SVT	Initial dose 500mcg BID max Decrease dose by 50% if CrCl<60 or QT prolonged	↑QT; CI: thiazide, dolutegravir, trimethoprim, verapamil, hypoK, hypoMg, CrCl<20
IV	Diltiazem (IV, PO)	CCB→slows AV node conduction & phase II of cardiac action potential	AF, AFlutter, SVT, MAT, angina, HTN	IV: 0.25mg/kg (<25mg) q15min prn; gtt 5-15mg/h PO: 120-320mg ER QD or ≤480mg/d IR q6h IV infusion: 5-10mg, repeat q15-30min PRN (≤20-30mg); gtt 5-20mg/h if needed PO : 120-360mg ER QD or ≤480mg/d IR q8h	Contraindicated in SSS, bradycardia, 2°/3°AVB, VT, AF + WPW, hypotension, pulmonary edema, HFrEF
	Verapamil (IV, PO)			IV (initial): total dose 8-12mcg/kg IBW (≤0.75-1.5mg) 3 divided doses, 50% over 5min as 1st, then 25% for 2nd & 3rd, q6h. Follow with maintenance. Goal: 0.5-0.8 (HF), <1.2 (AF) Oral (maintenance): 0.125-0.25mg QD	Digoxin tox (>2ng/mL usually), N/V, visual disturbance, atrial tachycardia with AV block, PVCs, VT, VF. CI: VF
Misc.	Digoxin (IV, PO)*	Inhibits Na/K ATPase→Ca influx. Suppresses AV node conduction, ↑vagal tone, +inotrope	AF, AFlutter, HFrEF, SVT	IV (admin over 1-2sec, PIV): 6mg→12mg after 1-2min if ineffective, repeat x1 if needed, flush immediately. Halve dose if patient s/p heart transplant, using central line, or receiving carbamazepine or dipyridamole	Arrhythmia, angina, HA, flushing, GI distress, dyspnea. CI: 2°/3° AVB, SSS, sx brady, lung dz, asthma
	Adenosine (IV)	Slows AV node, coronary vasodilation	SVT		

*Renal dosing required

Pulmonary & Critical Care

Respiratory Distress

Respiratory distress is a constellation of symptoms that portends impending respiratory collapse. It is different from **dyspnea**, which is the subjective sensation of shortness of breath. Key symptoms of **respiratory distress** are:

- Tachypnea (go look at the patient and measure yourself. RR ≥ 20)
- Cyanosis (typically SpO₂ $< 80\%$)
- ↑WOB (nose flaring, retractions, grunting, tripod-ing, diaphoresis)
- Obstruction (wheezing, stridor)

APPROACH

1) Confirm code status

2) Low threshold to call Rapid Response for assistance

3) Assess airway, breathing, circulation & confirm access

- Place on supplemental O₂: NRB to start, can always wean later
- Red flags (RICU STAT): GCS < 8 (hard criteria for intubation), pooling secretions, hemoptysis, life-threatening hypoxemia despite supplemental O₂ (SpO₂ $< 80\%$, PaO₂ $< 55\text{ mmHg}$), severe hypercapnia despite BiPAP, tiring out (\uparrow WOB, progressive hypercapnia), RR > 35
- Temporize: suction, head-tilt chin lift (preferred if no concern for Cspine injury) vs jaw-thrust to open airway, bag-mask ventilation (enough volume to see chest rise, no more than 8-10cc/kg or 5-6cc/kg during CPR; 8-10 breaths/min). If use of bag-mask will not be brief & pt unresponsive, consider OP airway prior to intubation

4) Initial workup:

- CXR (order STAT, must call x6-3050): look for new infiltrate (aspiration, PNA), pulmonary edema, lobar collapse (mucus plug), PTX. x4-1533 for read. If nl, consider ischemia, PE, acidosis, etc
- ABG: worrisome if PaCO₂ $> 45\text{ mmHg}$ (poor ventilation), PaO₂ $< 60\text{ mmHg}$ (poor oxygenation), pH < 7.25
- Labs: VBG (& ABG if possible, correlate to VBG. Widened A-a gradient > 20 = abnormal gas exchange vs nl < 20 = global hypoventilation), hs-Trop, NT-proBNP, lactate, BMP, CBC
- Additional studies based on clinical suspicion: CT-PE (if stable to travel), TTE (acute valvular dz, RV strain), NCHCT (suspected stroke)

TREATMENT

• Supplemental oxygen therapy (see [Oxygen Delivery Therapies](#) for more detail):

- NC: for every liter increase in O₂, \uparrow FiO₂ 0.03/L (max: 6L = 0.40 FiO₂)
- NRB: can give FiO₂ ~ 0.90 , but in tachypneic patient, FiO₂ ~ 0.60 (due to entrainment of room air)
- HFNC: FiO₂ 0.6 to 1.0 at 10-60 L/min (humidified air); \downarrow 90d mortality vs NIPPV for pts with hypoxic respiratory failure not due to cardiogenic pulmonary edema or obstructive lung disease ([NEJM 2015;372:2185](#))

• NIPPV (BiPAP for COPD; CPAP for CHF): RR $> 25-30$, accessory muscle use, pH < 7.35 , PaCO₂ $> 45\text{ mmHg}$

• Intubation: see red flags above

DISEASE SPECIFIC TREATMENT

- CHF: CPAP, IV diuresis, nitrates (paste or drip, if BP room)
- COPD: BiPAP, nebulizers (stacked DuoNebs x3), steroids (PO pred 40mg = IV methylpred 32mg); if severe exacerbation, consider methylpred 60-125mg q6h; abx if 2/3: ↑sputum volume, purulence, dyspnea
- PE: if high suspicion and no contraindication, start **empiric AC** (LMWH therapeutic faster vs UFH gtt)
- PTX: if unstable, bedside needle thoracostomy (**STAT page Thoracic Surgery**, 14G angiocath, 5th ICS at mid-axillary line or 2nd ICS at mid-clavicular line); page Thoracic Surgery or IP for chest tube
- Pleural effusion: thoracentesis (see [Thoracentesis](#); must be performed by IP or supervised by pulm attending)
- Opioid overdose: Narcan 0.4-2mg IV/IM q2min, observe response, uptitrate to adequate RR. Given short half-life, consider gtt if responsive to bolus at 2/3 of bolus dose per hour (ex: 0.2-0.6 mg/h)
- Anaphylaxis: Initial: Epi (1:1000) 0.3mL = 0.3mg IM, q5-15min PRN. Other agents may follow: diphenhydramine 25-50mg IV, nebulized albuterol, methylprednisolone 1-2mg/kg IV
- ACS (see [ACS](#)): ASA 325mg, atorva 80mg, nitrates (SL → gtt), heparin, βB, ACEi/ARB, etc

DYSPNEA DDX

- CV: MI, HF, VHD, arrhythmia, tamponade, PE, PHT
- AIRWAYS: asthma, COPD, mucus plugging, angioedema, anaphylaxis, foreign body
- ALVEOLI: edema, PNA, hemorrhage
- PLEURAL: large effusion, PTX
- CNS: CVA, intox (CO, ASA, BZD), met. acidosis (sepsis, DKA, etc), psych/anxiety
- OTHER: anemia, ↑abd girth, ALS/GBS/MG, spinal cord, hypothyroidism

Rapid Response x6-3333 for Senior On, nursing supervisor, RT, pharmacy

DECISION TO INTUBATE:

RICU: x6-3333, ask for "STAT RICU"

RICU Communication Guide: have information ready prior to intubation

Code status & urgency/acute of decline

Hemodynamics: LV, RV, valves, volume status, access

Aspiration risk: NPO, last meal, RFs

Difficult airway (from prior intubation notes)

Allergies

Have ready: sedation (propofol, fentanyl, midaz), pressor (Neo >> Levo), IVF w/ push line; RICU brings paralytic

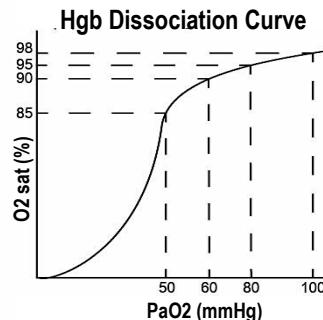
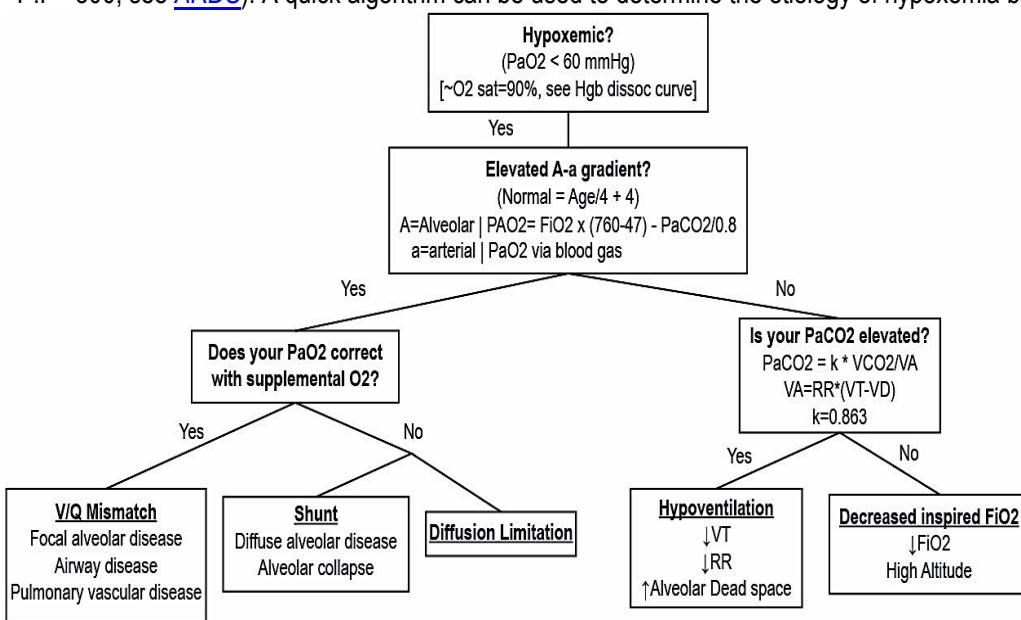
MICU/CCU: Resource RN will call for RICU; make sure attending/OI, fellow, RT, RN aware

INTUBATION IS NOT AN ACT OF WEAKNESS:
do not delay intubation in patients with impending respiratory failure

Pulmonary & Critical Care

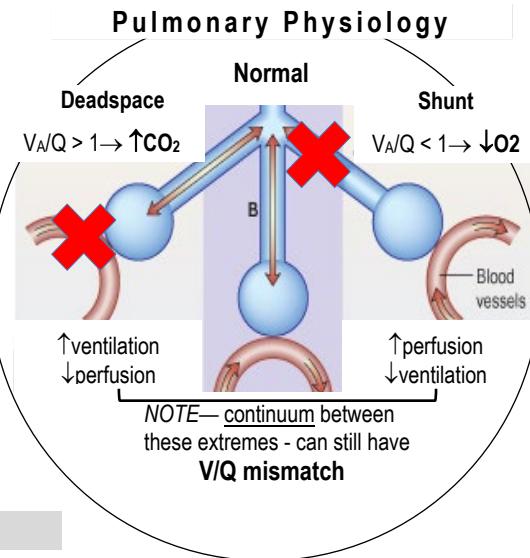
Hypoxemia & Hypercapnia

Respiratory Failure: inability to oxygenate (deliver O₂) or ventilate (blow off CO₂). Can be **hypoxicemic** (PaO₂ < 60 mmHg), **hypercapnic** (PaCO₂ > 45 mmHg), or both. **P:F Ratio** (P=PaO₂/F=FiO₂) quick surrogate for A-a gradient (consider ARDS if P:F < 300; see [ARDS](#)). A quick algorithm can be used to determine the etiology of hypoxemia based upon ABG results:



HYPOXEMIC RESPIRATORY FAILURE

- **Hypoventilation; low FiO₂:** decreased O₂ delivery to lungs (e.g. mouth breathing with O₂ via nasal canula)
- **V/Q mismatch:** imbalance in delivery of oxygenated air & blood flow
 1. FOCAL alveolar infiltrates: **PNA, edema, hemorrhage**
 2. Airway: **asthma, COPD, bronchiectasis**
 3. Vascular: **pHTN, PE**
 4. Iatrogenic: too much **PEEP**
- **Shunt:** flow of blood through lung without encountering oxygenated air, “perfusion without ventilation” (severe V/Q mismatch)
 1. DIFFUSE alveolar infiltrates: **above + ARDS**
 2. Alveolar collapse: **PTX, atelectasis, mucus plug**
 3. Intra-cardiac/intra-pulm shunt: **PFO, AVM** (e.g. hepatopulm.)
- **Impaired diffusion (↓DLCO):** hypoxemia worse w/ exertion
 - o ILD (correlates with severity on CT), pHTN, advanced COPD



HYPERCAPNIC RESPIRATORY FAILURE

- **“Won’t breathe” (↓RR): sedatives, obesity hypoventilation, brainstem stroke/tumor/infection, central sleep apnea, compensation for metabolic alkalosis (chemoreceptors), hypothyroidism (myxedema coma)**
- **“Can’t breathe” (↓V_T): nerves/muscles/chest wall/airways**
 1. ↑Alveolar dead space (airspace which does not participate in gas exchange; “ventilation without perfusion”)
 - Dead space = anatomic (~150cc upper airway air without perfusion) + alveolar (~0 normally; in disease, capillaries get destroyed or compressed → $\uparrow V_D$)
 - Parenchyma: emphysema, ILD/fibrosis, CHF, PNA, ARDS
 - Airway: asthma, COPD, CF, bronchiectasis, OSA, tumor, foreign body, high PEEP
 - Vascular: severe PE (wasted ventilation due to blocked circulation; more often see $\downarrow pCO_2$ 2/2 hyperventilation)
 2. Chest wall/pleural constraints → \downarrow lung volume: effusion/fibrosis, obesity, kyphosis/scoliosis, abd distension, PTX
 3. Neuromuscular ([Neurol Clin 2012;30:161](#)): trend at bedside with single breath test (non-intubated pts), negative inspiratory force (NIF) (intubated pts). **Consider EMG.** Ddx: **neuropathy** (C-spine/phrenic nerve, GBS, ALS, polio), NMJ disorder (MG, botulism), myopathy (polymyositis/dermatomyositis, hypophosphatemia), critical illness
- **↑CO₂ production (V_{CO₂}):** **TWOB, fever, seizure, sepsis, steroids, overfeeding, thyrotoxicosis**

ACID-BASE INTERPRETATION

- Hypercapnia** → Resp acidosis ($\uparrow pCO_2$)
 - Acute: HCO₃ ↑ by 1 (per pCO_2 ↑ 10)
 - Chronic: HCO₃ ↑ by 3-4 (per pCO_2 ↑ 10)**Hypocapnia** → Resp alkalosis ($\downarrow pCO_2$)
 - Acute: HCO₃ ↓ by 2 (per pCO_2 ↓ 10)
 - Chronic: HCO₃ ↓ by 5 (per pCO_2 ↓ 10)

OXYGEN DELIVERY DEVICES

Mask Type	Flow (LPM)	FiO2 (%)	Notes	Aerosol?
Nasal Cannula	1 - 6	24 - 40	Patient able to eat/speak. Consider humidification if >4LPM	N
Oxymizer	1 - 15	24 - 45	20mL reservoir allows for higher FiO2 compared to NC	N
Simple Facemask	5 - 10	30 - 60	Flow rates <5LPM lead to re-breathing of CO ₂	N
Face Tent (Shovel mask)	5 - 10	24 - 50	Less claustrophobic, FiO2 variable Offers humidification without a mask	Y, if humidified
Non-Rebreather	10 - 15	60 - 100	Consider first for acute hypoxemia (easily accessible) ↑FiO2 with tachypnea and ↑Vt due to entrainment Titrate flow rate to avoid reservoir bag collapse (<1/3) on inspiration	N
Venturi	Var. color	24 - 50	Color-coded adapters determine flow and FiO2 independent of ventilatory demand. Useful for set SpO ₂ goals (e.g. COPD) NOT for acute respiratory distress	Y, if >15 LPM or humidified
HFNC	10 - 60	30 - 100	~2-3cm H ₂ O of PEEP w/ mouth closed (~0.7cm H ₂ O per 10LPM) In acute hypoxic resp. failure not 2/2 cardiogenic pulmonary edema or obstructive lung disease, ↓90-day mortality but no Δ in intubation rates vs. NIPPV (NEJM 2015;372:2185) Extubation to HFNC non-inferior to extubation to NIPPV re: reintubation and postextubation resp. failure in high risk pts (JAMA 2016;316:1565)	Y, if >15 LPM

Caution: liberal supplemental O₂ to ↑SpO₂ >94-96% in acutely ill adults a/w ↑mortality ([Lancet 2018;391:1693](#))

NONINVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)

- **NIPPV:** both continuous positive airway pressure (**CPAP**) & bilevel positive airway pressure (**BLPAP or BiPAP™**)
 - In acute cardiogenic pulm. edema, NIPPV ↓intubation, ↓mortality ([NEJM 2008;359:142](#); [Cochrane Rev 2013](#))
 - In acute hypoxic resp. failure (not 2/2 COPD or ADHF), NIPPV may ↓mortality & intubation ([JAMA 2020;324:57](#))
- **CPAP:** provides positive end-expiratory pressure (PEEP) to ↓upper airway obstruction (for OSA), ↓atelectasis, ↓venous return (↓LV & RV preload), ↓LV afterload (hence useful in acute cardiogenic pulmonary edema)
- **BLPAP:** provides PEEP (same as “expiratory positive airway pressure” or EPAP) and inspiratory positive airway pressure (IPAP), which helps ↑tidal volume and minute ventilation (e.g. useful in AECOPD and acute cardiogenic pulm. edema)
 - In acute exacerbation of COPD with resp. acidosis, BLPAP ↓mortality, intubation, & LOS ([Cochrane Rev 2017](#))

Strong Indications for NIPPV (ERS/ATS: [ERJ 2017;50](#))

- Acute cardiogenic pulm. edema (CPAP/BLPAP)
- AECOPD with resp. acidosis (BLPAP)

Weak Indications for NIPPV

- Specific other resp. failure (e.g. asthma, hypoxemic, immunocompromised pt)
- Ppx against extubation failure in high risk pts
- Patient is DNI w/ indication for intubation
- Palliation for increased WOB, dyspnea

Contraindications to NIPPV

- **Risk of delay:** emergent indication for intubation, acute life-threatening non-respiratory organ failure
- **Risk of aspiration:** cannot clear secretions, AMS if pt cannot remove mask (exception: AMS due to hypercapnia)
- **Risk of injury:** pneumothorax (can induce tension physiology), recent esophageal anastomosis or tear, patient cannot tolerate decreased preload (↓venous return), facial trauma or recent facial surgery
- **Will not work:** patient cannot initiate breath, anatomic deformity or facial hair interrupting seal

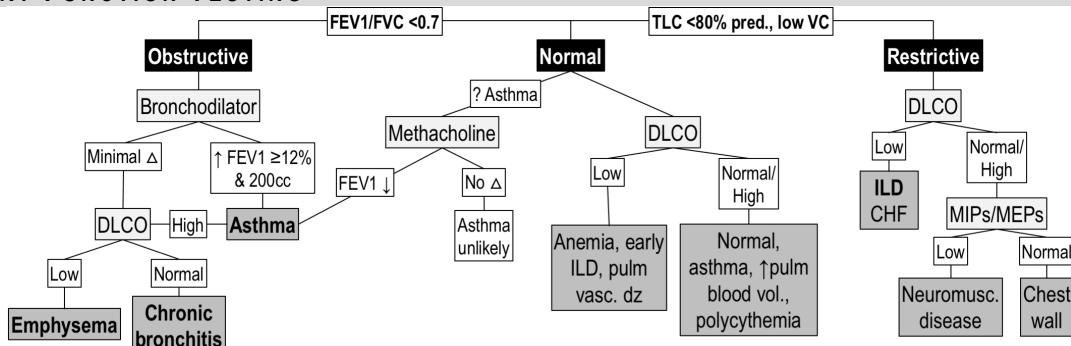
BLPAP/HFNC on the floor: huddle with nursing and RT (also notify Senior On). Trial BiPAP or HFNC no more than 2-3 hours and assess response; consider ABG/VBG to assess change in oxygenation or ventilation. If no improvement, discuss escalation of care to ICU

REMEMBER: BLPAP/HFNC MUST NOT DELAY AN INDICATED INTUBATION!

Pulmonary & Critical Care

PFTs & Asthma

PULMONARY FUNCTION TESTING



ASTHMA - DIAGNOSIS & OUTPATIENT CARE

DEFINITION: chronic, variable airway narrowing with intermittent dyspnea, wheeze, and/or cough ([JAMA 2017;318:279](#))

DIAGNOSIS:

Spirometry	Obstructive, reverses w/ bronchodilator, worsens w/ methacholine (can be nl before provocation)
Peak expiratory flow (PEF)	Estimates degree of control. <80% personal best c/w poor control
Allergy testing	If allergic component suspected (sx w/ exposure/persistent sx): ✓ IgE, CBC/diff (Eos), refer to Allergy
New-onset adult cases unusual differential includes: systemic disease (ABPA, EGPA, systemic mastocytosis), occupational asthma (10-25%; NEJM 2014;370:640), aspirin-exacerbated resp. disease (esp. if nasal polyps; J Allergy Clin Immunol 2015;135:676)	

MANAGEMENT: ([GINA 2020:51](#); [ERJ 2019;53:1901046](#))

- **Controller + reliever:** stepwise based on severity (see below); step up if not controlled; step down if well controlled 3mo
 - Note: changes in recent guidelines to recommend that all receive ICS-containing controller; no longer rec. SABA only tx as a/w ↑ allergic responses & airway inflammation, ↓ response when SABA needed, & overuse a/w ↑ severe exacerbations
 - In mild asthma, PRN budesonide-formoterol (Symbicort) > PRN SABA ([NEJM 2019;238:2020](#); [NEJM 2018;378:1865](#)) & non-inferior to maintenance ICS for preventing exacerbations (though ↑ sx; [NEJM 2018;378:1877](#))
 - In mild/mod., maintenance ICS-LABA + PRN ICS-LABA also > + PRN SABA ([AJRCCM 2005;171:129](#); [Chest 2006;129:246](#)). PRN ICS w/ SABA > PRN SABA alone ([Lancet 2011;377:650](#))
 - May be some phenotypes however w/ low eos. inflamm. (<2% in sputum) in whom ICS ↓ effective ([NEJM 2019;380:2009](#))
- **Trigger avoidance:** e.g. exercise, cold air, irritants (smoke, perfume), allergens, infxn, drugs (ASA, NSAIDs, β-blockers)
- **Exacerbations:** short course pred. 40-50mg x5-7d on top of controller/reliever regimen
 - Consider 4x controller ICS for mild exacerbations ([NEJM 2018;378:902](#))

	Mild Step 1	Mild Step 2	Moderate Step 3	Severe Step 4	Severe Step 5
Preferred Controller	PRN low dose ICS-LABA	Daily low-dose ICS or PRN low-dose ICS-LABA	Low-dose ICS-LABA	Medium-dose ICS-LABA	High-dose ICS-LABA + referral to specialist (consider biologics)
Other Options	Low-dose ICS taken w/ SABA (if combo not available)	Low-dose ICS taken w/ SABA; or LTRA	Med-dose ICS or low-dose ICS + LTRA	High-dose ICS, add-on tiotropium or add-on LTRA	Low-dose oral corticosteroids
Preferred Reliever	PRN low-dose ICS-LABA NOTE: Pt must also be ICS on maintenance				
Other Options	PRN SABA				

ICS: inhaled corticosteroids || LABA: long-acting β-agonists || SABA: short-acting β-agonist
 LTRA: leukotriene receptor antagonist || Biologics: anti-IL4 (dupilumab), anti-IgE (omalizumab), anti-IL5 (mepo-, res-, benra- lizumab, tezepelumab)
 Contraindicated to use LABA without ICS ([CHEST 2006;129:15](#); [NEJM 2010;362:1169](#))

ASTHMA - INPATIENT CARE

- ✓ PEF (via RT; severe <50%), CXR ± RVP; ABG if severe. Expect resp. alkalosis; nl/↑ pH may = impending resp. failure

Floor Patient	ICU Patient (Thorax 2003;58:81)
<ul style="list-style-type: none"> - Bronchodilators: albuterol ± ipratropium <ul style="list-style-type: none"> ○ DuoNeb in ED a/w ↓ admit (Cochrane Rev 2017) ○ Can Δ to SABA alone after admit unless severe/worsening - Steroids: pred 40-60mg or IV methylpred 40-60mg q12-24 (if ○ PO/impending arrest); total x5-7d (Cochrane Rev 2016) - O2 >92% (93-95% in severe; >95→↑pCO2; Thorax 2011;66:937) - If impending respiratory failure: stacked DuoNeb (x3/h), methylpred IV 60-125mg, Mg IV 2g/20min, transfer to ICU 	<ul style="list-style-type: none"> - Bronchodilators: albuterol + ipratropium - Methylpred 125mg IV q6h - BLPAP: limited data, can trial but generally avoided in adults - Rescue therapies: Mg IV 2g/20min, continuous albuterol nebs (CAB). Less data: ketamine, Heliox, ECMO as last resort - Mechanical ventilation: large ET tube, high insp flow rate (80-100L/min), low VT (6-8cc/kg), low RR (10-14), paralysis; Goal: maximize expiratory phase, permissive hypercapnia

ASTHMA/COPD OVERLAP (ACO) ([GINA 2020:129](#); [AJRCCM 2017;196:375](#); [NEJM 2015;373:1241](#))

- Some patients have persistent airflow limitation together w/ clinical features c/w both asthma & COPD
- **ICS-containing treatment is essential;** LAMA or LABA should not be given without ICS. Can escalate to triple therapy, biologics

Pulmonary & Critical Care

COPD

DEFINITION: persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities

DIAGNOSIS AND STAGING (GOLD: AJRCCM 2017;195:557)

- Diagnosis:** actual FEV1/FVC <0.7 without significant change w/ bronchodilator on spirometry
- GOLD Grade** (1-4) is defined by severity of airflow limitation (FEV1 % of predicted), helps establish prognosis & guide non-medical therapy
- GOLD Group ("ABCD")** is defined by exacerbations & sx ([mMRC](#), [CAT score](#)), guides therapy

	mMRC 0-1 OR CAT <10	mMRC >=2 OR CAT >=10
0 or 1 exacerbations without admission	A	B
>=2 exacerbations OR >=1 admission	C	D

GOLD Grade	FEV 1 (% of predicted)
1 (Mild)	≥80
2 (Moderate)	50-79
3 (Severe)	30-49
4 (Very Severe)	<30

MANAGEMENT OF STABLE COPD (GOLD 2020; NEJM 2019;381:1257)

Pharmacologic interventions: based on GOLD ABCD groups

	GOLD A (Fewer sx, low risk)	GOLD B (More sx, low risk)	GOLD C (Fewer sx, high risk)	GOLD D (More sx, high risk)
Starting tx:	PRN SABA, SAMA or SABA+SAMA	LAMA or LABA + PRN SABA (or SAMA)	LAMA (+ PRN SABA)	LAMA (+ PRN SABA) Severe sx (e.g. CAT >20): LAMA+LABA Eos >300 or asthma component: LAMA+ICS
Escalate to:	LAMA	LAMA+LABA or LABA+ICS	LAMA+LABA or LABA+ICS	LAMA+LABA+ICS (unless Eos <100) If persistent sx: PDE4i, azithro, theophylline If refractory: lung vol. reduction, transplant
Notes	- SABA+SAMA > monox (↑FEV1) (Chest 1994;105:1411) - Tiotropium may slow decline in FEV1 in early-stage COPD (NEJM 2017;377:923)	- Tiotropium > LABA (Cochrane Rev 2012; NEJM 2011;364:1093) - LAMA+LABA > monox (Chest 2014;145:981; Cochrane Rev 2015) - LAMA+LABA > LABA+ICS (NEJM 2016;374:2222; Chest 2008;134:255) but LABA+ICS may be pref. if asthma/allergies/rhinitis, hx of exacerbations, Eos >300 - LABA+ICS may have ↓ mortality vs. LABA but no Δ in exacerbations and ↑ in PNA (AJRCCM 2008;177:19) - Little benefit to ICS if Eos <100 (Lancet RM 2018;6:117)		- LAMA+LABA+ICS > LAMA+LABA to ↓ exacerbations, but may ↑PNA (Lancet 2018;391:1076; NEJM 2018;378:1671) - Consider d/c ICS if persist. exacerb., PNA (if Eos >300, high risk of ↑exacerb. w/ d/c) - PDE4i → ↓ exacerb. (Lancet 2015;385:857) - Azithro → ↓ exacerb. but ↑ hearing loss, risk of abx resistance (NEJM 2011;365:689; Lancet RM 2014;2:361; Cochrane Rev 2018)

- Vitamin D supplementation → ↓ exacerbations if baseline level <25 ([Thorax 2019;74:337](#))

Non-Rx interventions: ⊖ smoking (↓ mortality; [Annals 2005;142:233](#)), vaccines (flu, PCV13, PPSV23)

- Lung CA screening:** annual low-dose CT (age 50-80 & ≥ 20 pack-years & has smoked in last 15y) ([USPSTF 2021](#))
- Home O₂:** if PaO₂ ≤55 or SpO₂ ≤88% (PaO₂ ≤59 or SpO₂ ≤89 if pulmonary HTN or Hct >55% or CHF)
- Nocturnal NIPPV:** if daytime pCO₂ ≥52 & nocturnal SpO₂ ≤88% (despite 2L O₂) or if recent exacerb. & persistent pCO₂ >53 (↓ risk of readmit & mortality: [JAMA 2017;317:2177](#))
- Pulmonary rehab:** ↑QoL, ↑exercise capacity ([Cochrane Rev 2015](#)), possibly ↓ mortality ([JAMA 2020;323:1813](#))

COPD EXACERBATION (AECOPD) (ERS/ATS: ERJ 2017;49, GOLD 2020)

- Hx: ↑dyspnea, ↑Δ sputum, and/or ↑cough; ask re: URI sx, CHF sx, VTE risk fx, tob., prior exacerbations/steroids/intubations/abx
- Work-up:** CXR, CBC/diff, BMP, ABG/VBG (for pH/pCO₂) ± EKG, trop, NT-proBNP. Consider flu, COVID-19, PE eval (PE in 25% w/ severe exacerbations w/o clear trigger: [Annals 2006;144:390](#))

Management:

- SpO₂ 88-92%:** hyperoxia → ↓ vent. via Haldane effect & hypoxic vasoconst., ↑V/Q mismatch; ↑ mortality ([BMJ 2010;341:c5462](#))
- Bronchodilators:** albuterol, ipratropium, DuoNebs (combo)
 - “Stacked” DuoNebs (x3 in 1h) initially → space to standing DuoNebs q4 w/ albuterol PRN q2 → space further as able
- Steroids:** pred 40mg x5d. PO ~ IV ([Chest 2007;132:1741](#)) & 5d ~ 14d ([REDUCE JAMA 2013;309:2223; Cochrane Rev 2018](#)); some may need higher dose/longer course if severe
 - If severe: IV methylpred 60-125mg q6-q12 x72h
- NIPPV:** if resp acidosis, severe dyspnea, ↑WOB. ↓ mortality, intub., LOS ([Cochrane Rev 2004](#)). (NB: **need for emergent intubation is a contraindication to NIPPV** & NIPPV should not delay intubation)
- Antibiotics:** controversial; ↓ mortality but challenging to identify who will benefit ([Chest 2008;133:756; Cochrane Rev 2012](#))
 - Indicated if: ↑all 3 cardinal sx, 2/3 w/ ↑sputum purulence, or require NIPPV/mechanical ventilation
 - CRP may be useful output ([NEJM 2019;381:111](#))
 - PCT may be useful but ↑ mortality when utilized in ICU setting ([Eur Resp Rev 2017;26; ICM 2018;44:428](#))
 - Abx choice: based on PsA risk, prior SCx, resistance
 - ⊖ PsA RFs: FQ, CTX; amox/clav, azithro, doxy
 - ⊕ PsA RFs: FQ, cefepime, pip/tazo
 - Duration: 5-7d inpt; 3-5 outpt (varies by drug)
 - Concurrent CAP: treat by CAP guidelines
- Antivirals:** oseltamivir if influenza⊕, even if ≥48-72h

INHALED THERAPIES FOR ASTHMA & COPD

Class	Example Meds
Short-acting β-agonist (SABA)	Albuterol, levalbuterol (<u>SE</u> : ↑HR; levalbuterol more selective so less HR effect but \$\$)
Short-acting muscarinic antagonist (SAMA)	Ipratropium (Atrovent) (<u>SE</u> : urinary retention, dry mouth)
Long-acting β-agonist (LABA)	Salmeterol, formoterol (NB: in asthma, do not use without ICS)
Long-acting muscarinic antagonist (LAMA)	Tiotropium (Spiriva), umeclidinium (Incruse Ellipta)
Inhaled corticosteroid (ICS) + LABA	Fluticasone-salmeterol (Advair), budesonide-formoterol (Symbicort), mometasone-formoterol (Dulera), fluticasone-vilanterol (Breo Ellipta)
LAMA + LABA	Umeclidinium-vilanterol (Anoro Ellipta)
LAMA + LABA + ICS	Fluticasone-umeclidinium-vilanterol (Trelegy Ellipta)

Pulmonary & Critical Care

Bronchiectasis & Hemoptysis

BRONCHIECTASIS

DEFINITION: permanent airway dilatation from recurrent infection/inflammation ([AJRCCM 2013;188:647](#); [NEJM 2002;346:1383](#))

Symptoms	Chronic productive cough, recurrent bronchitis/pneumonia, wheezing, dyspnea, hemoptysis, recurrent pleurisy			
Etiology	Recurrent insult: infection (PNA, MAC, TB, PsA, childhood infections, ABPA), inhalation, GERD/aspiration Impaired immunity: ↓ mucus clearance (CF, 1° ciliary dyskinesia [PCD]), immunodeficiency (e.g. HIV, CVID, ↓ IgG) Obstruction: foreign body, tumor, COPD, tracheomalacia/tracheobronchomegaly, CTD (Marfan's), radiation Systemic disease: RA, Sjogren's, SLE, IBD, A1AT Idiopathic = ~50%			
Workup	Initial: MDCT or DLDCT, PFTs, CBC/diff, Ig levels, sputum Cx (bacterial, mycobacterial, fungal) - CT: bronchial diameter > adj artery; thickened bronchi w/ lack of tapering (Thorax 2019:74)			
Natural Hx	Exacerbations (avg 1.5/y), progressive ↓ in FEV ₁ , PsA colonization → worsening disease			
Chronic Management				
CF: AJRCCM 2013;187:680 , AJRCCM 2009;180:802 ; non-CF: AJRCCM 2013;188:647 , ERS: Eur Resp J 2017:50 , BTS: Thorax 2019:74				
<i>Principles originally arose in CF population then applied to non-CF</i> <ul style="list-style-type: none"> Airway clearance: nebs (albuterol, 3% NaCl) + chest PT (acapella, vest) <ul style="list-style-type: none"> CF: add DNase to neb bundle; not effective in non-CF Antimicrobials/anti-inflammatories: <ul style="list-style-type: none"> Non-CF: <ul style="list-style-type: none"> Azithro has some benefits w/ ↓ exacerb. but c/f ↑ abx resistance (Lancet 2012;380:9842; JAMA 2013;309:1251; Coch Rev 2018; Lancet RM 2019;7:845). Ensure no NTM first Trial inhaled abx if PsA colonization & ≥3 exacerb./y Consider eradication of new PsA isolate CF: azithro + inhaled tobramycin (for PsA; alt: aztreonam, colistin) Disease specific treatment: <ul style="list-style-type: none"> Non-CF: treat underlying cause if found; consider PPI/H2 blocker CF: <i>CFTR mut</i> → defective Cl⁻/HCO₃⁻ transport on airway surface <ul style="list-style-type: none"> Potentiators open CFTR channel (ivacaftor); correctors bring CFTR to surface (lumacaftor, tezacaftor, elexacaftor) Dual/triple tx → long-term FEV1 benefits (NEJM 2015;373:220; NEJM 2017;377:203; NEJM 2018;379:1599; NEJM 2019;381:1809) Pancreatic enzyme supplementation, vitamins ADEK 				
Acute Exacerbation				
<ul style="list-style-type: none"> Sx: ↑ cough/sputum/dyspnea; usually ⊖ fever Obtain resp cx prior to abx, CXR Micro: PsA + <i>S. aureus</i> > <i>H. flu</i>, <i>Moraxella</i>, <i>Burkholderia</i>; treat <i>Stenotrophomonas</i> and <i>Achromobacter</i> as pathogenic; <i>Aspergillus</i> in CF not treated Abx: use previous Cx data; tx 14d <ul style="list-style-type: none"> No prior Cx data: empiric FLQ (for PsA) If prior R-PsA: IV abx; 2 agents – β-lactam & either FLQ or IV tobra (dosed QD) <ul style="list-style-type: none"> No great evidence for double coverage of PsA though is standard of care in CF If β-lactamase⁺ <i>H. flu</i> or <i>Moraxella</i>: amox/clav, doxy, macrolide, or FQ Home abx: continue azithro ± inh tobra (practice varies) Steroids not used unless concomitant asthma, COPD, or ABPA Continue chronic treatment (airway clearance) 				

HEMOPTYSIS (expectoration of blood from lower respiratory tract)

Etiology	<ul style="list-style-type: none"> Airway: bronchitis, bronchiectasis (incl. CF), CA (usually primary lung CA), trauma (incl. foreign body) Pulmonary parenchyma: infection (PNA, abscess, TB, aspergilloma), vasculitis (ANCA, anti-GBM, immune-complex, drug-induced; see Vasculitis and Autoantibodies), coagulopathy, endometriosis, inhalation injury, sarcoid, pulmonary hemosiderosis Pulmonary vascular: PE, CHF (esp if on AC), mitral valve dz, bronchovascular fistula, aneurysm, AVM
Work-up	<ol style="list-style-type: none"> Consider other sources (GI or nasopharyngeal) CXR (most important), CBC, coags, U/A (vasculitis, anti-GBM), sputum Cx, CTA chest (if stable), bronch Consider NT-proBNP, D-dimer, ESR/CRP, C3/C4, ANA, ANCA, anti-GBM, APLAS, IGRA/AFB
Non-massive: if minimal (<30mL) & likely benign (ex: infxn/bronchiectasis): observe. If active, recurrent, >1w: CT → bronch	
MASSIVE HEMOPTYSIS (>500mL/d or >100mL/h) = life-threatening emergency with mortality 50-80%. <u>Asphyxiation</u> , NOT exsanguination, is mechanism of death (maximum pulmonary blood volume ~500mL, CCM 2000;28:1684)	
<ul style="list-style-type: none"> LIE PATIENT WITH SIDE OF SUSPECTED BLEED DOWN (preserve gas exchange in unaffected lung) Control airway: if very dyspneic, poor gas exchange, or rapid bleed, STAT RICU consult (x6-3333), largest ETT possible (8mm+). Note: ensure suction (± IP) available upon intubation as blood can rapidly fill ETT Ensure hemodynamic stability, correct coagulopathy. Inhaled TXA may be beneficial (Chest 2018;154:1379) Call IP → bronch to localize; temporize w/ balloon tamponade, bronchial blockade, electrocautery, topical vasoconstriction Call IR → if stable, can CTA to localize; otherwise bronchial angiography to embolize site. <i>If refractory</i>, call thoracic surgery Can consider pulse dose methylprednisolone if vasculitis suspected 	

DIFFUSE ALVEOLAR HEMORRHAGE (DAH, disruption of alveolar-capillary basement membrane, alveolar bleeding)

Presentation: hemoptysis (can be absent in 1/3), cough, fever, dyspnea, diffuse radiographic opacities, abnl gas exchange

Etiology: capillaritis (Rheum, drugs), bland hemorrhage (AC, low Plt), diffuse alveolar damage (ARDS, infxn, PE, drugs)

Workup: CXR, CT (diffuse ground glass, central > peripheral), BAL (progressively more blood), labs guided by clinical picture

OVERVIEW

Diverse group of disorders that cause scarring/fibrosis in the lungs, often leading to structural changes in the parenchyma (alveoli, interstitium, alveolar-capillary interface) & loss of lung volume/compliance

Presentation: progressive dyspnea, non-prod. cough, hypoxemia (esp. w/ exercise); some w/ systemic sx (AIP, HSP, COP)

History: tempo, hx CTD/IBD/malig., rheum ROS, meds, exposures (chemicals, dust, humidity, pets, barns), smoking, FH

Exam: “velcro-like” crackles, clubbing, e/o CTD (heliotrope rash, Gottron’s papules, mechanic’s hands, joint disease, muscle weakness, skin fibrosis, sicca), extrapulmonary manifestations of other systemic diseases

Etiologies: known & idiopathic causes broken down by subcategories (ATS/ERS: [AJRCCM 2013;188:733](#))

Idiopathic Interstitial PNAs (IIPs)			Known Causes					
Chronic	Acute/subacute	Smoking-rel.	Systemic Diseases	Connective Tissue Disease	Exposures			
					Inhalation			
Idiopathic pulmonary fibrosis (IPF; UIP pattern), idiopathic non-specific interstitial PNA (NSIP)	Acute interstitial pneumonia (AIP; DAD pattern*), cryptogenic organizing pneumonia (COP)	Resp. bronchiolitis-ILD (RB-ILD), desquamative interstitial PNA (DIP)	Sarcoid, amyloid, ANCA-vasculitis, IBD, CA	Scleroderma, poly/dermato-myositis, RA, SLE, Sjogren's, MCTD	Organic Grains, molds, AC/humidifier, birds, etc.	Inorganic Silica, asbestos, coal, metals, etc.		
				Hypersensitivity pneumonitis	Pneumoconiosis			
Others: Lymphangioleiomyomatosis (LAM): seen in young women with reticular opacities on CXR & thin-walled cysts on CT chest								
Pulmonary Langerhans Cell Histiocytosis (PLCH): young adults w/ upper-zone-predominant cysts (can be bizarrely shaped) & nodules								
Eosinophilic PNA: acute form (AEP) w/ <1mo of sx, BAL with >25% eos; chronic (CEP) with >1 mo. of sx, peripheral eos (>6%), & BL peripheral consolidations (classically described as the “photo negative” of pulmonary edema); Tx w/ steroids								
Idiopathic PNA w/ Autoimmune Features (IPAF): IIP (NSIP, UIP) w/ features of autoimm. dz not meeting criteria for CTD dx								
*Diffuse alveolar damage (DAD) pattern: diffuse, typically bilateral, central>peripheral ground glass or consolidative opacities								

DIAGNOSTIC EVALUATION

- Approach: remove potential environmental causes.** If improves → no further w/u. If not → **assess for systemic dz.** If unlikely systemic dz, HRCT (now called **Diffuse Lung Dz CT**) → consider **bronch** and/or **biopsy** based on findings
- Labs:** CBC/diff, CMP, U/A, ESR/CRP, CPK/aldolase, C3/C4, autoantibodies (ANA, RF/CCP, RNP, Ro/La, Scl-70, ANCA, hypersensitivity panel, myositis panel 3, Jo1 and MDA-5 [part of myositis panel but come back faster])
- Radiology: DLD CT;** upper (HSP, smoking-rel., inh. dusts) vs lower predom. (IPF, NSIP), LAD (CA, sarcoid)
 - UIP (top): usual interstitial pneumonia** = radiographic corollary of IPF. **Basilar-predom., traction bronchiectasis, honeycombing**
 - NSIP (bottom): nonspecific interstitial pneumonia** = pattern a/w many non-IPF pathologies. **Ground glass, mosaic attenuation** due to air trapping, ↑ reticular markings, **subpleural sparing**
- PFTs:** restrictive (↓TLC, ↓FRC, ↓RV; FEV1/FVC normal to ↑); ↓DLCO can be early sign
- BAL:** if acute or hemoptysis (eval AEP, alveolar hemorrhage, CA, infxn); if chronic, consider (eval HSP, sarcoidosis, infxn, PLCH). Not useful for IPF
- Lung biopsy:** if diagnosis unclear & will change management, rec against for definite UIP ([AJRCCM 2018;198:e44](#))



TREATMENT

- IPF:** ([AJRCCM 2015;192:e3](#))
 - Acute exacerbations:** Ddx includes infxn, PE, HF; **pred** ~1mg/kg/d & broad-spectrum **abx** (x7d) generally given (can re-pulse & slowly taper if tx failure during taper)
 - Chronic therapy:** consider **pirfenidone** (antifibrotic; SE: nausea, fatigue; [NEJM 2014;370:2083](#)) or **nintedanib** (TKi; SE: diarrhea; [NEJM 2014;370:2071](#)). Both ↓FVC decline, do not Δ overall survival. Consider **lung transplant**. AZA, pred, NAC tx ↑mortality ([NEJM 2012;366:1968](#)). GERD tx & aspiration prec. may be beneficial ([Lancet RM 2013;1:369](#))
- NSIP:** remove inciting exposures, tx underlying condition; can be **steroid-responsive** (pred 0.5-1mg/kg/d or pulse methylpred if requiring hospitalization); **2nd agent** (AZA, MMF, ritux, CYC) pending response. **Nintedanib** may benefit non-IPF progressive fibrotic disease irrespective of underlying ILD diagnosis ([NEJM 2019;381:1718](#); [Lancet RM 2020;8:453](#))
- COP:** monitor; if sx persist/progress → **pred** ~0.75-1mg/kg/d (pulse if fulminant)
- AIP:** idiopathic ARDS; usually not steroid-responsive, but often trial steroids & abx as **in-hospital mortality is >50%**

Pulmonary & Critical Care

VTE Diagnostics

CLINICAL MANIFESTATIONS

Signs/Symptoms

DVT

- S/Sx: pain, warmth, erythema or cyanosis, edema (esp. asymm.), palpable cord, venous distention, Homan's sign (sudden dorsiflexion of ankle w/ knee flexed to 30° → pain in upper calf); **none Sn/Sp** ([JAMA 1998;279:1094](#)) & can be asx
- Types:** **proximal** = iliac, femoral, popliteal veins; **distal** = calf veins below knee (ant./post. tibial, peroneal, soleal, gastrocnemius)
 - Massive iliofemoral DVT: *phlegmasia alba dolens* (edema, pain) → *phlegmasia cerulea dolens* (cyanosis, venous gangrene)
 - May Thurner syndrome: anatomic variant → compression of L common iliac vein by R iliac artery → LLE DVT
- Ddx:** superficial thrombophlebitis, cellulitis, arthritis, arterial occlusion, varicose veins, lymphedema, ruptured Baker cyst, chronic venous insufficiency ([Arch IM 1998;158:2315](#))

PE ([EHJ 2020;41:543](#))

- Sx:** **dyspnea** (73-79%), **pleuritic CP** (47-66%), **cough** (37-43%), orthopnea (36%), leg swelling/pain (26-42%), syncope (10%; [NEJM 2016;375:1524](#); [JACC 2019;76:744](#)), hemoptysis (13%), diaphoresis (4-11%), palpitations (10%), angina (4%); many asx
- Signs:** **tachypnea** (57-70%), **tachycardia** (26-30%), rales (21-51%), S4 (24%), 1P2 (15-24%), ↓ breath sounds (21%), JVD (13%), fever (2-7%), wheezing (3-5%), RV heave (4-5%), pleural friction rub (1-3%), S3 (3%)
- EKG Δs:** sinus tach., atrial arrhythmias (AF, AFL), RBBB, inf. Q, anterior STΔs/TWIs, S1Q3T3 (McGinn-White sign) ([ERJ 2005;25:843](#))

Risk Factors: Virchow's triad of venous stasis, vascular injury, hypercoagulability ([Circulation 2003;107:I9](#); [JAMA 2003;290:2849](#))

Strong (OR >10)	Moderate (OR 2-9)	Weak (OR <2)
<ul style="list-style-type: none"> - Fracture (hip/leg) - Hip or knee replacement - Major gen. surgery - Major trauma - Spinal cord injury 	<ul style="list-style-type: none"> - Arthroscopic knee surgery - CVC (PICC: Lancet 2013;382:311) - Hormone replacement tx/OCPs - Pregnancy (postpartum) - Hospitalized/SNF (w/o surgery) - Previous VTE, thrombophilia 	<ul style="list-style-type: none"> - CHF (JACC 2020;75:148) - Resp. failure - Asthma (ERJ 2014;43:801) - Malignancy/chemotherapy - Paralytic stroke - IBD, nephrotic syndrome - Sepsis (Chest 2015;148:1224)

DIAGNOSIS/RISK STRATIFICATION (ASH: [Blood Adv 2018;2:3226](#); AHA: [Circ 2011;123:1788](#); ESC: [EHJ 2019;41:543](#); [JAMA 2018;320:1583](#))

- Pre-test prob:** [Wells' for LE DVT](#), [Constans'](#) for UE ([Thromb Haemost 2008;99:202](#)), [Wells' for PE](#) ([Annals 2001;135:98](#))
 - If **low** (or mod. DVT), can r/o w/ D-dimer (see below) or [PERC score for PE](#); if D-dimer \oplus need further eval. If **high** (or mod. PE) → imaging
- DVT diagnosis:** venous Doppler US ("LENIs" = Lower Extremity Non-Invasives; "UENI" = Upper Extremity Non-Invasives)
- PE diagnosis:**
 - PE-CT:** study of choice; may also detect alternate dx ([NEJM 2006;354:2317](#))
 - V/Q scan:** validated ([JAMA 1990;263:2753](#)). Performed if CI to CT I+. **Need nl CXR** (minimize other causes of V/Q mismatch)
 - LENIs:** if suspect PE, unable to CT or V/Q, & \oplus , can treat; if \ominus , however, does not exclude PE (clot may have migrated or be from another source)
 - Echo:** most useful for risk stratification (not dx), though demonstration of clot or new RV strain can provide presumptive diagnosis if needed rapidly
 - ABG:** hypoxemia (\uparrow A-a gradient, normal in ~20%), respiratory alkalosis
- PE risk stratification:**
 - PESI** (PE Severity Index): **prediction of morbidity/mortality in patients w/ newly diagnosed PE** using 11 clinical criteria, including PMH (cancer, HF, lung dz) & abnormal vital signs (e.g. HR>110, RR>30, SpO₂<90%)

INTERPRETING D-DIMER (nl <500)

- DVT/PE:** if nl + low pretest prob, excludes DVT/PE ([NEJM 2003;349:1227](#); [JAMA 2006;295:199](#); [Thromb Haemost 2009; 101:886](#))
- Adjusted D-dimer:** → ↓ imaging w/o ↑ in PE
 - Age-adjusted:** if >50, use age × 10 as cut off ([JAMA 2014;311:1117](#))
 - Prob.-adjusted:** use of <1000 cutoff w/ low prob. ([NEJM 2019;381:2125](#))
- Ddx for ↑D-dimer:** arterial thrombus (MI, stroke, AF/intracardiac, acute limb ischemia), DIC, CA, inflammation/infection, ESLD, CHF, renal disease, ↑age, aortic dissection, trauma, surgery

High Risk (Massive)	Intermediate Risk (Submassive)	Low Risk (Nonmassive)
<p>Hemodynamically unstable</p> <ul style="list-style-type: none"> SBP <90 or requiring vasopressors & not due to hypovolemia, arrhythmia, etc Cardiac arrest 	<p>Right heart strain w/o hypotension</p> <ul style="list-style-type: none"> Biomarkers: <ul style="list-style-type: none"> ↑NT-proBNP >500; >600 cut-off ↑Sp (ERJ 2014;43:1669) ↑hs-TnT; age-adjusted cut-off of ≥14 in age <75 & ≥45 in age >75 may ↑NPV (ERJ 2015;45:1323) Echo: RV overload/dysfunction – enlarged RV, flattened IVS, mod/severe TR, McConnell's sign (RV free wall akinesis sparing apex), ↓TAPSE (marker of RV fxn, nl = 15-25mm; JEM 2020;58:449) CT: RV/LV diameter ratio >0.9 (EHJ 2011;32:1657) PESI: class III-V; short PESI (sPESI) ≥1 <p>ESC further classifies into:</p> <ul style="list-style-type: none"> -intermediate-high risk (both ↑TnT & RV dysfunction on TTE or CT) -intermediate-low risk (\oplus biomarkers or imaging or neither w/ PESI III-V) 	<p>No right heart strain or hypotension</p> <ul style="list-style-type: none"> Normal biomarkers Low risk per PESI & sPESI

Pulmonary & Critical Care

VTE Management

MANAGEMENT OF VTE (CHEST: [Chest 2016;149:315](#); ESC: [EHJ 2020;41:543](#))

Proximal DVT (popliteal, femoral, iliac vv.)	Distal DVT (calf, ant./post. tibial, peroneal vv.)
<p>Anticoagulate (unless contraindications), regardless of sx</p> <p>Agent: DOAC > VKA > LMWH; if malig.: DOAC or LMWH > VKA (for dosing & info on choosing agent, see AC and AC Mgmt sections)</p> <p>Duration: at least 3mo for all. Extend >3mo if:</p> <ul style="list-style-type: none"> • 1st or 2nd unprovoked prox. DVT & low/mod. bleeding risk. If high bleeding risk (see below), stop at 3mo. Unprovoked have ↑ recurrence rate (10% <1y off AC, 5% each subsequent yr) • If stop AC after 1st VTE, D-dimer at 1mo may help decide whether to resume, esp. in ♀ (NEJM 2006;355:1780; Blood 2014;124:196; Annals 2015;162:27) • If stop AC, ASA 100mg if no Cl (NEJM 2012;367:1979 & 366:1959; Circ 2014;130:1062) <p>If contraindications to AC (active bleeding, recent/planned high bleeding-risk procedure, major trauma, acute ICH) → IVC filter</p> <ul style="list-style-type: none"> • Remove once no longer needed. Complications incl IVC thrombosis, acute/recurrent DVT or PE, filter migration/erosion/fracture 	<p>Serial imaging vs. anticoagulation</p> <p>Serial imaging: if asx, low risk for extension, or high risk for bleeding</p> <ul style="list-style-type: none"> • Repeat US at 1-2w (1/3 will extend; ↓ risk in muscular veins: soleal, gastrocnemius) <p>Anticoagulate if:</p> <ul style="list-style-type: none"> • Severe symptoms • RFs for extension: ⊕ D-dimer, extensive (>5cm, mult. veins, >7mm in diam.), close to prox. veins, no reversible provoking factor, active CA, h/o VTE, inpt • On serial imaging, extends into proximal veins. AC also suggested if extends but remains in distal vein
<p>UE DVT (NEJM 2011;364:861): brachial, axillary, subclav. vv.; ↓ complications vs. LE DVT. Tx same as LE DVT. If PICC/CVC, <u>no need for catheter removal if needed/functional/</u> ⊖ infected. AC continued while catheter in place (esp. if CA), though no data</p>	
<p>Bleeding risk: <u>low</u> = 0 RFs (1.6%/3mo; 0.8%/y after 3mo); <u>mod</u> = 1 (3.2%/3mo; 1.6%/y); <u>high</u> = ≥2 (12.8%/3mo; ≥6.5%/y)</p> <p>RFs: age >65-75, previous bleeding, CA, renal failure, liver failure, thrombocytopenia, prior CVA, DM, anemia, anti-platelet tx, poor AC control, ↓ functional capacity, recent surgery, frequent falls, AUD, NSAID use</p>	
<p>Testing in unprovoked VTE: age-appropriate cancer screening (found in 1/20 within 1y; Annals 2017;167:410) & symptom-directed studies. Hypercoagulability workup limited at time of acute VTE while on AC (see Coagulation Disorders for details)</p>	

High Risk PE	Intermediate Risk PE	Low Risk PE
PERT consult (x47378)		
<p>Resuscitation:</p> <ul style="list-style-type: none"> • Limit IVF: can try 500cc if CVP low, but ↑RV distention → ↓CO • Vasopressors: NE generally preferred • O2: HFNC pref. for severe hypoxemia. Mech vent. ↑↑↑risk: HoTN from induction & PPV → ↓ venous return → ↓ RV CO, ↑RV failure • Circulatory collapse/arrest: VA ECMO <p>Anticoagulation: UFH (w/ bolus)</p> <p>Thrombolysis: systemic unless contraindicated</p> <p>Embolectomy: if thrombolysis contraind/fails; can be catheter-directed; surgery if all options contraind/fail or if clot in transit in RA/RV, PFO</p>	<p>Anticoagulation: LMWH preferred > UFH (faster time to therapeutic range) unless impending hemodynamic collapse, thrombolysis (or CrCl <30 or severe obesity)</p> <p>Thrombolytic therapy (systemic or catheter-directed) in select pts: (Circ 2011;123:1788)</p> <ul style="list-style-type: none"> • No strict guidelines, indications include: <u>developing shock, resp failure, mod/severe RV dysfunction</u> on TTE (RV hypokinesis, RVSP >40) w/ ↑↑ hs-TnT/NT-proBNP (>900) • <i>May be observed x24h on AC first, pending trajectory</i> • Routine tPA in int. risk PE → ↓ hemodynamic decomp., no clear long-term Δ in mortality; ↑ major bleeding & hemorrhagic CVA (NEJM 2014;370:1402; JACC 2017;69:1536) 	<p>Anticoagulation: See above (DVT) and AC, AC Mgmt sections</p> <p>Discharge: if no other reasons for hospitalization, can d/c</p>
<p>Thrombolysis: → ↓ mortality (Am J Card 2019;123:684; JAMA 2014;311:2414)</p> <p>Systemic: alteplase 100mg/2h (bolus 50mg/2min if cardiac arrest). Hold AC during infusion (but do not delay if got LMWH). No convincing evidence to support <u>routine</u> use of lower dose tPA (Am J Card 2013;111:273)</p> <ul style="list-style-type: none"> • Absolute contraindications: intracranial neoplasm, CNS surgery/trauma <2-3mo, h/o ICH, active bleeding, non-ICH stroke <3mo <p>Catheter-directed: may be preferred if high-risk for bleeding, failed systemic thrombolysis, or otherwise selected pts; can couple w/ US-assisted thrombolysis (EKOS) to enhance mechanical breakdown of thrombus or suction thrombectomy. ↓ in RVSP, ↓RV/LV ratio, no data for mortality benefit (Circ 2014;129:479; JACC Card Interv 2015;8:1382; Am J Med 2019;132:240; Am J Card 2019;124:1470)</p>		
<p>Anticoagulation: if started on LMWH/UFH, transition to DOAC after pt has stabilized (unless another agent indicated)</p>		

PERT (x47378): call if large PE w/ abnormal VS (tachycardia, hypotension), evidence of RH strain (TTE, EKG, biomarkers), saddle PE. Order: CBC/diff, BMP, LFTs, lactate, D-dimer, ABG, PT/INR, PTT, T&S, NT-proBNP, hs-Tn, EKG, CT-PE, LENIs, TTE

Pulmonary & Critical Care

Pulmonary Hypertension

Pulmonary Hypertension = mean PA pressure (mPAP) ≥ 20 PVR = (mPAP - PCWP) / CO; rearranged: mPAP = (PVR x CO) + PCWP ∴ ↑ in PVR or PCWP can → pulmonary hypertension (PH) <ul style="list-style-type: none">▪ Pre-capillary PH: PVR ≥ 3, PCWP ≤ 15, ↑DPG & TPG▪ Post-capillary PH: PVR < 3, PCWP > 15, nl DPG & TPG▪ Mixed PH: PVR ≥ 3, PCWP > 15, ↑DPG & TPG Transpulmonary gradient (TPG) = mPAP – PCWP; nl <12 Diastolic pulmonary gradient (DPG) = PA diastolic (PAD) – PCWP; nl <7	CLINICAL MANIFESTATIONS S/Sx: nonspecific; 2y delay to dx in 20% (Chest 2011;140:19) <ul style="list-style-type: none">- <u>Early:</u> DOE, lethargy, fatigue (2/2 inadequate CO w/ activity)- <u>Late:</u> exertional CP, syncope, edema, anorexia, abdominal distention (2/2 progressive RV failure)- <u>Rare:</u> cough, hemoptysis, hoarseness (Ortner's syndrome) Exam: loud P2; ↑JVP, edema, ascites, TR murmur, R-sided gallop, parasternal heave (LSB), PA tap (L 2 nd ICS), edema, hepatomegaly, ascites Imaging: CXR w/ enlarged PA, RA, RV (↓retrosternal space on lat.), pruning of peripheral vessels; CT w/ PA/Ao diameter ≥ 1 EKG: normal vs signs of RV hypertrophy/strain: RAD, R/S >1 in V1, RBBB, P pulmonale in II (RAE) TTE: TR peak velocity ≥ 3.4 = high prob for PH, RVSP >35mmHg, PA diameter >25mm; RVOT acceleration time <105ms, RV dilation/hypokinesis, RV/LV>1, IVC>21mm
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DIAGNOSIS ([ERJ 2019;53:1801904](#))

- RHC: gold standard (may not be needed in all circumstances) \pm **iNO vasoreactivity testing** (+ response = ↓mPAP ≥ 10 mmHg to reach mPAP ≤ 40 mmHg w/ ↑ or = CO; guides treatment in idiopathic PH)
- Evaluation for etiology:
 - **TTE:** eval for left HF (& whether severity explains PH)
 - **PFTs, DLD-CT, polysomnography:** chronic lung disease, OSA
 - **CPET:** determine etiology of exercise intolerance (cardiac vs pulmonary vs other)
 - **V/Q scan:** eval for CTEPH
 - **Labs:** NT-proBNP, BMP, LFTs, eval for systemic disorders in groups 1 & 5 (if not already known) – HIV, connective tissue diseases (ANA, RF/CCP, ANCA, Scl-70, Ro/La), schistosomiasis (if clinically appropriate), urine & serum toxicology

WHO CLASSIFICATION (6th World Symposium on PH: [ERJ 2019;53:1801913; JACC 2013;62:D34](#))

Pre-Capillary	Post-Capillary
Group 1: pulmonary arterial hypertension (PAH)	Group 2: left heart disease
<ul style="list-style-type: none"> - Idiopathic ($\text{♀} > \text{♂}$) - Heritable (e.g. <i>BMPR2</i>) - Drug/toxin-induced: cocaine, anorexigens, dasatanib, amphetamines - Associated with: CTD (MCTD, SSc, SLE), HIV, portal HTN, congenital heart disease, schisto - PAH long-term responders to CCBs - PVOD and/or pulmonary capillary hemangiomatosis - Persistent PH of newborn 	<ul style="list-style-type: none"> Obstructive: COPD Restrictive: ILD Mixed obstructive/restrictive: Chronic hypoxia w/o lung disease: OSA, OHS Developmental lung dz: (ERJ 2019;53:1801914)
Group 5: Misc. - chronic hemolytic anemia (e.g. sickle cell), MPN, sarcoid, metabolic d/o, complex congenital heart dz	

WHO Functional Classes: similar to NYHA for CHF & guides intensity of therapy. Class I = asx w/ ordinary activity, class II = sx w/ ordinary activity, class III = sx w/ minimal activity, class IV = sx at rest

MANAGEMENT

Treat underlying etiology: CTD, CHF, hypoxemia, VTE, etc. Advanced therapies (see below): guided by WHO functional class (reserved for II-IV). **Most evidence in Group 1.** Surgery: pulmonary thromboendarterectomy (CTEPH), atrial septostomy (R → L shunt), lung txp in select pts. General: exercise/pulm rehab, O₂, diuresis (for RHF), contraception in ♀

Mechanism	Medication	Route	Indication	Side effects
Endothelin receptor antagonists	Bosentan, ambrisentan, macitentan	PO	Group 1: ↓sx, ↑6MWT (NEJM 2002;346:896, Circ 2008;117:3010) Macitentan: ↓ morbid/mortality (NEJM 2013;369:809)	Anemia, PNA, edema, hepatotoxicity Macitentan: also flu, HA, UTI, bronchitis
(NO)-cGMP enhancers	PDE5 inhibitors: sildenafil, tadalafil	PO	Group 1: ↓sx, ↑6MWT (NEJM 2005;353:2148, NEJM 2009;361:1864)	Erythema, flushing, indigestion, HA, insomnia, epistaxis, rhinitis, retinal hemorrhage
	sGC stimulator: riociguat	PO	Group 1 & Group 4: ↓sx, ↑6MWT (NEJM 2013;369:330)	↓BP, n/v/d/const., GERD, anemia, dizziness, HA, hemorrhage
Prostacyclin pathway agonists (PPA)	Analogues: epoprostenol, treprostинil, iloprost Receptor agonist: selexipag	IV or inh.; treprostинil also SC PO	Group 1: ↑6MWT, ↑QOL; reserved for sickest patients (NEJM 1996;334:296) Group 5: some etiologies Group 1: ↓ hospitalization; no Δ mortality (NEJM 2015;373:2522)	CP, ↓BP, ↑HR, flushing, abd pain, anorexia, n/v/d, jaw pain, MSK pain, dizziness, HA, hemorrhage Diarrhea, nausea, jaw pain, HA, anemia
	Nifedipine, diltiazem	PO	⊕ iNO vasoreactivity test. ⊖ RV failure	↓BP, LE edema

Initiating Therapy based on ERS/ESC risk stratification guidelines ([ERJ 2015;46:903; ERJ 2019;53:1801914](#)): refer to Pulm HTN clinic

- Low/intermediate risk: dual oral therapy (typically targeting ERA/NO pathways)
- High risk: IV prostacyclin + 1 or 2 oral agents

Goal of therapy is to attain ≥3 low risk criteria: CI > 2.2 , RAP < 8 , WHO/NYHA class I or II, 6MWT > 440 m. May add IV/SQ prostacyclin if low risk criteria are not met 3-6mo after initiation of oral agents ([ERJ 2017;50:1700889](#))

Pulmonary & Critical Care

Mechanical Ventilation

INDICATIONS FOR INTUBATION

- Failure of NIPPV:** no clinical improvement
- Poor ventilation:** $\text{PaCO}_2 > 60$ with severe acidemia (COPD/asthma, sedation, neuromuscular disease, resp. muscle fatigue, trauma)
- Poor oxygenation:** worsening P:F ratio (PNA, pulmonary edema, ARDS, PE)
- Airway protection/instability:** ↓ consciousness (GCS < 8), shock, facial/head trauma, n/v/UGIB, severe secretions, severe bronchospasm/anaphylaxis
- Persistent increased work of breathing:** severe bronchospasm, airway obstruction, inability to compensate for severe acidemia
- Hemodynamic instability:** unstable arrhythmia, severe shock

Call RICU for intubation: x6-3333

RICU will ask: AMPLE

A = allergies

M = medications (current)

P = past medical hx (incl. h/o LVEF and RV function, prior intubations or difficult airway)

L = last meal/K (succinylcholine can cause hyperK)

E = events (prompting intubation)

During intubation, have at bedside:

- (1) Good access
- (2) IVF
- (3) sedative agent (e.g. propofol)
- (4) pressors (neo >> levo)

HEMODYNAMIC CONSEQUENCES OF INTUBATION

PPV increases intrathoracic pressure → ↓ LV & RV preload, variable effects on RV afterload → ↓ LV & RV stroke volume → ↓ BP (sedation can also contribute)

GENERAL PRINCIPLES: ([NEJM 2001;344:1986](#); [Respir Care 2017;62:629](#))

Five main variables: (1) RR, (2) tidal volume (V_T), (3) FiO_2 , (4) positive end-expiratory pressure (PEEP), (5) mode of ventilation

- Ventilation determines PaCO_2 : ↓ PaCO_2 by increasing RR and/or V_T** (↑ minute ventilation where $MV = RR \times V_T$)
 - 1) RR: often adjust this first; avoid >RR 30-35 due to risk of inadequate expiratory time → air trapping/auto-PEEP
 - 2) V_T (often set at ≤6cc/kg IBW): when ↑, ensure $P_{plat} \leq 30$ & driving pressure ($\Delta P = P_{plat} - \text{PEEP}$) ≤ 15 to minimize lung injury
- Oxygenation: ↑ PaO_2 by ↑ FiO_2 and/or PEEP**
 - 3) FiO_2 : avoid $\text{FiO}_2 > 0.6$ for prolonged periods due to oxygen toxicity
 - 4) PEEP: ↑ alveolar recruitment, improves V/Q match; if ↑PEEP → ↑P:F & P_{plat} stable, recruitable lung; if ↑PEEP → no Δ/↓P:F or ↑ PaCO_2 , not recruitable & ↑ shunt or dead space (should ↓PEEP)

VENTILATOR MODES: ([Respir Care 2007;52:301](#))

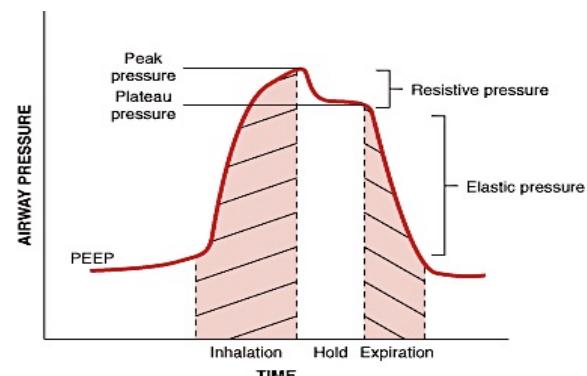
MODE	SET Indep. Var.	MEASURED Dep. Var.	PROS/CONS	HOW TO READ	WHEN TO USE
AC/VC <u>Assist Control/Volume Control</u> : delivers a breath until set tidal volume is reached	V_T PEEP RR FiO_2 I:E or flow	PIP & P_{plat} I:E or flow	☺: ↑ control (fixed V_T prevents barotrauma or atelectrauma) ☹: fixed insp. flow regardless of effort, ↑ dyssynchrony	"Pt is on Volume Control w/ V_T of 400 (4cc/kg), set at a rate of 16 breaths/min, PEEP of 8, and FiO_2 0.6; breathing at set rate of 16 (or over) with $V_T \sim 400$ for MV of 6.4L"	-Acute resp failure -ARDS -Airflow limitation (e.g. COPD, asthma) -@MGH, used more often than AC/PC
AC/PC <u>Assist Control/Pressure Control</u> : delivers a breath until set pressure is reached	P_{insp} PEEP RR FiO_2 I:E	Flow V_T	☺: variable flow (& V_T) during inspiration to satisfy pt demand, ↓ dyssynchrony ☹: can cause volutrauma as compliance or pt effort changes	"Pt is on Pressure Control of 18 (P_{insp}) over 5 (PEEP), set at a rate of 16 breaths/min, and FiO_2 0.3; breathing $V_T \sim 400$, at set rate of 16 (or over) for a MV of 6.4L."	-Air leak (e.g. PTX) -May trial in situations of vent dyssynchrony
PSV <u>Pressure Support Ventilation</u> : delivers a set pressure triggered by patient's spontaneous breaths	P_{insp} PEEP FiO_2 RR (backup)	I:E Flow V_T RR	☺: better tolerated, less sedation, trial pre-extubation (e.g. SBT on 0/0 or 5/5) ☹: ↓ control over parameters, volutrauma possible, no fixed RR (only backup)	"Pt is on Pressure Support of 10 (P_{insp}) over 5 (PEEP) with an FiO_2 0.3; breathing V_T of ~500 at 20 breaths/min. for a MV of 10L."	-Intubated for non-cardiac or lung failure (e.g. AMS) -Weaning vent -Severe met acidosis

MONITORING MECHANICS

Parameter	Target	Evidence
Tidal Volume (V_T)	ARDS: 4-8 cc/kg PBW Non-ARDS: 6-8 cc/kg PBW	ARDS: V_T 6cc/kg had ↓ mortality and vent-free days vs 12cc/kg (NEJM 2000;342:1301) Non-ARDS: V_T 10cc/kg vs 4cc/kg → no Δmortality or vent-free days (JAMA 2018;320:1872)
Plateau pressure (P_{plat}) Driving pressure ($\Delta P = P_{plat}-\text{PEEP}$)	<30 <15	ARDS: ↓ driving pressure a/w ↑ survival (NEJM 2015;372:747) Non-ARDS: driving pressure not a/w 30d mortality (Crit Care 2019;23:424)
Compliance ($V_T/\Delta P$) Airway Resistance ($\text{PIP}-P_{plat}$)	>50 <10	Maximizing O ₂ transport and minimizing dead-space occurred at the greatest total static compliance (NEJM 1975;292:284)

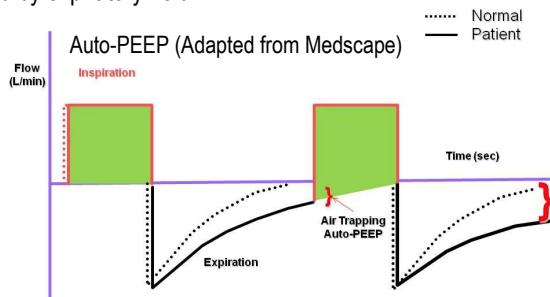
VENTILATOR MANEUVERS FOR MONITORING MECHANICS

- Inspiratory hold:** end inspiratory pause; measure P_{plat} → calculate ΔP , airway resistance, compliance
- Expiratory hold:** end expiratory pause; quantifies auto-PEEP

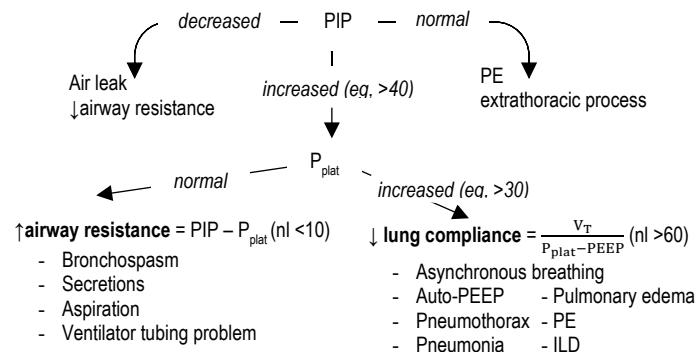


VENTILATOR COMPLICATIONS

- Dynamic hyperinflation (auto-PEEP):** 2/2 incomplete alveolar emptying; quantified by expiratory hold
 - Diagnosis:** end-expiratory flow >0 (residual pressure)
 - RFs:** vent strategy causing hyperinflation (high RR, $\uparrow I:E$ ratio) or obstructive disease (asthma, COPD, CF)
 - Consequences:** adverse hemodynamic effects (HoTN 2/2 \downarrow venous return), alveolar over-distension (\rightarrow volu-/barotrauma); \uparrow effort to trigger breath
 - Tx:** longer exhalation ($\downarrow I:E$ ratio, \downarrow RR), set exogenous PEEP to 2/3 auto-PEEP, bronchodilators for obstruction
 - If severe hemodynamic or resp. compromise, transiently disconnect pt from ventilator** and manually bag ventilate to allow deflation
- Ventilator-induced lung injury (VILI):** alveolar injury \rightarrow \uparrow alveolar permeability, interstitial & alveolar edema, alveolar hemorrhage, hyaline membranes, & alveolar collapse (similar to ARDS) ([NEJM 2013;369:2126](#)). Avoid w/ lung protective ventilation (see [ARDS](#))
 - Volutrauma:** over-distension of alveoli due to high V_T ; or, if there is heterogenous consolidation or atelectasis, a disproportionate volume from each breath is delivered to open alveoli
 - Atelectrauma:** shear forces from cyclic alveolar recruitment and de-recruitment injure adj alveoli/airways
 - Biotrauma:** cytokine release from lung epithelium \rightarrow multi-organ dysfunction
 - Oxytrauma:** $\uparrow \text{FiO}_2 \rightarrow$ free radical production, lung injury
 - Barotrauma:** injury from high P_{plat} (highest risk >35) \rightarrow PTX, subcutaneous emphysema, pneumomediastinum
- \uparrow Peak inspiratory pressure (PIP) = airway resistance + P_{plat} (normal < 35); can be elevated due to \uparrow airway resistance or \downarrow airway compliance (aka \uparrow elastic pressure), tx: steroids, nebs, bronch to clear secretions/mucus plugs**
- Other complications:** VAP, laryngeal edema, tracheal stenosis



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



ALGORITHM FOR RESPIRATORY PLAN (REMIX)

R	Reason for intubation	ARDS, PNA, COPD, pulmonary edema, aspiration, hypoventilation, altered mental status, etc
E	Exchange (gas exchange)	Recent ABG; how to improve PaO_2 (i.e. diuresis, pulmonary vasodilators) and/or PCO_2 (i.e. $\uparrow \text{RR}$)
M	Mechanics	P_{plat} , PIP, resistance pressure, elastic pressures; chest wall/respiratory muscle strength
I	ID/infection	Sputum cx data, abx day #, source control, need for bronchoscopy; assess for VAP
X	eXtubation barriers	Daily SAT/SBT, secretion clearance, mental status, planned procedures
(S)	Sedation	Current sedation, whether Δ needed (e.g. start dexmedetomidine/quetiapine as bridge peri-extubation)

LIBERATION & EXTUBATION: (ATS/CHEST: [AJRCCM 2017;195:115](#) & [Chest 2001;120:375S](#); NEJM 2012;367:2233; ERJ 2007;29:1033)

- Requirements for extubation:** (1) adequately treated underlying disease, (2) adequate oxygenation and ventilation: $\text{PaO}_2/\text{FiO}_2 \geq 150-200$, PEEP $\leq 5-8$, $\text{FiO}_2 \leq 0.4-0.5$, pH > 7.25 , (3) ability to cough, (4) able to manage secretions, (5) hemodynamic stability. Ideally sufficient mental status (alert, following commands), but as long as protecting airway, AMS does not preclude extubation
 - Rapid Shallow Breathing Index (RSBI) = RR/V_T ; RSBI >105 predicts extubation failure ($\text{Sn} > \text{Sp}$)** ([NEJM 1991;324:1445](#))
- Liberation protocol:**
 - Daily Spontaneous Awakening Trial (SAT) + Spontaneous Breathing Trial (SBT)**
 - SAT:** \downarrow ventilator time, ICU LOS, & mortality if paired with SBT ([NEJM 2000;342:1471](#); [Lancet 2008;371:126](#))
 - SBT:** ~30-120min daily trials w/ min support (PEEP ≤ 5 on PSV) = \downarrow vent time ([NEJM 1996;335:1864](#); [NEJM 1995;332:345](#))
 - Ways to fail:** hypoxemia ($\text{SaO}_2 < 90\%$, $\text{PaO}_2 < 60$), hypercapnia ($\text{PaCO}_2 \uparrow$ by > 10), low V_T , respiratory distress ($\uparrow \text{HR}$, $\uparrow \text{RR}$, HTN, accessory muscle use, diaphoresis), arrhythmia, hemodynamic instability, anxiety/agitation, somnolence
 - Causes of SBT failure:** underlying etiology not corrected, volume overload, cardiac dysfunction, neuromuscular weakness, delirium, anxiety, metabolic abnormalities
- Extubation strategies:**
 - Extubation to **NIPPV or HFNC** in patients with hypercapnia/RFs for reintubation, not done routinely $\rightarrow \downarrow$ post-extubation respiratory failure ([Lancet 2009;374:1082](#); [JAMA 2016;316:1565](#)). HFNC w/ intermittent NIV post-extubation $\rightarrow \downarrow$ reintubation compared to HFNC alone ([JAMA 2019;322:1465](#))
 - Check for **absence of cuff leak** before extubation (concerning for laryngeal edema) \rightarrow consider methylpred 20mg q4h 12h prior to extubation or methylpred 40mg x1 4h prior or IV dexamethasone 5mg q6h ([Eur J Anaesthesiol 2010;27:534](#))
 - If **agitation** is limiting ability to extubate, consider dexmedetomidine \rightarrow may improve odds of extubation ([JAMA 2009;301:489](#))
- Post-extubation respiratory failure:** due to poor secretion clearance, CHF, aspiration, bronchospasm, laryngeal edema
 - NB:** no benefit to NIPPV as rescue therapy during post-extubation respiratory failure and may be associated w/ worse outcomes ([NEJM 2004;350:2454](#)). Not recommended per ERS/ATS guidelines ([ERJ 2017;50](#))
- Tracheostomy:** usually performed once intubated for ~14d
 - Early tracheostomy (7d)** if expect intubation >14d $\rightarrow \uparrow$ comfort, allows \downarrow sedation, \downarrow risk of tracheal stenosis, \downarrow vent-free & ICU days, no ΔVAP rate ([JAMA 2010;303:1483](#); [Crit Care 2015;19:424](#); [Br J Anaesth 2015;114:396](#))

Pulmonary & Critical Care

ARDS

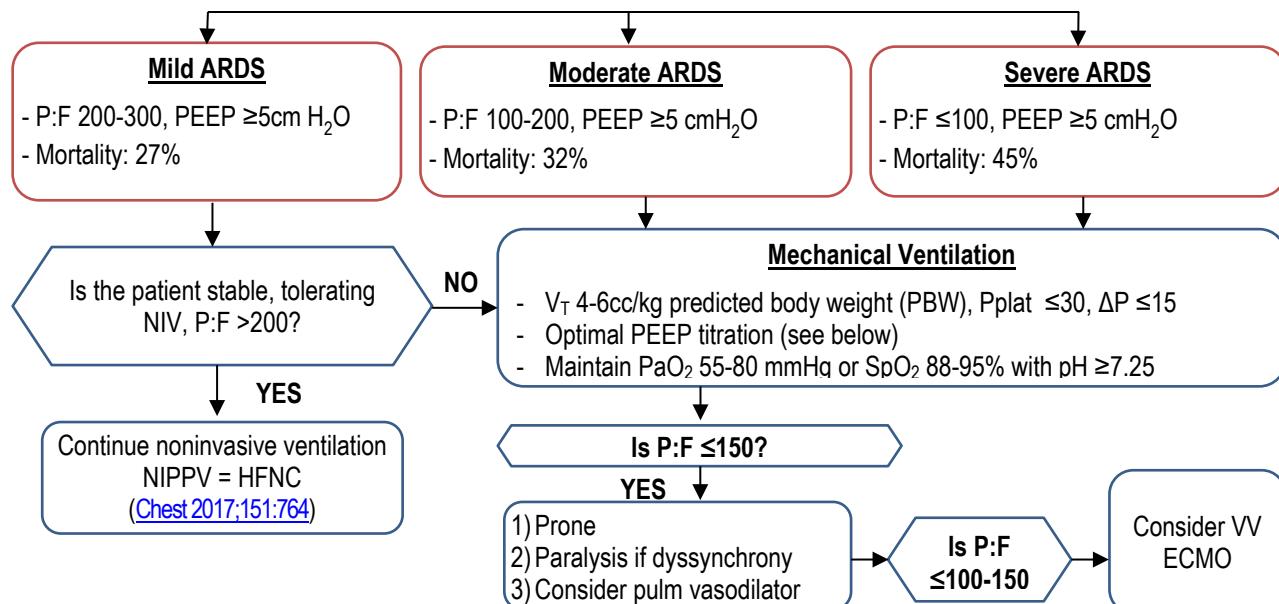
PATHOPHYSIOLOGY OF ARDS

Direct lung injury: pneumonia, aspiration, inhalational injury, near drowning, pulmonary contusion; indirect lung injury: sepsis, trauma, pancreatitis, drugs, burns, cardiopulmonary bypass/pump, transfusion-related acute lung injury (TRALI)

Pathway: diffuse, immune-mediated lung injury causing pulmonary capillary and alveolar epithelial damage leading to increased vascular permeability, impaired gas exchange, and decreased lung compliance ([NEJM 2017;377:562](#))

Berlin Definition for ARDS & Management Summary ([JAMA 2012;307:2526](#))

- 1) Onset within **1 week** of insult (usually 72h)
- 2) **Not primarily due to hydrostatic/cardogenic pulmonary edema**
- 3) Imaging showing **bilateral opacities** on CXR
- 4) **PaO₂:FiO₂ (P:F) ratio ≤300** with PEEP/CPAP ≥5cm H₂O



MANAGEMENT PRINCIPLES IN ARDS: (ATS/ESICM/SCCM: [AJRCCM 2017;195:1253](#))

	Strategy (in order of decreasing level of evidence)	Effects
Low Tidal Volume Ventilation (LTVP) (NEJM 2007;357:1113) (NEJM 2000;342:1301)	<ul style="list-style-type: none"> Maintain oxygenation while preventing ventilator-induced lung injury (VILI) V_T 4-6 cc/kg PBW w/ goal Pplat ≤30, driving pressure (Pplat-PEEP) ≤15 <ul style="list-style-type: none"> May allow ↑Pplat if ascites, obesity, etc. as may not accurately reflect transpulmonary pressure (see “esophageal balloon catheter” on next page) Permissive hypercapnia: pH goal ≥7.20-7.25 allows for lower V_T to minimize VILI <ul style="list-style-type: none"> Contraind: ↑ICP, RV fail./PH (↑pulm. vasoconst.), TCA/ASA o/d, pregnant 	↓mortality (31% vs 39.8%) and ↑vent-free days vs “traditional” V_T (12 cc/kg, Pplat <50)
Prone Positioning (PROSEVA NEJM 2013;368:2159)	<ul style="list-style-type: none"> ↓V/Q mismatch by ↓compressive atelectasis from heart & diaphragm → more homogenous vent. → ↑alveolar recruit. → ↓regional volutrauma & ↑compliance Contraind.: hemodynamic instability, ↑ICP, inability to turn neck (fixed/unstable C-spine), 2/3rd tri. pregnancy, recent sternotomy 	↓mortality (28d & 90d) in mod/severe ARDS
Conservative Fluid Management (NEJM 2006;354:2564)	<ul style="list-style-type: none"> Minimize pulmonary edema: “dry lungs are happy lungs” Avoid ± fluid balance after reversal of shock Dynamic assessment of volume responsiveness (i.e. pulse pressure variation, passive leg raise) (CCM 2017;45:1538) FACTT Trial: CVP<4 (conservative) vs. CVP ≤10-14 (liberal) 	↓ICU LOS & vent-free days, no Δ in 60d mortality or AKI
Positive End-Expiratory Pressure (PEEP) (NEJM 2004;351:327) (JAMA 2010;303: 865)	<ul style="list-style-type: none"> Maximize recruitment, minimize trauma from cyclic atelectasis Higher PEEP distributes V_T over more alveoli → less over-distention → improves oxygenation (via ↓V/Q mismatch and ↓shunt fraction) & compliance CV effects of PEEP: ↓preload/SV, RV afterload varies, ↓LV “afterload”, ↓BP Harms of PEEP: barotrauma, ↑dead space, hemodynamic effects 	No clear mortality benefit. Possible benefit for ↑PEEP if P:F ≤200
Neuromuscular Blockade (ROSE NEJM 2019;380:1997)	<ul style="list-style-type: none"> Maximize oxygenation by ↓vent dyssynchrony and chest wall compliance No survival benefit to routine early paralysis for mod-severe ARDS (P:F <150) Can use as bolus/infusion to maintain vent synchrony in mod-severe ARDS 	no Δ in 90d mortality. Risk: ↑ICU-acquired weakness

Pulmonary & Critical Care

ARDS

SUMMARY OF RESCUE THERAPIES FOR HYPOXEMIA (6 P's of refractory hypoxemia)

- **Pee:** consider diuresis to reduce pulmonary edema (see “conservative fluid management” above)
- **PEEP:** optimize PEEP (see “PEEP” below)
- **Prone positioning:** should be implemented early (12-24h) if P:F <150 (or 200) despite optimal PEEP titration
 - Maintain prone ≥16h. If supine and P:F remains >150 (or 200) and ΔP ≤15 after 2h, can remain supine
- **Pulmonary vasodilators:** start with iNO trial (40ppm; up to 80ppm); if effective, use inhaled epoprostenol (Veletri)
 - Should see at least 20% ↑PaO₂, otherwise do not continue therapy due to cost and risks, including hypotension
 - ↓V/Q mismatch by selectively dilating vessels that perfuse well-ventilated lung; also ↓PVR and ↓RV afterload
 - No mortality benefit and ↑risk of renal failure, but may improve oxygenation in first 24h and total lung capacity at 6mo ([Cochrane Rev 2016; Crit Care 2012;16:R36](#)). *NB:* risk of methemoglobinemia w/ iNO
- **Paralysis:** can be used to maintain vent synchrony (see “neuromuscular blockade” above). Start w/ intermittent boluses & transition to infusion if persistent dyssynchrony >3 boluses/2h (cisatracurium 0.1-0.2mg/kg q30min PRN → 0-5mcg/kg/min; rocuronium 0.6-1.2mg/kg q30-60min PRN → 0-20mcg/kg/min, start at 8-12mcg/kg/min)
- **Perfusion (ECMO):** for severe, refractory hypoxemia; see [ECMO](#) for more information

LUNG PROTECTIVE (ARDSNET) VENTILATION

- **Initial ventilator set-up:** $V_T = 6 \text{ cc/kg PBW}$, RR to approximate baseline MV (RR <35), moderate PEEP (8-10)

Adjustments: (also see [Mechanical Ventilation](#))

- **Oxygenation:** goal PaO₂ 55-80 mmHg or SaO₂ 88-94%
 - SpO₂ <94% a/w ↓mortality; hyperoxia ↑ → mortality ([JAMA 2016;316:1583; Crit Care 2014;18:711](#))
 - If persistent hypoxemia requiring FiO₂ >~0.6, optimize PEEP (see below)
- **Mechanics:** goal **plateau pressure (Pplat) ≤30 & driving pressure (ΔP) ≤15** (obtain with inspiratory hold)
 - If Pplat >30 and/or ΔP >15: ↓ V_T by 1 cc/kg PBW (minimum V_T 4 cc/kg PBW); limit on ability to ↓ is ↓MV → ↑pCO₂ & ↓pH
 - If Pplat <25 and V_T <6cc/kg PBW: can ↑ V_T by 1 cc/kg until Pplat >25 or V_T 6 cc/kg PBW
- **pH:** goal **7.20-7.25 to 7.45** (“permissive hypercapnia” unless contraindicated, lower boundary context dependent)
 - **pH below goal:** ↑RR (up to 35/min) until pH at goal or PaCO₂ <25; watch for auto-PEEP development at high RR
 - **If RR = 30-35/min & pH goals not met:** can ↑ V_T (may cause ↑Pplat >30)

Mechanical Ventilation Goals in ARDS

Measure	Goal
Oxygenation	PaO ₂ 55-80mmHg SaO ₂ 88-94%
Mechanics	Plateau pressure (Pplat) ≤30 Driving pressure (ΔP) ≤15
pH	7.20-7.25 to 7.45

OPTIMAL PEEP FOR ARDS

- **ARDSNet FiO₂/PEEP scale:**
 - If P:F <150 w/ PEEP 5cm H₂O, assess ability to recruit lung by increasing PEEP from 5 → 15cm H₂O
 - If improvement, use ARDSNet high PEEP/low FiO₂ scale; if no improvement, use low PEEP/high FiO₂ scale (see right)
- **Best PEEP trial:** select the PEEP corresponding to best global recruitment with lowest risk for overdistention based on **resp system compliance (CRs = $V_T / [Pplat - PEEP]$)**
 - Keep V_T constant and use **decremental titration of PEEP**; choose best PEEP based on balance of highest compliance, lowest driving pressure (<15), Pplat <30, acceptable oxygenation, and stable hemodynamics
- **Driving pressure:** $\Delta P = Pplat - PEEP$ (goal: ≤15)
 - Represents the relationship between tidal volume and lung compliance ($\Delta P = V_T/CRs$)
 - Lower ΔP associated with ↑survival independent of other variables (V_T , PEEP, Pplat) ([NEJM 2015;372:747](#))
- **Recruitment maneuvers** (if hemodynamically stable):
 - Used to open collapsed alveoli to ↓tidal opening and closing (**atelectrauma**) and ↑participation in gas exchange
 - Begin with **high PEEP** to open up alveoli, then decremental PEEP titration to optimize mechanics ([JAMA 2008;299:637](#))
 - Outcomes are mixed w/ ↑ ([JAMA 2017;318:1335](#)) and ↓mortality (low quality, [Cochrane Rev 2016](#)); **avoid ↑↑PIP's (>50)**
- **Esophageal balloon catheter:** estimates intrapleural pressure; used to calculate **transpulmonary pressure (P_{tp} = alveolar pressure [Pplat] - intrapleural pressure)**. PEEP then titrated to maintain optimal P_{tp} (<25 at end-inspiration to prevent VILI, 1-2 at end-expiration to prevent atelectrauma) ([NEJM 2008;359:2095](#))
 - No effect on mortality, ventilator free days, or ICU days, despite improved oxygen and lung compliance, but ↓risk of needing advanced rescue therapy ([JAMA 2019;321:846](#))
 - Consider in cases of high intra-abdominal pressure (e.g., obesity, ascites, abdominal compartment syndrome)

NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary

Lower PEEP/higher FiO ₂							
FiO ₂	0.3	0.4	0.4	0.5	0.5	0.6	0.7
PEEP	5	5	8	8	10	10	10
FiO ₂	0.7	0.8	0.9	0.9	0.9	1.0	
PEEP	14	14	14	16	18	18-24	

Higher PEEP/lower FiO ₂							
FiO ₂	0.3	0.3	0.3	0.3	0.3	0.4	0.4
PEEP	5	8	10	12	14	14	16
FiO ₂	0.5	0.5-0.8	0.8	0.9	1.0	1.0	
PEEP	18	20	22	22	22	22	24

STEROIDS FOR ARDS

- For indication & use in COVID-19, see [MGH guidance](#) (directory in Handbook), RECOVERY trial ([NEJM 2021;384:693](#))
- Non-COVID-19 ARDS: conflicting data; Dexa-ARDS ([Lancet RM 2020;8:267](#)) → ↑ventilator-free-days & ↓mortality in mod-severe ARDS. Other trials: possible benefit in early mod-severe ARDS, ↑mortality if ARDS ≥14d ([Chest 2007;131:954; NEJM 2006;354:1671](#))

Pulmonary & Critical Care

ECMO

TYPES OF ECMO ([JACC 2014;63:2769](#))

1. **Venoarterial (VA, replaces heart and lungs)**: treats cardiogenic shock and hypoxic resp. failure
 - o Venous blood is removed, oxygenated, CO₂ extracted, and returned to arterial system
 - o Venous cannula in com. femoral vein (drainage from IVC or RA); arterial cannula in R fem. artery
2. **Venovenous (VV, replaces lungs)**: treats hypoxic resp. failure; relies on native cardiac output
 - o Venous blood is removed, oxygenated, CO₂ extracted, and returned to venous system
 - o Either two venous cannulae (common fem. vein and SVC) or a single bicaval device via R IJ (Avalon) that allows for early mobility

To call ECMO consult:

- MGH Heart App
- Directory: type "ECMO Consult" or **p24252**
- # 857-310-0335

Indications: (criteria suggested by [ELSO](#), MGH Heart App)

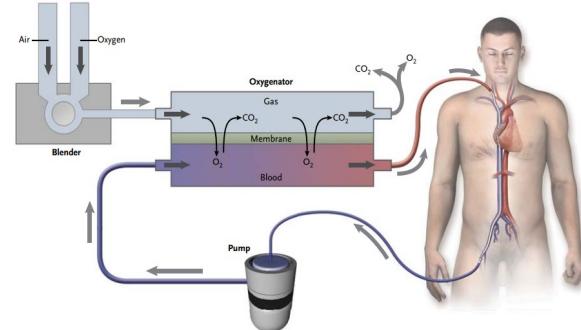
- **Acute resp failure (VV)**: PaO₂/FIO₂ <100-150 despite optimization, unable to achieve safe inflation pressures (Pplat <30), uncomp. CO₂ retention (>80) with inability to mechanically ventilate
- **Cardiogenic shock (VA)**: refractory low cardiac index (<2L/min/m²) & HoTN despite adequate volume, inotropes, & IABP
- **Reversible etiology** (ARDS, massive PE, cardiac arrest)
- **Bridge to definitive therapy** (transplantation, VAD, recovery)
- **Less invasive strategies have failed** (see [ARDS](#) and [Inpatient HF](#))

Contraindications:

- **Absolute (VA or VV)**: non-recoverable multi-organ failure/neurological disease; unwitnessed arrest/CPR >30min w/o ROSC; active severe bleeding; contraindication to AC, recent NSGY procedure/active intracranial bleed (<10d)
- **Absolute VA**: BMI>40; AoD; severe AI; ESLD/ESRD
- **Absolute VV**: severe right or left HF
- **Relative**: age>70; multi-organ failure; severe pHTN; unknown neuro status; GVHD; active malignancy; significant immunosuppression; ventilated >7d; DIC; survival <30% based on [RESP](#) and [SAVE](#) scores

ECMO VARIABLES

- **Sweep** (replaces ventilation): ↑sweep → ↓P_aCO₂ in blood returning to pt; titration of sweep affects **CO₂ elimination**
- **FdO₂** (fraction of delivered oxygen): usually set at 1.0
- **RPM**: RPM is predominant determinant of **blood flow** (2-5L/min; also affected by cannula size & native CO)
- **Baseline lab goals**: Hgb >7.5g/dL; Plt >75K; fibrinogen >150
- **AC**: UFH, follow PTT, Xa, AT-III. Goals: d/w attending/pharmacist



COMPLICATIONS ([HeartLung Circ 2014;23:10](#))

- **CLOTS** (oxygenator, pump, tubing, hemofilter; 0.13-22%); **bleeding** (cannulation site, GI, intracranial, hemolysis, DIC; 5.3-79%); **neurologic** (ICH, stroke, seizure, encephalopathy; 10-33%); **limb ischemia** (13-25%); **infxn** (17-49%); **AKI** (30-58%); **multi-organ failure** (10%); **cannulation problems** (0.8-8%); **hyperbili** (27%)

TROUBLESHOOTING THE CIRCUIT

- **Chatter**: "shaking" sound caused by high ⊖ pressure in the tubing; usually due to **hypovolemia**. Tx: volume (**5% albumin**)
- **Poor oxygenation** (as measured on patient ABG):
 - a) Recirculation: blood travels from the outflow (return) catheter back into the inflow (drainage) catheter, bypassing body; usually due to catheter malposition → Dx: **discordant circuit O₂ & patient O₂** content. Tx: reposition cannula, ↓RPM
 - b) Machine malfunction: hypoxemia on **post-membrane ABG**. Tx: replace membrane
 - c) Shunt: occurs if native CO >> ECMO flow (large fraction of blood travels through diseased lungs rather than ECMO circuit and is poorly oxygenated) → hypoxemia on **patient ABG only**. Tx: ↑RPM, ↓fever, ↓inotropes, ↑phenylephrine, βB, CCB
- **Harlequin (North-South) syndrome (VA only)**: **hypoxia of upper extremities, heart, brain** – can occur only when fem. artery cannulated. Cardiac recovery, but poor lung fx → native CO (deoxygenated) pushes against oxygenated ECMO blood in aortic arch leading to hypoxia of UE, brain, heart. Tx: relocate arterial cannula to R subclav or aorta ([HeartLung Ves 2015;7:320](#))

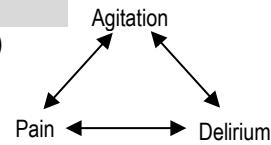
OUTCOMES

- **Acute respiratory failure**: 2 major studies show ↓mortality, though unclear if benefit from referral to ECMO center or **ECMO itself**
 - o 75 matched pairs ARDS d/t H1N1; transfer to ECMO center ↓mort. (23% vs 52%); 85% tx w/ ECMO ([JAMA 2011;306:1659](#))
 - o **CESAR**: RCT, 180 pts w/ severe ARDS; referral to single ECMO center vs. conventional management. ECMO-referred group ↑survival w/out disability at 6mo (63% vs 47%) ([Lancet 2009;374:135](#))
 - o **EOLIA**: RCT, 249 w/ severe ARDS; ECMO w/in 7d vs conventional tx; ECMO ↑days w/out renal failure (46 vs 21), ↓ischemic stroke (0% vs 5%), no sig. Δ 60d mortality ([NEJM 2018;378:1965](#)); stopped early (prelim results ⊕ for ECMO; [NEJM 2018;378:2031](#))
- **Refractory cardiogenic shock**: ~40% survive to discharge; ECMO placed under CPR = best predictor of death ([CCM 2008;36:1404](#); [ASAIO 2017;63:60](#))
- **ECPR**: ECMO as extension of CPR in cardiac arrest. In-hospital cardiac arrest: ↑survival (OR: 0.17) compared to CPR ([CCM 2011;39:1](#)); OHCA: 22% w/ meaningful neurologic recovery ([Resuscitation 2016;101:12](#)); overall: 29% survive to discharge ([ASAIO 2017;63:60](#)). Consider calling ECMO team if 10 minutes w/o ROSC to discuss ECMO
- **ECMO in COVID-19 ARDS**: international cohort study, 90d mortality 37-39% (similar to non-COVID 19 ARDS, [Lancet 2020;396:1071](#))

Pulmonary & Critical Care

Sedation

- GOAL OF ICU SEDATION:** addressing ICU triad of pain, agitation, & delirium ([NEJM 2014;370:444](#))
- Agitation:** target light sedation in intubated pts; no benefit to non-sedation approach ([NEJM 2020;382:1103](#))
 - Pain:** common, ↑energy expenditure; analgesia alone adequate in some ([Lancet 2010;375:475](#))
 - Delirium:** 16-89% ICU pts; a/w ↑mortality, ↓QOL, poor cognitive outcomes ([JAMA 2004;291:1753](#); [CCM 2010;38:1513](#); [CCM 2010;38:2311](#)); ↑risk w/ deeper sedation ([Intensive Care Med 2007;33:66](#))



ABCDE BUNDLE

A/w ↑vent-free days, ↓delirium ([CCM 2014;42:1024](#))

A – Spontaneous awakening trial (SAT): daily interruptions of sedation → ↓ICU LOS, vent days ([NEJM 2000;342:1471](#)), PTSD sx ([AJRCCM 2003;168:1457](#))

B – Spontaneous breathing trial (SBT): for pts who pass SAT, assess for suitability of extubation ([Lancet 2008;371:126](#))

C – Choice of sedation: see below

D – Delirium: assess CAM-ICU daily

E – Early mobility: ↓pressure sores, ↑functional status, ↓vent days, ↓delirium ([Lancet 2009;373:1874](#); [NEJM 2014;370:1626](#))

RASS (Richmond Agitation Sedation Scale) (AJRCCM 2002;166:1338)

+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube/catheters; aggressive
+2	Agitated	Frequent, non-purposeful mvmt; fights ventilator
+1	Restless	Anxious, but mvmt not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Sustained awakening to voice (≥10sec)
-2	Light sedation	Briefly awakens w/ eye contact to voice
-3	Mod. sedation	Mvmt or eye opening to voice but no eye contact
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
-5	Cannot be aroused	No response to voice or physical stimulation

SEDATION AGENTS (SCCM: [CCM 2018;46:e825](#))

Usual Initial Agents

Non-BZD Sedatives (targeting agitation/delirium)		For pain control, add:
Propofol 5-50mcg/kg/min (max 83) <i>GABA modulator</i>	1st line sedative. Immediate onset/rapid awakening. ↓ICP & controls seizures → use in status epilepticus & EtOH w/d. Earlier extubation & ↓mortality vs BZDs (AJRCCM 2014;189:1383) <ul style="list-style-type: none"> SEs: HoTN, bradycardia, hypertriglyceridemia, propofol infusion syndrome (PRIS) (>48h): acidosis, bradycardia, renal/liver failure, rhabdo, HLD, HSM No Δ w/ renal/liver failure; accumulates in adipose 	Opioids (targeting analgesia) <ul style="list-style-type: none"> Start w/ push doses, gtt for more sedation SEs: resp depression, tolerance, constipation/ileus
Dexmedetomidine (Precedex) 0.2-1.5mcg/kg/h <i>Central α2 agonist</i>	Sympathomimetic, anxiolysis w/o resp. depression or amnesia. Can use w/o ETT (EtOH w/d, post-extubation). A/w ↓delirium & earlier extubation (JAMA 2016;315:1460); ↓vent days vs midaz (JAMA 2012;307:1151 ; JAMA 2009;301:489), ↓delirium vs loraz (JAMA 2007;298:2644) & propofol (Eur J Anaesthesiol 2020;37:121); nightly admin. may prevent delirium (AJRCCM 2018;197:1147). No Δ in mortality (NEJM 2019;380:2506) <ul style="list-style-type: none"> SEs: bradycardia, HoTN, withdrawal syndrome Dose-reduce in renal, liver failure 	Hydromorphone bolus 0.25-1mg q1h, gtt 0.5-5mg/h <ul style="list-style-type: none"> Accumulate in liver/renal failure
		Fentanyl bolus 25-50mcg q30m, gtt 50-200mcg/h <ul style="list-style-type: none"> Bolus t_{1/2} 30-60m; gtt t_{1/2} 9-16h SE: chest wall rigidity Accumulates in adipose No renal metabolites
		Morphine bolus 2-4mg q1h, gtt 2-30mg/h <ul style="list-style-type: none"> Inexpensive, generally tolerated SEs: pruritus, bradycardia, HoTN Accumulates in renal failure

If deeper sedation is required or propofol contraindicated, add/switch to:

Benzodiazepines (targeting amnesia, anxiolysis) <i>GABA agonist</i>	AND/OR	"Dissociated amnesia" & analgesia w/o resp depression ; some bronchodilation
↑mortality, time to light sedation & extubation, & delirium • SEs: resp depression, agitation, withdrawal/tolerance		<ul style="list-style-type: none"> SEs: hallucinations, sympathetic stimulation (HTN, bronchodilation, hypersalivation), delirium upon withdrawal, false ↑BIS activity Metabolites accumulate in renal/liver failure
Midazolam bolus 0.5-4mg q2h, gtt 2-8mg/h	Shorter t _{1/2} vs lorazepam (~2-6h vs 14h), both w/ fast onset (2-5min); only IV BZD not in propylene glycol <ul style="list-style-type: none"> Note CYP3A4 metab med interactions (fluconazole, azithro, flagyl, amio) Metabolites accumulate in liver/renal failure; accumulate in adipose 	
Lorazepam bolus 1-2mg	Preferred > midaz in renal, liver failure but caution in severe liver dz <ul style="list-style-type: none"> Propylene glycol (solvent) toxicity w/ ↑dose (lactic acid, HoTN, arrhythmia) Risk of oversedation 2/2 delayed response/accumulation 	Strategies for weaning off prolonged analgesia/sedation: <ul style="list-style-type: none"> ↓opioids ~25% per day; can replace w/ PO opioid (incl methadone) ↓benzos ~25% per day; can replace w/ phenobarb or lorazepam ↓dexmed. ~25% q6h; can replace w/ clonidine q8-12h or patch <p>For refractory agitation, consider antipsychotics, incl quetiapine (50mg q6-12h, max 400mg/d) & haloperidol (2.5-5mg IV q4-8h)</p>

Pulmonary & Critical Care

Shock

OVERVIEW (NEJM 2013;369:1726)

- Definition:** state of tissue hypoxia due to decreased or dysregulated oxygen delivery or extraction, resulting in end-organ damage
 - Initially reversible, but rapidly progresses: cell death → end-organ damage → multiorgan failure → death
- Clinical manifestations:** **hypotension** (SBP <90mmHg or ↓SBP >40mmHg from baseline); **end-organ dysfunction:** oliguria (UOP <0.5cc/kg/h), **altered mental status**, metabolic acidosis (\pm anion gap, ↑lactate); cool & clammy vs. warm & flushed extremities. (**NB:** any of these can be **normal**—including BP—in a patient who is in shock, so a **high index of suspicion** is needed)
- Initial workup:** focused H&P, ensure **access**, review meds, EKG/CXR, ABG/VBG, CBC/diff, CMP, TnT, lactate, CVO2

MAP: determined by **CO** (cardiac output) & **SVR** (systemic vascular resistance)

$$\text{MAP} = \text{RAP} + \text{CO} \times \text{SVR}$$

SVR determined by vessel diameter/length and blood viscosity

(2/3) DBP + (1/3) SBP
HR x SV

SV determined by preload, afterload, & contractility

Lactic Acidosis (NEJM 2014;371:2309)	
Type A: due to tissue hypoperfusion , typically seen in shock; can be profound in setting of bowel ischemia, necrosis	Type B: NOT marked tissue hypoperfusion. Metformin, malignancy (e.g. Warburg), EtOH, thiamine deficiency, albuterol, D-lactate, mito. dysfunction, liver disease

ETIOLOGIES OF SHOCK

Signs of ↑CO:		SHOCK		Signs of ↓CO:	
- Widened pulse pressure	- Low diastolic BP	↑CO	↓CO	- Narrow pulse pressure	- Cold extremities
- Warm extremities	- Normal cap refill			- Slow cap refill	
Distributive (66%)	Hypovolemic (16%)	Cardiogenic (16%)	Obstructive (2%)		
Pathophys.	↓SVR & altered oxygen extraction	↓ cardiac output → inadequate oxygen delivery			
Examples	Sepsis, SIRS, anaphylaxis, adrenal insufficiency, liver failure, toxins/meds, neurogenic (NEJM 2013;369:840; NEJM 2001;345:588)	Hemorrhagic (GI, RP, abdomen, thigh), GI losses, 3rd spacing (pancreatitis) (NEJM 2018;378:370)	MI, HF, myocarditis, severe valve disease, arrhythmias	Extra-cardiac causes: PE, tension PTX, tamponade	
Extremities	Warm and dry	Cold and dry	Cold and wet	Cold and dry	
CVP/PCWP	↓/normal	↓↓	↑↑	↑/normal	
CO or CVO2	↑/normal	↓	↓	↓	
SVR	↓↓	↑	↑	↑	
TTE Findings	Normal chamber size, normal/↑ contractility	Small chambers, normal/↑ contractility	Large chambers, poor contractility	Tamponade: pericardial effusion PE/PTX: dilated RV	
Basic Management	All causes: fluids, pressors <u>Sepsis:</u> source control, abx <u>Adrenal insuff:</u> steroids (hydrocort) <u>Anaphylaxis:</u> IM epi, H1RA, H2RA, methylpred, albuterol	Ensure adequate access! <u>Most cases:</u> fluids <u>Hemorrhage:</u> pRBCs, hemostasis via surgery/IR/GI	HF: diuresis, inotropes, ± PA line <u>Arrhythmias:</u> electricity, anti-arrhythmics	Tamponade: fluids, pericardiocentesis <u>PE:</u> AC/lysis <u>PTX:</u> chest tube vs. needle decompression	

If the etiology of shock is unclear, useful ways to quickly distinguish include:

- Vitals:** wide vs narrow pulse pressure (proxy for CO; PP <25% SBP suggests low CO); **exam:** warm/cold; dry/wet; rashes, mottling
- Data points:** if central access, **CVO2** (normal CvO2 = 70%, >70% in sepsis, <70% in other states of shock), **CVP** (normally 5-7, elevated in cardiogenic/obstructive, low in hypovolemic). **TTE** (POCUS and/or STAT TTE)
- Consider:** PAC, no mortality/LOS/cost benefit in unselected ICU or CHF pts (Cochrane Rev 2013; JAMA 2005;294:1625; Lancet 2005;366:472)

MANAGEMENT CONSIDERATIONS

- Antibiotics:** if septic shock is on the differential, obtain cultures & start broad spectrum antibiotics
- Fluid resuscitation:** crystalloid bolus (not infusion). Can predict **fluid responsiveness** by pulse pressure variation, passive leg raise, IVC diameter (see [Sepsis](#)). Good approximation = improvement in BP/UOP/lactate with fluid challenge. **Appropriate fluid challenge should raise CVP by 2.** Be more cautious with fluids if possible cardiogenic shock (NEJM 2013;369:1243)
- Vasoactive agents** (see [Vasopressors](#)): titrate to **MAP >65 mmHg** (if cardiogenic, MAP >60 mmHg)
- Ventilatory support:** intubate if necessary (concomitant respiratory failure, unable to compensate for metabolic acidosis, marked hemodynamic instability) & have pressors available as **intubation can worsen hypotension** (including hemodynamic collapse in RV dysfunction); SpO2 may be unreliable due to peripheral vasoconstriction (even on earlobe) & may require frequent ABG
- Steroids:** if known adrenal insufficiency or chronic steroid use, stress-dose steroids (hydrocortisone 50mg q6h or 100mg q8h x5-7d, pending clinical improvement); unclear role for septic shock (see [Sepsis](#))
- Bicarbonate:** if pH <7.1 or <7.2 w/ severe AKI, can temporize while addressing underlying etiology w/ bicarb amps or bicarb gtt. No mortality benefit except in AKI (Lancet 2018;392:31) (see [Sepsis](#))

SPECIALIZED TEAMS

STEMI (x6-8282)
PERT (x4-7378)
SHOCK (p11511; IABP, Impella)
ECMO (p24252, 857-310-0335)

Pulmonary & Critical Care

Sepsis

OVERVIEW

- Definitions:** updated in 2016 by Sepsis Definitions Task Force (Sepsis-3) ([JAMA 2016;315:801](#))
 - Sepsis:** life-threatening organ dysfunction (\uparrow SOFA ≥ 2) caused by dysregulated host response to infection
 - Septic shock:** sepsis + (1) pressors to sustain MAP > 65 AND (2) lactate > 2 w/o hypovolemia
- Diagnosis:** SIRS + infectious source failed to identify 1/8 w/ sepsis & organ failure ([NEJM 2015;372:1629](#))
 - Sequential Organ Failure Assessment (SOFA) score:** includes PaO₂/FiO₂, plts, bili, BP, GCS, & Cr
 - Quick SOFA (qSOFA) ≥ 2** can help identify pts w/ suspected infection w/ **early sepsis outside of ICU** (\uparrow ICU LOS, \uparrow mortality)

qSOFA
1. RR > 22
2. AMS
3. SBP ≤ 100

PATHOPHYSIOLOGY/CLINICAL MANIFESTATIONS ([NEJM 2013;369:840](#); [BMJ 2016;353:i1585](#))

- Microbial components** bind immune cells \rightarrow **↑ inflammatory mediators**, PMN migration; if exceeds boundaries of local environment \rightarrow **sepsis** (generalized inflammatory response) \rightarrow **tissue ischemia** (thrombosis in microcirculation 2/2 altered coag., \downarrow RBC deformability \rightarrow \downarrow O₂ extraction), **cytopathic injury** (mitochondrial dysfunction), **impaired endothelial barrier** (\rightarrow edema) \rightarrow **organ dysfunction**

Cardiovascular	Vasodilation \rightarrow hypotension; ventricular function may be either hyperdynamic or depressed
Pulmonary	Pulmonary edema, ARDS
GI	\uparrow intestinal permeability \rightarrow \uparrow bacterial translocation \rightarrow worsening systemic inflammation
Hepatic	Cholestasis ("sepsis-induced cholestasis"), impaired reticuloendothelial function
Renal	AKI of multifactorial etiology, including microvascular dysfunction, oxidative stress, global hypoperfusion
Hematologic	Early inflammation, late immunosuppression; procoagulant and anticoagulant disequilibrium: DIC , \downarrow plt
Endocrine	Altered glycemic control, adrenal dysfunction, sick euthyroid syndrome
Neurologic	Encephalopathy

INITIAL MANAGEMENT (2016 Surviving Sepsis: [Intensive Care Med 2017;43:304](#))

Sepsis & septic shock are **medical emergencies**, so **early recognition** is critical. Components of initial management include:

1) Antibiotics: empiric broad spectrum IV antibiotics should be administered within one hour of recognition. Order STAT.

- Delay \rightarrow \uparrow mortality by 7.6%/h ([CCM 2006;34:1589](#); [CCM 2010;38:1045](#)). More rapid abx \rightarrow \downarrow mortality ([NEJM 2017;376:2235](#))
- Abx selection:** guided by site of infection, prior pathogens, exposures (SNF, lines, recent abx, etc), immunocompromise, etc.
 - Consider **double coverage of PsA** if known/suspected PsA infection w/: severe sepsis/septic shock, bacteremia in neutropenic pt, burn pt, or otherwise high incidence of resistance to chosen class (10-15%). Usually β -lactam + (FLQ or aminoglycoside)
 - If there is suspicion of **toxic shock syndrome**, add **clindamycin** for anti-toxin effects (& additional staph/strep coverage)
 - If RFs for **invasive Candida infection** (neutropenia, chemotherapy, transplant, indwelling catheters, TPN, recent major surgery [esp. abdominal], prolonged admission/abx), consider empiric antifungals (typically **micafungin**)
 - In nonneutropenic pts w/ *Candida* colonization, empiric antifungals not a/w \uparrow fungal infection-free survival but did \downarrow invasive fungal infections ([JAMA 2016;316:1555](#))
- De-escalation:** once causative organism identified, Δ to narrowest effective agent, w/ duration individualized to pt/etiology/trajectory
 - Procalcitonin may be useful in guiding cessation ([Lancet 2010;375:463](#); [Lancet ID 2016;16:819](#); [CCM 2018;46:684](#))

2) Resuscitation: initial fluid resuscitation with 30 mL/kg of crystalloid completed within 3 hours

- Balanced crystalloids** (e.g. LR) with \downarrow mortality and \downarrow renal impairment in critically ill adults compared to NS ([NEJM 2018;378:829](#)); no mortality benefit to colloids ([NEJM 2004;350:2247](#); [JAMA 2013;310:1809](#); [NEJM 2014;370:1412](#))
- Targets of resusc:** **lactate clearance** (normalization or $> 20\%$ /2h) ([JAMA 2010;303:739](#)); **cap. refill** (<30s) ([JAMA 2019;321:654](#))
- After the initial resuscitation effort, further fluid administration should be guided by dynamic measures of fluid responsiveness (see table below). Lack of volume responsiveness \rightarrow use/increase **vasopressors** instead

ASSESSING FLUID RESPONSIVENESS (JAMA 2016;316:1298)	
Method	Fluid responsive if:
Pulse pressure variation: validated in mechanically ventilated w/ $V_T \geq 8$ cc/kg, not spontaneously triggering ventilator, & in NSR (Crit Care 2014;18:650)	PPV $\geq 13\%$
Mech ventilation = pos. pressure during inspiration \rightarrow \downarrow venous return & RV preload \rightarrow \uparrow LV filling/output \rightarrow PPmax in inspiration, PPmin in expiration PPV = (PPmax - PPmin)/PPmean	If on ascending portion of Starling curve, sensitive to Δ s in preload. Volume responsive pts will show larger variations in PP or SV during resp cycle
Passive leg raise: raise legs to 45° w/ torso horizontal x1min in any mech. ventilated pt \rightarrow "autotransfusion" of ~250-350cc; assess Δ in hemodynamics	\uparrow PP $\geq 10\%$ (surrogate for \uparrow SV if no invasive measure of CO)
Δ in IVC diam: measure 1cm prox. to hepatic vein junction in M-mode; if mech. vent, calc. distensibility : dIVC = (Dmax-Dmin)/Dmin; if spont. breathing, calc. collapsibility : cIVC = Dmax-Dmin/Dmax	dIVC $\geq 15\%$ cIVC $\geq 40\%$
Fluid challenge: bolus 250-500cc fluids; check CVP before & immediately after, if \uparrow by ≥ 2 then was adequate volume challenge	Improvement in hemodynamics, UOP, lactate; \uparrow PP $\geq 10\%$

3) Vasopressors: target a mean arterial pressure (MAP) of >65mmHg ([NEJM 2014;370:1583](#)) (see [Vasopressors](#) for full details)

- Norepinephrine (NE, Levophed): first choice vasopressor
- Vasopressin: add when NE at 5-15mcg/min to ↑ kidney funx. Not usually titrated, on or off at 0.04U/min ([NEJM 2008;358:877](#))
- Epinephrine: recommended when 2nd or 3rd agent is needed; consider trial when NE escalating >25mcg/min
- Phenylephrine (Neo): recommended primarily when (a) NE is associated with serious arrhythmias, (b) CO is high & BP persistently low, (c) NE + vaso have failed to achieve MAP target at >25mcg/min and pt is ↑ tachycardic (d) hypotension a/w AFRVR
- Dopamine: reserved for highly selective patient population with bradycardia and low risk of tachyarrhythmia; a/w ↑ risk of arrhythmias/mortality in all-comers ([CCM 2012;40:725](#); [NEJM 2010;362:779](#))
- Methylene blue: uncommonly used, pressor of last resort when NO-mediated vasoplegia is suspected
- Angiotensin II: not currently available at MGH; ATHOS-3 trial ([NEJM 2019;377:419](#))

4) Source Identification and Control

- Cultures: obtain cultures prior to antimicrobials (unless will significantly delay administration) as 1Sn ([Annals 2019;171:547](#)). Get at least 2 sets of BCx with at least one drawn percutaneously (see [Bloodstream Infections](#))
 - Consider 1,3 beta-D-glucan, galactomannan, and/or cryptococcal Ag if concerned for fungemia
- Identify conditions that require source control: necrotizing soft tissue infection, abscess, cholangitis, cholecystitis, GI perforation/ischemia, pyelo a/w obstructive renal stone or abscess, empyema, septic arthritis, devices
- Failure to improve on broad spectrum antibiotics should prompt evaluation for an occult source with imaging

Where to draw blood cultures?

Drawing cultures from vascular access devices can lead to high rates of false positives. Obtain cultures from vascular access devices only if concerned for CRBSI (rigors with infusion, erythema/induration around line site); otherwise obtain only peripheral blood cultures

OTHER ASPECTS OF MANAGEMENT

AKI

- Timing: no mortality benefit to early (<12h) vs delayed (>48h) initiation of RRT in patients with septic shock and severe AKI without urgent indication ([NEJM 2018;379:1431](#); [NEJM 2016;375:122](#); [NEJM 2020;383:240](#))
- Modality: CVVH and HD are largely equivalent for treating AKI, but CVVH minimizes fluid shifts in hemodynamically unstable patients

Metabolic Acidosis/Lactic Acidosis

- Ultimately, need to correct underlying etiology. Can temporize with bicarbonate if:
 - Severe acidemia w/ pH <7.1: used as cutoff as evidence in animal/tissue studies of myocardial depression, ↓ catecholamine efficacy, arrhythmias, though generally not replicated in human studies & pts w/ DKA can have pH <7 w/o these effects
 - Less severe acidemia (pH <7.2) w/ AKI: BICAR-ICU → NaHCO₃ gtt to keep pH >7.3 (≤1L/24h) ↓ mortality ([Lancet 2018;392:31](#))
- Bicarbonate administration: 1 amp = 50mEq/50mL (or 8.4%); or infusion of solution of 150mEq (3 amps) in 1L of D5W
 - Caution: HCO₃ → pCO₂ that must be ventilated off, so must have sufficient resp. drive/be intubated. Also → ↓ iCa

Transfusions

- Transfusion goal of Hgb 7g/dL similar to 9g/dL unless cardiac ischemia or active hemorrhage ([NEJM 2014;371:1381](#))

CONTROVERSIAL MANAGEMENT STRATEGIES

Corticosteroids

- Rationale: critical illness affects HPA axis, may cause relative “critical illness-related corticosteroid insufficiency” (CIRCI)
- Diagnosis: cortisol levels/stim. have not reliably predicted pts who will benefit from steroids, but random AM cortisol ≤10 or Δcortisol ≤9 after 250mg cosyntropin stim. are indicators of likely adrenal insufficiency (NB: etomidate can interfere w/ stim.)
- Controversy: “Annane/French trial” ([JAMA 2002;288:862](#)) ↓ mortality w/ IV hydrocort 50mg q6h + fludrocort 50mcg/d x7d in pts w/ septic shock & cort stim Δ≤9, replicated ([NEJM 2018;378:809](#)). No Δmortality in ([NEJM 2008;358:111](#); [JAMA 2016;316:1775](#); [NEJM 2018;378:797](#))
- Conclusion: if refractory septic shock (esp. if e/o CIRCI), consider IV hydrocort 50mg q6h or 100mg q8h (≤400mg/d) ± fludrocort (hydrocort likely has sufficient mineralocorticoid effect) for 5-7d w/ taper guided by response ([Intensive Care Med 2017;43:1751](#))

Vitamin C

- Rationale: Vitamin C is an antioxidant; may also act synergistically with hydrocortisone to ↓ inflammation
- Controversy: small, 1-center cohort ([Chest 2017;151:1229](#)) ↓ mortality w/ high dose **Vit C, hydrocort**, & IV **thiamine**, not validated. No benefit to Vit C alone ([CCM 2019;47:774](#); [JAMA 2019;322:1261](#)) or w/ thiamine + hydrocort ([JAMA 2020;323:423](#))
- Conclusion: no proven benefit to Vitamin C, either alone or in combination w/ thiamine & hydrocortisone

Esmolol

- Rationale: β-blockade may attenuate harmful effects of sympathetic adrenergic response in septic shock
- Controversy: single RCT ↓ mortality in pts w/ septic shock w/ esmolol to keep HR 80-94 ([JAMA 2013;310:1683](#)), but control group ↑↑ mortality rate (80.5%). Not validated in subsequent studies
- Conclusion: need further validation of findings; esmolol **not routinely used** in septic shock

Pulmonary & Critical Care

Vasopressors

Category	Name	α	β_1	β_2	D	PVR	SVR	CO
Vasoconstrictors	Phenylephrine	5+	0	0	0	2+	↑	↓
	Vasopressin			V1		±	↑	-/↓
Inoconstrictors	Norepinephrine	4+	2+	(+)	0	1+	↑	↑
	Dopamine (low)	0	1+	0	2+	±	-/↑	↑
	Dopamine (med)	1+	2+	0	2+	±	↑	↑
	Dopamine (high)	2+	2+	0	2+	±	↑	↑
	Epinephrine	4+	3+	2+	0	1-	-/↑	↑
Inodilators	Dobutamine	(+)	3+	2+	0	1-	↓	↑
	Milrinone			PDE inhibitor		2-	↓	↑
Chronotrope	Isoproterenol	0	3+	3+	0	0	↓	↑

α_1 : vasoconstriction, ↑ duration of heart contraction
 α_2 : sedation/analgesia, vasoconstriction (if peripheral) vs vasodilation (if central, e.g. clonidine)
 β_1 : ↑ inotropy, ↑ chronotropy
 β_2 : ↑ vasodilation
D: renal/splanchnic/coronary/cerebral vasodilation
V1: vasoconstriction (especially splanchnic)

*If vasopressor extravasates into surrounding tissue, give **phentolamine** 5-10mg in 10cc NS directly into area of extravasation

VASOPRESSORS & INOTROPES (Circulation 2008;118:1047)								
	Name	Mechanism	Uses			Side effects		Dosing
VASOPRESSORS	Norepinephrine (NE) Levophed "Levo"	$\alpha_1 > \beta_1$ agonist: ↑↑SVR, ↑CO Reflex brady from vasodilation can negate ↑HR from chronotropy	Septic shock (1 st) Cardiogenic shock (1 st) Hypovolemic shock (1 st)			Arrhythmia Digital ischemia ↑FSBG		Initial: 2-12mcg/min (0.1-0.15mcg/kg/min)
	Phenylephrine Neosynephrine "Neo"	Pure vasopressor α_1 agonist: ↑↑ SVR	Septic shock if ↑↑HR from NE or ↑CO w/ ↓BP or 3 rd agent needed AFRVR, HOCM, AS, RV failure			Reflex bradycardia ↓CO, ↑PAP, ↑SVR Digital ischemia		Initial: 50-180mcg/min (0.5-2mcg/kg/min)
	Vasopressin Pitressin "Vaso"	V1 agonist: ↑SVR V2 agonist: ↑renal H ₂ O reabsorption	Septic shock (2 nd), add when NE 5-15 mcg/min (↓ mortality vs. NE alone) (NEJM 2008;358:877) Anaphylaxis (2 nd) Pulmonary HTN/RV failure Hepatorenal syndrome			Coronary ischemia Mesenteric ischemia ↓Na		Usual: 0.04U/min Consider when NE 5-15
	Epinephrine Adrenalin "Epi"	<u>Low:</u> $\beta_1 > \beta_2 > \alpha_1$: ↑CO, neutral SVR <u>High:</u> $\alpha_1 > \beta_1 > \beta_2$: ↑CO, ↑SVR	ACLS (1 st) Anaphylaxis (1 st) Symptomatic bradycardia (2 nd) Septic shock Bronchospasm			↑HR, arrhythmias Myocardial ischemia ↑lactate ↑splanchnic SVR ↑FSBG		<u>Low:</u> 1-4mcg/min <u>High:</u> 5-35mcg/min
	Dopamine Intropin "Dopa"	<u>Low:</u> D ₁ > β ₁ : ↑CO, ↑UOP <u>Med:</u> β ₁ > D ₁ : ↑CO, ↑SVR <u>High:</u> α ₁ > β ₁ > D ₁ : ↑SVR	Symptomatic bradycardia Septic shock w/ bradycardia ↑mortality vs. NE in septic (CCM 2017;45:486) & cardiogenic shock (NEJM 2010;362:779)			Tachyarrhythmia Myocardial ischemia ↓BP (low dose) ↑PCWP, pulm shunt ↑FSBG		<u>Low:</u> 1-2mcg/kg/min <u>Med:</u> 5-10mcg/kg/min <u>High:</u> 10-50mcg/kg/min
	Methylene blue	↓NO and cGMP, ↑smooth muscle tone: ↑SVR	Refractory vasoplegia due to sepsis/anaphylaxis Post-cardiopulm bypass Amlodipine overdose Metformin overdose Methemoglobinemia			False ↓SpO ₂ Arrhythmias ↑PVR Rash, hemolysis, serotonin syndrome ∅∅∅ in G6PD		Initial: 1-2mg/kg Max: 5mg/kg
	Angiotensin II	ANG-II agonist: ↑SVR	Refractory septic shock (NB: not available at MGH)			Peripheral ischemia		10-20ng/kg/min; max 40
INODILATORS	Dobutamine Dobutrex "Dobuta"	$\beta_1, \beta_2 > \alpha_1$ agonist: ↑CO, ↓SVR	Cardiogenic shock Sepsis + ↓LV EF (add to NE/vaso)			↓BP, ↑HR Arrhythmias Myocardial ischemia Tachyphylaxis		Initial: 0.5-1mcg/kg/min (2.5 if more severe) Max: 20-40mcg/kg/min
	Milrinone Primacor	PDE inhibitor (↑cAMP), ↑inotropy, vasodilation: ↑CO, ↓PVR/SVR	Cardiogenic shock RV failure (↓PVR, ↓LVEDV)			Hypotension Arrhythmias Myocardial ischemia		Initial: 0.125mcg/kg/min Max: 0.75mcg/kg/min
	Isoproterenol Isuprel	$\beta_1 = \beta_2$ agonist: ↑HR, ↓SVR	Symptomatic bradycardia Mg-refractory torsades de pointes			↓BP, ↑HR Arrhythmias Myocardial ischemia Flushing, anxiety		Initial: 2-10mcg/min (can bolus 2-6mcg first) Max: 30mcg/min

Pulmonary & Critical Care

Toxicology

Toxicology resident pager 21827 • Toxicology/Poison Control Center 1-800-222-1222 • <http://mghlabtest.partners.org>
 MGH Laboratory Toxicology Screen Guru: Dr. Jim Flood (jflood@partners.org; great resource for questions re: tox screens)

	Drug/Toxin	Presenting Symptoms	Diagnostic Workup	Management
Toxidromes	Anticholinergic Atropine, Benztropine, Scopolamine, Diphenhydramine	Mydriasis, hyperthermia, ↓ sweating, flushing, delirium, urinary retention, ileus, tachycardia, HTN	Hx, EKG, CPK	Supportive, cooling for hyperthermia; charcoal (1g/kg) if <1h, BZDs for agitation & seizure (szr), physostigmine if severe (ICU, atropine at bedside; not for TCA ODs)
	Cholinergics Organophosphates, carbamate insecticides, nicotine	"DUMBBELLS": Diaphoresis/Diarrhea, Urination, Miosis/Muscle spasm, Bronchoconstriction/Bronchorrhea, Bradycardia, Emesis, Lacrimation, Lethargy, Salivation/Seizure	ABG, ECG, Chem 7, CPK, lactate. Can monitor RBC AChE inhibitor if available	100% O ₂ , atropine (2-5mg, redose to effect q3-5min, no effect on muscular symptoms); pralidoxime (30mg/kg over 30min → 8-20mg/kg/h. Only for organophosphate toxicity)
	Sympathomimetics Amphetamines, MDMA, cathinones "bath salts"	Agitation, mydriasis, hallucinations, paranoia, tachycardia, HTN, diaphoresis, hyperthermia, piloerection, szr	EKG, chem 7, lactate, CPK, LFTs, coags	IV BZDs, atypical antipsych. if refractory agitation, avoid succinylcholine and ketamine
	Neuroleptic Malignant Syndrome (NMS) Dopamine blockade, dopaminergic w/d	AMS, "lead pipe" rigidity, sialorrhea, hyperthermia, dysautonomia, diaphoresis <u>Typically no N/V/D or hyperreflexia</u>	Search for causative agent. CPK (often ↑↑), CBC (↑WBC), LDH, LFTs, BMP, serum iron (often ↓); consider brain imaging, LP, EEG	D/c causative agent (restart dopamine if DCd), IVF, cooling blanket, nitroprusside for HTN, BZD for agitation. Dantrolene, bromocriptine, amantadine
	Serotonin Syndrome Antidepressants, Linezolid, Tramadol	AMS, hyperreflexia (LE predominant), hyperthermia, mydriasis, ↑HR, HTN, diarrhea, diaphoresis, clonus, rigidity	Search for causative agent. CBC, CPK, BMP, coags, LFTs, UA, CXR	BZDs for agitation (avoid antipsychotics); supportive care for altered VS (esmolol, nitroprusside for ↑HR & HTN, cooling). If all else fails, consider cyproheptadine
Psychiatric Medications	Benzodiazepines	Depressed MS, ataxia, slurred speech, hyporeflexia, ↓RR, coma	Hx, urine tox can give qualitative result	Supportive; avoid flumazenil as it precipitates withdrawal + szr
	Antipsychotics	Physiologic depression, miosis, anticholinergic effects, extrapyramidal reactions/NMS, tachycardia	CMP, CBC, CPK, LDH, LFTs, serum iron, EKG, EEG	NaHCO ₃ for QTc prolong.; Mg, isoprot., overdrive pacing if torsades. Avoid class IA, IC, and III antiarrhythmics
	TCAs	Prolonged QRS, arrhythmia, hypotension, anticholinergic toxicity, myoclonus, hyperthermia, AMS, coma, szr	CPK, tox screen, EKG: ↑QRS duration (>100ms, 26% szr risk; >160, 50% risk), terminal R wave >3mm in aVR. Watch for ventricular arrhythmia	NaHCO ₃ (for the Na) if QRS >100ms or HoTN. BZDs for szr. Salvage: 3% NaCl, lipid emulsion
	Lithium	N/V/D, tremor, hyperreflexia, clonus, ataxia, AMS, szr, AV block, sinus brady, long QT, hyper/hypothyroid, nephrogenic DI if chronic	BUN/Cr, Li levels (nl 0.5-1.5mmol/L), EKG. Toxicity common w/ AKI from NSAIDs, ACEi, diuretics	Frequent neuro checks; IVF (NS preferred), maintain UOP, HD if encephalopathy, renal dysfunction
Pain Medications	Acetaminophen	Malaise, vomiting, sweating, RUQ pain, DILI/ALF	See Acute Liver Injury & Failure	
	Opioids	↓RR & VT, CNS depression, ↓bowel sounds, miosis	EKG, core temp, FSBG, CPK	IV or intranasal naloxone (0.4-2mg). See Opioid Use Disorder & Withdrawal
	Salicylates	Tinnitus, fever, vertigo, N/V/D, ↑RR, pulmonary edema, AMS (can have neuroglycopenia w/ nl FSBG)	ABG (mixed resp alkalosis/met acidosis), BMP, CXR, salicylate level (>30-50mg/dL). Trend levels & ABG q2h	Avoid intubation (if required, hyperventilate to avoid acidemia), IVF, charcoal (1g/kg), glucose (100mL D50), NaHCO ₃ , alkalinize urine to pH 7.5-8, avoid acetazolamide. Consider HD
Cardiac Medications	CCBs	N/V, HoTN, CHF, ↓HR, AV block, stupor, cardiac arrest, ↑FSBG	Hx, EKG (↓HR, long PR), blood levels (slow, correlate poorly). Extended release more dangerous. High FSBG = poor prognosis	Calcium, pressors, glucagon, HIGH DOSE-insulin (1U/kg bolus, then 0.5-1U/kg/h gtt, adjust to cardiac response), IVF; consider pacing, atropine, ECMO
	B-Blockers	HoTN, ↓HR, AV block, long QTc (sotalol), CHF, bronchospasm, ↓FSBG, stupor, ↑K, szr (propranolol), miosis	Hx, EKG, blood levels (slow, correlate poorly); propranolol highest mortality	Pressors, calcium, glucagon (0.05-0.15mg/kg bolus q3-5min or gtt), high-dose insulin (see above), IVF; atropine, pacing, ECMO
	Digoxin	↓HR, AV block, N/V/abd pain, ↑K, AMS, xanthopsia (yellow-green halo), bidirectional VT, "regularization of AF"	EKG, BMP, UOP, dig level (nl 0.9-2ng/mL; may not be accurate if drawn w/in 6h of last dose, as includes bound Fab fragments)	Digoxin-specific Fab fragments (if K>5.5, severe end-organ dysfxn, or life-threatening arrhythmia), Mg, <u>AVOID</u> hypokalemia

Pulmonary & Critical Care

Toxicology

	Drug/Toxin	Presenting Symptoms	Diagnostic Workup	Management
Alcohols	EtOH	Disinhibition, stupor, nystagmus, memory loss, discoordination, ↓RR, coma	EtOH level, methanol and ethylene glycol if + osmol gap. BMP, LFTs	See Alcohol-Related Liver Disease and Alcohol Use Disorder & Withdrawal
	Ethylene glycol Antifreeze	Inebriation, AMS; flank pain, hematuria	AGMA (severe), osmol gap, CaOx crystalluria, AKI, hypocalcemia, ↑↑lactate	Fomepizole (15mg/kg bolus over 30min then 10mg/kg q12h), NaHCO ₃ if pH<7.3, leucovorin 50mg IV, consider HD
	Methanol Windshield fluid, "moonshine"	Inebriation, retinal injury (visual blurring, papilledema, blindness)	AGMA (severe), osmol gap, visual acuity testing	As above, fomepizole (or EtOH), NaHCO ₃ , HD
Other Exposures	Cocaine	Agitation, psychosis, szr, HTN, ↑HR, vasospasm/MI, arrhythmia, stroke, vasculitis, lung injury, rhabdo	Serum/urine tox (metabolites detectable for 2-5d), ECG, cardiac biomarkers if chest pain, CPK, UA	Hyperthermia treatment (cooling, BZDs), treat chest pain with ASA, CCB, nitrates, labetalol (no pure βB)
	Carbon Monoxide	<u>Minor sx:</u> headache, N/V <u>Major sx:</u> confusion, LOC, szr, coma, cardiac ischemia, arrhythmias	Hx (house fire, winter w/ space heaters), cyanide & carboxyhemoglobin levels, co-oximetry (SpO ₂ invalid), AG acidosis, EKG, TnT	100% O ₂ (t½ 6h→60 min); hyperbaric O ₂ (t½ 6h→20min); watch for delayed neuropsychiatric sequelae
	Cyanide	HA, nausea, AMS, szr, coma, shock. Suspect in structural fires, prolonged nitroprusside infusion	Lactate, AGMA, cyanide & carboxyhemoglobin levels	Hydroxocobalamin (5g over 15min, use amyl nitrate if unavailable) & sodium thiosulfate
	Gamma-hydroxybutarate (GHB)	Agitation, ↓HR, ↓RR, ↓BP, coma (sudden onset/resolution), co-intoxicants common	Not detected on routine tox screen, need 100mL urine & 10-30mL blood for send-out. EKG, r/o other causes, βhCG	Supportive; BZDs for withdrawal. <u>Note:</u> OD at low dose if on protease inhibitors
	Synthetic Cannabinoids "Spice" or "K2"	Anxiety, paranoia, sedation, memory impairment, hallucinations, psychosis, szr, tachycardia, HTN, N/V, AKI	Not detected on routine tox screen, can send blood & urine for send-out	Supportive care. BZDs for agitation and szr. Antipsychotics for agitation

([Pharmacotherapy 2015;35:189](#); [Chest 2011;140:795](#); [Crit Care Clin 2012;28:479](#))

ANION AND OSMOL GAPS

Anion Gap	Osmol Gap
Methanol Uremia (CKD) Ketoacidosis INH Iron Lactic Acidosis Ethylene/propylene glycol Salicylates CO Cyanide Sympathomimetics	With normal AG: EtOH, isopropyl-OH Ether Glycine/sorbitol/mannitol Hyperproteinemia Hyperlipidemia With elevated AG: Ethylene/propylene glycol Methanol Ketoacidosis Lactic Acidosis

Anion Gap = (Na⁺) – (Cl⁻ + HCO₃⁻)
*Normal 8-16 (avg = 12)

Osmol Gap = Osm_{plasma} - Osm_{calc}
*Normal ≤10, but wide variability, so interpret with caution

Osm_{calc} = 2×[Na⁺] + [BUN]/2.8 + [gluc]/18 + [EtOH (mg/dL)]/4.6

DECONTAMINATION THERAPIES

- Activated Charcoal
 - Most effective if given when substance is **still in stomach** (usually considered to be **within 1h of ingestion**, but data is lacking)
 - Not useful for: cyanide, lithium, ethanol/methanol, glycols, mineral acids (e.g. sulfuric acid, nitric acid), alkali metals (potassium, magnesium, sodium, including sodium hydroxide [Drano]); iron; ammonia
 - Other therapies not routinely used: whole bowel irrigation (with polyethylene glycol), gastric lavage, Ipecac
- Dialysis and Acid/Alkaline Diuresis (consult Nephrology):

Dialyzable Toxins	Acid Diuresis →give Vitamin C	Alkaline Diuresis →give NaHCO ₃
Methanol, isopropyl alcohol (rarely EtOH) Glycols Acetone Lithium Salicylates Barbiturates INH Atenolol, sotalol	Quinine PCP	Phenobarbital Salicylates Methotrexate TCAs

Gastroenterology

Upper GI Bleeding

MGH GI Taskforce Protocol for Acute Upper GI Bleeding Management

- **Criteria:** BP <90 and HR >100 x2 30min apart; Hct <20/Hgb <7 regardless of vital signs, and evidence of active significant bleed in 12hrs; require >2L IVF or 2U pRBCs to prevent instability/keep Hct >25; ATLS hemorrhagic shock class III; clinical judgment
- **Consults:** page/call GI fellow; call Med Sr for MICU bed; consult Trauma team and/or Interventional Radiology when needed
- **Resuscitation:** crystalloid IVF via 2x 18G or larger PIVs; pRBC to keep **Hb >7** or Hb >8 if co-morbidities (i.e. CAD); IV PPI (+ octreotide if portal HTN), fix coagulopathy if needed
- **Urgent EGD in the ICU:** performed after effective resuscitation and securing safe airway; ideally w/in 8 hr. If no ICU bed, should be performed in ED Acute (sedation and intubation if needed); IV erythromycin/azithromycin is recommended 30 mins prior to EGD

URGENT ASSESSMENT & MANAGEMENT OF GI BLEEDING

- Assess & reassess V/S for hemodynamic stability
- Attempt to quantify **amount & rate** of blood loss; NGT Cl with varices
- **≥2 PIV** (18G or larger) – rarely done by IV nurse; look at their arms (green = 18; pink = 20; blue = 22)
- **Type & screen** (type & cross if plan to transfuse), **IVF** (and blood if indicated): liberal transfusion if active bleed or unstable VS. Hct drop lags 24-72h from onset of bleeding
- **Correct coagulopathy:** IV vit K, FFP (if INR >1.7), Plt, PCC. If severe/life-threatening, consider reversal agent. If uremic, consider ddAVP (0.3 mcg/kg); if ESLD avoid FFP (\uparrow volume $\uparrow \rightarrow$ portal pressure) as INR not accurate in these patients
- **Transfusion goals:** **Hb >7** (avoid overtransfusion if EVs), Plt >50k, INR <2 (unless ESLD), PTT <50, Fibrinogen >100
 - See [Transfusion Medicine](#) for **Massive Transfusion**; generally start after 4U
- **GI consult** for EGD and/or colonoscopy (make NPO)
- **Surgery or IR consult** if hemodynamic instability or difficult endoscopic correction
- **Intubation:** if large volume hematemesis, AMS, variceal bleeding requiring balloon tamponade

Etiologies of Upper GIB ([Dig Dis Sci 2018;63:1286](#))

- **PUD** (~50%; duodenal>gastric): H. pylori, NSAID, ETOH, Tobacco, Cameron lesion (in hiatal hernia), ZE
- **Varices** (~5%): EVB (esophageal) > gastric
- **Esophagitis or gastritis** (~30%): GERD, pill, ASA, NSAIDs, clopidogrel, EtOH, infectious
- **Vascular malformation** (~5-10%): Dieulafoy's, AVM, GAVE, HHT, XRT, aortoenteric fistulae
- **Traumatic** (~5%): Mallory-Weiss, foreign body, Boerhaave's
- **Neoplastic** (~5%): primary > metastatic
- **Post-procedural** (varies): polypectomy, sphincterotomy
- **Biliary**: hemobilia, hemosuccus pancreaticus

High Risk Features in UGIB

- Hypotension
- Tachycardia
- Coagulopathy (INR > 1.5)
- AMS
- Syncope
- Age > 65
- Liver Dx
- CHF

ACUTE UPPER GI BLEEDING ([Annals 2019;171:805](#); [NEJM 2016;374:2367](#))

- **Definition:** bleeding proximal to ligament of Treitz
- **S/Sx:** hematemesis, melena (+LR 25); brisk UGIB can p/w hematochezia, orthostasis; BUN/Cr >30 (\oplus LR 7.5; [JAMA 2012;307:1072](#)), especially >35 (100% Sp; [J Clin Gastro 1990;12:500](#))
- **Risk stratification** (30d mortality): New [ABC score](#) better at classifying than AIM65 ([Gut 2020](#)); [Glasgow-Blatchford Score](#) recommended over [AIMS65 \(Annals 2019;171:805, BMJ 2017;356:6432\)](#); [Machine Learning Scoring System](#) w/ >Sp (100%) than both ([Gastro 2020;158:160](#))
- **Management:** EGD generally within 24hrs (debated), but no Δ in outcomes if between 0-6hrs vs. 6-24hrs for non-variceal or -HDUS bleeds ([NEJM 2020;382:1299](#)); TXA/amicar: no Δ bleeding/mortality, \uparrow VTE risk especially in ESLD ([Lancet 2020;395:1927](#))
- **Prognosis:**
 - **PUD rebleeding w/o med management:** 90% if active bleed, 50% if visible vessel, 30% if clot, 20% if oozing, else < 10%
 - **Esoph variceal bleed:** 40-50% resolve spontaneously; 30% mortality \rightarrow 70% if continued bleeding; 60% risk re-bleeding overall

Pre-EGD

Post-EGD

- | | |
|--|--|
| <ul style="list-style-type: none">- Transfusion: Hb >7 (NEJM 2013;368:11). Consider higher threshold if CVD (Annals 2019;171:805). Avoid overtransfusion in variceal bleed – can \uparrow portal pressures and worsen bleeding- IV PPI: \downarrow high-risk lesions requiring endoscopic therapy, but unclear clinical impact pre-EGD (Cochrane Rev. 2010)- IV erythromycin or azithromycin: 250mg 30m prior to EGD \uparrow gut motility & visualization (AJG 2006;101:1211)- If cirrhosis: IV octreotide: 50 mcg x1 \rightarrow 50 mcg/hr + IV CTX 1g q24hr x7 days for ppx against bacterial infections (Gastro 2006;131:1049; APT 2011;34:509); stop β-blockers- ddAVP (if uremia) | <ul style="list-style-type: none">- If high risk PUD, intensive PPI x72 hr \rightarrow \downarrow re-bleeds & need for repeat EGD; pantoprazole 40mg IV BID (intermittent dosing non-inferior to bolus+gtt; JAMA IM 2014;174:1755). Oral PPI may replace IV PPI. D/c with Oral PPI QD x8weeks- Treat H. pylori if positive- If variceal bleed: continue octreotide x 3-5d, consider TIPS or BRTO if refractory to EGD- If angiodysplasia: consider long-term octreotide (APT 2012;36:587), bevacizumab or thalidone w/ GI help- If re-bleed: repeat EGD, consider angiography, surgical/IR consult. If variceal, consider balloon tamponade, TIPS, BRTO |
|--|--|

Management of anticoagulation/antiplatelet agents (ASGE: [Gastrointest Endosc 2016;83:3](#))

Warfarin: hold during bleed; resume after hemostasis (w/ UFH bridge at ~48hrs if indicated; see [Hematology: Anticoagulation Bridging](#) section); \downarrow risk of thrombosis, death in AF if resumed w/in 7d ([Am J Cardiol 2014;113:662](#))

DOAC: hold during bleed; no data to guide, but generally resume 48-72hr after hemostasis

ASA: continue during bleed if low-moderate risk, hold if high risk (unless recent PCI/ACS – see below); **resume** in pts w/ CAD (2° prev.) after hemostasis, best if w/in 1-7d; \uparrow risk of 30d mortality if not resumed ([Annals 2010;152:1](#)); if PUD, add PPI to \downarrow risk of bleeding **DAPT for PCI/ACS:** d/w cardiologist; generally if very recent (<30d PCI, <90d ACS) continue both unless life-threatening; if more distant, continue ASA but less risk in holding P2Y2i. Resume w/in 1-7d if able, esp if low rebleed risk

In general, restarting AC/AP sooner $\downarrow \rightarrow$ risk of vasc. events, though \uparrow risk of bleeding ([APT 2019;50:8](#))

Gastroenterology

Lower GI Bleeding

ACUTE LOWER GI BLEED (NEJM 2017;376:1054)

- Definition:** hematochezia from colon or rectum; classically, distal to lig. of Treitz
- Sx:** hematochezia (maroon stools, bright red blood, or blood clots); less commonly melena (dark, sticky; requires that blood spend 14hr in GI tract) Stool appearance is a poor indicator of bleeding source; hematochezia can also be seen with brisk UGIB
- Diagnosis:**
 - Exonerate UGIB first with EGD if brisk bleed/hemodynamic instability (10-15% of patients with severe hematochezia)
 - Consider NGT if moderate suspicion for UGIB (not done often at MGH; contraind. with hx of varices)
 - Coffee-ground material, bright red blood → EGD
 - No blood or bile seen: indicates indeterminate source → consider EGD before colonoscopy
 - Bilious fluid: no active UGIB source → colonoscopy
 - Colonoscopy is mainstay of diagnostic therapy; imaging can also be used to help localize active bleed
 - CT angiography: (bleeding rate 0.3-0.5mL/min); available, fast, minimally invasive; first line ([ACR Approp. Criteria](#))
 - IR angiography: (>0.5 mL/min); allows for intervention (e.g. embolization) but risk of bowel ischemia, vascular injury

History	Etiologies (NEJM 2017;376:1054)
Painless	Divertic. (30-65%), angioectasias (5-10%), hemorrhoid (5-20%)
Abd. pain	IBD (3-5%), ischemic colitis (5-20%), perforation
Weight loss	Malignancy (2-15% neoplasm or polyp), IBD (3-5%)
Fever/diarrhea	IBD (3-5%), acute mesenteric ischemia, infectious colitis (2-5%)
AS/ESRD/LVAD	Angioectasias (5-10%)
Recent colo.	Post-polypectomy (2-7%)
Constipation	Stercoral ulceration (0-5%)
Abd/pelvic XRT	Radiation proctopathy/colitis (0-2%)
NSAIDs	NSAID-induced colopathy (0-2%)
Liver disease	Colorectal varices (0-3%)
AF	Acute mesenteric ischemia
Prior GI surgery	Anastomotic ulcers
AAA repair	Aortoenteric fistula
HDUS(↑HR,↓BP)	Brisk UGIB (13%)

- Risk stratification:**
 - New ABC score (age, blood test, comorbidity) can predict 30d mortality for lower GI bleed ([Gut 2020](#))
 - Oakland Score: Age, Sex, Prior GI admission, DRE, HR, BP, Hgb; Score >8 consider admission ([Lancet 2017;2:635](#))
- Management:** ([ACG Guidelines](#), see Figure 1 for flow chart)
 - Transfusion goals: Hgb >7 (consider >9 in active CAD), Plt >50k, INR <1.5 (INR 1.5-2.5 ok to perform endoscopic hemostasis before reversing; INR >2.5 consider using reversal agent)
 - Initial labs: CBC, CMP, coags, T&S; trend Hgb Q2-8 hrs depending on severity of bleed
 - IF HEMODYNAMICALLY STABLE: prep for colonoscopy (after discussion with GI); need 8 hrs w/o solid food prior
 - If ongoing bleeding or high risk, colonoscopy within 24hr; order set "Gastroenterology Bowel Prep" → "Suprep" ([Am J Gastro 2019;114:305](#))
 - Colonoscopy at 24-36hrs may be a safe approach in most stable patients ([Gastro 2020;158:1](#)); remains controversial, may reduce identification of stigmata of recent hemorrhage, ↑LOS
 - For refractory angioectasias, can treat with thalidomide and bevacizumab
 - IF HEMODYNAMICALLY UNSTABLE: EGD to r/o UGIB causing brisk hematochezia followed by urgent colonoscopy, IR (embolization), surgical consult (subtotal colectomy if cannot locate colonic bleed), massive transfusion protocol
 - Diverticular hemorrhage, angioectasia, post-polyp. bleed, hemorrhoids, rectal varices amenable to endoscopic treatment
 - Anticoagulation/antiplatelet management: generally extrapolated from UGIB data
 - ASA for 1° prev. should be stopped & generally not resumed. ASA for 2° prev. should not be held; if it is, should be resumed soon after bleed resolves ([Gastro 2016;151:271](#)). If on DAPT for recent PCI/ACS (<30d PCI, <90d ACS), should continue unless life-threatening bleed. If less recent, can likely hold P2Y12i for 1-7d, d/w cardiologist

UNIDENTIFIED SOURCE AFTER EGD/COLONOSCOPY: ~75% small bowel, 25% UGIB/LGIB (ACG: [AJG 2015;110:1265](#))

- Small bowel causes:** Angiectasia (20-30%), IBD (esp. <40), Dieulafoy's, neoplasm, Meckel's (esp. <40), polyposis synd. (esp. <40), NSAID ulcers Rare: small bowel varices, portal hypertensive enteropathy, amyloid, HHT, Kaposi, inherited connective tissue disorders & congenital vascular abnormalities; rare non-small bowel: aortoenteric fistula, hemobilia, hemosuccus pancreaticus
- Diagnosis/management:** ([ASGE 2017;85:22](#), see Figure 1 for flow chart)
 - Video capsule (VCE): 1st line; dx in 38-83%, may miss duodenal/prox. jejunal lesions; contraind. if strictures (retention)
 - 2nd look EGD ± push enteroscopy (prox 60cm jejunum) if recurrent UGI sx; 2nd look colo. if recurrent hematochezia
 - CT/MR enterography: CTE if ⊖VCE or if risk of strictures (IBD, XRT, prior SB surgery, suspected stenosis); CTE>MRE
 - Deep enteroscopy: if strong suspicion of SB lesion and therapy required; can use to intervene after ⊕VCE
 - If brisk bleed: CTA if stable, angio. if unstable; can intervene w/ embolization, enteroscopy, or surgery
 - If no source identified: iron repletion, consider octreotide, antiangiogenic tx; replace AV if Heyde's & ongoing bleeding

Gastroenterology

Abdominal Pain

Anatomic Approach to Acute Abdominal Pain Adapted from (Am Fam Physician 2008;77:971)		
Right Upper Quadrant Liver pathologies (hepatitis, abscess, Budd-Chiari, portal vein thrombus, Fitz-Hugh-Curtis) Biliary pathologies (cholelithiasis, cholecystitis, cholangitis, Sphincter of Oddi dysfunction) Extra abdominal: PE, PNA, CHF	Epigastric Pancreatitis Gastric pathologies (esophagitis, GERD, dyspepsia, PUD, gastritis, gastroparesis) Mesenteric ischemia Extra abdominal: MI, Aortic dissection	Left Upper Quadrant Spleen pathologies (splenomegaly, abscess, infarction, rupture, trauma) Gastritis, PUD Subdiaphragm or abdominal abscess (either side)
Right Lower Quadrant Appendicitis, lymphadenitis	Periumbilical Early appendicitis PUD, bowel obstruction (SBO > LBO) Umbilical Hernia	Lower Quadrant Intestinal pathologies (diverticulitis, colitis, constipation, IBD, IBS) Renal pathologies (nephrolithiasis, pyelonephritis) Pelvic pathologies (ectopic, fibroids, cyst, endometriosis, torsion, PID, abscess, epididymitis) Hernia Hematoma
RED FLAGS of abdominal pain <ul style="list-style-type: none"> • HDUS, rigidity, guarding, or rebound • "Pain out of proportion" • Gross distention + cannot tolerate PO • Bilious emesis, hematemesis, hematochezia • "Tinkling" or absent bowel sounds "Can't miss" Dx: vascular infarct, perforation, extra-intestinal hemorrhage, obstruction, ectopic pregnancy	Diffuse Obstruction, perf, ischemia, AAA Peritonitis, gastroenteritis, dietary SBO, LBO, SBP, toxin, meds (iron), cancer Ketoacidosis, adrenal insufficiency FMF, hereditary angioedema, AIP	
	Suprapubic Cystitis, prostatitis, urinary retention	

Key elements of H&P Pain history: Δ w/ eating or BMs, Δ BMs, jaundice, recent medications (NSAID, abx), surgeries Special pops: immunosuppressed, sexually active, elderly (Am Fam Physician 2006;74:1537) Exam: distention, abdominal veins, caput medusa, rigidity, guarding, rebound pain, percussion pain, Carnett's sign (AJG 2017;112:760), Castell's sign, McBurney's point, Rovsing's sign, obturator sign, HSM, flank/shifting dullness, DRE	Imaging/Testing (ACR Appropriateness Criteria) <ul style="list-style-type: none"> • Acute, nonlocalized with fever: CT AP I+ • Epigastric pain, suspected PUD: H.pylori stool antigen, EGD • RUQ, suspect biliary: RUQUS followed by MRCP w/ clinical suspicion • RLQ, suspect appendicitis: CT AP I+ vs Ultrasound • Lower quadrant, suspect diverticulitis: CT AP I+ • Lower quadrant/flank, suspect kidney stone: CT AP I- • Suspect bowel obstruction: CT AP I+ over plain film (no need for PO contrast) • Suspect mesenteric ischemia: CTA AP • Lower quadrant/pelvic, b-hCG+: pelvic and transvaginal US • AAA suspected: HDS stable→CTA AP; HDUS→STAT surgery consult
Initial Tests to Consider BMP, Ca, Mg, CBC w/ diff, LFTs, lipase, lactate, ESR/CRP, UA, b-hCG, troponin, coags, T&S Infectious studies as appropriate including COVID-19 (Gastro 2020;159:320)	

IMAGE NEGATIVE ABDOMINAL PAIN

Metabolic: DKA, Ca, uremia, heavy metal, AI, AIP

Meds/Toxins: EtOH, opioids/opioid withdrawal, cocaine, anticholinergics, lead/heavy metal

Functional: IBS, abdominal migraine, functional dyspepsia

Episodic: Passed stone, sphincter of Oddi dysfunction

Other: angioedema, VZV, eos, gastritis, polyradiculopathy, abdominal epilepsy

Centrally Mediated Pain Syndrome (CAPS) and Narcotic Bowel Syndrome (NBS) ([Gastro 2016;150:1408](#))

CAPS: multimodal approach with clear boundaries + goals. Trial SSRI (least analgesic), SNRI, or TCA for 4-6 weeks → dose titration → potentially dual therapy. Early psychologic, behavioral, or mindfulness referral (such as [Benson-Henry Institute](#) at MGH). Psychiatry referral for refractory patients.

NBS: reduce opioid while controlling pain (consider antidepressants and nonpharmacologic therapy). Patient education key, esp. re: hyperalgesia. Expert consensus favors inpatient opioid detox, though only small studies ([AJG 2012;107:1426](#))

Common Etiologies of Chronic Abdominal Pain Adapted from (Chronic Abdominal Pain 2015)		
Visceral	Somatosensory	Functional
Chronic pancreatitis, IBD, mesenteric ischemia, adhesions, cancer, pelvic etiologies	Anterior cutaneous nerve entrapment (PE: Carnett sign), myofascial pain, slipping rib syndrome, radiculopathies, post-herpetic, diabetic neuropathy	Centrally mediated (functional) pain, functional dyspepsia, IBS, narcotic bowel syndrome (NBS)

Gastroenterology

GERD & Peptic Ulcer Disease

GASTROESOPHAGEAL REFLUX DISEASE (GERD) (ACG: [AJG 2013;108:308](#), AGA: [Gastro 2008;135:4](#))

Signs & Sx: “heartburn” w/ food (i.e. spicy foods, coffee, soda, chocolate, EtOH) or position (reclining), regurgitation, sour taste after awakening, sore throat, dysphagia, globus, chronic cough/throat clearing, hoarseness, asthma exacerbation, chest pain

- Alarm symptoms: dysphagia/odynophagia, wt loss, GIB, IDA, persistent vomiting, anorexia, new onset age ≥60

Ddx: infectious esophagitis, pill esophagitis, eosinophilic esophagitis (EoE), motility disorder, reflux hypersensitivity/functional dyspepsia

Evaluation: if sxs suggestive of GERD, PPI trial is dx test of choice (though has limitations: Sn 78% / Sp 54%; [Annals 2004;140:518](#))

- If alarm symptoms → EGD w/ biopsy: look for tissue damage and/or complications, alternative DDx (i.e. EoE, malignancy)
- Ambulatory pH monitoring/impedance testing: if endoscopy ⊖ but persistent symptoms
- Esophageal manometry: if GERD sx w/ CP and/or dysphagia and normal EGD → assess for motility disorder

Management: ([Gastro 2018;154:302](#))

- Lifestyle Δs: wt loss (goal BMI <25), tobacco cessation, drinking <2 cups of coffee/tea/soda, “prudent” diet (i.e., high intake of fruits, vegetables and whole grains); ≥30 min exercise daily, no eating 2-3 hours before bed ([JAMA IM 2021;e207238](#))
- PPIs: > than antacids/H2RAs for sx relief in empiric tx and optimal for erosive esophagitis ([Cochrane Rev 2013](#))
 - Start low-dose PPI (e.g. 20mg omeprazole) 30min before AM meal. Reassess 4-8wk, uptitrate to high-dose (e.g. 40mg omeprazole), then BID if no relief. Assess at 8w if able to d/c
 - Maintenance PPI: if continue to have sx after PPI discontinued or if severe complications (erosive esophagitis, Barrett's)
 - Discontinuing PPI: if on PPI >6mo., taper by 50% per wk to prevent rebound hypersecretion
 - PPI risks: probable association: Mg wasting (↑QTc), AIN, iron deficiency; possible association (controversial) C.diff/other enteric infxn, ↑ risk of osteoporosis, CKD, ([Gastro 2017;152:706](#)); no demonstrated risk of dementia ([Gastro 2020;115:671](#))
- H2RAs (ranitidine, famotidine): can be given for nighttime sx PRN w/ PPI, tachyphylaxis common after wks
- Others: PRN antacids, sodium alginate ([APT 2013;38:1059](#); [APT 2014;39:595](#)), baclofen (as adjunct)

Severe/Refractory Symptoms:

- If no relief after 8w on high-dose BID PPI, refer for EGD/impedance testing & consider alternative dx such as functional dyspepsia (symptoms >3mo; [Gastro 2020;158:2286](#)), NERD, reflux hypersensitivity, EoE, rumination (effortless regurgitation), hiatal hernia
 - EoE: dysphagia, GERD sx, food impaction; a/w allergic conditions. Eos on bx. PPI, topical steroids ([Gastro 2020;158:1776](#))
 - Hiatal hernia: Type I (sliding)– asx; Type 2-4 (paraesophageal hernias) – refractory GERD; surgery controversial
 - Reflux hypersensitivity: dx w/ pH impedance w/ acid exposure time <4% + reflux symptom association (normal manometry)
- Gastric fundoplication may be superior to medical tx for refractory heartburn ([NEJM 2019;381:1513](#))

Complications:

- **Barrett's Esophagus (BE)**: squamous epithelium → columnar intestinal epithelium. **AdenoCA** risk 0.1-2%/yr. Screen w/ EGD in: men w/ chronic (>5yrs) or freq. (>weekly) GERD sx + ≥2 RFs (>50, white, central obesity, tobacco hx, FH of BE or adenoCA) ([AJG 2016;111:30](#)). Mgmt: indefinite PPI; some evidence for NSAIDs/ASA ↓ risk of CA ([Lancet 2018;392:400](#))
- **Esophageal stricture**: p/w progressive solid food dysphagia. Endoscopy w/ biopsy can differentiate stricture from cancer

PEPTIC ULCER DISEASE (PUD) ([BMJ 2019;367:l5495](#); [Lancet 2017;390:613](#))

Signs & Sx: intermittent gnawing, dull, aching, or “hunger-like” epigastric pain relieved w/ antacids though 70% are asx; duodenal ulcers p/w pain 2-5hrs after meal & at night (persistent acid w/o buffer). **Associated sx:** early satiety, bloating, n/v

Etiology: 90% caused by *H. pylori* or NSAIDs. **Others:** meds (bisphosphonates, steroids, clopidogrel, sirolimus), ZES, mastocytosis, HSV, CMV, EBV, fungal infxn, post-surgical, XRT, ischemia (crack cocaine), Crohn's, sarcoid, critical illness

Ddx: other causes of dyspepsia: biliary disease, gastric CA, celiac, chronic pancreatitis, drug-induced, functional dyspepsia

Evaluation: *H. pylori* testing in all w/ dyspepsia; if >60 → EGD to exclude CA ([AJG 2017;112:988](#))

- ***H. pylori* testing**: Stool Ag or urea breath test (not avail. at MGH) preferred to assess for active infection though affected by PPI & abx (↑ false ⊖). Serology (IgG) not affected by PPI/abx/bismuth but cannot accurately distinguish active vs. past infection; a ⊖ serology is helpful in excluding infection if low pre-test probability. Bx w/ urease, histology, cx
- **EGD**: biopsy malignant-appearing & select benign-appearing ulcers; obtain samples for *H. pylori* testing

Management: PPI (duration depends on etiology), add sucralfate if duodenal ulcer 2/2 ↑ acid, *H. pylori* tx, d/c offending agents; if need to continue ASA, continue w/ PPI ([NEJM 2005;352:238](#); [Gastro 2010;138:82](#)). F/u EGD after 8-12w if refractory sx (see below) or gastric ulcer w/o clear etiology ([Gastrointest Endosc 2010;71:663](#))

H. pylori treatment: ([Gastro 2017;112:2](#))

- First line = **quadruple therapy** (if clarithromycin resistance >15%): PPI BID, bismuth 300mg QID, tetracycline 500mg QID (alternative: doxy 100mg BID), metronidazole 500 QID x 14d. Combo pill (Pylera) available; add PPI BID for quad tx
- Triple therapy: clarithromycin 500mg BID, amoxicillin 1g BID (or flagyl 500mg TID if PCN-allergic), PPI BID x14d. Addition of bismuth may ↑ eradication ([CGH 2020;18:89](#))
- **Confirmation of eradication**: stool Ag, urea breath test (not avail. at MGH) or EGD >4 wks after completion of abx and PPI

PUD: ulcer that does not heal after 8-12wks adequate tx; 5-10% of ulcers are refractory to PPI tx

- Ensure *H. pylori* eradicated, NSAIDs & other contributing meds discontinued. Test for ZES w/ fasting serum gastrin (↑ if on PPI, recheck 1 week s/p cessation); secretin stimulation test if non-diagnostic

- Continue PPI x additional 12w and then reassess w/ EGD. If still refractory, surgical tx: resection, vagotomy, partial gastrectomy

Complications and Management: ulcer consider **complicated** if any of the following are present: **Bleeding**: see [Upper GI bleeding](#).

Perforation: IVF, IV PPI, abx ± surgery. **Penetration.** Gastric outlet obstruction: pyloric channel/duodenal ulceration → spasm, edema, inflammation, dysmotility → fibrosis/scarring; Tx: IVF, correct electrolytes, NGT; may need endoscopic dilatation or surgical tx if persists w/ medical mgmt

Gastroenterology

Nausea & Vomiting

GENERAL APPROACH TO PATIENT WITH NAUSEA/VOMITING ([Gastro 2001;120:1](#))

- (1) Seek out etiology. Make sure to consider chronicity & comorbidities
- (2) Treat underlying cause if possible; symptom management based on underlying etiology
- (3) Anticipate and address complications of N&V (aspiration, volume depletion, hyperchloremic metabolic alkalosis, hypokalemia, MW tear)

Evaluation	Etiologies (VVOOMMIIITING)		Receptor	Targeted treatment	
History <ul style="list-style-type: none"> - Acute <1mo. or chronic (AJG 2018;113:5) - Relation to time of day - Triggers: relation to POs, recent foods/meds, sick contacts, headache, head trauma, last BM - Hematemesis, melena - Abd pain, heartburn - Prior abd surgery - CP, SOB, diaphoresis - Vertigo, uncontrolled DM Labs to consider <ul style="list-style-type: none"> - BMP, LFTs, lipase - hCG, UTox, VPAIN - UA, ABG, lactate - Cort stim - Troponin Studies to consider <ul style="list-style-type: none"> - KUB - EKG - CT abdomen (I+/O+) - Barium swallow or EGD - Gastric emptying study - CT head "Can't-miss" diagnoses <ul style="list-style-type: none"> - SBO, mesenteric ischemia - Cardiac ischemia - Pancreatitis, pyelo, cholecystitis - Pregnancy - AI, DKA - ↑ ICP 	Vestibular & Vertigo	Acute/gait instability; Labyrinthitis, BPPV, vestibular neuritis, Meniere's disease	ACh H ₁	Scopolamine, dimenhydrinate, diphenhydramine, meclizine, Dix-Hallpike → Epley maneuver	
	Obstruction	Adhesions, hernia, volvulus, constipation, gastric outlet obstruction	Multiple	Prochlorperazine, ondansetron, bowel rest, NGT, IVF, surgery consult, serial exams/KUB, NO metoclopramide (risks perf)	
	Operative	Post-op nausea/vomiting (Risk factors: F > M, nonsmoker, post-op opioids, hx of condition, type of surgery), 1/3 cases	Multiple	Serotonin antagonist, aprepitant, dexamethasone (use 2 in combo as ppx if 3+ RFs), gabapentin	
	Motility	Gastroparesis (common in uncontrolled DM), autonomic dysfunction, cyclic vomiting syndrome, chronic idiopathic nausea (see Motility Disorders)	D ₂ (periph)	Low fat & insoluble fiber diet, metoclopramide, erythromycin (tachyphylaxis after 4 wks; motilin agonist), diphenhydramine, cannabis abstinence, TCAs, gabapentin, olanzapine, benzos, SSRI/SNRI	
	Meds (drugs & withdrawal)	Antibiotics, AEDs, chemo, opioids, cannabis hyperemesis, anti-arrhythmics	D ₂ (central)	Stop offending med if possible, prochlorperazine, haloperidol	
	Inflammation/Infection/Ischemia	Chemo, XRT, bowel ischemia, gastroenteritis, PUD, hepatitis, pancreatitis, cholecystitis, pyelonephritis	5-HT ₃ NK1	Ondansetron, prochlorperazine, dexamethasone, olanzapine & aprepitant (chemo), treat underlying disorder (antibiotics, surgery, etc.)	
	Toxins	Uremia, ketoacidosis, hypercalcemia, food poisoning, hypo/hyperglycemia	D ₂ (central)	Prochlorperazine, haloperidol, treat underlying disorder	
	Intracranial	Elevated ICP, migraine, meningeal irritation, acute glaucoma	ACh H ₁ 5-HT ₃	Dexamethasone (if ↑ICP), treat underlying disorder	
	Nerves	Anxiety, depression, anticipatory nausea, pain	Multiple	Lorazepam (anticipatory N/V), dexamethasone, pain control	
	Gums/mouth	Mucositis thrush, oral HSV	Multiple	Treat cause; magic mouthwash	
Management	Recep.	Med	Dose	QTc	Other side effects
Address underlying cause while treating sxs <ul style="list-style-type: none"> - Non-pharm options: Acupuncture, meditation, ginger root, inhaled alcohol (AEM 2018;72:2) - Chemo PPX: dex ± lorazepam ± ondansetron ± aprepitant ± olanzapine (NEJM 2016;375:134) - Adhesive SBO (prior GI surg): conserv. mgmt x 48h (NGT, NPO) → gastrografin per NGT ↓ surgery by 74% (BJS 2010;97:470) 	5HT ₃	Ondansetron (Zofran)	4-8 mg PO/IV q8h	↑	constipation, HA
		Palonosetron (Aloxi)	0.075-0.25mg IV x1	-	more potent
	D ₂	Metoclopramide (Reglan)	10-20 mg PO/IV q6-8h	↑	EPS (black box), dystonia (peripheral), promotility agent
		Prochlorperazine (Compazine)	5-10 mg PO/IV/PR q6h	↑	EPS, sedation
		Haloperidol (Haldol)	0.5-4 mg PO/IV q6h	↑	EPS, sedation
	Cortical	Dexamethasone (Decadron)	4-8mg PO q4-6h	-	Psychosis, CHF, ↑appetite
		Lorazepam (Ativan)	0.5-2 mg PO/IV q6h	-	Delirium, sedation
	NK ₁	Aprepitant (Emend)	125mg day 1, 80mg days 2-3	-	CYP3A4 inhib, GI upset
	CB ₁	Dronabinol (Marinol)	2.5-10 mg q4-6h	-	Dysphoria, asthenia, ↑appetite
	5HT _{2A} , D ₂	Olanzapine (Zyprexa)	5-10mg PO QD	↑	Metabolic (wt gain, ↑lipids); ↑ mortality in dementia (black box)
	H ₁ ,ACh, D ₂	Promethazine (Phenergan)	12.5-25 mg PO/IV/PR q4-6h	-	EPS, sedation , tissue injury (black box)
	ACh,H ₁	Scopolamine	0.3-0.6 mg q24h	-	Delirium, sedation, dry mouth, urinary retention, ileus, blurry vision
		Hyoscymamine	0.125-0.25 mg SL/PO/IV q4h	-	
		Diphenhydramine (Benadryl)	25-50 mg PO/IV q6h	-	

Gastroenterology

Diarrhea

ACUTE DIARRHEA: ≥3 loose stools/d for <14d (ACG: [AJG 2016;111:602](#); IDSA: [CID 2017;65:e45](#); NEJM 2014;370:1532)

- Evaluation:** small bowel (absorbs ~10L) = watery, large vol., +cramping/bloating; large bowel (absorbs 1L) = freq., small vol., painful, ± fever, blood, mucus
Exposure hx: travel, abx/hospitalization, food, sick contact, daycare
Patient features: immunocompromised, s/sx hypovolemia
- Workup:** BMP if hypovolemic; BCx if fever/ill, immunocompromised; stool Cx if severe (>6BM/d, severe pain), inflammatory, high-risk host (age >70, immunocompromised, IBD), or persistent >2w; O&P if >2w, immunocompromised, MSM; *C. diff* if RFs
- Common pathogens:** See table. Immunocompromised: CMV, *C. diff*, *Cryptosporidium*, *Isospora*, *Microsporidium*, MAC, TB, *Histoplasma*, *Cryptococcus*
- Treatment:** Volume & electrolyte repletion critical. Empiric abx: controversial; if febrile, septic, inflammatory diarrhea: FQ or azithro. Consider in age ≥70, hospitalized, serious comorbidities. **Avoid abx if suspect EHEC** as can ↑ risk of HUS. Caution w/ loperamide (OK if no fever or bloody stool). Probiotics controversial: not recommended by ACG except for post-abx diarrhea

CHRONIC DIARRHEA: ≥3 loose stools/d for >4w

5 types: secretory, osmotic, functional, malabsorptive, and inflammatory.

See table below

Evaluation: ([Gastro 2017;152:515](#); [CGH 2017;15:182](#); [Gut 2018;67:1380](#))

- Hx: freq., stool vol., tenesmus, abd pain, fever, bloating, wt loss, nocturnal sx, postprandial sx, steatorrhea, past surgical hx, travel, immunocompromised, meds, radiation
- Labs: CBC, BMP, ESR/CRP, LFTs; TSH; stool lytes (Na, K, pH), fecal calprotectin (marker of neutrophil activity)/lactoferrin (marker for fecal leukocytes), fecal fat (24-48h collection), FOBT
 - Utility of stool testing? Negative fecal calprotectin/lactoferrin rules out IBD (useful for IBD vs IBS); ⊕ FOBT w/ diarrhea suggestive of chronic infection, IBD (poor sensitivity for CRC)
 - Other tests to consider: *C. diff* (recent antibiotics), *Giardia* (common in MA)/*Cryptosporidium/Cyclospora* (travel; exposure to infants in daycares), *Microsporidium* (immunocompromised)
- Stool osmotic gap for watery diarrhea:** $290 - 2^*(\text{stool } [\text{Na}] + [\text{K}])$; normal 50-100mOsm/kg

Pathogen	Details
Viral (most cases)	
Norovirus	Outbreaks during winter; n/v prominent
Rotavirus	Daycare-associated
Adenovirus	A/w conjunctivitis + pharyngitis
Bacterial (most severe cases)	
E. coli	Toxigenic = traveler's diarrhea; hemorrhagic, O157:H7 = undercooked meats, a/w Shiga toxin, HUS
Campylobacter	Undercooked/unpasteurized foods, can be a/w reactive arthritis or GBS
Salmonella	Eggs, poultry, milk, often bacteremic
Shigella	Low inoculum, often hematochezia
Vibrio spp.	Shellfish/salt water; RF: cirrhosis
Yersinia	Undercooked pork, "pseudoappendicitis"
<i>C. diff</i>	See C. diff
Parasitic	
Giardia	In MA, outdoor streams; watery stool progressing to malabsorptive/greasy
<i>Cryptosporidium</i>	Water-related outbreaks
<i>Cyclospora</i>	Contaminated produce
<i>E. histolytica</i>	Contaminated food/water outside US, a/w liver abscesses

	Watery			Fatty	Inflammatory
	Secretory	Osmotic	Functional	Malabsorptive/Maldigestive	
Etiologies	Addison's, neuroendocrine tumors, hyperthyroid, medullary CA of thyroid, mastocytosis, microscopic colitis (lymphocytic or collagenous) , DM autonomic neuropathy, amyloidosis, bile salt (4-5%) , lymphoma, villous adenoma	Lactose intolerance, mannitol, sorbitol, magnesium, laxative use	IBS, functional diarrhea (see Motility Disorders)	<u>Malabsorption</u> : mesenteric ischemia, mucosal disease (CD, Whipple's), short gut syndrome, SIBO <u>Maldigestion</u> : bile acid malabsorption (ileal disease) or ↓ synthesis, pancreatic exocrine insufficiency	IBD, invasive bacteria/parasite (<i>C. diff</i> , <i>E. histolytica</i> , <i>Yersinia</i> , TB), ulcerating virus (CMV, HSV), colon CA, lymphoma, radiation
Mechanism	Secretagogue, rapid transit, ↓ surface area	Osmotic substance	Multi-factorial	Structural problem, mucosal disease, panc. or bile acid insufficiency	Inflammation interferes w/ function/absorption
Osmotic gap	<50	>125	50-100		
Response to fasting	No change	Improves	Variable	Improves	No change
Further Testing	Exclude infxn. +/- colo with bx (esp. if immunosupp). As appropriate: chromogranin, gastrin, somatostatin, calcitonin, 5-HIAA, TSH, ACTH stim, SPEP	Stool pH (<6), H2 breath test, laxative screen	None	Sudan stain, 24hr fecal fat (>20g likely panc dysfxn, 14-20g likely small bowel cause), stool elastase or chymotrypsin, see Celiac	Exclude infxn. ESR/CRP, calprotectin, colo w/ biopsies
Treatment	Bile salt : cholestyr. 4g QD-QID Microscopic colitis : budesonide VIP : somatostatin (octreotide 50-250 ug TID SQ) Other : opiates via mu receptor (eg loperamide 2-4mg QID, diphenoxylate 2.5-5mg QID)	D/c offending agent; dietary review	Fiber (Citrucel > Metamucil), Viberzi (+pain), Rifaximin (+bloating)	Pancreatic enzyme replacement therapy (pancrealipase 500-2500 units/kg/meal)	Abx vs. immunosuppression

Gastroenterology

Constipation, IBS, & Colonic Disorders

CONSTIPATION

Definition: dissatisfaction with defecation; at least 2 of: straining during defecation, lumpy/hard stool, sensation of incomplete defecation, manual facilitation of BM, <3 BMs per week

Etiologies

• 1° constipation:

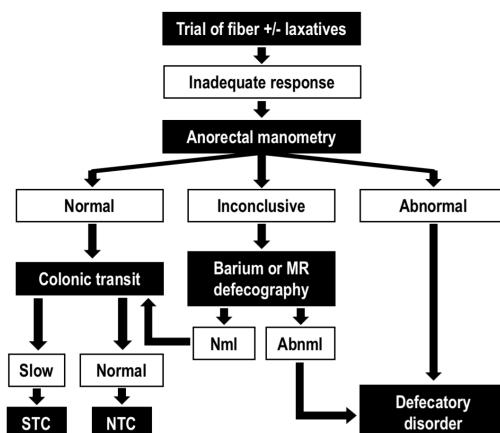
- Slow-transit constipation (STC): sitz-marker study shows delay in colonic transit; associated with bloating & pain
- Normal-transit constipation (NTC): normal testing, does not meet criteria for IBS-C, but has constipation sx
- Defecatory disorders: impaired rectal evacuation w/ normal or delayed colonic transit; inadequate rectal propulsive forces or increased resistance to evacuation (e.g. failure to relax or inappropriate contraction)
- IBS-C: see below; recurrent abd. pain or discomfort a/w hard or infrequent stools or relieved by defecation

• 2° constipation:

- Lifestyle: low fiber, sedentary
- Medications: analgesics, opioids, anticholinergics (antihistamines, antidepressants, antipsychotics), iron, aluminum (antacids, sucralfate), diuretics, clonidine, amiodarone, CCB, ondansetron
- CTD: amyloidosis, sarcoidosis
- Metabolic: ↑Ca, hypothyroid, ↓Mg, ↓K, uremia, heavy metal poisoning, pregnancy
- Neuro: autonomic neuropathy, DM, Hirschsprung's, multiple sclerosis, spinal cord injury, PD, stroke
- Obstruction: anal stenosis, colon cancer, stricture, rectocele, compression

Diagnosis/Treatment (AGA: [Gastro 2013;144:211](#); [Gastro 2013;144:218](#); [JAMA 2016;315:185](#))

- History: duration of sx, frequency & consistency of stools, straining, incomplete evacuation, use of manual maneuvers, alarm sx (sudden change in BMs in >50 y/o, blood, weight loss, strong FH of CRC), **medications**
- Initial workup: DRE (fissures, hemorrhoids, tone), CBC (for anemia); colonoscopy if +FOBT or alarm sx or fevers (or if concern for IBD/CD); other labs not needed unless otherwise clinically warranted
- Further workup (primarily outpatient): see [algorithm](#) from AGA guidelines
 - **Anorectal manometry (ARM), balloon expulsion test**: identifies defecation disorder
 - **Barium, MR defecography**: useful when ARM inconsistent with clinical impression, can identify anatomic abnormalities
 - **Colonic transit study**: via radio-opaque makers (Sitz markers) or wireless motility capsule study (less commonly used)
- Management: see medications below
 - **Secondary constipation**: treat underlying cause
 - **STC/NTC**: fiber, laxatives (PEG, stimulant); add secretory agents if persists; consider UGI eval if still no improvement
 - **Defecatory disorder**: biofeedback/pelvic floor PT; if persists, eval. for STC/NTC; surgery if structural abnormality



Hospital Constipation Prophylaxis and Bowel Regimens

- Risk factors: >60 yo, prolonged immobility, decreased fluid intake, preexisting constipation, meds (see above)
- Docusate (Colace) lacks evidence in hospitalized pts ([J Pain Symp 2000;2:130](#)) & increases cost & pill burden ([JAMA Int Med 2016;178:1216](#)); senna 2 tabs QHS > senna + colace ([J Pall Med 2008;11:575](#))
- General ppx for at-risk patients: **senna 2 tabs QHS or BID standing + Miralax 17 gm daily prn**
- High-risk ppx for patients on opioids: **senna 2 tabs BID standing + Miralax 17 gm daily standing**
- Stepwise approach: **senna → miralax → mag citrate/MOM → bisacodyl PR → enemas → disimpaction**
(NB: disimpaction can cause vasovagal syncope; all rectal procedures are contraindicated in neutropenic pts)
 - Types of enemas (stepwise): **tap water → soap suds/mineral oil → milk and molasses (MGH specific) → Fleet's**
- Avoid Mg and Phos containing products in renal insufficiency (MOM, Mg citrate, Fleet's enema) → can cause nephrocalcinosis

IRRITABLE BOWEL SYNDROME (IBS) (AGA: [Gastro 2019;157:851](#))

Definition (Rome IV Criteria): recurrent abd discomfort ≥ 1x/wk on average for 3 months a/w 2+ of the following: (1) related to defecation, (2) change in stool frequency, (3) change in stool form. No nocturnal pain, weight loss, bleeding, or ↑ calprotectin/lactoferrin

Types: IBS-C (constipation-predominant), IBS-D (diarrhea-predominant), IBS-M (mixed), IBS-U (unclassified), by [Bristol Stool Scale](#)

Epidemiology: 10-12% of US adults; ↑ risk w/ younger age, ♀ > ♂, psychosocial stressors, low QoL, hypochondriasis; gastroenteritis may be trigger. **Treatment**: all: exercise, diet Δ (low FODMAP), fiber (psyllium), rifaximin (esp. non IBS-C), anti-spasmodics (dicyclomine), peppermint oil, TCAs, CBT. IBS-C: laxatives (linaclotide, plecanatide, lubiprostone); IBS-D: eluxadoline, loperamide, alosetron (♀) (ACG: [AJG 2018;113:1](#) AGA: [Gastro 2014;147:1146](#))

COLONOSCOPY PREP

Adequate preparation = essential. Place pt on clear at noon the day prior to colonoscopy; the prep should start no later than 6PM.

SUPREP ↑ tolerability with equivalent bowel preparation vs GoLYTELY ([AJG 2019;144:305](#))

To prep: 6oz SUPREP + 10oz water → 32oz water over the following hour → repeat both steps in the morning

If stool is not clear after full prep, give additional 6oz SUPREP. Contact GI team if not completely see-through to reschedule procedure

Gastroenterology

Constipation, IBS, & Colonic Disorders

COLONIC DISORDERS

Stercoral Colitis:

- Definition:** inflammation of the colonic wall due to pressure from impacted fecal material → increased intraluminal pressures → ischemic pressure necrosis
- Epidemiology:** nursing home residents; bedridden; hypothyroidism; diabetic enteropathy; opioids; clozapine; other constipating meds
- Treatment:** fecal disimpaction if no defects in colonic wall on CT; consider as cause of sepsis in right clinical setting

Diverticulosis

- Definition:** herniation of colonic mucosa into muscularis propria, where vasa recta penetrate
 - Risk factors:** low fiber diet ± chronic constipation, obesity, physical inactivity, ↑ age (present in 50% of patients >60yo; common incidental finding), smoking, NSAIDs, red meat consumption, ♀ = ♂. Nuts, seeds, popcorn consumption is **not** associated
 - Location:** 90% L-sided (primarily sigmoid) in "Western" populations; 75-85% R-sided in Asia
 - Bleeding:** **painless** bleeding of vasa recta within the diverticuli. 75% are self-limited & resolve with bowel rest. Recurrence is common.
- Tx if bleeding does not stop: 1) endoscopic, 2) angio (IR embolization), 3) surgery. See [Lower GI Bleed](#)

- Diverticulitis develops in 4% of pts with diverticulosis

Diverticulitis

- Definition:** infection of diverticuli: micro-perforation 2/2 erosion of the diverticular wall by increased intraluminal pressure
 - Uncomplicated** (75%): abdominal pain (LLQ), fever, leukocytosis, anorexia, Δ in BMs (diarrhea or constipation)
 - Complicated** (25%): bowel obstruction, abscess, fistula (potentially with bladder, vagina, skin or peritoneum), or perforation
- Diagnosis:** characteristic s/sx + imaging findings (diverticula, bowel wall >4mm, inflammation w/in pericolic fat +/- abscess/fistula)
- Management:** (AGA: [Gastro 2015;149:1944](#))
 - Uncomplicated (medical):** PO abx x7d (Cipro/Flagyl, Bactrim/Flagyl, or Augmentin), bowel rest. Per AGA, *use of abx should be selective* (immunosupp., pregnant, significant comorbid disease, chronic steroid use, SIRS/sepsis). No abx is noninferior to abx in uncomplicated diverticulitis ([Clin Gastroenterol Hepatol 2021;19:503](#); [Br J Surg. 2019;106:1542](#))
 - Complicated (surgical):** IV abx (GNR + anaerobe coverage), bowel rest, and surgical evaluation (peritonitis typically present; evaluation for abscess drainage or colonic resection)
- Diet:** high fiber diet is recommended for patients w/ hx acute diverticulitis ([Gastro 2015;149:1950](#))
- Follow-up:** colonoscopy 6w after acute diverticulitis to evaluate for malignancy (if no colonoscopy within prior year)

MEDICATIONS FOR CONSTIPATION ([Gastro 2013;144:218](#); [JAMA 2016;315:185](#); ACG: [AJG 2014;109:S2](#))

Type	Agent	Dose	Notes
Bulk agents	Psyllium (Metamucil), Methylcellulose (Citrucel)	1tsp up to TID (for psyllium: up to 30g/d)	In some (esp. STC), can ↑ bloating in large amounts. Start low & ↑
Surfactants	Docusate (Colace)	50-360mg QD	Less effective than other laxatives; may be inferior to psyllium, not recommended (JHM 2019;14:110)
Stimulants	Senna	1-4 tabs QD or BID	↑ colon secretions, motility. Can cause cramping
	Bisacodyl (Dulcolax)	5-15 mg up to 3x/w	↑ colon motility, can cause cramping. PO QHS or PR AM
Non-absorbed substances (osmotic)	Polyethylene glycol Miralax (PEG alone) GoLyteLy/NuLyteLy (PEG+salts)	17 g QD; max 34g/d	Modestly more effective and better tolerated (less bloating) than lactulose (Cochrane Rev 2010). Dose daily. If 17g does not work, increase to 34g
	Lactulose, sorbitol	15-30 ml QD or BID	↑ flatulence/bloating. Less effective than PEG
	Milk of magnesia (MOM)	15-30 mL QD or BID	Benefit of simultaneous neutralization of gastric acidity and water retention in stool. Avoid if renal failure
	Magnesium citrate	150-300 mL QD	Exact mechanism unknown. Can be used as a lower-volume alternative to PEG bowel prep (2+ bottles + Dulcolax PR). Avoid if renal failure
Enemas	Tap water, soapsuds mineral oil, Fleet's (sodium phos.), milk & molasses	Varies	All work via lubrication. Soapsuds also stimulates peristalsis. Fleet's is hypertonic and also has osmotic effect. <u>Avoid Fleet's in elderly or renal failure (phos).</u>
Secretory drugs	Lubiprostone (Amitiza)	24µg BID for STC/NTC; 8µg BID for IBS-C	Binds Cl- channel & increases secretion, ↑ small bowel & colon transit. Most common side-effect is nausea
	Linaclotide (Linzess), Plecanatide (Trulance)	Linaclotide: 145µg QD for STC/NTC; 290µg QD for IBS-C Plecanatide: 3g daily	Guanylate cyclase-C agonists; ↑ Cl/HCO3 secretion & colonic transit
Peripheral opioid receptor antagonists	Methylnaltrexone, Naloxegol (pegylated naloxone), Alvimopan	Methylnaltrexone: 1 dose SQ QOD PRN - 38-62kg: 8mg - 62-114kg: 12 mg - CrCl <30: 1/2 dose	At MGH, methylnaltrexone approved only if on stable dose of opioids ≥ 2 weeks x3d w/o BM AND failed multiple other laxatives. Contraindicated in obstruction, small risk of perforation (AGA guidelines for OIC: Gastro 2019;156:218 ; Gastro 2019;156:229)

Gastroenterology

Motility Disorders & Celiac Disease

		OROPHARYNGEAL DYSPHAGIA	ESOPHAGEAL DYSPHAGIA
Symptoms		Difficulty initiating swallowing; drooling, coughing, aspir.	Difficulty seconds after initiation, food stuck in esophagus
Etiologies	Neuro-muscular (solids + liq.)	<u>Central</u> : tumor, stroke, PD, ALS, MS, polio <u>Peripheral</u> : neuropathy, myasthenia gravis <u>Muscular</u> : polymyositis, muscular dystrophy	<u>1^o</u> : achalasia, esophageal motility disorders (e.g. distal esophageal spasm, hypercontractile "Jackhammer" esoph.) <u>2^o</u> : diabetes, scleroderma, amyloid, Chagas (Chicago classification: Neurogastro Motil 2015;27:160)
	Structural (solids > liquids)	<u>Intrinsic</u> : tumor, XRT, trauma/surgery, Zenker's <u>Extrinsic</u> : anterior mediastinal mass, goiter, cervical spondylosis	<u>Intrinsic</u> : tumor, stricture, infxn, EoE, rings, webs (e.g. Plummer-Vinson), pills (NSAIDs, doxy, tetracyc., bisphosph) <u>Extrinsic</u> : vascular rings (e.g. dysphagia lusoria), Ao. enlarge., LA compression, mediastinal, substernal thyroid, LAD
Work-up		<u>History</u> : onset & duration, solid/liq & localization, +/- odynophagia, underlying conditions (e.g. CNS, malignancy, thyroid, DM, scleroderma), offending meds (pill esophagitis), immunocompromise (Cand., CMV, HSV esophagitis or lymphoma in HIV), radiation. Dysphagia in older adults is not normal aging <u>PE</u> : appearance (systemic disease or CNS issue), HEENT exam (evidence of LAD, tumor, asymmetry), FOB <u>Labs</u> (consider): CBC, TFTs, ANA, α -Scl-70, α -centromere, α -RNP, α -Jo, HgbA1C, iron studies, HIV, AChR-Ab	
Diagnostics		1) Modified barium swallow, ENT and neuro evals, +/- EGD to identify obstructive structural problem 2) Consider chest/neck CT to dx extrinsic compression	
Selected Conditions		Zenker's diverticulum : p/w halitosis, regurgitation of food/aspiration, cough. Tx: endoscopic surgery (rigid vs. flexible) Strictures & rings : if lumen <13mm, dysphagia common. Tx: PPI, dilation, intralesion steroid inj, stent Distal esophageal spasm : uncoordinated peristalsis a/w intermittent chest pain & regurgitation; barium swallow: corkscrew (vs. nml). Hypercontractile esophagus : similar sx; nml barium swall. Tx (both): PPI, nitrates/CCB/PDEi, TCA Infectious esophagitis : odynophagia; often immunosuppressed – Candida, HSV, CMV Eosinophilic esophagitis (EoE) : dysphagia, refractory GERD sx. EGD w/ stacked rings, strict. Bx >15 eos/hpf. Tx: PPI, diet Δ s (dairy, wheat > soy, eggs, nuts, fish), topical steroids (MDI/neb/liq.); consider dilation (AGA: Gastro 2020;158:1776) Achalasia : progressive dysphagia solids/liquids, + regurgitation ; <u>barium swallow</u> with bird's beak appearance of distal esophagus; <u>manometry</u> : absent distal peristalsis, incomplete LES relaxation; EGD to r/o pseudo-achalasia (2/2 CA); tx w/ pneumatic dilation, Heller myotomy, POEM, botox, CCBs (AGA: AJG 2013;108:1238 ; JAMA 2015;313:1841)	

GASTROPARESIS (ACG: [AJG 2013;108:18](#))

Definition: decreased gastric motility w/o obstruction

Sx: **n/v, early satiety**, postprandial fullness, bloating \pm abd pain

Etiologies: **diabetes** (vagus nerve damage 2/2 hyperglycemia), post-surgical (e.g. vagus nerve injury post-bariatric surgery), **post-viral**, systemic disease (thyroid, critical illness, Parkinson's, CTD), **meds** (opiates, CCB, anti-cholinergics)

Exam: \pm TTP in epigastrium, succussion splash (sloshing on abd auscultation)

Dx: exclude mech obstruction w/ EGD, CTE/MRE/SBFT \rightarrow gastric emptying study (hold motility meds 48h prior)

- Gastric emptying studies: gastric scintigraphy >> wireless capsule motility testing, ^{13}C breath testing; \oplus if retained solids @ 4h
 - **Indications**: post-prandial n/v, abd pain, early satiety; reflux unresponsive to therapy; patients with DM w/ poor glycemic control; evaluate for rapid gastric emptying; w/u of cyclic vomiting syndrome
 - **Contraindications**: hyperglycemia at time of test > 275 mg/dL

Labs: TSH, ANA, A1c, tot protein, alb, CBC/diff

Treatment: small meals w/ low fat & non-digestible fiber, prokinetic agents before meals (metoclopramide or erythromycin; give drug holidays due to tachyphylaxis/to assess benefit), antiemetics; venting G-tube if refractory, J-tube for nutrition if wt loss.

CELIAC DISEASE ([NEJM 2012;367:2419](#); ACG: [Gastro 2019;156:885](#))

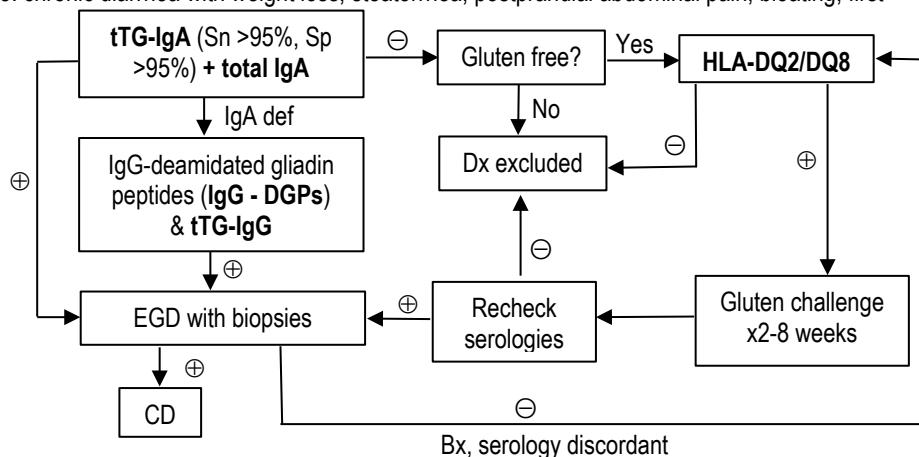
Pathophysiology: abnormal immune response to gluten \rightarrow diarrhea, wt loss, abd pain, IDA, vit D def

Who: s/sx or laboratory e/o malabsorption i.e. chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain, bloating; first degree relative; unexplained elevated LFTs; unexplained IDA; diarrhea in T1DM; dermatitis herpetiformis

Diagnosis: see **flow sheet**.

Biopsy findings: ↑ intraepithelial lymphs, elongation of crypts, villous atrophy (ACG: [AJG 2013;108:656](#))

Treatment: strict adherence to gluten-free diet; IgA anti-tTG titer should decrease and return to normal over time. Ensure no deficiency in vitamins (A, D, E, B12), Cu, Zn, carotene, folic acid, Fe \pm thiamine, vit B6, Mg, and selenium



Gastroenterology

Inflammatory Bowel Disease

Epidemiology: onset 15-40y, bimodal in CD w/ 2nd peak 50-80y. Genetic predisposition (up to 25% variance per GWAS studies; ↑ incidence in Jewish, white) + environment (↑risk: Western diet, abx, NSAIDs; smoking ↑ risk for CD & ↓ risk for UC)

Pathophysiology: defective mucosal barrier, genetic factors, effects of microbiota, impaired mucosal immunity ([NEJM 2020;383:2652](#))

	Ulcerative Colitis (Lancet 2017;389:1756)	Crohn's Disease (Lancet 2017;389:1741)
S/S	Bloody diarrhea, lower abd pain, cramps, tenesmus Extra-GI: rheum (seroneg. arthritis, sacroiliitis), cutaneous (erythema nodosum, pyoderma gangrenosum, aphthous ulcers), ophthalmic (uveitis, iritis, episcleritis), heme (DVT, AIHA), GI (PSC), GU (Ca-Ox / UA stones), pulm (bronchiectasis, ILD)	Abd pain, grossly nonbloody diarrhea, n/v, wt loss, perianal dz
Dx	Continuous colonic mucosal inflammation spreading proximally from rectum , crypt abscesses, pseudopolyps	Skip lesions (including TI & upper GI), strictures, fistulae, transmural inflamm., noncaseating granulomas , cobblestoning
Complic.	Toxic megacolon, anorectal strictures/dysfxn ↑risk CRC: colo after 8y of active disease, q1-3y w/ random 4-quadrant bx q10cm of colon; 2° amyloid	Obstruction (2/2 strictures), abscesses, fistulae, malabsorption
Classif.	Montreal Criteria: UC: proctitis/L-sided/extens.; CD: age at dx, dz location, behavior (stricture, penetrating) (Gut 2006;55:749)	

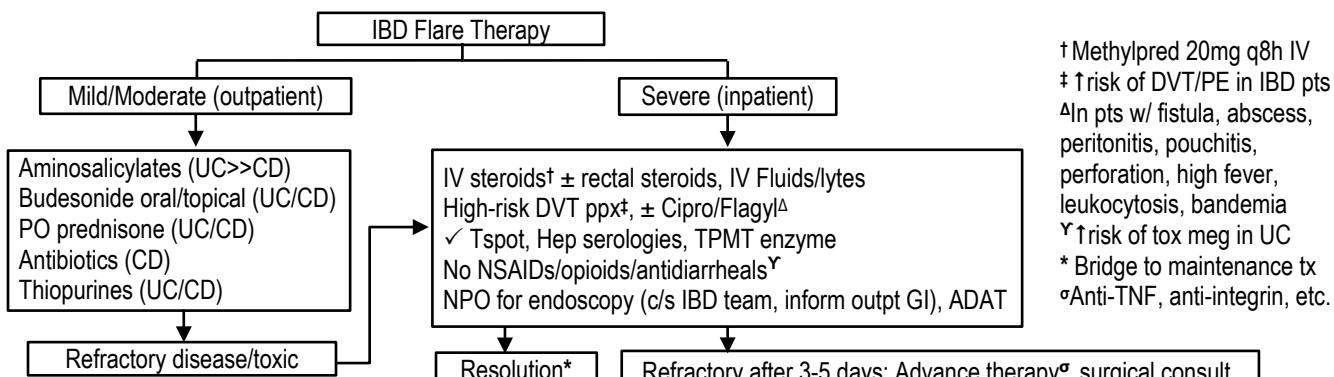
INPATIENT WORK-UP AND MANAGEMENT

Labs: CBC, Chem 10, LFTs (↑ALP→?PSC), ESR/CRP, Mg, fecal calprotectin, C. diff, Stool Cx, O&P, Fe/TIBC/B12 (if anemic). *Prior to medication initiation:* Hep serologies and TSpot (immunomodulators), TPMT enzyme (azathioprine)

Imaging: if concern for peritonitis/obstruction/mass (abscess) → KUB, CT A/P. Consider MRE to eval small intestine

Ddx: Infectious colitis, celiac disease, lactose intolerance, IBS

Severity	UC (Truelove Witts, Mayo Clinic Score)	CD (CD Activity Index)
Mild	<4 stools (bloody or not), afebrile, nml ESR, Mayo score 3-5	Ambulatory, tolerates PO/no dehydration, no pain/toxicity
Moderate	4-6 BM, bloody BM, low fever, ↑ pain, mild anemia, Mayo score 6-10	Failed 1st line tx, low fever, N/V, wt loss, pain, anemia
Severe	>6 BMs, Hb <10.5, fever, HR >90, wt loss, ESR >30, Mayo score 11-12; <u>Pred. of aggressive disease course</u> include <40 yo, disease severity, and early steroid need (Gastro 2020;158:1450)	Failed advanced tx, toxic, abscess, obstruction, peritonitis, cachexia



Indications for Surgery: CD: severe stricture, fistulae, abscess, failing medical tx. UC: refractory disease, perforation, toxic megacolon

Management Guidelines: CD: ACG: [AJG 2018;113:481](#), AGA: [Gastro 2017;152:271](#); UC: ACG: [AJG 2019;114:384](#), AGA: [Gastro 2020;158:1450](#)

Class	Drug	Use	Notes & Adverse Effects (AE)
Steroids	Budesonide (PO/PR), Pred (PO), Methylpred (IV)	Induction	PO budesonide 1st-line in mild CD, 2nd-line to ASA for mild UC, but can be 1st-line for mod. AE: osteoporosis, infection, AVN, AI, delirium
Amino-salicylates (UC>>CD)	Sulfasalazine Mesalamine (PO: Pentasa, Ascol, Lialda, Apriso. PR: Canasa, Rowasa)	Induction + Maintenance for moderate disease	Sulfasalazine: pro-drug with more AEs, also systemic effects Mesalamine forms differ in gut penetration: Pentasa (ileum, R>L colon), Ascol (R>L colon), Lialda & Apriso (pancolon), Canasa & Rowasa (distal). AE: HA, fever, rash, diarrhea, pancreatitis, ↓ sperm count, AKI
Thiopurines	Azathioprine (pro-drug) 6-MP	Induction + Maintenance	Typically as combination therapy for induction; can be monotherapy for maintenance. 6-TGN for monitoring. AE: n/v, hepatitis, BM suppression
Antimetabolites	Methotrexate	Induction + Maintenance	For pts unable to tolerate thiopurines. Typically as combination therapy. Give with folic acid. AE: n/v, hepatotoxicity, BM suppression, lung injury
Anti-TNF	Infliximab (Remicade) (IV) Adalimumab (Humira) (SQ) Certolizumab (Cimzia)-CD Golimumab (Simponi)- UC	Induction + Maintenance for mod-severe	Infliximab for induction in pts naïve to biologics. Contraindicated if toxic megacolon, pyogenic infxns. If flare during maintenance: measure trough (24hrs prior to dose) and antidirug Ab. If non-responsive despite adequate levels → another class. AE: infxn, TB/HBV reactiv., malignancy
Anti-integrin	Vedolizumab (Entyvio) (IV) (NEJM 2013;369:699 ; NEJM 2013;369:711)	Induction + Maintenance for mod-severe	Induction in pts naïve to biologics. VARSITY (NEJM 2019;381:1215): in mod-severe UC, achieved ↑ clinical remission at 52wks vs. Humira, but w/ greater steroid use. AE: infusion reactions, nasopharyngitis
IL-12, -23 inhibitor	Uztekimab (Stelara) (NEJM 2019;381:1201)	Induction + Maintenance	Consider if previously failed infliximab AE: infection, HA, nasopharyngitis, nausea, abdominal pain, arthralgias
JAK inhibitor	Tofacitinib (Xeljanz) (NEJM 2017;376:1723)	Induction + Maintenance	Consider if previously failed anti-TNFs AE: infection, herpes zoster, HA, nasopharyngitis, arthralgias
Calcineurin inhib (IV)	Cyclosporine	Induction only for severe UC	C/i in s/o toxic megacolon. Labs: troughs (q2-3d) Cr, Mg, lipids, LFTs AE: renal injury, ↑K, infxn, neurotox/seizures (esp. if ↓Mg or cholesterol)

Diet: ↓ processed foods, no unpasteurized dairy. UC: ↓ red meat. CD: ↓ saturated fats, ↑ fruits & veg ([Clin Gastro Hep 2020;18:1381](#))

Gastroenterology

Intestinal Disorders

ILEUS AND SMALL BOWEL OBSTRUCTION ([J Trauma Acute Care Surg. 2012;73:S362](#); [J Trauma Acute Care Surg. 2015;79:661](#))

	Ileus	Small Bowel Obstruction
Definition	Slow gut motility without obstruction	Obstruction of intestinal flow, can be partial or complete
Risk Factors	Intra-abdominal surgery, peritonitis, ischemia, meds (opioids, anti-cholinergics); worsened by ↓K	Prior surgery (adhesions), hernia, inflammation (e.g. IBD), malignancy, radiation, foreign body ingestion, gallstones
Signs/ Symptoms	N/V, mild diffuse pain , obstipation (↓BMs and ↓flatus), bloating/gassiness, abd distention, tympany to percussion, ↓BS , no peritoneal signs	N/V (may be bilious/feculent), severe cramping pain , obstipation, abd distention, tympany to percussion, high pitched or absent BS, dehydration, ± peritoneal signs
Studies	<u>KUB or CT</u> : dilated bowel loops, air in colon, no transition point , no peritoneal free air	<u>KUB (less useful)</u> : decompressed colon, air-fluid levels <u>CT w/ PO + IV contrast</u> : transition point, decompressed colon, ± peritoneal free air , ischemic signs, closed loop obstruction
Treatment	Bowel rest, decompression via NGT if mod/severe sx, avoid opioids, replete lytes. Methylnaltrexone if hx opioid use	<u>Initial mgmt</u> : Bowel rest, decompression via NGT for N/V and distension, IVF, replete lytes. Broad spectrum abx if c/f ischemia/necrosis or bowel perf <u>Nonsurgical mgmt</u> : Gastrografin challenge (adhesive SBO only) <u>Indications for surgery</u> : any suspicion of ischemia/necrosis or perf , closed loop obstruction (volvulus), hernia, intussusception, tumor, foreign body, gallstone, SBO persists after 3-5 days

Acute colonic pseudo-obstruction (Ogilvie's): typically elderly, hospitalized pts. A/w severe illness (e.g. sepsis, pancreatitis, peritonitis), systemic dz (thyroid, DM, renal or liver failure), neuro (spinal cord compression/trauma, PD, MS), meds (opiates, CCB, anticholinergics). Tx: conservative (NPO, IVF, NGT/rectal tube), neostigmine if cecal diam. >12 or if fail conservative tx. Colonic decomp. if fails.
(ASGE: [Gastro Endosc 2020;91:228](#))

INTESTINAL ISCHEMIA (ACG: [AJG 2015;110:18](#); [NEJM 2016;374:959](#))

	Ischemic Colitis	Acute Mesenteric Ischemia	Chronic Mesenteric Ischemia
Signs/ Symptoms	- Cramping pain (mostly LLQ) → mild/mod hematochezia - Uncommon: gangrenous bowel or fulminant colitis (uncommon)	- <u>Arterial</u> : sudden, pain out of proportion to exam - <u>Venous</u> : often insidious onset, waxing/waning abd distention, N/V , diarrhea ± occult blood	- Recurrent, post-prandial pain ("intestinal angina"); dull, crampy, starts 10-30m after PO, lasts 1-3h - N/V, early satiety, BM Δs - Wt loss, fear of eating
Pathophys. and Risk Factors	Non-occlusive (95%): - <u>Watershed areas</u> (splenic flexure, rectosigmoid) most susceptible; 25% R-sided - <u>Risk factors</u> : cardiopulmonary bypass, extreme exercise - <u>Vessels</u> : SMA, IMA - <u>Prognosis</u> : favorable, 85% spontaneously resolve in 2w, 5% recurrence	SMA occlusion (~75%): <u>embolic</u> (40-50%); AF/endocarditis/aortic plaque, <u>thrombotic</u> (20-35%): underlying ASCVD, <u>dissection/inflammation</u> (<5%) Non-occlusive (5-15%): hypoperfusion or vasospasm after CV event/surgery, cocaine, vasculitis Mesenteric vein thrombosis (5-15%): trauma, surgery, thrombophilia, local inflammation (pancreatitis, diverticulitis, biliary infxn), stasis due to cirrhosis/portal HTN, malignancy <u>Prognosis</u> : mortality 50%, but can be 70-90% if delay in diagnosis leads to intestinal gangrene	- Progressive atherosclerotic narrowing at origins of vessels - <u>Risk Factors</u> : tobacco, HTN, DM, HLD (ASCVD RFs), >60 yo, female, dissection, vasculitis, fibromuscular dysplasia, radiation - <u>Vessels</u> : SMA, IMA, celiac artery - If pain is constant, consider acute thrombosis (see left)
Diagnosis	Labs : - ↑lactate, WBC, LDH, CK, & amylase if advanced - Stool guaiac ⊕ in ~50% - ✓ Stool Cx, O+P, C. diff Imaging : CT AP (I+/O+): wall thickening, edema, thumbprinting, pneumatosis, no vessel occl. . Colonoscopy (to assess extent): petechial blood, pale mucosa, segmental edema/ulceration	Labs : most abnormalities arise after progression to necrosis. ↓pH, ↑lactate, AGMA (in 50%), WBC >15K (75%), stool guaiac ⊕ in ~50% Imaging : - <u>KUB</u> : ileus, colonic dilatation, pneumatosus - <u>CT AP</u> (ideally CTA; no oral contrast): wall thickening, pericolonic fat stranding, pneumatosis, arterial occlusion, portomesenteric venous gas - <u>Angiography</u> : if CTA non-diagnostic but high suspicion, or if vasculitis affecting small-medium size vessels. Can stent/tPA	Imaging : - <u>CTA</u> (preferred; alt. = MRA): ⊕ if stenosis of ≥ 2/3 major vessels (celiac, SMA, IMA). 91% with 2 vessels, 55% with all 3 vessels - <u>Doppler U/S</u> to measure mesenteric blood flow and r/o median arcuate ligament syndrome - <u>Gastric tonometry</u> exercise testing - <u>Angiography</u> (see left)
Treatment	- Bowel rest - IVF - D/C vasoconstrictive meds - GNR/anaerobic abx if mod/severe disease (no data) - If suspicion for necrosis, gangrene, or perf, call surgery	Occlusive disease : - NGT/NPO, IVF/blood product - broad-spectrum abx - Anticoagulation if not bleeding (heparin +/- tPA) - If <u>infarction/peritonitis/perforation</u> → surgery - Thrombectomy/embolectomy vs. intra-arterial vasodilators vs. thrombolysis Non-occlusive : treat underlying cause Mesenteric vein thrombosis : anticoag x3-6m	- <u>Elective revascularization</u> : open vs. endovascular. Peri-op mortality 0-16%; no role for prophylactic intervention if asymptomatic - Restenosis common (7% open revasc; 34% endovascular) - TPN for nutrition support - AC if acute-on-chronic ischemia

Gastroenterology

Nutrition & Feeding

GENERAL APPROACH (ACG: [AJG 2016;111:315](#))

1) Assess nutritional status ([Clin Nutr ESPEN 2018;26:13](#))

- **Hx/Exam:** dietary intake/tolerance, n/v/d, muscle/fat wasting, **weight loss**, functional capacity (grip strength, ADLs). **Screen** for food insecurity ([Hunger Vital Sign](#))
- **Weight loss as indicator of malnutrition:** >2% in 1 wk, >5% in 1 month, >7.5% in 3 months, >10% in 6 months, >20% in 1 yr
- **Labs:** albumin/pre-albumin, transferrin, retinol binding protein should be **avoided** as indicators of nutrition. INR prolongation may indicate malnutrition. Consider vitamin levels if history/exam is suggestive
- **24-hr calorie count; nutrition consult** if c/f malnutrition (**screen** with [NRS-2002](#) or [NUTRIC Score](#) in hospitalized pts)

2) Determine dietary route (oral > enteral [EN] > parenteral [PN]):

- **Oral:** assess aspiration risk, dysphagia, odynophagia. Consider SLP c/s for dietary modifications (e.g. pureed, thick liquids etc.)
- **Enteral (EN):** if pt unable to tolerate oral diet safely or meet caloric needs through oral diet alone, may need NGT. Place tube **post-pyloric** if gastroparesis, obstruction, n/v, or high aspiration risk. **Gastric residuals not recommended** ([NEJM 2014;370:1227](#))
- **Parenteral:** TPN (central access) or PPN (peripheral). Used when GI tract non-functional

3) Initiate diet: early EN initiated within 24-48 hours of admission, advance to goal within 48-72 hours (as tolerated, 3-4 days if refeeding risk). Nutrition/TPN consult for specifics. Watch for refeeding (see below)

ARTIFICIAL NUTRITION

Supplements (order “Adult/Pediatric Nutrition Supplements”): Ensure Plus (standard), Ensure Clear (low fat), Mighty Shake (standard, has lactose), Magic Cup (pudding, dysphagia), Glucerna Shake (DM), Nepro (CKD), Beneprotein (protein powder), Prosource Protein (liquid)

TUBE FEED FORMULAS	
Indication	Formula
Normal absorptive capacity	Osmolite 1.0
Long-term TF Prevent constipation (high fiber)	Jevity 1.5
Wound healing (high protein) ICU patients (on propofol)	Promote
IBD, pancreatitis Post-abdominal surgery	Vital (semi-elemental)
Respiratory failure/ARDS Volume overload (high protein)	Osmolite 1.5
Renal or liver failure (low Na/K/phos)	Nepro
Wound healing	Beneprotein/ProSource Liq Protein (modular protein)
Max fluid restriction	TwoCal HN (normal protein, no fiber)

TPN: “TPN (Nutritional Support Team)” in PPD

Consider if NPO ≥7d. Need central access w/ clean dedicated lumen. Order by 1PM to start same day

- Monitor for complications of TPN (if applicable):
 - **Metabolic effects:** hyperglycemia (2x > enteral), serum electrolyte alterations, refeeding syndrome (see below), Wernicke's encephalopathy, hepatic dysfunction, biliary sludge/gallstones. Small amt of insulin included but can be adjusted if needed
 - **Monitor BMP, Mg, Phos, LFTs, and TGs**
 - **Bloodstream infection:** increased risk of infection (fungal and bacterial)
- If no central access, **Clinimix** (amino acid solution in dextrose, no fats) can be given as PPN
- **To stop TPN**, coordinate careful transition to EN w/ nutrition; stop when EN provides >60% energy needs ([AJG 2016;111:315](#))

REFEEDING SYNDROME

Electrolyte/fluid shifts caused by initiation of nutrition in severely malnourished patient, can be fatal; most likely to occur within 72h of starting nutritional therapy ([Nutrition 2018;47:13](#))

- **Risk factors:** minimal/no intake for 5 (minor) to 10 (major) days, significant wt loss, age, excessive alcohol use, malnutrition 2/2 chronic dz/malabsorptive conditions, anorexia nervosa, persistent n/v/d, low initial lytes ([J Clin Med 2019;8:2202](#))
- **Characteristics: early:** ↓Phos, ↓K, ↓Mg, vitamin deficiency (thiamine); **late:** cardiac damage (CHF), respiratory failure (volume overload); **other s/s:** AMS, n/v, diarrhea, tremors, paresthesias
- **Prevention and management:** close lab monitoring (**at least BID when concerned**) w/ aggressive repletion of electrolytes (Phos, K, Mg, Ca; IV preferred) for first 3 days & administer thiamine **before** refeeding regardless of level, slow/hypocaloric initial feeding, consider fluid/sodium restriction, cardiac monitoring in high risk patients. Stop feeding if electrolyte abnormalities persist

SPECIAL CONSIDERATIONS

- **IBD flares, pancreatitis:** early enteral feeding (ideally within 24-72 hrs of admission)
- **Critical care:** enteral feeding should start within 48 hrs of ICU stay (superior to TPN if GI tract functional); contraindications include significant GI pathology (e.g. GI bleed or obstruction) for which patient should be NPO ([Clin Nutr ESPEN 2019;38:48](#))
- **Dementia:** avoid dietary restrictions, use nutritional supplements as needed; guidelines recommend against TFs in advanced dementia (a/w higher mortality), lack of evidence to support appetite stimulants ([Nutr Clin Pract. 2014;29:829; Clin Nutr 2015;34:1052](#))

TIPS FOR ORDERING INPATIENT DIETS

Consistent carbohydrate for DM (no calorie restrictions), **low fat (cardiac)** for CAD/cardiac disease, **low fat (GI)** for gallbladder disease/fat malabsorption/pancreatitis, **low K** for hyperkalemia/renal disease (2g), **no added salt** – 4g Na vs **2g Na** (renal/liver/cardiac disease), **low protein** some CKD cases but NOT for dialysis patients, **low phos** for ESRD. **Neutropenic/BMT** diet (no garnishes), **PET scan** diet is carbohydrate restricted (will NOT restrict glucose or make patient NPO), **red dye restricted** for pre-EGD/colonoscopy

Gastroenterology

Weight & Weight Loss

OBESITY

Definition: BMI: <18.5 underweight; 18.5-24.9 normal weight; 25-29.9 overweight; **30-34.9 class I obesity; 35-39.9 class II obesity; >40 class III ("severe") obesity.** NB: avoid using stigmatizing terms such as "morbid" or "extreme"

- Increased waist circumference: >40 inches men, >35 inches women

Epidemiology: 30-45% Americans; Midwest, South > NE, West; non-Hispanic Black > Hispanic > non-Hispanic White >> Asian; associated with lower SES, income, education ([CDC 2020; NEJM 2019;381:2440](#))

Associated with: HTN, HLD, T2DM, CAD, stroke, GB disease, OA, sleep apnea, certain cancers, all-cause mortality

Goal: 5-10% weight loss within 6 months. Benefits at 3-5% weight loss → improved TG, ↓ risk of DM; >5% → ↓BP, improved BG

Treatment:

- Diet:** 1200-1500 kcal/d for women; 1500-1800 kcal/d for men; a diet that is 500-750 kcal/day less than usual; or a diet that restricts certain food types. Variety of diets – all achieve calorie deficit: balanced low calorie, higher protein, low carbohydrate, low-fat vegan, vegetarian, macronutrient targeted, Mediterranean style, intermittent fasting ([Circ 2014;129:S102](#))
- Lifestyle:** comprehensive program – dieting, exercise, behavioral techniques (Weight Watchers, outpatient programs)
- Medications:** see *table*. Indicated for weight loss & management in combination with diet for adults with initial BMI ≥30 or BMI ≥27 with other weight-related comorbidities (DM, HTN, HLD)

MEDICATIONS FOR WEIGHT LOSS ([APJ 2016;43; JAMA 2016;315:2424](#))

Agent	Mechanism of Action	Dose	Side effects	Notes
Orlistat (Xenical, Alli OTC)	Inhibit GI lipases that hydrolyze TGs into FFA; increases fecal excretion of TG	60-120mg TID AC	GI complaints including fecal incontinence (>10%); reduced vitamin absorb; drug-drug interactions. Rarely liver, kidney injury	Reduced BG, lipids, BP; no longer first-line due to GI effects
Phentermine/topiramate (Qsymia)	Phentermine = stimulant, anorectic, increases satiety by action at hypothalamus Topiramate = mechanism for weight loss unknown	3.75/23mg x14d → 7.5/46mg x12w; Can increase to max 15/92mg	Teratogenic. Drug-drug interaction with metformin. Activating. Paresthesia, HA, constipation, dry mouth, URI, insomnia, dysgeusia	Should not be used w/ HTN or CAD, caution in patients with anxiety
Naltrexone/bupropion (Contrave)	Works at hypothalamus to increase satiety and through inhibition of mesolimbic dopamine circuit (reward circuit)	8/90mg daily 16/180mg BID	Nausea, constipation, HA, vomiting; lower seizure threshold; increase BP; cannot be taken with opioids	Not first line due to side effects, helpful in patients w/ AUD
Liraglutide (Saxenda)	GLP-1 receptor agonist; injectable	0.6mg titrated to full dose 3mg daily (↑ from DM doses)	N/V (typically resolve w/ time); delay in GE; thyroid C cell tumors in rodents (must ask if hx of thyroid cancer)	Benefit to DM, CAD, NAFLD; insurance limitations

Choice of agent: all approved medications effective at reducing weight. Typically choose liraglutide as first line for tolerability; few head-to-head comparisons (liraglutide > phenteramine/topiramate > orlistat, naltrexone/bupropion); consider patient characteristics. Metformin can produce modest weight loss in overweight patients (<5% weight loss) but not FDA approved for weight loss. Other GLP1ras (e.g. semaglutide, [NEJM 2021;384:989](#)) may attain weight loss indication in near future

Discontinuation: lack of at least 5% weight loss within 3 months on full dose. If weight loss 5-10% achieved, continue indefinitely

Therapies not recommended: lorcaserin (withdrawn by FDA 02/2020, ↑ risk of cancer); dietary supplements; hCG injections

WEIGHT LOSS SURGERY ([NEJM 2007;356:2176](#))

Indications: adults with BMI > 40 or BMI > 35 with obesity-related comorbid conditions & who have not responded to behavioral treatment w/ or w/o pharmacotherapy. Consider [Weight Center referral](#) at MGH

Mechanism of weight loss: restriction (reduced stomach capacity) ± malabsorption (↓ nutrient absorption by shortening the absorption length of SI)

Types: Restrictive: sleeve gastrectomy, gastric banding, intragastric balloon;

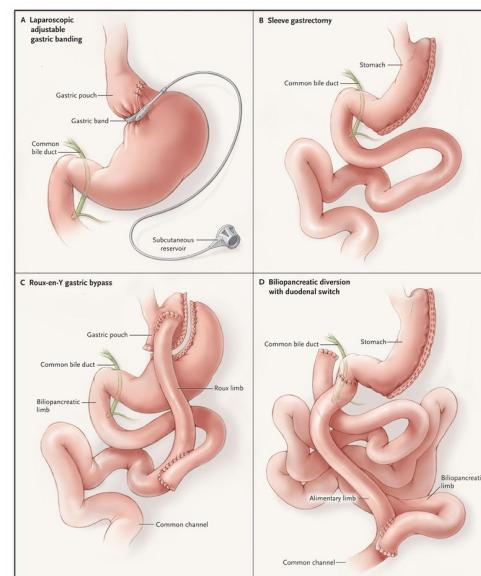
Malabsorptive: jejunoileal bypass (JIB) and the biliopancreatic diversion (BPD) ± duodenal switch; Restrictive + malabsorptive: Roux-en-Y gastric bypass (RYGB), single-anastomosis duodenoileal bypass with sleeve gastrectomy

Benefits: 23.4% weight lost at 2y; 16.1% at 10y ([NEJM 2004;351:2683](#)); remission of DM, HTN, HLD, OSA; ↓ cardiovascular and cancer mortality rates (30-50%), extended life expectancy by 3 years ([NEJM 2020;383:1535; Annals 2020;173:694](#))

Post-surgical diet: thin liquids for several days → full liquids x 10-14 days → soft solids x ~3 months, ADAT → regular diet

Complications:

- <30d: anastomotic leak, MI, and PE (total 0-1.55%) ([Obes Rev 2018;19:529](#))
- Long term:** food aversions/intolerances, **vitamin deficiencies** (absorbed in SI: fat soluble vit ADEK; thiamine, B12, folate; iron, zinc, selenium, copper, Ca), psychosocial impairment, **dumping syndrome**, **osteoporosis**, weight re-gain



Gastroenterology

Pancreatitis

Etiology

- **Gallstones/sludge** (40-75%): #1 in women
- **Alcohol** (30%): #1 in men
- **Hypertriglyceridemia** (10%): #3; suspect if TG>1000
- **Anatomic**: ampullary diverticula/stenosis, duodenal stricture, tumor, divisum, parasites, foreign body
- **Post-ERCP**: 4.5% of ERCP; **rectal NSAIDs** ↓ risk ([Endoscopy 2020](#), [Endosc Int Open 2019;7:477](#))
- **Autoimmune**: ↑ IgG4, +ANA (rare)
- **Hypercalcemia**: Ca activates pancreatic enzymes
- **Genetic**
- **Trauma**: blunt, especially s/p MVA

- **Drugs** (<5%): **Class Ia**: ACEi, dapsone, Lasix, Flagyl, pentamidine, statins, sulfa, tetracycline, valproate, mesalamine; **Class Ib**: amiodarone, azathioprine/6-MP, dexamethasone; **Class II**: didanosine, estrogen, propofol, tamoxifen, HCTZ ([CGH 2007;5:648](#))
- **Toxins**: **smoking**, organophosphates, scorpion venom, methanol
- **Infections**: **viral** (Coxsackie, EBV, CMV, HIV, Mumps, VZV, HAV, HBV, HSV), **bacterial** (Mycoplasma, Legionella, Salmonella), **fungal** (Aspergillus), **parasitic** (Toxoplasma, Crypto, Ascaris)
- **Ischemia**: vasculitis (SLE, PAN), hypoTN/shock, cholesterol emboli
- **Tropical**: pt from low SES in SE Asia, first bout as child
- **Idiopathic** (10-25%)

Diagnosis (Revised Atlanta Classification: [Gut 2013;62:102](#), [Pancreatology 2014;14:324](#))

- **Presentation**: abd pain (90%, band-like pain to back in 50%), N/V (90%), ileus, jaundice, flank/umbilical ecchymoses
- **History**: prior episodes, EtOH/smoking, prior GI procedures (e.g. CCY, ERCP), meds, infx sx, autoimmune hx, FH
- **Diagnosis – need 2/3**: 1) consistent clinical presentation, 2) lipase >3x ULN, 3) characteristic imaging
- **Labs**: lipase (*no need to trend*; false ⊕ in CKD, DKA), CBC (often ↑Hct), BMP (Ca), LFTs (↑ALT > 3.5x ULN has 95% PPV for gallstone pancreatitis: [AJG 1994;89:1863](#)), lipid panel (TGs)
- **Imaging**: CT if need to establish dx or to eval. for complications; RUQUS to r/o gallstones. MRI/MRCP can detect necrosis, stones
- **Severity**: mild: absence of organ failure and local or systemic complications; moderate: organ failure that resolves within 48 hours or local/systemic complication; severe: organ failure >48h (22% mortality)
- **Prognosis**: many scoring systems; [BISAP](#) is quick. SIRS ↑mortality. [Ranson](#), [APACHE II](#) scores less practical

Management (AGA: [Gastro 2018;154:1096](#))

- **IV fluids**: aggressive in first 24hrs: boluses + infusion 150-250/hr. **Can give LR or NS**, avoid LR if ↑Ca. Goal-directed: ↓HR, ↓Hct, ↓BUN, UOP 0.5-1cc/kg/hr. Avoid aggressive resuscitation after 24-48h (↑risk of abdominal compartment syndrome, intubation)
- **Pain control**: IV opioids | **Abx**: no role for prophylactic abx
- **Nutrition**: start PO (low fat) within 24h as tolerated. At 5-7d, if PO not tolerated start TFs (NG or NJ). Enteral > TPN: maintains intestinal barrier, prevents gut flora translocation. TPN a/w ↑risk of infections, organ failure/death
- **Reverse precipitants**: treat ↑Ca or ↑TG, stop culprit meds. For gallstone pancreatitis, urgent ERCP (24hrs) if cholangitis or CBD obstruction. CCY ideally prior to discharge as ↑biliary complications if CCY is delayed ([Lancet 2015;386:1261](#))
 - **HyperTG**: insulin gtt (0.1-0.3U/kg/hr) + D5, q1h FSBG (initially), q12h TG. Goal TG <500 (may take several days). No good evidence for apheresis so typically not done at MGH. Once can take PO, fibrates are first line. DC: lifestyle Δs, lipid clinic referral

Complications (AGA: [Gastro 2020;158:67](#); [NEJM 2016;375:1972](#))

Local		Vascular	Systemic
	<4 weeks	>4 weeks	
Interstitial edematous pancreatitis	Acute peripancreatic fluid collection : w/o features of pseudocyst; <u>resolve spontaneously</u> w/o drainage	Pancreatic pseudocyst : fluid collection w/ well-defined wall. If dx unclear, EUS w/ FNA (↑amylase). Drain if sx, rapidly ↑, infxn (endo vs. perc/surg)	Thromboses : splenic, portal, SMV; AC if portal vein or bowel ischemia Pseudoaneurysm : erosion of GDA/splenic artery → bleeding into pseudocyst. Suspect if ↓Hgb, expansion of fluid collection, unexplained GIB. Dx: arterial phase CT Tx: IR embo. prior to drainage of fluid collection
Necrotizing pancreatitis	Acute necrotic fluid collection : intra- or extrapancreatic Infected necrosis : 1/3 become infected, usually later in course; abx: (cefepime or cipro) + flagyl vs. pip/tazo vs. carbapenem in critically ill. <u>Necrosectomy</u> – can delay 4w if stable	Walled off necrosis : encapsulated necrotic collection. Drain if sx or infxn (endo vs. perc)	Abd. compartment syndrome : intra-abd pressure >20 w/ new organ failure. ✓ bladder pressure if in ICU ARDS : via phospholipase degradation of surfactant Metabolic : ↓Ca, ↑Glc, ↑TG GIB : via pseudoaneurysm AKI DIC

Chronic Pancreatitis (ACG: [AJG 2020;115:322](#))

Repeat acute attacks (esp EtOH & smoking) → fibrosis & loss of glandular tissue → chronic abd pain, exocrine insufficiency (steatorrhea, wt loss), endocrine insufficiency (brittle DM). Lipase/amylase may be ↑ early but nml/low as more tissue lost. ⊕ Fecal fat, ↓stool elastase. CT/MRI to dx calcifications, ductal dilation. ↑risk of pancreatic CA.

Tx: pancreatic enzyme replacement (Creon), ensure vit ADEK replete, pain control. Refer to MGH Pancreas Center: 617-726-5523

Pancreatic Masses (Curr Gastro Rep 2013;15:347)

- **Solid**: adenoCA (85-90%), autoimmune panc, neuroendocrine (1-5%), 1° lymphoma (<1%), mets (melanoma, RCC, etc.)
- **Cystic**: inflammatory (pseudocyst, paraduodenal wall cyst), IPMN (mucinous cystic or serous adenoma or adenoCA) ([AJG 2018;113:464](#); [Gastro 2015;148:819](#))
- **Imaging**: **CT abd pancreatic mass protocol**: EUS with FNA allows biopsy (87% Sn, 96% Sp); MRI useful in <2 cm lesions or when vascular involvement needs to be delineated better); consider PET-CT, MRCP for malignancy in IPMN (70% Sn, 92% Sp)
- **Labs**: CA 19-9 (⊕ in 80% of panc CA, 86% Sn, 87% Sp), CEA (mucinous), ANA, IgG4 (if autoimmune suspected)

Gastroenterology

Liver Chemistry Tests

Upper Limit of Normal (ULN): ALT (IU/L): 33 (males), 25 (females); ALK-P: 115 (males), 100 (females) (ACG: [AJG 2017;112:18](#))

Patterns of Liver Chemistry Test Elevation:

Hepatocellular: ↑ALT & AST

Cholestatic: ↑ALK-P & direct hyperbilirubinemia

Infiltrative: ↑ALK-P w/o significant bilirubin or AST/ALT elevation

Non-hepatic: indirect hyperbilirubinemia, non-hepatic ↑ALK-P, non-hepatic ↑AST

R factor = (ALT/ULN) ÷ (AlkPhos/ULN)

Hepatocellular: R factor >5

Cholestatic: R factor <2

Mixed: R factor 2-5

Causes of hepatocellular injury: Always consider relevant history (meds, OTCs, herbals) and clinical picture

Borderline to mild AST or ALT elevation (<5x ULN):

- Meds/toxins: see list below
- Alcohol-related (acute alc hep: typically 2:1 AST:ALT ratio, <400)
- Viral infections (HBV, HCV)
- Sepsis/ischemia/hypoperfusion
- Biliary obstruction (mixed picture)
- NAFLD (often AST & ALT <4x ULN)
- Cirrhosis (usually normal or only mildly elevated)
- Congestive hepatopathy (usually w/ indirect hyperbili)
- Autoimmune hepatitis (AIH)
- Wilson's disease (AST>ALT often >2; nml/↓ ALP & ALP/Tbili <4)
- Other systemic diseases: celiac, thyroid, hemochromatosis, A1AT (even in absence of lung disease), tickborne illness

Extreme AST or ALT elevation >1000:

- Ischemia:** shock, cardiac arrest, Budd-Chiari, cocaine
 - Natural history: ↑ALT/AST (often >50xULN) then ↑bilis (lag behind) and peak 1w later
 - ALT:LDH ratio <1.5 favors dx of ischemia > viral hepatitis (Sn 94%/Sp 84%) ([JCG 1994;19:118](#))
- Meds/toxins:** most commonly Tylenol
- Acute viral infection:** Hep A-E, reactivation of HepB in immunocompromised, HSV, EBV, CMV
- Acute autoimmune hepatitis
- Acute biliary obstruction
- Acute Wilson's (rare if age > 40)
- Malignant infiltration

Workup and Management

- Stop potentially offending medications/toxins
- Viral: HBsAg, HBsAb, HBcAb, HCV ab (PCR to confirm if HCV+)
- RUQUS: steatosis (NAFLD vs. EtOH), cirrhosis → Fibroscan
- AIH: ANA, ASMA, LKM-1, IgG
- Wilson's: ↓ceruloplasmin, ↑urine Cu (if chronic ↑AST/ALT)
- Hemochromatosis: iron panel: ♂: TSAT≥45% & ferritin >200; ♀ TSAT ≥40% & ferritin >150 without acute hepatitis → HFE test
- See [ESLD](#)

- ✓ INR, assess for HE (acute liver injury vs. failure)
- Stop offending meds/toxins, send tox screen
- Viral: HAV IgG/IgM, HBsAg, HBcAb IgG/IgM, HBsAb, HCV Ab and PCR, HSV, EBV, CMV, HDV/HEV if suspicious
- AIH: ANA, ASMA, LKM-1, IgG
- RUQUS with Doppler
- See [Acute Liver Injury & Failure](#)

Commonly used drugs that cause hepatocellular injury: acetaminophen, allopurinol, amoxicillin-clavulanate, amiodarone, aspirin, carbamazepine, clindamycin, fluconazole/ketoconazole, fluoxetine, glyburide, heparin, hydralazine, INH, labetalol, lisinopril, losartan, methotrexate, niacin, nitrofurantoin, NSAIDs, phenytoin, protease inhibitors, statins, sulfa drugs, trazodone, valproic acid

Herbal remedies/supplements: kava-kava, black cohosh, green tea extracts, Asian herbal medicines, weight loss supplements

Illicit drugs: anabolic steroids, cocaine, ecstasy, PCP. **Environmental:** *Amanita* mushrooms

See [livertox.nih.gov](#) for full list. ([J Hepatology 2019;70:1222](#); [NEJM 2019;381:264](#); [US Gastro Hep Rev 2010;6:73](#))

Causes of cholestatic injury pattern: ↑ALK-P and bili; R ratio <2

- Biliary obstruction:** choledocholithiasis, malignancy (cholangio, pancreatic, ampullary), primary sclerosing cholangitis (PSC), chronic pancreatitis with strictures
- Intrahepatic cholestasis:** meds (anabolic steroids, **Augmentin**, penicillins, cephalosporins, captopril, macrolides, estrogens, Bactrim, carbapenems), TPN, sepsis, primary biliary cholangitis (PBC)
- Biliary epithelial damage:** hepatitis, cirrhosis

Workup and Management

- Stop offending meds/toxins
- RUQUS for biliary obstruction
- MRCP/ERCP if obstruction
- ✓ ANA/AMA/SMA if no obstruction
- If chronic, consider liver bx/MRCP

Causes of infiltrative pattern: primarily ALK-P elevation

- Sarcoidosis or other granulomatous disease (e.g. TB, certain fungal infxns)
- Malignancy: lymphoma, metastasis to liver, HCC
- Amyloidosis
- Abscess
- Hepatic extramedullary hematopoiesis
- PSC can also have ↑ALK-P with normal bilirubin

- ✓ GGT to confirm liver origin
- RUQUS for biliary obstruction
- MRCP/ERCP if obstruction
- ✓ ANA/AMA/SMA if no obstruction
- If chronic, consider liver bx

Non-hepatic causes of abnormal LFTs:

- Indirect hyperbilirubinemia:** Gilbert's syndrome, hemolysis, resorption of hematoma
- Alk phos elevation:** also expressed in bone (e.g. ↑ in Paget's, bony mets, Potts), intestines (e.g., ↑ in SBO), and placenta (third trimester pregnancy)
- AST elevation:** AST is most abundant in liver tissue but also present in muscle (e.g., ↑ rhabdomyolysis, heat stroke, acute MI), kidney, brain, and RBCs

- If indirect bili: hemolysis labs
- If ALK-P: GGT, fractionated alk phos (bone, gut, hepatic)
- If AST/ALT: CK

Gastroenterology

Biliary Disease

GALLSTONE DISEASES ([J Hep 2016;65:146](#))

Choledolithiasis: presence of stones in GB (6% of ♂, 9% of ♀)	Choledocholithiasis: stones in common bile duct
<ul style="list-style-type: none"> Sx: asx (<20% develop clinical events). Larger, multiple, older gallstones and ♀ ↑events (Gastro 2016;150:156) vs biliary colic (dull RUQ/epigastric pain, 30m-6h, caused by GB contracting around sludge/stone, often postprandial & w/ n/v) Dx: RUQUS (Sn 84%, Sp 99%) > CT (Sn 55-80%); EUS if ⊖; labs wnl Stone types: <i>cholesterol</i> (most common); <i>pigment</i>: Crohn's/ileal disease, extravasc. hemolysis, TPN Tx: <i>asymptomatic</i>: observe; CCY only if at risk for GB CA (stone >3cm, porcelain GB, GB adenoma); <i>symptomatic</i>: elective CCY Complications: cholecystitis, choledocholithiasis, pancreatitis, GB CA, gallstone ileus, Mirizzi syndrome (compression of CBD/CHD) <p>Cholecystitis: stone in cystic duct → inflammation of GB ± infxn</p> <ul style="list-style-type: none"> Sx: RUQ pain (w/ radiation to back/shoulder), Murphy's sign, n/v, fever Labs: ↑WBC; may have mild ↑ALP, Bili; but if ↑↑, c/f CBD obstruction Acalculous cholecystitis: GB stasis/ischemia w/o obstruction. Unexplained fever, ↑WBC. Risk factors: trauma, burns, TPN, severe illness, fasting, sepsis, immunosuppression (CGH 2010;8:15) Dx: RUQUS (GB wall thickening, pericholecystic fluid, sonographic Murphy's) → HIDA scan if ⊖; pre-tx w/ 2mg IV morphine ↑Sn (given by nuclear rads at MGH) (AJR 2016; 207:865). Tokyo Guidelines for dx & severity (based on deg. of organ dysfunction) (J Hep Panc Sci 2018;25:41) Tx: abx (Zosyn or CTX/Flagyl). Early (<7d) CCY during hospitalization → ↓ morbidity (Br J Surg 2015;102:1302). If critically ill or high surgical risk & fails to improve after 1-3d abx, perc. cholecystostomy. Stop abx 24h post-CCY unless septic/perc chole: 4-7d. (JAMA Surg 2019;154:873) Complications: gangrenous cholecystitis, emphysematous cholecystitis (gas-forming org.), perforation, enteric fistula, gallstone ileus 	<ul style="list-style-type: none"> Sx: RUQ pain, n/v, jaundice; may be asx Labs: ↑ALP, ↑Bilis ± ↑AST/ALT Dx: RUQUS to look for CBD dilation >7mm (poor Sn for visualizing stones themselves); MRCP or EUS if equivocal Tx: ERCP w/ stone removal; interval CCY Complications: ascending cholangitis, acute pancreatitis <i>NB:</i> can occur in pts s/p CCY if de novo formation in CBD <p>Cholangitis: ascending biliary infxn 2/2 obstruction in CBD</p> <ul style="list-style-type: none"> Etiologies: stone, stricture (malig., PSC, AIDS), liver fluke Sx: <i>Charcot's triad</i>: RUQ pain, fever, jaundice; <i>Reynold's pentad</i>: + shock and AMS Labs: ↑WBC, ↑ALP, ↑Bili, ± ↑AST/ALT (can be ↑↑) Dx: RUQUS (ductal dilation), MRCP/ERCP. Tokyo Guidelines for dx & severity (J Hep Panc Sci 2018;25:17) Tx: broad spectrum abx (Zosyn or CTX/flagyl; carbapenem if life-threatening) x7d; urgent ERCP w/ decompression (<24-48h) if severe (associated organ dysfunction/shock) or if fails to improve on abx x24h. Perc drainage if ERCP not feasible. Interval CCY if due to gallstones Higher risk for cholangitis after palliative CBD stent placement in patients with malignant obstruction Complications Post-ERCP: (GIE 2017;85:32)

AUTOIMMUNE BILIARY DISEASES

Primary Biliary Cholangitis (PBC) (AASLD: Hepatology 2019;69:394)	Primary Sclerosing Cholangitis (PSC) (NEJM 2016;375:1161)
<p>Autoimmune destruction of intrahepatic bile ducts</p> <ul style="list-style-type: none"> Clinical manifestations: ♀>♂; asx, (50-60%), pruritus, fatigue, sicca symptoms, cirrhosis (late) Dx: ≥2 of the following: ALP ≥1.5x upper limit of normal; AMA >1:40 titer (95% pts); biopsy findings SPATA31A3 and GARP new biomarkers for diagnosis (Liver International 2019;39:2124) Associated with: hypothyroidism (20% pts), anemia, metabolic bone disease, Sjogren's, autoimmune hepatitis (overlap) Tx: ursodiol: first line, ↓progression & ↑survival (NEJM 1994;330:1342); obeticholic acid: adjunctive/replacement for ursodiol, fibrates: off label altern.; cholestyramine for pruritus; modafinil for fatigue; liver transplant: 22% recurrence in 5yrs 	<p>Affects intra- + extrahepatic bile ducts</p> <ul style="list-style-type: none"> Clinical manifestations: ♂>♀; asx (50%), pruritus and fatigue (most common), cirrhosis (late); cholangitis due to strictures Dx: ↑ALP ± bili; may have +auto-Abs but of unclear significance; MRCP (segmental strictures), ± biopsy; ✓ AMA/IgG4 to exclude alternative dx Associated with: IBD (60-80%; UC>Crohn's), cholangioCA (10-15% pts), metabolic bone disease, AIH (overlap) Tx: none; liver transplant (MELD exceptions for recurrent cholangitis, intractable pruritus): 20% recurrence 5 years post-LT Hepatobiliary CA surveillance (imaging, CA 19-9, AFP) improves survival (Hepatology 2018;67:2338)

MALIGNANT DISEASE OF THE BILIARY TRACT

Gallbladder carcinoma: risk factors: gallstone disease (34x more likely to develop CA), porcelain GB, GB polyps, PSC, chronic infxn

- Diagnosis:** LFTs usually normal, ↑CA19-9/CEA; RUQUS best screening test, then CT/MRI/MRCP

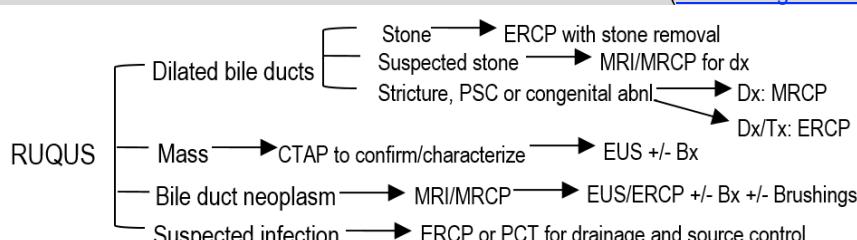
Cholangiocarcinoma: may be extrahepatic (90%) or intrahepatic (10%); risk factors: PSC, liver flukes, intrahepatic gallstones

- Diagnosis:** ↑ALP, Bili, CA 19-9/CEA ± ↑AST/ALT depending on deg. of obstruction; RUQUS screening test, then ERCP/MRCP/EUS

SPHINCTER OF ODDI DYSFUNCTION

- Biliary: abdominal pain, ↑liver enzymes, and CBD dilation; Pancreatic: pancreatic-type pain + dilated pancreatic duct + elevated pancreatic enzymes, or recurrent acute pancreatitis ([Curr Gastro Rep 2015;17:31](#))

RADIOGRAPHIC ASSESSMENT OF SUSPECTED BILIARY PATHOLOGY ([Am J Roentgenol 2011;197:551](#))



Gastroenterology

Acute Liver Injury & Failure

Acute Liver Failure (ALF): encephalopathy & coagulopathy (INR >1.5) of <26w in pts without cirrhosis or known liver dz
Acute Liver Injury (ALI): acute liver injury <26w with coagulopathy but NOT encephalopathy

Presentation: fatigue, lethargy, anorexia, n/v, RUQ pain, pruritis, ± jaundice → confusion in ALF (and may progress to coma)

Initial diagnostics: CBC, CMP, PT/INR, T&S, lactate, ABG, arterial NH₃, FSBG, hCG, HIV, APAP, tox screen, viral serologies (see below), autoimmune serologies (see below), amylase/lipase, RUQUS w/ Doppler ([JHM 2017;12:184](#))

Type	Etiologies	Diagnostics
Drugs	Acetaminophen: most common cause of ALF in US, dose-depend. (>4g) Herbal supplements: including <i>Amanita phalloides</i> mushroom Idiosyncratic DILI: see LiverTox ; abx (*Augmentin), AEDs, anti-TB, etc. (Alcohol-related hepatitis: considered acute-on-chronic and not ALF)	<u>History:</u> all APAP-containing meds, herbal supplements, new meds/OTCs, EtOH use <u>Labs:</u> APAP level, EtOH, tox screen
Viral	HAV, HBV, HCV (rare w/o HBV co-infection), HDV (↑risk co-infection > superinfection > HBV alone), HEV (pregnant or in endemic areas) Others: HSV (may be anicteric, ↓WBC), adenovirus, EBV, CMV, VZV (if immunocompromised)	<u>History:</u> travel, IVDU, occupational exposures, sexual exposures, vesicular rash, blood transfusion, immunocompromised state <u>Labs:</u> HAV IgM, HBsAg & core IgM, HCV Ab & PCR, HSV Ab; ✓ HDV if +HBV, HEV if preg. VZV if immunocompromised
Ischemic/vascular	Systemic hypoTN (sepsis, cardiac dysfunction), vasoconstricting drugs (cocaine, meth.), Budd-Chiari (hepatic vein thrombosis), veno-occlusive disease (post-HSCT); ALT/LDH <1.5 suggestive of ischemic	<u>History:</u> HoTN, hypercoag. state, drugs/meds <u>Imaging:</u> U/S w/ Doppler; CT or MRI/MRV are alternatives; consider TTE if no known cause
Autoimm.	AIH: F>M; can present as ALF but uncommon	<u>Labs:</u> IgG(↑), ANA, ASMA, anti-LKM-1
Genetic	Wilson's: <40, F>M; AST>ALT often >2; nml/↓ ALP & ALP/Tbili <4; a/w DAT-neg. hemolytic anemia, ↓uric acid, rapidly progressive renal failure	<u>History/exam:</u> FH, slit-lamp exam for KF rings <u>Labs:</u> ceruloplasmin (though may be nml/↑ in ALF)
Others	HELLP, acute fatty liver of pregnancy, malignant infiltration (breast CA, SCLC, lymphoma, myeloma), HLH, heat stroke, hepatectomy	<u>Labs:</u> U/A if pregnant Liver bx if dx remains elusive after thorough eval

MANAGEMENT OF ACUTE LIVER FAILURE (AASLD: [Hep 2012;55:965](#); AGA: [Gastro 2017;152:644](#); NEJM 2013;369:2525)

- Consult Hepatology for OLT workup.** Urgency based on HE severity (ASAP if grade 3-4)
- Triage/monitoring:** **ICU if HE grade ≥2;** freq. INR, CBC, ABG, Glc, Na, K, Cr, Mg, Phos; freq. exams to assess for signs of worsening HE or ↑ICP (esp. grade 3-4), e.g. Cushing's triad
- Hemodynamics:** IVF and/or pressors (norepi ± vaso); goal MAP ≥75 for cerebral perfusion
- N-Acetylcysteine (NAC):** tx APAP toxicity, may benefit non-APAP ALF w/ grade 1-2 HE ([Gastro 2009;137:856](#)). Initially for all APAP pts. 150mg/kg/h, 1h → 12.5mg/kg/h, 4h → 6.25mg/kg/h, 67h
- Encephalopathy:** intubation for HE gr. ≥3; ↑cerebral edema in HE gr. 3 (25-35%) & 4 (65-75%)
 - Lactulose in ALF controversial: ↑bowel distent. may worsen outcomes
 - If ↑↑risk for cerebral edema (gr. 3-4, aNH₃ >150, ARF, pressors), prevent w/ 3% NaCl for Na 145-155 ([Hep 2004;39:464](#)), HOB 30, ↓stimulation, avoid: overhydration & ↑PEEP
 - Treat cerebral edema w/ IV mannitol (0.5-1g/kg bolus x1-3); if impending herniation, hyperventilate to PaCO₂ ~25-30 (temporary; may worsen edema by → ischemia). Pentobarbital/thiopental if other measures fail (may cause hoTN which → ↓CPP)
- Seizures:** phenytoin; benzos if refractory. Consider routine EEGs for subclinical seizure
- Infection:** high risk for bacterial (Staph, Strep, GNRs) & fungal. ✓ serial BCx, UCx, SCx, CXR. May not fever, ↑WBC, or have localizing s/s, though worsening HE or AKI may be sign. Low threshold for empiric abx ± antifungal (esp. if prolonged hosp., abx, steroids, CVVH)
- Coagulopathy/bleeding:** can trial vit K, routine FFP not recommended. In ICU, ppx w/ PPI. High risk for bleed and/or clotting

Hepatic Encephalopathy		
Grade	Mental Status	Asterixis
I	Attention deficit	±
II	Lethargy Moderate confusion	+
III	Somnolence Marked confusion	+
IV	Coma	+

Complications of Acute Liver Failure	
Neuro	HE, cerebral edema
CV	Shock, high-output state
Pulm.	Pulm. edema, ARDS
GI	GIB, pancreatitis (esp. APAP)
Endo.	↓Glc, adrenal insuff.
Renal	Renal dysfxn in >50%; met. acid. (↑lactate), ↓Na, ↑K, ↓P
Heme	Coagulopathy, ↓Plt, DIC
Infection	In ~90%; bacterial + fungal

ETIOLOGY-SPECIFIC MANAGEMENT

- APAP → NAC w/in 8h, [Rumack-Matthew Algorithm](#)
- HBV/HCV → OLT. Possible role for antivirals in HBV
- HAV/HEV → supportive care, possible OLT
- AFLP/HELLP → delivery. Follow up for need for OLT
- HSV/VZV → acyclovir (5-10mg/kg q8h); may need OLT
- AIH → glucocorticoids; OLT if needed
- Wilson's → OLT. Chelation ineffective
- Budd-Chiari → TIPS, surgical decompression, lysis, OLT

King's College Criteria – list for OLT if:

Acetaminophen-induced ALF:

Arterial pH <7.3 OR **all 3 of:** INR >6.5, Cr >3.4, grade 3-4 HE

Other causes of ALF: INR >6.5 OR **3/5:** age <10 or >40, Tbili ≥17, INR >3.5, time from jaundice to encephalopathy >7d, unfavorable etiology (seronegative hepatitis, DILI, Wilson's)

Prognosis: MELD score >30.5 = poor prognosis. HBV, Wilson's, Budd-Chiari, AIH, DILI also associated with poor prognosis.

Gastroenterology

Viral Hepatitis

HEPATITIS A ([J Hep 2018;68:167](#))

Fecal-oral transmission from personal contact or contam. food/water, international travel. Sx: abrupt n/v, anorexia, malaise, fever, jaundice, RUQ/abd pain, \uparrow ALT>AST (often >1000), 1 bilirubin, ALP. 70% of adults w/ sx, last 2-8w, jaundice peaks after 2w. Dx: \oplus anti-HAV IgM, persists 3-6mo. Anti-HAV IgG forms at 2-3w, persists for life, confers immunity. Tx: supportive unless ALF (rare). Vaccinate if: MSM, IVDU, chronic liver disease, travel, homeless, occupational exposures (caring for at risk). Havrix (2 doses, at 0, 6-12mo)

HEPATITIS B (AASLD: [Hepatology 2018;67:1560](#); USPSTF: [JAMA 2020;324:2452](#))

Risk Factors	Vertical transmission (SE Asia), sexual contact, IVDU, needlestick, unvaccinated (US before 1994), immunosuppress.
Clinical Pres.	Acute: 70% subclinical, 30% w/ jaundice, <1% ALF. S/S: anorexia, nausea, fatigue, RUQ discomfort. ALT>AST in 1000s, +/- \uparrow Bili. Chronic: \oplus HBsAg >6mo. (often w/ persistent \uparrow ALT), occurs <5% adults. 40% \rightarrow cirrhosis
Extrahepatic	PAN, membranous nephropathy/MPGN, aplastic anemia, arthritis
Diagnosis	Screening: HBsAg, anti-HBs, anti-HBc total (identifies all infected). Interpretation below
Treatment	First line: tenofovir or entecavir (Hepatology 2016;63:284). Goal: suppress HBV DNA, lose HBsAg & HBeAg
HCC Screen.	Indications: all HBsAg+ w/ cirrhosis, HBsAg+ & high-risk (Asian/Black ♂ >40; Asian ♀ >50; +HDV; +FH HCC)

HBsAg	Anti-HBs	Anti-HBc (total)	Interpretation	Next Steps
\oplus	-	\oplus	Hepatitis B infected (acute or chronic)	\checkmark anti-HBc IgM (acute vs. chronic), HBV DNA, HBeAg, total anti-HDV
-	\oplus	\oplus	Past infection (resolved)	None; \uparrow risk of reactivation w/ chemo/immunosuppression
-	-	\oplus	(1) Recovery from remote acute infxn (w/ anti-HBs titers that have waned), (2) chronic infxn (& low level HBsAg), (3) acute HBV in window period, (4) false \oplus anti-HBc or false \ominus HBsAg	Differentiate possibilities w/ anti-HBc IgM (acute infxn vs. others), anti-HBe, HBV DNA, repeat anti-HBc (later). NB: "occult HBV" = DNA \oplus w/ HBsAg \ominus +/- HBcAb \oplus . Low risk reactivation but \uparrow if chemo/immunosuppression
-	\oplus	-	HBV-immune from prior vaccination	None
-	-	-	Uninfected, non-immune	Vaccinate. Engerix-B (3 doses, at 0,1,6mo). NB: If receiving HD, double dose, at 0,1,2,6mo

HBV reactivation: indicated by: (1) \uparrow in HBV DNA vs. baseline or (2) reverse seroconversion from HBsAg-/anti-HBc+ to HBsAg+. **Check serologies before high-risk therapies:** rituximab, anti-TNF, high dose steroids (>20mg pred/d x4w), HSCT, chemotherapy, anti-rejection therapy. HBsAg+ is greatest risk, need ppx. HBsAg-/anti-HBc+ is lower risk, ppx vs monitor for reactivation

Management: **Acute:** unless severe, supportive. **Chronic:** tx if decompensated cirrhosis or if compensated w/ DNA >2k (& consider if <2k) regardless of ALT to reduce risk of decompensation. If no cirrhosis, depends on eAg/ALT/DNA

HEPATITIS C (AASLD/IDSA: [Hepatology 2020;71:686](#); [Lancet 2019;394:1451](#))

Screening	\checkmark HCV Ab. If positive, order RNA Viral Load (PCR). MGH does not have reflex testing. Everyone: universal one-time screening (CDC: MMWR Rec Rep 2020;69:1 ; USPSTF: JAMA 2020;323:970). IVDU or MSM w/ HIV: annual
Risk Factors	IVDU, blood products before 1992 or from infected individual, MSM, HIV, chronic HD, incarceration, immigration from high prevalence area, birth to HCV infected mother, sex with HCV partner
Diagnosis	\oplus Ab, \oplus RNA = current infection. \oplus Ab, \ominus RNA = cleared or treated (NB: can still get reinfected)
Natural History	Acute HCV: 75% subclinical. If sx, develop 2-26w after exposure, last 2-12w. Fulminant rare (<1%) Chronic HCV: 80% \rightarrow chronic; if younger, ♀, genotype 1, IL28B, jaundice, \uparrow ALT more likely to clear spontaneously 20% \rightarrow cirrhosis (\uparrow risk if ♂, EtOH, obesity, HIV, immunosuppr.). HCC risk 1-13%/yr
Extrahepatic	Mixed cryo., porphyria cutanea tarda, lichen planus, LCV, thyroiditis, Sjogrens, renal dz (e.g. MPGN), NHL
Treatment	If no cirrhosis, prior HCV tx, HCC, current pregnancy, HIV, or HBsAg \oplus : 1) Confirm no cirrhosis with FIB-4 score <3.25, U/S Elastography (FibroScan), or FibroSure 2) Confirm HIV, HBsAg, and urine pregnancy test neg. Get CBC, LFTs, GFR baseline 3) Start pan-genotypic Rx: Mavyret (Gle/Pib) x8wks or Epclusa (Sof/Vel) x12wks. If on coumadin, monitor for subtherapeutic INR. No other monitoring needed. Note: patients do not need to be abstinent from drugs or EtOH. If have compensated cirrhosis, see (AASLD, IDSA 2020). If decompensated cirrhosis, refer to GI
Follow-up	\checkmark HCV RNA >12 weeks after therapy to assess SVR. If \oplus cirrhosis, need ongoing HCC surveillance via U/S (q6mo)

HEPATITIS D (Gastro 2019;156:461)

Can have coinfection or superinfection with HBV. **Coinfection** similar to HBV but more severe, \uparrow risk ALF; often biphasic ALT course.

Superinfection most severe, highest risk ALF & chronic infxn (90%) \rightarrow cirrhosis in 80% in 5-10y. 3x \uparrow risk HCC vs. HBV mono-infection. \checkmark total anti-HDV once in all HBV infected patients. If suspect false negative Ab, confirm with HDV RNA PCR

HEPATITIS E (APT 2017;46:126; Gastro 2012;142:1388)

Most common cause of viral hepatitis in endemic areas. **Transmission:** fecal-oral, vertical, zoonotic (swine organ meats). Most asx, resolve spontaneously. **Extra-hepatic:** neuro (e.g. GBS), renal, arthritis, anemia, pancreatitis. \uparrow risk of ALF/mortality in pregnant women ([Annals 2007;147:28](#)). Rarely chronic HEV in transplant recipients. **Dx:** HEV IgG+IgM, high false \oplus/\ominus . **Tx:** supportive care (if immunocompetent)

Gastroenterology

Alcohol-Related Liver Disease

ALCOHOL-RELATED LIVER DISEASE (ALD): (AASLD: [Hepatology 2020;71:308](#); ACG: [AJG 2018;113:175](#))

Risk factors: sex (F>M), pattern (\uparrow daily, \pm \uparrow binge), obesity, genetics (e.g. PNPLA3), smoking, comorbid HCV/NAFLD/etc.; coffee \downarrow risk

Pathophysiology: EtOH \rightarrow fat accumulation; EtOH \rightarrow \uparrow gut permeability \rightarrow \uparrow innate immune response, liver cell inflammation, injury, necrosis, fibrosis; may be important role for gut microbiota ([Nature 2019;575:505](#))

Disease spectrum:

- Steatosis: usually asx; may have mild \uparrow AST>ALT, GGT; develops in 90% w/ >60g/d EtOH after 2w; reversible w/ 4-6w abstinence
 - 20-40% develop fibrosis \rightarrow 8-20% to cirrhosis \rightarrow 20-40% decomp./acute-on-chronic liver failure. HCC in 3-10% w/ cirrhosis
- Steatohepatitis: histopathologic correlate of AH; can develop at any stage of ALD; often \rightarrow to fibrosis (40-50%) & cirrhosis (>75%)
- Alcohol-related hepatitis (AH): an acute inflammatory syndrome that can occur at any stage of ALD

Alcohol Liver Evaluation Team (ALiVE, p26299): eval. inpts w/ ALD or AUD w/o known ALD

ALCOHOL-RELATED HEPATITIS:

Presentation: varies from few sx to liver failure; jaundice, anorexia, fever, abd pain (tender hepatomegaly), malaise, weakness, nausea

- Can lead to portal HTN & its sequelae (EVs, ascites, HE) in the absence of cirrhosis due to hepatic swelling & portal venous obstruct.
- Alcoholic ketoacidosis can often be observed

Dx: jaundice w/in prior 8w, ongoing heavy EtOH (F >3 std. drinks/d, M >4 std. drinks/d for >6mo). <60d abstinence before onset of jaundice, AST moderate \uparrow (50-400) w/ AST/ALT >1.5, Tbili >3 ([Gastro 2016;150:785](#)). Often \uparrow WBC (<20k, \uparrow PMNs), \uparrow INR

- Ddx: other etiologies of acute hepatitis/jaundice (viral, meds/herbs, ischemia, AIH, Budd-Chiari, biliary obstruct.), decompensated cirrhosis (can often be superimposed). ✓HAV/HBV/HCV, U/S w/ Doppler, \pm others. Assess for signs of cirrhosis
- Transjugular Bx: consider if atypical presentation and/or labs (e.g. AST or ALT >400), uncertain alcohol intake hx, confounding factors such as use of hepatotoxic meds w/in last 30 days, possible ischemic insult (e.g. HoTN, cocaine use) or other etiology

Exclude infection: ✓ BCx, U/A, UCx, diag. para if ascites, CXR \pm sputum Cx if indicated. Some will have SIRS/fever due to inflamm., but important to screen for infxn as at high risk (esp. if severe AH: 12-26% at admission), can be difficult to dx, and has tx implications

Prognostic tools:

Tool	Use	Components	Stratification
<u>Maddrey Discriminant Function (MDF)</u>	Consult ALiVE (p26299) to consider steroids	PT, PT control (14.5 at MGH), Tbili	$\geq 32 =$ severe \rightarrow 1mo. mortality 30-50%; GI consult re: steroids (Gastro 1978;75:193)
<u>MELD</u>		Tbili, INR, Cr, Na	$>20 =$ 3mo. mortality 20%; GI re: steroids (Hepatology 2005;41:353)
<u>Lille</u>	Perform on day 7 re: whether to d/c steroids	Day 0: Age, Albumin, PT, Cr Day 0 & Day 7: Tbili	≥ 0.45 : Nonresponse \rightarrow stop steroids <0.45 : Response \rightarrow continue steroids (Hepatology 2007;45:1348)

TREATMENT OF ALCOHOL-RELATED HEPATITIS:

Corticosteroids: see algorithm

- No MDF ceiling but if very severe (e.g. MDF >90, MELD >30), need to closely assess for occult infxn or other contraindications. Single study w/ MDF >54 a/w \uparrow mortality has not been replicated ([Alc Clin Exp Res 1995;19:635](#))
- Prednisolone used as not metabolized by liver (methylpred 32mg is IV alternative): 40mg x 28d w/ 2-4w taper (e.g. \downarrow 10mg q4d until 10mg then \downarrow 5mg q3d)
- No mortality difference at 28d or 90d, \uparrow infxn ([NEJM 2015;372:1619](#)). No effect on all-cause mortality up to 3mo after randomization ([Cochrane Rev 2019](#))

NAC: may benefit, no harm (though is large volume load)

Supportive therapy: hold BB if MDF ≥ 32 as \uparrow AKI incidence ([Liver Int. 2015;35:8](#))

Nutrition: ensure adequate kcal, protein; supplement w/ MVI, thiamine, folate, B6, consider Zn. Low kcal in severe AH a/w \uparrow infxn & \uparrow 16mo mortality ([Gastro 2016;150:903](#))

Abstinence: can result in rapid improvement in outcomes w/in 3mo. Combination of psychosocial + pharmacotherapy achieved best outcomes ([J Hepatol 2016;65:618](#)). Age and lack of past alcoholism treatments were independently associated with complete abstinence ([Hepatology 2017;66:1864](#))

LIVER TRANSPLANTATION:

Definitive therapy for ALD. Traditionally required 6mo abstinence. \uparrow 16mo survival with low risk of alcohol relapse and low impact on donor pool in appropriately selected pts ([NEJM 2011;365:1790](#), [Am J Transplant 2016;16:841](#))

- **MGH** offers early LT eval. prior to abstinence for pts w/ 1) 1st alcohol-related decompensating event (i.e. no prior knowledge of alcohol-related liver disease or alcohol-related legal issues), 2) MDF ≥ 32 , 3) no response to steroids, 4) no grade 3-4 HE (to allow for psych eval), 5) strong social support, 6) no severe psychiatric co-morbidities, and 7) no other SUD. Consult hepatology for candidacy

MDF ≥ 32 or MELD >20

Contraindic. to steroids:

- Uncontrolled infection
- Uncontrolled GIB
- AKI (excluded from trials)
- Concomitant HBV, HCV, HCC, DILI, panc., HIV, TB
- Multiorgan failure/shock

Prednisolone 40mg/d +/- NAC

Day 7: Lille model

Response

No Response

Stop steroids

Complete 4w & 2-4w taper

Other therapies with potential efficacy:

- **NAC:** w/ steroids x5d, \downarrow mortality at 1mo, not 3 or 6mo ([NEJM 2011;365:1781](#), [Gastro 2015;149:958](#))
- **Pentoxifylline:** consider if steroids contraind. No convincing data on \downarrow mortality, but \downarrow AKI/HRS ([Gastro 2000;119:1637](#), [APT 2013;37:845](#))
- **G-CSF:** in clinical trials ([Hepatology 2019;70:802](#), [AJG 2014;109:1417](#))
- **Fecal transplantation:** new ongoing RCT

Gastroenterology

NAFLD

DEFINITIONS

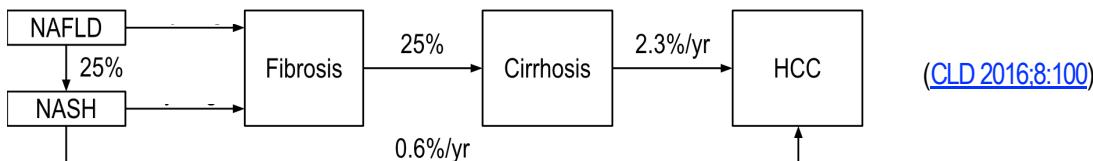
Nonalcoholic Fatty Liver Disease (NAFLD): presence of hepatic steatosis (imaging or bx) w/o 2° cause (includes NASH)

Nonalcoholic Steatohepatitis (NASH): hepatic steatosis and inflammation with hepatocyte injury ± fibrosis

NASH cirrhosis: cirrhosis with current or previous histological/clinical evidence of steatosis or steatohepatitis

EPIDEMIOLOGY ([Gut 2018;67:963](#))

- Prevalence:** 10-46% in US; >95% in pts w/ obesity undergoing bariatric surg, 33-66% in pts w/ T2DM, and 50% in pts w/ dyslipidemia, ↑ with ↑TC:HDL & TG:HDL (but growing number of lean NAFLD)
- Risk factors for progression:** insulin resistance, DM, weight gain, HTN, AST/ALT >1 ([JAMA 2015;313:2263](#)); mortality and liver complications associated with advanced fibrosis ([Hepatology 2011;53:1874](#))



DIAGNOSIS ([NEJM 2017;377:2063](#); [Hepatology 2018;67:328](#); [Hepatology 2011;54:344](#))

- Presentation:** mild ↑AST, ALT (2-4x ULN with AST:ALT ratio <1) or imaging w/ hepatic steatosis (~70% w/ nl LFTs)
 - No indication for routine screening in high-risk pts due to limited tx options
- History & Physical:**
 - DDx:** EtOH use, viral hepatitis, parenteral nutrition, Wilson's disease, malnutrition, hemochromatosis, autoimmune liver disease, α-1 AT deficiency, DILI, celiac disease, thyroid disease
 - Screen for significant EtOH consumption (>21 standard drinks/wk in men, >14 in women)
 - Evaluate for associated comorbidities (T2DM, obesity, dyslipidemia, DM, hypothyroidism, PCOS, OSA)
 - Assess for signs of cirrhosis and insulin resistance (e.g. acanthosis nigricans)
- Labs:** LFTs, CBC, PT/INR, HCV ab, lipid panel, HgbA1c, celiac serologies, TSH
- If elevated LFTs: consider iron studies, α-1AT, ANA, ASMA, SPEP, HBV
 - Ferritin may be ↑ in hemochromatosis and NAFLD, so if iron sat also elevated, consider HFE testing
- Imaging:** ultrasound to confirm hepatic steatosis, rule out other pathology
 - Non-invasive evaluation for advanced fibrosis (F3-4); assess q3y – if indeterminate, consider 2nd test ([J Hepatol 2015;63:237](#); [Hepatology 2019;70:1521](#); [DDS 2016;61:1356](#); [Hepatology 2018;67:260](#))

Diagnostic	Considerations	Rule Out	Rule In
NAFLD fibrosis score (NFS)	Use to triage pts 35-65yo w/ ↓ risk of advanced fibrosis & monitor progression; quick but not liver-specific	< -1.455 (Sn 90%, Sp 60%)	≥ 0.676 (Sn 67%, Sp 97%)
FIB4		< 1.3 (Sn 82%, Sp 57%)	> 2.67 (Sn 36%, Sp 93%)
VCTE (FibroScan)	Most used/validated; high user variability, limited in pts w/ severe obesity and ascites	< 9.9 kPa (Sn 83%, Sp 61%)	≥ 11.4 kPa (Sn 75%, Sp 71%)
Ultrasound elastography	Similar to FibroScan, also provides imaging; obtain if need for ultrasound	< 7.1 kPa (Sn 94%, Sp 52%)	> 9.2 kPa (Sn 93%, Sp 81%)

- Referral to Hepatology:** persistent/significant transaminitis, advanced fibrosis, need for liver bx
- Biopsy:** consider for pts at high risk of advanced fibrosis/NASH or competing etiologies of liver disease

MANAGEMENT ([CLD 2020;15:4](#))

- Lifestyle intervention:** weight loss ≥5% ± ↓500-1000 kcals/d reduces hepatosteatosis; 7-10% weight loss may improve fibrosis; Mediterranean diet, low carb, higher protein diet associated w/ improvement in weight loss; reducing fructose consumption helpful; exercise can significantly improve insulin resistance & outcomes
- Pharmacotherapy:** pioglitazone improves histology; vitamin E 800IU/d improves histology in pts without DM in bx-proven NASH (PIVENS trial, [NEJM 2010;362:1675](#)); omega-3 FAs improve hyperTG in pts with NAFLD ([APL 2010;31:679](#)); GLP-1ra in pts with F2/F3 fibrosis to ↑NASH resolution w/o improved fibrosis ([NEJM 2021;384:1113](#))
 - Not recommended currently: metformin (give if T2DM for ↑weight loss), UDCA, obeticholic acid, elafibranor
- Surgery:** consider bariatric surg in eligible pts with obesity and NAFLD or NASH
- Other considerations:** vaccinate for HAV/HBV, tx comorbidities, avoid EtOH consumption, statin if risk factors

Gastroenterology

End Stage Liver Disease

DEFINITIONS

- Cirrhosis: state of irreversible fibrosis and formation of regenerative nodules that distorts hepatic architecture and vasculature
- Compensated cirrhosis: no ascites, encephalopathy, jaundice or GI bleeding. May have nonbleeding varices. Usually asx.
- Decompensated cirrhosis: development of ascites, hepatic encephalopathy, jaundice, variceal bleeding or hepatorenal syndrome
- End-stage liver disease (ESLD): accompanying pathophysiologic state of impaired liver function

CLINICAL MANIFESTATIONS AND DIAGNOSIS ([JAMA 2012;307:832](#))

- **Symptoms**: fatigue/weakness, jaundice, pruritus, nausea, anorexia, abdominal distention, GIB, confusion, muscle cramps
- **Exam**: ↓BP, splenomegaly, caput medusae, ascites, jaundice, spider angiomas, gynecomastia, testicular atrophy, palmar erythema, asterixis, white nails, Dupuytren's contracture
- **Labs**: ↑TBili, ↑INR, ↓alb, ↓Na, ↓PLT, ± ↓Hgb/Hct, ↓WBC; AST, ALT, alk phos, and GGT may be ↑ or normal
- **Diagnostics**: viral hepatitis panel, iron studies, ANA, ASMA, AMA, α1AT, ceruloplasmin, SPEP
- **Imaging**: RUQUS (with Doppler) to assess echogenicity/morphology of liver, ascites, vascular patency, biliary tree, HCC
- **Biopsy**: gold standard but performed less often. Main indications are dx uncertainty or indeterminate fibrosis severity ([NEJM 2017;377:756](#)). Perc. (cannot do through ascites, massive obesity) or transjugular (allows HVPG measurement; pref. if coagulopathy)

ETIOLOGIES

- **Most common**: alcohol, viral (HCV, HBV), non-alcoholic fatty liver disease (NAFLD)
- **Genetic disorders**: hemochromatosis, Wilson's, α1AT deficiency, CF, inherited disorders of glucose metabolism
- **Immune-related**: autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), celiac disease
- **Vascular**: post-hepatic portal HTN (right heart failure, Budd-Chiari syndrome, veno-occlusive disease)
- **Other**: infection (i.e. schistosomiasis), meds (e.g. MTX, isoniazid, amiodarone; see [LiverTox](#)), cryptogenic/idiopathic

NATURAL HISTORY AND RISK STRATIFICATION ([J Hepatol 2006;44:217](#))

- **MELD score**: predicts 90d mortality, used for transplant allocation
- **Child-Pugh class**: assesses cirrhosis severity, predicts 1-2y mortality
- **Compensated**: Child-Pugh Class A. Median survival 12y, 1y survival >95%. 5-10% risk of decompensation per year.
- **Decompensated**: Child-Pugh Class B/C. Median survival 2y, 1y survival 40-80%

COMPLICATIONS OF CIRRHOsis

- **Portal hypertension**: esophageal varices, portal hypertensive gastropathy, hypersplenism (→cytopenias), ascites, SBP, hepatorenal syndrome, hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension, cirrhotic cardiomyopathy
 - Hepatic venous pressure gradient (HVPG) measurement can confirm portal HTN (gradient b/w portal vein and IVC)
 - Normal HVPG <5mmHg; Portal HTN ≥6; Clinically-significant portal HTN: ≥10; Risk of EV bleed: ≥12
- **Hepatic encephalopathy**: see [ESLD: HE](#)
- **Immune dysfunction**: increased risk of infection; bacterial and fungal infections are major causes of morbidity & mortality
- **Endocrinopathies**: hypoglycemia, thyroid dysfunction, hypogonadism, hyperestrinism (palmar erythema, spider angiomas)
- **Coagulopathy**: see [ESLD: Hematologic Abnormalities](#)
- **Portal vein thrombosis**: ↑risk due unbalanced hemostasis & slowing of portal flow. Start AC for acute PVT w/ LMWH (unless high bleeding risk); transition to DOAC or warfarin once stable & continue at least 6mo (AGA: [Gastro 2019;157:33](#))
- **Hepatocellular carcinoma**: see [ESLD: HCC](#)
- **Frailty**: encompasses sarcopenia, functional decline, deconditioning, malnutrition, impaired cognition. A/w decompensation, hospitalization, and mortality. ([Hepatology 2017;66:564](#); [Am J Gastroenterol 2016;111:1759](#))

VIBES: a systematic approach to the management of cirrhosis

General: etiology of cirrhosis, complications, compensated/decompensated, etiology of decompensation (infection [including new/reactivation of HBV/HCV], GIB, EtOH, HCC, dehydration, meds, surgery, etc.), Child-Pugh class, MELD score

Volume (ascites, edema, hepatic hydrothorax, hepatorenal syndrome)

- Current diuretics & response; dietary Na+ restriction (<2 g/d), fluid restriction 1.5L (if Na<125)
- Prior history of LVPs, thoracentesis for hepatic hydrothorax, consideration of TIPS if refractory

Infection

- Prior history of SBP, whether has indication for 1° or 2° ppx
- Current treatment or ppx

Bleeding (esophageal/gastric varices, portal hypertensive gastropathy, coagulopathy)

- Prior history/source of bleeding, therapies (e.g. banding, sclerotherapy, TIPS), current prophylaxis (β blocker)
- Current bleed: severity, IV access, H/H trends, medical therapy (PPI/octreotide), results/plan for EGD, SBP ppx as above

Encephalopathy

- Prior history, precipitant, and treatment
- Current severity, trend, precipitant, medicines, goal #BM (e.g. 4 BM/day, 500cc stool, mental status improvement)

Screening/Surgery (transplant)

- Vaccinations: HAV, HBV, Influenza, Pneumovax, Prevnar, all other standard vaccines, see [Transplant ID](#)
- Maintenance: alcohol abstinence, avoid NSAIDs, HCC screening with q6mo RUQUS ± AFP
- Transplant status: listed or not listed, MELD score, Milan criteria if HCC, classically requires 6 months sobriety

Gastroenterology

End Stage Liver Disease

ASCITES (AASLD: [Hepatology 2013;57:1651](#))

- Most common cirrhosis complication (50% in 10 years); development of ascites → 15% 1y mortality, 44% 5y mortality
- Pathophysiology: portal hypertension → ↑NO, prostaglandins → splanchnic vasodilation → ↓intravascular volume → ↑RAAS, ADH → Na & water retention. Severity of hypoNa (from ADH secretion) correlates with worsening survival
- Diagnosis: dx para indicated for all new-onset or worsening ascites & pts w/ ascites w/ acutely decomp. cirrhosis or hospitalized
 - Studies: **cell count w/ diff, albumin, total protein, GS/Cx ± glucose, LDH, amylase, cytology (malignancy), AFB Cx/ADA (TB)**
 - DDx: **portal HTN** vs. non-portal HTN. **SAAG** differentiates 97% of time ([Annals 1992;117:215](#))

SAAG ≥1.1 g/dL		SAAG <1.1 g/dL	
Etiology related to portal hypertension	Etiology not related to portal hypertension	Etiology related to portal hypertension	Etiology not related to portal hypertension
<ul style="list-style-type: none"> Cirrhosis (ascites fluid total protein [AFTP] <2.5) CHF, constrictive pericarditis (AFTP >2.5) Acute hepatitis (including EtOH) Massive liver metastases Hepatocellular carcinoma Budd-Chiari syndrome (AFTP >2.5) Portal vein thrombosis 		<ul style="list-style-type: none"> Secondary bacterial peritonitis TB peritonitis Peritoneal carcinomatosis (+cytology) Chylous ascites (triglycerides >200) Hypoalbuminemia (nephrotic synd., protein-losing enter.; AFTP <2.5) Serositis (e.g. SLE) Pancreaticobiliary 	

- Management of ascites:
 - 1st line: <2g Na, ○EtOH, ○NSAIDs, diuretics (see below), avoid ACEi/ARB; fluid restrict 1.5L if Na <125
 - Initiating therapy*: **100mg/d spironolactone + 40mg/d furosemide is usual starting dose (5:2 ratio)**. Combo maintains eukalemia & mobilizes fluid faster. May start lower if older. Consider spironolactone alone for mild first ascites if output ↓
 - Ongoing therapy*: ↑dose q3-5 days if inadequate diuresis (5:2 ratio, though can adjust PRN if abnormal K). **Max doses**: 400mg spironolactone and 160mg furosemide. Δ to amiloride 10-40mg qd if painful gynecomastia w/ spironolactone
 - If unsuccessful*: Check U_{Na}/U_K ratio if pt gaining weight/requiring LVPs on diuretics; U_{Na}/U_K <1 suggests ineffective diuretic dose or resistance; U_{Na}/U_K >1 suggests >2g Na dietary intake; stricter dietary Na restriction may be more helpful
 - Weight loss goals: 0.5 kg/d** (TBB -500) if no peripheral edema (AKI risk if too fast); if edema, 1kg/d or -1L. **Avoid IV diuretics** (azotemia risk ↑). Ascites mobilizes fluid slower than other compartments ([Gastro 1986;90:1827](#))
 - Therapeutic LVP**: indicated for tense or refractory ascites or inability to use diuretics; **if >5L, transfuse 6-8g albumin for every L ascites removed**
 - Albumin: long term administration may offer survival benefit ([Lancet 2018;391:2417](#)), but expensive.
- Refractory ascites:
 - Defined as: (1) unresponsive to Na-restricted diet and high-dose diuretics or (2) rapid reaccumulation after LVP
 - Management: consider d/c βBs (↑mortality in refractory ascites; [Hepatology 2010;52:1017](#)), avoid ACEi/ARB (↓renal perfusion), midodrine TID ([J Hepatol 2012;56:348](#)), serial LVPs (usually ~q2w), TIPS as bridge to OLT

SPONTANEOUS BACTERIAL PERITONITIS (SBP) (AASLD: [Hepatology 2013;57:1651](#))

- Must r/o SBP in all inpatients w/ cirrhosis & ascites w/ dx para; 10-30% hospitalized pts w/ cirrhosis have SBP
- Diagnosis: >250 PMN/L w/ positive GS/Cx (SBP) or negative GS/Cx (CNNA = similar mortality to those w/ +Cx; treated similarly)

⊕ Ascites culture		⊖ Ascites culture
PMN ≥250/μL	Spontaneous bacterial peritonitis (SBP) (secondary peritonitis → polymicrobial)	Culture negative neutrocytic ascites (CNNA)
PMN <250/μL	Non-neutrocytic bacterascites (NNBA)	Normal

Hemorrhagic ascites: RBC >50,000/mm³, often due to traumatic tap → correct PMN count by subtracting 1 PMN for every 250 RBCs

- Usually monomicrobial; GNR 70% (*E. coli*, *Klebsiella*), GPC 25% (*S. pneumoniae*), anaerobes 5%
- If polymicrobial, consider secondary bacterial peritonitis 2/2 perforation vs. loculated abscesses
- Bowel perf. suggested if ≥2 of the following: TP >1, LDH >ULN, or Glc <50; also CEA >5 & ALP >240 (Runyon's criteria)
- Treatment:
 - CTX 2g q24h x5d AND 25% albumin** (1.5g/kg on day 1, then 1.0g/kg on day 3, max 100g; indicated if Cr >1, BUN >30, or TBili >4); IV cipro (400mg q12) is alternative if unable to take cephalosporin (unless taking cipro for ppx)
 - Discontinue βBs indefinitely given increased risk of AKI & HRS once SBP is diagnosed ([Gastro 2014;146:1680](#))
 - Repeat para if no improvement in 48h** to rule out 2° peritonitis → add anaerobic coverage, CT A/P ± surgery c/s
 - Patients w/ NNBA w/ s/s of infection (e.g. temperature >100°F, abdominal pain, tenderness) should receive empiric abx
- Prophylaxis:
 - IV CTX 1g q24 x7 days if GIB**; can switch to tx dose PO cipro (500mg q12) or PO Bactrim (DS BID) if not bleeding & stable
 - All patients w/ prior SBP should receive 2° PPX (after full tx above) w/ **PO cipro 500 qd** (at MGH) or **PO Bactrim DS qd**
 - Consider 1° prophylaxis if ascitic TP <1.5 AND impaired renal function (creatinine ≥1.2, BUN ≥25 or serum Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3) ([Gastro 2007;133:818](#))

Gastroenterology

HEPATIC ENCEPHALOPATHY (HE) ([NEJM 2016;375:1660](#); AASLD: [Hepatology 2014;60:715](#))

- Pathophysiology: ↑NH₃ → neurotoxic effects, abnl neurotransmission, ↑GABA- & BDZ-like neurotransmitters & altered glutaminergic inputs → ↓excitatory transmission. In ALF, acute ↑NH₃ → cerebral edema
- Diagnosis:** clinical. Serum NH₃ should not be used to screen for HE. ↑NH₃ **does not add diagnostic, staging, or prognostic value** in CLD ([JHM 2017;12:659](#)). Only helpful in ALF (predicts mortality). **Trend via exam findings** (see grades)
- Asterixis:** “flapping tremor” is **negative myoclonus** w/ loss of postural tone; **alternative is hand grip:** oscillates b/w tight and loose ([APT 2010;31:537](#))
- Precipitants:** infection, dehydration/overdiuresis, GIB, ↓K or alklosis (↑renal NH₃), constipation, sedatives/BZD, new HCC, new clot, TIPS
- Treatment:** ↓GI NH₃ absorption, avoid/correct precipitating factors
 - Lactulose:** Δs gut microbiome, has laxative effect; 30mL q2h until BM → titrate to 3-4 soft BM/day (PO, PR or NG)
 - Lactulose + rifaximin 550mg BID > lactulose alone** for HE reversal (NNT = 3) & all-cause mortality (NNT = 4) ([AJG 2013;108:1458](#)); prevents recurrence of HE ([NEJM 2010;362:1071](#)). Add rifaximin if refractory or 2nd admission
 - If refractory, consider non-standard therapies: oral branched-chain AAs ([Cochrane Reviews 2017;5](#)), IV L-ornithine L-aspartate ([Hepatology 2018;67:700](#)), probiotics ([Cochrane Rev 2017;2](#)), PEG ([JAMA Int Med 2014;174:1727](#))
 - FMT may have role ([Hepatology 2017;66:1727](#); [Gastro 2019;156:1921](#))
 - Maintain K >4 to improve ammonia clearance

Grades of Hepatic Encephalopathy (West Haven Criteria)		
Covert	Grade 1	Inattention, euphoria/ anxiety, altered sleep pattern , ↓attention span
Overt	Grade 2	Lethargy, behavior Δs, time disorientation, asterixis , personality Δs, hypoactive DTRs
	Grade 3	Somnolence to semi-stupor, responsive to stimuli, time & place disorientation, asterixis, hyperactive DTRs
	Grade 4	Coma

VARICEAL BLEEDING (AASLD: [Hepatology 2017;65:310](#))

- Screening:** esophageal varices most common (50% of patients). Baseline EGD at cirrhosis diagnosis unless liver stiffness <20kPa (by transient elastography) & platelets >150 (very low probability)
 - Repeat EGD q2yrs (if ongoing injury/condition), q3yrs (if injury quiescent), or if decompensation event & previously no/small EVs

1° PPX	EVs identified → ppx if high risk of bleeding:	<ul style="list-style-type: none"> - Medium/large: non-sel. βB (see below), carvedilol (6.25mg qd x3d → ↑ to 6.25mg BID), OR serial endoscopic variceal ligation (EVL) q2-8w until eradication - Small: non-selective βB
	Episode of variceal bleeding → ppx to prevent recurrence w/ combination of non-selective βB + EVL	<ul style="list-style-type: none"> - Non-selective βB: nadolol 20-40mg qd or propranolol 20-40mg BID; adjust every 2-3d to goal HR 55-60, SBP>90; max daily dose in patients with/without ascites: propranolol 160 320mg/d or nadolol 80 160mg/d - Serial EVL: q1-4w until obliteration; repeat EGD 3-6mo after & then q6-12mo

- Acute bleeding:** IV access, IVF, pRBC, PPI, octreotide, CTX, EGD. May need intubation for EVL, Blakemore as a bridge (GI), urgent TIPS (IR) if cannot band. **Conservative transfusion:** goal Hgb 7-9 ([NEJM 2013;368:11](#)). See [Upper GI Bleeding](#)
- Indications for TIPS:** early “preemptive” TIPS (<72h) in pts with high risk of treatment failure or rebleeding ([NEJM 2010;362:2370](#); [Hepatology 2019;69:282](#)); “rescue” TIPS if uncontrolled bleeding or if recurs despite max medical & endoscopic therapy
- Gastric varices:** similar mgmt. of acute bleed. Can consider TIPS, BRTO, or endoscopic glue or coil injection. TIPS favored if also EV
- Stop βB if:** SBP, refractory ascites, HRS, low BP, sepsis; “window hypothesis” (βB have no effect on survival or prevention in early cirrhosis, have survival benefit in middle stages, & reduce survival in advanced cirrhosis) ([J Hepatol 2014;60:643](#); [Gastro 2014;146:1597](#))

HEMATOLOGIC ABNORMALITIES (AGA: [Gastro 2019;157:33](#); [NEJM 2011;365:147](#); [CGH 2013;11:1064](#); [Thromb Haemost 2018;118:1491](#))

- Cytopenias:** **thrombocytopenia** (splenomegaly, ↓TPO), **leukopenia** (splenomegaly), **anemia** (bleeding, spur cell anemia); may have BM suppression from EtOH/infection, nutritional deficiencies (e.g. folate), direct effect of HCV/HBV
- Coagulation abnormalities:** ↓**coagulation factors** (except for FVIII), ↓**anticoagulant proteins** (C, S, ATIII), **dysfibrinogenemia**, **accelerated fibrinolysis** (↑tPA) → ↑**risk of both clotting and bleeding** & patients not auto-anticoagulated; balance tends to favor thrombosis in early stages vs bleeding in late stages of cirrhosis
 - Labs:** ↑PT/INR, ↑PTT, ↑/nml fibrinogen (though does not function normally; ↓ if fulminant), ↑/nml D-dimer (vs ↑↑ in DIC), ↑factor VIII (vs ↓ in DIC); note PTT and PT/INR do **NOT** correlate with risk of bleeding or clotting
- Anticoagulation:** ([J Hepatol 2017;66:1313](#); [JACC 2018;71:2162](#))
 - VTE ppx:** should not be withheld unless high risk of bleeding or plts<50
 - Systemic AC:** ok unless CPS C or high risk of bleeding. EGD for EVs prior. VKA, LMWH, or DOAC all options. VKA dosing c/b baseline PT/INR; LMWH c/b ↓ATIII levels; DOACs relatively safe – can use all except rivaroxaban w/ caution in CPS B
- Bleeding:** consider role of coagulation factor deficiency, dysfibrinogenemia, hyperfibrinolysis, thrombocytopenia
 - If suspect vitamin K deficiency, give **vitamin K** 10mg x3d to correct nutritional component
 - pRBCs** Hgb <7, **platelets** <50k, **cryo** for fibrinogen <100-120. FFP if persistent (though large volume → ↑portal pressures)
 - Delayed bleeding or oozing from mucocutaneous sites → **Amicar** (3g PO QID or 4-5g IV over 1h → 1g/h) or TXA (1g IV q6h)
- Procedures:**
 - Platelets:** >50k for surgery, TIPS, liver biopsy, or other procedure w/ high bleeding risk; TPO agonists can reduce need for peri-procedural PLT transfusions but take ~10d to ↑PLT ([NEJM 2012;367:716](#); [Gastro 2018;155:705](#))
 - PT/INR:** **NO** benefit to giving FFP pre-procedure to “correct” INR. ↑volume can ↑bleeding risk by ↑portal pressures

Gastroenterology

End Stage Liver Disease

HEPATOCELLULAR CARCINOMA (HCC) (AASLD: [Hepatology 2018;68:723](#); [Hepatology 2018;67:358](#))

- 2-4% risk per year. May be asx, lead to decompensation, and/or have sx related to mass effect (pain, early satiety, palpable mass)
- Screening indicated in:
 - **Cirrhosis due to any etiology**, except in Child-Pugh Class C pts not on transplant list (due to low survival time)
 - HBV carriers without cirrhosis if: Asian M >40, Asian F >50, African/African-American, or FHx HCC
- Screen with: RUQUS ± AFP q6mo; if U/S inadequate, can use multiphase CT or MRI
 - If nodule <1cm, repeat US in 3-6mo
 - If nodule ≥1cm or AFP ≥20ng/mL, obtain multiphase CT or MRI & proceed according to [LI-RADS class](#)
- Staging:
 - [AJCC TNM system](#) (for patients getting surgical resection or transplant)
 - [Barcelona system](#) (medical mgmt): size, # of nodules, LN & portal vein involvement, mets, Child-Pugh score, performance status
- Management:
 - **Curative:** surgical resection (1st line if Child-Pugh A & T1-T2 nodule), OLT (if non-resectable but within [Milan criteria](#))
 - **Noncurative:** ablation, chemoembolization (TACE), radioembolization (TARE), radiation, chemo (sorafenib), immunotherapy
 - Within Milan criteria → local-regional tx (LRT) as bridge to OLT. Outside Milan → LRT to downstage to w/in Milan → OLT
 - Not OLT candidate (and non-resectable) → LRT and/or systemic chemotherapy
- Prognosis: survival by Barcelona stage: 0-A (early): >5y, B (intermediate): 2-5y, C (advanced): >1y, D (terminal): 3mo

HEPATIC HYDROTHORAX (AASLD: [Hepatology 2013;57:1651](#))

- Transudative effusion due to **shift of ascites into pleural space** (due to neg. intrathoracic pressure) via small diaphragmatic defects. Can be seen w/o significant ascites. Usually **unilateral**: R (~75%) > L-sided (~15%) > bilateral (~10%) ([Medicine 2014;93:135](#))
- Diagnosis: exclude other causes of transudative effusion; can visualize w/ radioisotope injection into ascites if dx unclear
- Treatment: first line: **diuretics, 2g Na restriction**. Therapeutic thora for dyspnea. TIPS if refractory. **Chest tube not recommended**
- Spontaneous bacterial empyema: can become infected (~15%) due to translocation of bacteria from abd. cavity. ~40% occur in absence of SBP ([Hepatology 1996;23:719](#)). Dx: >250 PMNs w/ +Cx or >500 PMNs w/o +Cx. Tx: same as for SBP

HEPATOPULMONARY SYNDROME (HPS) (NEJM 2008;358:2378; EASL: [J Hepatol 2018;69:406](#); ILTS: [Transplantation 2016;100:1440](#))

- Syndrome of **shunting through intrapulmonary vascular dilatations**; mechanism unclear, **possibly due to circulating NO**
- Presentation: shunting tends to occur at bases → **platypnea** (dyspnea when upright, relieved when supine) & **orthodeoxia** (upright hypoxemia, PaO₂ ↓ by 4 mmHg or ≥5%), clubbing, cyanosis, diffuse telangiectasias, hypoxemia (PaO₂ <70-80)
- Diagnosis: **TTE with late bubbles** (3-6 cardiac cycles after RA), **↑A-a gradient ≥15mmHg** (or ≥20mmHg if age >64)
 - ^{99m}Tc MAA scan is alternative to TTE but more invasive, less sensitive. May be useful in quantifying shunting if severe hypoxemia and coexisting intrinsic lung disease
 - Pulmonary angiography performed if severe hypoxemia poorly responsive to 100% O₂ & areas amenable to embolization
 - PFTs can be performed to evaluate for intrinsic lung disease; ↓DLCO in HPS
- Risk stratification: on RA → *mild:* PaO₂ ≥80, *moderate:* 60-79, *severe:* 50-59, *very severe:* <50 **OR** PaO₂ <300 on 100% O₂
- Management: O₂ to maintain sat >88%; no effective medical therapies. OLT can significantly improve (and reverse) HPS – MELD exception points given for severe HPS

PORTOPULMONARY HYPERTENSION (EASL: [J Hepatol 2018;69:406](#); ILTS: [Transplantation 2016;100:1440](#))

- Rare cause of **group 1 pulmonary hypertension** in setting of portal HTN
- Pathogenesis: ↓blood flow to pulm. arterial bed. Mechanisms unclear but include vasoconstrictors normally cleared by liver (e.g. endothelin-1, estradiol) reaching pulmonary circulation, ↓prostacyclin synthase, endothelial proliferation and PLT aggregation. 3x higher risk in women than men. More common in autoimmune liver disease
- Presentation: DOE, fatigue, chest pain, palpitations, lightheadedness, orthopnea, leg edema, hemoptysis; often w/ TR, JVD, EKG w/ RVH, RAD, RBBB
- Diagnosis: RHC w/ PAH (mPAP ≥20mmHg, PCWP <15 mmHg, PVR >3) in pt with portal hypertension in absence of other etiology
- Risk stratification: *mild:* mPAP <35, *moderate:* mPAP 35-44, *severe:* mPAP ≥45
- Management: may benefit from advanced therapies (epoprostenol, bosentan, sildenafil, iloprost). OLT can improve PAH (MELD exception points given for moderate PPH). β-blockers and TIPS may be harmful and should be avoided
- Transplant: increased risk of morbidity/mortality with mPAP ≥35; mPAP ≥45 is an absolute contraindication to transplant

CIRRHOTIC CARDIOMYOPATHY (Hepatology 2020;71:334; EASL: [J Hepatol 2018;69:406](#))

- Chronic cardiac dysfunction in cirrhotic pts w/o known cardiac disease; characterized by 1) impaired cardiac contractility in response to stress, 2) altered diastolic relaxation, 3) electrophysiological abnormalities such as prolonged QTc
- Pathophysiology: myocardial dysfunction 2/2 systemic inflammation; shear stress from portal hypertension → mechanical force on myocardial fibers; other possible mechanisms involve collagen configuration, sodium retention and activation of RAAS
- Prevalence: up to 50% of pts undergoing liver transplantation have signs of cardiac dysfunction
- Diagnosis: echocardiography with dynamic stress testing
- Treatment: same as HF management in non-cirrhotic pts
- Prognosis: largely subclinical; poses risk with stressors (infection, TIPS, OLT). Detailed cardiac assessment prior to interventions

Gastroenterology

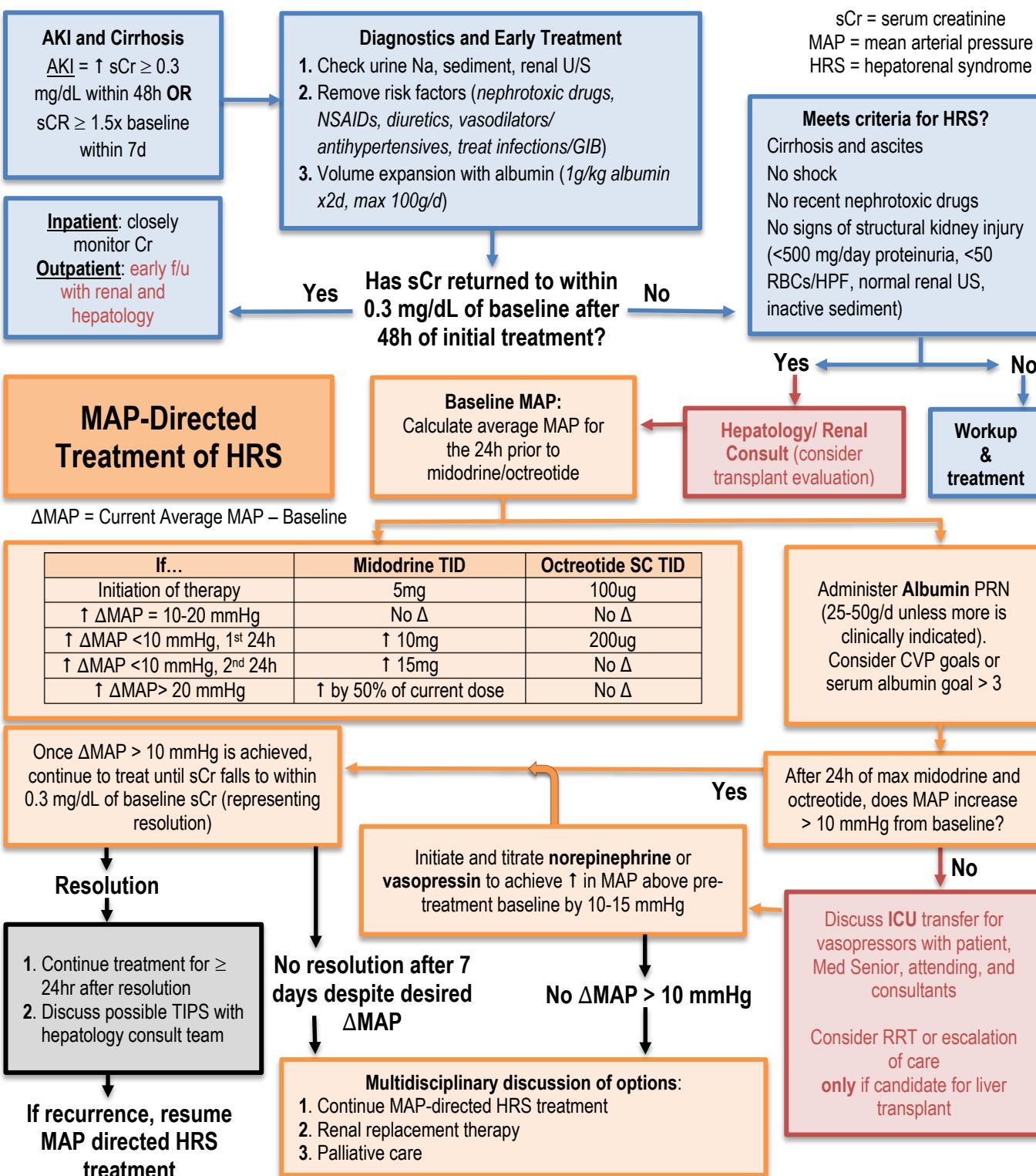
Hepatorenal Syndrome

HEPATORENAL SYNDROME (HRS) (NEJM 2009;361:1279; Clin Gastro Hep 2018;16:162; BMJ 2020;370:2687)

- Pathophysiology:** portal HTN → ↑NO, prostaglandins → splanchnic vasodil. → ↓EABV → ↑RAAS, ADH, SNS → renal vasoconstr.
- Diagnosis:** **dx of exclusion:** need: (1) chronic or acute hepatic disease w/ portal HTN, (2) ↑Cr >0.3/48hrs or >50%/7d, (3) absence of shock, (4) no parenchymal disease, (5) no current/recent nephrotoxins, (6) no improvement after 2d cessation of diuretics + **albumin challenge** (1g/kg of 25% albumin x2d, max 100g/d; goal is ↑ oncotic pressure, not volume expansion)
- Type I (AKI-HRS):** ↑Cr 2x b/l and >2.5 mg/dL in <2w + multiorgan dfxn; **Type II (CKD-HRS):** slower ↓, often have refractory ascites
- Precipitants:** infection (SBP > other), GI bleed, fluid shifts after LVP, alcohol-related hepatitis
- Management:** see below. Use albumin + octreotide + midodrine or norepinephrine to increase MAP & albumin levels. No diuretics, βB, or other vasodilators or nephrotoxins. Poor prognosis, RRT does not improve survival. Consider only if management ineffective and a candidate for OLT. OLT is definitive treatment

MGH Algorithm for the Diagnosis and Treatment of Hepatorenal Syndrome

(Int. Club of Ascites: Gut 2015;64:531; Dig Dis Sci 2014;59:471; Dig Dis Sci 2015;60:1474; Nephron 2015;131:191)



INDICATIONS FOR LIVER TRANSPLANT (AASLD: [Hepatology 2014;59:1144](#))

- Acute liver failure: see [Acute Liver Injury & Failure](#)
- Cirrhosis with MELD ≥ 15 or complication (e.g. ascites, HE, EV bleed, HRS, chronic gastropathy bleed). Survival benefit of OLT $>$ risk at MELD ≥ 15 ([AJT 2005;5:307](#))
- HCC: *first-line option* within [Milan criteria](#) but unsuitable for resection ([NEJM 1996;334:693](#); [Hepatology 2018;69:182](#)); can be “down-staged” to within Milan with treatment; composite criteria (surrogates of tumor biology such as AFP, treatment response, tumor size, number of nodules) are likely to replace conventional criteria. See [ESLD: HCC](#)
- Liver-based metabolic disorders w/ systemic manifestations: A1AT deficiency, familial amyloidosis, Wilson’s disease, hemochromatosis, glycogen storage disease, primary oxaluria
- Systemic complications of chronic liver disease: hepatopulmonary syndrome, portopulmonary HTN
- Condition qualifying for exception (see below under “Prioritization for Liver Transplant”)

Milan Criteria:

One lesion ≤ 5 cm or up to 3 lesions all ≤ 3 cm
No extra-hepatic involvement
No major vessel involvement

CONTRAINDICATIONS TO LIVER TRANSPLANT

- Absolute: severe cardiac or pulmonary disease, AIDS, HCC w/ metastatic spread, ongoing EtOH/illicit substance use within 6mo (changing for EtOH in select cases; see [Alcohol-Related Liver Disease](#)), uncontrolled sepsis, anatomic abnormality that precludes LT, intrahepatic cholangiocarcinoma, extrahepatic malignancy (not meeting criteria for cure), fulminant hepatic failure with sustained ICP >50 mmHg or CPP <40 mmHg, hemangiosarcoma, persistent nonadherence to medical care, lack of adequate social support system
- Relative: BMI ≥ 40 , HIV (all center-specific)

PRIORITIZATION FOR LIVER TRANSPLANT

- Prioritized based on MELD Score ([AJT 2015;15:2552](#)) & stratified by blood type. Updated regularly & more frequently if more severe disease
- Certain conditions result in impaired survival but are not directly accounted for in the MELD score \rightarrow specific disease-related criteria for MELD exceptions that upgrade MELD score w/ subsequent automatic upgrade q3mo
- Standard MELD exceptions: HCC (w/in Milan criteria, AFP <1000), hepatopulmonary syndrome (RA PaO₂ <60 mmHg), portopulmonary HTN (mPAP <35), familial amyloid polyneuropathy (TTR mutation), primary hyperoxaluria, CF (FEV1 $<40\%$), hilar cholangiocarcinoma, hepatic artery thrombosis (w/in 14d of LT but not meeting status 1A criteria)
- Can also petition review board for non-standard exceptions (e.g. recurrent cholangitis in PSC, intractable pruritus in PBC, refractory complications)

TRANSPLANT EVALUATION PROCESS

- Laboratory testing: order set in EPIC; BMP, Ca, Mg, Phos, LFTs, GGT, CBC w/ diff, PT/PTT, T&S, Fe/TIBC, ferritin, ceruloplasmin, A1AT level, autoimmune (ANA, ASMA, AMA, SPEP), viral hepatitis (HAV IgG, HBsAg, HBsAb, HBcAb [total], HBeAb, HBV DNA, HCV Ab & PCR, HDV Ab), HIV, EBV, CMV, VZV, HSV, RPR, toxo, measles/mumps/rubella titers, IGRA, AFP, PSA, amylase, uric acid, total cholesterol, U/A, UCx
- Additional tests: ABG (on RA), EKG, CXR, U/S w/ Doppler, abdominal CT or MRI (!+) (eval for HCC), age-appropriate cancer screening (colonoscopy, mammogram, pap smear), bone density (outpt), cardiopulmonary eval as below
- Immunizations: HAV, HBV, pneumococcus, influenza, Tdap
- Consults: transplant surgery, psychiatry, social work (address psychosocial issues, adequacy of support, financial screening, insurance counseling), nutrition
- Cardiopulmonary eval: TTE w/ bubble \pm PFTs. Dobutamine stress echo may be indicated (typically if >40 or CAD RFs). Optimal strategy debated – AASLD: stress testing in all candidates; AHA/ACC: if multiple CAD RFs ([JACC 2012;60:434](#))
- ID eval: eval for LTBI as above and tx pre-LT if able. Coccidiomycosis, strongyloides testing if from endemic area. Dental extractions pre-LT. HIV not a contraindication if immune function adequate. HBV tx pre-LT. HCV can be tx pre- or post-LT (timing depends on if LT imminent, access to HCV+ donor, comorbidities). Transplant ID consult
- Combined kidney transplant: eligible if CKD w/ GFR ≤ 30 or ESRD on HD; sustained AKI w/ dialysis ≥ 6 wk or GFR ≤ 25 for ≥ 6 wk; or metabolic disease (e.g. hyperoxaluria) (UNOS/OPTN: [AJT 2016;16:758](#))
- Living Donor Transplant (LDLT): recipients should fulfill same minimal listing criteria as for deceased donor

Nephrology

Acute Kidney Injury

DEFINING AKI (KDIGO 2012 Guidelines)

Stage	Serum Creatinine	Urine Output	Work-up and management
1	↑ ≥0.3 mg/dl w/in 48h or ↑1.5-1.9x baseline w/in last 7d	<0.5 ml/kg/h for ≥6h	(1) H&P (2) monitor Cr and UOP (3) UA and sediment (4) urine electrolytes (5) renal U/S and other tests (below)
2	↑2-2.9x baseline	<0.5 ml/kg/h for ≥12h	Above measures plus:
3	↑3x baseline, Cr ≥4, ↓eGFR to <35 (<18 yo), or RRT	<0.3 ml/kg/h for ≥24h, or anuria ≥12h	(1) renally dose meds (2) eval need for RRT (3) consider ICU for CRRT, pressors for renal perfusion (4) avoid subclavian CVCs/PICC (to preserve potential fistula sites)

Diagnostic Tips

- Serum Cr approximates GFR at steady state only (unable to estimate GFR w/ ΔCr): **must assume GFR <10 if ΔCr >1/day**
- Drugs can impair Cr excretion without ΔGFR (BUN remains stable): trimethoprim, H2 blockers (cimetidine), dronaderone
- ↑BUN out of proportion to Cr: pre/post-renal, UGIB, steroid
- ↑Cr out of proportion to BUN: rhabdomyolysis, AIN, TMP-SMX, vancomycin toxicity, malnutrition

STEPWISE WORKUP

1) **History/exam**: vitals (HTN/HoTN), volume status, exposures (contrast, meds), recent infection (IgA nephropathy 1-2d, post-strep GN in 10-14d), active infection (sepsis can induce ATN independent of BP or ↓RBF ([JASN 2011;22:999](#))), trauma/myalgias (rhabdomyolysis), rashes (AIN, vasculitis)

2) **Urinalysis (UA)**: see [Urinalysis](#)

3) **Urine chemistries**:

- FENa: FENa <1% c/w pre-renal AKI, >2% c/w ATN. **ONLY** verified in oliguric AKI, not useful if on diuretics. Note: GN, rhabdo, & IV contrast can all cause FENa <1%. Overall limited use, except to rule out HRS with ↑FeNa ([J Hosp Med 2016;11:77](#))
- FEUrea: if on diuretics and high pretest prob. of pre-renal physiology. FEUrea <35% c/w with pre-renal ([Kid Int 2002;62:2223](#))
- Urine Osm: >500 is consistent with a pre-renal etiology. Patients with ATN are only rarely able to concentrate to this degree
- Urine protein: if proteinuria on UA, send serum albumin, urine total protein, urine microalbumin, & urine Cr. Urine albumin/protein ratio (APR) >0.4 suggests glomerular > tubulointerstitial process (Sn 88%, Sp 99%) ([Nephro Dial Trans 2012;27:1534](#)). Note: dipstick detects albumin; will not help identify light chains/paraprotein

4) **Urine sediment**: see [Urinalysis](#). Important if clinical history/above studies are not strongly suggestive or if AKI fails to respond to initial management

5) **Eosinophilia/eosinophiluria**: poor test for AIN. Urine eos >1% has Sn 31%, Sp 68% ([J Hosp Med 2017;12:343](#))

6) **Renal U/S**: exclude hydronephrosis. In absence of a suggestive history, <1% of renal U/S for AKI showed post-renal etiology; can provide evidence of chronic processes if no known hx ([BMC Nephrol 2013;14:188](#))

7) **Monitor Cr**: assess response to empiric treatment of presumed cause

8) **Next**: if sediment or history suggests glomerular disease, broaden workup with C3/4, ANCA, anti-GBM, ANA, anti-dsDNA, HBV/HCV/HIV, cryo, SPEP w/ IMFX/SFLC as per below. Consider biopsy if expected to change treatment

DIFFERENTIAL DIAGNOSIS OF AKI ([Kid Int 1996;50:811](#))

PRE-RENAL (21%)	INTRINSIC	POST-RENAL (10%)		
↓ Absolute volume <ul style="list-style-type: none"> Bleeding GI or skin loss Diuretics Osmotic diuresis Cerebral salt wasting ↓ Effective volume <ul style="list-style-type: none"> CHF/cardiorespiratory Cirrhosis/hepatorenal Nephrotic syndrome Sepsis/third-spacing Δ renal dynamics <ul style="list-style-type: none"> NSAIDs/COX-2s ACEi/ARBs Abd compart. syndr. Relative hypotension	GLOMERULAR (<4%) <ul style="list-style-type: none"> Anti-GBM ANCA + <ul style="list-style-type: none"> Microscopic polyangiitis Granulomatosis with polyangiitis (GPA) Eosinophilic GPA Drug-induced ANCA Immune complex <ul style="list-style-type: none"> <u>Low complement</u>: PSGN, SLE, cryo, MPGN, MGRS <u>Normal complement</u>: IgA nephropathy/HSP Fibrillary/immunotactoid 	TUBULO-INTERSTITIAL <ul style="list-style-type: none"> ATN (45%) <ul style="list-style-type: none"> Ischemia, sepsis, toxic Contrast, rhabdo, aminoglycosides AIN (2%) <ul style="list-style-type: none"> Meds (see below) Infectious: CMV, leptospiral, legionella Autoimmune/infiltrative: TINU, IgG4 disease, sarcoid Crystals <ul style="list-style-type: none"> TLS, acyclovir, ethylene glycol Proteins <ul style="list-style-type: none"> MM, amyloid, Ig deposition 	VASCULAR <ul style="list-style-type: none"> Microvascular (<4%) <ul style="list-style-type: none"> TTP/HUS APLAS HELLP/Eclampsia Scleroderma Meds (calcineurin inhib/CIN, gemcitabine) Macrovascular (1%) <ul style="list-style-type: none"> RAS (athero, FMD) Dissection Renal artery/vein thrombosis 	Urinary retention <ul style="list-style-type: none"> BPH, meds, neurogenic Foley dysfunction Urinary obstruction (bilateral) <ul style="list-style-type: none"> Stones (single kidney/transplant) Malignancy Retroperitoneal fibrosis

Common medications related to AKI (not comprehensive):

AIN: NSAIDs, β-lactams, ciprofloxacin, sulfa drugs, rifampin, PPIs (delayed effect), cimetidine, mesalamine, allopurinol

Direct tubular injury: NSAIDs, calcineurin inhibitors, ACEi/ARB, methotrexate, acyclovir (IV>>PO), protease inhibitors, amphotericin, tenofovir (proximal tubule), vancomycin (esp w/ pip-tazo), numerous cytotoxic, targeted, & immunotherapy cancer rx ([CID 2017;64:116](#))

MANAGEMENT

"A Euvolemic Kidney is a Happy Kidney; Fluids are NOT always the answer"

1. **Optimize hemodynamics, avoid nephrotoxins:** correct volume status - IVF if hypovolemic, diuretics if hypervolemic. Stop NSAIDs/ACEi/ARBs, spironolactone, diuretics (if prerenal). Avoid ↑glucose and contrast. No evidence of benefit for empiric diuretics in oliguria ([JAMA 2002;288:2547](#)). If fluids, LR > NS ([NEJM 2018;378:819](#); [NEJM 2018;378:829](#))
2. **Renally dose meds:** antibiotics, narcotics, LMWH → UFH, leviteracetam. Pre-hydrate if GFR <30 for contrast (MGH protocol)
3. **Manage complications:**
 - **HyperK:** calcium gluconate, insulin/dextrose → patiromer/sodium zirconium, bowel reg, furosemide
 - **Hyperphos:** sevelamer vs. phoslo depending on calcium
 - **Metabolic acidosis:** sodium bicarb PO/IV (see [Acid-Base Disorders](#))
 - **Bleeding** with concern for uremic platelets: DDAVP 0.3 mcg/kg IV, onset 1h, lasts 4-8h
4. **Indications for HD (AEIOU):** Acidosis (esp. pH <7.0, refractory to bicarb), Electrolytes (refractory hyperK⁺), Intoxication (lithium, ethylene glycol, metformin, salicylates, theophylline), refractory Volume Overload, Uremia (encephalopathy, neuropathy, pericarditis)

RENAL EMERGENCIES (WHEN TO PAGE THE RENAL FELLOW OVERNIGHT)

- **Acidosis:** severe metabolic acidosis, unstable patient, usually in the ICU with pH <7.0. Temporize with bicarb pushes and isotonic bicarb gtt, intubation and hyperventilation if unable to compensate by breathing off CO₂. May need RRT. CVVH does not remove lactic acid and is similar in correction rate to bicarbonate infusion
- **Hyperkalemia:** marked hyperkalemia leading to ECG changes or arrhythmia (K >6.5). Temporize with Ca gluconate, furosemide, insulin/D50, albuterol, etc. Note HD much faster at clearing K than CVVH
- **Hyponatremia:** call if severely symptomatic (AMS with low GCS, seizures, etc) requiring bolus hypertonic saline +/- DDAVP clamp
- **Anuria w/ ADHF:** place Foley, monitor UOP/SpO₂/signs of shock. Improving cardiac output (volume optimization with diuretics or HD, ± inotropes) will raise GFR
- **Ingestions:** ethylene glycol, methanol (elevated osmolar gap) with end organ damage (i.e. renal failure, vision loss), see "Indications for HD (AEIOU)" above
- **RPGN:** when suspected, urgent renal consultation to consider pulse dose steroids ± plasmapheresis. See [Glomerular Disease](#)
- **Scleroderma renal crisis:** ACEi (captopril) at maximum tolerated dose (starting at 6.25 or 12.5mg, titrating up q4h). Avoid steroids

SPECIFIC MANAGEMENT BY CAUSE

- **Acute interstitial nephritis (AIN):** stop offending agent, consider prednisone 40-60mg qd for 1-2w if biopsy-confirmed or high pre-test probability though not great evidence ([CJASN 2018;13:1851](#))
- **Cardiorenal syndrome (type 1):** ([Nat Rev Neph 2013;9:99](#); [Circ 2019;139:e840](#))
 - **Definition:** 5 phenotypes that impact the heart and kidneys with various causal relationships. Type 1 is HF resulting in AKI
 - **Pathophysiology:** decreased renal perfusion from ↑venous congestion ± ↓CO lead to a low trans-renal perfusion pressure. More of a problem with "underdraining" (congestion) than "underfilling" (perfusion)
 - **Treatment:** relief of renal venous congestion. Trend Cr against TBB to test hypothesis, expect a lag effect
 - Loop diuretics are first line for type 1 ± addition of thiazide (metolazone/chlorothiazide); see [Advanced Diuresis](#)
 - No benefit of low dose dopamine or nesiritide to improve forward flow ([JAMA 2013;310:2533](#))
 - Ultrafiltration showed similar outcomes re: weight loss and CHF sx, but worsened renal function compared to pharmacologic therapy with loop/thiazide diuretics ([NEJM 2012;367:2296](#))
- **Contrast-Induced nephropathy (CIN):** ([Circ 2012;122:2451](#))
 - **Definition:** ↑Cr ≥0.5 or 25% within 48-72h of contrast without other causes
 - **Clinical syndrome:** starts 24-48h, **peaks 3-5d**, resolves 10d; usually non-oliguric
 - **Pathophysiology:** vasospasm vs acute tubular injury due to osmotic injury. Recent studies: unclear risk of AKI following contrast, likely lower than previously estimated ([Ann Emerg Med 2017;69:577](#)). Weigh risk of CIN against risk of not performing a study
 - **Risk factors:** higher contrast load, hyperosmolar contrast, intra-arterial injection, DM, proteinuria, concomitant AKI
 - **Prophylaxis:** for high-risk pts (GFR <30 or 30-45 + DM) receiving arterial or IV contrast, consider IV NS per MGH protocol (see [Contrast](#)). If treating volume overload, hold diuretics day of contrast with no additional IVF. No added benefit for IV bicarb or NAC ([NEJM 2018;378:603](#)) or pre/post/intra HD ([Am J Med 2012;125:66](#))
- **Crystalline nephropathy:** discontinue drug; fomepizole/HD if ethylene glycol toxicity; rasburicase if TLS
- **HRS:** see [Hepatorenal Syndrome](#)
- **Myeloma kidney (Cast Nephropathy):**
 - **Dx:** TP/Cr, SPEP/UPEP, SFLC, kidney bx if dx unclear
 - **Tx:** IV hydration to target UOP >3L/d to minimize precipitation (volume overload can be treated with diuretics), chemotherapy to decrease production of SFLC per oncology. Unclear benefit of plasmapheresis given rebound of light chain production
- **Post-renal:** Foley, α-antagonists; 5α-reductase inhibitor (effect not immediate); urology/LR if perc nephrostomy tube needed
- **Rhabdomyolysis:** AKI unlikely unless CK >2k-5k; aggressive IVF for UOP >250cc/h with NS. Consider isotonic sodium bicarb if marked acidosis ([NEJM 2009;361:62](#)), but no convincing evidence that HCO₃ is superior to NS. Monitor for electrolyte abnormalities: hyperK, hypoCa. Continue aggressive IVF until CK <5000; continue IVF and add diuresis if volume overload

Nephrology

Glomerular Disease

NEPHROTIC SYNDROME (NS)

Etiology: ↓ podocyte integrity (foot process effacement) → **Triad:** proteinuria >3.5g/day (albuminuria), Alb <3.0g/dL, edema
Associated sequelae: HLD + premature atherosclerosis, foamy urine, hypercoagulability (10-40% VTE risk 2/2 loss of antithrombin & plasminogen), Vit D deficiency (loss of binding protein), infectious risk (↓ IgG/opsonins, esp. strep pneumo), protein malnutrition

Workup: Basic: UA/sed, spot urine P/C (if abnl, send 24h urine protein). First send HbA1c (most proteinuria 2/2 DM) to r/o DM
 Advanced: ANA, anti-dsDNA, anti-PLA2R, SPEP, SFLC, HBV, HCV, HIV, C3/C4, nephrology c/s for possible renal biopsy

Labs: 3+ protein (dip detects albumin) or spot urine P/C > 3000mg/g, fatty casts or oval fat bodies = epithelial cells w/ engulfed lipid (Maltese crosses when polarized), Cr normal or ↑, may have mild nephritic features (hematuria, HTN more common in primary dz)

Treatment: edema: diuretics + low Na diet; HLD: statin; VTE risk: ppx AC; consider ACE/ARB (↓ glom pressure). Steroids may have role

Disease	Associations	Biopsy Findings
Diabetes	T1DM > 5-10y, T2DM, retinopathy. Most common cause of NS	Nodular glomerulosclerosis
FSGS	1°: ↑ in Black patients (APOL1) 2°: viral (HIV, parvo, EBV, CMV), drugs (NSAIDS, pamidronate, INF, rapamycin, heroin), adaptive (2/2 nephrectomy, CKD, obesity, reflux, HTN), chronic hypoxemia (OSA, sickle cell)	Mesangial collapse & sclerosis. Collapsing variant rapidly progresses to ESRD
Membranous	1°: Abs to podocyte PLA2R (75%) (NEJM 2009;361:11) or THSD7A 2°: SLE, HBV, syphilis, drugs (NSAIDs, penicillamine, gold), solid tumors	Thick BM w/ electron-dense subepithelial deposits
Minimal change	Idiopathic, a/w NSAIDs, lymphoma (HL #1), children > adults	Foot process effacement (EM)
MPGN	Mixed nephritic/nephrotic. <u>Immune complex mediated</u> : chronic infxn (HBV, HCV+cryos), SLE, lymphoma, MM. <u>C3 glomerulopathy</u> : dense deposit disease or C3 glomerulonephritis	Thick BM, mesangial proliferation, subendothelial ± subepithelial deposits
Amyloidosis	AL (myeloma) and AA (systemic inflammation, e.g. RA)	Diffuse amorphous hyaline glomerular deposits; +Congo red. IF κ/λ, LC if AL

GLOMERULONEPHRITIS (GN)

Etiology: immune-mediated inflammation of the glomerulus leading to endothelial and podocyte injury → hematuria w/ active sediment (dysmorphic RBC; specific but less sensitive), RBC casts (rare but very specific), subnephrotic proteinuria (<3.5g/d, but 10-30% >3g/d)

Clinical presentation: AKI, HTN, edema, proteinuria, and hematuria. If systemic vasculitis, often fatigue, fever, weight loss, small-vessel involvement of other organ systems (palpable purpura, DAH, mononeuritis multiplex)

- 1) Asymptomatic urinary abnormalities: subnephrotic proteinuria, +/- microscopic hematuria; no renal impairment, edema, or HTN
- 2) Rapidly progressive GN (RPGN): ↓ GFR >50% in ~3 mo, glomerular crescents on bx, 0.5-2.5 g/d proteinuria, dysmorphic RBC. Consult Renal ASAP, consider methylpred (0.5-1g IV QD x3d). Per etiology/biopsy: cyclophosphamide (CYC) or mycophenolate ± rituximab (RTX). Plasma exchange has fallen out of favor ([NEJM 2020;382:622](#))
- 3) Chronic GN: persistent proteinuria, +/- hematuria, slow progression

Workup: UA/sed, C3/C4, ESR/CRP, HBV/HCV/HIV, SPEP/SFLC, ANA (dsDNA, Sm), ANCA, anti-GBM, RF/cryos, anti-DNAse, ASO

Disease	Associations	Labs
Renal-Limited Immune Complex Deposition		
Post-strep GN	~1-2w post-pharyngitis, 3-6w post-cellulitis	⊕ASO, ↓C3
Fibrillary GN	Idiopathic; cancer; autoimm (Crohn's, SLE, Graves', ITP)	Normal C3, C4, (bx IF +DNAJB9)
IgA nephropathy	1°: ~1-2d post-viral URI or GI infx. 2°: liver dx, Celiac, HIV	+/- ↑IgA, normal C3
Systemic Immune Complex Deposition		
SLE (Classes 3, 4)	Photosensitivity, malar rash, sicca, pleuritis, cytopenias, arthralgias	⊕ANA, ⊕anti-dsDNA, ⊕anti-Sm, ↓C3, ↓C4
Cryoglobulinemia (Type 2)	HCV > HBV, ESLD, MM	⊕Cryos (↑↑⊕RF), ⊕HCV, ↓C3, ↓C4
Endocarditis	Fever, valve dx, emboli	⊕BCx, ↓C3
HSP	Post-URI, malignancy, IgA nephropathy, purpura, arthritis, GIB	+/- ↑IgA, normal C3 (IgA does not fix complement)
ANCA Vasculitis		
Granulomatosis with polyangiitis (GPA)	Multi-system, granulomatous sinusitis/otitis, other ENT sx, pulmonary sx (DAH, granuloma), arthritis, palpable purpura, RPGN	c-ANCA/anti-PR3 (80%), p-ANCA/anti-MPO (10%)
Eosinophilic granulomatosis w/ polyangiitis (EGPA)	Multi-system, new-onset asthma, allergic rhinitis/sinusitis, mononeuritis multiplex	p-ANCA/anti-MPO (50%), eos ≥1500
Microscopic polyangiitis (MPA)	Multi-system, non-granulomatous	Anti-MPO (60-70%)
Drug-induced vasculitis	Hydralazine, PTU, allopurinol, adulterated cocaine (levamisole → ear necrosis)	↑titer p-ANCA (95% drug-ind; MPO, HNE); c-ANCA (50%; anti-histone)

ANCA Vasc: Tx: Induction: Steroids + RTX or CYC ([NEJM 2010;363:221](#)). Maintenance: RTX > AZA ([NEJM 2014;371:1771](#)). Induction w/o plasma exchange and w/ lower-dose steroids appears non-inferior and lowers infx risk ([NEJM 2020;382:622](#))

Anti-GBM: RPGN, DAH (=Goodpasture), linear IgG along BM. **Alport's:** mutant COL4A (renal, hearing, eye dx). EM w/ split GBM

Nephrology

Chronic Kidney Disease

OVERVIEW

- CKD definition:** GFR <60mL/min OR presence of kidney damage (typically albuminuria $\geq 30\text{mg/d}$) for $\geq 3\text{mo}$ ([JAMA 2015;313:837](#))
 - Estimating GFR: [CKD-EPI \(Annals 2009;150:604\)](#) preferred (cystatin C adds accuracy); Cockcroft-Gault overestimates, MDRD underestimates
 - Albuminuria is an independent predictor of mortality and CKD progression. UA detects albumin but not other proteins
 - Race in GFR calculations can lead to underdiagnosis, undertreatment, and underreferral for transplant for Black pts ([NEJM 2020;383:874](#))
- Etiologies of ESRD:** DM (47%), HTN (28%), GN (7%), cystic kidney (3%), other (15%) ([USRDS 2018](#))
- Epidemiology:** 15% US adults w/CKD; ESRD prevalence 3.8x higher in Black pts than White pts ([USRDS 2020](#))
- Staging/Action:** G1-G3a: risk factor reduction, dx and tx, slow progression. G3a-G3b: evaluate & treat complications. G4 (or A3): renal referral, prep for RRT/transplant. G5: RRT (if indicated), transplant eval

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006. Colors represent risk for progression, morbidity, and mortality: green (low), yellow (moderate), orange (high), red (very high). [Lancet 2012;379:165](#)

		Persistent albuminuria categories Description and range			
		A1	A2	A3	
		Normal to mildly increased	Moderately increased	Severely increased	
<30 mg/g	<3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol		
G1	Normal or high	≥ 90	55.6	1.9	0.4
G2	Mildly decreased	60-89	32.9	2.2	0.3
G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2
G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2
G4	Severely decreased	15-29	0.2	0.1	0.1
G5	Kidney failure	<15	0.0	0.0	0.1
			93.2	5.4	1.3
					100.0

MANAGEMENT

- BP control:** goal BP <130/80 ([Circ 2019;140:e596](#))
 - If proteinuria: ACEi, then CCB; if edema: loop diuretic if eGFR <30, thiazide if >30; if resistant HTN or HFrEF: spironolactone
- Proteinuria:** reduce to goal <300mg/d with RAAS blockade (ACEi or ARB; not both simultaneously) ([NEJM 2013;369:1892](#))
- DM:** goal HgbA1c <7%. 1st line agents: metformin (if eGFR >45), SGLT2i (if eGFR >45), GLP-1r agonists (if eGFR >30). Insulin safe at any eGFR. ↓ rate of CKD progression with SGLT2i ([NEJM 2019;380:2295](#)) & GLP-1r agonists ([NEJM 2017;377:839](#)). Finerenone (aldosterone antagonist) ↓ risk of CKD progression and CV events in pts with T2DM ([NEJM 2020;383:2219](#))
- HCV:** treat to slow progression ([Kidney Int 2020;97:193](#))
- CVD:** risk 2-4x general population. Statin if >50 y/o and no ESRD/tx ([Kidney Int 2014;85:1303](#)), encourage exercise, ⊖ smoking. Dapagliflozin ↓ CKD progression/mortality/CVD outcomes, regardless of DM status ([NEJM 2020;383:1436](#)). No benefit seen in initial invasive vs. conservative strategy in stable CAD + advanced CKD, and mod/sev ischemia ([NEJM 2020;382:1608](#))
- Avoid nephrotoxins:** NSAIDs, herbs w/ aristocholic acid, aminoglycosides, acyclovir, phosphate-based bowel prep, PPIs (can cause AIN and CKD), contrast (see [AKI](#) and [Contrast](#)), baclofen (stage G4/5)
- Renally dose meds:** anti-infectives, atenolol, colchicine, DOACs, DM rx, gabapentin, levetiracetam, metoclopramide, opioids
- Nutrition:** nephrocaps (B-complex + C), Na <2 g/d, K/phos/fluid restriction as needed. Protein 0.6-0.8 gm/kg/d only if GFR <60 and nephrotic syndrome is not present. Very low protein diet not clearly shown to be beneficial ([AJKD 2009;53:208](#))
- Monitoring:** q4-12mo Cr & electrolytes, annual UAlb/Cr & UProt/Cr ratios, PTH, 25-vitD, CBC, Fe studies. Renal U/S at time of dx
- Nephrology referral:** GFR → 30, sudden ↓ in GFR, severe proteinuria (Alb:Cr >300), active urine sediment with ↓GFR, resistant HTN
- Prognosis:** based on 1) cause of CKD, 2) GFR category, 3) albuminuria category, 4) other risk factor/comorbidity; use [Tangri risk score](#) to assess 2 and 5-year risk of requiring HD ([JAMA 2016;315:164](#))

COMPLICATIONS

GFR thresholds: hyperPTH (50), anemia (44), acidosis (40), hyperK (39), hyperPhos (37) ([JASN 2009;20:164](#))

- Hyperparathyroidism:**

Type	Ca	PO ₄	PTH	VitD	Pathophysiology
1 ^o HyperPTH	↑	↓	↑	nI	Excess PTH production by parathyroid gland
2 ^o HyperPTH (2/2 ↓ Vit D)	↓	↓	↑	↓	Decreased Ca absorption stimulates PTH secretion
2 ^o HyperPTH (2/2 CKD)	nI/↓	nI/↑	↑	nI/↓	↓ PO ₄ excretion increases PTH secretion
3 ^o HyperPTH	↑	↑	↑↑	nI/↓	Longstanding 2 ^o hyperPTH leads to PTH gland hyperplasia

- Mineral and bone disorder:** check Ca, PO₄, ALP, 25-OH vit D (1,25-OH vit D level will fluctuate) ([Annals 2018;168:422](#))
 - PTH rising/persistently above goal (2-9x ULN, based on CKD stage): restrict dietary phos, non-Ca phos binders (sevelamer preferred, w/ meals & snacks) ([CJASN 2016;11:232](#)), calcium/Vit D supplements not recommended unless on HD
 - Severe/refractory PTH > 1000: calcitriol vs calcium mimetic vs parathyroidectomy if non-responsive to medical therapy
- Anemia:** Hb <13 (M), <12 (F). Screening: annual if eGFR >45, q6m if <45, q3-6m if anemic. Goal Hb 10-11.5 ([Kidney Int 2012](#))
 - Iron repletion (PO or IV) when Tsat <30% and ferritin <500ng/mL. Check q3m if on ESA. IV > PO ([Cochrane 2019;2:7857](#))
 - When Fe replete and Hgb <10, consider erythropoiesis stimulating agents (ESA), which ↓ transfusions, risk of Fe overload, Ab formation; contraindicated in cancer, SBP>160, HF, stroke. Hb >13 with ESA increases risk of CVA ([NEJM 2009;361:2019](#))
- Metabolic acidosis:** NaHCO₃ 650-1300mg up to TID for goal HCO₃ >22. Alternative: dietary acid reduction (↑fruits/veg, ↓meat). Slows progression of CKD and improves bone health, diet also ↓BP ([CJASN 2019;14:1011](#))
- Uremic bleeding:** no need to treat unless pre-procedure with DDAVP
- Preparation for HD access:** avoid BP measurements and venipuncture in non-dominant arm, avoid subclavian/PICC lines due to risk of central stenosis (precludes future AVF placement), prefer small bore tunneled IJ placed by IR

Nephrology

Dialysis & Transplant

OVERVIEW (NEJM 2012;367:2505)

- Diffusion: concentration gradient drives small molecules (e.g. urea, creatinine) across selectively permeable membrane
- Convection: hydrostatic pressure forces medium-weight molecules across membrane
- Ultrafiltration (UF): removal of plasma water by hydrostatic pressure

IMPORTANT CONSIDERATIONS

- Timing: controversial, individualized for each patient
 - ELAIN (JAMA 2016;315:2190): early RRT ↑ renal recovery, ↓ RRT time/LOS/90d mortality
 - IDEAL-ICU (NEJM 2018;379:1431): no Δmortality w/ early RRT (pts w/ septic shock+AKI)
 - STARRT-AKI (NEJM 2020;383:240): early RRT did not Δ90d mortality vs. standard RRT (clinical indication); more pts in early arm remained dialysis dependent
- Access: dialysis lines can only be accessed by dialysis/ICU RNs (except in codes); contact dialysis unit (x63700) for new access
- PICCs: HD or future HD candidates cannot receive PICC unless first cleared by Renal (to preserve options for vascular access)
- Abx: dose abx based on IHD vs. CRRT vs. PD and w/ pharmacy; communicate directly w/ dialysis fellow to give during HD

Emergent Indications for RRT (AEIOU)

- Acidosis*: pH <7.2, refractory to bicarb
- Electrolytes: refractory K >6.0 mEq/L or rapidly rising K
- Ingestions: dialyzable toxins (eg: Li, ASA, methanol, ethylene glycol, metformin, phenobarbital, dabigatran)
- Overload: diuretic-refractory volume
- Uremia: encephalopathy, pericarditis, coagulopathy with uremic bleeding

*Lactate clearance via HD cannot overcome production in shock/hypoperfusion

INTERMITTENT HEMODIALYSIS (IHD) (NEJM 2010;363:1833)

- consider in critically ill pts (Lancet 2006;368:379)
- Mechanism: Cr, Urea, K⁺ move from blood to dialysate; Ca²⁺ and HCO₃⁻ move from dialysate to blood (down concentration gradients)
 - Volume removal: occurs via UF; HD can rapidly remove solute and volume; usually three 4h sessions weekly (MWF or TThSa)
 - Access: double-lumen central catheter (tunneled or temporary, ↑infection); AV graft (↓maturation time but ↑thrombosis & long-term complications); AV fistula (↓infection, ↓overall mortality vs. catheters/AVG, but 6+ week maturation time + 50% primary failure rate)
 - Intradialytic medications: erythropoietin, iron, vitamin D analogues, antibiotics, heparin (to prevent clotting of HD circuit)
 - Complications: HoTN, cramps, dialyzer rxn (SOB, urticaria, diffuse pain), HIT, hemolysis, EtOH withdrawal (rapid clearance of EtOH), myocardial stunning, arrhythmia/peri-dialytic cardiac arrest

PERITONEAL DIALYSIS (PD) (Lancet 1999;353:823)

- call PD RN on call 24/7 for any inpatient on PD
- Mechanism: peritoneum acts as membrane; infusion of fluid rich in osmotic agent (e.g. dextrose) → solute removal via diffusion and osmotic gradients → similar survival to pts on IHD (AJKD 2018;171:110)
 - Benefits: preserves residual GFR longer than IHD, better middle molecule clearance, fewer access interventions, pt independence
 - Modalities: (1) continuous ambulatory PD (**CAPD**): manual exchanges occurring both day and night, all inpatients receive CAPD; (2) Automated PD (**APD**): multiple automated exchanges overnight with long dwell during day
 - Complications: peritonitis, encapsulating peritoneal sclerosis, hernia, pleural effusion, hyperglycemia, HLD, ↓K, ↑Na, catheter leaks

CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

- Principles: depends on high UF rate to achieve clearance → replacement fluid must be added back to restore volume, acid base balance + electrolytes. Less effective in toxin removal/significant volume overload compared w/ HD.
 - **CVVH**: continuous veno-venous HF, removes solute via convection; **AVVH**: intermediate CVVH circuit setting w/ ↑flow rates/12h
 - **CVVHD**: continuous veno-venous HD, removes solute by diffusion; **CVVHDF**: combines convection and diffusion to remove solute
- Indications: (1) **hemodynamic instability** (2) significant volume overload not able to do intermittent HD (2) significant and continued acidemia (3) risk of cerebral edema w/ IHD; not ideal for hyperK/toxins, acidosis (can correct with isotonic bicarb gtt instead)
- Volume management: run negative (up to -250cc/h), even, or slightly positive. Replacement fluid w/ bicarb, lactate acetate or citrate
- Anticoagulation: used to ↓risk of circuit clotting, use heparin + bicarbonate OR citrate, citrate achieves regional AC by Ca chelation → follow iCa levels (will see ↑total Ca but ↓iCa), metabolized in liver → ↑AG = possible citrate toxicity (avoid in liver failure)
- Complications: HoTN, arrhythmias, hypothermia, ↓iCa/K/PO₄, bleeding, thrombocytopenia (mechanical destruction in circuit), HIT
- Drug dosing: drugs can bind to circuit resulting in ↑V_D → work with pharmacy to re-dose all meds based on flow rate

RENAL TRANSPLANT

- Basics: mortality & QOL benefit, more cost-effective than HD; LDKT > DDKT; racial disparities exist in transplant access
- Listing: refer EARLY (GFR <30), pts can be listed when GFR <20; pt & graft survival are improved if transplant occurs PRIOR to HD
- Contraindications: short life expectancy, active malignancy, SUD, nonadherence; age/HIV/psych comorbidities NOT contraindications
- Allograft dysfunction: **delayed graft function**: <1w (prerenal, ATN, thrombus, obstruction), **early**: 1-12w (prerenal, CNI tox, infxn [BK virus, CMV], acute rejection), **late acute**: >3mo (prerenal, CNI tox, noncompliance), **late chronic**: yrs (HTN, CNI toxicity, BK virus, recurrence of original renal pathology, chronic allograft nephropathy)

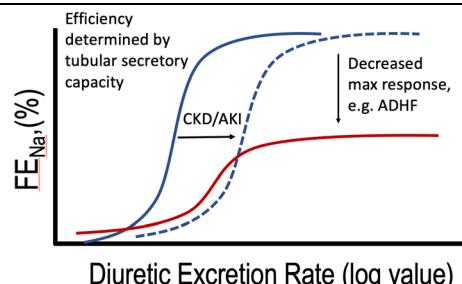
IMMUNOSUPPRESSION			
Class	Examples	Mechanism of Action	Adverse Events
Calcineurin inhibitor (CNI)	Cyclosporine Tacrolimus (FK506)	Inhibits calcineurin-mediated activation of NFAT → blocks T-cell cytokine production	Nephrotoxicity (long-term fibrosis), HTN, tremor, insomnia, hirsutism (CsA only)
mTOR inhibitor	Sirolimus (Rapamycin)	Inhibits mTOR → blocks IL-2 production	Pulmonary edema, ↓wound healing, hyperTG, mouth ulcers
Antimetabolite	Mycophenolate	Inhibits de-novo purine synthesis	N/V/D, cytopenias
	Azathioprine	Purine analogue	BM suppression, N/V/D, hepatitis

Nephrology

Advanced Diuresis

GENERAL PRINCIPLES

- Obtain daily standing weights, Na^+ restriction 2g/day, consider fluid restriction
- Loop diuretics have a sigmoidal dose-response curve indicating need to reach diuretic threshold, so double dose until adequate response is achieved; natriuresis determined by total time above the natriuretic threshold
- Transient ↑ in serum Cr are common in diuresis, can be tolerated if effective decongestion. No assoc. between ↓renal function during diuresis and biomarkers of tubular injury; ↑survival in HF ([Circ 2018;137:2016](#))



	Loop Diuretics			Thiazide Diuretics
	Furosemide	Torsemide	Bumetanide	Chlorthalidone, HCTZ, metolazone, chlorothiazide (IV/PO)
Mechanism of Action	Inhibit Na-K-2Cl transporter in ascending limb of loop of Henle to ↓Na reabsorption and “break” medullary concentrating gradient (unable to concentrate urine)			Inhibit NaCl channel in DCT to ↓Na reabsorption and prevent urinary dilution (avoid if SIADH); no effect on medullary concentrating gradient
PO Bioavailability	20-50%	80-90%	80%	Variable
Duration	~6 hours	6-8 hours	4-6 hours	Variable
Dosing considerations	1 Bumetanide IV/PO = 20 Torsemide PO = 40 Furosemide IV = 80 Furosemide PO			Administer 30 min before loop diuretic to “disable” DCT (PO metolazone, IV chlorothiazide)
Side effects	↓K, ↓Mg, ↓Ca, ↑urate, ↑ HCO_3 , ototox., allergy			↓Na, ↓K, ↓Mg, ↑Ca, ↑urate, HLD, pancreatitis
Other	Consider dosing BID-QID to avoid anti-natriuresis seen in QD dosing			Try metolazone 2.5-10mg PO before chlorothiazide 500-1000mg IV (\$\$\$)

OTHER DIURETICS

- Carbonic anhydrase inhibitors: acetazolamide 250-1000mg PO QD, can do TID x1d vs QD x3d for metabolic alkalosis (pH >7.6)
- Aldosterone antagonists: spironolactone 25-200mg QD-BID, eplerenone 25-50mg QD-BID
 - ↑K, gynecomastia (10%, only spironolactone); eplerenone has ↑aldosterone receptor selectivity but more expensive

DISEASE-SPECIFIC CONSIDERATIONS

Condition	Mechanism	Treatment
Renal Insufficiency	- ↓GFR → ↓delivery of diuretic to nephron → higher doses needed in patients with CKD - Organic acids accumulate and compete with diuretics	- High-dose loop ± thiazide augmentation
Chronic Diuretic Use	- “Braking phenomenon” of compensatory DCT hypertrophy leads to ↑Na reabsorption	- Add metolazone or chlorothiazide
CHF	- GI edema leads to ↓absorption of PO furosemide (consider torsemide/bumex given better bioavailability) - ↓GFR in ADHF is driven by renal venous HTN (↑CVP, ↑PCWP) more so than low perfusion (↓CI) - High sympathetic tone → ↑RAAS, Na reabsorption	- DOSE (NEJM 2011;364:797) : in ADHF, no Δ sx or renal fxn for pts receiving low vs high dose diuretics and continuous vs bolus dosing - No benefit of RRT over stepwise diuresis - Consider sequential nephron blockade
Hypoalbuminemia	- Loop diuretic (binds to albumin) leaks out of vasculature ($\uparrow V_D$) resulting in ↓delivery to nephron	- Consider bumetanide (lower albumin-binding) - No evidence for benefit of albumin + loop diuretic
Cirrhosis	- Decreased delivery to nephron in setting of hypoalbuminemia - Splanchnic vasodilation → ↓EABV → renal hypoperfusion (pre-renal azotemia) - SNS and RAAS → ↑Na reabsorption	- Avoid IV diuretics unless respiratory distress - See ESLD: Ascites
Nephrotic Syndrome	- Decreased delivery to nephron due to low albumin - Urinary albumin binds drug → loss of diuretic in urine	- Use 2-3x normal dose of diuretic

STEPWISE APPROACH IN HEART FAILURE (NEJM 2017;377:1964)

- IV loop diuretic**. Starting dose: 2.5x home dose as IV furosemide (CHF) (e.g. if home 80mg PO, give ~80-120mg IV) or Cr×30 as IV furosemide (e.g. if Cr 4, use lasix 120mg IV); if unknown, start with furosemide 20-40mg IV
- Reassess in 1-2 hrs** and double dose Q1H until response achieved. An adequate dose should cause brisk diuresis
- Consider loop diuretic **bolus + gtt** (should bolus when initiating gtt and re-bolus every time gtt increased)
- If refractory edema, consider adding a **thiazide** (metolazone PO or chlorothiazide IV) to achieve sequential nephron blockade
 - Counteracts natural ↑ in DCT Na reabsorption from loop diuretics; **monitor closely** ↓K, ↓Mg, ↓ HCO_3
- Nephrology consult for consideration of short term UF/RRT as a bridge to advanced therapies

Nephrology

Acid-Base Disorders

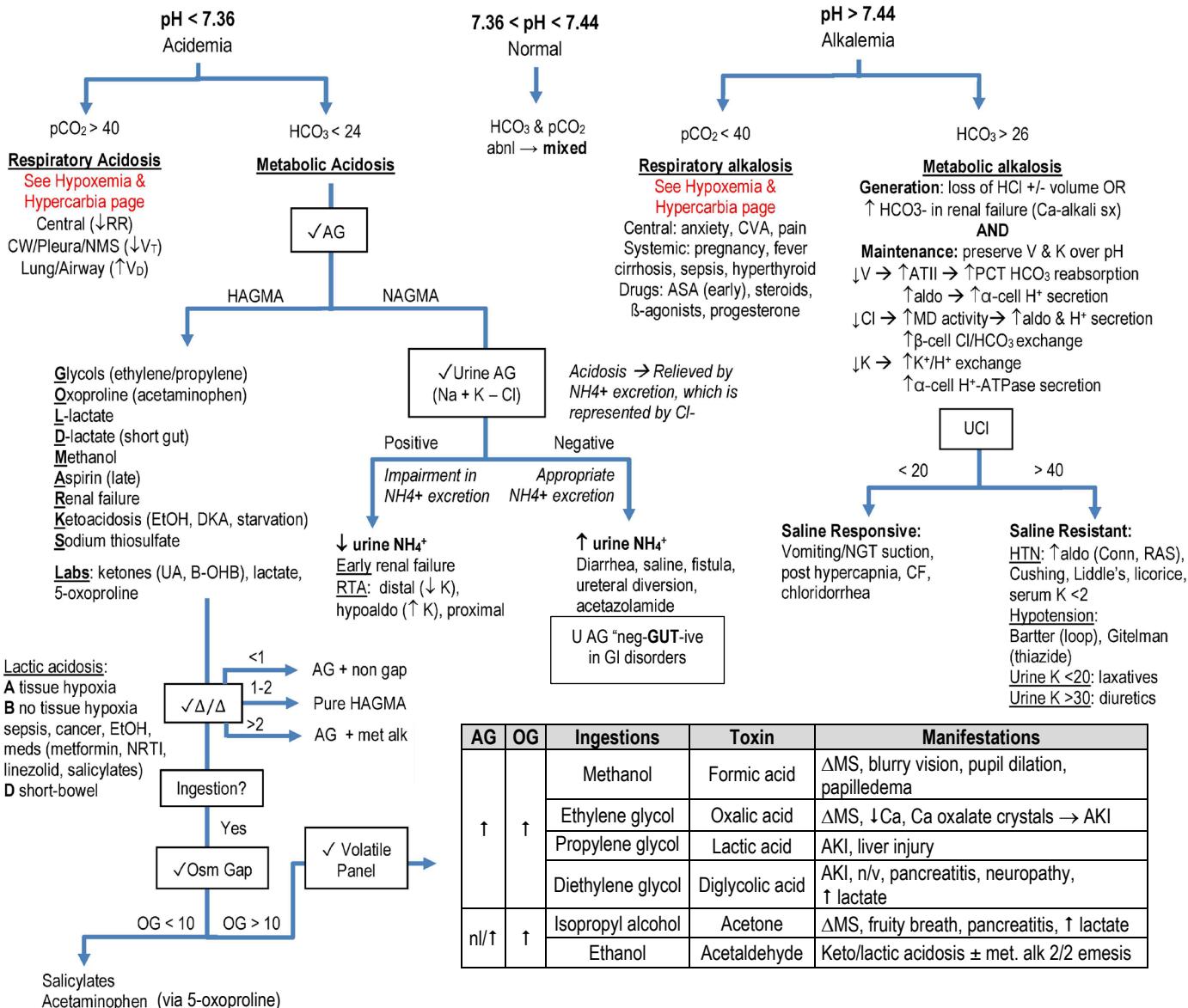
OVERVIEW

- ABG vs VBG:** pH VBG~0.04 lower, HCO_3 (VBG~2mEq lower; calculated value on blood gas, BMP more accurate), CO_2 (VBG~8 mmHg higher). VBG can screen for hypercapnia w/ pCO_2 cutoff $\geq 45\text{mmHg}$ (100% SpO₂) but does **NOT** accurately assess degree of hypercapnia. **When in doubt, check ABG** ([AJEM 2012;30:896](#))
- Severe acidemia** (pH <7.2) → vasodilation, ↓ inotropy/MAP, ↓ response catechols/pressors, arrhythmia, ↑K, insulin resist., AMS
- Severe alkalemia** (pH >7.6) → vasoconstriction, ↓ coronary/cerebral perfusion, SVT/VT, ↓K/Ca/Mg/Phos, AMS, seizure, hypoventilation

STEP-WISE APPROACH ([NEJM 1998;338:26](#); [NEJM 2014;371:1434](#))

- Is there **acidemia** (pH <7.36) or **alkalemia** (pH >7.44)?
- Is 1° disorder **metabolic** (parallels pH Δ) or **resp** (opposite pH Δ)?
- Is pt compensating? (respiratory takes min-hrs, renal 3-5d)
- Is there an **anion gap**? Calculate regardless of pH or HCO_3
 $\text{AG} = \text{Na} - (\text{Cl} + \text{HCO}_3)$ = unmeasured anions – unmeasured cations
 Correct AG for albumin: $\text{AG}_c = \text{AG} + 2.5(4 - \text{albumin})$
 Negative AG: ↑↑Na, lipids (interfere w/ chloride), bromide intox
- If there is ↑AG metabolic acidosis (AGMA), calculate “**delta-ratio
 $\Delta/\Delta = \Delta \text{AG} / \Delta \text{HCO}_3 = \text{AG} - (\text{albumin} \times 2.5) / (24 - \text{HCO}_3)$**
- Consider Osm gap = $2(\text{Na} + \text{K}) + \text{Urea}/2.8 + \text{glucose}/18 + \text{EtOH}/4.6 - \text{serum Osm}$

ALGORITHMIC APPROACH



MANAGEMENT OF ACID-BASE DISORDERS: treat the underlying cause!

- **Metabolic acidosis:**
 - **Acute:**
 - In BICAR-ICU ([Lancet 2018;392:31](#)), pts with metabolic acidosis (pH <7.2) tx w/ IV HCO₃ for goal pH >7.3 had no Δ in overall mortality but ↓RRT initiation. A subset of pts w/ AKIN stages 2-3 had improved mortality at 28d
 - For pH <7.1 or HCO₃ <6: if HDS, can start **isotonic HCO₃ gtt.** Monitor VBG/ABG q1h. Bolus admin is controversial due to c/f CO₂ accumulation → hypercapnia, hypernatremia, hypocalcemia, hypertonicity, hypervolemia, overshoot alkalosis
 - For bicarb to have full effect on serum pH, pt must be able to increase minute ventilation to ventilate off CO₂
 - **Special considerations:**
 - **Toxic alcohols:** tx with NaHCO₃, **fomepizole**, or HD (if vision Δ, AKI, methanol >50mg/dL, ethylene glycol >300mg/dL)
 - **Salicylate poisoning:** NaHCO₃ to urine pH >6.5 or HD (if level >80mg/dL, coma, AKI, hypervolemia)
 - Chronic: in CKD, replete with PO NaHCO₃ for goal HCO₃ >22. See [CKD](#)
- **Metabolic alkalosis:** replete volume, K, & Cl
 - Treat both (1) underlying cause of metabolic alkalosis & (2) cause of renal retention of HCO₃
 - If **saline responsive:** NS w/ KCl until urine pH >7. For pts w/ CHF/cirrhosis & alkalosis 2/2 diuresis, consider K⁺-sparing diuretic
 - If **saline resistant:** for mineralocorticoid excess → use K⁺-sparing diuretic (**amiloride**) & consider surgical removal of adenoma
 - If pH >7.6 & persistently volume overloaded, give **acetazolamide** vs KCl + loop diuretic with close K⁺ monitoring
- **Respiratory acidosis:** treat underlying process; adjust vent settings if intubated. NaHCO₃ unlikely to be helpful, theoretically harmful if unable to ventilate subsequent CO₂ produced. For every 100mEq HCO₃ administered, 2.2L CO₂ must be exhaled
- **Respiratory alkalosis:** address underlying cause (correct hypoxemia, treat pain/anxiety/fever); adjust vent settings if intubated

RENAL TUBULAR ACIDOSIS (RTA) ([Int J Clin Pract 2011;65:350](#))

Consider in any pt w/ hyperchloremic or non-AG metabolic acidosis (NAGMA) or hyperK (Type IV). R/o GI losses & excessive Cl use first!

Pathophysiology: inappropriate net retention of acid or inadequate excretion of bicarb

- In acidemia, kidney should ↑NH₄⁺-Cl⁻ excretion; urine pH should be <5.3; this process is defective in RTAs
- **Caveat:** CKD of any etiology is associated with ↓NH₄⁺ production & acidosis

Etiologies:

- **Proximal RTA (Type II):** new ↓setpoint for proximal tubule HCO₃⁻ reabsorption so more HCO₃ spills into urine
 - Primary (rare): Na-HCO₃ cotransporter defect
 - Acquired: **amyloidosis**, MM, post-renal transplant, heavy metals (Pb, Cd, Hg, Cu), ↓Vit D, Wilson's disease, PNH
 - Meds: acetazolamide, cisplatin, tenofovir, aminoglycosides, topiramate
 - Often a/w Fanconi Syndrome: glycosuria (w/ serum gluc <180), hypouricemia, aminoaciduria
- **Distal RTA (Type I):** inability to secrete H⁺ in distal tubule
 - Primary: genetic loss of H⁺ or HCO₃⁻ transporters in intercalated cells
 - Acquired: **autoimmune disease** (RA, SLE, SS); **hypercalciuria** (any cause); obstructive nephropathy; SCD, MM, amyloid, cryoglobulinemia, tubulointerstitial injury, renal transplant rejection, cirrhosis, glue sniffing (toluene)
 - Meds: amphotericin B, Li⁺, ifosfamide
- **Type IV:** effective hypoaldosteronism: ↓aldo secretion OR tubular resistance → ↑K → ↓NH₃ synthesis → ↓NH₄⁺ excretion
 - Acidosis due to inhibition of ammonia-genesis by hyperkalemia of any cause
 - **Hyporeninemic hypoaldosteronism** (most common): diabetic nephropathy, CIN, NSAIDs, calcineurin inhibitor, HIV
 - ↓ Aldo production: ACEi/ARB > heparin > adrenal insufficiency, severe illness
 - Aldosterone resistance: (ENaC inhibition) K-sparing diuretic, trimethoprim, pentamidine

Workup: clinical history (PMH – autoimmune or malignancy, med review, stones), response to HCO₃ supplementation

- ABG/VBG, BMP (AG, HCO₃, K), UA (pH). Consider urine Ca/Cr to differentiate proximal vs distal RTA
- Estimate of Urine NH₄⁺: **UAG** = Na + K - Cl (less useful when ↑urine anions or UNa < 25)

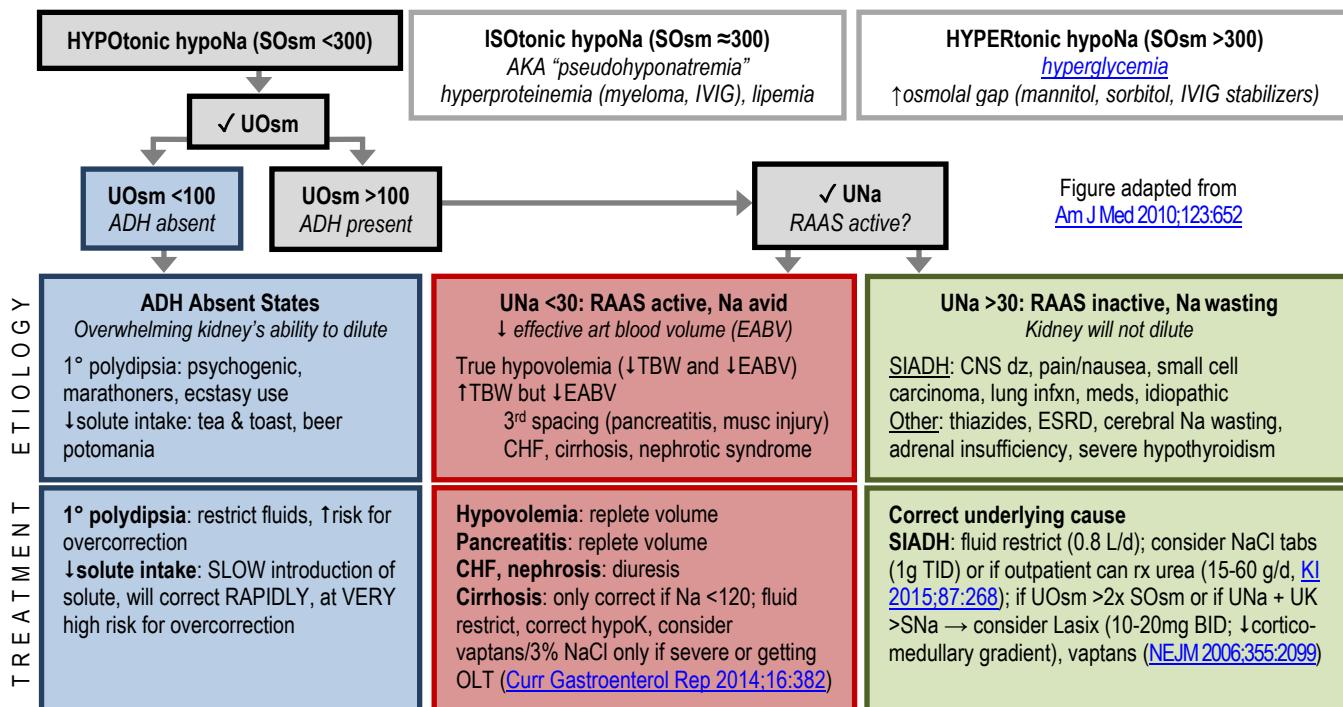
	PROXIMAL RTA (TYPE II)	DISTAL RTA (TYPE I)	TYPE IV RTA
Defect	Proximal HCO ₃ ⁻ resorption	Distal H ⁺ secretion	Hyperkalemia
Serum HCO ₃ ⁻	12 – 20	<10	>17
Serum K	↓ or normal	↓ or normal	↑
Urine pH during acidemia	Varies, but >5.5 after HCO ₃ ⁻	>5.5	<5.5, but cannot buffer w/ NH ₄ ⁺
Urine AG = Na + K - CL	⊖	⊕	⊕
Additional dx testing	Urine Ca/Cr nml	Urine Ca/Cr elevated	Renin, aldosterone, cortisol
Complications	Rickets, osteomalacia	CaPO ₄ urinary stones	Hyperkalemia
Tx (Goal HCO ₃ 22-24)	Challenging. NaHCO ₃ (10-20 mEq/kg) or KCitrate. K supplement	NaHCO ₃ (1-4mEq/kg)	Treat hyperK: loop, low K diet If hypoaldo, can give fludrocort

HYPONATREMIA: free water excess relative to serum sodium ([NEJM 2015;372:55](#))

Symptoms: often asymptomatic; AMS, HA, vertigo, N/V, weakness, seizures

Workup: H&P focused on symptoms, etiology, chronicity, volume status

- Serum studies: BMP, Osm. Consider uric acid, TSH, AM cortisol. Urine studies: UA, Osm, Na. Consider uric acid with creatinine, K
- Determine if ADH is present ($\text{UOsm} > 100$). Can approx UOsm from UA: last 2 digits of SG x 30 (e.g., SG 1.010 \approx UOsm 300)
- If ADH is present, determine if ADH is appropriate ($\text{UNa} < 30$). UNa is less reliable if on diuretics
- Other diagnostic clues ([Eur J Inter Med 2016;29:22](#); [JCEM 2008;93:2991](#); [Ann Intern Med 1980;93:716](#); [Cureus 2020;12:e7762](#)):
 - Other solutes: SIADH: often serum uric acid (sUA) < 4 , BUN < 5 , fractional excretion of uric acid (FEUA) $\geq 10-12\%$ (small studies: 100% PPV for SIADH/thiazide hypoNa; FEUA $\leq 8\% = 100\%$ NPV for SIADH). $\downarrow \text{EABV}$: often sUA > 5 , BUN \uparrow , FEUA $< 4\%$
 - IVF: SIADH: NS initially $\uparrow \text{SNa}$ but then will $\downarrow \text{SNa}$ (Na is excreted while H_2O retained). Hypovolemia: NS will $\uparrow \text{SNa}$



Treatment: depends on acuity, severity, and etiology ([JASN 2017;28:1340](#))

- **Rate/goal:** $\uparrow \text{Na} 4-6 \text{ per 24h}$, to short-term goal ≥ 125 ; typically, $\uparrow \text{Na} 4-6$ will alleviate sx
- **Severe symptomatic** (sz, AMS): 3% NaCl via 100mL bolus over 10min ($\uparrow \text{Na} 1.5-3$); repeat up to 3X until sx resolve or Na $\uparrow 4-6$
- **Severe asymptomatic** (Na < 120): 3% NaCl at [Na Correction Rate](#), usually 15-30mL/h, until Na ≥ 125
- **Mild/mod** (Na 130-134/Na 120-129): etiology-specific treatment (e.g., fluid repletion, fluid restriction, diuresis, hold diuresis)
- **Overcorrection:** Na $\uparrow > 8$ in 24h or > 18 in 48h
 - Osmotic demyelination syndrome (ODS): delayed onset (2-6d) dysarthria/dysphagia, paresis, AMS, locked-in syndrome
 - Dx with MRI ~4w after sx onset
 - RFs: starting Na ≤ 105 (ODS unlikely if starting Na > 120 , [Hosp Pract 1995;37:128](#)), malnutrition, EtOH use, cirrhosis, $\downarrow \text{K}$
 - Be mindful of rapid correction in pts where ADH stimulus is removed (e.g. IVF for hypovolemia)
 - If Na trajectory predicts overcorrection, consider **DDAVP clamp** (recommend Renal consult) ([Am J Kidney Dis 2013;61:571](#)):
 - DDAVP 2-4mcg IV/SC q6-8h with Na measured q4-6h, until Na ≥ 125 . If needed, add 3% NaCl at [Na Correction Rate](#)
 - If already overcorrected, relower Na to a goal level where it would not be considered overcorrected:
 - D5W 6mL/kg IBW over 2h ($\downarrow \text{Na by 2}$) and continue with q2h Na measurements until at goal level, PLUS
 - DDAVP 2-4mcg IV/SC q6h for 24-48h even after relowering goal initially achieved
- **Concurrent hypokalemia:** K and Na freely exchanged, giving 1mEq of K = giving 1mEq of Na; can overcorrect w/ K supplementation

HYPERNATREMIA: free water loss in excess of NaCl loss ([Crit Care 2013;17:206](#), [NEJM 2015;372:55](#))

Etiologies: ↓ access to free water or ↓ thirst, DI (↓ production or efficacy of ADH)

- **Renal losses:** UOsm < 800 ; ↓ ADH release or kidney response: post-ATN, osmotic, DI, loop diuretic, hyperCa, elderly
- **Extrarenal losses:** UOsm > 800 ; GI loss from NGT, vomiting, diarrhea, insensible losses, hypodipsia

Treatment: BMP q12-24h, strict I/O. Aim to $\downarrow \text{SNa}$ by 12 per 24h (accidental overcorrection unlikely to be dangerous, complications of more rapid correction (e.g. cerebral edema) are rare in adults, [CJASN 2019;14:656](#))

1. Calculate current free water deficit. Shortcut FWD (L) = (Current Na – Goal Na)/3. Target Na should be 24h goal
2. Account for ongoing losses:
 - insensible losses: 700-900 mL/d typically but \uparrow if burns, diarrhea (cannot measure, so \uparrow replenishment if inadequate)
 - urine: 24h UOP x (1 - (UNa+UK)/SNa)); alternative = (0 x 1st L) + (0.5 x 2nd & 3rd L) + (1 x urine beyond 3L)
3. FW to give today = current FWD + ongoing losses. Give via PO, TF (FWB), or IV (D5W). If DI see [Pituitary Disorders](#) for DDAVP

Nephrology

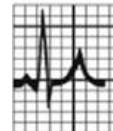
Potassium Disorders

NORMAL POTASSIUM HANDLING/HOMEOSTASIS (NEJM 2015;373:60)

- Ingested K⁺ absorbed in intestines → taken up primarily by liver/muscle cells via insulin & β2 receptors → ↑Na-K ATPase activity
- 98% of K⁺ is intracellular; remaining extracellular levels trigger aldosterone secretion → principal cell K⁺ secretion → excretion in urine
- Excretion also driven by Na⁺ delivery to distal nephron. ↑Na⁺ delivery → K⁺ excretion; ↓Na⁺ delivery → K⁺ retention

HYPERKALEMIA

- S/S: muscle cramps, paralysis, conduction delay (e.g. CHB, BBB, sinus arrest), arrhythmia (VT/VF, asystole, idioventricular rhythms) ([CCM 2008;36:3246](#))
- Dx: confirm K⁺ not d/t hemolyzed sample, plt>500K, WBC>120, or infusion of K⁺-containing IVF; consider blood gas K⁺
- ECG: peaked T waves → flat P → ↑PR interval ± AVB → wide QRS ± BBB → sine wave pattern → PEA/asystole/VF
 - ECG does not correlate w/ K⁺ level* ([Clin J Am Soc Neph 2008;3:324](#))
- Etiologies: Acidosis, ↓ Aldosterone; B-blocker, Blood; Cell lysis/turnover; Drugs, DM, Decreased GFR
 - Redistribution:** cell lysis (hemolysis, rhabdo, TLS, pRBCs, crush injury), acidosis, ↓insulin (DM, octreotide), hyperosm, meds (digoxin, β-blockers, succ, calcineurin inhib [CNI], minoxidil), hyperK periodic paralysis, post-hypothermia
 - Usually transient unless impaired renal K⁺ excretion
 - ↓Renal K excretion:** required for persistent hyperK⁺
 - ↓Aldo production/action: ACEi/ARBs, NSAIDs, K⁺-sparing diuretics, CNI, pentamidine, TMP, type IV RTA
 - Impaired Na delivery to distal nephron: hypovolemia, CHF, cirrhosis
 - AKI/CKD (esp. if oliguric): usually GFR<15
 - Other: ureterojejunostomy – urine K⁺ reabsorbed
- Management: *acute changes are most dangerous* → **STAT ECG**. Treat if ECG changes, K⁺>6, rapid rise, or sx (e.g. weakness)
 - Key is **elimination**, other measures are temporizing. Address reversible factors (optimize volume status, low K⁺ diet, meds)

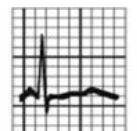


HYPERKALEMIA TREATMENT					
Strategy	Treatment	Onset	Duration	Notes	
Stabilize	Calcium: calcium gluconate or CaCl ₂ (central line) 1-2g IV, can repeat after 5 min PRN	1-3m	30-60m	1 st line if any ECG Δs . Stabilizes cardiac membrane. Avoid if on dig	
Redistribute	Bicarb (sodium bicarbonate 1-2 amps IV vs gtt)	5-10m	1-2h	Drives K ⁺ into cells. Only if ↓↓ pH	
	Insulin (10U IV; 5U if ESRD) + D50 25g (if BS<250)	10-30m	4-6h	Drives K ⁺ into cells. ↓K ⁺ 0.5-1.5mEq/L	
Eliminate	Albuterol (10-20mg neb preferred over IV)	15-30m	15-90m		
	Furosemide ≥40mg IV; can approx. as 30xCr if K>6.	30m	Variable	Urinary K ⁺ excretion	
	Patiromer (8.4g/d PO) or sodium zirconium cyclosilicate* (Lokelma, 10g TID initially) favored over Kayexalate** (15-30g PO/PR)	*1h 7h	24h	Swaps K ⁺ for Ca ⁺⁺ or Na ⁺ in gut	
	Hemodialysis lowers K immediately	N/A	3h	Removes K ⁺ , may rebound d/t shifts	

**GI ischemia/necrosis reported w/ Kayexalate, contraindicated post-op, ileus, bowel obstruction, colitis ([JAMA Intern Med 2019; 179:1023](#))

HYPOKALEMIA

- Signs and symptoms: usually with K⁺<2.5 → cramps, ileus, weakness (LEs > trunk/UEs > respiratory muscle paralysis), rhabdo ([Nat Rev Neph 2010;7:75](#))
- ECG: flat T waves, ST dep, U waves, ↑QT, atrial or ventricular ectopy → VT, VF (esp if K<3, susceptible pts, or on digoxin)
- Etiologies:
 - Lab artifact** (pseudo-hypokalemia): WBC >100 absorb K⁺ if sample sits out (check K⁺ on blood gas)
 - Inadequate intake**: unlikely to be 1° cause, usually combined with another etiology
 - Redistribution**: ↑pH, ↑insulin, refeeding syndrome, ↑β-adrenergic activity (e.g. albuterol, epi), ↑blood cell prod (e.g. s/p G-CSF), hypothermia, toxins (cesium, barium, chloroquine), hypoK/thyrox periodic paralysis
 - Extrarenal losses**: diarrhea (esp. if chronic, VIPoma, villous adenoma, laxatives), vomiting/NGT
 - Renal losses (w/o HTN)**: ↑urine flow (1° polydipsia, excess IVF), ↓Mg⁺⁺, meds (ampho B, ifosfamide, cisplatin, gent)
 - Acidemia: DKA, RTA (proximal and some distal)
 - Alkalemia: diuretics, UGI losses (2° hyperaldo), Bartter's (~loop diuretic), Gitelman's (~thiazide)
 - Other: ↑urine excretion of anions (β-OH-butyrate in DKA, bicarb [e.g. UGI losses], toluene + PCN metabolites)
 - Renal losses (with HTN)**:
 - 1° hyperaldo: ↑aldo, ↓renin (e.g. adrenal adenoma); 2°: ↑aldo, ↑renin (e.g. renal art. stenosis, tumor)
 - Other: ↑glucocorticoid or ↑ENaC activity (e.g. Cushing's, Liddle's syndrome, black licorice)
- Management: 10mEq raises K⁺ by 0.1mmol/L; caution if ↑Cr or if due to transcellular shifts
 - Oral KCl (ER = pill, IR = powder) preferred for tx as SAFER, quick acting, ↑retention of K⁺, and many pts are Cl⁻ depleted
 - IV formulation KCl if unable to take PO or if severe/symptomatic → max 10mEq/h (floor), 20mEq/h (ICU)
 - Always replete Mg⁺⁺, otherwise K⁺ repletion ineffective ([JASN 2007;18:2649](#))
 - Avoid dextrose-containing solutions → can acutely worsen hypoK (dextrose ↑insulin secretion → K⁺ shifts into cell)



Nephrology

Magnesium & Phosphorus Disorders

HYPOMAGNESEMIA ([Med Sci \(Basel\) 2019;7:56](#))

- **S/Sx:** other electrolyte disturbances ($\downarrow K$, $\downarrow Ca$), weakness, anorexia, confusion, hyperreflexia, tetany, $\uparrow PR$, $\uparrow QRS$, $\uparrow QTc$, peaked/inverted T waves, U waves, VT/torsades de pointes, accentuation of digitalis toxicity
- **Etiologies:**
 - $\downarrow GI$ absorption: \downarrow intake (malnutrition), \uparrow loss (diarrhea, pancreatitis, malabsorption, small bowel resection, PPIs)
 - \uparrow Renal loss: thiazide, loops, Gitelman's, amphotericin, aminoglycosides, foscarnet, tacrolimus/cyclosporine, cisplatin, pentamidine, EtOH, glycosuria
 - Distinguish GI vs. renal with **FEMg** ($>3\%$ suggests renal wasting)
- **Treatment:** oral (slow) vs. IV (fast, typically used inpatient) ([Am J Health Syst Pharm 2012;69:1212](#))
 - IV: $MgSO_4$ 1-2g over 15min, max 1-2g/h; can give 4-8g over 12-24h; $\frac{1}{2}$ dose if eGFR <30
 - PO: $MgCl_2$ 6-8 tabs/day causes less diarrhea than Mg oxide 800-1600mg/day, **always use in divided doses**
 - If hypoMg due to thiazide or loop diuretic, can add K-sparing diuretic to decrease Mg excretion

HYPERMAGNESEMIA (rarely pathologic w/o renal insufficiency)

- **S/Sx:** (typically if Mg >6): neuromuscular (hyporeflexia [first sign], lethargy, weakness, resp failure), CV (HoTN, bradycardia, conduction defects [$\uparrow PR$, $\uparrow QRS$, $\uparrow QTc$, CHB, arrest]), hypocalcemia (hyperMg can suppress PTH)
- **Etiologies:** Mg intake/repletion $>$ renal clearance (only method of excretion)
 - Medication overdose (Epsom salts, laxatives, Maalox, Mg enemas) \rightarrow avoid these agents in ESRD
 - Increased Mg absorption with gastritis/PUD/colitis
 - Mild hyperMg may be seen in DKA, hypercatabolic states (TLS), lithium, adrenal insufficiency
- **Treatment** (symptomatic only): Ca gluconate 1g IV over 10 min vs gtt to counteract resp depression/hypotension; **IV fluids**, loop diuretics to enhance renal excretion. If oliguric/anuric ESRD, requires HD for removal

HYPOPHOSPHATEMIA

- **S/Sx:** (typically only if phos <1.0 mg/dL, esp. if acute): \downarrow intracellular ATP \rightarrow AMS/encephalopathy, seizures, CHF, resp depression, proximal myopathy, rhabdo, dysphagia/ileus, hemolysis, mineral Δ (bone pain, hypercalcemia, rickets/osteomalacia) ([JASN 2007;18:1999](#))
- **Etiologies:**
 - **Redistribution (into cells):** \uparrow insulin (DKA, HHNK, **refeeding**), acute resp alkalosis ($\uparrow pH \rightarrow \uparrow$ glycolysis), hungry bone syndrome (deposition of Ca and phos in bone immediately following parathyroidectomy)
 - $\downarrow GI$ absorption: poor PO, chronic diarrhea, \downarrow vit D, antacids or phos binders (e.g. aluminum, Mg, sevelamer)
 - \uparrow Renal excretion: \uparrow PTH (1° or 2° hyperPTH), Fanconi syndrome (multiple myeloma, tenofovir), \uparrow FGF-23 (genetic/paraneoplastic), meds (acetazolamide, metolazone, IV iron) ([QJM 2010;103:449](#)), osmotic diuresis (glycosuria), CVVH (esp at high bicarb dose)
 - Distinguish GI/redistribution vs renal with **FEPO₄** ($>5\%$ suggests renal wasting)
- **Treatment:**
 - **Severe (<1 mg/dL) or symptomatic:**
 - Na or K phos 30mmol q4-6h with frequent levels (can give 15, 30, or 45mmol doses at MGH). Change to PO once >1.5 mg/dL. Give $\frac{1}{2}$ dose in CKD/ESRD
 - Aggressive IV tx can cause Ca precipitation, hypotension (often due to hypocalcemia), AKI, arrhythmia
 - **Asymptomatic (<2 mg/dL):** Na or K phos 1mmol/kg/d PO in 3-4 divided doses (total 40-80mmol)
 - NeutraPhos: 1 packet = 250mg phos (8mmol); 7.1mEq K, 6.9mEq Na; *preferred if need K or want lower Na*
 - K-Phos Neutral: 1 tab = 250mg phos (8mmol); 1.1mEq K, 13 mEq Na; *preferred if do not need K*
 - If poorly tolerated (can cause diarrhea), can give scheduled skim milk (8oz = 8mmol phos)

ACUTE HYPERPHOSPHATEMIA (for chronic hyperphosphatemia, see [CKD](#))

- **S/Sx:** results from Ca precipitation \rightarrow hypocalcemia (muscle cramps, tetany, tingling, perioral numbness)
- **Etiologies:**
 - **Acute phos load** (TLS, rhabdo, exogenous/phosphate-containing laxatives)
 - **Acute extracellular shift** (DKA, lactic acidosis, severe hyperglycemia)
 - **Acute kidney injury** due to decreased clearance (including acute phosphate nephropathy)
 - **Increased tubular reabsorption** (vit D toxicity)
 - **Pseudohyperphosphatemia** (hyperglobulinemia, hyperlipidemia, hyperbilirubinemia, hemolysis)
- **Treatment:** normal saline (though can worsen hypocalcemia), dialysis

Nephrology

IV Fluids & Electrolyte Repletion

IV FLUIDS

- Types:** **crystalloid** (e.g. NS or LR), **free water** (e.g. D5W), & **colloid** (e.g. albumin, blood products)
 - Crystalloid can be isotonic (NS, LR), hypotonic (1/2 NS, 1/4 NS), or hypertonic (3% saline)
- Bolus fluids** = volume expansion in shock, sepsis, hemorrhage (initial resuscitation), GI losses, burns
 - Rate: ~500cc-1L over 30min-2h. If concerned about volume overload, start w/ smaller volume (250-500cc)
 - NS in large volumes can cause hyperchloremic non-AG metabolic acidosis (NAGMA) and ↑ need for RRT
 - LR possibly associated with better renal outcomes compared with NS ([NEJM 2018;378:829](#); [NEJM 2018;378:718](#))
 - LR has **minor** quantities of K & lactate. ↑K & lactate ([JEM 2018;55:313](#)) are **NOT** contraindications to LR
 - Colloid is NOT superior to crystalloid for volume resuscitation in shock ([JAMA 2013;310:1809](#))
- Maintenance fluids** = replace daily losses (~1.6L/d in adults w/ normal renal function & perspiration). Also used at higher rates in conditions such as pancreatitis & rhabdomyolysis ([NEJM 2015;373:1350](#))
 - If patient is taking PO, there is no need for maintenance IV fluids. **Always order with time limit**
 - D5-1/2 NS is typical maintenance fluid for NPO patients. Insufficient calories to replace a diet (~170 kcal/L)
 - Maintenance rate:** 60mL/h + 1mL/kg/h for every kg above 20 kg → ex. 60kg adult = 100mL/h

Fluid	pH	Osm	[Na ⁺]	[Cl ⁻]	[K ⁺]	[Ca ²⁺]	Dextrose	Other
Human plasma	7.35-7.45	275-295 mOsm/L	135-145 mEq/L	94-111 mEq/L	3.5-5.0 mEq/L	2.2-2.6 mg/dL	60-100 mg/dL	1-2 mEq/L lactate
Normal Saline	4.5-7	308	154	154				
Lactated Ringers	6-7.5	280	130	109	4	1.35		29 mEq/L lactate
1/2 NS	5	154	77	77				
D5-1/2 NS	3.5-6.5	406	77	77			5 g/dL	
D5W	3.5-6.5	252					5 g/dL	Used in hyperNa (see Sodium Disorders)

Albumin: [MGH Albumin Policy](#) put in place to prevent non-evidence-based overuse ([ASA Choosing Wisely](#))

Albumin 25% = 12.5g albumin in 50mL solution; Albumin 5% = 12.5g albumin in 250mL solution

Indications: use to replace serum oncotic pressure, not usually for volume resuscitation

- SBP:** improves renal outcomes. Dosing: albumin 25% at 1.5g/kg w/in 6h (max 100g), decrease to 1g/kg on Day 3
- Large volume paracentesis in cirrhosis:** only if >5L removed. Dosing: Albumin 25% at 6-8g/L ascites removed
- Augmenting diuresis in ARDS:** already on high dose loop diuretic AND albumin <2.5 or Total Prot <6 Dosing: Albumin 25% at 25g q8h for 3 doses (requires attending approval; stop once alb >2.5. Max 3 days)
- Hepatorenal syndrome:** see [Hepatorenal Syndrome](#)
- Other:** chiller in ECMO, mechanical circulatory support, burns, nephrotic syndrome
- NOT helpful in decompensated cirrhosis unless for the above indications ([NEJM 2021;384:808](#))

ELECTROLYTE REPLETION (see [Potassium, Magnesium & Phosphorus, & Calcium Disorders](#))

	Potassium	Magnesium	Phosphorus	Calcium
Goal	- CAD/arrhythmia: ≥4 - Everyone else: ≥3.5 - Do not replete if on HD unless <3.0	- CAD/arrhythmia: ≥2 - Everyone else ≥1.7	- Replete if sx or phos <1 - At risk for refeeding: >2	- Replete if sx, long QTc, Ca <7.5, iCal <1.15mmol/L
PO or IV?	PO > IV	IV > PO	PO > IV	IV if severe, PO if mild
PO repletion	- KCl IR (powder): q4-6h - KCl ER (pills): giant pills - If K <3.5, ≥20 mEq KCl IR	- Mg oxide 400mg (240mg elemental Mg) TID x1d	- K-Phos: 1 packet QID - Neutra-Phos: 1 packet QID	- Ca carbonate 1250mg PO BID
IV repletion	- Peripheral: 10mEq/h - Central: 20mEq/h w/ telemetry monitoring	- Mg sulfate 2g IV	- Give 15-45mmol Phos at a time - K-Phos (1.5mEq K/mmol Phos) - Na-Phos (1.3mEq Na/mmol Phos)	- Ca gluconate 1-2g IV; - CaCl ₂ used in codes, 0.5-1g q2-5min
Comments	- 10mEq K ↑serum K by 0.1 - Max 80mEq → re-check K - Correct hypoMg	- 2g ↑serum Mg by 0.5 - ↓Mg can cause ↓K/Ca	- IV Phosphate can precipitate Ca → causing hypocalcemia	- Correct for low Alb & hyperphos first - 1g Ca gluconate ↑serum Ca by 0.5

Nephrology

Urinalysis & Nephrolithiasis

URINALYSIS

URINE DIPSTICK – urine should be analyzed within 2-4h

Specific Gravity	Can help approximate urine osm: decimal of SG x 30 (e.g. SG 1.020 → 20 x 30 → ~ 600mosms) SG <1.010: post-ATN (concentrating defect), diuretics, DI, polydipsia, hypovolemic hypoNa after resuscitation SG 1.010 – 1.025: normal SG >1.025: prerenal, contrast (esp >1.030), ↓EABV, glycosuria (DM), proteinuria, SIADH
pH	Normal 4.5 - 8, but strongly depends on serum pH and dietary intake If normal urine pH + metabolic acidosis, suspect type I RTA (kidney not secreting H ⁺ ions) If pH ≥7, suspect urease-producing organisms (Proteus, PsA), strict vegetarians (low protein diet), type I RTA
LE	Released from lysed PMNs; FP : ↑pH or ↓SG (lyses WBCs); FN : proteinuria, glycosuria. For UTI, Sn 80% , Sp low
Nitrite	Indicates nitrate-reducing GNR (E. coli, Klebsiella, Proteus, PsA – NOT Enterococcus). For UTI, Sn 60% , Sp>90%
WBC	UTI; if sterile pyuria, consider AIN, GN, chlamydia, ureaplasma, urethritis, TB, foreign body, exercise, steroid use, cyclophosphamide
Blood	Detects heme (glomerular, renal, or urologic); FP : hemoglobinuria (hemolysis), myoglobinuria (rhabdo), semen, drugs (rifampin, chloroquine, iodine), peroxidase producing bacteria
Protein	Detects albumin when excretion >300mg/d: does NOT detect light chains, insensitive to LMW proteins Falseley elevated by high SG, heavy hematuria (heme protein), and iodinated contrast (w/in 24h)
Ketones	Detects only acetoacetate, NOT β-hydroxybutyrate; yield decreases as collected urine sits
Glucose	Reflects glomerular overflow (serum glucose >180mg/dL or SGLT-inhibitor/mutation) OR PCT failure (glycosuria w/ normal serum glucose → consider Fanconi's syndrome 2/2 MM, heavy metal, drugs, etc.)

URINE SEDIMENT (MICROSCOPY)

- **Urine microscopy room:** to the left of Harris room, outside White 10
- Nephrology fellow/attending (day) or Security (night) can let you in
 1. Obtain 10cc of **fresh urine**
 2. **Centrifuge** using a balance @ 3000 RPM x3-5min
 3. **Invert/drain supernatant** and **resuspend** sediment in the few drops of urine that remain in the tube. Place one drop of sample on slide and place coverslip
 4. Bright Field Microscopy: keep light source subdued, lower condenser to maximize contrast, start at **low power** (10x) to obtain a general impression. Pay attention to **coverslip edge** where casts tend to migrate
 5. **Phase contrast microscopy:** maximizes contrast and definition and allows better visualization of casts and cells. Raise condenser up high and turn light source to maximum brightness. Objective and condenser annulus should always match

Findings	Description
RBCs	Glomerular (dysmorphic RBCs "mickey mouse ears") vs non-glomerular (normal)
WBCs	UTI/cystitis, pyelonephritis, AIN, atheroembolic, glomerular injury, renal/bladder TB, nephrolithiasis
Epithelial Cells	Tubular (ATN), transitional (proximal urethra to renal pelvis), squamous (contamination by genital secretions)
Casts	Viewed best w phase contrast: Hyaline, RBC, WBC, Muddy brown, Granular, Waxy, Fatty
Crystals	Viewed best w phase contrast: Acyclovir ("needles"), Tenofovir, Struvite (NH4·Mg·PO4), ethylene glycol (oxalate)

CONDITION	UA	CELLS	CASTS/CRYSTALS	COMMENTS
Pre-renal azotemia	SG >1.010		Hyaline, granular	↓FENa, ↓FEUrea
Nephrotic syndrome	3+ protein		Oval fat bodies, hyaline	
Glomerulonephritis	3+ heme	Dysmorphic RBCs	RBC casts, WBC, granular	
ATN	SG ~ 1.010	Tubular cells	Granular, muddy brown	
Rhabdomyolysis, hemolysis	3+ heme w/o RBCs	NO cells	Acellular hyaline casts with red or brown pigmentation	↓FENa, red/brown urine
AIN		WBCs; ± eos	WBC casts, granular	Urine eos NOT sens or spec
Renal infarct	Sterile pyuria; +pro	+Eos, RBCs, WBCs		↑urine LDH (↑serum LDH)
Cholesterol emboli	Sterile pyuria	+Eos	Cholesterol	
Myeloma kidney		Bland	Bland	Proteinuria NOT detected by UA
Ethylene glycol			Ca oxalate	
CKD			Waxy	± impaired ability to concentrate

NEPHROLITHIASIS

Composition and prevalence: CaOxylate > CaPhosphate > Urate = Struvite > Cysteine

Risk factors: male, obesity, DM, white, southeastern US, oral antibiotics, CKD, ESRD, family history (2% attributed to inherited disease)

Workup: CT (I-) > US (urological procedures require CT for planning). Can strain urine to type stone. Can also get 24h urine ("Litholink") at home both before and after interventions (usually dietary) are made

Precipitating factors: low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, hypercystinuria, urea splitting bacteria, high sodium intake, acidic urine (urate, cysteine), or basic urine (calcium phosphate, struvite)

Acute management: IVF, pain management, alpha blockers (>5 mm), urologic intervention if >10mm, infection, or >4 days of obstruction

Chronic management: fluid intake >2.5L/d, low Na diet, high K diet, low oxalate diet (no nuts, chocolate, green leafy veggies, etc.), increase Ca intake, avoid excess vitamin D, thiazide diuretics if calcium stones, allopurinol if hyperuricosuria

Citrate supplementation: used for inhibition of Ca and uric acid stone formation. Leads to metabolic alkalosis. ↓new stones, stone size

Infectious Disease

Empiric Antibiotics

PRINCIPLES OF ANTIBIOTIC SELECTION ([IDSA Guidelines](#), [Sanford Guide](#), [Johns Hopkins Abx Guide](#))

1. Is my patient **stable**? If not start broad spectrum abx quickly; **time to ABX correlates with mortality in septic shock!**
2. *** Get cultures BEFORE starting antibiotics ***
3. What **evidence** is there of infection? (fever, localizing symptoms, leukocytosis, hypotension, inflammatory markers)
4. Is my pt **immunocompromised** (more likely infected, less likely symptomatic) systemically (age, DM, immunosuppression, HIV, neutropenia, ESLD, ESRD) or anatomically (prostheses, lines, altered anatomy, structural organ dz, prior surgeries)?
5. **Where** did it come from (most common sources: PNA, UTI, SSTI, lines, GI translocation), **where** did it go? (blood, CNS, valve, bone)
6. **What bugs** do I need to cover? (likely source, prior pathogens, recent IV abx, immunocompromise, community v facility)
7. How will I **narrow**/stop abx? Re-eval w/in 48h if nothing growing, rely on **MGH antibiogram** (below) while susceptibilities pending
8. **Abx failure**: poor source control (lines, hardware, abscess, effusion, unidentified source), poor penetration, resistance (least likely)
9. **BROADEST IS NOT ALWAYS BEST**, you may lose penetration or efficacy

Suspected Process	Microbiology	Empiric Antimicrobial Therapy	Additional Info
Meningitis (CID 2004:39:1267 ; CID 2017:64:e34)	-Viral, HSV, S. pneumo > N. meningitis -If >50yo, immunocompromised, EtOH: Listeria -If hardware or nosocomial: Staph, PsA; C. acnes if VP shunt	-Vanc + CTX 2g Q12 -Listeria → ampicillin -HSV → acyclovir	-S. pneumo: dex 10mg q6h x 4d -Healthcare-assoc, hardware, VP shunt, IVDU: cefepime, ceftaz, or meropenem instead of CTX
Community Acquired Pneumonia (CAP) (AJRCCM 2019:200:e45)	-VIRAL (MOST COMMON) -Legionella, Mycoplasma, Chlamydia ("atypical") -S. pneumo (classic lobar PNA) -H. flu, Moraxella -S. aureus (usually very sick) -Klebsiella (EtOH)	-Healthy outpt: AMOX >> azithro +Comorbid: amox/clav+macrolide, or levoflox -Most inpts: CTX+azithro, or levoflox -Prior MRSA/PsA OR [IV abx in past 90d]: vanc + cefepime + azithro	-High levels of resistance to azithro -Consider flu testing + oseltamivir -Post-flu/cavitory/empyema: vanc -Structural lung dz: levoflox>azithro -Legionella: levoflox>azithro
Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP) (CID 2016:63:e61)	-CAP organisms + S. aureus + GNRs incl. PsA -Acquired IN HOSPITAL, "HCAP" not included	-Vanc + cefepime	-consider local MDRO prevalence
Endocarditis (Circ 2015:132:1435)	-Native: S. aureus, Strep, Enterococcus, few GNRs, HACEK <5% -Prosthetic: S. aureus, S. epi	-Native: vanc+CTX -Prosthetic: vanc/gent (or vanc/CTX if prosthetic valve >1yr), but ask ID	-ID c/s improves mortality! -MSSA: β-lactam >> vanc
Cholecystitis/Cholangitis (CID 2010:50:133)	-E. coli, Klebs, Enterococcus, anaerobes -Often polymicrobial → broad abx for 48h even if BCx growing only 1 org	-CTX+MNZ -If nosocomial/severe: pip/tazo or penem (mero, imi)	-Source control with CCY, ERCP, or perc cholecystostomy
Other Intra-abdominal (CID 2010:50:133)	-Abscess: GNRs, anaerobes, Enterococ, Candida; S. aureus, Strep rare -Diverticulitis: Polymicrobial, enteric GNR, anaerobes, role of Enterococcus unclear	-[CTX or Cipro]+MNZ -If nosocomial/severe: pip/tazo or penem (mero, imi)	-If abscess: drain -Surgical eval if peritonitis, perf, fistula, recurrent diverticulitis
Spontaneous Bacterial Peritonitis (Hep 2013:57:1651)	-Enteric GNR (incl. Enterobacter), Strep, Enterococcus; rarely anaerobes	-CTX	-Cipro reserved for patients w/ β-lactam allergies and for ppx -Initiate PPX after first episode
UTI (non-pregnant) (CID 2011:52:e103 ; CID 2010:50:625)	Uncomplicated: E.coli, Klebsiella, S. saprophyticus, Proteus Complicated (i.e. systemic infxn, pyelo): + Enterococcus, PsA, Serratia, Providentia Catheter-associated (CAUTI): + other GNRs	-Uncomp: NFT, TMP/SMX, or fosfo -Comp: CTX -CAUTI: vanc+CTX -Cefepime if c/f PsA, penem if c/f ESBL; add vanc if GPC in ucx	-Generally, tx only if symptomatic -CAUTI: exchange Foley, consider repeat UA/UCx 48h later
Osteomyelitis (CID 2012:54:e132 ; CID 2015:61:e26)	-Hematogenous source: S. aureus -Direct inoculation/vascular (e.g. DM ulcer): S. aureus > Strep, PsA (diabetic), GNR, Enterococ, Eikenella (human bites), Pasteurella (animal bites)	-If stable, can hold off abx until after blood and bone cultures -Vanc+CTX; cefepime if DM/PVD/ulcer or direct inoculation	-Dx: ESR/CRP, MRI, bone bx -Debride (ortho/vasc surg/plastics) w/ bone bx+cx -Bite: amp/sulbact 1.5-3g q6h
Septic Arthritis (Curr Opin Rheumatol 2008:20:457)	-Staph, Strep, N. gonorrhoea, E. coli; Salmonella (sickle cell); PsA (IVDU); Lyme; viruses (poly-articular)	-Blood+joint fluid cx prior to abx -Vanc+CTX (consider cefepime if IVDU, other risk factor for PsA)	-Consult ortho for joint washout
Skin/Soft Tissue (SSTI) (CID 2014:59:e10)	-Impetigo: S. aureus > Strep -Cellulitis/Erysipelas: Strep > Staph -Nec Fasc: Strep, C. perfringens, MRSA	-Purulent: vanc -Non-purulent: cefazolin -Nec Fasc: vanc+[pip/tazo or mero] + clinda	-DM/PV ulcer: vanc+[CTX or cefepime] -If abscess: drain -If nec fasc: URGENT SURG EVAL
Septic shock, no source (Intensive Care Med 2017:43:304)	-GNRs, S. aureus, Strep, PsA, anaerobes -Consider toxic shock syndrome (TSS)	-Vanc+cefepime or ceftaz ± MNZ (if c/f anaerobes) -If TSS: add clinda 900mg IV q8h	-MDRO: meropenem/imipenem -Critical illness: consider 1 dose aminoglycoside

For up to date MGH Antibiogram & Guidelines for Empiric Therapy for Inpatients: [click](#) (VPN or hospital WiFi) & scroll down

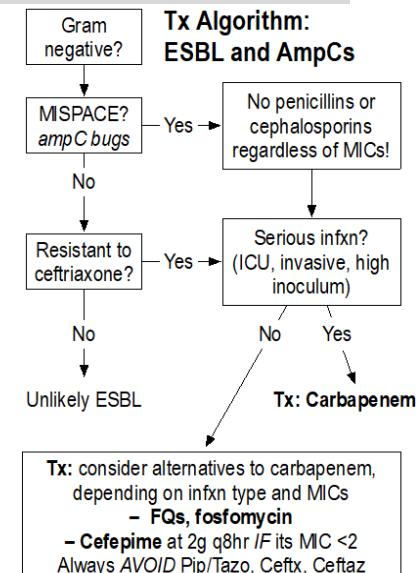
Infectious Disease

Multidrug Resistant Organisms

MDR GNRs ([CID 2020; Dosing table](#) [does not include cefepime])

Extended-Spectrum Beta Lactamases (ESBL)

- Mechanism: plasmid-mediated enzymes seen in **GN organisms** conferring resistance to most beta-lactams (PCNs, cephalosporins, aztreonam)
 - MGH infection control definition of potential ESBL: **GNR resistant to CTX**
- Pathogens: Klebsiella (#1), E. coli (#2), Proteus mirabilis (#3), other GNs
- RFs: abx within past 6mo, long inpt hosp., nursing home, >65yo, lines/cath/tubes/vent, TPN, HD, travel to Asia
- Treatment: avoid PCNs/cephalosporins incl. pip-tazo even if "susceptible" ([MERINO: JAMA 2018;320:984](#))
 - If not critically ill, can use cefepime if MIC≤2 ([CID 2014;58:1554](#)) or beta-lactam alternatives if susceptible (e.g. FQ [E. coli]) ([CID 2017;64:972](#)). TMP/SMX, NFT preferred for cystitis
 - If critically ill or prior ESBL \oplus BCx, empiric tx w/ meropenem



AmpC Beta-Lactamases (Cephalosporinases – aka MISPACED organisms)

- Mechanism: enzymes that neutralize 3rd gen ceph., pip-tazo. Constitutive or inducible expression (can appear S to CTX)
- Inducible AmpC producers include **MISPACED** (aka SPICE, SPACE-M) **organisms**: Morganella, Indole-positive Proteus (non-mirabilis species), **Serratia**, Providencia, Acinetobacter, **Citrobacter**, Enterobacter
- Treatment: do not treat these organisms with 3rd gen. cephalosporin (i.e. CTX) or pip/tazo, even if "susceptible"
 - If critically ill, tx w/ meropenem or cefepime if MIC ≤2. Pip-tazo being studied (MERINO II)
 - If not critically ill, can use beta-lactam alternatives (e.g. FQ, TMP/SMX, or NFT [only cystitis]) if susceptible

Carbapenem Resistant Enterobacteriaceae (CRE) – resistant to at least one carbapenem or possessing carbapenemase

- Mechanisms: 1) Carbapenemase or 2) AmpC/ESBL (some hydrolyze penems) + porin loss (limits penem entry)
- RFs: cephalosporin/carbapenem use in past 3mo (*penem exposure not req*), medical care in India/Pakistan
- Laboratory detection: suspicious when MIC >2 for imi-, mero-, or ertapenem
- Treatment: preferred option is usually ceftaz-avibactam (+aztreonam if care in India/Pakistan); alternatives may include AG (if UTI), extended-infusion meropenem (if susceptible), cefiderocol or tigecycline (if intra-abdominal), **c/s ID**
 - If uncomplicated UTI – use FQ, TMP/SMX, NFT, fosfomycin, or single dose AG

Difficult-to-Treat Resistance Pseudomonas (DTR-PSA)

- Definition: non-susceptibility to pip-tazo, ceftaz, cefepime, aztreonam, FQ, meropenem, AND imipenem-cilastatin
- Treatment: ceftolozane-tazobactam, ceftaz-avibactam, imipenem-cilastatin-relebactam, single dose AG (if cystitis); **c/s ID**

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

Community-associated MRSA: no healthcare exposure, SSTI in young & healthy

- RFs: HIV, IVDU, prior abx use; outbreaks: incarceration, military, sports, sharing needles/razors

Healthcare-associated MRSA: occurs >48h following hospitalization or w/in 12mo of healthcare exposure

- RFs: recent hospitalization/surgery, HD, LTC facility residence
- Nasal swab: NPV in CAP = 96.5%, if \ominus consider d/c MRSA coverage ([CID 2018;67:1](#)), use [Antimicrobial De-escalation Guidelines](#) in HAP/VAP

Treatment: check the vanc MIC

- MIC ≤2 mcg/mL = vanc-susceptible (though ↑tx failure and mortality when MIC=2). Vanc-intermediate (VISA) when 4≤MIC≤8. Vanc-resistant (VRSA) if MIC ≥16
- Serious infections (i.e. bacteremia): **vanc** (w/ full loading dose) and **ID c/s**. If persistent bacteremia or MIC ≥2, consider **dapto** (not in PNA [inactivated by surfactant] or meningitis [does not cross BBB]) or add ceftaroline
- Mild infections (e.g., SSTI): TMP-SMX, doxycycline >> clindamycin (increased resistance at MGH); linezolid

VANCOMYCIN RESISTANT ENTEROCOCCI (VRE)

- Low virulence, colonizer. **E. faecium**: often resistant & generally less virulent. **E. faecalis** is facile: i.e. **less** resistance
- RFs: prior abx, Foley, indwelling lines; proximity to other VRE pts; long hosp/SNF; immunocompromised
- Clinical sites of infection: UTI (often an **asymptomatic colonizer**); bacteremia (2nd most common CLABSI); intra-abdominal and pelvic infections; endocarditis (esp. if prosthetic valve); meningitis (immunocompromised or VP shunt)
- Treatment:
 - Invasive infection (e.g. bacteremia, endocarditis): dapto (+ amp or CTX or ceftaroline) OR linezolid, **c/s ID**
 - Uncomplicated UTI: fosfomycin x1 (consider repeat dose on days 4 and 7) OR NFT

Infectious Disease

Community Acquired Pneumonia

COMMUNITY ACQUIRED PNEUMONIA (CAP) ([AJRCCM 2019;200:45](#))

- **Definition:** PNA acquired in the community, including patients from nursing homes, dialysis, or with outpatient clinic exposure
- **Diagnosis:** new CXR opacity AND s/sx (e.g. fever, cough, leukocytosis, purulent sputum, hypoxemia)
 - Elderly at ↑ risk of blunted s/sx but also ↑ prevalence of atelectasis/aspiration
 - Radiographic consolidation NOT specific for bacterial vs viral PNA
 - If CXR ⊖ but high clinical suspicion → tx and repeat CXR in 24h (PNA may "blossom" after fluid resuscitation and/or time); if still ⊖ → consider chest CT or other dx
- **Triage:** CURB-65 (Confusion, BUN>20, RR>30, BP<90/60, age>65) → outpatient if score 0-1, inpatient if 2, consider ICU if 3-5. Pneumonia Severity Index (PSI) more comprehensive → outpatient if <70, inpatient if >90
- **Severe CAP: 1 Major** (pressors or mech vent) OR **3 Minor** (RR>30, P:F<250, multilobar infiltrates, confusion, BUN>20, WBC<4K (not due to chemo), Plt<100K, T<36C, HoTN requiring aggressive fluid resuscitation)
- **Micro:** S. pneumoniae (most common in inpts, ICU), H. influenzae, GNRs, S. aureus, Legionella. Most common pathogens identified are viruses – rhinovirus, influenza, others ([NEJM 2015;358:415](#))
- **Work-up (inpatient):**
 - **Sputum culture and gram stain** (ET aspirate if intubated): adequate sample if >25 PMN/lpf and <10 SEC/lpf. NOTE: "abundant squamous cells" or more squamous cells than polys suggests the sample is saliva
 - **Blood cultures:** controversial benefit, positive <20% of inpt PNA, 2/3rd of positive Cx are S. pneumoniae
 - Obtain Scx and Bcx if: severe CAP, empiric treatment for MRSA/PsA, prev. MRSA/PsA, or hosp. w/ IV abx ≤90d
 - **Procalcitonin (PCT):** not routinely used at MGH, data show it may not change antibiotic management
 - ↑ in acute resp. infxn from bacterial causes, unclear cut-off to distinguish from viral. Not validated in immunocompromised
 - **Legionella urine Ag** (Sn 70%, Sp 99%); detects only serogroup 1 (80-90% in US). ✓ if severe CAP or recent exposure/travel. Clinical predictors include hypoNa, fever, diarrhea, and recent travel ([CID 2019;68:2026](#))
 - **MRSA nasal swab:** high NPV (~98%). ⊖ test → consider d/c MRSA coverage ([CID 2018;67:1](#))
 - **Influenza:** test seasonally. **Tx:** oseltamivir regardless of duration of illness (though best if initiated <48h)
- **IDSA/ATS CAP Empiric Treatment** (NOTE: additional considerations for travelers, immunocompromised)

Outpatient	Preferred	Alternative/Other info
No Comorbidities or MRSA/PsA RFs	Amox 1g TID OR doxy 100mg BID OR macrolide (azithro OR clarithro) (<u>if resist. <25%</u>)	<u>NOTE: U.S. has high rates of macrolide- and doxy-resistant S. pneumo</u>
Comorbidities°	[Amox-clav 2g BID <u>AND</u> azithro] <u>OR</u> levofloxacin 750mg QD monotherapy	Cefpodox or cefurox. can replace amox-clav, doxy can replace azithro
Inpatient	Preferred	Alternative/Other info
Non-Severe	(β-lactam (CTX) <u>AND</u> macrolide [azithro]) <u>OR</u> levofloxacin monotherapy**	Amp/sulb can replace CTX, clarithro can replace azithro
Severe/ICU	β-lactam (CTX 1-2g QD) <u>AND</u> (azithro OR levofloxacin)	In ICU, azithro >> levofloxacin (anti-inflamm. effect); consider add'l agents for drug-resistance (see below)
MRSA/PsA RFs#	Vancomycin <u>AND</u> ceftazidime	Obtain Cx and nasal MRSA swab to inform de-escalation. Do not use daptomycin (poor lung penetration)

°Chronic heart, lung, liver, or renal disease; DM; AUD; malignancy; or asplenia. **CAP START showed β-lactam monotherapy noninferior to combo β-lactam/macrolide or fluoroquinolone alone, however trial was conducted in areas with lower rates of atypical organisms ([NEJM 2015;372:1312](#)). #Prior respiratory isolation of MRSA/PsA or recent hospitalization w/ IV abx (≤90d)

- **Risk factors for drug-resistant pathogens in CAP:**
 - General: hospitalization & IV abx in past 90d; prior respiratory isolation of MRSA, PsA or other resistant organisms
 - PsA: GNR on gram stain, h/o PsA, bronchiectasis, COPD w/ freq exacerbations req abx/steroids. **Tx:** (for normal renal function) ceftazidime 2g q8h, ceftazidime 2g q8h, pip-tazo 4.5g q6h, mero/imipenem; double coverage usually not necessary
 - MRSA: GPC clusters on gram stain, recent flu-like illness, necrotizing/cavitation/empyema, ⊕ nasal swab, risk factors for colonization (ESRD, IVDU, prior abx [esp. fluoroquinolones]). **Tx:** vancomycin or linezolid
- **Anaerobic coverage:** only if suspicion for empyema or lung abscess, see [HAP/VAP & Aspiration Pneumonia](#)
- **Steroids:** some data for benefit in severe CAP but routine use not rec. by IDSA/ATS unless o/w indicated for refractory septic shock or COPD/other comorbidity ([Cochrane Rev 2017](#)). **AVOID** in INFLUENZA as might ↑ mortality ([Cochrane Rev 2016](#))
- **Duration:** usually **5d; 7d** in suspected or proven MRSA or PsA CAP, assuming clinical stability (afebrile x48h + ≤1 sign of CAP instability: HR >100, RR >24, O2<90%, AMS, no PO intake). MRSA should be treated longer if not improving within 72h (e.g. 10-14d in critically ill, 2-6w with ID consult if c/b bacteremia or necrotizing PNA)
 - If have not achieved clinical stability, extend course & eval. for resist. pathogen, complication (empyema, abscess), alt. source
 - Convert IV → PO when clinically improving; **no need to observe x24h on PO**
- **Response to therapy:** tachycardia resolves by 2-3d; fever resolves by 2-4d; hypoxemia resolves by 3-6d
 - CXR clears by 1mo in 50% (up to 12wks in elderly, lung disease); **do not** need repeat CXR if clinical improvement
 - If no response to therapy after 72h: consider chest CT (± BAL) to evaluate for empyema, abscess, fungal infxn
- **Parapneumonic effusion:** exudative, develops adjacent to a pneumonia, 20-57% of PNA hospitalizations ([CID 2007;45:1480](#))
 - Uncomplicated (smaller, free flowing, ~normal pH/glucose, ⊖ GS/Cx) → complicated (larger, loculated, ↓pH/glucose, ⊕ GS/Cx) → empyema (purulent)
 - **Large enough** for dx ± tx thoracentesis or chest tube → **c/s** IP, IR, or Thoracic Surg. Small effusions often regress w/ abx
 - Duration of abx, utility of surgery, timing of repeat imaging: guided by severity and clinical/radiographic progression

Infectious Disease

HAP/VAP & Aspiration Pneumonia

HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA (IDSA/ATS: [CID 2016;63:e61](#))

Definitions:

Hospital-acquired pneumonia (HAP)	Pneumonia that develops ≥48h after admission
Ventilator-associated pneumonia (VAP)	Pneumonia that develops ≥48h after endotracheal intubation
Dx criteria: new/progressive infiltrates on CXR + 2/3 of fever, leukocytosis, purulent tracheal secretions	

Common microbiology: enteric GNRs (*Klebsiella, E. coli*), MRSA/MSSA, *PsA*, *Acinetobacter*

Workup: CXR, SpCx, BCx, MRSA swab; consider induced sputum, bronch with BAL

MDRO RFs: IV abx use w/in 90 days preceding onset (most important); high local prevalence (>10%) of MDR GNRs & MRSA; structural lung disease (CF, bronchiectasis); prior hx of MDRO infection

- **MDR VAP RFs:** septic shock/ICU, ARDS, onset ≥5d in hospital, or RRT preceding onset

Empiric Tx of HAP/VAP w/ MDRO risk: 1 anti-PsA (β -lactam pref.) AND 1 anti-MRSA agent (typically **vancomycin**)

- Consider double PsA coverage if: septic shock, rapid progression of PNA requiring mech. ventilation, hx of MDR PsA

Antipseudomonal β -lactams	Antipseudomonal non- β -lactams	Anti-MRSA agents
<ul style="list-style-type: none">- <u>Cefepime 2g IV q8h</u>- Ceftazidime 2g IV q8h- Pip/Tazo 4.5g IV q6h- Meropenem 1g IV q8h- Aztreonam 2g IV q8h (only if severe PCN allergy: ellucid)	<ul style="list-style-type: none">- Levofloxacin 750mg IV qd (*PsA susceptibility only 70% at MGH)- Ciprofloxacin 400mg IV q8h- Tobramycin 5-7mg/kg IV x1, then dose by level- Polymyxin B (call ID)	<ul style="list-style-type: none">- <u>Vancomycin IV</u>- Linezolid 600mg q12h
<i>Always adjust dosing for renal function. When in doubt, call Pharmacy!</i>		

• Tailoring therapy:

- Improvement after 48h or pathogen ID'd: narrow abx and d/c MRSA+PsA coverage if possible. ⊖ MRSA swab w/ 96% NPV for MRSA infection, most evidence comes from swab on admission and not further into course ([CID 2018;18:67](#); [CID 2020;71:1142](#)). VAP: ⊖ tracheal aspirate NPV 94%, consider d/c abx after 72h ([IJD 2010;14:18](#))
- No improvement after 48h: broaden to cover MDROs (if not already), consider other sites of infection/abscess, non-infectious causes of clinical syndrome

• Duration: 7d. Consider serial procalcitonin → d/c abx when <0.25ng/mL ([ERJ 2009;34:1364](#))

ASPIRATION PNEUMONIA

- **Definition:** pneumonia caused by the excessive entry of secretions, particulate matter, or fluid into airways. Micro-aspirations are common and the definition of aspiration pneumonia as a distinct clinical entity remains unclear
- **Predisposing factors:** AMS, esophageal dysmotility, post-bronchial obstruction, gum disease/poor dentition
- **Microbiology:** most common organisms are GNRs and standard CAP/HAP organisms ([AJRCCM 2003;167:1650](#)). Role of anaerobes is likely overstated ([Chest 1999;115:178](#))
- **Characteristics:** indolent, putrid sputum, pulmonary necrosis w/ cavitation/abscess/empyema
- **Workup:** CXR, SpCx (anaerobic respiratory culture not performed at MGH due to low utility)
- **Empiric treatment:** same as CAP/HAP empiric treatment ([AJRCCM 2019;200:e45](#); [JHM 2020;15:754](#))
 - **Anaerobic coverage:** only recommended in pts w/ **suspected lung abscess** or **empyema**. First line: ampicillin-sulbactam (or amox-clavulanate if not severely ill); alternative: (CTX+MNZ) OR clindamycin
 - **Duration:** 7d unless complicated by cavitation/abscess/empyema

ASPIRATION PNEUMONITIS

- **Definition:** aspiration of chemical substances into the airways without bacterial infection
- **Clinical manifestations:** abrupt onset (2h), low-grade fever, ↑WBC, hypoxemia, CXR consolidation (RML/RLL upright, RUL supine) → often indistinguishable from pneumonia in the acute setting!
- **Treatment:** if concern for aspiration pneumonia (i.e. bacterial infection), **cover with abx for 48h** → d/c if no consolidation develops on CXR OR if signs/sx/consolidation resolve rapidly

Infectious Disease

Viral Respiratory/Head & Neck Infections

VIRAL RESPIRATORY INFECTIONS (for COVID-19 [VPN/MGH wifi]; for bacterial pharyngitis see [HEENT Concerns](#))

- **Epidemiology**
 - >200 viral pathogens may cause VRIs, most common include rhinovirus, influenza, coronavirus, parainfluenza
 - LRTI (bronchitis, bronchiolitis, PNA): coronavirus, influenza, RSV, parainfluenza, adenovirus ([Lancet 2011;377:1264](#))
 - In immunocompromised hosts, consider reactivation of latent viruses (HSV, CMV, adenovirus)
- **Presentation**
 - Transmission: hand contact, droplet, peak viral shedding at 2-3d of illness
 - Symptoms: nasal congestion, dry throat, cough, wheeze, fever, myalgias with symptoms peaking at 3-5d and lasting 10-14d (if significant systemic illness consider influenza, measles, SARS, Hantavirus)
 - Complications: bacterial PNA (occurs in 1/800 w/ initial improvement → worsening after ~7d, micro: S. pneumo, S. aureus), asthma/COPD exacerbation, bacterial sinusitis (occurs 2/100), otitis media, ARDS
- **Diagnosis**
 - Clinical diagnosis that generally does not require microbiological testing except for influenza and COVID-19
 - Respiratory viral panel: NP swab PCR for adenovirus/parainfluenza/metapneumovirus; can help avoid unnecessary abx; collect w/in 5d of sx onset, though ~15% healthy persons harbor resp viruses ([Ped ID J 2008;27:1103](#))
 - Influenza testing: (IDSA: [CID 2019;68:47](#))
 - RT PCR most sensitive and specific; can differentiate A, B and subtypes (1-8h)
 - Rapid molecular assay 92% Sn, 96% Sp, can differentiate A, B (15-30min)
 - Rapid ag test 62% Sn, 98% Sp (<15min); during season ⊖ test does not exclude, not sufficient to stop tx
- **General VRI Treatment**
 - Sx management with decongestants, nasal sprays, anti-inflammatory agents, humidified air. No role for ppx abx
 - COVID-19 specific treatments: dexamethasone ([NEJM 2021;384:693](#)), remdesivir ([NEJM 2020;383:1813](#)) in select patients. See [Handbook](#) (VPN or MGH wifi) for most up to date guidance
- **Influenza Treatment and Post-Exposure Prophylaxis**
 - Treatment: oseltamivir 75mg BID x5d (can extend in severely ill or immunocompromised)
 - Indications: severe dz (hospitalized or PNA), ↑ risk (age >65, long-term care facility residence, pregnant, <2 wks post-partum, immunosuppressed, cirrhosis, DM, CHF/CAD, CKD, COPD, SCD, asthma, BMI >40, neuro dz)
 - Consider: outpts with sx <48h or those with high risk household members
 - Prophylaxis: oseltamivir 75mg daily after last day of exposure (x7d if **vaccinated**, x14d + vaccine if **unvaccinated**)
 - Initiate w/in 48h of exposure
 - Consider: unexposed unvaccinated pts/house contacts w/ ↑ complication risk; facility residents during outbreak

HEAD AND NECK INFECTIONS ([Principles of Crit Care. Chow AW. 4th edition. McGraw-Hill, NY 2015](#))

- Epidemiology: often from odontogenic, otogenic or sinogenic infection with contiguous spread
- Organisms: streptococci, H flu, oral anaerobes. PSA in otogenic source. MRSA in sinogenic source and IVDU
- Diagnostics: blood cultures, **CT Neck**, MRI (consider to evaluate for osteo), IR or ENT for tissue or abscess culture
- Empiric Treatment: varies based on likely source; odontogenic - CTX+MNZ, otogenic - cefepime+MNZ; sinogenic - vancomycin+CTX+MNZ. **Involve ENT early** for drainage and airway monitoring
 - **Submandibular space** (Ludwig's angina): periodontal infection → mouth pain, tongue swelling, neck stiffness, can progress to airway compromise, most commonly strep viridans
 - **Internal jugular septic thrombophlebitis** (Lemierre's syndrome): pharyngitis and septic embolic phenomena. Most commonly *fusobacterium*. Treat with abx and anticoagulation
 - **Deep neck space**: involving retropharyngeal, "danger," and paravertebral spaces. Presents with neck pain and systemic toxicity. Can progress to carotid sheath abscess, mediastinitis, vertebral osteo, paravertebral abscess

ORBITAL AND PRESEPTAL CELLULITIS ([Surv Ophthalmol 2018;63:505](#))

Preseptal

- Epidemiology: local trauma
- Organisms: staph, strep
- Symptoms: eyelid pain and edema **without** orbital congestion
- Diagnosis: clinical; CT orbit and sinus can distinguish from orbital cellulitis
- Empiric Treatment: amoxicillin + TMP-SMX or clindamycin

Orbital

- Epidemiology: sinusitis, oral abscess, dacryocystitis, local trauma, direct inoculation
- Organism: staph, strep; in immunocompromised mucor and aspergillus
- Symptoms: pain with eye movement, proptosis, decreased visual acuity and corneal sensation, extraocular muscle deficits
- Diagnosis: blood cultures, CT of orbit and sinus, LP if c/f CNS extension, MRI if concern for cavernous sinus thrombophlebitis
- Empiric Treatment: vancomycin+CTX; add MNZ if concern for CNS involvement or odontogenic/sinogenic spread, **involve ophthalmology early**
- Complications: vision loss, subperiosteal abscess, orbital abscess, CNS spread, cavernous sinus thrombophlebitis

Infectious Disease

Urinary Tract Infections

ASYMPTOMATIC BACTERIURIA

Definition: bacteriuria ($\geq 10^5$ CFU/mL) w/o sx referable to a UTI, irrespective of pyuria

- **Treatment:** asymptomatic bacteriuria or pyuria should NOT be treated (exceptions: pregnant woman, s/p renal transplant in past 1mo, ppx for invasive urologic procedures) (IDSA: [CID 2019;68:1611](#))

UTI

Clinical features: frequency, urgency, dysuria (premenopausal), incontinence, nocturia, suprapubic tenderness in otherwise healthy nonpregnant women

Fever, other s/sx of systemic illness, occurring in pregnant women, men, obstruction, immunosuppressed, renal failure/transplant, RFs such as indwelling catheters

No ↓

↓ Yes

Uncomplicated UTI (Cystitis) ([JAMA 2014; 312:1677](#))

- **Diagnosis:** clinical; U/A can be used to confirm; pyuria (>10 WBC); nitrite and LE both \oplus on dipstick \rightarrow Sn 68-88%
 - **Women:** dysuria + ↑frequency w/o vaginal discharge/irritation \rightarrow >90% likelihood of UTI. Outpatient, U/A unnecessary unless immunocompromised or RFs for complicated UTI
 - Absence of pyuria **strongly suggests against cystitis**
 - **Nitrite:** \oplus w/ Enterobacteriales (convert nitrate \rightarrow nitrite)
 - Outpatient, get UCx if: male, atypical sx, persist 48-72h after abx initiated, or recur w/in 3 mo of tx
- **Differential diagnosis:** vaginitis, urethritis, structural abnormality, PID, nephrolithiasis
- **Microbiology:** *E. coli*, Klebs, *Proteus*, *S. Sapyrophyticus*
Enterococcus rarely causes true infection
- **Treatment:** NFT 100mg BID x5d OR T/S DS BID x3d OR **fosfomycin** 3g x1; alternatives: oral β -lactam (e.g. Augmentin 500mg BID, Cefpodoxime 200mg BID) x7d
 - Avoid NFT if CrCl <40
 - Avoid empiric T/S if resistance >20% (*E. Coli* resistance 27% at MGH)

Complicated UTI

- 30% w/ UTI **and** fever are bacteremic (usually older, flank / suprapubic pain, ↑CRP, ↓BP) ([JAMA 2018;378:48](#))
- **Pyelonephritis is a complicated UTI**, & may itself be complicated by perinephric or renal abscess
 - WBC casts on U/A are suggestive of pyelo
- **Microbiology:** same as uncomp. UTI plus *Serratia*, *Morganella*, *Providencia*, *Pseudomonas*, *Citrobacter*. Gram-positives rare. If *S. aureus*, think bacteremia. Increasingly resistant organisms (especially to FQ, TMP/SMX)
- **Dx:** UCx in all; imaging if ill, suspect obstruction, persistent sx
- **Treatment:** Outpt: CPO 500mg BID OR LVO 750mg x5-7d OR T/S DS BID x7-10d. Can give 1x IV CTX prior to oral tx.
Inpt: CTX OR CEFE OR P/T; CBPN if c/f ESBL. Narrow to oral if improving. Add **vanc/linezolid** if GPC on urine GS.
Duration for inpt: depends on clinical course & oral agent chosen (5-7d for FQ; 7-10d for T/S; 10-14d for β -lactam)
 - Avoid **NFT & fosfomycin** (poor soft tissue penetration)
 - Remove/replace coated urologic devices
 - **Prostatitis:** FQN preferred for better penetration; tx duration up to **6w**

CATHETER-ASSOCIATED UTI (CAUTI) (IDSA: [CID 2010; 50:625](#))

- **Definition:** leading healthcare-assoc. infection; requires: (1) s/sx with no other identified source of infection; **AND** (2) UCx with one uropathogenic species $>10^3$ CFU/ml from single catheterized urine specimen (catheter in place >2 d) **OR** midstream voided specimen from pt whose catheter was removed w/in previous 48h
 - In pts w/ neurogenic bladder and ↓ sensation, other signs of UTI include new onset incontinence, autonomic hyperreflexia, malaise, lethargy, bladder pain ([Urology 2015;6:321](#))
- **Prevention:** restrict catheters to pts w/ appropriate indications; remove catheters ASAP; consider short-term straight cath
- **Dx:** do not screen asx patients; pyuria, turbidity, odor cannot differentiate asymptomatic bacteriuria from CAUTI
 - **Remove** catheter ASAP, obtain repeat UA/UCx from new catheter PRIOR to abx. Urinary catheters may become coated with a biofilm that acts as a reservoir for microorganisms and can compromise the action of antibiotics and host defenses
 - Purple urine bag syndrome: occurs due to byproducts from bacterial enzymes in urine; benign and \neq UTI
- **Micro:** same as complicated UTI, with addition of *Candida* (see below); can be polymicrobial
- **Treatment:** same abx as complicated UTI, use Cx to narrow. If recent catheterization/instrumentation, h/o MRSA in urine, add vanc, then narrow pending culture results. Duration: 7d if improving; 10-14d otherwise

FUNGURIA (IDSA: [CID 2016;62:e1](#))

- Asymptomatic colonization common; only treat if symptoms present OR neutropenic OR before urologic procedure
- Tx: **Fluc** 200-400mg (pyelo) PO QD 14d **OR** for resistant *C. glabrata* or *krusei*, **Amphotericin** 0.3-0.6 mg/kg QD x1-7d

RECURRENT UTI

- Abx ppx (usually ↓ dose T/S or NFT) may be used in some ♀ w/ recurrent simple cystitis (≥ 2 UTI/6mo) if behavior Δs ineffective. Either post-coital or continuous ([Cochrane Rev 2004](#)). D-mannose 2g daily, 2-3L water intake daily also effective
- Pts w/ recurrent admission for complicated UTI, review prior micro & consider resistant orgs. Consider ID +/- urology involvement. Abx ppx is not indicated for recurrent complicated UTI with resistant organisms due to risk of ↑ resistance

Infectious Disease

Skin & Soft Tissue Infections

CELLULITIS (IDSA: [CID 2014;59:147](#); [JAMA 2016;316:325](#))

- Clinical features:** erythema, warmth, tenderness, edema, induration ± purulence; smooth, poorly demarcated (vs. erysipelas). May have lymphangitis, LAD, vesicles/bullae, fever (20-77%), leukocytosis (34-50%)
- RFs:** trauma, venous stasis, chronic edema (esp. lymphedema), DM, obesity, XRT, IVDU, neutropenia, eczema, prior surgery/biopsy, toe web abnormalities
- Differential diagnosis:** (*NB*: if "bilateral cellulitis," strongly consider alternative diagnosis)
 - Non-infectious: inflammatory (contact dermatitis, drug rxn, angioedema, Sweet syndrome, gout, bursitis, erythema nodosum, pyoderma gangrenosum, eosinophilic cellulitis, sarcoidosis, GVHD); vascular (stasis dermatitis, lymphedema, DVT, superficial thrombophlebitis, calciphylaxis), neoplastic (leukemia, lymphoma, breast CA, extramammary Paget's)
 - Infectious: abscess (may coexist), erysipelas, necrotizing fasciitis, septic joint, osteo, zoster, HSV, erythema migrans
- Diagnosis:**
 - CLINICAL.** Can use [ALT-70 score](#) (reduces abx use) ([J Am Acad Derm 2017;76:618](#); [JAMA Derm 2018;154:529](#)). Consider US to assess for presence of drainable abscess
 - BCx & wound Cx NOT recommended due to low yield (pos in <5%). Obtain if: systemic toxicity, extensive skin involvement, immunosuppression, surgical wounds, special exposures (bites, water), recurrent/persistent cellulitis
- Treatment:** based on 1) **purulence** and 2) **severity**. Duration: 5d; up to 14d if delayed signs of improvement

Severity	Purulent (abscess or fluctuance)	Non-purulent †
Mild	MRSA (67%) > MSSA (17%) > Strep (5%) I&D only	Strep >> <i>S. aureus</i> > aerobic GNRs PO: cephalex., diclo., pen VK, amox-clav
Moderate: systemic signs of infxn‡ <u>OR</u> abscess >2cm	I&D+Cx. <u>Empiric:</u> T/S <u>OR</u> doxy <u>MSSA:</u> diclo. <u>OR</u> cephalex. <u>MRSA:</u> T/S	IV: cefazolin, CTX, pen G Severe β-lactam allergy: vanc, telavancin
Severe: systemic signs of infxn‡ <u>AND</u> HoTN, immunocomp., rapid evolution, deeper infection, or failed PO tx	I&D+Cx. <u>Empiric:</u> vanc <u>OR</u> LZD <u>OR</u> daptomycin <u>OR</u> ceftaroline. <u>MSSA:</u> naftillin <u>OR</u> cefazolin	Vanc+(mero <u>OR</u> cefepime+MNZ). <u>Nec fasc or TSS:</u> add clinda for toxin inhibition

†Non-purulent w/ **MRSA risk factors** (prev. MRSA infx/colonization, hosp./surgery/abx in prev 8wks, IVDU, penetrating trauma, hemodialysis, HIV, athletes, prisoners, military, LTC facility residents): add empiric PO/IV MRSA coverage (T/S or doxy)

‡Systemic signs of infection include: T >38C or <36C, tachycardia (HR >90), tachypnea (RR >24), WBC >12 or <4

NB: erythema may worsen initially; should improve w/ 72h of abx. **Take pictures and draw margin lines** to track progress

- Additional coverage:** anaerobes (if necrosis, crepitus, certain diabetic infxns [see below], animal bite); GNRs (cirrhosis w/ severe infection, immunocompromise, certain diabetic infxns [as below]); PsA (neutropenic, trauma, post-op)
- Specific associations:** gas gangrene → *C. perfringens*; dog/cat bite → *Capnocytophaga, Pasteurella*; human bite/IVDU → *Eikenella*; water exposure → *Aeromonas* (freshwater); saltwater → *Vibrio vulnificus* (esp. in cirrhosis)
- IVDU:** numerous sources of infection (water, syringes, cotton filter, skin flora), discuss safe injection practices and PreP with patient. Links to printable patient resources: ([CDC 1](#); [CDC 2](#))

NECROTIZING FASCIITIS (NEJM 2017;377:2253)

- Microbiology:** Type I: polymicrobial (mixed aerobes/anaerobes); Type II: monomicrobial (usually GAS, less often other Strep or Staph, *Vibrio*, *Aeromonas*), associated with TSS; myonecrosis (i.e., gas gangrene): caused by *C. perfringens*, presents with gas in tissues, severe pain, toxin-mediated shock
- RFs:** immunosupp., DM (esp. Fournier's gangrene – necrotizing fasciitis of the perineum), cirrhosis, neutropenia, EtOH, trauma (even minor), skin/mucosal breach, PVD
- Clinical manifestations:** pain out of proportion to exam, bullae, induration (risk of compartment syndrome), tissue anesthesia, rapid skin changes (purple-red → blue-grey), crepitus (suggestive of myonecrosis); systemic toxicity, ↑CK, lactate, Cr, WBC
- Diagnosis:** early suspicion and involvement of a **surgeon for surgical exploration** and ID is critical
 - LRINEC score** ≥6 raises high suspicion for nec fasc; 90% Sn, 95% Sp ([CCM 2004;32:1535](#))
- Treatment:** urgent surgical debridement + abx: vanc + mero or cefepime/MNZ + clinda (*NB:* LZD also inhibits toxin production)

DIABETIC FOOT INFECTIONS (IDSA: [CID 2012;54:e132](#))

- Severity:** mild (superficial ulcer, no involvement of deeper structures, erythema <2cm); moderate (ulcer with involvement of deeper structures or erythema >2cm); severe (moderate + systemic signs of infxn)
- Initial evaluation:** cleanse, debride, probe, culture. Check pulses/sensation, ABIs (40% have PAD), consider XR/MRI
- Diagnosis:** wound culture. Most polymicrobial w/ GPC>GNR, anaerobes. For mod-severe infxn: add blood Cx + ESR/CRP
 - Osteomyelitis:** if suspicious for OM (see [Osteomyelitis](#)), obtain MRI ± surgery c/s for bone/tissue bx ± ID c/s
- Treatment:** definitive tx based on deep Cx obtained **PRIOR** to the initiation of abx. Appropriate wound care is critical
 - Mild:** oral → target GPCs (cephalexin, amox-clav, diclo, levoflox); T/S or doxy for MRSA; 1-2w
 - Moderate/severe:** IV → target GPCs, GNRs, ± anaerobes: (CTX or FQ) + MNZ; or amp-sulb. MRSA coverage w/ vanc, LZD, or daptomycin if: severe infxn, prior MRSA infxn/colonization, other RFs (see above). PsA coverage w/ cefepime or pip/tazo if: severe infxn, immunocompromised, neutropenic, water exposure, burn/puncture, nosocomial
 - If improving, may de-escalate IV to highly bioavailable PO regimen to complete course

Infectious Disease

Osteomyelitis

CLINICAL MANIFESTATIONS

- **Acute:** <2w of sx & absence of necrotic bone or sequestrum. Sx: localized pain & diminished function or evidence of inflammation (fever/chills/night sweats/erythema). Pts can be afebrile
- **Chronic:** previously failed tx, >3w sx, presence of bony sequestrum, persistent drainage or sinus tract; pain (absent if neuropathy), erythema, swelling; poorly healing ulcers; hallmark is necrotic bone
- **Etiologies:** hematogenous seeding (usually monomicrobial) from bacteremia (\uparrow risk if endocarditis or indwelling device) or contiguous spread (polymicrobial) via direct inoculation after surgery/trauma
 - Hip, vertebra, pelvis: often have fewer symptoms, can present as septic arthritis
 - Vertebral: point tenderness, unremitting, >50yo (except IVDU), \pm fever ([NEJM 2010;362:1022](#), IDSA: [CID 2015;61:e26](#))
 - Pelvic: a/w bacteremia, sacral pressure ulcers, trauma (esp. athletes), urogyn/pelvic surgery, femoral access site; many present subacutely, may have localized pain or poorly localized, may not have fever
 - Sternoclavicular: ant. chest wall swelling, pain, tenderness; may be mistaken for abscess or atypical cellulitis; can occur via hematog. spread or post-CT surgery \pm mediastinitis (33% mortality: [J Thor. Card Surg 2006;132:537](#))
 - Mandibular: usually contiguous spread of oral flora/odontogenic infxn; often w/ anaerobes

DIAGNOSTIC APPROACH ([JAMA 2008;299:806](#))

- **Exam:** probing to bone sufficient for dx in patients w/ DM (83% Sp, 87% Sn) w/o need for further imaging ([CID 2016;63:944](#))
- **Blood Cx:** often \oplus with hematogenous infxn involving vertebra, clavicle, pelvis (**always obtain BCx x2 before starting antibiotics**)
- **Labs:** ESR/CRP (if high can use for monitoring response), \pm leukocytosis
- **Imaging:**
 - **>2w of sx:** obtain plain XR 1st. XR non-diagnostic and concerning story: obtain advanced imaging (MRI)
 - **<2w of sx, suspected vertebral OM, or DM:** start w/ advanced imaging (MRI), contrast preferred for vertebral OM
 - MRI: Sn 90%, Sp 82%, high NPV ([Arch Intern Med 2007;167:125](#)); best in DM or if c/f vertebral osteo ([CID 2015;61:e26](#))
 - CT: if MRI not available; can demonstrate periosteal reaction & cortical/medullary destruction
 - Radionuclide bone scan: very sens, but non-spec (false \oplus if soft tissue inflamm.); option if hardware prevents MRI
- **Bone biopsy: gold standard diagnostic test**
 - C/s surgery vs. MSK IR; Surg $>$ IR if concern for overlying cellulitis to mitigate risk of seeding. Open Bx preferred to percutaneous ([CID 2009;48:888](#)). If perc. Bx \ominus and suspicion high, repeat vs. obtain open biopsy
 - Bone Cx may be \oplus even on abx; need 2 specimens: GS/Cx (aerobic, anaerobic, mycobacterial, fungal) + histopath
 - If evidence of OM on imaging or \oplus probe to bone, bone biopsy \oplus up to 86% of cases ([CID 2006;42:57](#)). Biopsy not required if \oplus blood Cx and clinical/radiographic findings of OM

Risk Factors	Likelihood Ratio
Ulcer area >2cm	7.2 (1.1-49)
Probe-to-bone	6.4 (3.6-11)
ESR >70mm/h	11 (1.6-79)
Abnormal XR	2.3 (1.6-3.3)
MRI c/w OM	3.8 (2.5-5.8)
Normal MRI	0.14 (0.08-0.26)

TREATMENT

- **Antibiotics** (tx based on culture data, see table)
 - Delay empiric tx until biopsy if pt HD stable, no neurologic compromise or epidural abscess
 - Common organisms: **MSSA/MRSA**, CoNS, Strep, Enterococci, aerobic GNRs. Other: Brucella, mycobacteria, fungi
 - Can consider adding rifampin if Staph + hardware (for biofilm) ([Arch Intern Med 2008;168:805](#))
 - Duration: **≥6w**, PO may be adequate after sufficient response to IV but d/w ID ([NEJM 2019;380:425](#)). If PO, FQ+RIF most common
 - No residual infected bone (i.e. amputation): abx 2-5d \rightarrow up to 10-14 if associated SSTI
 - Consider rechecking ESR/CRP; if elevated at end of abx, consider further w/u (**NB:** NO routine repeat MRI, findings take weeks to months to resolve)
- **Surgical debridement:** indicated if failure to respond to medical therapies, chronic OM, complications of pyogenic vertebral OM (e.g., early signs of cord compression, spinal instability, epidural abscess), or infected prosthesis

Empiric Tx	
Vancomycin + GNR coverage (typically CTX 2g q24). Include PsA coverage (cefepime) for IVDU	
Organism-Specific Tx	
MSSA	Nafcillin 2g IV q4h; cefazolin 2g IV q8h (not if CNS infxn)
MRSA or CoNS	Vanc; dapto
PCN-S Strep	Pen G 4 mill U IV q4h; amp 2g q4; CTX 2g q24; vanc
Enterococci	Pen G 4 mill U IV q4h; amp 2g q4 +/- CTX 2g q24; vanc; dapto
GNR	CTX 2g q24; cipro 750mg PO BID; levoflox 750mg PO/IV q24; Cefepime 2g q12h (q8h if PsA)

Infectious Disease

Bloodstream Infections & Endocarditis

BLOODSTREAM INFECTIONS (BSI)

Evaluation ([JAMA 2012;308:502](#))

- Sources: lines, procedures, meningitis, endocarditis, osteomyelitis (OM), septic arthritis, PNA, UTI, SSTI, abscesses
- When should I/should I not send blood cultures? ([JHM 2017;12:510](#); [JHM 2016;11:336](#))

Predictive signs/symptoms	Predictive clinical scenario	Other Considerations
Fever+chills (+LR 1.1-6.1); rigors (+LR 4.7, Amer J Med 2005;118:1417); SIRS (-LR 0.09), normal food intake (-LR 0.18)	<u>High risk:</u> septic shock (38-69% \oplus BCx), meningitis (53%) <u>Medium risk:</u> pyelonephritis (19-25%) <u>Low risk:</u> cellulitis (2%), CAP (7%), other community-onset fever (13%)	Immunocompromised (neutropenia, HIV); hard-to-isolate source (OM, septic arthritis)

- How should I send blood cultures?
 - PRIOR to abx, 2 sets minimum, ideally 3 peripheral venipunctures over 1h; draw from central line only if c/f catheter-related infxn (criteria: catheter CFUs 3x peripheral blood OR cath. growth 2h before peripheral) (IDSA: [CID 2009;49:1](#))
 - Signs of contaminant: only 1 bottle growing, certain organisms (e.g. CoNS, GPRs), no systemic sx
- Further testing:
 - Staph aureus and Staph lugdunensis: very sticky. **Daily surveillance cultures** (not necessary for GNRs) ([CID 2017;65:1776](#)), **remove lines/hardware**, TTE/TEE to r/o endocarditis, consider back imaging for discitis/OM if having back pain
 - Consider TTE for high grade Strep spp. No routine TTE for GNRs
 - Yeast: **TTE, optho c/s** to r/o fungal endophthalmitis, **remove lines**

Antimicrobial selection:

Gram stain	Empiric abx	Other considerations
GPCs	Vanc+CTX	<u>S. aureus</u> : ID c/s \downarrow mortality. Adding β -lactam (cefazolin/nafcillin) <i>may</i> improve outcomes (CID 2013;57:1760) MSSA: β -lactam \ggg vanc (CID 2015;61:361)
GPRs	Call ID	More likely true infection in immunocomp hosts, multiple bottles, hardware, or known GPR infection
GNRs	Cefepime	Consider mero if prior MDRO/ESBL, add MNZ or switch to PTZ if \uparrow suspicion for abdominal source/cholangitis
Candida	Micafungin	ID c/s \downarrow mortality (Lancet ID 2019;19:1336); ALWAYS treat as true infection in blood

ENDOCARDITIS (AHA/IDSA: [Circ 2015;132:1435](#); ESC: [EHJ 2015;36:3075](#))

- Etiology: cutaneous (40%), oral (29%), GI (23%) – source often unknown
- Clinical manifestations: BSI s/sx; valvular complications \rightarrow acute HF, AV block; septic emboli (CVA/CNS, pulm/PE, MI, kidneys, spleen, joints), immune-complex deposition (arthritis, GN)
- Exam: new murmur, arthritis, embolic phenom. (petechiae, splinter hemorrhage)
- Diagnosis: **Duke criteria** \rightarrow 2 major OR 1 major + 3 minor OR 5 minor
 - TTE in all; TEE if: \ominus TTE w/ high susp; PVE; intracardiac device; suspected complications (AHA/ACC: [JACC 2014;63:e57](#))
 - Consult ID**
 - May be role for PET in PVE (less so in NVE) ([CID 2020;70:583](#))
- Monitoring:
 - Repeat BCx** q24h until sterile x48h
 - Serial ECGs** for: new AV block (prolonging PR most common); p mitrale; low QRS voltage, TWI, arrhythmias
- Microbiology: **Native Valve:** Strep, Staph, CoNS/Enterococcus, HACEK; **PV (<12mo):** CoNS, Staph, Enterococc./GNR/fungus; **PV (>12mo):** similar to NVE (w/ more CoNS)
- Indications for surgical consult: **emergent:** new-onset HF (acute valvulopathy), annular/aortic abscess (new AV block on EKG); **other:** L-sided S. aureus/fungus/MDRO, persistent infxn after 5-7d abx, PVE w/ recurrent infxn, large vegetation (>10mm on L, >20mm on R), embolic phenomena despite abx (AATS: [JTCVS 2017;153:1241](#)); **can c/s surgery for all PVE** (\pm streptococcal)
- AC/antiplatelet: generally ok to continue but no indication to initiate; if CVA/ICH, hold x2w
- IVDU-assoc IE: refer to MGH Drug Use Endocarditis Team (DUET, Epic phrase: .MGHDUET). Includes CT surgery, ID, ACT
- IV \rightarrow PO may be non-inferior to IV in **carefully selected** L-sided IE pts ([POET; NEJM 2019;380:415](#))

Modified Duke Criteria for Infective Endocarditis	
MAJOR CRITERIA	
\oplus BCx (likely org. in 2 Cx 12h apart or 3 Cx 1h apart) or <i>C. burnetii</i> IgG titer 1:800	
Endocardial involvement on imaging: vegetation, abscess, dehiscence, or new regurgitation	
MINOR CRITERIA	
RFs: valve dz, IVDU, prior infxn, indwelling line, prosthetic	
Temperature $>38C$ or $100.4F$	
Vascular phenomena: septic arterial/pulm emboli, mycotic aneurysm, ICH, conjunctival hemorrhages, Janeway lesions	
Immunologic phenomena: GN, Osler, Roth spots, \oplus RF	
\oplus BCx not meeting major criteria	

ORGANISMS AND ANTIMICROBIAL REGIMENS (ID will help guide)

Organism	Therapy	Notes
Streptococci (VGS [<i>mitis, mutans, anginosus, etc.</i>]; <i>bovis</i> [a/w colon cancer]; <i>Gemella</i> spp.; <i>Abiotrophia</i> [treat as \pm MIC])	-PCN OR CTX x4w (some infxns may have 2w options) -may add gent based on PCN MIC and severity of infection -PVE: generally requires gent	-Dosing: PCN varies; CTX 2g q24; amp 2g q4; gent 1mg/kg q8, peak 3-4, trough <1 -Vanc inferior to beta-lactams
Staphylococci (<i>aureus</i> ; <i>lugdunensis</i> [virulent, treat like SA]; CoNS [often methicillin-resistant])	-MSSA: oxacillin (better for CNS penetration), nafcillin (some risk for nephrotoxicity), cefazolin (good for kidneys) x6w -MRSA: vanc OR dapt x6w -PVE: may add rifampin	-Dosing: ox and naf 2g q4; cefazolin 2g q8; dapt 8-12mg/kg q24; gent as above -Vanc inferior to beta lactams for MSSA
Enterococci (<i>faecalis, faecium</i>)	-Amp AND CTX x6w, may add gent or streptomycin -Vanc if amp-resistant. VRE: dapt + amp OR linezolid	-Dosing: as above -4w amp+gent sufficient if NVE and <3 mo sx; 6w if >3 mo or PVE
Gram \ominus (HACEKs mostly, PsA, other GNRs possible)	-HACEK: CTX OR amp OR cipro x4w -GNRs: β -lactam + (AG or FQ) x6w	-Rare etiology, minimal data to firmly direct treatment modalities
Fungi (<i>Candida, Aspergillus</i>)	-Candida: ampho B 3-5 mg/kg/d (\pm flucytosine) OR Micafungin 150mg q24. C/s surgery	-RFs: TPN, lines, PPM/ICD, prosthesis, IVDU

Infectious Disease

Meningitis & Encephalitis

BACTERIAL MENINGITIS

Clinical Features

- History: 95% have ≥2 of: fever, nuchal rigidity, AMS, HA ([NEJM 2004;351:1849](#)). Lethargy, hypothermia may be common in elderly. Abd pain, peritonitis can be seen w/ VP shunts
- Exam: most findings more Sp than Sn. Nuchal rigidity 30% Sn, 68% Sp; Kernig's 5% Sn, 95% Sp; Brudzinski's 5% Sn, 95% Sp ([CID 2002;35:46](#)); jolt sign (worsening HA with horizontal rotation of the head) 64% Sn, 43% Sp ([Am JEM 2013;31:1601](#)). Meningococcemia associated with petechial rash, palpable purpura

Diagnosis ([CID 2004;39:1267](#))

- Blood cultures **STAT, BEFORE** antibiotics; **DO NOT** delay antibiotics for LP or imaging
- Lumbar puncture **ASAP**
 - Head CT prior to LP only indicated if: immunocompromised, known CNS disease (mass lesion, CVA, focal infection), new seizure, papilledema, ↓ level of consciousness, focal neurologic deficit
 - Obtain opening pressure with simple column manometer (nml 200mm H₂O; mean 350mm H₂O in bacterial meningitis)
 - For a list of what studies to send and CSF analysis/interpretation, see [Procedures: Fluid Analysis](#)
 - Repeat LP if no clinical improvement after 48h of appropriate antibiotics

Microbiology ([NEJM 2011;364:2016](#); [NEJM 2010; 362:146](#))

Community			Nosocomial (intracranial procedure, >48h in hospital, head trauma)
Adults 18-34	Adults 35-49	Adults >50	
S. pneumoniae (50%)	S. pneumoniae (75%)	S. pneumoniae (76%)	Gram neg bacilli (40%)
N. meningitidis (35%)	N. meningitidis (10%)	GBS (8%), Listeria (7%)	S. aureus (10%)
H. influenzae (7%)	GBS (7%)	H. influenzae (6%)	Coag neg Staph (10%)
GBS (6%)	H. influenzae (5%)	N. meningitidis (5%)	C. acnes (takes 10 days to grow!)
Listeria (2%)	Listeria (3%)	Aerobic gram neg bacilli	

Empiric Treatment ([Lancet 2012;380:1693](#))

Adults < 50	Adults > 50	Immunocompromised	Nosocomial	SEVERE β-lactam allergy
Vanc + CTX 2g q12h	Vanc + CTX 2g q12h + ampicillin 2g q4h	Vanc + [cefepime 2g q8h OR meropenem 2g q8h] + ampicillin 2g q4h (not needed if on mero) (consider fungal & viral)	Vanc + [cefepime 2g q8h OR ceftazidime 2g q8h OR meropenem 2g q8h]	Vanc + meropenem 2g q8h OR moxifloxacin 400mg QD [if >50 or immunocomp., for Listeria: Bactrim 5mg/kg IV QD div q6-12h] if not on mero

Note: vancomycin is added empirically to cover PCN-resistant S. pneumo, not MRSA

- Duration: N. meningitidis/H. flu (7d); S. pneumo (14d); Listeria (2-4w if immunocompetent; 4-8w if immunocompromised)
- Dexamethasone:** greatest benefit in suspected or confirmed pneumococcal meningitis w/ GCS 8-11 (↓ mortality, hearing loss, and short-term neuro sequelae in high-income countries) **0.15 mg/kg q6h x 4d**; start **prior to or with** 1st dose of abx, but **do not delay abx**
- CSF shunts:** consult Neurosurgery for assistance with mgmt and/or shunt removal (IDSA: [CID 2017;64:701](#))
- BBB penetration:** meningeal inflammation ↑ BBB permeability esp when severe. Abx with poor penetration into CSF in cases of mildly-inflamed meninges include β-lactams (overcome by ↑ dosage), aminoglycosides, tetracyclines, daptomycin

ASEPTIC MENINGITIS: meningeal inflammation with negative bacterial cultures

Clinical Features: similar to bacterial, usually less toxic. LP: lymphocytic pleocytosis

Etiology: Infectious: enteroviruses (most common), HSV, VZV, partially tx'd bacterial meningitis (usually days-wks), any stage of syphilis, Lyme, leptospira, mumps, Nocardia, TB, HIV (primary infxn), LCMV, fungal (see below), brain/parameningeal abscess; Non-infectious: autoimmune (Behcets, sarcoid, SLE, SJS), neoplastic (leukemia, lymphoma), drugs (NSAIDs, antimicrobials, IVIG)

Treatment: tx underlying cause (if possible) & supportive care. If suspect TB, c/s ID re: tx, addition of steroids; see [Tuberculosis](#)

FUNGAL MENINGITIS: see [Invasive Fungal Infections](#)

Causes: Primary (immunocompetent): Cryptococcus, Blastomyces, Histoplasma, Coccidioides, other dimorphic fungi; Secondary (immunocompromised): Cryptococcus, Candida, Aspergillus, other molds

Diagnosis: submit CSF for CRAG, fungal wet prep, fungal culture. Obtain large volumes (40-50 mL) for Cx

ENCEPHALITIS (IDSA: [CID 2008;47:303](#))

Presentation: AMS w/ focal neuro deficits or seizures. Abnormal brain function (vs. normal cerebral function in meningitis)

Etiology: Infectious: HSV, VZV, arbo (**West Nile**, WEE/EEE, St Louis, Japanese), enteroviruses, HIV, CMV (extremely rare), JC, echo, adeno, influenza, Powassan virus; Non-infectious: post-infectious demyelination (ADEM), autoimmune, paraneoplastic (anti-Hu [(SCLC)], anti-Ma2 [testicular], anti-CRMP5 [SCLC/thymoma], anti-NMDA receptor [ovarian teratoma, idiopathic])

Diagnosis: send CSF for HSV, VZV PCR; other viruses less common, only send if clinical suspicion high (West Nile IgM, JC, CMV/EBV [extremely rare]); consider MRI (HSV → temporal lobe enhancement, W. Nile → basal ganglia/thalamic foci); EEG

Treatment: HSV, VZV → acyclovir 10 mg/kg IV q8h; otherwise supportive care

- If sx recur s/p tx, consider viral relapse vs. autoimmune enceph. – high rates of autoimm. dz wks later ([Lancet Neurol 2018;17:760](#))

Infectious Disease

C. Difficile Infection

OVERVIEW (IDSA: [CID 2018;66:987](#); ACG: [AJG 2013;108:478](#))

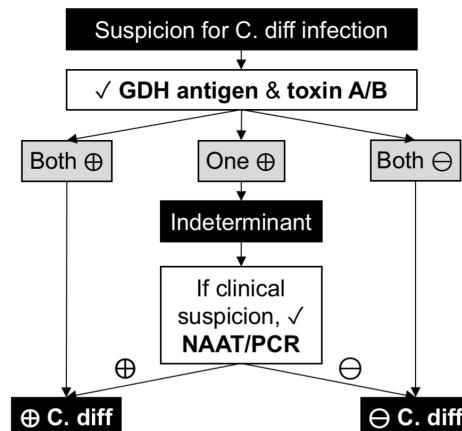
- **Definition:** C. difficile infection (CDI): acute-onset sx (usually ≥ 3 episodes/d of watery diarrhea) + e/o toxin-producing C. difficile or histopathology c/w pseudomembranous colitis
- **RFs:** abx w/in 3mo (all abx, particularly associated with 2nd/3rd/4th gen ceph, FQ, carbapenems, clinda), age (≥ 65 yo), recent hosp or ↑ LOS, IBD, chemo/immunocompromise, GI surgery, tube feeding, PPI/H2RA
- **Pathogenesis:** fecal-oral, colonized host; most often infection requires both acquisition of C. diff plus loss of gut microbial abundance/diversity (e.g. due to abx). Symptoms are toxin-mediated: toxin A (enterotoxic) & toxin B (cytotoxic)
- **Community-acquired CDI:** ~1/3 new cases; p/w diarrhea w/o traditional RFs. **Potential sources:** contam. food/H₂O, pets, asx colonization in family, babies, outpatient visits ([AJG 2012;107:89](#); [JAMA IM 2013;173:1359](#))

CLINICAL MANIFESTATIONS

- **Features:** **watery diarrhea** (≥ 3 loose stools in 24h) +/- mucus/blood; fever, abd pain, ↑WBC, ileus
- **Ddx:** non-C. diff abx-associated diarrhea, infectious diarrhea, post-infectious IBS, IBD, microscopic colitis, Celiac disease
- **Severity:** see table below; severe colitis may be c/b hypovolemia, AKI, marked leukocytosis, lactic acidosis, protein-losing enteropathy; fulminant colitis characterized by hypotension/shock, ileus, toxic megacolon w/ ↑↑ mortality

DIAGNOSIS

- **MGH protocol:** see algorithm to right. **NB:** indeterminant results can be 2/2 asymptomatic (non-toxin-producing) colonization
 - **GDH:** enzyme produced by all C. diff strains; assay sensitive but cannot distinguish toxigenic & non-toxigenic strains
 - **Toxin A/B:** assay detects toxin production; high Sp but poor Sn
 - **NAAT/PCR toxin gene:** high Sn but can be \oplus even in the absence of active infection (strain may have toxin gene but not produce it)
- **DO NOT** retest within 7d w/o significant clinical change
- **DO NOT** test for “cure” (may remain \oplus for up to 6w despite resolved sx)
- **CT A/P:** if severe illness or fulminant colitis to assess for complications warranting surgical intervention (e.g. toxic megacolon, bowel perf)
- **Flex sig:** in rare cases when alt dx suspected and need visualization/bx



TREATMENT (IDSA: [CID 2018;66:987](#))

Category	Criteria	Treatment
Non-severe	WBC <15 <u>AND</u> Cr <1.5	-Vanc 125mg PO q6h or fidaxomicin* 200mg BID -Alternative: metronidazole 500mg q8h (↑resistance → <i>not first line</i>) -D/c antimotility agents, non-essential abx, cholestyramine (binds vanc)
Severe	WBC >15 <u>OR</u> Cr >1.5	-Vanc 125mg PO q6h or fidaxomicin* 200mg BID
Fulminant	Hypotension/shock, ileus, megacolon	-Vanc 500mg PO q6h <u>AND</u> metronidazole 500mg IV q8h -If ileus: can add vanc PR 500mg in 100cc NS as retention enema Q6H - Surgery c/s; consider FMT if ileus, not responsive to tx, or recurrent dz

Duration: 10d for non-fatal; if receiving concurrent abx, duration may be **extended** until course is completed (± after)

***Fidaxomicin:** bactericidal, ↓ recurrence vs. vanc, may ↑ rate of cure but \$\$\$ ([CID 2011;53:440](#); [Cochrane Rev 2017](#))

RECURRENCE

- follows initial resolution of sx in up to 25% (usually w/in 30d), often due to relapse as opposed to reinfection vs. **refractory disease** (no resolution on therapy → consider alt diagnosis and ID or GI c/s)
- **1st recurrence:** pulse-tapered PO vanc x6-8w OR fidaxomicin 200mg BID x10d (unless was used for initial episode)
- **2nd recurrence:** pulse-tapered PO vanc x6-8w OR 125mg PO vanc q6 x10d followed by rifaximin 400mg TID x20d OR fidaxomicin 200mg BID x10d (unless used for prior episode). IDSA recommends evaluation for **fecal microbiota transplant (FMT)** after 2nd recurrence; more effective than vanc or fidaxomicin alone ([NEJM 2013;368:407](#); [CID 2019;68:1351](#); [Gastro 2019;156:1324](#)). At MGH, consult ID for FMT evaluation

OTHER CONSIDERATIONS

- **Prophylaxis:** secondary ppx w/ PO vanc (standard or reduced dose 125-250mg BID) may ↓ recurrence in pts w/ prior CDI receiving systemic abx ([AJG 2016;111:1834](#); [CID 2016;63:651](#); [ICHE 2019;40:662](#)). May also be effective as primary ppx in high-risk patients (≥ 60 yo, current or recent <30 d systemic abx) w/ 125mg daily dosing ([CID 2020;71:1133](#))
- **Probiotics:** insufficient evidence, not in guidelines; some evidence supports use w/ abx to reduce abx-associated diarrhea ([JAMA 2012;307:1959](#)) and prevent CDI ([Gastro 2017;152:1889](#)) but use w/ caution in immunocompromised pts ([CID 2015;60:S129](#))

Infectious Disease

Invasive Fungal Infections

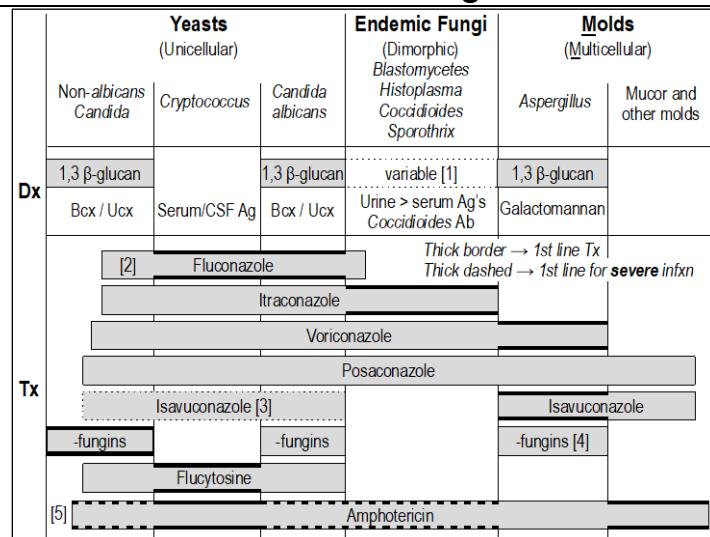
RFs

Heme malignancy, HSCT > SOT > biologic Tx

DIAGNOSTIC TESTING

Fungal markers:

- 1,3-β-D Glucan (BDG)** ([CID 2011;52:750](#)): cell wall polysaccharide, detects *Candida*, *Aspergillus*, *Pneumocystis* (PJP), *Fusarium*, *Trichosporon*, *Histo*, *Coccidioides* with Sn 77%, Sp 86% (cutoff 80). **CANNOT** dx Mucor, Rhizopus, Blasto, Crypto
 - False \oplus w/ IVIG, albumin, HD, meds (e.g. cefepime)
- Galactomannan (GM)** ([Cochrane Rev 2015](#)): detects *Aspergillus* cell wall component; Sn (serum 65-80%, BAL 90-95%), Sp 88%
 - False \oplus w/ some TPN formulations
- Histo Ag**: UAg Sn 90% if disseminated (vs. sAg 80%); Sp limited by cross-reactivity
- Crypto Ag (CrAg)**: serum Sn&Sp >90% if disseminated, less w/ pulm dz only, high Sn for pulm if HIV
- Blastomycoses**: uAg > sAg; high Sn, modest Sp d/t cross-reactivity



Notes: [1] See left/below [2] 87% of MGH *C. glabrata* is fluc-S [3] Only approved for invasive Aspergillosis/Mucor [4] In aspergillosis, vori + mica not superior to vori alone [5] Covers all invasive fungi w/ rare exceptions, e.g., *C. lusitania*. Always order amphoB w/ pre & post hydration AND BMP, Mg BID. Adapted from JA Freed and AJ Hale, [IDModules.com](#)

ID consultation is advised for these diagnoses

Invasive Opportunistic Fungi

YEAST	Candida CID 2016;62:e1	RFs: neutropenia, immunocompromised (heme malign, transplant), TPN, IVDU, CVC, prior abdominal surgery, ICU Spectrum of illness: sepsis (25% mortality), macronodular skin lesions (10%), endophthalmitis, endocarditis, osteomyelitis, UTI Dx: BCx (never a contaminant in BCx, c/s ophtho & ID, TTE, repeat Cx daily); ↓Sn if deep tissue/hepatosplenic infxn; \oplus RCx usually colonization not infxn Tx: BSI → micafungin → azole (or amphoB for resistant strains); remove CVCs. Endophthalmitis : may need intravitreal amphoB/vori. UTI: see UTI . Duration: BSI: 2w after 1 st ⊖ Cx w/ no dissemination, deep-seated infxn: longer, see BSI & Endocarditis Source: non-neutropenic: lines most likely source; neutropenic: GI most likely source, consider G-CSF Ppx: fluconazole, posaconazole or micafungin (for SOT, SCT, neutropenic)
	Cryptococcus CID 2010;50:291	RFs: immunocompromised, liver disease, HIV, can occur in immunocompetent Spectrum of illness: meningoencephalitis, pulmonary (acute resp failure), cutaneous nodules, liver abscesses Dx: serum/CSF CrAg, LP/CSF: OP >20, ↓gluc, ↑TP, lymphs, +India ink & CrAg Tx: amphoB + flucytosine (x2w) → fluc (≥8w), serial LPs if OP≥25 or symptoms of 1ICP, fluc for mild pulm dz
	Pneumocystis HIV.gov	RFs: HIV (CD4 <200), steroids equiv. to pred 20mg/day x4w, transplant, heme malignancy Spectrum of illness: pulm sx onset over days/weeks, PTX, hypoxemia out of proportion to CXR (diffuse GGO on CT) Dx: LDH >500 (Sn not Sp), BAL > induced sputum for silver stain/DFA/PCR, 1,3-BDG (Eur J Clin Micr ID 2014;33:1173) Tx: T/S (IV 5mg/kg q6H, adjust PRN renal fxn). Consider pred 40mg BID if severe hypoxemia; Alternatives: TMP+dapsone, clinda+primaquine, atovaquone or pentamidine; Duration: 21d Ppx: T/S (1 DS qD > SS qD, 1 DS MWF), atovaquone, dapsone, pentamidine; Indications: pred 20mg ≥4w, SCT, leuk, etc.
MOLD	Aspergillus CID 2016;63:e1	RFs: immunocompromised esp. neutropenia/steroids/transplant, COPD with prolonged ICU stay, anti-TNF-α, cannabis use Spectrum of illness: invasive pulm (IPA), PTX, aspergilloma, sinusitis, CNS, endophthalmitis, disseminated infxn, necrotic skin lesion Dx: CT with halo sign, BAL/sputum culture + silver stain ± biopsy, 1,3-BDG (not Sp), GM (Sp; can trend in tx, BAL > sputum) Tx: vori (monitor trough, drug-drug int) ± mica, isavuconazole, or amphoB; consider debridement if necrotic lesion Duration: 6-12w minimum for pulm dz Ppx: consider posa (prolonged neutropenia, GVHD [NEJM 2007;356:348]), vori/itra/inhaled amphoB (lung transplant ± h/o IPA)
	Mucor	RFs: DKA, iron overload, heme malig, prolonged neutropenia, immunocompromise (Semin Respir Crit Care Med 2015;36:692) Spectrum of illness: rhino/orbital/cerebral invasion, pulmonary, GI, renal; black eschars over ulcers, rapidly progressive Dx: biopsy, culture, wet prep/silver stain (broad non-septate hyphae), CT with reverse halo sign Tx: DEBRIDEMENT, amphoB, consider posaconazole or isavuconazole (for salvage therapy or if renal disease)

Endemic Fungi

Histoplasmosis CID 2007;45:807	Endemic areas: central/eastern US esp OH/MS River valleys, Central America, Asia, Africa Spectrum of illness: PNA, meningitis, mediastinal disease, disseminated disease; pericarditis, arthritis Dx: urine/serum/BAL Ag, histology, Cx; NB: chest imaging may appear similar to sarcoid Tx: itra or no tx (mild-mod), amphoB → itra (severe); NSAID for extrapulm; Duration: 6-12w Ppx: for both Histo and Blasto (below), consider itraconazole for HIV (CD4 <150) in hyperendemic areas
Blastomycosis CID 2008;46:1801	Endemic areas: midwest, south-central, SE US esp OH/MS River valleys and Great Lakes, Canada Spectrum of illness: fever, PNA (acute or chronic), ARDS, ulcerated skin lesions, osteomyelitis, prostatitis, CNS Dx: wet prep (broad-based, budding yeast), Cx, uAg > sAg, never a colonizer Tx: itra (mild-mod), amphoB → itra (severe); Duration: 6-12mo
Coccidioidomycosis CID 2016;63:e112	Endemic areas: desert regions: SW and S US, Mexico, Central and South America Spectrum of illness: PNA (+/- nodules), fever, rash (erythema nodosum), HA, eosinophilia, meningitis, osteomyelitis Dx: serologies, Cx (if high concern, alert lab for biohazard), spherules on bx/aspirate, Ag for extrapulm (urine, blood, CSF) Tx: no tx (mild-mod, immunocompetent); fluc or itra, consider amphoB (severe); Duration: 3-12mo Ppx: fluc for 1° ppx ONLY for transplant (not HIV) in endemic areas; fluc for 2° ppx

Infectious Disease

Tuberculosis

Epidemiology and RFs

- World: 1/4 infected; US: incidence 2.8/100,000, w/ 5.6% HIV coinfection and 1% MDR ([CDC MMWR TB US 2017](#))
- Acquisition: travel hx to/from high-prevalence area, homelessness, incarceration, IVDU, healthcare work, racial/ethnic minority
- Reactivation: risk 5% first 2y, 5-10% lifetime, higher if ≥ 1 RF: HIV, immunosupp, CKD (esp. RRT), DM, CA, txp, TNF α inhib., silicosis, malabsorption/malnutrition, tobacco, EtOH ([NEJM 2011;364:1441](#))

Screening for Latent TB

Test based on likelihood of exposure & progression to active disease. **IGRA preferred** (TSPOT test of choice at MGH); **TST acceptable** (NB: only 60% Sp in pts who received BCG vaccine). Both IGRA and TST are 80-90% Sn and >95% Sp in immunocompetent, ↓ Sn in immunocomprom. Neither rules in/out active TB, can be **discordant ~30%** of the time. If \oplus test w/ no RFs, repeat either IGRA or TST prior to tx. If \oplus test in ↑risk pt, proceed to tx (**[TST/IGRA Interpreter](#)**, ATS/CDC/IDSA: [CID 2017;64:111](#))

TST at 48-72h	Patient Population
≥5mm	HIV, prior TB hx, CXR c/w prior TB, silicosis, immunosuppression
≥10mm	Diabetes, CKD, IVDU
≥15mm	No risk factors
NB: size reflects skin induration, NOT erythema	

Clinical Manifestations

- Primary TB: fever, chest pain, cough, arthralgia. CXR often normal or \oplus hilar LAD
- Reactivation TB: fever, cough, hemoptysis, night sweats, wt loss; CXR often w/ posterior/apical involvement or cavitation (seen in 1/3 of pts, a/w ↑org. burden → ↑infectious, AFB \oplus) ([J Clin Microbiol 2007;45:4064](#)); more common than primary TB

DIAGNOSTICS: ACTIVE PULMONARY/EXTRAPULMONARY TB (ATS/CDC/IDSA: [CID 2017;64:111](#); [Lancet 2007;369:9578](#))

Site of Infection		Diagnostic Tests
Lung	Sputum	Expectorated or induced, AFB smear/Cx x3 ≥8h apart, add NAAT/PCR to one of the specimens; smear may be \ominus if low burden (~20% if HIV-, ~60% if HIV+)
	Bronch	AFB smear, NAAT/PCR (Xpert), and Cx; +/- transbronch bx, post-bronch induced sputum ↑yield
Ascites or pleural fluid		Adenosine deaminase (ADA) >39 units/L → high Sn/Sp; free IFN-γ elevated → high Sn/Sp; AFB smear, NAAT/PCR (Xpert), & Cx (poor Sn but helpful if positive)
Pericardial fluid		AFB, Cx, cell counts (typically exudative, ↑prot, lymphocytes), ADA. No evidence for free IFN-γ
CSF		At least 3 large volume (10-15cc) serial LPs if possible (↑yield). ↓glucose, ↑protein, lymphocyte predominance; ↑ADA useful adjunct. AFB smear, Cx, and NAAT/PCR (Xpert)
Wound/Tissue		AFB-positive staining and caseating granulomas; cytopenias → consider bone marrow bx
Urine		UA w/ "sterile" pyuria; send first AM void (large vol ~50cc) Cx x3d. Urine LAM not available at MGH
Blood		Can send mycobacterial cultures (isolators) for AFB

Patient Isolation

- clinical decision based on likelihood of active TB
- When: cough, dyspnea, or hemoptysis + ≥ 1 RF (HIV+, foreign born, substance use disorder, homelessness, recent incarceration, prior TB/exposure). First obtain CXR; if CXR normal (and HIV- or CD4>200), TB less likely. If CXR abnormal-equivocal (or HIV+ and CD4<200), maintain isolation and obtain sputum x3 as above. Consider ID c/s
 - Discontinue: if alt dx OR AFB smear \ominus x3 w/ very low suspicion OR on TB tx x2w + AFB smear \ominus x3 + clinical improv

Approach to Treatment (ATS/CDC/IDSA: [CID 2016;63:e147](#); [NEJM 2015;373:2149](#))

- Prior to starting treatment:**
 - Check baseline LFTs/Cr, visual acuity/color discrimination, screen for HIV, Hep A/B/C, DM, EtOH use, pregnancy
 - Before treating latent TB: rule out active TB (obtain relevant history and CXR. Sputum AFB if ↑clinical suspicion)
 - Before treating active TB: c/s ID, send TB for drug sensitivity testing
- Treatment regimens:**
 - Active TB: isoniazid (INH) + rifampin (RIF) + pyrazinamide (PZA) + ethambutol (EMB) x2mo, followed by INH+RIF x4mo
 - Obtain monthly sputum AFB smear/cx until \ominus x2 consecutive months to assess tx response
 - Latent TB: INH+rifapentine (RPT) qw x12 (3HP) OR RIF x4mo (4R) OR INH+RIF x3mo (3HR) OR INH+B6 x6-9mo (6H, 9H, less preferred) ([CDC Tx Table](#); [R and R 2020;69:1](#))
 - Quinolones: 1st line w/ MDR-TB, **avoid in bacterial PNA** if suspicious for active TB (↓dx yield & ↑risk of resistance)
- Drug-resistant TB: suspect if previously treated, treatment failure, from prevalent area (India, China, Russia, S. Africa), or known exposure. Treatment regimen depends on drug susceptibility profile; usually 12-24mo course. 80% mortality
 - Combination of bedaquiline/pretomanid/linezolid for 6mo approved for tx of highly MDR-TB ([NEJM 2020;382:893](#))
- HIV co-infection: discuss timing of ART initiation w/ ID
- Extrapulmonary TB: highly variable presentation/therapy, duration depends on site of infection & response. For CNS TB: 12mo tx, glucocorticoids confer 25% short term reduction in mortality ([Cochrane Rev 2016](#))
- Medication side effects: hepatotoxicity (INH, RIF, PZA), optic neuritis (EMB), peripheral neuropathy (INH → add pyridoxine [B6] with initiation of treatment), orange bodily fluids (RIF), numerous drug-drug interactions (especially RIF)

Infectious Disease

HIV/AIDS & Opportunistic Infections

DEFINITION AND CLINICAL MANIFESTATIONS:

- Acute HIV: mono-like syndrome w/ rash, LAD, fever, oral ulcers, pharyngitis, myalgias, diarrhea; **presents 3-6w after infection**
- AIDS: HIV w/ CD4 count <200 or CD4 T-cell <14% of total lymphs or AIDS-defining illness

HIV SCREENING AND DIAGNOSTICS:

- Screen all 13-64yrs once, every pregnancy, dx of another STI, pts w/ IVDU annually, commercial sex (CS), MSM >1 partner since last test, partners of all 1risk pts. MA: verbal informed consent req. HCP **cannot** consent for incapacitated pt (e.g. ICU)
- Preferred test: 4th gen HIV 1/2 Ab/p24 Ag assay: mean detection limit **18d** ([STD 2017:44:739](#))
- HIV RNA PCR (viral load, VL): mean **12d**, high Sn/Sp but slow, expensive; used for: 1) concern for acute HIV (Ab/Ag testing are negative early in disease course); 2) confirmation of HIV diagnosis; 3) treatment efficacy in known HIV

PROPHYLAXIS:

- PrEP (Pre-Exp): offer to any pt w/ ↑ risk of acquiring HIV: **serodiscordant couple**, **STI** last 6mo, **MSM** w/ inconsistent condom use, IVDU, ↑ risk sex, **CS, transgender** pts (USPSTF: [JAMA 2019:321:2203](#)). If partner w/ HIV has undetectable VL, risk of HIV transmission is near zero (undetectable = untransmissible) ([JAMA 2016:316:171](#))
 - Prior to initiation: negative HIV test, screen for HBV/HCV, other STIs, Cr, pregnancy test
 - Daily regimen: **TDF/FTC (Truvada)** qd ↓ risk (40-75%, >95% w/ excellent adherence), **d/c** when risk is no longer present. **TAF/FTC (Descovy)** also FDA-approved (except for pts w/ receptive vaginal intercourse) → ↑ cost ↓ renal/bone issues
 - Event-driven PrEP: Truvada “2-1-1”: double dose 2-24h before sex, then 1 dose daily x 2d (not FDA-approved, limited evidence in non-MSM). If discrete exposure (e.g. vacation), start Truvada qd 1w prior and for 1mo after (MSM only)
 - Monitoring: HIV q3mo, Cr q3-6mo (stop Truvada if eGFR <60, consider Descovy eGFR 30-60), STIs q3mo, pregnancy q3mo
- nPEP (Non-Occupational Post-Exp): persons presenting at ≤72h after non-occupational ↑ risk exposure to HIV; case-by-case decision if HIV status of source unknown; baseline HIV Ab/Ag, HBV, HCV, STI testing
 - Regimen: **Truvada + raltegravir or dolutegravir x28d**; if ≥1 course nPEP in last year, consider PrEP

BASIC EVALUATION FOR NEWLY DIAGNOSED HIV: **ID consultation is advised**

- CD4 count w/ %, quantitative HIV RNA (VL), genotype/resistance, CBC/diff, BMP, UA, lipids, 3-site GC/CT, syphilis Ab, TST/IGRA if no prior TB hx, HA/B/CV, MMR w/ vax PRN, VZV if nonimmune, hCG, cervical and/or anal Pap, ± HLA B*5701 (IDSA: [CID 2020](#))
- Initiate ART early through referral (p36222) at all CD4 levels to ↓ mortality ([NEJM 2015:373:795](#)). ART can often be initiated on site prior to genotype return, even in 1risk pts ([AIDS 2018:32:17](#))
- Recheck VL after 2-4w, then q4-8w until suppression achieved → monitor VL q3-4mo

TREATMENT: choose based on individual pt factors, drug-drug interactions, resistance, HLA B*5701 (abacavir hypersens.)

- ART naïve: 1st line: 2 NRTI “backbone” (typically TAF/FTC or TDF/FTC) + 1 from diff class, often integrase inhibitor (e.g. dolutegravir)
- Pregnancy: if new dx, 1st line TDF/FTC or abacavir-lamivudine (ABC/3TC) + dolutegravir; if prev well treated, cont existing regimen

HOSPITAL MANAGEMENT OF PEOPLE WITH HIV:

- Patient on ART: determine regimen & adherence; typically **continue ARVs** (interruptions can ↑ disease progression)
 - If ARVs must be held, hold **all** ARVs and **c/s ID**. Beware drug-drug interactions esp boosted PIs (check [DDI database](#))
- Patient not yet on ART: prioritize OI tx, ppx, **c/s ID** re: early inpt vs outpt initiation of ART
- IRIS: worsening sx of underlying infxn (TB, MAC, CMV, others) 1-3mo post-ART initiation, ↑ risk if ↓ CD4 count
 - Early ART initiation safe after OI dx ([PLoS ONE 2009:4:e5575](#)) (except in CNS TB or crypto)

Opportunistic Infections Prophylaxis Summary Recommendations for HIV in the US (HIV.gov 2020: [Full](#), [Tables](#))

CD4	Opportunistic Infection	Prophylaxis	Criteria for D/C
All	Influenza, HAV, HBV, HPV, VZV, S. pneumonia (most common OI), TB	Vax: Flu; HAV, HBV, HPV, PCV13, PPSV23 after 8w; no live vax w/ CD4<200; LTBI: see Tuberculosis	None
<200	Pneumocystis jirovecii (or hx of thrush)	TMP-SMX DS qd (preferred) or 1 SS qd or dapsone 100mg qd or atovaquone 1500mg qd	CD4 >200 x 3mo
<150	Histo (endemic or exposure; not in MA)	Itraconazole 200mg PO qd	CD4 >150 x 6mo
<100	Toxoplasma	TMP-SMX DS qd or dapsone 50mg qd + pyrimethamine 50mg qw + leucovorin 25 qw	CD4 >200 x 3mo
<50	Mycobacterium avium complex (MAC)	Ppx not recommended if ART initiated immediately	CD4 >100 x3mo

Treatment of Specific OIs in Adults with HIV

Pathogen	Diagnosis	1st Line Treatment
See Invasive Fungal Infections for diagnostics and therapeutics for PJP and Cryptococcus, Tuberculosis for TB		
Herpes Simplex Virus (HSV)	Oral/genital: DFA, PCR, viral Cx CNS: LP + CSF PCR	Orolabial: acycl 400mg PO q8h or valacycl 1g PO q12h x5-10d; Genital: tx x5-14d; CNS: acycl 10mg/kg IV q8h x3w
Cytomegalovirus (CMV)	Retinitis: ophtho exam; Colitis/esophagitis: bx; PNA: bronch w/ cytopath; Neuro: CSF PCR, brain Bx, Blood: PCR	Gancic IV → valgan PO w/ improvement. Consider foscarnet for resistant dz
Toxoplasma gondii	CT/MRI: ring-enhancing; most pts IgG+ but not IgM+, brain Bx if tx fails (to r/o CNS lymphoma)	Pyrimeth 200mg x1; then by wt + sulfadiazine + leucovorin qd x6w
PML	MRI: non-enhancing lesions; LP: JCV PCR	Only disease-modifying tx is ART
Mucocutaneous candidiasis (esophageal/oral)	Clinical dx. White plaque removed w/ tongue depressor, +KOH; EGD + Bx	Oral: fluc 100mg PO x7-14d; Eso: fluc 100-400mg PO/IV or itra oral soln 200mg PO qd x14-21d
MAC	Cx (blood/sputum/bronch/marrow/tissue), AFB stain	(Clarithro 500mg BID > azithro 600mg qd) + ethambutol 15mg/kg qd

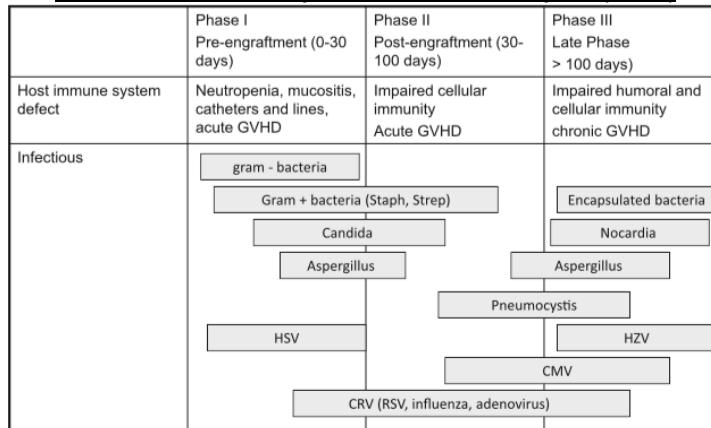
Infectious Disease

Transplant ID

GENERAL PRINCIPLES (AJT 2017;17:856)

- Early infections:** donor-derived, nosocomial/reactivation early, followed by OIs as immune suppression peaks
- Late infections:** community-acquired infections, fungal infections
- Pre-transplant evaluation:** ✓ mumps/measles/rubella/VZV/CMV/EBV/HAV IgG, HBV (sAb, sAg, cAb), HCV, HIV, syphilis, Toxoplasma, TST/IGRA. Consider: endemic fungi, T. cruzi, Strongy. Goal: immunize or treat prior to txp
 - Serologic tests are helpful to identify latent infection pre-transplantation, but less useful after transplant for acute disease

Infections After Hematopoietic Stem Cell Transplant (HSCT)



Infections After Solid Organ Transplant (SOT)

	<4wk.	1-12mo.	>12mo.
Virus		Adeno, BK	
		EBV, HCV, HBV	
		HSV	
		HHV 6,7	HPV, JC/PML, PTLD
		VZV	
Fungus		CMV, community-acquired	
		Aspergillus	Aspergillus
		Candida	Endemic fungi
Bact.		Mucor	Crypto
			PCP
	Surg.-related		Mucor
Para.			Listeria, Nocardia
			TB, non-TB mycobacteria
		Toxo, leishmaniasis	
		Strongy, T. cruzi	

HSCT PROPHYLAXIS (JNCCN 2016;14:882)

- Candida:** fluconazole 400mg daily (d0-365 at MGH)
- HSV/VZV:** famciclovir 250mg BID, acyclovir 400-800mg BID or valacyclovir 500mg BID (d0-365)
- PJP:** T/S (1 DS > SS qD, 1 DS MWF); also covers *Toxo*, *Nocardia*, *Listeria*; alternatives: atovaquone, dapsone (d0-180 or 365)
- High-risk HBV reactivation:** entecavir, tenofovir, or lamivudine (duration varies)
- CMV: pre-emptive monitoring** of VL in high-risk pts & initiate tx (valganciclovir or ganciclovir) when ↑ vs. ppx in high-risk pts. Letermovir (CMV-specific; no activity against HSV) can be considered for ppx in select cases (NEJM 2017;377:2433)

Select Transplant-Associated Infections (<i>ID c/s is advised</i>)			
Pathogen	Clinical Syndrome	Diagnosis/Treatment	Additional comments
CMV	Fever, leukopenia, +/- hepatitis, colitis/esophagitis, pneumonitis, retinitis	Dx: serum PCR (may be ⊖ in colitis, 15%) ± bx involved organ (GI, BAL w/ cytopath) Tx: PO valganciclovir vs. IV ganciclovir. Consider resistance testing if not improving (UL97, UL57). <u>Alt Tx:</u> foscarnet or cidofovir	Most common infxn s/p SOT. <i>Highest risk:</i> D+/R- in SOT and D-/R+ in HSCT. May ↑ rejection and susceptibility to OIs. Repeat VL at least 7d apart ($t_{1/2}$ of CMV), not comparable between labs Adapted from AJT 2017;17:856
PJP	Subacute dyspnea, hypoxemia, fever	See <i>Invasive Fungal Infections</i>	In contrast to HIV, there is limited data to support the use of steroids
BK Virus	Nephritis w/ AKI, ureteral stenosis, hemorrhagic cystitis	Dx: BK PCR +/- bx Tx: ↓ immunosuppression	Mainly in renal txp (nephritis) and HSCT (hemorrhagic cystitis) pts
Strongyloides	<i>Hyperinfection syndrome:</i> fever, n/v/d, cough/wheeze, hemoptysis, ⊖ eos; 2° polymicrob. bacteremia (GNRs)	Ivermectin 200mcg/kg/d until stool ⊖ x2w	Identify at-risk individuals and tx pre-txp

Symptom-Driven Diagnostics

SOB	CXR, CT chest I+, induced sputum (GS/Cx, consider AFB stain, MB Cx, PJP exam), Legionella urine Ag (Sn 70-90%, Sp 100%), viral resp panel. If cavitating or nodular lesions: 1,3-β-D-glucan/galactomannan, sCrAg, urine/serum histo Ag, early bronch w/ BAL. <u>NB:</u> engraftment syndrome, cryptogenic organizing PNA also on DDX
Diarrhea	Stool Cx, O+P (consider micro add-on for: <i>Cryptosporidium</i> , <i>Isopora</i> , <i>Cyclospora</i> , <i>Microsporidia</i>), C. diff, CMV PCR. If high suspicion for viral colitis (e.g., CMV, adeno), c/s GI re: colo w/ Bx. In HSCT, consider typhilitis (NEC) and GVHD
AMS/HA	CT head, LP (OP, GS/Cx, glucose, TP, HSV PCR, CrAg, save extra for additional tests). <u>NB:</u> fludarabine, cytarabine and calcineurin inhibitors (via PRES) can also lead to encephalopathy
Rash	Mark outline and photos, may require skin biopsy. GVHD, medication allergy, HSV, cellulitis, fungal infection
Leukopenia	CMV PCR, EBV PCR, consider tickborne illnesses during the correct season or if frequent blood transfusions
Hepatitis	If post-HSCT, consider viral (HAV, HBV, HCV, EBV, CMV, HSV, adenovirus & more rarely enterovirus and HHV6), <i>Candida</i> , and non-infectious (GVHD, iron toxicity, DILI, hepatic sinusoidal obstruction syndrome)
AKI	UA/UCx, renal U/S, BK PCR if renal transplant. Consider med toxicity and check levels (esp tacrolimus, cyclosporine)

Infectious Disease

STIs & Travel Medicine

SEXUALLY TRANSMITTED INFECTIONS

Routine STI testing in asymptomatic adults: HIV, syphilis, GC, chlamydia

	Lesions	Symptoms	Diagnosis	Treatment
Painless	Syphilis (<i>T pallidum</i>) (CDC Pocket Guide ; PCOI)	1°: painless, firm, round ulcer 2°: fever, condyloma lata of skin/mucus membranes, LAD, uveitis 3°: aortitis/aneurysm, disseminated gummas, CN palsies, tabes dorsalis (impaired gait, sensation, reflexes) Latent = asx (early <1y; late >1y or unknown). Highly infectious in 1°, 2°	1st: "TrepSure" (Sn 96%, Sp 98%); <i>T pallidum IgG ELISA</i> ; + for life If +: confirm w/ VDRL/RPR titers (Sn 86%, Sp ~90%); false + with anti-cardiolipin. CSF titers if concern for neurosyph (IJSTD AIDS 2006;17:768) If TrepSure +, RPR -: 2nd treponemal test (e.g. FTA-Abs)	1°/2°/early latent: benzathine PCN G 2.4milliU IM x1 3°/late latent: benzathine PCN G 2.4milliU IM qw x3 Neuro: IV PCN G 3-4milliU q4h or infusion x10-14d (CID 2011;53:S110) PCN allergy: consider desens
	LGV (<i>C trachomatis</i> serovars L1-3)	1°: transient, painless anogenital lesion 2°: 2-6w later, painful inguinal LAD 3°: pelvic/abd LAD, inflamm diarrhea, abscess ("genitoanorectal syndrome")	Chlamydia NAAT detects LGV serovars LGV-specific PCR available as sendout test	Doxy 100mg BID x21d + aspiration of buboes
	GI (<i>K granulomatis</i>)	Painless progressive beefy red ulcerative genital lesions	Presence of Donovan bodies in phagocytes on bx specimen	Azithro 1g qw/500mg qd x3w until healed (MMWR 2015;64:1)
Painful	Genital herpes (HSV2>1)	Prodrome → painful vesicles → ulcers 1° infection: systemic sx ± LAD	Confirm clinical dx with PCR	Acyclovir/valacyclovir. Consider episodic vs. chronic suppressive tx based on frequency & severity & risk of partner spread
	Chancroid (<i>H ducreyi</i>)	Painful genital/perianal ulcer 5-7d post-exposure w/ inguinal LAD ± drainage	Usually clinical with negative syphilis/HSV; GS/Cx, PCR in some labs	Azithro 1g or CTX 250mg IV; often empiric PCN for syph; eval partners
Other ddx for genital ulcer: drug rxn, Behcet, neoplasms, Crohn's, trauma, tuberculosis, amebiasis, and leishmaniasis				

Discharge	Symptoms	Diagnosis	Treatment
Gonorrhea (<i>N gonorrhoeae</i>), Chlamydia (<i>C trachomatis</i>)	♀: frequently asx, mucopurulent cervicitis, urethritis, PID ♂: dysuria, purulent discharge, epididymitis, proctitis All: pharyngitis	♀: can self-swab, vaginal > urine NAAT (Sn >65%, >57%) ♂: first-catch urine NAAT > urethra All: pharyngeal/anal swab based on hx (can self-swab) (BMJ Open 2019;9) NB: Cx if c/f resistance	Gonorrhea: CTX 500mg IM x1 Chlamydia: azithro 1g PO x1 or doxy 100mg BID PO x7d Concurrent infxn/empiric tx for both: CTX + doxy (azithro-R gonorrhea) (MMWR 2020;69:1911)
Mycoplasma genitalium	Suspect in pts who fail tx for GC/CT ♀: cervicitis, PID, often asymptomatic ♂: dysuria, purulent discharge, proctitis	♀: vaginal swab PCR ♂: urine or urethral swab PCR (send out test)	If failed tx for GC/CT: moxifloxacin 400mg qd x7-14d (CID 2015;60:1228)
Trichomoniasis (<i>T vaginalis</i>)	♀: purulent malodorous discharge, pruritus, dysuria, dyspareunia ♂: usually asymptomatic	Wet mount → vaginal swab NAAT	Metronidazole or tinidazole 2g PO ±GC/CT tx; tx partner Retest after 3 months

TRAVEL MEDICINE

Pre-Travel Counseling

- Patient: medical conditions, medication supply, dosing schedule changes for travel (e.g. insulin), supplemental oxygen needs, allergies (epi pen), pregnancy, immunization history, prior malaria exposure
- Trip: duration, season, purpose of trip, exposures based on itinerary (urban v rural, cruise ship, animals, cave or water exposure)
- General Counseling: sunscreen (SPF 50+), seatbelt/helmet, safe sexual practices, hand hygiene, animal avoidance, considerations around tap water and raw foods, considerations around travel and evacuation insurance. Provide patient with [CDC Travel Tips](#)
- Arthropod bite avoidance: ↓ exposed skin, insect repellant (DEET, picaridin, Metofluthrin, IR3535), treated clothing, mosquito nets

Immunizations

- Ensure routine vaccinations are up to date, then use MGH developed "[Pre Travel PREP](#)" or [CDC site](#) for country-specific recs
- Common travel vaccines: Yellow Fever, Meningococcal, Typhoid, HAV, HBV, Japanese Encephalitis, pre-exposure rabies, Cholera

Malaria Prophylaxis (typically South/Southeast Asia, Africa, Central/South America)

- [CDC tool](#): Rx options based on resistance. ~1w pre-travel, up to 4w after. Daily: atovaquone-proguanil (Malarone), doxy, primaquine Weekly: mefloquine, chloroquine

Traveler's Diarrhea ([CDC Yellow Book](#))

- Common pathogens: ETEC, C. Jejuni, Shigella spp, Salmonella spp, Vibrio spp, norovirus, rotavirus, Giardia lamblia, etc.
- Tx: mild: loperamide; severe (fever, dysentery, interference with travel): azithro 1g x1 > FQ or rifaximin, avoid loperamide

Infections in a Returning Traveler

- Broad ddx, consider geography, exposure risk, pt vulnerability, incubation periods. Common culprits: Malaria, dengue, EBV/CMV, tick-borne, typhoid fever, respiratory viruses, TB, STIs, typical infections (CAP/UTI etc.) ([NEJM 2017;376:548](#))

Infectious Disease

Tickborne Diseases

TICKBORNE DISEASES ([CDC Guide](#))

Approach to tick bites and prevention:

Physical prevention: daily tick check, shower after outdoors when feasible, treat pets, safe household practices ([CDC handout](#))

Chemical prevention: DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-diol, 2-undecanone; 0.5% permethrin for fabrics

Removal: ASAP, pull **straight out** w/ clean straight-tip **tweezers**, **wash** w/ soap/water, can submit tick for species identification

Approach to tickborne illness:

Hx: hiking/outdoor activity, late spring-early autumn. **Most (50-80%) will NOT recall tick bite** ([Tick Borne Dis 2019;10:694](#))

Sx/signs/labs: fever, myalgias, arthralgias, rash; ↓WBC & PLT, ↑AST & ALT. **Coinfection is common**

Empiric tx: if high suspicion, send all dx incl. babesia smear (not tx by doxycycline), **start empiric doxycycline 100mg PO BID**

Other similar zoonoses to consider: tularemia (rabbits), leptospirosis (rats), brucella/coxiella (cows/sheep), though less common

Tick identity and geography:

Amblyomma americanum (lone star/turkey tick, **HME**): South, MW, Atlantic

Dermacentor variabilis (American dog/wood tick, **RMSF**): SE and SW USA, Mexico, Central/South America

Ixodes scapularis (deer/bear/black-legged tick, **all others below**): **Northeast**, Mid-Atlantic, and central Midwest

Disease	Presentation	Diagnosis	Treatment
Lyme IDSA: CID 2021;72:e1 ; Lancet 2012;379:461 ; NEJM 2014;370:1724	<p><u>Early localized (>1mo)</u>: erythema migrans (EM, red ovoid lesion ± central clearing), ± fever, myalgia, arthralgia, asx in 30%</p> <p><u>Early disseminated (days-mos)</u>: multiple EM lesions, sx above; neuro: CN palsies, meningitis, mononeuritis, radiculopathy; cardiac: heart block, myopericarditis</p> <p><u>Late disseminated (mos-one year)</u>: arthritis (mono- or polyarthritis of large joints, esp. knee), neuro (mild encephalopathy, peripheral neuropathy)</p> <p><u>Post-infectious syndromes</u> (yrs): fatigue, depression attributed to Lyme exposure, NOT a "chronic infection" so no role for abx (NEJM 2007;357:1422)</p>	<p>Avoid serologic testing w/o objective s/sx</p> <p>Early: clinical suspicion only (serology converts >1w after EM appears)</p> <p>Late (2 tier testing):</p> <ol style="list-style-type: none"> Screening ELISA IgM/IgG Western blot (WB) if screen ⊕ or equivocal <p>IgM⊕ = 3 particular bands IgG⊕ = any 5/10 total bands</p> <p>IgG⊕ at 6-8w; if ELISA/WB IgM⊕ IgG⊖ at 6-8w: false ⊕</p>	<p>Early: doxy 100mg PO BID x14d</p> <p>Disseminated (neuro, cardiac involvement): CTX 2g q24h x14-28d based on severity</p> <p>Ppx: doxy 200mg PO x1 IF tick attached & engorged ≥36h in endemic area AND ≤72h after tick removed</p>
Babesiosis IDSA: CID 2021;72:e49 ; NEJM 2012;366:2397	<p><u>Common exposure</u>: blood transfusion (not screened for)</p> <p><u>Mild-to-moderate</u>: viral-like sx (fever, fatigue, chills, sweats), arthralgias, myalgias, HA, n/v, cough – can be subacute (up to 6mo)</p> <p><u>Severe</u> (usually immunosupp, HIV, <u>asplenic</u>, <u>rituximab</u>, >50yo): severe hemolysis, DIC, ARDS, multiorgan failure</p> <p><u>Labs</u>: DAT⊖ hemolytic anemia, ↓PLT, ↑ALT/AST</p>	<p>Blood smear: ring forms in RBC (Maltese cross rare); malaria appears similar, parasitemia = %infected RBCs</p> <p>PCR: very Sn & Sp, not widely available</p>	<p>Mild-mod: atovaquone 750mg q12h + azithro 500mg q24h</p> <p>Severe: add clinda 600mg IV q8h (prev. w/ quinine), c/s ID</p> <p>Severe hemolysis, parasitemia ≥10%, or end-organ failure: c/s heme re: plasma exchange</p>
<i>Borrelia miyamotoi</i> (NEJM 2013;368:2910)	<u>Relapsing fever</u> (e.g. qOD), HA, AMS, photophobia, chills; ↓WBC/PLT, ↑ALT/AST (mimics anaplasmosis); rash usually absent	PCR > serology NB : EIA cross-reacts w/ Lyme	Doxy 100mg BID x14d
Powassan virus (CID 2016;62:707)	Fever, encephalopathy <u>MRI</u> : T2/FLAIR hyperintensities (esp. basal ganglia) <u>CSF</u> : lymphocytic pleocytosis (can also be neutrophilic)	Serum/CSF serology (send-out to state lab)	Supportive care, no antivirals known to be effective
Anaplasmosis (HGA)	<u>Common</u> : high fever, myalgias, headache; rash is less common (<30%), can be ill-appearing	PCR : morulae in 20-80% of neutrophils on smear	Dox 100mg BID x10d
Ehrlichiosis (HME)	<u>Labs</u> : ↓WBC/PLT, ↑ALT/AST, ↑CK	PCR : morulae in 0-20% of monocytes on smear	
Rocky Mountain Spotted Fever (<i>Rickettsia rickettsii</i>)	3-5d prodrome (fever, malaise, myalgias, HA) → progressive petechial rash (limbs → trunk, spares face) <u>Severe</u> : meningoencephalitis, shock, ARDS, DIC, organ failure; 20% mortality if untreated; 5% if treated <u>Labs</u> : WBC variable, ↓PLT, ↓Na, AKI, ↑LFTs, coagulopathy	Clinical dx , start empiric tx Serology : undetectable until 7-10d after sx onset; repeat 14-21d after sx onset to confirm dx Skin biopsy : 70% Sn	Dox 100mg BID x5-7d minimum + ≥3d after afebrile (tx for all ages)

Infectious Disease

Fever of Unknown Origin

DEFINITION ([CCM 2008;36:1330](#); [Medicine 1961;60:1](#))

- Classically T>38.3C on multiple occasions for ≥3w w/o obvious cause. After inpt eval, duration can vary by subpopulation (nosocomial, neutropenic, HIV-associated) ([Br J Hosp Med 1996;56:21](#))
- Far more often an atypical presentation of a more common dz than very rare dz
- Etiologies: 1) rheumatologic dz, 2) infection, 3) malignancy, 4) other (including meds)

WORKUP ([AJM 2015;128:1138e1](#))

- Ddx:** most commonly **rheumatologic > ID > cancer > meds**
 - 25-50% of cases, no source is identified ([Medicine 2007;86:26](#))
- History:** review fever pattern, B symptoms, PMH (incl. dental, immunocompromise), valvular dz, exposures including travel, birthplace, animal, arthropod, food, blood products, sick contacts, sexual contact, drugs, occupation, TB RFs, meds (antimicrobials, vaccines), procedure/hospitalization, family history
- Exam:** dental caries/thrush, sinus and temporal artery tenderness, thyromegaly, murmur, abd tenderness, HSM, eyes, fundi, lymph nodes, joints, skin/nails, rectal, urogenital
- Initial:** CBC/diff, BMP, LFTs, ESR/CRP, UA/UCx, BCx x3 (diff. sites), CXR
 - ESR: measure of chronic inflammation. Falsely elevated in ESRD, paraproteinemia, anemia, obesity, advanced age
 - Correction for age → ♂: age/2, ♀: (age/2)+10**
 - CRP: rises more acutely than ESR; may be falsely low in cirrhosis
- Other labs to consider:** IGRA, HIV, syphilis Ab, LDH, TFTs, SPEP/SFLC, ANA, ANCA, RF/CCP, cryo, CK/aldolase, EBV serologies, CMV PCR, ferritin, blood smear, HBV/HCV
- Imaging** ([Arch Intern Med 2003;163:545](#)): CT C/A/P (71% Sn, 71% Sp), LENls, TTE, FDG-PET/CT (Sn 67-100%, Sp 33-88% [Am J Med Sci 2012;344:307](#)), tagged WBC scan (Sn 45-60%, Sp 78-86%), maxillofacial CT
- Tissue diagnosis:** LN, liver bx (14-17% yield), BM (low yield at 0-2%), temporal artery biopsy (GCA), kidney (RPGN), consider LP if CNS findings

TREATMENT

- Try to avoid empiric antibiotics** and observe (unless hemodynamic instability or immunocompromised)
- D/C possible offending meds
- If ↑ suspicion for GCA/vasculitis, strongly consider empiric steroids (prior to bx) to prevent vision loss/end-organ damage
- If extensive workup ⊖, prognosis usually good, most cases defervesce ([AJM 2015;128:1138e1](#))

Etiologies of FUO	
*bold = common causes (AJM 2015;128:1138e1)	
Infectious	Abscess (perianal, brain, dental), HIV, EBV, CMV, HHV6-8, HBV, HCV, endocarditis (fastidious/HACEK, nutritionally variant <i>Strep</i>), nosocomial infection, hardware/graff infection, osteomyelitis, septic arthritis, sinusitis, prostatitis, TB (miliary) , tick-borne infections, endemic fungi (e.g. cocci/histo/paracocci), malaria, cat-scratch disease, toxoplasmosis, Q fever, brucellosis , Bartonella, salmonella, typhus, melioidosis, schistosomiasis, visceral leishmaniasis, Whipple's disease, lymphogranuloma venereum
Malign.	Lymphoma, leukemia, MM, myeloproliferative disorders, RCC , HCC, pancreatic, cervical, metastases, myxoma
Rheum.	Cryo, PMR/ GCA/TA , RA, Adult Still's, (JRA)/MAS , SLE, dermatomyositis, sarcoid, HSP, PAN, Kikuchi's, Takayasu's, Behcet's, GPA/MPA/EGPA
Other	Drug fever , serotonin syndrome, NMS, DVT/PE/hematoma, hypothalamic dysfunction, pheo, thyroiditis, alcoholic hepatitis, cirrhosis , IBD, factitious, HLH, familial periodic fever syndromes (FMF, Hyper-IgD Syndrome, Schnitzler's, TRAPS)

ETOIOLOGIES BY PATIENT POPULATION

Patient Population	Etiologies
General (Am J Med Sci 2012;344:307)	Infection 14-59%, rheumatic 2-36%, malignancy 3-28%, miscellaneous 0-18%, undiagnosed 7-51%
Elderly patients (Am Geriatr Soc 1993;41:1187)	Infx 25% (abscess 4%), rheum 31% (most common GCA/PMR), malignancy 12%
Uncontrolled HIV* (CID 1999;28:341)	Infx 88% (dMAC 31%, PJP 13%, CMV 11%, histo 7%, other viral 7%), malignancy 8% (lymphoma 7%) *Mean CD4 count 58/mm ³
Neutropenic (refractory to abx) (NEJM 2002;346:222)	Fungal infx 45%, bacterial infx 10-15% (resistant, biofilms), GVHD 10%, viral infx 5%, misc 25%

SELECT CAUSES OF FUO

- Drug fever:** dx of exclusion, broadly refers to any febrile response to medication. Can occur at any time while taking drug, with resolution post-cessation (resolution can take up to 1w)
 - Fevers can be in excess of >102F. Rarely, ⊕ accompanying signs (e.g., morbilliform rash, LFT elevations, eosinophilia)
 - Mechanisms include: hypersensitivity rxn (incl. SJS/TEN), dysfunctional thermoregulation, aseptic meningitis, Jarisch-Herxheimer reaction, NMS/serotonin syndrome, G6PD deficiency
 - Medications commonly associated: antimicrobials (β-lactams, sulfa, macrolides), AEDs, dexmedetomidine, chemo
- VTE:** DVT, PE, thromboplebitis may cause fever. Usually low grade (6% w/ fever >101F and 1.4% >102F) ([Chest 2000;117:39](#))
- Central fever:** most commonly associated with SAH, intraventricular bleed, brain tumors ([JAMA Neurol 2013;70:1499](#))

Infectious Disease

Rare Diseases at MGH

Organism/Syndrome	Epi & Transmission	Symptoms	Labs	Diagnostic Tests	Treatment
Malaria (<i>Plasmodium</i> spp)	Africa, Latin Am, Asia, Mid East, Eastern Europe	12-35d incub (up to yrs if <i>P. vivax</i>); fever, HSM, AMS, jaundice, petechiae	Anemia, ↓PLT, AKI, ↑LFTs, ↓glucose, acidemia	BinaxNOW (RDT) + thick/thin blood smear w/ Giemsa	Variable, d/w ID
	<i>Anopheles</i> spp. (nocturnal)				
Mosquito-borne viruses: Dengue, Chikungunya, and Zika are often indistinguishable clinically/epidemiologically; consider testing for all 3 if concerned					
Dengue fever (DENV serotypes 1-4; <i>Flavivirus</i>)	India, Asia/Pac, Africa, Lat Am	Fever, retro-orbital HA, arthralgia "break bone fever", petechiae, shock	Lymphopenia, thrombocytopenia, ↑Hct	Serum RNA early → IgG/IgM (cross-rxn w/ Zika); tourniquet test	Rest, fluid; avoid NSAIDs due to ↑ hemorrhagic sx
	<i>A. aegypti</i> and <i>A. albopictus</i> (diurnal feeders)				
Chikungunya fever (<i>Alphavirus</i>)	Africa, Asia/Pac, Caribbean, Lat Am, S USA	1-14d incub; fever (>102 in chik), HA, polyarthralgia, rash, conjunctivitis, GBS + fetal microcephaly (Zika)	Chik: lymphopenia, thrombocytopenia, ↑LFTs, AKI	Chik: PCR if <7d sx; serology if ≥7d Zika: serum/urine PCR if <14d sx → serology/plaque reduct.; serology if ≥14d of sx	Rest, fluid; avoid NSAIDs unless definitely not dengue
	<i>A aegypti</i> and <i>A albopictus</i> (diurnal feeders); STI (Zika)		Zika: labs freq. nml		
West Nile virus (<i>Flavivirus</i>)	Africa/MEast, Europe, Americas	Asx; fever, HA, myalgia, 1% meningitis	CSF pleocytosis (lymphs)	Serum + CSF Abs > PCR	Rest, fluid
	<i>Culex</i> spp. (nocturnal feeders)				
Leishmaniasis, cutaneous/visceral (<i>Leishmania</i> spp)	C/S America, S Europe, Mid East, E Africa, S Asia	CL: painless ulcer(s), regional LAD	VL: cytopenias, ↑LFTs	Clinical dx, tissue smear/cx; rarely Ab	Variable, d/w ID; abx if superinfected lesions
	<i>Lutzomyia/Phlebotomus sandfly</i>	VL: fever, HSM, ↓wt			
Bacterial Zoonoses: <i>Coxiella</i> , <i>Bartonella quintana</i> , and <i>Brucella</i> are important causes of culture-negative endocarditis					
Cat scratch disease (<i>Bartonella henslae</i>)	Worldwide	Fever, LAD 1-3w, neuro, ocular	↑ESR/CRP, ↑LFT	PCR 1-3d; Ab 1-2w; histology	Variable, d/w ID
	Cat bite/scratch, fleas				
Leptospirosis (<i>Leptospira</i> spp.)	Worldwide; tropics > temperate	Fever, HA, myalgia, jaundice, conjuc. suffusion	AKI, ALF, rhabdo, anemia, hypoNa,	Serology if 3-5d sx	Outpt: doxy 100mg BID x7d; inpt: PCN G, doxy, or CTX
	Water contaminated by animal urine/sewage, esp. after floods				
Q fever (<i>Coxiella burnetii</i>)	Worldwide (not New Zealand)	Fever, HA, myalgia, PNA, endocarditis	↑AST/ALT, ↑Bili, ↓PLT, ↑CK	PCR <7d, serology ≥7d	Doxy 100mg BID x14d
	Aerosolized ungulate fluid				
Brucellosis (<i>Brucella</i> spp)	Worldwide	Fever, arthritis (SI/spine), endocarditis	↑AST/ALT, ↓WBC w/ relative ↑lymph	Serology if 7-10d sx	Doxy 100mg BID x6w + gent/rifampin
	Dairy products, ungulate contact, lab exposure				
Tularemia (<i>Francisella tularensis</i>)	N America, Europe > Asia	Regional LAD: 6 syndromes: PNA, glandular, etc.	Nonspecific; ↑ESR/CRP; ↓PLT	Serology if sx ≥2w; GS, Cx (cysteine + media)	Streptomycin 7-10d; cipro or doxy 10-21d if mild dz
	Arthropod bite, animal contact (rabbit), food/water, airborne				
Rickettsia: in general, rickettsial diseases with eschars are scrub typhus, African tick-bite fever, RMSF, Mediterranean spotted fever, and rickettsialpox					
Murine typhus (<i>Rickettsia typhi</i>)	SE Asia, N Africa, N America	Fever, centrifugal rash , HA, myalgia	↓Plt, ↑AST/ALT	Serology performed 2w apart	Doxy 100mg BID x7d
	Feces of infected rat fleas				
Scrub typhus (<i>Orientia tsutsugamushi</i>)	India → E Asia; Pacific, Chile	Eschar , fever, lymphadenopathy, centrifugal rash, HA	↓Plt, ↑AST/ALT, ↑Bili, AKI, WBC usually wnl	Serology performed 2w apart; consider eschar bx	Doxy 100mg BID x7d; azithromycin if tetracycline-R
	Bites from infected mite larvae (AKA chiggers)				
Helminths: if concerned about intestinal worms, albendazole is an effective and safe medication to give empirically while awaiting lab results					
Schistosomiasis (<i>Schistosoma</i> spp)	Africa, Brazil, MidEast, Asia	Acute (3-8w): fever, urticaria, HA Chronic : HSM, portal HTN, hematuria	↑Eos (30-60%) in acute, ↓Plt; LFTs usually wnl	Serology at 6-12w; stool/urine microscopy for speciation	Acute: pred 20-40mg x5d + praziquantel Chronic: 40-60 x1 of praziquantel
	Fresh water with free cercariae from infected snails				
Trichinellosis (<i>Trichinella</i> spp)	Worldwide, esp. Europe	Abd pain, n/v, diarrhea → myalgia, weakness, ± fever	↑Eos, ↑WBC, ↑CK, ↑LDH	Serology 2-8d; muscle biopsy	Albendazole 400mg BID + pred 30-60mg qd x8-14d
	Undercooked meat, esp. pork				
Strongyloidiasis (<i>Strongyloides stercoralis</i>)	Rural tropics/subtropics; Appalachia, SE USA	Skin rxn, epigastric pain, diarrhea, resp. sx; fever, n/v, sepsis/shock if hyperinfection	↑Eos, ↑WBC; in immunosupp. pts → hyperinfection & disseminated dz (normal eos)	Serology more Sn than stool but less Sp. ✓ BCx, may have GN bacteremia (gut translocation)	Ivermectin 200 mcg/kg/day x2d; treat for 5-7d if disseminated dz
	Skin contact with soil contaminated w/ human feces, fecal-oral, autoinfection				
Other Infections					
Typhoid fever (<i>Salmonella enterica</i> serotype Typhi)	India, SE Asia, Africa	Fever, lethargy, abd pain, 'rose spots', diarrhea (>50%), constip. (30%), HSM	↓HR, ↑LFTs, ↓WBC (↑WBC sign of intest. perf.), anemia, abnl coags	Stool/blood Cx. BMBx 90% Sn. Serology effective in non-endemic regions	Azithro/ciprofloxacin Severe: CTX (meropenem if Pakistan)
	Fecal oral; asymptomatic carriers				
Melioidosis (<i>Burkholderia pseudomallei</i>)	India → SE Asia; N Australia	Fever, PNA, skin abscess, community-acquired sepsis, GU	↑WBC; other nonspecific values c/w organ failure	Blood Cx on Ashdown's agar, GS	Abscess I&D + IV mero/ceftaz x2w → T/S x3mo
	Soil; aspiration, inhalation, percutaneous inoculation				
Hantavirus (Sin nombre, Andes)	SW USA, Lat Am, Europe, Asia	Hemorrhagic fever, renal failure, ARDS	↑PTT, ↓Plt, AKI, proteinuria	Serology via state department of health	Supportive care
	Aerosolized rodent excreta				
Toxoplasmosis (<i>Toxoplasma gondii</i>)	Worldwide	Mono-like symptoms	Atypical lymphs, ↑AST/ALT	Serology 1-7d; CSF 2-5d	Tx if CNS, preg, or choriorretinitis
	Cats; contaminated meat/water				

Multiple: NEJM 2017:376:548, NEJM 2018:379:557, NEJM 2007:357:1018, NEJM 2015:372:954, JAMA 2002:287:2391; Malaria: JAMA 2010:304:2048; Dengue: NEJM 2012:366:1423; Zika: NEJM 2016:374:1552; Chikungunya: NEJM 2015:372:1231; West Nile: JAMA 2013:310:308; Brucellosis: NEJM 2005:352:2325;

Schistosomiasis: NEJM 2002:346:1212; Typhoid: NEJM 2002:347:1770; Melioidosis: NEJM 2012:367:1035

Infectious Disease

Infection Control

Resources: [Infection Control Website](#) on ellucid for the most up to date MGH policies and list of disease/conditions requiring isolation. For additional support, work with unit-specific nursing leadership and contact Infection Control (x62036) or refer to [Who to Call For What](#)

Standard Precautions: apply to *all* patients. Hand hygiene (HH) is the most important action to stop the spread of infection

- Disinfect hands with an alcohol-based hand rub (ABHR)
 - Before entering and upon exiting the patient room
 - After contact with the patient or items in the patient environment
 - When glove use is indicated, HH is performed **before** donning AND **after** doffing gloves
 - Hands are visibly soiled: wash hands with soap/water, dry hands, then apply ABHR
- **Gloves/gowns** for contact w/ blood, bodily fluids (e.g., wound), secretions, excretions, mucous membranes, broken skin
- **Mask + eye** protection for procedures that can **splash** blood, bodily fluids, or secretions (e.g., ABGs, paracenteses)
- **Dispose** of materials **heavily soiled** with blood or bodily fluids into biohazardous waste (**red bag**)
- **Disinfect** reusable patient equipment (e.g., personal stethoscope, U/S) with hospital-approved disinfectant **wipes** after patient contact

Transmission-Based Precautions (follow links in isolation column for additional details)

Isolation	Risk & Transmission	Description	Examples
Contact	Direct or indirect contact w/ pt or his/her environment	<ul style="list-style-type: none">◦ Hand hygiene + nonsterile gloves + isolation gowns◦ Do not touch phones, beepers, notes while in room◦ Remove gown and gloves <i>together</i> only touching <i>inside</i> of PPE with bare hands, dispose of PPE inside or immediately outside the room◦ Dedicate the use of equipment (stethoscope, BP cuff) to avoid sharing w/ other pts. All equipment w/in the room is presumed contaminated◦ Disinfect reusable non-critical equipment (stethoscope) using hospital-approved disinfectant wipes for pathogen of concern	MRSA VRE MDROs CRE Lice/Scabies Uncontained drainage (abscesses)
Contact PLUS	Spore forming & alcohol-resistant orgs transmitted by indirect/direct contact	<ul style="list-style-type: none">◦ Contact precautions + hand wash soap/water + ABHR + private room◦ After doffing PPE; wash hands with soap/water x15-20sec, dry, then apply ABHR; use bleach wipes for equipment◦ Isolate pt empirically while awaiting results	C. diff Norovirus C. auris Cutaneous anthrax
Enhanced	Cystic Fibrosis	<ul style="list-style-type: none">◦ Contact precautions + private room and limitations on use of shared spaces	
Droplet	Large respiratory droplets (coughing, sneezing, talking)	<ul style="list-style-type: none">◦ Surgical mask + eye protection + private room◦ Isolate pt empirically while awaiting results	N. meningitidis Influenza Adenovirus Pertussis
Enhanced Respiratory	COVID-19	<ul style="list-style-type: none">◦ Contact precautions + N95/PAPR + eye protection + private room (may cohort known with known COVID-19)◦ Airborne Infection Isolation Room (AIIR, "negative pressure") preferred when aerosol-generating procedures anticipated	COVID-19
Airborne	Small droplet nuclei that remain suspended in air & disperse widely	<ul style="list-style-type: none">◦ Standard precautions + N95/PAPR + AIIR	Tuberculosis Varicella Disseminated herpes zoster
Strict	Highly pathogenic organisms	<ul style="list-style-type: none">◦ Contact precautions + N95/PAPR + eye protection + AIIR. If suspected, isolate, contact Biothreats (Non-COVID) Pager #26876	SARS/MERS Avian Influenza

Immunocompromised Hosts:

- BMT, lung txp, neutropenic patients: standard precautions + positive pressure room + N95 for pt during travel + dietary precautions
 - BMT: gloves and surgical mask for healthcare workers
 - Lung transplant: gown, glove, and surgical mask for healthcare workers

How Infection Statuses are Resolved and Transmission-Based Precautions Discontinued:

Use CORAL/NEMO for all COVID-related infection statuses. For screening for resolution of prior MRSA, VRE, MDRO status, contact Infection Control Unit referencing [Who to Call for What](#). Discuss resolving any other infection status w/ Infection Control directly

Bloodborne Pathogen Exposure: (needlestick, splash to eyes, mouth, nose, open cut)

1. Immediately wash affected area
2. Normal business hours: call MGH OHS (6-2217). Outside business hours: page on-call OHS clinician, pager #21272
3. Notify supervisor

Pregnant Health Care Workers and Infectious Disease

Infectious Disease

Antimicrobial Dosing

Drug (By Class)	Usual Dosing	CrCl 50-25	CrCl 25-10	CrCl<10	HD
PENICILLINS					
Ampicillin IV (bacteremia)	2g q6h	CrCl 50-10: 2g q8-12h		CrCl <10: 2g q12h	2g q8-12h*
Ampicillin IV (endocarditis, meningitis)	2g q4h	CrCl 50-10: 2g q6-8h		CrCl <10: 2g q12h	2g q8-12h*
Ampicillin-sulbactam IV (blood, intra-abd, PID)	3g q6-8h	CrCl 30-15: 3g q8-12h		CrCl <15: 3g q12h	3g q12h*
Piperacillin-tazobactam IV (non-Pseudomonas)	3.375g q6h	CrCl 40-20: 2.25g q6h		CrCl <20: 2.25g q8h	2.25g q8h
Piperacillin-tazobactam IV (Pseudomonas)	4.5g q6h	CrCl 40-20: 3.375g q6h		CrCl <20: 2.25g q6h	2.25g q8h
CEPHALOSPORINS					
Cefazolin IV	2g q8h	CrCl 50-10: 2g q12h		CrCl <10: 2g q24h	1g daily q24 OR 2g post-HD
Ceftriaxone IV	1-2g q24h	No change with renal function; meningitis dosing is 2g q12h to max 4g/day; on HD days, give post-HD			
Ceftazidime IV (most except UTI, meningitis)	2g q8h	CrCl 50-31: 2g q12h	CrCl 30-16: 2g q24h	CrCl 15-5: 1g q24h; CrCl <5: 1g q48h	2g x1 → 1g daily* OR 2g post-HD
Cefepime IV (febrile neutropenia, PNA, CNS)	2g q8h	CrCl 59-30: 2g q12h	CrCl 29-10: 2g q24h	CrCl <10: 1g q24h	1g q24h* OR 2g post-HD
Cefepime IV (others)	1-2g q8-12h	CrCl 59-30: 1g q12h	CrCl 29-10: 1g q24h	CrCl <10: 1g q24h	1g q24h* OR 2g post-HD
FLUOROQUINOLONES					
Ciprofloxacin IV (for systemic Pseudomonas, q8 dosing)	400 mg q8-12h	CrCl <30: 400mg q24h			400 mg q24h*
Levofloxacin IV/PO (CAP, complicated infx)	750mg q24h	CrCl 49-20: 750mg q48h	CrCl <20: 750mg x1 → 500mg q48h		750mg x1 → 500mg q48h
CARBAPENEMS					
Meropenem IV (most except meningitis, CF, in which case double dose)	1g q8h	CrCl 50-26: 1g q12h	CrCl 25-10: 500mg q12h	CrCl <10: 500mg q24h	1g q24h*
OTHER ANTI-INFECTIVES					
Acyclovir IV (higher dose for CNS/VZV, adjusted wt if obese)	5-10mg/kg q8h	CrCl 49-26: 5-10mg/kg q12h	CrCl 25-10: 5-10mg/kg q24h	CrCl <10: 2.5-5mg/kg q24h	2.5-5mg/kg q24h*
Clindamycin IV	600-900mg q8h	Usual dose since Clindamycin not renally eliminated; max 2,700mg/day			
Fluconazole IV/PO	12mg/kg x1 → 6mg/kg q24h OR 800mg x1 → 400mg q24h	CrCl <50: 6mg/kg x1 → 3mg/kg q24h OR 400mg x1 → 200mg q24			6mg/kg x1 → 3mg/kg q24h* OR 400-800mg x1 → 200mg q24 (or 400 post-HD)
Metronidazole IV/PO	500mg q8h	Usual dose. Can use q6h dosing interval for CNS dosing			

***Dialysis dosing:** if drug dosed multiple times/day, administer 1 of the doses after HD. If drug dosed QD, administer after HD on HD days

Adapted from **MGH/Partners antimicrobial dosing guidelines** (contains more info on renal dosing for other antimicrobials, including **CVVH dosing**). To access, sign into VPN or Epic Resources → Handbook → Clinical Topics → Infectious Disease → Antimicrobial Renal Dosing Guideline (3a)

VANCOMYCIN DOSING including HD/CVVH dosing:

Typical dosing regimen: **20-25mg/kg LOAD** (can choose **higher dose for obesity or critical illness, max 2g regardless of wt**) → **15mg/kg q8-12h** (using adjusted body wt if obesity) maintenance for stable renal function; adjustments for renal function (page 2 of empiric dosing guideline above). Dose by level for unstable renal function including AKI

- **Dose monitoring:** Trough versus area under the curve (AUC) depending on indication - see table below. Check trough **1h prior to 4th dose** (or 3rd/5th to avoid overnight levels). AUC monitoring: PK calculation assistance from pharmacist, requires peak 1-2h after completion of (typically) 4th dose (usual infusion 60min/g) and trough 30-60min prior to next dose

SUMMARY OF THERAPEUTIC VANCOMYCIN GOALS	
Confirmed or high suspicion for serious MRSA infection (bacteremia, bone & joint, endocarditis/vascular, intra-abdominal, pneumonia, necrotizing infxns)	AUC _{24h} 400-600mg-h/L as determined by peak and trough, followed by patient-specific trough (pharmacist will place note in chart)
Serious non-MRSA infection or empiric use	Trough 13-18mcg/ml
Skin/soft tissue & urinary tract infections	Trough 10-15mcg/ml
Central nervous system	Trough 15-20mcg/ml
Unstable renal function (dose by level)	10-20mcg/ml

- **Subtherapeutic level:** first trough ≤1mcg from target (e.g. 9.3, w/ goal 10-15): continue same dose; first trough >1 to <5mcg lower than target (e.g. 11 w/ goal 13-18): ↑dose by 250mg (e.g. 1000mg → 1250mg); first trough >5mcg lower than target: shorten dosing interval (e.g. q12 → q8h)
- **Supratherapeutic level:** ≤2mcg from target: delay next dose by ~½ dosing interval (e.g. 4h for q8h dosing), reinitiate at 250mg less (e.g. 1250mg → 1000mg); 3-5mcg from target, delay next dose by ½ dosing interval, adjust dosing to next longer interval (e.g. q8 → q12); >5mcg from target: hold, repeat level in 12-24h and discuss with pharmacist

Hematology

Pancytopenia & Anemia

PANCYTOPENIA

Etiologies	
BM	↓cellular (aplastic, myelofibrosis, chemo, PNH, mets), nml cellular (MDS, PNH), ↑cellular (leukemia, lymphoma, MM)
Systemic	↑spleen (cirrhosis), toxin (EtOH, cocaine), nutrition (↓B12/folate, Cu), CTD (SLE, RA), sepsis, HLH/MAS
Meds	NSAIDs, PPIs, sulfas, antihistamine, chemo, anticonvulsants, antiprotozoals, heavy metals, many others
Infxn	viral (HIV, HBV/HCV, CMV/EBV, parvo), bacterial (Brucella, TB), fungal (Histoplasmosis), parasitic (leish, malaria, schisto)
Work-up	
Initial/Mild	✓ meds, CBC/diff, retic, smear, LFTs, TSH, B12, folate, PT/PTT, fibrinogen, HIV, HBV, HCV
Severe	✓ Hct/MMA, Cu, Zn, LDH, DAT, ANA, RF/CCP, ESR/CRP, SPEP, CMV, EBV, Parvo, Tox, Abd US+Doppler
Heme	✓ BMBx (strongly consider if pancytopenic w/o obvious systemic causes), flow cytometry (if c/f PNH)

- HLH: infxn/malig/rheum dz (MAS)/CART/checkpoint inhib. → hyperinflamm. → in some, cytokine storm. Dx: 5/8 of fever, ↑spleen, 2/3 cytopenias, ↑TG /↓fibrinog, ferritin ≥500 (usually >7-10k), ↑sIL-2R, hemophagocytosis in BM, low/no NK activity. Usually ↑LFTs, hepatomegaly, ↑LDH, ↑D-dimer. [H-score](#) for probability. Tx: depends on etiology (ASH: [Blood 2019;133:2465](#))

ANEMIA ([Williams Hematology 2021](#))

S/Sx: ↓O2 delivery → fatigue, lightheaded, DOE, pallor, angina (if CAD), claudication, cramps, abd pain, N/V; compensatory mechanisms, incl ↑RR, ↑CO (↑HR, palpitations, flow murmur, later: high-output HF), ↑erythropoiesis (bone pain)

Other findings: jaundice (hemolysis), glossitis (folate/B12/Fe def), motor/sensory deficits (B12 def), PICA/koilonychias/angular cheilitis (Fe def), splenomegaly (cirrhosis, infxn, thalassemia, malig., chronic hemolysis), constipation/bone pain (myeloma), melena (GIB), Mediterranean/Asian/Black (thal/SS), unusual thromboses (PNH), petechiae/purpura (coagulopathy, pancytopenia)

Initial labs (draw/add on prior to transfusion): CBC/diff (Δs in other cell lines, MCV, RDW), retic, special slide, T&S

- Calculate [reticulocyte index](#) (RI) = [% retic x (Hct/nl Hct)] / maturation factor, adjusts for Hct/early release of retics. Determines if adequate BM response: hypo- (<2%) vs hyper-proliferative (>2%); RI <0.1% indicative of aplastic anemia or red cell aplasia

Additional labs depend on RI and clinical history:

- RI <2% → "Anemia labs": Fe/TIBC/ferritin, folate/B12 (in last 6mo), BMP, LFTs, TSH, CRP
 - If unrevealing/otherwise indicated by history: ± SPEP/SFLC, Hgb electrophoresis, AM testosterone, Epo, BMBx
- RI >2% → "Hemolysis labs": LDH, bilirubin, haptoglobin, DAT (Coombs), coags, UA

CLASSIFICATION OF ANEMIA ([NEJM 2014;371:1324](#); [Lancet 2018;391:155](#); [JACC: Heart Failure 2019;7:36](#); [Williams Hematology 2021](#))

UNDERPRODUCTION (RI < 2%)		
Microcytic (MCV <80 μm^3)	Normocytic (MCV 80-99 μm^3)	Macrocytic (MCV ≥100 μm^3)
Iron deficiency anemia (IDA) <ul style="list-style-type: none"> ↓Fe, ↑TIBC, ↓ferritin (<30 high Sp; <15=○Fe in BM), Fe/TIBC <16%, ↑RDW Anemia of chronic inflammation (ACI) <ul style="list-style-type: none"> ↓Fe, ↓nl TIBC, ↑ferritin (<100 if ACI+IDA or <200 in ESRD), Fe/TIBC ↓/nl (>18%) In CHF, ferritin <100 (or <300, if Tsat <20) Thalassemias <ul style="list-style-type: none"> Fe studies nml, MCV ↓↓ (often <70), Mentzer index (MCV/RBC <13; high Sp); Hb electrophoresis Sideroblastic anemia <ul style="list-style-type: none"> ↑ferritin, Fe/TIBC nml; smear: basophilic stippling (Pb); BMBx: ringed sideroblasts 	Inflammation & variant: <ul style="list-style-type: none"> Early IDA or early ACI Mixed IDA & ↓folate/B12 (dimorphic: nml MCV w/ ↑RDW) Organ-specific: <ul style="list-style-type: none"> Renal (CKD/ESRD): ↓Epo (should ↑10x per 10% Hct drop) Endocrine (thyroid, pituitary, adrenal, parathyroid, testosterone; ↓metab. Rate→↓O2 demand): ↓Epo Marrow (red cell aplasia, aplastic anemia, MDS, myelofibrosis, myelophthisis, PNH, MM): ✓ SPEP, serum FLC, BMBx 	Megaloblastic: smear shows hyper-seg PMNs and macro-ovalocytes <ul style="list-style-type: none"> ↓Folate: ↑homocysteine, nl MMA ↓B12: ↑homocysteine, <u>↑MMA</u> (anti-IF Ab, ↑gastrin if pernicious anemia; falsely nml B12 possible) Non-megaloblastic: MCV usually <110 <ul style="list-style-type: none"> Cirrhosis, EtOH Reticulocytosis: lysis or bleed Hypothyroidism MDS (refractory anemia) & MM Meds: antifolates, pur/pyr analogs, AEDs, HAART, AraC, Hydrea
DESTRUCTION/LOSS (RI > 2%)		
Extrinsic (to RBC)	Intrinsic (to RBC)	
MAHA (-DAT, +schisto): see Thrombocytopenia <ul style="list-style-type: none"> Smear (≥2 schisto/HPF), PLT ~25K, ↑LDH, ↑indir bili, ↓hapt Immune (+DAT, +spherocytosis): Ab- and/or complement-mediated <ul style="list-style-type: none"> Warm autoimmune (CLL, HIV, lymphoma, SLE): +DAT anti-IgG/C3 Cold autoimmune (EBV, lymphoid malig., Mycoplasma): +DAT anti-C3 Drugs (PCN, cephalosporins), alloimmune (hemolytic transfusion rxn) Non-immune (-DAT): <ul style="list-style-type: none"> Infection: Babesia, Malaria, Bartonella, C. perfringens, H. flu (type B) Toxin: lead, copper, insect/spider/snake bites, hypotonic infusion Hypersplenism: many; massive SM usually 2/2 heme malignancy 	Hereditary: <ul style="list-style-type: none"> Hb disease (SS, HbC, thal): Hb electrophoresis Enzyme deficiency (G6PD, PK): G6PD levels often nml in attack; check 4w later & repeat in 3mo if ○ Membrane defect: spherocytosis, elliptocytosis Acquired (new onset): <ul style="list-style-type: none"> PNH (paroxysmal nocturnal hemoglobinuria): flow cytometry ± FLAER for GPI anchor, smear nml, UA (Hgb/hemosiderin), thrombosis (intra-abd/cerebral) Acute blood loss: GI blood loss, hematoma	
Intravascular: ↑↑LDH, ↓hapt, hemoglobinemia & -uria; Extravascular: ↑indir bili ± ↑LDH ± ↓hapt (if free Hb escapes spleen), SM		

IRON DEFICIENCY ANEMIA ([NEJM 2015;372:1832](#); [Blood 2019;133:30](#))

- Etiology:** ↑loss due to chronic bleeding (PUD/UGIB [↑BUN w/o ↑Cr], LGIB/CRC, menses, parasites, intravascular hemolysis), ↑demand (Epo, pregnancy, blood donation), ↓intake (malnutrition) or ↓absorption (Crohn's, ↑pH [e.g. PPI], post-gastrectomy, Celiac)
- Evaluation:** GI bleed eval, H. pylori; consider Celiac (esp. if not responsive to PO iron)
- Treatment:** PO 325mg FeSO₄ x1-3 QD or QOD (↑absorp. w/ QOD: [Lancet Haematology 2017;4:e524](#)). ~6w to correct anemia, ~3-6mo to replete stores. ↑absorp. on empty stomach, w/ VitC, ↓w/ Ca foods, antacids. GI SE: constipation, epigastric pain, N/V
 - IV iron if excessive SEs, CKD, malabsorption, IBD, intolerant to PO, or CHF ([NEJM 2009;361:2436](#)). Typical dose: **iron sucrose 200mg QOD x5 or 300mg QOD x3**. SE: n/v, pruritus, flushing, myalgia/arthritis, CP; ○ by 48h. Anaphylaxis rare

Hematology

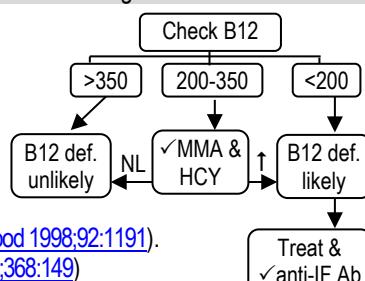
Pancytopenia & Anemia

ANEMIA OF CHRONIC INFLAMMATION (NEJM 2019;381:1148; Blood 2019;133:40)

- Etiology:** autoimmune, infection, malignancy, chronic disease (CHF, CKD); inflammatory cytokines (IL-1, IL-6 & TNF α) \rightarrow \uparrow hepcidin \rightarrow \uparrow ferroportin degradation/internalization \rightarrow \downarrow intestinal Fe absorption, \downarrow Fe recycling by macrophage & hepatic Fe mobilization
- Time course:** usually 1-2mo to develop, but can \downarrow Hgb 2-3g/dL in 1-2d in acute illness
- Treatment:** tx underlying disease. Fe if concomitant Fe deficiency: Tsat <15-20%, or no response to EPO; can \checkmark soluble transferrin receptor/ferritin index to distinguish pure ACI vs. ACI+IDA but typically hx & Fe studies sufficient
 - Erythropoiesis stimulating agents (ESA):** FDA-approved for anemia a/w CKD & HIV on HAART. Controversial in cancer pts, (JCO 2019;37:1336). Evidence against use in CHF (NEJM 2013;368:1210). Maintain Tsat \geq 20%, ferritin \geq 100 for EPO therapy

MEGALOBLASTIC ANEMIA: ↑RBC size due to abnormal cell division in BM; macrocytic & can be non-megaloblastic

- \downarrow **Folate:** foliage, 3mo stores; ↓intake (EtOH, elderly), ↓absorption (Celiac, jejunal processes), ↑demand (pregnancy, hemolysis, malig.), meds (MTX, TMP, AEDs); severe form a/w hemolytic anemia, pancytopenia; ↑homocysteine, MMA nml; Tx: 1-5mg PO QD (must \checkmark B12 before tx)
- \downarrow **B12:** beef, 3y stores; ↓intake (EtOH, vegan), pernicious anemia (Ab to IF, gastric parietal cells), ↓absorption (gastrectomy, Celiac, Crohn's, PPI, chronic pancreatitis), ↑competition (bacterial overgrowth, tapeworm); severe form a/w pancytopenia & subacute combined degeneration (dorsal columns, corticospinal tract) w/ dementia, ataxia, paresthesia, ↑homocysteine, ↑MMA. Tx: 1-2mg PO B12 QD (as effective as IM if not 2/2 malabsorption) (Blood 1998;92:1191). For pernicious anemia, typically given IM. Post-tx, neuro sx start to improve 3mo-1y (NEJM 2013;368:149)



AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) (NEJM 2019;381:647)

- Mechanism:** antibody-mediated (warm) or complement-mediated (cold) hemolysis. DAT detects IgG/C3 bound to RBCs
- Warm AIHA:** Etiology: **idiopathic**, CLL/lymphoma, SLE/autoimmune disease, HIV, Babesia, meds. Extravascular hemolysis in spleen and liver > intravascular hemolysis. Dx: +DAT anti-IgG ± C3d, \downarrow haptoglobin, \uparrow LDH, \uparrow indirect bili, \uparrow retic. Tx: transfuse for Hb<6 & prednisone 1-2mg/kg/d for up to 3w with slow taper; 2nd line: rituximab, splenectomy. **Notify Blood Bank** if rapid hemolysis
- Cold AIHA:** Etiology: most often **cold agglutinin disease** (lymphoid malignancies, EBV, Mycoplasma, autoimmune dz). Intravascular > extravascular hemolysis. Dx: +DAT anti-C3 at room temp + C3d (can \checkmark thermal amplitude, consider titer). Tx: avoid cold; if sx/transfusion-dependent, plasmapheresis/IVIG temporizing, **rituximab** (1st line), treat underlying cause; NO steroids or splenectomy
- Drugs:** both Ab & non-Ab-mediated; abx (PCN, cephalosporins, sulfa); NSAIDs; CV (methyldopa, procainamide); rasburicase (G6PD)
 - If +DAT but no hemolysis, think **drugs**, \uparrow IgG (IVIG/Rhlg/myeloma), **CTD** (e.g. controlled SLE)

SICKLE CELL ANEMIA (NEJM 2017;376:1561)

- Definitions:** Sickle Cell allele: autos. recessive β globin gene A->T (Glu6Val) missense mutation. Sickle Cell Trait (SCT): heterozyg for β^S globin w/o aberrancy in partnered β globin gene. Sickle Cell Anemia (SCA): homozyg for β^S globin. Sickle Cell Disease (SCD): any inherited hemoglobinopathy w/ formation of Hemoglobin S (HbS) leading to sickle shape of RBCs
- Epidemiology:** ~300K born w/ SCA per y worldwide. ~90-100K w/ SCD in U.S, 1.2K families in Boston area. ~2-3mil worldwide
- Pathophysiology:** deoxygenated HbS polymerization \rightarrow sickle shaped RBCs, impacts RBC membrane integrity, adherence to vascular endothelium \rightarrow vaso-occlusive events (**VOE**), potential to affect **any organ**
- Diagnostics:** baseline Hb electrophoresis and HPLC: tests to separate HbS from other variants (HbA, HbF)
- Clinical Manifestations & Tx:** most severe in SCA, intermediate for SC, or S/Thal dz
 - Acute Pain Episodes:** Sx: swelling, tenderness, HTN, N/V. Frequency peaks age 19-39. \uparrow risk when Hb >8.5 and \downarrow HbF. Triggers: dehydration, infxn, stress, menses, EtOH, many w/o clear etiology
 - Acute Chest Syndrome:** #2 cause of hospitalization. Pulmonary arterial circ \downarrow O₂ tension \rightarrow \uparrow risk VOE. Complications incl PNA, thromboses, fat embolism. Def: imaging infiltrate + pulm sx/fever. Dx: CXR, \uparrow WBC, r/o PE & MI. Tx: abx (CTX+azithro or FQ), **transfusions** (simple v exchange), **bronchodil**. NB: 50% preceded by or a/w acute pain episodes
 - Other organ systems:** 1) Splenic sequest: 20% pts; acute 2g/dL \downarrow Hb; 2) Infxn: \uparrow risk of encapsulated org. If febrile, send BCx and cover empirically w/ CTX (+azithro if c/f acute chest; +vanc if HDUS or c/f meningitis); 3) Card: major cause of death, CM (2/2 chronic anemia, hemosiderosis), \uparrow MI risk; 4) Neuro: stroke \rightarrow neurocog impairment, epilepsy; 5) Hepatobili: ischemia, iron overload, pigmented gallstones; 6) Bone: \uparrow rate VitD def & osteoporosis, osteonecrosis; 7) Hyperhemolytic episode: rare; pain, fever, \downarrow Hb w/in 7-15d of transfusion, Tx: notify blood bank, hydration \pm steroids, IVIG, ritux, eculizumab
- Management:** Sickle Cell Pager (p28439) and consult Hematology for every admission!
 - W/u: CBC/d, BMP, LFTs, coags, hemolysis labs, BCx, UA/UCx; CXR; special slide (polychrome., sickle cells, Howell-Jolly)
 - All inpts:** VTE ppx, pain ctrl, O₂ (SpO₂ <92%), incnt. spirometry (\downarrow acute chest, NEJM 1995;333:699), often IVF for acute pain episodes. See Acute Care Plan. Utilize Epic Order Set. **Pain ctrl:** opioids \pm NSAIDs; if unknown prior dose: IV morphine \leq 10mg or Dilaudid 0.02-0.05mg/kg (max 1.5mg) \rightarrow PCA
 - Neutral language:** misperceptions interfere w/ mgmt, biased language a/w poor pain control and \ominus attitude to pt (JGIM 2018;33:685). **Avoid stigmatizing terms**, incl: "sickler, freq. flyer, pain seeking," etc.
 - Transfusions:** dilute HbS, \downarrow EPO, \uparrow SpO₂. Indicated in stroke, multiorgan failure, acute chest, sequest., peri-op. **No e/o benefit in acute pain episode**. Exchange $>$ simple (risk of hyperviscosity). Judicious w/ transfusion (risk of iron overload) (Blood Adv 2020;4:327). Iron chelators: deferoxamine (daily inj., slow), deferiprone and deferasirox (PO, poorly tolerated)
 - Outpt:** hydroxyurea (\uparrow HbF; continue inpt), folate/MVI, L-glutamine (\downarrow oxidative stress in RBCs; NEJM 2018;379:226), voxelotor (inhibits HbS polymerization; NEJM 2019;381:509), crizanlizumab (P-selectin antag, \downarrow RBC adhesion; NEJM 2017;376:429). Vaccines for encapsulated bacteria (Mening, HiB, Pneumo), HBV, flu, CoV-19
 - Other therapies:** allogeneic BMT only curative option. Gene therapy evolving (incl CRISPR use) (NEJM 2021;384:205)

Hematology

Thrombocytopenia

THROMBOCYTOPENIA ([Hematology 2012;2012:191](#))

Definitions: 100-150k mild, 50-99k mod, <50k severe. **Bleed risk:** <50k w/ surgery/active bleed, <30k w/ mild trauma, <10k spontaneous

↓ PRODUCTION	↑ DESTRUCTION	SEQUESTRATION/DILUTION
<ul style="list-style-type: none"> - Infxn: sepsis, HIV/HCV, VZV/CMV/EBV, parvo, tickborne - Nutrition: EtOH, ↓B12, ↓folate - Drugs: abx, chemo, ASH Edu 2018;2018:576 - Neoplasm: MDS, BM infiltration, 1° heme - Other: cirrhosis (↓TPO), aplastic anemia, some vWD 	<ul style="list-style-type: none"> - Immune: ITP, SLE/APLS, RA, lymphoma, post-transfusion - Drugs: heparin, MTX, abx, anti-GPIIb/IIIa, quinine, NEJM 2007;357:580 - MAHA: DIC, TTP, HUS, mHTN, preeclampsia/HELLP - Shearing: CVVH, bypass, IABP, vasculitis, hemangioma (Kasabach-Merritt) 	<ul style="list-style-type: none"> - Hypersplenism (cirrhosis, portal HTN) - Massive transfusion - Hypothermia - Gestational

Workup:

- H&P focused on bleeding (GI, GU, epistaxis, HA, mucocutaneous), etiology, timing of plt ↓. If new HA: consider CTH
- R/o alarming causes: HIT, TMA, catastrophic APLS. Identify common causes: infxn, drug, immune, nutrition, hypersplenism, MDS
- Initial labs: CBC/d, BMP, LFTs, coags, special slide, T+S, HIV, HCV, pregnancy test, citrated plt count (r/o pseudo-thrombocytopenia)
- If c/f MAHA (e.g. schistocytes on slide): add LDH, haptoglobin, DAT, retics, D-dimer, fibrinogen
- If c/f SLE/APLS: add ANA, lupus anticoagulant, anti-cardiolipin, anti-β2GP1
- If c/f BM disease: consider BM biopsy (rarely done)

PRIMARY IMMUNE THROMBOCYTOPENIA (ITP) ([Blood Adv 2019;3:3829](#); [Blood 2017;129:2829](#); [NEJM 2019;381:945](#))

AutoAbs against pltts and megakaryocytes. Defined by isolated plt <100k, dx of exclusion (anti-plt Ab not useful)

Presentation: asx or mucocutaneous bleeding; 10% of ITP has AIHA = Evan's syndrome. Screen for H. pylori (tx may ↑pltts in ITP)

Prognosis: <10% spontaneous resolution, up to 50% recover with 1st line tx. 1.4% risk of ICH, 9.5% risk of severe bleeding

Management: “response” = plt ↑2X to ≥30k within 3mo

- Plt ≥30k & asx/minor bleed: observe; consider steroids if elderly, comorbidities, on AC/anti-pltts, upcoming procedures, & plt near 30k
- Plt 10k-29k: steroids ± IVIG; if not bleeding, do not give pltts (will be destroyed)
 - steroids (takes 4-14d to work): dexamethasone 40mg/d x4d, methylpred 1g/d x3d, or prednisone 60mg/d x3w w/ taper
 - IVIG (takes 2-4d to work, lasts 2-3w): 1g/kg/d x2d
- Plt <10k: steroids + IVIG, consider romiplostim, do not give pltts unless c/f bleeding
 - romiplostim (takes 5-14d to work): 3-5mcg/kg SQ and repeat weekly until response
- Severe bleeding: plt transfusions, IVIG, steroids, Amicar (0.1g/kg/30min → gtt 0.5-1g/h)/TXA, romiplostim
- Refractory/recurrent: romiplostim at increasing doses, rituximab, fostamatinib; last resort = splenectomy (itself only 50% effective)

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) ([Blood Adv 2018;2:3360](#); [Blood 2017;129:2864](#); [NEJM 2015;373:252](#))

IgG anti-PF4-heparin complex binds & activates pltts, hypercoagulable state. Can occur with any heparin (UFH, LMWH, heparin flushes)

Presentation: 5-10d after exposure, ↓plt >50%, nadir 40-80k, thrombosis in 30-50% (skin necrosis, DVT/PE, arterial)

- Consider rapid-onset HIT if <24h with prior exposure within 100d; delayed-onset can present up to 3w after last heparin

Diagnosis/Management:

- Calculate 4Ts Score. If 0-3: HIT unlikely (NPV 99%), OK to continue heparin. If ≥4:
 - 1) **Stop heparin, reverse warfarin** (prevent skin necrosis), and **start non-heparin AC**. No plt transfusion unless severe hemorrhage
 - 2) Send **anti-PF4**. Send **serotonin release assay (SRA)** (gold standard, long to result). Do not wait for results to do Step 1
 - PF4 neg: HIT unlikely; OK to resume heparin. PF4 OD ≥2, or OD ≥1.5 with 4Ts ≥6: HIT likely. Otherwise: decide based on SRA
- Duration of AC: if no thrombosis, until plt >150k; if thrombosis, typically 3-6mo. AC options:
 - **Fondaparinux** (IV or SQ): for stable non-surgical patients, contraindicated if GFR <30, irreversible
 - **Argatroban** (IV): preferred in renal failure & surgical pts, monitor w/ chromogenic Xa (goal 20-40%)
 - **Bivalirudin** (IV): only approved for HIT undergoing PCI, preferred in liver failure
 - **DOACs for non-urgent AC**: apixaban, edoxaban, rivaroxaban, dabigatran
 - **Warfarin**: not until plt >150k for 2 consecutive days
- Add heparin to allergies. Avoid future heparin (use alt. AC for VTE ppx), though if compelling indication (e.g., bypass) small studies suggest no ↑risk of HIT in pts with h/o HIT >100d prior if anti-PF4 now neg ([NEJM 2001;344:1286](#); [NEJM 2000;343:515](#))

THROMBOTIC MICROANGIOPATHY (TMA) ([NEJM 2014;371:654](#))

Microthrombi → **MAHA** (↓Hb, ↑LDH, ↓haptoglobin, +schistos, -DAT), ↓↓plt (consumption), **end-organ injury** (vascular occlusion)

- **Drug-induced (DITMA):**
 - 1) Immune-mediated: gemcitabine, oxaliplatin, quetiapine, quinine
 - 2) Dose-dependent: gemcitabine + other chemo, tacrolimus, cocaine
- **TTP** (plt <30K): inherited/acquired ADAMTS13 def. → vWF multimers. S/Sx: purpura, GI sx, neuro sx; fever uncommon, AKI rare, pentad rare. Dx: [PLASMIC score](#) → if mod/high, ✓ADAMTS13. Tx: **plasma exchange**, steroids, ritux, caplacizumab. **Avoid pltts**
- **HUS** (plt >30K): Shiga-toxin-mediated (O157:H7 *E. coli*, *Shigella*). S/Sx: bloody diarrhea, severe AKI; severe neuro sx rare (SZ, coma, hemiparesis). Dx: stool ⊕ for organism or toxin; Tx: supportive (IVF, HD) ([Blood 2017;129:2847](#))
- **Complement-mediated** (“atypical HUS”): S/Sx: **severe AKI** + 20% w/ extra-renal sx (CNS, cardiac, pulm hemorrhage, panc.); Dx: complement genotyping, anti-complement Ab. Tx: plasma exchange; eculizumab ([NEJM 2013;368:2169](#))
- **2° Etiologies**: DIC, infxn, malignancy, SLE/APLS, scleroderma, mHTN, HELLP, post-HSCT

Hematology

Eosinophilia

OVERVIEW ([Am J Hematol 2017;92:1243](#); [Hematology 2015;2015:92](#))

- **Eosinophilia:** AEC >500. **Hypereosinophilia:** AEC >1500. **Hypereosinophilic syndromes (HES):** AEC >1500 + organ dysfunction
 - Eosinophils are quickly eliminated by steroids → eosinophilia may be unmasked as pts taper off chronic glucocorticoids
- Primary = due to clonal expansion (HES/leukemia). Secondary (reactive) = due to infection, atopy, meds, rheum dz, etc

Infections	Helminthic: strongyloides, toxocariasis, shistosomiasis, ascaris, filariasis, trichinellosis, hookworm, fascioliasis. Fungal: aspergillus (ABPA), coccidiomycosis, histoplasmosis. Protozoal: isospora. Viral: HIV, HTLV1/2
Malignancy	Primary HES (PDGFRA-assoc.), eosinophilic leukemia, CML, NHL, HL, mastocytosis; less common with solid tumors
Autoimmune	EGPA (see Vasculitis), PAN, eosinophilic fasciitis, RA, IBD, IgG4, sarcoidosis, GVHD, blistering disease
Allergic	Drugs, DRESS, asthma/atopy, ABPA, hyper IgE syndrome, AIN, episodic angioedema (Gleich syndrome)
Misc	Adrenal insufficiency, cholesterol emboli syndrome, acute arterial thrombosis, radiation exposure

WORKUP ([Br J Haematol 2017;176:553](#); [J Allergy Clin Immunol Pract 2018;6:1446](#); [Hematology 2015;2015:92](#))

- **Hx:** meds/supplements (<6w), diet, travel, occupational exposures, atopy, infxn, malignancy, rheumatic dz, full ROS, Δ in sx
- **Exam:** assess for rashes, cardiac/pulmonary abnormalities, nasal/sinus involvement, LAD, hepatosplenomegaly, neuropathy
- **Initial diagnostics:** CBC/diff (repeat), special slide, BMP, LFTs, LDH, ESR/CRP
 - If AEC 500-1500: check troponin, B12/tryptase, CXR if clinically indicated
 - If AEC >1500, assess for HES: check U/A, CK, troponin, EKG, CXR, PFTs, CT C/A/P (for adenopathy, organomegaly, masses, organ infiltration), tissue biopsy of affected organs; also B12, tryptase, serum Ig levels
- **Additional diagnostics** (as clinically indicated): Strongyloides serology, stool O&P, other serologies if potential exposure; ANCA if c/f EGPA; ANA, RF, CCP if c/f rheum dz; IgE levels, allergy testing if c/f allergy; imaging/bronch, serologies (e.g. aspergillus IgE) if c/f pulm. dz; imaging/endoscopy if c/f GI dz; TTE/CMR if c/f cardiac dz; periph. flow ± BMBx if c/f MPD or >1500 & no obvious 2° cause

TREATMENT ([Hematology 2015;2015:92](#))

- Urgent Tx: if cardiac, neuro, or thromboembolic complications, AEC >100,000/rapidly rising, or s/sx of leukostasis → 1mg/kg to 1g methylpred (+empiric ivermectin 200mcg/kg if potential Strongyloides exposure); obtain HES diagnostics above prior to initiating
- Non-urgent Tx: symptomatic or evidence of end-organ damage but does not need urgent Tx; see below for Tx by condition
- No Tx: if asymptomatic, no organ involvement, & no identified cause to treat, can monitor for resolution & organ damage

DRUG RXNS

- Can be isolated ↑Eos or accompanied by systemic illness (DRESS, hepatitis, AIN, etc). In hospital, PCNs/cephalosporins common culprits. Suspect DRESS if new drug 2-8w prior, fever, rash, facial edema, LAD, abnml LFTs, ± organ involvement, atyp. lymphs

ORGAN-SPECIFIC PATHOLOGY

Cardiac: ([Immunol Allergy Clin North Am 2007;27:457](#); [JACC 2017;70:2363](#))

- Eosinophilic endomyocarditis: necrosis → thrombus formation (→ embolic events) → fibrosis → restrictive CM, valve involvement
 - May be due to hypersensitivity myocarditis, parasitic infections, malignancy, idiopathic HES
 - Dx: TTE (LV/RV apical dysfunction, signs of restriction, intracardiac thrombi) and cardiac MRI (+subendocardial LGE)
 - Tx: high dose steroids & remove culprit med (if hypersensitivity), treat underlying disorder (parasite, HES)
- Eosinophilic coronary arteritis: rare complication of EGPA; may mimic ACS

Pulmonary: ([Clin Microbiol Rev 2012;25:649](#); [Chest 2014;145:883](#); [J Allergy Clin Practice 2014;2:703](#))

- Acute eosinophilic PNA: <7d fever, cough, SOB; a/w smoking; ↑periph. Eos often absent at presentation; Dx: BAL Eos ≥25%
- Chronic eosinophilic PNA: subacute fever, cough, SOB, wt loss; a/w asthma; Dx: BL periph/pleural infil, UL-predom; BAL Eos ≥25%
- Allergic bronchopulmonary aspergillosis (ABPA): asthma/CF c/b recurrent exacerbations w/ fever, malaise, brown mucus plugs; Dx: ↑Eos, ↑total IgE, ↑Aspergillus IgE & IgG, imaging w/ central bronchiectasis, UL/ML consolidations; Tx: steroids + itraconazole
- Loeffler syndrome: transient/migratory pulm. opacities, ↑Eos 2/2 helminth larvae; Dx: larvae in resp secretion (stool usually ⊖)

GI: (AGA EoE: [Gastro 2020;158:1776](#); [NEJM 2015;373:1640](#); [Clin Rev Allergy Immunol 2016;50:175](#))

- Eosinophilic esophagitis (EoE): dysphagia, food impaction, GERD-like sx/refractory GERD, assoc w/ allergic conditions; Dx: EGD w/ bx, exclude other causes (GERD, motility d/o, Crohn's, infxn, CTD, etc.); Tx: dietary Δs, PPI, topical steroids (MDI/neb, PO liquid)
- Eosinophilic gastroenteritis (EGE): stomach/duod. ± esoph., colon; Sx: n/v/d, abd. pain, ascites; Tx: dietary Δs, PO steroids

Others: neuro (peripheral neuropathy, encephalopathy, CVA/TIA from thromboemboli), thrombotic complications, skin Δs

PRIMARY HYPEREOSINOPHILIC SYNDROMES (HES) ([Am J Hematol 2017;92:1243](#); [Hematology 2015;2015:92](#))

- **Myeloproliferative HES** (~20% of HES in US): acute/chronic eosinophilic leukemia, PDGFRA-associated MPN → clonal expansion of Eos; 80% pts have *FIP1L1-PDGFRα* fusion gene; remainder have PDGFRA, FGFR1, JAK2 rearrangements
 - Dx: anemia, thrombocytopenia, ↑tryptase, ↑B12, special slide (dysplastic eosinophils), flow cytometry (PDGFRA, BCR-ABL1, JAK2, FGFR1, KIT), BM Bx (fibrosis, hypercellularity)
 - Tx: if PDGFR+, imatinib; if JAK2+, JAK2 inhibitor; if FGFR1+, chemo; 2nd line or no rearrangement: hydroxyurea, IFN-α, other TKI/empiric imatinib
- **Lymphocytic HES:** clonal T-cell expansion → ↑IL-5 → ↑Eos. Often p/w skin/soft tissue involv., polyclonal hyper-IgG, ↑IgE. Episodic angioedema (Gleich syndrome) is very rare subset of L-HES. Up to 25% risk of progression to lymphoma.
 - Dx: flow cytometry for CD3, CD4 (clonal IL-5-secreting CD3+ CD4+ T-cells)
 - Tx: steroids; 2nd line: IFN-α, hydroxyurea, mepolizumab (anti-IL-5; [NEJM 2008;358:1215](#)), alemtuzumab
- **Idiopathic HES:** eosinophilia without identified cause and evidence of end-organ damage → consider ANCA-neg EGPA (50% cases)
 - Tx: steroids; 2nd line: hydroxyurea, IFN-α, imatinib, mepolizumab, alemtuzumab

Hematology

Coagulation Disorders

HYPERCOAGULABLE STATES ([NEJM 2017;377:1177](#))

WORKUP OF FIRST VTE			
Presentation	Provoked by strong trigger: <ul style="list-style-type: none"> - Major surgery/trauma - Immobility ≥3d - CA, pregnancy/OCP/HRT, SLE, IBD, nephrotic synd., MPN, HIT - Paget-Schroetter, May-Thurner 	Unprovoked/provoked by weak trigger & <ul style="list-style-type: none"> - Recurrent thrombosis - Young (<45yo) - Strong FH 	Unusual site: <ul style="list-style-type: none"> - Arterial thrombosis - Portal, hepatic, splenic, renal, mesenteric, or cerebral venous thrombosis
Workup	<ul style="list-style-type: none"> - No role for hypercoag. testing - Age-appropriate cancer screen 	<ul style="list-style-type: none"> - Consider if mgmt altered (OCP, AC duration or agent [VKA in APLAS], s/p pregnancy loss) - APLAS if young or recurrent events 	<ul style="list-style-type: none"> - Arterial: test for APLAS - Cerebral and splanchnic veins: inherited, APLAS, JAK2, PNH

Hypercoag testing considerations:

- **1st unprovoked VTE:** typically no need to test as inherited thrombophilia does **NOT** sig. ↑ risk of recurrent VTE ([JAMA 2005;293:2352](#))
- **DO NOT test at time of event.** If performed, should be **>2w following d/c of AC** to avoid confounded results
- **Testing** includes: APC resistance (reflexes to FVL), protein C/S (reflexes to FVIII/fibrinogen), ATIII, LA, prothrombin G20210A (PTG), anti-cardiolipin, anti-β2 glycoprotein. Only FVL, PTG, aPL Ab are reliable in acute VTE or on AC

CONDITION	CLINICAL PEARLS	TESTING
Inherited Conditions		
Factor V Leiden	- Most common inherited cause of hypercoagulability	- APC resistance assay (reliability iso heparin products depends on assay) → reflex FVL genetic test
Prothrombin gene mutation	- 2 nd most common cause of hypercoagulability - ↑ prothrombin (FII)	- PCR for PTG G20210A mutation (most common)
Protein C/S deficiency	- Activated protein C/S inactivate FVa and FVIIIa; ↓ level (more common) or function leads to hypercoagulability - A/w warfarin-induced skin necrosis (screen if hx)	- Free protein C/S functional assays - ↓ by acute thrombosis, VKA, liver dz, DIC, chemo, uremia (PC), pregnancy/OCP/nephrotic syndrome (PS) - ↑ by DOAC (C/S), HLD and nephrotic syndrome (PC)
Antithrombin III deficiency	- ↓ level or function - NB: heparin works via ATIII to inactivate FIIa and FXa; if ATIII defic., will be heparin-resistant & require ↑↑↑ doses	- ATIII functional assay assessing FXa inhibition - ↓ by acute thrombosis, UFH/LMWH, liver dz, nephrotic - ↑ by DOAC, direct thrombin inhibitors
Others	Homocysteine and MTHFR mutational analysis should NOT be performed	
Acquired Conditions		
APLAS	<ul style="list-style-type: none"> - Sapporo criteria = 1 clinical + 1 lab criterion - Clinical criteria: venous/arterial thrombosis, pregnancy complications - Catastrophic APS: ⊕ aPL w/ ≥3 organ thromboses in <1w, mortality ~50% (Autoimm. Rev 2010;10:74) Tx: LMWH → warfarin ± ASA (if arterial) 	<ul style="list-style-type: none"> - Lab criteria: ⊕ LA, anti-cardiolipin, or anti-β2 glycoprotein >2x ULN, twice 12w apart - LA unreliable on AC (false ⊕) and acute thrombosis (false ⊖); anti-CL and β2GP not affected - NB: ⊕ aPL Ab can be seen in infxn, rheum dz, malig, meds w/o clinical APLAS; unclear significance - False ⊕ VDRL (NEJM 2018;378:2010)

COAGULOPATHY ([NEJM 2014;370:847](#))

Disorders of **1° hemostasis** (↓ platelet # or function, VWD → mucocutaneous bleeding, petechiae, menorrhagia) or **2° hemostasis** (factor deficiency/↓ activity → deep tissue bleeding, joint, organ, brain; prolonged PT/PTT)

- Rule out **artifact, anticoagulant use, or systemic disease** (cirrhosis, DIC, abx, malnutrition, renal disease, cancer)
 - Consider diseases affecting vascular function (e.g., HHT, scurvy, EDS)
- If prolonged PT/PTT and etiology is not clinically apparent, order **mixing study** w/ normal plasma ([JAMA 2016;316:2146](#))
 - If PT/PTT corrects: supports **clotting factor deficiency** (confirm w/ factor specific assays)
 - If no/partial correction: supports **presence of inhibitor** (confirm w/ inhibitor specific assays)
 - Types: drugs (e.g. heparin), acquired factor inhibitor (VIII, V>>IX, XI; autoimmune d/o, malig.), nonspecific inhib. (e.g. LA)
 - If work-up is unrevealing, consider vWD testing, platelet function testing, thrombin time (TT), fibrinogen, factor XIII
- Tx: replace missing factor, eliminate inhibitor (immunosuppressants), treat underlying condition

Coagulation Defect	Normal aPTT	Prolonged aPTT
Normal PT	Platelet dysfunction (VWD, other platelet disorders), ↓ Factor XIII	Intrinsic pathway: ↓ VIII, IX (hemophilias), or XI (Ashkenazi). VWD (variable subtypes). ↓ XII, PK, HMWK (no clinical bleeding). Lupus anticoagulant (prothrombotic)
Prolonged PT	Extrinsic pathway: ↓ Factor VII, warfarin, liver dz, Vit K deficiency	Common pathway: liver disease, DIC, Vit K deficiency, warfarin. Rarely common pathway deficiency/inhibitor

DIC: massive activation of coag cascade → consumption of coag. factors (→ **bleeding**), microvascular **thrombosis** (→ MAHA, organ ischemia). 2/2 various inflamm. etiologies (sepsis, CA, trauma, pancreatitis)

Dx: ↑PT/PTT, ↑D-dimer, ↓fibrinogen, ↓plts, +schistos, ↑LDH, ↓hapt. **NB:** often normal coags in chronic DIC. Can differentiate DIC from liver dz w/ ↓FVIII (in endothelium, not liver), [DIC score](#)

Tx: underlying cause, transfuse plts if <10k (or serious bleeding <50k), cryo if fibrinogen <100, FFP if INR >2. Amicar generally contraind.

Hematology

Anticoagulation Agents

ORAL AGENTS (ASH: [Blood Adv 2018;2:3257](#); CHEST: [Chest 2012;141:e152S](#); [Chest 2012;141:e44S](#))

Agent	Dosing	Bridging/Switching/Reversal
Warfarin (Coumadin) - Vitamin K antagonist: inhibits vitamin K-dependent gamma-carboxylation of F ₂ , VII, IX, X, & Protein C+S - t _{1/2} 40h (variable)	- Initiation: 5mg qd x2d; frail, HF, kidney/liver dz: consider 2.5mg; BMI >40: consider 7.5mg - Adjust by INR, which lags 48h behind dose Δ Monitoring: (UW Dosing Nomogram) INR <2: ↑ up to 10-20%/w or consider booster dose INR 2-3: no change INR 3-4: ↓ 10%/wk or consider holding 0.5-1 dose INR >4: hold until INR 2-3, restart ↓ 5-15%/w If overlap w/ direct thrombin inhibitor: check chromogenic FXa: goal 20-40%	Bridging: (see below to bridge from parenteral AC): To parenteral AC: start IV w/o bolus when INR <2 Reversal: IV vitamin K faster than PO at 6h; ~ at 24h - Active bleeding: 1) IV vit K 10mg + FFP (10mL/kg ; 1U = 200-250mL) 2) Kcentra (4-factor PCC) 50U/kg if life-threatening (Circ 2013;128:1234 ; Transfusion 2016;56:799) - No active bleeding: 1) INR >10 → PO vitamin K 2.5-5mg OR IV 1-2.5mg 2) INR <10 → hold warfarin, no need for reversal
Dabigatran (Pradaxa) - Direct thrombin (IIa) inhibitor, t _{1/2} 12-17h - 80% renal clearance - P-gp substrate - Other: ↑ dyspepsia, ?↑ coronary events	- Non-valvular AF: 150mg PO BID if GFR >30, 75mg PO BID if GFR 15-30 (RE-LY NEJM 2009;361:1139); some use 100mg PO BID dose if high bleeding risk - VTE: 150mg PO BID after 5d UFH/LMWH (RE-COVER NEJM 2009;361:2342) - PPX: 110mg x1 then 220mg PO QD (RE-NOVATE II Thromb Haemost 2011;106:721)	Bridging/switching: To parenteral AC: start 12h after last dose (24h if CrCl <30). From parenteral AC: start <2h before next dose. To warfarin: start 3d before dabigatran ⊕ if CrCl ≥50; 2d if CrCl 31-50, 1d if GFR 15-30; bridge PRN. From warfarin: hold and start when INR < lower limit of therapeutic range Reversal if life threat.: can be dialyzed, lipophilic - Idarucizumab 5g (RE-VERSE NEJM 2017;377:431)
Rivaroxaban (Xarelto) - Direct Xa inhibitor - t _{1/2} 5-9h; 11-13 in elderly - 66% renal clear. - Avoid with CYP3A4 and P-gp dual inhibitors	- NV AF: 20mg PO QD if GFR >50, 15mg if GFR 15-50 (ROCKET AF NEJM 2011;365:883) - VTE: 15mg PO BID x2d, then 20mg QD. After 6mo, consider ↓ to 10mg QD if ongoing risk for VTE (NEJM 2010;363:2499 ; 2012;366:1287 ; 2017;376:1211) - PPX: 10mg PO QD (MAGELLAN NEJM 2013;368:513)	Bridging/switching: (J Thromb Thrombolysis 2016;41:206) - To parenteral AC: start when next DOAC dose due - From LMWH/fonda: start w/in 0-2h of next dose - From UFH: start immediately after ⊕ gtt (for edoxaban , start 4h after stopping UFH) - From warfarin: <ul style="list-style-type: none">• Start rivaroxaban when INR <3• Start apixaban when INR <2• Start edoxaban when INR ≤2.5 - To warfarin: (NB all ↑ INR; ✓ just before dose if able) <ul style="list-style-type: none">• Rivaroxaban/apixaban: coadminister until INR ≥2• Edoxaban: cut edoxaban dose by ½ and begin warfarin, ⊕ edoxaban once INR ≥2 - DOAC to DOAC: start when next dose due Reversal if life-threat.: not dialyzed off, protein-bound - Andexanet alfa (recombinant FXa): low or high-dose bolus depending on dose/timing → 2h gtt (NEJM 2015;373:2413 & 2019;380:1326)
Apixaban (Eliquis) - Direct Xa inhibitor - t _{1/2} 12h - lower renal clear. (25%) (Can use in ESRD)	- NV AF: 5mg PO BID, 2.5mg BID if 2/3: Cr ≥1.5, Wt ≤60kg, age ≥80; some use 2.5mg BID if CrCl 15-29 (ARISTOTLE NEJM 2011;365:981) - VTE: 10mg BID x7d, then 5mg BID x6mo; after 6mo, consider ↓ to 2.5mg BID (NEJM 2013;369:799 & 368:699) - PPX: 2.5mg BID (NEJM 2009;361:594)	
Edoxaban (Savaysa) - Direct Xa inhibitor - t _{1/2} 10-14h - 50% renal clear. - Avoid if CrCl >95 or <15 - P-gp substrate	- NV AF: 60mg PO QD; 30mg if CrCl 15-50 or wt ≤60kg; do not use if CrCl >95 (ENGAGE AF NEJM 2013;369:2093) - VTE: 60mg QD after 5d UFH/ LMWH, 30mg QD if CrCl 15-50, ≤60kg, or taking P-gp inhib. (NEJM 2013;369:1406) - PPX: not FDA-approved (15-30mg PO QD)	

PARENTERAL AGENTS

Agent	Dosing/Monitoring	Bridging/Switching	Reversal	Other
Heparin (UFH) - Binds & activates ATIII → inactivates Xa & IIa - t _{1/2} 60-90min	- ACS: 60U/kg → 12U/kg/h; PTT 63-83 - VTE: 80U/kg → 18U/kg/h; PTT 70-100 - PPX: 5,000U SC q8-12h - Monitoring: PTT; anti-Xa (goal 0.3-0.7) if baseline ↑ PTT or high doses; ACT if ↑↑	- To LMWH: give LMWH & ⊕ UFH at same time - To warfarin: ⊕ UFH once therapeutic ≥2d	- Protamine: 1mg per 100U heparin or 1mg LMWH (max 50mg). 60% reversal for LMWH, most effective if last dose within 8h - To warfarin: ⊕ LMWH once therapeutic INR ≥2d	- Preferred in renal failure (CrCl <30), peri-procedure, poor absorption, pregnancy
Enoxaparin (LMWH, Lovenox) - Binds & activates ATIII → inact. Xa>>IIa - t _{1/2} 4.5-7h	- ACS/VTE: 1mg/kg BID; QD if GFR <30 - PPX: 40mg SC QD; 30mg BID if ↑↑ risk; ↑30% if BMI ≥40; 30mg QD if GFR <30 - Monitoring: not routine; can ✓ anti-Xa 4h after 4 th dose, goal 0.5-1.0	- To UFH: ⊕ LMWH & start UFH w/o bolus 1-2h before LMWH dose due - To warfarin: ⊕ LMWH once therapeutic INR ≥2d	- Acute VTE: LMWH > UFH (Cochrane Rev 2017) - Prolonged t _{1/2} in renal failure	
Fondaparinux (Arixtra) - Binds & activates ATIII → inact. Xa only - t _{1/2} 17-21h	- VTE: <50kg → 5mg QD 50-100kg → 7.5mg QD >100kg → 10mg QD - PPX: 2.5mg SC QD - CrCl <30: contraindicated - Monitoring: not routine; can ✓ 4h anti-Xa	- To warfarin: ⊕ fonda. once therapeutic INR ≥2d - To UFH: start UFH (no bolus) 1-2h before due - From UFH: start 1h after UFH ⊕	- No reversal agent	- ↑ aPTT at therapeutic doses - If CrCl 30-50, consider Δ agents
Argatroban - Direct IIa (thrombin) inhibitor - t _{1/2} 45min	- HIT: 1-2mcg/kg/min - Monitoring: PTT, goal 1.5-3x baseline - Caution in critically ill, cardiac dysfunction, liver disease	- To warfarin: ⊕ once chromogenic factor Xa 20-40% (argatroban ↑INR)	- No reversal agent	- Idarucizumab is only for dabigatran

Hematology

Anticoagulation Management

CHOOSING AN ANTICOAGULATION AGENT

Guidelines: CHEST for VTE: [Chest 2016;149:315](#), ASH for VTE: [Blood Adv 2021;5:927](#), ASCO for VTE in CA: [JCO 2020;38:496](#); ACC/AHA/HRS for AF: [JACC 2019;74:104](#), CHEST for AF: [Chest 2018;154:1121](#); AHA/ACC for Valvular HD: [JACC 2017;70:252](#)

VTE	Obesity	Avoid DOACs if BMI ≥ 40 or wt $\geq 120\text{kg}$, though rivarox. may be ok. If use, ✓ peak/trough level (ISTH: JTH 2016;14:1308)
	Active Malignancy	Apixaban (CARAVAGGIO NEJM 2020;382:1599), edoxaban (NEJM 2018;378:615), rivaroxaban (JCO 2018;36:2017), LMWH > warfarin (CLOT NEJM 2003;349:146). Edox/rivarox ↑ bleeding risk v LMWH, avoid in GI/GU CA w/ intralum. lesions. DOAC > LMWH for short-term VTE tx, either long-term. Apix/rivarox ppx ↓ VTE in high-risk outpts, suggest in mod-risk: consider if Khorana ≥ 2 (AVERT NEJM 2019;380:711 ; CASSINI NEJM 2019;380:720). LMWH ppx OK in high-risk outpts
	Recurrent	If on non-LMWH: switch to LMWH. If on LMWH: increase LMWH dose
	All Others	DOACs > warfarin > LMWH
AF	Non-valvular	DOACs > warfarin for stroke risk, mortality, and bleeding risk
	Valvular	Warfarin if mod/severe MS (regardless of CHADS2/VASC)
	+ PCI	Dual (P2Y12i+OAC) v triple therapy (+ASA): dual w/ ↓ bleeding, likely no ↑ events (Annals 2020;172:474 ; EHJ 2019;40:3757) Dual therapy: DOAC + clopidogrel x12mo. Rivaroxaban 15mg QD (some use 20mg) (PIONEER AF NEJM 2016;375:2423) & dabigatran 150mg BID (RE-DUAL PCI NEJM 2017;377:1513) in guidelines, also data for apixaban (5mg BID unless 2.5mg indicated) (AUGUSTUS NEJM 2019;380:1509) & edoxaban 60mg QD (*though didn't ↓ bleeding v VKA) (ENTRUST-AF PCI Lancet 2019;394:1335). Warfarin + clopi or ticag also option (WOEST Lancet 2013;381:1107). Ticag may be used in-hospital or if very high thrombotic risk. After 12mo, can likely Δ to OAC alone (AFIRE NEJM 2019;381:1103) If triple therapy chosen due to high thrombotic/low bleed risk, typically d/c ASA & transition to dual therapy at 4-6w
	Mechanical	Warfarin + ASA. Warf > dabigatran (RE-ALIGN NEJM 2013;369:1206). INR for AVR 2.5 (3 if +AF, VTE, etc.); MV & TV = 3
Valve	Bioprosthetic	SAVR: Warfarin (INR 2.5) + ASA 3-6mo → ASA . TAVR: ASA/clopi 3-6mo → ASA . If AF/VTE, OAC+clopi → OAC (evolving)
	APLS	Warfarin. Warfarin > rivaroxaban in high-risk APLS (TRAPS Blood 2018;132:1365)
CAD	ACS (PCI)	Very low dose rivaroxaban (2.5mg BID) added to ASA/clopidogrel → ↓ CV mortality but ↑ major bleeding (NEJM 2012;366:9)
	2° prevention	Very low dose rivaroxaban (2.5mg BID) + ASA → ↓ MACE vs. ASA alone; ↑ major bleeding but no Δ in ICH or fatal bleeding (COMPASS NEJM 2017;377:1319). Can consider if high risk for events & low bleeding risk

ANTICOAGULATION BRIDGING

Guidelines: ACC: [JACC 2017;69:871](#); ASH: [Blood Adv 2018;2:3257](#); CHEST: [Chest 2012;141:e419s](#)

Indication	AF		VTE		Mechanical Valve	
	Risk Factors	Bridge?	Risk Factors	Bridge?	Risk Factors	Bridge?
Thrombotic Risk						
High	- CHA ₂ DS ₂ -VASc ≥ 7 (or CHADS2 5-6) - CVA/TIA, or systemic embolism <3mo - Rheumatic valv. HD	Yes unless major bleed/ICH <3mo	- VTE <3 mo - Severe thrombophilia: protein C/S or ATIII def, APLAS, multiple abnormalities	Yes	- Any mechanical MV - Caged ball/tilt disc AVR - Any mechanical valve w/ CVA/TIA <6mo	Yes
Moderate	- CHA ₂ DS ₂ -VASc 5-6 (or CHADS2 3-4) - CVA/TIA or systemic embolism >3mo	Likely bridge if prior CVA/TIA and if no ↑ risk of bleeding	- VTE 3-12mo - Recurrent VTE - Active malignancy - Non-severe thrombophilia: heterozygous factor V Leiden, PTG mutation	No	- Bileaflet AVR w/ ≥1 CVA risk factor: age >75, AF, prior CVA/TIA, HTN, DM2, CHF	Consider based on risk of bleeding in pt from procedure
Low	- CHA ₂ DS ₂ -VASc ≤4 (or CHADS2 0-2) - No prior CVA/TIA or systemic embolism	No	- VTE >1y & no other risk factors	No	- Bileaflet AVR w/o AF or CVA	No

- BRIDGE trial** ([NEJM 2015;373:823](#)) demonstrated ↑ risk of bleeding w/ bridging in pts with AF undergoing invasive procedure requiring interruption of VKA (NB: excluded pts w/ mech. valves, stroke/TIA <12w, major bleeding <6w, CrCl <30, Plt <100k)
- Bridging VKA w/ UFH or LMWH:
 - Stop VKA 5d prior to procedure if therapeutic INR. Start UFH or LMWH when INR <2
 - Stop UFH 4-6h prior to surgery and LMWH 12 or 24h prior to surgery (depending on dosing interval)
 - Restart UFH/LMWH at 24h postop. if low postprocedural bleeding risk or 48-72h if high risk. ⊖ when INR >2
 - Resume VKA w/in 24h postop if no bleeding complications (will not ↑ early bleeding risk because effect takes 24-72h)
- DOACs:** no bridging required; most can be stopped 24-72h prior to surgery, depending on procedural bleeding risk & renal function:

	High Bleed Risk		Low Bleed Risk	
	CrCl >50	CrCl <50	CrCl >50	CrCl <50
Dabigatran	≥48h (4 doses)	≥96h (8 doses)	≥24h (2 doses)	≥48h (4 doses)
Rivaroxaban	≥48h (2 doses)	≥48h (2 doses)	≥24h (1 dose)	≥24h (1 dose)
Apixaban	≥48h (4 doses)	≥48h (4 doses)	≥24h (2 doses)	≥24h (2 doses)
Edoxaban	≥48h (2 doses)	≥48h (2 doses)	≥24h (1 dose)	≥24h (1 dose)

- If low bleeding risk, can resume 24h after procedure. If high bleeding risk, wait 48-72h. If unable to take PO for prolonged period or second procedure is anticipated, start UFH/LMWH at the above time points instead

See [Peri-Procedural Anticoagulation](#) for MGH-specific peri-procedural guidance for cardiac cath. lab & IR procedures

TRANSFUSION MEDICINE TERMINOLOGY

- **ABO typing:** front type: **A/B antigens** (pt's RBC + reagent anti-A or B); back: anti-A or B in plasma (pt's plasma + reagent RBCs)
- **Rh(D) typing:** tests for **D antigen** on RBC (pt's RBC + reagent anti-D) – *NB: anti-D is not a naturally occurring antibody*
- **Screening (T&S):** tests for **unexpected antibodies** in pt's plasma (pt's plasma + screening RBC + Coomb's reagent), “active” $\times 3d$
- **Crossmatching (T&C):** final confirmation test by mixing pt's plasma & **donor** RBC; performed just prior to transfusion
- **Direct antiglobulin test (DAT/Coomb's Test):** tests for Ab or complement on RBCs (RBCs + Coomb's reagents [anti-IgG, anti-C3])

BLOOD PRODUCTS

Product	Description	Indications	Notes
Red Blood Cells	1U ~ 330cc <u>Processing</u> 1. Leukocyte reduction 2. Irradiation 3. Washing (rarely)	- Hgb <7 (NEJM 2014;371:1381 ; NEJM 2013;368:11) - Hgb <8 if CAD/ACS, ortho/cardiac surgery - Acute hemorrhage (>15% intravascular volume) - AIHA (no specific Hgb threshold) - Sickle cell disease (see Anemia: Sickle Cell Disease)	- Each unit has Hct ~55% - Response: 1U ↑Hgb ~1
Platelets	1U = 6pk = 300cc <u>Types</u> 1. Apheresis platelets derived from 1 donor 2. Pooled platelets from multiple donors <u>Processing</u> 1. Leukocyte reduction 2. Irradiation	Low platelets or functionally abnormal platelets - <10k: PPX spont bleeding (NEJM 1997;337:1870), antifibrinolytics in refractory thrombocytopenia in CA - <50k: major bleed, intra- or post-op bleed, ppx prior to invasive operative procedures (<30k bedside procedures) - <100k: post-bypass bleed, ICH/ophthalmic (no data) - ITP: only if life-threatening CNS/GI/GU bleed (often preceded by wet purpura, mucus membrane bleeding)	- Response at 30-60m: 1U ↑PLT ~30K - No evidence that apheresis > pooled pts - No evidence that platelets reverse anti-platelet agents (Lancet 2016;387:2605) - CI: TTP/HUS, HIT
Fresh Frozen Plasma	1U = 250cc Typical starting dose 2U Non-cellular portion of blood containing all coag factors; separated and frozen after collection	- Active bleed d/t deficiency in multi coag. factors or isolated coag factors for which concentrate is not available - ALF: consider for ↓Plt or ↑INR only if bleed or pre-op - Cirrhosis: cryo preferred, as treating INR w/ FFP can ↑bleeding due to ↑portal pressures - Trauma, DIC in presence of bleeding, congenital TTP - Ppx prior to bedside invasive procedures for INR >2.0	- Response: 2U ↑coag activity ~10% - Max correction INR 1.7 - Effect <6h due to short t _{1/2} of FVII - Potentiates effect of heparin by providing ATIII
Cryoprecipitate	10U = 150cc Contains factor VIII, factor XIII, VWF, and fibrinogen	- Fibrinogen <100: 50-100mg/dL, give 10U; <50, give 20U - Massive transfusion w/ ↓fibrinogen or abnl ROTEM/TEG - Complex cardiac surgery (JAMA 2017;217:738) - Postpartum hemorrhage (Br J Anaesth 2015;114:623) - FVIII deficiency, VWD - Cirrhosis: fibrinogen <100-120 or c/f dysfibrinogenemia	- 10U cryo should ↑fibrinogen ~85mg/dL - Fibrinogen t _{1/2} 3-5d - FVIII or vWF replacement: cryo is last resort therapy
Coagulation Factors	1-factor: VIII, IX, rF VIIa (NovoSeven), ATIII 3: II+IX+X (Profilnine) 4: PCC=II+VII+IX+X (Kcentra) FEIBA (anti-inhib. complx) vWF/FVIII (Humate-P)	- Coagulation factor deficiency/inhibitor - Von Willebrand's disease (Humate-P, NovoSeven) - VKA reversal (IV VitK first, for severe bleed PCC > FFP)	- Blood Transfusion Service approval required - S/E: allergic rxn, thrombosis
Antifibrinolytics	Contain Lysine derivatives that bind to plasminogen to ↓fibrinolysis and ↑hemostasis <u>Types</u> (topical, PO, IV) 1. Aminocaproic acid (Amicar) 2. Tranexamic acid (TXA)	- Trauma (Health Tech 2013;17:1) - Postpartum hemorrhage (Lancet 2017;389:2105) - Cardiac surgery (NEJM 2017;376:136 ; J Thor C Surg 2019;157:644), ECMO - Cirrhosis: when hyperfibrinolysis suspected (see ESLD) - Major orthopedic surgery, platelet refractoriness due to HLA alloimmunization, fibrinolysis of serosal surface and closed space bleeding, coagulation factor inhibitor	- Amicar: load 4-5g over 1h → 1g/h for 8h or until bleeding controlled - TXA: load 1g over 10min → 1g over 8h cont. infusion - S/E: risk of seizures w/ high dose TXA
Albumin	<u>Types</u> 1. 5% (iso-oncotic) 2. 25% (hyper-oncotic) Both contain 12.5g albumin & 154mEq Na (isotonic)	5% if hypovol/intravasc depl., 25% if fluid/Na restricted - Cirrhosis: HRS, SBP, LVP (see ESLD) - Shock: 4% albumin similar to 0.9% NS for IVF resuscitation (when alb. >2) (SAFE NEJM 2004;350:2247) - ARDS: 25% albumin (25g) q8h x3d + lasix gtt x3d → ↑O ₂ , neg. TBB (when alb. <2) (Crit Care 2005;33:1681)	- C/I: traumatic brain injury (Also see IV Fluids and Electrolyte Repletion)
IVIG	<u>Types</u> Polyclonal IgG and trace plasma contaminants Dose adjust for obesity	- Immunodeficiency: hypogammaglobulinemia IgG <400 - Immunosuppression in autoimmune disease (e.g. ITP, AIHA, post-transfusion purpura, acquired VWS) - Neuro: CIDP, myasthenia gravis, GBS - ID: toxic shock syndrome, Kawasaki disease	- SE: infusion reactions, aseptic meningitis, hyperosm renal tubular injury, thrombosis

TRANSFUSION MODIFICATIONS

- **Leukoreduction (LR):** filters leukocytes to (1) ↓ HLA sensitization in chronically transfused pts / **heme malignancies**, bone marrow / kidney / heart / lung **transplant candidates** (not liver transplant) (2) ↓ CMV risk & (3) ↓ febrile non-hemolytic transfusion reaction
- **Irradiation:** prevents proliferation of donor lymphocytes from attacking the recipient (transfusion-associated-GVHD in 1st degree directed donors); indications: **heme malignancy** & BMT to prevent GVHD; not indications: solid tumor, solid organ transplant, HIV
- **Saline-washing:** removes anti-IgA Ab & plasma proteins; indications: severe anaphylaxis to blood products (w/ or w/o IgA def.)

ADMINISTERING BLOOD PRODUCTS

- **Consent:** required for administration of all blood products, discuss type of product, indication, benefits/risks, possible alternatives
- **Ordering:** “Prepare RBC” (or platelets/FFP/cryo) → select number of units to prepare, indication, applicable modifications (see below) and “Transfuse RBC” → select number of units to administer, and rate of admin (usually over 2-4h)
- **Monitoring response:** order post-transfusion CBC to be drawn 15-30min after transfusion (if not actively bleeding)

MASSIVE TRANSFUSION: call Blood Bank (x63623) & physically run down w/ pick-up slip to Gray/Bigelow 2 to pick up cooler

- Activate when anticipate transfusing 50% TBV (~5U pRBC) in 2h OR 100% TBV (~10U pRBC or 5L plasma) in 24h
- Occurs most commonly in trauma, GI bleeding, cardiac surgery, obstetric complications, rupture of major blood vessel
- Emergency release un-crossmatched pRBCs (O- for pre-menopausal females, O+ ok for males and older females)
- **No universally accepted ratio:** for 2-4U pRBCs, transfuse 1U FFP, 1U PLT, & 10U cryo (can modify to goals below as stabilizes)
 - Goals: Hb >7-10, INR <2.5, PLT >50k, fibrinogen >100
 - No evidence for 1:1:1 transfusion protocol ([JAMA 2015;313:471](#))
 - Excessive FFP a/w ARDS in pts not requiring massive transfusion
- Correct coagulopathy → IV vit K, FFP 15cc/kg; platelet dysfunction (ASA, plavix, uremia) → PLTs, DDAVP 0.3mcg/kg
- Consider IV amicar or IV TXA (dosing on previous page)
- **Complications:** dilutional coagulopathy, hypothermia, hypocalcemia (citrate), metabolic alkalosis (citrate metabolized to bicarb)

PLATELET REFRACTORINESS: failure to achieve acceptable ↑ platelet count following transfusion. Normal t_{1/2} of 3 days

- **Alloimmune: Ab to class I HLA antigens** (e.g. +PRA) or PLT-specific antigens. RFs for HLA alloimmunization: multiple pregnancies, prior transfusions with non-leukoreduced blood products, organ transplants ([NEJM 1997;337:1861](#)). Drug-associated ITP (heparin, sulfa, vanc, linezolid, piperacillin, rifampin, thiazide, anti-GpIIb/IIIa)
- **Non-alloimmune: non-HLA Ab-mediated;** 2/3 of cases; Ddx: sepsis/DIC, HIT, TTP, CVVH/bypass/IABP, splenomegaly, liver dz, HSCT, viral infection (HIV/HCV) & drugs (amphotericin)
- **Evaluation:** check plt post-transfusion on 2 occasions and assess plt recovery (15min-1h later) & plt survival (18-24h later)
 - Inadequate plt recovery: corrected count increment <5k on 2 occasions; also usually indicated by plt ↑ <10k x2 → alloimmune refractoriness ([JCO 2001;19:1519](#))
 - Normal plt recovery but ↓ survival → non-alloimmune refractoriness
- **Alloimmune refractoriness workup:**
 - Consult Blood Transfusion Service [p21829](#). Studies will *not* be processed without discussing w/ them first
 - Send Panel Reactive Antibody: HLA class I Ab screen; test for alloreactivity against HLA antigens. Normal is 0%, range 0-100%
 - **If platelets required urgently** (i.e. actively bleeding), notify Blood Bank and ask for send out to Red Cross
- **Management:** with each platelet transfusion, **must** check a post-transfusion CBC w/in 15-60min of completion
 - Compatible platelets (specific HLA-antigen negative) or crossmatch compatible
 - ABO/HLA-matched apheresis single-donor plts from Red Cross. Takes days to process. Each unit has a shelf life ~3 days
 - Consider Amicar if bleeding (contraindicated in thrombotic DIC); correct coagulopathy with DDAVP if e/o uremia

MANAGEMENT OF ANEMIA IN JEHOVAH'S WITNESSES ([Am J Hematol 2017;92:1370](#))

- Discuss management with patients on a case-by-case basis
- **Acceptable products:** hematins (iron, folate, B12, recombinant human EPO), non-blood volume expanders (NS, LR, hydroxyethyl starches), hemostatic agents (amicar, TXA, DDAVP, albumin-free clotting factors)
- **Acceptable to some:** autotransfusion, HD/apheresis/bypass/ECMO, hemostatic products w/ blood fractions (coag. factors, PCC), plasma-derived products (albumin, cryo, Ig), products potentially containing albumin (rhEPO, vaccines), BM/organ transplantation
- **Unacceptable products:** whole blood, pRBCs, platelets, FFP, cryo, autologous blood transfusion
- Bleeding, preop: consider IV iron + rhEPO to speed up erythropoiesis → rhEPO onset 2-6 days if Fe/folate/B12 replete
- **Critically ill:** no expert consensus, consider rhEPO 200-300U/kg IV q24h or 250-500U/kg SQ q48h for goal periop Hb >10-12 → can be extrapolated to hemodynamically unstable/bleeding pts

THERAPEUTIC APHERESIS

- **Plasmapheresis (plasma exchange):** removes plasma, replaces with saline, albumin or plasma (depending on pt. condition) Indications: TTP (replace ADAMTS13 [NEJM 1991;325:393](#)), hyperviscosity, cryo, Guillain-Barre, CIDP, MG, ANCA, anti-GBM
- **Cytapheresis:** removes abnormal or excessive # blood cells Indications: leukapheresis for hyperleukocytosis (goal WBC <100); erythrocytapheresis for sickle cell crisis, severe babesiosis (high grade parasitemia >10, severe hemolysis, or pulm/liver/renal dz); platelet removal for thrombocytosis rarely done (goal plts <1000)

Hematology

Transfusion Reactions

INITIAL EVALUATION: Blood Bank (x63623, p21829) (BrJ Haematol 2012;159:143)		
<ul style="list-style-type: none"> S/Sx: f/c/rigors, hives/flushing, infusion site pain, shock/oliguria, wheezing, crackles 		
1. <u>STOP</u> transfusion, ABCs, VS q15min, notify blood bank		
2. If only urticarial sx or isolated T ≤39C → treat sx, resume transfusion once resolved		
3. Initial workup to consider: <ul style="list-style-type: none"> High suspicion for hemolysis: DAT, Bili, LDH, haptoglobin, crossmatch, UA, smear High suspicion for sepsis: GS/BCx of both pt & blood product High suspicion for TRALI/TACO: JVP, NTproBNP, ABG, portable CXR 		

	Acute	Delayed
Immune-mediated	AHTR FNHTR Urticaria/hives Anaphylactic TRALI	DHTR TA-GVHD Post-tx purpura
Non-immune mediated	Cold toxicity Citrate toxicity Sepsis TACO	Iron overload Viral infection

Reaction/Per-Unit Risk	Presentation/Diagnosis	Pathophysiology	Treatment/Prevention
ACUTE TRANSFUSION REACTIONS (<24h)			
Acute Hemolytic (AHTR) 1/76,000-137,000	Sx: 15min to 2-4h; <u>fever/chills</u> , back/flank pain, bleeding, DIC Dx: +Hb (blood/urine), +DAT, +Bili/LDH, +smear (spherocytes)	- ABO/Kidd incompatibility (preformed Abs) → <u>intravascular hemolysis</u> (IgM), cytokine/complement activation - Rh/Kell/Duffy incompatibility → less severe <u>extravascular hemolysis</u>	Tx: IVF (± diuresis) for goal UOP >100cc/hr x24h - Monitoring: HoTN, AKI, DIC, mortality ∝ volume transfused PPX: careful monitoring
Febrile Non-Hemolytic (FNHTR) 1/14 (PLT) 1/200-2,500 (RBC)	Sx: 1-6h; <u>low-grade fever</u> , chills, HA, flushing Dx: hemolysis workup negative	- Donor WBCs produce TNFα, IL1, IL6 - <u>RBC</u> : donor WBCs activated by recipient anti-HLA Abs - <u>PLT</u> : donor WBCs make cytokines before transfusion	Tx: APAP ± meperidine PPX: leukoreduction, little evidence for pre-medication
Sepsis (Bacterial Contamination) 1/75,000 (PLT)	Sx: 15-60min; high fever, <u>rigors</u> , abd sx, HoTN/shock Dx: GS/BCx of both pt & bag	- Bacteria >> viruses in donor blood - <u>RBC</u> : Yersinia, PsA (endotox-GNRs) - <u>PLTs</u> : Staph epi (GPCs)	Tx: antibiotics, quarantine all other similar products PPX: routine screening
Urticaria/Hives 1/33-100	Sx: <u>anytime</u> during/after transfusion; localized or diffuse hives & redness Dx: no work-up necessary	- IgE-mediated hypersensitivity to donor plasma proteins	Tx: pause → diphenhydramine → resume if urticaria resolves PPX: washed products, no evidence for pre-medication
Anaphylactic/Anaphylactoid 1/20,000-50,000	Sx: <u>within min</u> ; acute <u>HoTN</u> , angioedema, urticaria, wheezing, abd pain Dx: clinical; consider IgA def.	- IgE-mediated hypersensitivity in recipient lacking <u>IgA</u> or <u>haptoglobin</u> - Bradykinin-mediated flushing/HoTN in pt taking <u>ACEi</u> or neg charged filters (e.g. plasma exchange w/ albumin)	Tx: ABCs, O2, IVF ± pressors, epi IM Q15min, methylpred 125mg, diphenhydr. 25-50mg PPX: washed products
Transfusion-Related Acute Lung Injury (TRALI) 1/12,000 (RBC) 1/38,000 (PLT)	Sx: 1-6h; noncardiogenic pulm edema (ARDS); ± fever Dx: NTproBNP nml, bilateral CXR infiltrates w/o CHF	- Pre-transfusion stress activates lung endothelial cells & primes PMNs - Donor anti-HLA Abs/bioactive factors attack primed PMNs of recipient	Tx: ABCs, O2, intubation PPX: male donor plasma (fewer anti-HLA, anti-PMN Abs); defer donors w/ prior assoc. TRALI
Transfusion-Assoc. Circulatory Overload (TACO) 1/100 (RBC)	Sx: 1-6h cardiogenic pulm. edema 2/2 vol. overload Dx: elevated NTproBNP, CXR	- Highest risk in elderly, HF, CKD, chronic anemias	Tx: O2, IV diuretics, ± nitrates, NiPPV PPX: slower rate (1cc/kg/hr)
IVIG Transfusion Reactions 5-15% of infusions	- <u>Inflammatory rxn</u> : fever, chills, flushing, myalgias - <u>Anaphylactoid rxn</u> : urticaria, flushing, chest pain, N/V, HTN	- <u>Inflammatory rxn</u> : Ab/Ag interaction i/s/o concurrent infxn - <u>Anaphylactoid rxn</u> : unknown, potentially kinin-mediated, rare	Tx: IVF, sx mgmt PPX: slow, space out infusions
DELAYED TRANSFUSION REACTIONS (>24h, <28d)			
Delayed Hemolytic (DHTR) 1/2,000	Sx: ~3d; <u>fever</u> , anemia, jaundice, flu-like illness Dx: +DAT, +DBili/LDH, +smear w/ spherocytes	- Anamnestic IgG against previously exposed antigen (Kidd/Duffy/Kell) → extravascular hemolysis	Tx: none NB: delayed serologic transfusion reaction is the same except w/o hemolysis
TA-GVHD Rare (typically immunosuppressed)	Sx: 2-30d; <u>fever</u> , rash, mucositis, diarrhea, hepatitis, pancytopenia	- Donor T cells attack non-HLA matched recipient organs in s/o immunosuppression or 1 st degree relative donor	PPX: irradiation
Post-Transfusion Purpura (PTP) Rare (women>>men)	Sx: 3-14d; purpura, mucocutaneous bleed Dx: PLT <10,000, anti-HPA-1A	- HPA-1A neg women develop Abs to HPA-1A (common in donor PLTs)	Tx: 1 st line: IVIG 2 nd : PLEX PPX: HPA-1A negative PLTs

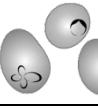
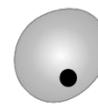
Hematology

Peripheral Smear Interpretation

GENERAL APPROACH ([NEJM 2005;353:498](#); [MGH Slide Rounds](#))

- For Cellavision access, see **Core Lab Supervisors** (G/B 539B, in Hematology lab across from the physician microscope)
- Low power (20x): scan slide for WBC distribution. Identify the “thick” edge and the “feathered” or thin edge where RBCs are just apart
- Med power (40x): examine feathered edge for rouleaux, parasites, abnormal WBC, platelet aggregation/microsatellites
- Oil Immersion (100x): assess the size, shape, and morphology of major cell lineages:
 - RBC:** examine where RBCs are close but not touching. Assess size (compare to a lymphocyte nucleus for scale), morphology (membrane irregularities, fragmentation), color (pallor, reticulocytes)
 - WBC:** examine at edges and thin end of film. Assess distribution of normal WBC, size, cytoplasm (including granules and vacuolation), and inclusions (such as Dohle bodies)
 - Plt:** assess for appropriate number (1 plt per HPF = 20K platelets in CBC), giant platelets, check for granulation

COMMON QUESTIONS ANSWERABLE BY PERIPHERAL SMEAR ([NEJM 2005;353:498](#); [Harrison's 18th Ed.](#))

RBC Lineage				
Question	Findings	Example	Clinical Significance	Next Steps
Intravascular hemolysis occurring?	Schistocytes (helmet cells, fragments, micro-spherocytes)		>1% schistocytes in HPF + absent alt diagnoses suggests TMA (Int J Lab Hematol 2012;34:107)	<ul style="list-style-type: none"> - Correlate with CBC, haptoglobin, LDH - Assess for clinical causes of TMA, valve hemolysis. Consider calculating <u>PLASMIC score</u>, Hematology c/s
Intra-erythrocytic forms present?	Ring forms in RBCs; less often, tetrad (Babesia)		84% Sn for babesiosis (Ann Rev Pub Health 1998;19:237); 65-74% Sn for malaria (Malar J 2008;7:22)	<ul style="list-style-type: none"> - Thick and thin smears for confirmation/parasite burden - Babesia, Lyme, anaplasma testing
Evidence of iron deficiency?	Hypochromic, microcytic cells; “pencil” cells		>5% hypochromic cells gold standard for functional IDA, incl in pts with active inflammation (Clin Chem 2002;48:1066)	<ul style="list-style-type: none"> - Iron studies if not yet sent - Supplementation if no contraindication
Are there rouleaux?	Linear aggregations of RBCs throughout smear (may be artifact at edges)		Sn but not Sp for MM (Arch Int Med 2002;162:1305). Reflects presence of \oplus charged proteins, incl. Ig & fibrinogen (Blood 2006;107:4205)	<ul style="list-style-type: none"> - Correlate for causes of elevated Ig/decreased albumin, incl. infection, inflammation, cirrhosis - Consider quant Ig, SPEP/UPEP. Correlate for CRAB criteria
Functional asplenia?	Howell-Jolly bodies		Sn only for severe splenic hypo-function; inversely prop to functional splenic volume (AJH 2012;87:484)	<ul style="list-style-type: none"> - Assess for causes of hyposplenism; consider vaccination & antibiotic adjustment accordingly
WBC Lineage				
Question	Findings	Example	Clinical Significance	Next Steps
Are PMNs hyper/hyposegmented?	Hyper: any 6-lobed or >3% w/ 5 lobes. Hypo: 2 lobes		Hyper: 98% Sn megaloblastic anemia, 77% Sp B12 def (Acta Haematol 1989;81:186). Hypo: 92% Sn MDS (Br J Haematol 1986;63:665)	<ul style="list-style-type: none"> - Check folate/B12, consider supplementation (hyper); MDS workup (hypo)
Are lymphocytes atypical?	Large lymphocytes, extra cytoplasm, prominent nucleoli		$\geq 10\%$ atypical lymphs \oplus LR for infectious mononucleosis (JAMA 2016;35:1502); part of RegiSCAR score for DRESS	<ul style="list-style-type: none"> - Apply to RegiSCAR scoring; consider EBV/CMV infection
Plt Lineage				
Question	Findings	Clinical Significance		Next Steps
Are giant platelets present?	Large platelets \geq size of RBC	Low MPV has OR 8.1 for thrombocytopenia d/t BM causes; giant plt more likely to indicate adequate proliferation (Clin Lab Haematol 2005;27:370)		<ul style="list-style-type: none"> - Consider peripheral causes of thrombocytopenia incl drug-induced, hemolysis, sequestration - Consider MYH9 and other hereditary plt disorders

OTHER COMMON FINDINGS AND IMPLICATIONS ([Harrison's 18th Ed.](#))

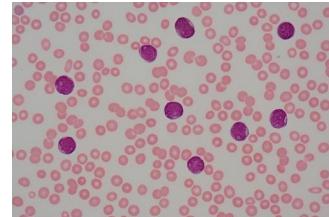
Target Cells	Acanthocytes (Spur Cells)	Echinocytes (Burr Cells)
 Membrane redundancy due to liver disease, thalassemia, HbC disease	 Irregular, dense membrane projections present in severe liver disease	 Small, uniform membrane projections present in uremia and MAHA

GENERAL ADMISSION APPROACH

- **History:** note sibling status (for donor search), and if pre/peri menopausal, obtain date of LMP, full ROS
- **Laboratory workup:**
 - **Peripheral smear:** anemia, thrombocytopenia, variable WBC, circulating **blasts**, Auer rods (*indicates myeloid origin*)
 - **Peripheral flow cytometry:** **DO NOT DELAY.** Collect in yellow top tube, then **hand-carry** to Warren 506 flow lab, inform them this is **RUSH** for New Leukemia. On Epic: Orders → Flow cytometry (not bone marrow flow); fill in clinical hx and check “Flow Cytometry CBC and differential, Special Slide Box, Leukemia Panel;” inpatient attending manages results, cc output onc
 - **Screening labs:** CBC/diff, BMP, LFTs, coags, UA, bHCG, HBV/HCV, CMV IgG, T&S
 - **DIC labs:** CBC/diff, PT/PTT/INR, fibrinogen, D-dimer (esp if concern for APML)
 - **TLS labs:** BMP, LDH, uric acid, Ca, Mg, Phos; **Cairo-Bishop criteria** = diagnosis requires 2 lab (\uparrow uric acid, \uparrow K, \uparrow Po4, \downarrow Ca) + 1 clinical (AKI, arrhythmia, seizure); see [Oncologic Emergencies](#)
- **BM Bx:** >20% blasts, flow cytometry, cytogenetics (karyotype, FISH), molecular testing (**FLT3 ITD/TKD, NPM1, IDH1/2**)
- **Studies:** EKG, CXR, TTE (prior to induction due to cardiotoxic chemotherapies), \pm **CT head** (if CNS sx)
- **Access:** double-lumen **Hickman** vs triple-lumen **PICC** in anticipation of chemotherapy. Coordinate central access with attending
- **LP \pm intrathecal chemo:** indications for LP include all ALL; AML w/ CNS or ocular symptoms; APML with systemic relapse
 - **CT or MRI before LP:** AMS, focal neurologic signs, papilledema, seizure within the last week
- **HLA-typing, HSCT work-up** (\leq 80yo): collect in 2 yellow top tubes, send to American Red Cross; siblings > parent/children as donor
 - On Epic: Orders → HLA Lab → Specimen Type: Blood → Pt: Recipient → Type: Bone Marrow/HSC → Test: Allotransplant, if HLA, to AmRedCross → if Panel-Reactive Antibody (PRA), Class I/II Ab screen
- **Utilize the Leukemia Admission Order Set:** includes Neutropenic precautions, BMT diet, PRNs, among others
 - TLS ppx: allopurinol 300mg qd | GI ppx: omeprazole 20mg qd | VZV reactivation ppx: Famvir 500mg qd | Hibiclens daily, Peridex mouthwash BID | No VTE ppx (thrombocytopenia)

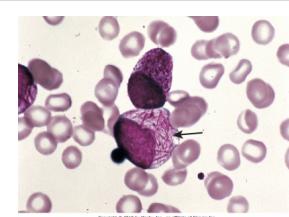
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

- Epi: bimodal. Peak incidence in 3-5yo, another peak in $>$ 45yo (68% 5y survival)
- S/Sx: pancytopenia sx, bone pain, masses (LAD, HSM, anterior mediastinal mass in T-ALL), CNS sx (CN palsy, n/v, HA), TLS, DIC
- Smear: lymphoblasts with scant cytoplasm, large nuclei containing nucleoli
- Subtypes: B-cell lymphoblastic leukemia/lymphoma (B-ALL/LBL) & T-cell ALL/LBL
- Risk stratification ([Lancet 2020;395:1146](#)):
 - B-ALL/LBL (subtyped by clinical/molecular features)
 - **Favorable:** WBC $<$ 30k, age $<$ 35; hyperdiploidy (trisomy 4, 10, or 17 most favorable), *ETV6-RUNX1*, *TCF3-PBX1*, *ERG* deletion, *DUX4*-rearrangement; rapid response to treatment ($<$ 0.01% minimal residual dz [MRD] on Day 29 BM)
 - **Unfavorable:** WBC \geq 30K, age \geq 35, hypodiploidy, *KMT2A* rearrangement, *BCR-ABL1* (Ph+), *BCR-ABL1*-like (Ph-like) ALL, *TCF3-HLF*, *MEF2D*-rearrangement, *IKZF1* deletion (esp. if w/ *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1* deletion), complex karyotype (\geq 5 chromosomal abnormalities), CNS or testicular involvement; slow tx response ($>$ 0.01% MRD on Day 29 BM)
- Treatment ([NEJM 2006;354:166](#); [JCO 2011;29:532](#)):
 - **General:** no single best regimen, many (e.g. CALGB 10403, R-Hyper-CVAD, BFM). Involves 1) induction, 2) consolidation (multiple rounds), 3) intensification (if needed), 4) CNS therapy (if needed), 5) maintenance, 6) allo-HSCT (high risk disease)
 - If pt is AYA (age 15-39), pediatric-inspired regimen often used (usually incorporating asparaginase)
 - If *BCR-ABL1*-positive, TKI is used in conjunction w/ chemotherapy (e.g. R-HyperCVAD plus dasatinib)
 - If elderly, low-intensity or chemotherapy-free regimens often used (e.g. dasatinib + blinatumomab; [NEJM 2020;383:1613](#))
 - **CNS ppx:** **intrathecal** MTX/cytarabine vs **systemic** high-dose MTX w/ leucovorin rescue
 - **Maintenance:** weekly **MTX/6-MP** + monthly **Vinc/Pred** x2-3y; **better prognosis** if young, WBC $<$ 30K, early CR
 - For relapsed/refractory B-ALL, **blinatumomab** (CD19 BiTE), **inotuzumab ozogamicin** (CD22 ADC), **CD19 CAR-T** cell therapy



ACUTE PROMYELOCYTIC LEUKEMIA (APML)

- Subtype of AML with distinct biology and excellent prognosis ([NEJM 2013;369:111](#))
- S/Sx: pancytopenia sx (fatigue, anemia, ecchymoses, infxn). High risk for DIC and bleeding
- Smear: **atypical promyelocytes** (large, “dirty” granular, bilobed nuclei, **+Auer rods**)
- Cytogenetics: **t(15;17) \rightarrow PML-RAR α (>97%),** rarely t(11;17), t(5;17)
- Treatment: **EARLY Tx w/ ATRA CRITICAL** given high early mortality 2/2 to coagulopathy; **start ATRA** if even mild suspicion for APL as there is **low drug toxicity** and **high mortality** with delay
 - **Induction:** If low risk (WBC \leq 10K): ATRA (all-trans retinoic acid) + ATO (arsenic trioxide) ([JCO 2017;35:583](#)). If high risk (WBC $>$ 10K): ATRA + idarubicin or daunarubicin/cytarabine
 - **Consolidation:** ATRA + (daunorubicin vs ATO, may depend on induction therapy) \rightarrow check for remission; goal **molecular complete remission** (absence of PML-RAR α on RT-PCR)
- Complications of ATRA therapy:
 - **Differentiation syndrome:** SIRS, hypoxemia, edema, pulmonary infiltrates, AKI \rightarrow high-dose steroids (dexamethasone 10mg q12h), consider temporary cessation of ATRA
 - **Hyperleukocytosis:** see [Oncologic Emergencies](#)
 - **Idiopathic intracranial hypertension:** HA, vision loss, papilledema \rightarrow hold ATRA, pain control \pm steroids/acetazolamide



Oncology

Acute Leukemia

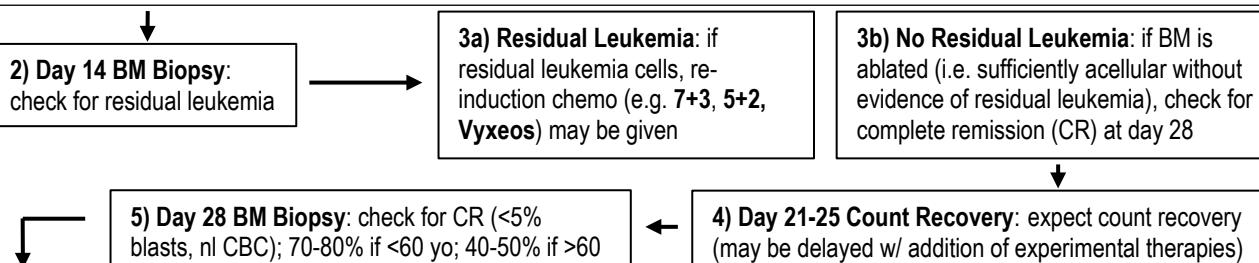
ACUTE MYELOID LEUKEMIA (AML)

- Pathophysiology: clonal disorder of the hematopoietic system w/ infiltration of BM, blood, & other tissues. Significant heterogeneity in underlying cytogenetic and molecular abnormalities (see table to right)
- Epi: most common leukemia in adults (80%). Median age at dx: 68yo
- S/Sx: **pancytopenia** (fatigue, petechiae, ecchymoses, infxn), myeloid sarcoma, **leukemia cutis** (non-tender red/brown papules/nodules), **neutrophilic dermatosis** (i.e. Sweet syndrome: tender red/violet papules/plaques), gingival hypertrophy (due to leuk. infiltration), joint swelling (leuk. infiltration, gout), **leukostasis** (AML > ALL; typically WBC >50-100K; SOB, HA, blurry vision, stroke; spurious ↑K (check ABG); falsely low PaO₂ (check pulse Ox) (see [Onc Emergencies](#))
- Dx: >20% blasts in BM or characteristic translocation (e.g. t(8;21)) or myeloid sarcoma
- Complications (see [Onc Emergencies](#) for 2-4): (1) **DIC** (if present, strong suspicion for APL); (2) **febrile neutropenia**; (3) **TLS** → allopurinol, IVF, consider rasburicase if uric acid >10; (4) **leukostasis** → hydroxyurea, IVF, consider leukapheresis, avoid transfusion
- Subtypes: t-AML (therapy-related from chemo, radiation), s-AML (secondary from preceding heme disorder, e.g. MDS, MPN, PNH)
- Risk stratification: based on cytogenetics, mutations, performance status ([Kamofsky/ECOG](#))
- Tx: intensive (see below, per [NEJM 2009;361:1249](#)) vs non-intensive (azacitidine + venetoclax; [NEJM 2020;383:617](#))

Risk Category	Genetic Abnormality (NCCN 2019 AML Guidelines)
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Biallelic mutated CEBPA Mutated NPM1 without FLT3-ITD or with FLT3-ITD ^{low}
Intermediate	Mutated NPM1 and FLT3-ITD ^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD ^{low} (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); MLL3-KMT2A Cytogen. abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Wild-type NPM1 and FLT3-ITD ^{high} Mutated RUNX1; Mutated ASXL1; Mutated TP53

1) Day 1 Induction Chemotherapy: standard regimen for “medically fit” pts: “7+3”, cytarabine continuous infusion x7d + ida/daunorubicin (bolus/short infusion) on Days 1-3. Regimen will kill leukemia & healthy BM cells but will not ablate the marrow. Additional/alternative targeted agents for pts with certain cytogenetic abnormalities:

- Midostaurin (tyrosine kinase inhibitor) added to 7+3 in AML with *FLT3* mutations ([NEJM 2017;377:454](#))
- Liposomal cytarabine/daunorubicin (Vyxeos): ↑ survival in t-AML & MDS-related AML ([JCO 2018;36:2684](#))
- Gemtuzumab ozogamicin added to 7+3 in CD33-positive AML ([Blood 2017;130:2373](#))



6) Consolidation Therapy: initiated soon after remission. Goal to eradicate residual disease & sustain lasting remission. Options include chemo or allo-HSCT. In general, allo-HSCT preferred in higher-risk disease if pt able to tolerate. Chemo in lower-risk disease & in pts who are not allo-HSCT candidates. **Risk stratification determines management (see table above)** ([Blood 2017;129:424](#)):

Favorable risk: **HiDAC (high dose AraC)** x3-4 cycles vs standard dose AraC

Intermediate risk: chemo vs allo-HSCT

Unfavorable risk: **allo-HSCT** vs clinical trial

Older pts with high-risk dz can be treated with intermed-dose cytarabine or hydroxyurea

Maintenance: oral azacitidine (CC-486) can be considered if CR & no HSCT ([NEJM 2020;383:2526](#))

- Relapsed/refractory AML treatment:** *IDH1* mut - Ivosidenib | *IDH2* mut - Enasidenib | *FLT3* mut – Gilteritinib | Chemotherapy (e.g. 7+3 (esp. if earlier durable response), HiDAC, mitoxantrone + etoposide) | if eligible, allo-HSCT, even if it is second HSCT

Oncology

Lymphadenopathy & Lymphoma

EVALUATION OF LYMPHADENOPATHY (AFP 2016;94:896)

- Generalized LAD DDx: HIV, EBV, mycobacteria, SLE, medications (e.g. phenytoin), sarcoid, lymphoma/malignancy
- Localized LAD DDx: cervical (EBV, CMV, toxo, TB, lymphoma), supraclav (malignancy), axillary (infxn, breast CA), inguinal (STDs)
- Hx: exposures, travel, meds, B Sx (fevers, drenching night sweats, >10% unintentional wt loss in 6mo), other s/sx of infxn or malig
- Exam: localization (think about area of nodal drainage), size (abnormal >1cm), consistency, fixation, tenderness (inflammation)
- Labs: CBC/diff, HIV (RNA if acute), LDH, HBV/HCV, PPD/TSpot, syphilis, ANA, heterophile Ab; consider HTLV & EBV serologies
- Imaging: CT C/A/P (+), PET (can define node size and distribution, more helpful for monitoring of disease treatment/progression)
- Biopsy: consider if large (>2cm), persistent 4-6w, or increased size, w/ immunophenotyping & cytogenetics. Empiric tx may decrease yield of biopsy! Excisional (cells & nodal architecture) > core needle (tissue for molecular studies) > FNA (high false neg)

LYMPHOMA

Lymphoma Staging: for Hodgkin lymphoma (HL), add "B" if presence of B symptoms

Stage I: ≥1 LN in a single LN group, or single extralymphatic organ

Stage II: ≥2 LN groups on same side of diaphragm

Stage III: LN groups above and below diaphragm

Stage IV: disseminated ≥1 extralymphatic organs

Workup: BM biopsy, PET (except in HL stage IA/IIA w/ favorable features, CLL by flow cytometry), labs above, HBV serologies if rituximab

Hodgkin Lymphoma: Reed-Sternberg cells (CD15+ CD30+ CD20-) in inflammatory milieu; bimodal age distribution ([Lancet 2012;380:836](#))

- WHO classification (classical HL, separate from NLPHL):
 - Nodular Sclerosis (70%): mediastinal mass, good prognosis
 - Mixed Cellularity (25%): periph LAD, HIV/EBV, poor resource areas
 - Lymphocyte Rich (5%): periph LAD, good prognosis
 - Lymphocyte Depleted (<1%): worst prognosis (late stage at presentation)
- Treatment: note risk of late effects – cardiotox, 2° malignancy, pulm tox
 - Stage I-II: ABVD + XRT (curative intent)
 - Stage III-IV: ABVD x6 cycles vs escalated BEACOPP ± XRT
 - Up-front PD1 blockade or BV ([Blood 2021;137:1318](#), [NEJM 2018;378:331](#))
 - Relapsed/refractory: salvage chemo + autoSCT; brentuximab vedotin; PD1 inhibitor ([JCO 2018;36:1428](#)); CD30 CAR-T ([JCO 2020;38:3794](#))

Hodgkin Lymphoma International Prognostic Score (IPS)		
1 point per factor (JCO 2012;30:3383)		
Age >45	Points	5y PFS
Male	0	88%
Stage IV	1	84%
Albumin <4	2	80%
Hb <10.5	3	74%
WBC ≥15,000	4	67%
Lymphocytes <600 or <8%	≥5	62%

Non-Hodgkin Lymphoma (NHL): a/w immunosupp. (HIV, txp), autoimm. dz, infection (H. pylori, HCV, HTLV1, EBV) ([Lancet 2012;380:848](#))

- Indolent:** incurable, but better prognosis, **follicular lymphoma international prognostic index (FLIPI)** ([Blood 2004;104:1258](#))
- Aggressive:** higher chance of cure, but worse prognosis, **revised international prognostic index (IPI)** ([Blood 2007;109:1857](#))

Diagnosis	Age	Prevalence	Clinical Features	Treatment
DLBCL	70	25-35%	Aggressive, rapid growth, nodal/extranodal BCL2, BCL6, or MYC translocation common *Double-hit lymphoma (DHL): more aggressive subtype w/ both MYC and either BCL2 or BCL6 translocations	- Stage I-II: R-CHOP + RT - Stage III-IV: R-CHOP, if relapsed/refractory, salvage R-ICE then, if response, autoSCT; or CD19 CAR-T; R-mini-CHOP if old/frail *DHL treated with aggressive tx similar to Burkitt (i.e. R-EPOCH, R-hyperCVAD, R-CODOX-M/IVAC) - Experimental tx adding drugs to R-CHOP failed in phase III RCTs
Follicular	60	20-25%	Indolent, painless LAD t(14;18) BCL2+	- Stage I/contiguous II: RT preferred - Stage II-IV: anti-CD20 ± bendamustine, lenalidomide, CHOP, or CVP (in III-IV observe to progression first)
SLL/CLL	65	<5%	Often indolent, painless LAD, IgM M-protein No risk of leukostasis unless WBC >400k Staging: Rai/Binet , IGHV (unmutated = HR), ZAP70 (+ = HR), CD38 (+ = HR), FISH (del17p = HR), genetics (TP53 mut. = HR)	- Treat when "active" (Blood 2018;131:2745), i.e. cytopenia, bulky dz, progressive lymphocytosis w/ increase >50% over 2mo, autoimmune dz (AIHA, ITP), significant constitutional sx - Regimens (evolving): ibrutinib ± rituximab or obinutuzumab, venetoclax (± BTKi, CD20 Abs, others), other BTKi, FCR, BR
Mantle Cell	60-70s	<5%	Aggressive, splenomegaly t(11;14) cyclin D1+	- Stage I/non-bulk II: BR, VR-CAP, R-CHOP, or LR + R maint - Stage II-IV: RDHA and platinum, R-CHOP/R-DHAP, NORDIC regimen or HyperCVAD + autoSCT w/ R maint, CD19 CAR-T
MALT	65	<5%	Good prognosis , mucosal sites (GI) associated with H. pylori	- Gastric: quad therapy if H. Pylori+ - Non-gastric: similar to follicular
Splenic MZL	70s	<5%	Indolent, splenomegaly associated with HCV	- HCV treatment can lead to regression - If HCV negative, tx with R (preferred) or splenectomy
Adult Burkitt	45	<1%	Aggressive, rapidly growing, extranodal sites (jaw-African, abdomen-American) t(8;14), cMYC+, a/w EBV & HIV	- R-CODOX-M/IVAC, R-EPOCH or R-HyperCVAD - Diff doses for low (single site, <10cm, nl LDH) vs high risk

ABVD = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine

BEACOPP = Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone

CHOP = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

CODOX-M/IVAC = Cyclophosphamide, Vincristine, Doxorubicin, HD-Methotrexate, Ifosfamide, Etoposide, HD-Cytarabine

BR = Bendamustine, Rituximab, LR = Lenalidomide, Rituximab

CVP = Cyclophosphamide, Vincristine, Prednisolone

EPOCH = Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin

HyperCVAD = Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, alternated w/ methotrexate + cytarabine, followed by maintenance POMP

VR-CAP = Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone

RDHA and platinum = Rituximab, Dexamethasone, Cytarabine and Carboplatin, Cisplatin, or Oxaliplatin

NORDIC regimen = dose-intensified Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (maxi-CHOP) alternating with Rituximab + high dose Cytarabine

Oncology

Plasma Cell Disorders

EVALUATION OF PLASMA CELL DISORDERS ([AFP 2005;71:105](#); [Leukemia 2009;23:215](#))

Evaluation		Utility	When to Send
Ig Levels	Quantify Ig levels in blood: IgG, IgM, IgA, IgD, IgE. Will not discern monoclonal vs polyclonal	If suspect a 1° (e.g. B cell deficiency) or 2° humoral immunodeficiency (e.g. immunosupp., marrow crowding)	
SPEP	Detect/quantify M-protein (monoclonal protein, paraprotein; typically, immunoglobulin from an abnormally expanded B/plasma cell = monoclonal gammopathy). Appears as "M-spike"		
Serum IF	Identify the type of M-protein (intact Ig [G, M, A, D, E], light chain only [LC: κ or λ], or heavy chain only [HC])		
SFLC Assay	Sn > IF for identifying abnormal LC abundance (i.e. outside normal κ/λ ratio of 0.26-1.65). Normal ratio w/: ↓LC = immunosupp./def., ↑LC = infxn/inflammation (i.e. polyclonal activation; includes some autoimm dz), or ↓LC renal clearance**		
UPEP	Detect/quantify Bence Jones Protein (BJP) (= urine monoclonal protein, typically κ or λ LC). Dipstick will miss BJP	After serum M-protein confirmed, to assess for nephrotoxic FLC/BJP. Use 24h urine to quantify	
Urine IF	Identify the type of BJP (κ or λ)	If UPEP positive for BJP	

Ig = immunoglobulin = antibody ≈ gammaglobulin (i.e in the gamma region on an electrophoresis gel; thus, "gammopathy")

**ESRD can ↑ serum LCs and skew ratio up to 3. Get UPEP + urine IF to rule out urine Bence Jones Protein

Note, some therapeutic antibodies may show up in above assays as false positives (e.g. daratumumab)

CLASSIFYING PLASMA CELL DISORDERS ([Lancet Oncol 2014;15:e358](#))

CRAB criteria: Ca⁺⁺ (>11mg/dL), Renal dz (Cr >2), Anemia (Hgb <10), Bone lesions (≥1 focal lesion on survey, CT, or PET)

All those with **M-protein** ≥1.5g/dL, **IgA M-protein** of any size, **abnormal SFLC assay**, or **CRAB** need **BM biopsy**

	MGUS	Smoldering MM	Multiple Myeloma (MM)	Waldenström (WM)	AL Amyloidosis
BM Involvement (%)	<10	10-60	≥10 (or plasmacytoma)	≥10	<10
Serum M-protein (g/dL)	<3	≥3 [<u>IgG</u> or <u>IgA</u>]	Present	Present (<u>IgM</u>)	<3
Clinical Signs	Absent	Absent	CRAB	LAD/HSM or hyperviscosity	Present

- Monoclonal Gammopathy of Undetermined Significance (MGUS):** premalignant clonal plasma or lymphoplasmacytic cells. ↑ w/ age (50+: 3%, 85+: 7.5%). Classified as non-IgM, IgM, or LC. IgG>M>A>D. κ>λ. BJP in 20%. Risk of prog to MM (or AL amyloid, LC deposition dz [LCDD], other lymphoproliferative dx). WM risk if IgM. ↑MM risk if IgD. Abnl SFLC ratio predicts prog to MM (~1%/y)
- Smoldering MM:** prog to MM ~10%/y for first 5y. If high risk by Mayo 20-2-20 rule ([BCJ 2018;8:59](#)), may consider tx (e.g. Rd)
- MM:** ≥10% BM clonal cells & CRAB. If ≥60% BM or SFLC ratio ≥100 or >1 bone lesion (on MRI), meets criteria even w/o CRAB
- Smoldering WM:** IgM MGUS ≥3g/dL or ≥10% BM but no sx (see below). Monitor for dz progression, no tx
- WM:** lymphoplasmacytic lymphoma in BM, IgM MGUS. Sx: LAD/HSM, hyperviscosity (IgM = large pentamer; HA, vertigo, vision Δ), anemia. "Bing-Neel" = CNS LPL. Measure viscosity (>4 CP = sx). Tx: anti-CD20, BTKi, etc. Can tx hyperviscosity w/ plasmapheresis
- AL amyloid:** S/Sx: cardiomyopathy, purpura, nephrotic syndrome, neuropathy, orthostasis, HSM, macroglossia. Congo-red stain (apple-green birefringence) on pathology
- Monoclonal Gammopathy of Renal Significance (MGRS):** collection of disorders leading to kidney disease, including light chain & heavy chain deposition disease, proliferative GN with monoclonal immunoglobulin deposits (PGNMID), C3 glomerulopathy, others
- POEMS syndrome:** (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes), a/w ↑VEGF, sclerotic bone lesions, & Castleman's disease. Polyneuropathy & MGUS required for dx. Endocrinopathy: hypo-gonad, -thyroid, etc.

MULTIPLE MYELOMA WORKUP AND MANAGEMENT ([Nat Rev Dis Primers 2017;3:17046](#); [NCCN 2020 MM Guidelines](#))

- Lab findings/workup:** ↓AG ratio, ↑globulin, ↑ESR, peripheral smear (rouleaux RBCs), ↑LDH, ↑β2M, SPEP/IF/SFLC, whole body low-dose CT ± PET (↑Sn than skel. survey), BMBx (IHC, flow, cytogenetics/FISH, Snapshot). 10% w/ concurrent AL amyloid
- Risk stratification:** by age, performance status, comorbidities, [R-ISS staging](#) (incorporates cytogenetics/FISH, LDH, β2M, albumin). High risk features: t(4;14), t(14;16), t(14;20), amp1q, **del17p**, extramedullary dz, circulating PC. ≥2 HR FISH = "double hit" (ultra HR)
- Treatment agents:** most common induction regimens combine a proteasome inhibitor, immunomodulator, & steroids/chemo:
 - Proteasome inhibitors: bortezomib (Velcade – V, Bor), carfilzomib (Cz, K), ixazomib (Ix)
 - Immunomodulatory agents (IMiDs): lenalidomide (Revlimid – R), pomalidomide (Pom), thalidomide (T)
 - Steroids/chemo: dexamethasone (low dose = d), prednisone (P), melphalan (M), cyclophosphamide (Cy), doxorubicin (dox)
 - Monoclonal Abs: anti-CD38 daratumumab (Dara; [NEJM 2019;380:2104](#)) & isatuximab (Isa); elotuzumab (Elo)
- Induction & consolidation:** NOT curative. Standard risk median OS approaching 10y. High risk median OS ~3y
 - Induction: triple w/ VRD most common; CyBorD if renal failure at diagnosis; DaraRd if older/frail; quad (DaraKRd) if high risk
 - If candidate for autologous SCT, usually performed early, but can delay until relapse w/o detriment in OS ([NEJM 2017;376:1311](#))
 - Maintenance (e.g. R or V) following SCT, or after induction if no SCT. A/w ↑OS ([JCO 2017;35:3279](#)), but ↑2° cancers
- Response criteria:** ↑depth a/w better outcomes: partial resp. (↓M-protein 50-90%); very good partial resp. (↓M-protein >90%); complete response (no M-protein, <5% BM PC); minimal residual disease negative (<1 PC in 10⁵ cells on flow or VDJ sequencing)
- Relapsed/refractory MM:** mix-match combos, salvage auto-SCT, **BCMA-directed CAR-T/ADC/BiTTEs**, venetoclax if t(11;14), others
- Other Tx:** aimed at reducing skeletal lesions/fractures (bisphosphonates, denosumab, XRT), hyperCa⁺⁺, renal damage, hyperviscosity, infection (PCP, HSV, fungal, VZV; depending on therapy), VTE (aspirin vs AC for IMiD-induced thrombotic risk), anemia (EPO)

Oncology

MDS & MPN

MYELODYSPLASTIC SYNDROME (MDS): clonal stem cell mutation → ineffective/dysmorphic hematopoiesis → risk of AML

- Presentation: median age 65-75, s/sx of unexplained cytopenias (~90% anemia). A/w autoimmune diseases
- RF: male, exposure (benzene, tobacco), chemotherapy-related, XRT, genetic (Down, Li-Fraumeni, Diamond-Blackfan)
- DDx: myelofibrosis (MF), aplastic anemia, PNH, CHIP, AML, MP/MPN syndromes, other causes for cytopenias (infxn, meds/toxins)
- Diagnosis: cytopenias, dysplasia >10% of nucleated cells in at least one lineage, <20% blasts, cytogenetics. [WHO classification](#)
 - Initial eval: CBC/diff, retics, smear, BM Bx w/ iron stain and cytogenetics, Epo, Fe studies, folate/B12, TSH, LDH, HIV/EBV/CMV, molecular/genetic testing for somatic mutations and hereditary predisposition. Consider flow for PNH/LGL
- Prognosis: based on [IPSS-R](#); median survival ranges from 0.7y in “very high” risk, to 8.8y in “very low” risk
 - IPSS-R is based on blast %, cytogenetics, cytopenias. Correlates w/ survival & progression to AML
- Treatment: based on IPSS-R, performance status & age; see [NCCN 2021 MDS Guideline](#)
 - Low/intermediate risk: supportive care. Consider Epo, ATG ± CyA, G-CSF, hypomethylating agents (azacitidine/decitabine). In selected patients, alloHSCT. Luspatercept for ringed sideroblastic-lower risk patients ([NEJM 2020;382:140](#))
 - Intermediate/high risk: if transplant candidate, alloHCT ± induction chemotherapy. If not, azacitidine or decitabine
 - Special variants: del(5q) = lenalidomide; hypoplastic MDS with PNH+ cells, HLA-DR15 or age <60 = ATG + cyclosporine

OTHER MYELOID DISORDERS:

- **Clonal Hematopoiesis (CH) of Undetermined Potential (CHIP)**: risk factor for MDS and other malignancies, variant allele frequency (VAF) ≥2% of leukemia-associated gene, normal peripheral counts, rate of progression to AML 0.5-1%/y, blasts on BM Bx <5%
- **Clonal Cytopenia of Unknown Significance (CCUS)**: unexplained cytopenia, CH w/ ≥2 %VAF of leukemia-associated gene
- **Idiopathic Cytopenia of Unknown Significance (ICUS)**: unexplained cytopenia, no CH; if leukemia-associated gene, VAF <2%

MYELOPROLIFERATIVE NEOPLASM (MPN): clonal expansion, ≥1 myeloid lineage (commonly involves JAK-STAT activation)

Most common: CML, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF). Sequelae vary depending on lineage; PV/ET can lead to 2° MF; all can transform to AML; all can cause vWF syndrome. Goals of Tx: improve sx, prevent thrombosis, prevent transformation to AML; only curative therapy is allo-HCT ([NCCN 2020 MPN Guideline](#); [NCCN 2021 CML Guideline](#))

	PV (↑Hgb ↑WBC ↑Plt)	ET (↑Plt)	Primary MF (↓Hgb ↓WBC ↓Plt)	CML (↓Hgb ↑WBC ↑Plt)
Sx	<u>Hyperviscosity</u> (HA, dizziness, Δ vision, abd pain, ruddy complexion), <u>thrombosis</u> (VTE, stroke, Budd-Chiari), aquagenic pruritus, erythromelalgia	Up to 50% asx at dx. Similar to PV (erythromelalgia), <u>bleeding</u> (acquired vWF syndrome, consider if plt >1 million)	Fatigue, night sweats, weight loss, abd pain, satiety, <u>HSM</u> , anemia, thrombotic & hemorrhagic events	Often asymptomatic; fatigue, night sweats, bleeding, abd pain, weight loss, <u>splenomegaly</u> (most common physical exam finding)
Dx	Major WHO criteria: <ul style="list-style-type: none"> - Hgb >16.5 (♂), Hgb >16 (♀) - BMBx: trilineage proliferation - <u>Mutations</u>: JAK2 V617F Minor WHO criteria: <ul style="list-style-type: none"> - Low Epo (below reference) <u>Note</u> : considerable overlap for PV, ET, & MF on BMBx	Major WHO criteria: <ul style="list-style-type: none"> - PLT >450k - BMBx: megakaryocytes w hyperlobulated nuclei <u>Mutations</u> : JAK2 (60-65%) > CALR > MPL Minor WHO criteria: <ul style="list-style-type: none"> - Other clonal markers 	Major WHO criteria: <ul style="list-style-type: none"> - BMBx: “dry” tap showing reticulin or collagen fibrosis - <u>Mutations</u>: JAK2 50%, CALR 40%, MPL 5% Minor WHO criteria: <ul style="list-style-type: none"> - Leukoerythroblastic smear, ↑LDH, anemia, splenomegaly 	Mutation : BCR-ABL (by FISH, RT-PCR) CBC w/ ↑granulocytes of all maturities, basophilia, eos. <u>Can be in chronic, accelerated (10-20% blasts), or blast phase (>20% blasts)</u> . Blast phase can convert to AML (80%) or ALL
Tx	All : phlebotomy (goal HCT <45), ASA 81 (if no bleeding), allopurinol, antihistamine If >60, ↑risk thrombosis : HU > interferon-α, 2 nd line: ruxolitinib (JAK2-inhib)	All : ASA 81 (unless vWF syndrome). If age>60 or ↑risk thrombosis : HU > interferon-α > anagrelide (PDE inhib, ↓plt prod.) (NEJM 2005;353:33)	Allo-HSCT (only cure), transfusion, hydroxyurea (HU), ruxolitinib (primarily symptom reduction) (NEJM 2012;366:787)	Chronic phase : BCR-ABL inhibitors: imatinib, nilotinib, dasatinib. Consider allo-HSCT if tx resistant Acute/blast phase : Manage as AML/ALL
DDx	↑Epo: hypoxia-induced (heart/lung dz, carboxy-Hb, smoking) vs Epo-producing tumor (rare). ↓Epo: activating Epo receptor mutation (rare)	Infection, inflammation, iron deficiency, splenectomy, neoplasm	Other MPNs (especially ET); MDS; hairy cell leukemia; other marrow-infiltrating malignancies	Leukemoid rxn (↑LAP), drugs (steroids, GCSF, ATRA), infxn (C. diff, EBV), severe hemorrhage, splenectomy, DKA, organ necrosis

MDS/MPN SYNDROMES/TYPES:

- **Chronic myelomonocytic leukemia (CMML)**: MDS/MPN overlap syndrome w/ moncytosis >1000 & splenomegaly, <20% blasts, dysplasia involving at least one myeloid lineage
- **Systemic mastocytosis**: see [Mast Cell Disorders](#)
- **Hypereosinophilic syndrome**: see [Eosinophilia](#)
- **Hemophagocytic lymphohistiocytosis (HLH)**: “cytokine storm” syndrome, 1° or 2° (infectious, inflammatory, neoplastic – esp. lymphoma); Dx: pathologic mutation or 5+: fever, cytopenia, splenomegaly, ↑TG, ↑ferritin, ↓NK cells, ↑CD25, hemophagocytosis in BM/Spleen/LNs. H-score for prob. Sx: fever, HSM, rash, sepsis; Tx: depends on etiology. HLH-94 protocol (dexamethasone/etoposide, then Cyclosporine A ± IT MTX if CNS involvement), survival ~2mo w/o therapy. Also see [Pancytopenia & Anemia](#)

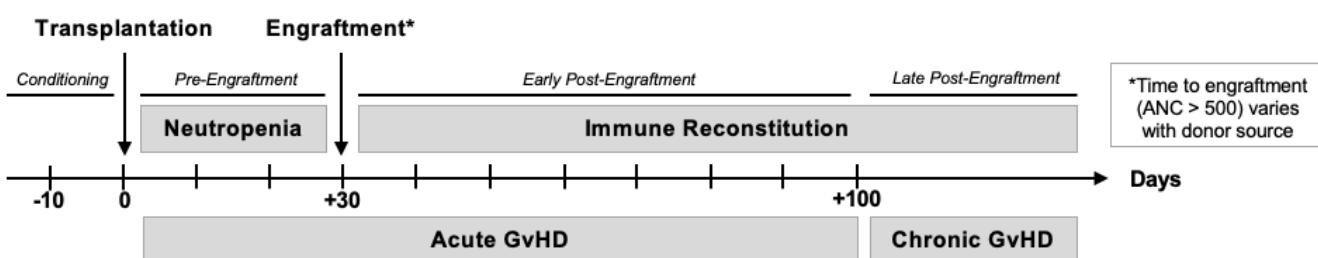
Oncology

Stem Cell Transplantation

TYPES OF TRANSPLANT

		Allogeneic Transplant	Autologous Transplant
Definition	Transplant of non-self (+donor) stem cells	Transplant of self (patient) stem cells	
Goals	Reconstitute hematopoiesis after ↑ dose chemo and graft-versus-tumor (GVT) effect to kill ↑ risk disease or treat profound marrow failure. Always curative intent		Reconstitute hematopoiesis after ↑ dose chemo to kill all cells in BM (tumor/nl). Intent mostly curative except for MM (prolong remission)
Indications	↑ risk AML (40-60% 5YS), ALL (40-50% 5YS), MDS (45% 5YS), ↑ risk myelofibrosis , TKI-resistant CML , indolent relapsed lymphomas , aplastic anemia , thalassemia, sickle cell dz, primary immunodeficiency (SCID), inborn errors of metab.		1 st relapsed lymphomas (40-50% 5YS), MM (35% 5YS); relapsed Waldenström , AL amyloidosis , select solid tumors (germ cell, neuroblastoma, Ewing sarcoma), autoimmune dz (MS, SS, Crohns, SLE)
Source of cells	Predominantly peripheral blood stem cells (PBSC), some use BM . Umbilical cord blood (CB) also used		Usually PBSC – less invasive, more rapid engraftment than BM
Time to engraftment	14-28 days (time for CB > BM > PBSC)		10-14 days
Graft-versus-host disease (GVHD)	Yes , skin, liver, GI most commonly affected. Acute (w/in 6mo, peri-transplant mortality) Chronic (>3mo, morbidity/mortality mo/years later)		Rare “GVHD-like” syndrome occurs in ~0.5% of autologous transplants (BMT 2020;55:1879)
Graft-versus-tumor (GVT) effect	Yes (<i>therapeutic mechanism</i> – goal for donor T cells to engraft and attack host tumor cells)		Likely no, but mechanism via CD8+ T cells under investigation (JCI 2019;129:48)
Immunosuppression	Yes (sometimes for 1-2y)		No

ALLOGENEIC STEM CELL TRANSPLANT ([NEJM 2006;354:1813](#))



- **Donor types:** matched to pt by HLA typing to **minimize GVHD**; matching at alleles A, B, C, DR, DQ
 - **Matched-related donor (MRD):** preferred, compatible siblings, matched at 10/10 HLA alleles
 - **Matched-unrelated donor (MUD):** common, NMDP database, matched at 8-9/10 HLA alleles
 - **Haploidentical:** any parent/sib/child (~universal), match at 5/10 HLA alleles, ↑ GVT via NK cells ([Front Immun 2020;11:191](#))

Stem Cell Source	Collection	Engraft	GVHD Risk	Notes
Bone marrow (BM)	Aspirated from iliac crest	18-21d	Reference	No longer favored despite lower cGvHD risk, due to higher graft failure rate than PBSC
Peripheral blood stem cells (PBSC)	Mobilization and peripheral apheresis	12-15d	Higher risk	Preferred source due to faster engraftment (Cochrane Rev 2014)
Cord blood (CB) (Blood 2013;122:491)	Immature SC from umbilical cord at delivery	28d (variable)	Lower risk	↑txp-mortality compared to MUD (similar DFS/OS); allows for more HLA disparity

- **Conditioning regimens** ([Blood 2014;124:344](#)): determined by underlying condition, disease status, performance status
 - **Myeloablative conditioning:** complete disease eradication & ablation of host BM/immune cells
 - Used for young healthy patients, in remission or with measurable residual disease (MRD) ([JCO 2020;38:1273](#))
 - ↑ toxicity, ↑ immunosuppr, ↑ txp-mortality, ↓ relapse
 - **Reduced intensity conditioning (RIC):** tumor debulking & allow engraftment
 - Permits transplant in elderly w/ co-morbidities; ↓ toxicity, ↓ txp-mortality, ↑ relapse ([JCO 2017;35:1154](#))
 - Agents: chemo (ex. alkylating agents - busulfan, cyclophosphamide, melphalan) ± total body irradiation

TERMINOLOGY

- One-liners include: underlying diagnosis; **autologous vs allogeneic** transplant; **day since transplant** (transplant = d0, day before = d-1, day after = d+1); **conditioning regimen** (myeloablative vs RIC/non-myeloablative); **donor type** (MRD, MUD, haploidentical) & **source** (BM, PBSC, CB); **GVHD prophylaxis** regimen
- Example one-liner: “35M w/ AML (FLT3-mutated) who is now day +4 from his **myeloablative** (Bu/Cy) matched related donor (**MRD**) peripheral blood stem-cell transplant (**PBSCT**) with tacrolimus/methotrexate GVHD prophylaxis (day 0 = 1/1/21).”

Oncology

Stem Cell Transplantation

INFECTIOUS COMPLICATIONS: 2/2 chemo-related pancytopenia & immunosuppression (ASBMT/IDSA: [BBMT 2009;15:1143](#))

	Day 0-30 Pre-Engraftment	Day 30-100 Early Post-Engraftment	Day 100+ Late Post-Engraftment
Immune Defect	Neutropenic, mucositis, lines Acute GVHD	Poor cellular immunity Acute GVHD	Poor cellular and humoral immunity Chronic GVHD
Bacterial	GPCs & GNRs (F&N) Neutropenic enterocolitis (typhlitis)	GPCs & GNRs	Encapsulated bacteria (SHiN) Nocardia
Viral	Resp/enteral (adeno, flu, RSV, paraflu), HSV	Resp/enteral (adeno, flu, RSV, paraflu), EBV (risk of PTLD), CMV, HHV6 (screen for in CB tx)	Resp/enteral (adeno, flu, RSV, paraflu), EBV (PTLD), VZV, BK (hemorrhagic cystitis), JC (PML)
Fungal	Aspergillus, candida	Aspergillus, candida, PJP	Aspergillus, PJP
Parasitic	-	Toxo	Toxo (can <u>mimic</u> PJP PNA)

- **Neutropenic enterocolitis (typhlitis):** polymicrobial infxn leading to necrotizing enterocolitis, most often involving cecum
 - S/Sx: fever, ANC <500, abdominal pain (often RLQ), n/v, watery/bloody diarrhea
 - Micro: polymicrobial (GPC/GNR/anaerobes/fungal), clostridium septicum a/w fulminant course & high mortality rate
 - Dx: CT (I+/O+) w/ bowel wall thickening, mesenteric stranding, bowel dilatation, mucosal enhancement, pneumatoasis
 - Tx: pip/tazo vs -penem vs ceftazidime/MNZ + **surgery c/s** + add fungal coverage if persistently febrile >72h
- **Infectious PPX:** items with asterisks (*) have well-established benefit and are employed at all institutions
 - **Bacterial:** cipro 500mg BID or levofloxacin 500mg qd (Day -1 to ANC >500)
 - **Viral (HSV/VZV)*:** acyclovir 400mg BID or famciclovir 500mg qd (Day -1 to +365 [auto]; 1y min & until off IS [allo])
 - **CMV:** ivermectin 480mg QD (dose-reduced w/ cyclosporine) used in CMV-seropositive recipients (Day +7 to +100)
 - Alternative: monitor weekly CMV VL (from day -1 to +100), with pre-emptive therapy for CMV viremia with IV ganciclovir or PO valganciclovir
 - **Fungal***: fluconazole 400mg QD, voriconazole 200mg BID, posaconazole 200mg TID (Day -1 to ANC>500 [auto] or 3-6mo [allo])
 - **PCP/Toxo*:** Bactrim SS QD (start after engraftment as outpatient for 6mo [auto], >1y or off IS [allo])

GRAFT VERSUS HOST DISEASE

- **Acute GVHD:** ~40% in MRD, ~60% in MUD (cellular immune response, T_H1 cell-mediated) ([NEJM 2017;377:2167](#))
 - Risk factors: ↑HLA mismatch, ↑age, female donor/male recipient, TBI-myeloablation, PBSC > BM > CB
 - Cause: donor T cell recognizes and attacks recipient native cells (usually **day 0 to +100**, but can be later)
 - S/Sx: skin (rash, graded by biopsy findings, % body surface, desquamation), liver (cholestatic injury, graded by bilirubin), GI (diarrhea, graded by volume of diarrhea/day)
 - DDx: skin (viral, drug, engraftment), liver (viral, drug, SOS, TPN), GI (C. diff, CMV, adeno, GNR, typhlitis, drug)
 - Tx: Grade I topical, II-IV **IV methylpred 1-2mg/kg**; if severe or steroid-refractory: vedolizumab, MMF, ruxolitinib ([NEJM 2020;382:1800](#)), antithymocyte globulin (ATG); many other agents proposed. Consider trial enrollment
- **Chronic GVHD:** 30-70% of patients s/p allo-HSCT (humoral immune response, T_H2 cell-mediated) ([NEJM 2017;377:2565](#))
 - Cause: both donor T cell & B cell mediated attacks on recipient **after day +100**
 - Risk factors: prior acute GVHD, HLA mismatch, ↑age, PBSC > BM
 - S/Sx: resembles **scleroderma** (sicca, dysphagia, arthritis, skin tightening, malar rash), lung (bronchiolitis obliterans), liver (cholestasis), cytopenias/immunodeficiency; any organ system (see NIH consensus scoring sheet in [BBMT 2015;21:389](#))
 - Tx: steroid ± broad immunosuppression, **photopheresis** for skin; novel therapies including ruxolitinib, ibrutinib, rituximab, & belimumab (ROCK2 inhibitor) have shown responses in steroid-resistant disease
- **GVHD PPX:** day -3 to indefinite (tapered over months to years), goal to prevent graft rejection & acute/chronic GVHD
 - **Immunosuppression regimens:** combined tacrolimus/methotrexate or tacrolimus/sirolimus most common
 - **T cell depletion regimens:** (ATG, decreased T-cell dose) no longer favored; ↓chronic GVHD but no effect on OS
 - **Post-transplant cyclophosphamide:** combined with tacrol/MMF, used more widely for haplo and MMUD, ↓a/cGVHD

Immunosuppressant	Mechanism	Dosing	Toxicities
Tacrolimus	Calcineurin inhibitor	Trough goal: 5-10ug/L	AKI, ↑K, ↓Mg, ↑LFTs, n/v, TMA, tremor, DM risk
Sirolimus (Rapamycin)	mTOR inhibitor	Trough goal: 3-12ug/L	AKI, sinusoidal obstruction syndrome (SOS), leukopenia, TMA, HLD, cytopenias
Methotrexate (MTX)	Anti-metabolite (inhibits thymidine)	Given on day +1,3,6,11 w/ tacrolimus	Mucositis , myelosuppression, hepatitis, AKI
Mycophenolate (MMF/Cellcept)	Anti-metabolite (inhibits purines)	N/A	Myelosuppression, n/v/d
Post-transplant cyclophosphamide (PTCy)	Kills early allogeneic T-cells (JCI 2019;129:2357)	Given days +3 and +4, particularly for haploid/identical	Hemorrhagic cystitis, ↑mucositis, cardiac toxicity

Oncology

Stem Cell Transplantation

NON-INFECTIOUS COMPLICATIONS: immune-mediated organ damage, toxic effects of chemo, or immunosuppression

- **Pre-Engraftment (Day 0-30):** common to have mucositis, nausea/vomiting, alopecia, rash, diarrhea
 - **Mucositis:** most HSCT patients get some degree of mucositis; duration & severity are worse in allogeneic HSCT.
Treatment is focused on pain & caloric intake. WHO grade: (1) erythema (2) ulcer, solid+liquid PO (3) liquid PO (4) NPO
 - Pain: topical/IV opiates; low threshold for PCA
 - Nutrition: TPN initiated if PO intake impaired by mucositis & expected to continue for ≥1w
 - Palifermin (recombinant keratinocyte growth factor): can reduce duration & severity in select ablative regimens
 - **Engraftment syndrome:** sudden PMN recovery causing cytokine storm and vascular leak
 - S/Sx: fever, rash, weight gain, bone pain; if severe – pulmonary edema, ↑LFTs, AKI, seizures
 - Dx: diagnosis of exclusion (DDx: infection, drug reaction, acute GVHD)
 - Tx: high-dose IV steroids (*discuss with attending prior to initiation of steroids)
 - **GI – nausea/vomiting:** optimal management varies based on timing relative to chemo initiation
 - Immediate (day 0-1): 5-HT₃ blockade (Zofran, A洛xi), neurokinin-1 antagonists (Emend), steroid (decadron)
 - Delayed (day 2-5 post chemo): dopamine (D2) blockade (Compazine, Reglan, Haldol)
 - Late (5+ days post chemo): lorazepam, steroids, dronabinol (more helpful in younger pts, marijuana users)
 - **Pulm – idiopathic interstitial pneumonitis/diffuse alveolar hemorrhage (DAH):**
 - Cause: direct cytotoxic injury to alveoli
 - S/Sx: fever, hypoxemia, diffuse lung infiltrates (**ARDS**)
 - Dx: bronchoscopy w/ serial lavage (r/o infection, blood) – progressively bloodier on serial lavage c/w DAH
 - Tx: high-dose steroids; + for DAH: FFP to correct coagulopathy, maintain plt >50k; limited data for recombinant FVIIa
 - **Liver – sinusoidal obstruction syndrome (SOS) (previously veno-occlusive disease [VOD]):**
 - Cause: direct cytotoxic injury to hepatic venules leading to hypercoaguable state and microthrombi
 - S/Sx: RUQ pain, jaundice, ascites/edema; ↑ALT/AST/TBili, ↑INR/Cr (if acute liver failure or HRS)
 - Dx: Doppler US c/w reversal of portal vein flow, liver bx; Dx criteria: Tbili >2mg/dL, hepatomegaly/RUQ pain, sudden weight gain (fluid) >2-5% baseline body weight
 - PPX: **ursodiol 300mg TID** (admit to Day +30); Tx: **defibrotide**
 - **Renal – AKI (DDx: ATN, hepatic SOS, aGVHD, thrombotic microangiopathy (TMA), TLS, ABO-mismatched transplant)**
 - Nephrotoxins: calcineurin inhibitors, acyclovir, amphotericin, aminoglycosides
 - TMA: subacute onset ~ day 20, caused by endothelial damage 2/2 calcineurin inhibitors, conditioning, & GVHD
 - TLS: considered in pts with significant disease burden at time of transplant; PPX: **allopurinol 300mg qd**
 - **Heme – graft failure, cytopenias, bleeding**
 - Primary graft failure: persistent neutropenia without engraftment
 - Secondary graft failure: delayed pancytopenia after initial engraftment (immune or infectious)
 - Rx: graft failure may require re-transplantation; transfusion support with irradiated & leukoreduced blood products
 - **Post-Engraftment (Day +30):**
 - **PTLD (post-transplant lymphoproliferative disease):** ~1% in allo-SCT; median **day +70-90** ([NEJM 2018;378:549](#))
 - Cause: IS leads to EBV reactivation (dormant in B cells) & clonal B cell proliferation (usually donor-derived)
 - Risk factors: T cell depleted donor graft, treatment with ATG, HLA-mismatch, CB transplant
 - Dx: rising plasma EBV DNA level, biopsy with immunophenotyping for definitive diagnosis
 - Tx: **reduce IS**, anti-viral, rituximab-based chemo (if systemic) vs surgery/RT (if localized), DLI, EBV-targeted T cells
 - **Pulm – bronchiolitis obliterans (cGVHD), pulmonary veno-occlusive disease**
 - **Liver – cGVHD, drug-induced liver injury, viral hepatitis reactivation, iron overload (secondary hemochromatosis)**
 - **Renal – TMA (chronic onset ~ day 100), drug toxicity (calcineurin inhibitors), nephrotic syndrome**

QUICK REFERENCE (Day -8 conditioning to Day +30 engraftment)

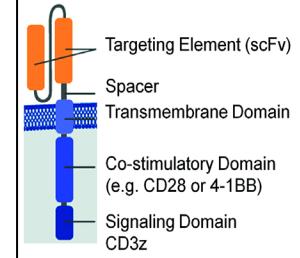
Monitor S/Sx	DDx fever	DDx abdominal pain	DDx dyspnea/hypoxemia
<ul style="list-style-type: none">• Chemo toxicity: mucositis, N/V/D, S/Sx of infection• GVHD: rash, jaundice, diarrhea (24h <u>volume</u>)• SOS: RUQ pain, jaundice, ascites, edema• Engraftment syndrome: fever, dyspnea, edema	<ul style="list-style-type: none">• Infection (bacterial, viral, fungal, parasitic)• Drug rxn• Engraftment syndrome (d7-9 for auto, d14-21 for allo)• Tumor (initial lysis & cytokine release)• Immobility (Atelectasis, aspiration, DVT/PE)• GVHD	<ul style="list-style-type: none">• Neutropenic enterocolitis• Colitis: C. Diff, CMV• SOS• GVHD• Obstruction, ileus, constipation	<ul style="list-style-type: none">• Existing dz: CHF, COPD, asthma• PNA: bacterial, fungal, aspiration• Volume (often on mIVF with chemo)• Drug: chemo-induced lung injury or cardiotoxicity• Engraftment (pulmonary edema from capillary leak)• Pneumonitis• Alveolar hemorrhage• PE, TRALI, GVHD

DISEASE RELAPSE: #1 cause of death post-HSCT. **Mechanisms:** immune escape, resistant clones that survive conditioning

- Treatment: donor lymphocyte infusion (DLI), second allo-HSCT, clinical trial enrollment for novel therapies, hospice

MECHANISM OF ACTION ([NEJM 2018;379:64](#))

- Chimeric antigen receptor T cells (CAR-T cells): type of autologous cell therapy; T lymphocytes collected from the patient, genetically modified with construct encoding a chimeric antigen receptor (CAR) that directs the T cells against a selected antigen on the patient's tumor
- CAR: transmembrane engineered protein consisting of extracellular immunoglobulin (antibody)-derived domains (ScFv), which target and bind a tumor antigen (e.g. CD19) fused to an intracellular T cell receptor domain (CD3z) and a costimulatory domain that signal for T cell activation (see figure)



FDA-APPROVED THERAPIES: anti-CD19 cell-based therapies

- Yescarta** (axicabtagene ciloleucel; usually called "axi-cel")
 - Aggressive, refractory adult B-cell lymphoma: ZUMA-1, Phase II, 54% CR ([NEJM 2017;377:2531](#))
- Kymriah** (tisagenlecleucel)
 - Relapsed/refractory B-ALL age <25y: ELIANA, Phase II: [NEJM 2018;378:439](#). Adult phase I long-term f/u: [NEJM 2018;378:449](#)
 - Adults with relapsed/refractory DLBCL: JULIET, Phase II, 52% ORR (40% CR), 65% w/o relapse at 1y ([NEJM 2019;380:45](#))
- Tecartus** (brexucabtagene autoleucel)
 - Relapsed/refractory mantle cell lymphoma: ZUMA-2, Phase II, 93% ORR (67% CR) ([NEJM 2020;382:1331](#))
- Clinical trials in heme malignancies, e.g. BCMA in MM ([NEJM 2019;380:1726](#)) & solid tumors, e.g. IL13Ra2 in GBM ([NEJM 2016;375:2561](#))
- Under investigation: combo w/ PD1-axis blockade ([Cancer Cell 2019;36:471](#)) & other cell types, e.g. CAR-NK cells ([NEJM 2020;382:545](#))

TOXICITIES ([JNCCN 2020;18:230](#); [BBMT 2019;25:625](#))

- Cytokine-release syndrome (CRS)**
 - Most common toxicity. Typically 2-3d post-infusion, lasts 7-8d. Fulminant cytokine release (IL-2, sIL2R, IFN γ , IL-6, GM-CSF) triggered by CAR-T engagement of antigen and T cell proliferation. ↑ risk in bulky disease and specific constructs
 - S/Sx:** fever, ↓BP, ↑HR, ↓SpO₂, malaise, anorexia, myalgia. Can affect any organ (CV, lung, GI/liver, renal, CNS) w/ arrhythmia, ARF, capillary leak, HLH/MAS
 - Diagnosis:** monitor for 7d post infusion for FDA-approved therapies (inpt or possibly close outpt); VS, basic labs, ferritin, coags, CRP, TLS labs. When suspect: admit, tele, r/o infection
 - Therapy:** if plan to treat CRS with steroids or anti-IL6, **first get clear approval by the treating attending (even if overnight)**
 - Broad-spectrum abx if fever or neutropenic until r/o infxn
 - MGH: tocilizumab (anti-IL6R) 8mg/kg IV over 1h ($\leq 800\text{mg}$); siltuximab (anti-IL6) also exists; 2nd line: steroids
- CAR-T cell-related encephalopathy syndrome (CRES)**
 - Etiology unclear; passive cytokine diffusion into brain (IL-6, IL-15 a/w neurotoxicity) vs CAR-T trafficking into CNS
 - Timing:** typical onset 4-10d post-infusion, duration 14-17d, variable. Can be concurrent w/ CRS or after
 - S/Sx:** toxic encephalopathy (see ICE & ICANS grade)
 - Diagnosis:** neuro consult, ICANS (or CARTOX-10) score. If \geq grade 3: MRI brain w/o contrast + EEG ± LP. Funduscopic exam
 - Therapy:** Ppx: if CAR-T known to cause neurotoxicity, start seizure ppx on day of infusion (levetiracetam 500-750 mg q12h for 30d). Tx: see chart
 - Prognosis:** generally reversible, rare fatal cases
- Hemophagocytic lymphohistiocytosis (HLH) / macrophage activation syndrome (MAS):** see [Pancytopenia & Anemia](#)
 - Profound systemic inflammatory state characterized by cytotoxic T cell hyperactivation (IFN γ) → macrophage activation (IL-6), lymphohistiocytic tissue infiltration, and multiorgan failure; occurs in ~1% of patients treated with CAR-T. **S/Sx:** fever, cytopenias, multiorgan dysfunction
 - When to consider:** rapidly rising ferritin $>5\text{K}$ with cytopenias in context of CRS, especially if any: oliguria or ↑Cr >4 or 3x b/l, pulmonary edema, ↑AST or ALT 5x ULN, or ↑Tbili 1.5x ULN; hemophagocytosis in bone marrow or other organs
 - Dx:** labs resemble HLH: CBC/diff, ferritin, sIL2R, LDH, fibrinogen, TGs, LFTs, Cr. BMBx rarely critical (low Sn/Sp)
 - Tx:** high mortality, do not delay diagnosis, escalate therapy aggressively. Manage as per CRS with addition of steroids. If no improvement in 48h, consider etoposide or intrathecal cytarabine for neurotoxicity

CRS Grade		Therapy
1	Fever	If $>3\text{d}$, consider tx as in grade 2
2	Fever w/: HoTN not requiring pressors or hypoxemia on NC	Tocilizumab q8h PRN up to x4, add steroids as below if still ↓BP after 1-2 doses, fluids
3	Fever w/: ↓BP requiring pressors or ↓SpO ₂ requiring HFNC, face mask, Venturi, NRB	Tocilizumab as above, dexamethasone 10mg IV q6h (or equivalent)
4	Fever w/: ↓BP requiring multiple pressors or ↓pO ₂ requiring NIPPV, MV	Tocilizumab + dex as above. If refractory, consider methylpred 1g/d IV x3d w/ taper

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool	
Max score: 10	AAOx3 (4 pts), naming x3 (3 pts), follows commands (1 pt), writes sentence (1 pt), serial 10s from 100 (1 pt)

ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grade		Treatment (if CRS, add tocilizumab)
Grade 1	ICE = 7-9	Supportive
Grade 2	ICE = 3-6, or does not awaken spontaneously	Dex 10mg IV x1
Grade 3	ICE = 0-2, or awakens only to tactile stimulus, or focal edema on neuroimaging	Dex 10mg IV q6h or methylpred 1mg/kg IV q12h
Grade 4	ICE = 0, difficult to arouse, szr $>5\text{min}$ or w/o return to b/l, deep focal motor deficit (e.g. paresis), diffuse cerebral edema, or ↑ICP	Methylprednisolone IV 1g/d x3d or equivalent w/ taper

Oncology

Solid Organ Malignancies

Organ	Risk factors/screening	Diagnostics	Treatment
Prostate <ul style="list-style-type: none"> Adenocarcinoma (95%) Transitional, basal cell, intraductal carcinomas; neuroendocrine, carcinosarcoma, lymphoma, stromal sarcoma <p>NCCN Guidelines Prostate Cancer 2020</p>	<p>Risk factors:</p> <ul style="list-style-type: none"> Age, AA race, genetic factors (BRCA1/2 and family history), smoking <p>Screening with PSA (JAMA 2018;319:1901):</p> <ul style="list-style-type: none"> 55-69: individualized risk-benefit discussion 70 and above: no testing 	<p>Diagnosis: Bx</p> <p>After diagnosis:</p> <ul style="list-style-type: none"> TRUS, MRI, biomarkers, CT C/A/P, bone scan <p>Germline testing:</p> <ul style="list-style-type: none"> High/very high NCCN risk Any risk level if \oplus FHx or intraductal histology 	<p>Androgen deprivation therapy (ADT):</p> <p><i>Orchiectomy, Androgen R blocker:</i> enzalut-, apalut-, darolut-, flutamide. <i>Androgen synthesis inhib:</i> abiraterone. <i>GnRH agonist:</i> leuprolide, gose-, hist-, triptorelin, <i>GnRH antagonist:</i> degarelix, relugolix</p> <p>Low risk: surveillance (PSA, DRE \pm Bx) vs external beam radiation therapy (EBRT) \pm brachytherapy (BT) vs radical prostatectomy</p> <p>Intermediate/high risk: combination of EBRT, ADT, BT \pm prostatectomy w/ lymph node dissection</p> <p>Metastatic/recurrent: ADT, if fail, ADT+doxetaxel. Bone mets: radium-223 or denosumab/zoledronic acid, palliative RT. MSI-H/dMMR: pembrolizumab</p>
Breast <ul style="list-style-type: none"> Infiltr. ductal (76%) Invas. lobular (8%) Ductal/lobular (7%) Mucinous (2%) Tubular (1.5%) Medullary (1%) Papillary (1%) <p>NCCN Guidelines Breast Cancer 2020</p>	<p>Risk factors:</p> <ul style="list-style-type: none"> Age, genetics (BRCA1/2, CHEK2, ATM, PALB2), FHx, obesity after menopause, menopause >55, chest RT, 1st birth >30, nulliparity, HRT, menarche <13y, ETOH, benign breast disease, tobacco <p>Screening:</p> <ul style="list-style-type: none"> USPTF: q2y mammo 50-74 NCCN: q1y mammo >40 or 10y before earliest FHx if >30 or 10y after RT if >30 ACOG: q1-2y mammo; offer 40-50, rec 50-75 	<p>Dx mammogram (Bi-RADS), US, FNA or core Bx (> excis. Bx), breast MRI if young or to assess extent (good Sn, but Sp 72%)</p>	<p>Early stage (I, IIA, IIB through T2N1):</p> <ul style="list-style-type: none"> Breast Conserving Surgery + RT vs mastectomy \pm RT, HR tx, HER2 tx, chemo if high risk <p>Locally advanced (Stage IIB T3N0, IIA-IIIC):</p> <ul style="list-style-type: none"> Surg + RT w/ (neo)adj. chemo & HR/HER2 tx <p>(Neo)adjuvant therapy:</p> <ul style="list-style-type: none"> ER/PR+, HER2-: tamoxifen or aromatase inhibitors (AI) (anastrozole, letrozole, exemestane); no AI if premenopausal; \pm ovarian suppression if high risk. Chemo: AC-T (doxo, cyclophosph [CYC], paclitax.) or TC HER2+: TCH(P) (traztuzumab, carboplatin, docetaxel, \pm pertuzumab) or ACTH(P) (doxorubicin, CYC, paclitaxel, trastuz, \pm pertuz) + ER/PR tx if HR+ Triple Neg (NEJM 2017;372:2147): capecitabine <p>Metastatic/recurrent (Stage IV):</p> <ul style="list-style-type: none"> ER+: as above \pm fulvestrant (ER antagonist); \pm CDK4/6 inhib. or everolimus (mTOR inhib.) HER2+: THP (1st line) or T-DM1 (trastuzumab-drug conjugate), trastuzumab+lapatinib BRCA mutation (NEJM 2017;377:523; NEJM 2018;379:753): olaparib or talazoparib Triple neg: systemic tx
Pancreas <ul style="list-style-type: none"> Exocr./adeno (94%) Endocrine (6%) <p>NCCN Guidelines Pancreatic 2020</p>	<p>Risk factors:</p> <ul style="list-style-type: none"> Tobacco, EtOH, obesity, DM, chronic pancreatitis, age, male, FHx, HNPCC, BRCA1/2 <p>Genetic mutations:</p> <ul style="list-style-type: none"> KRAS, p53, SMAD4, TGFbR1/2, CDKN2A, MLL2/3, KDM6A, ATM, NRTK, ALK, ROS1, BRAF, HER2, PALB2 	<ul style="list-style-type: none"> CT C/A/P pancreas, EUS+Bx, MRCP \pm ERCP, CA19-9, germline testing +tumor gene profile Bx metastatic site in metastatic dz 	<p>Resectable/Borderline: surgery \pm systemic tx: 1st line FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin), gemcitabine+nab-paclitaxel, gem+capecitabine, \pm chemoRT</p> <p>Locally advanced: systemic tx as above or stereotactic body radiation (SBRT)</p> <p>Metastatic: systemic tx. Olaparib for BRCA1/2 positive (NEJM 2019;381:317)</p> <p>NTRK fusions: larotrectinib, entrectinib</p> <p>MSI-H/dMMR (NEJM 2015;372:2509): pembrolizumab</p>

Oncology

Solid Organ Malignancies

Organ	Risk factors/screening	Diagnostics	Treatment
Colon and rectum ▪ AdenoCa (98%) ▪ Neuroendocrine ▪ Lymphoma NCCN Guidelines Colon Cancer 2020	Risk factors: <ul style="list-style-type: none">▪ FHx, genetic (FAP, HNPCC), IBD, obesity, tobacco, red/processed meat, ETOH, adenomatous polyps, age▪ ↑ death w/ R-sided (BRAF/KRAS mut) (JAMA Oncol 2018;4:e173695) Protective factors: ASA for 50-59yo and ≥10% CVD risk (Annals 2016;164:814) Screening: colo, flex sig, CT colo, FIT, FOBT for 50-75yo. Per ACS: 45-75yo	<ul style="list-style-type: none">▪ Colonoscopy w/ polyp, bx for path▪ CT C/A/P, CEA▪ MRI for liver mets▪ Pelvic MRI or endorectal US for rectal CA▪ Genetic testing: MSI/MMR status in all, K/N-RAS, BRAF, HER2	Colon: I-IIA: surgery + observation, or capecitabine or 5-FU/leucovorin (IIA) IIB-IV: surg, RT, systemic tx: FOLFOX (oxaliplatin, leucovorin, 5-FU), CAPEOX (capecitabine, oxaliplatin), FOLFIRI (irinotecan, leucovorin, 5-FU), FOLFOXIRI (irinotecan, oxaliplatin, leucovorin, fluorouracil), ± bevacizumab; nivo ± ipi or pembrolizumab BRAF V600E: encorafenib + EGFR inhib. (cetuximab, panitumumab) MSI-H/dMMR: immuno tx (pembrolizumab, nivolumab) HER-amp +RAS/BRAF WT: trastuzumab + pertuzumab/lapatinib Rectal: low anterior (LAR) v abdominoperineal resection (APR) ± neo v adj chemoRT. Chemo as in colon cancer
Lung ▪ NSCLC (84%): adeno, large>SCC ▪ SCLC (13%) NCCN Guidelines NSCLC 2020 NCCN Guidelines SCLC 2020	Risk factors (Nat Rev Ca 2007;10:778): <ul style="list-style-type: none">▪ Tobacco, asbestos, occup. exposures, lung fibrosis, age, male▪ 25% lung cancer worldwide not due to smoking → more likely single mutation Screening (Annals 2014;160:330): <ul style="list-style-type: none">▪ Annual low dose CT chest for pts 50-80yo with ≥20 pack-yr hx and smoking within last 15y	<ul style="list-style-type: none">▪ CT C/A/P, PET/CT, brain MRI▪ Evaluate pathologic LNs with biopsy▪ Molecular testing for NSCLC (EGFR, ALK, ROS1, NTRK1/2/3, METex14 skipping, RET, PD-L1) before starting systemic tx	NSCLC: IA: surgery v definitive RT; IB-IIIA: surgery if able ± adjuv chemoRT. IIB/IIIA unresectable, IIIB: definitive chemoRT + adjuvant durvalumab (NEJM 2018;379:2342). IV: targeted, immune tx, systemic tx Chemotherapy: cisplatin + docetaxel/etoposide/pemetrexed; carboplatin + pemetrexed/paclitaxel/gemcitabine/docetaxel Targeted inhibitors: EGFR (osimertinib 1 st line, erlotinib, afatinib, gefitinib, dacomitinib); ALK/ROS1 (alectinib, crizotinib, ceritinib, brigatinib, lorlatinib); BRAF/MEK (dabrafenib/trametinib); TRK (larotrectinib, entrectinib) Immunotherapy (PD-L1+) (Lancet 2016;387:1540 ; NEJM 2018;378:2078): pembrolizumab ± chemo. ipi/nivo, atezolizumab+platinum+taxane + bevacizumab (anti-VEGF) SCLC: <ul style="list-style-type: none">▪ Limited: surgery + chemo ± mediastinal RT▪ Extensive (NEJM 2018;379:2220): chemo & atezolizumab v durvalumab ± RT for lobar obstruction, SVC synd, bone/brain mets▪ Chemo: platinum agents, etoposide, irinotecan
Melanoma ▪ Superficial spreading (75%) ▪ Nodular (15-30%) ▪ Lentigo maligna (10-15%) ▪ Acral lentiginous (<5%) ▪ Amelanotic (2-10%) ▪ Ocular (5%) NCCN Guidelines Melanoma 2020	Risk factors: <ul style="list-style-type: none">▪ Sun exposure (UVB > UVA), atypical nevi, high nevi count, FHx or personal hx, immunosuppression▪ Familial melanoma: CDKN2A, CKD4, POT1▪ Most common somatic mutations: BRAF (V600E, V600K) 50%, NRAS 15-20%, cKit 10-15% (acral). Genetic testing for stage II-IV dz	<ul style="list-style-type: none">▪ Biopsy of primary tumor, LN sampling, CT C/A/P, brain MRI, & serum LDH for active surveillance and treatment response	Surgical excision primary tumor ± sentinel LN Adjuvant treatment for metastatic disease: <ul style="list-style-type: none">▪ Immunotherapy (NEJM 2015;373:23; NEJM 2015;372:2521): anti-PD-1 (pembrolizumab); anti-CTLA4 (ipilimumab), ipi+nivo (NEJM 2019;381:1535)▪ Targeted tx (NEJM 2014;371:1867): BRAF/MEK inhibitor combination (dabrafenib & trametinib, vemurafenib & cobimetinib, encorafenib & binimetinib), binimetinib for NRAS mutated after prior ICI, KIT inhib. imatinib▪ RT: sympt. localized disease (e.g. brain mets)▪ Talimogene laherparepvec (T-VEC) (JCO 2015;33:2780): intralesion. injection of HSV → tumor cell lysis & GM-CSF expression

Oncology

Chemotherapy & Toxicities

Drug	Mechanism of Action	Toxicities
ANTI-METABOLITES		
Azacitidine	DNA/RNA methyltransferase inhibitor	BM↓, constipation, n/v, renal tox, liver tox
Cytarabine (HiDAC)	DNA polymerase inhibitor	Acute cerebellar ataxia, PRES, BM↓, chemical conjunctivitis (Rx dexamethasone eye drops), ↑LFTs, cutaneous tox, hand-foot syndrome
Decitabine	DNA methyltransferase inhibitor	BM↓, constipation, n/v/d, hyperglycemia, URI sx, MSK pain
5-fluorouracil (5-FU)	Thymidylate synthase inhibitor, incorporation into DNA/RNA	Coronary vasospasm, acute cerebellar ataxia, hand-foot syndrome , stomatitis, hemorrhage, hiccups, diarrhea, BM↓
Capecitabine	5-FU prodrug	Monitor INR (if warfarin), hand-foot synd., SJS-TEN, n/v/d, BM↓, liver tox
Fludarabine	DNA polymerase, ribonucleotide reductase, DNA primase, ligase inhibitor	BM↓, autoimmune hemolytic anemia, neurotoxicity, fatal pulm toxicity (when used with pentostatin for CLL)
Gemcitabine	DNA polymerase and ribonucleotide reductase inhibitor	Capillary leak syndrome, PRES, TMA/HUS, ARDS, ↑LFTs, n/v, hematuria
Hydroxyurea	Ribonucleoside diphos. reductase inh.	BM↓, cutaneous tox, n/v/d, ↑LFTs, ↑Cr, ↑BUN
Mercaptopurine	Purine antagonist, incorporation into DNA/RNA	Biliary cholestasis & hepatocellular necrosis, BM↓ (consider TPMT SNP testing if severe BM↓), n/v/d
ANTI-FOLATES		
Methotrexate	Dihydrofolate reductase (DHFR) inhibitor	BM↓, aplastic anemia, AKI, ↑LFTs, hepatic fibrosis/cirrhosis, cutaneous tox, IS (PCP), pneumonitis/PF, teratogenic, ulcerative stomatitis/diarrhea
Leucovorin/Folinic Acid	Restores active folate stores	See methotrexate; used to diminish toxicities
Pemetrexed	DHFR inhibitor, broad anti-folate activity	BM↓, desquamating rash, pneumonitis, renal tox
ALKYLATING AGENTS (all cause BM↓, infertility, increased risk of MDS/AML)		
Busulfan	Alkylates DNA at N ⁷ of guanine	BM↓, sinusoidal obstruction/VOD, tamponade, ILD, seizures, renal tox
Ifosfamide	Crosslinks DNA to other structures	Hemorrhagic cystitis, encephalopathy , renal/pulmonary/cardiac tox
Melphalan	Cross-links strands of DNA	BM↓, hypersensitivity, amnesia, pulmonary fibrosis, mucositis, rash, IF
Carmustine	Alkylates and cross-links DNA and RNA	BM↓, pulm tox (dose-related), ↑LFTs, renal tox, ocular sx
Cyclophosphamide	Alkylates and cross-links DNA (prodrug)	Hemorrhagic cystitis, renal/cardio tox, pulm fibrosis, IF, sinusoidal obstruction/VOD, IS, hypoNa
Dacarbazine	Methylation of DNA at O ⁶ and N ⁷ of guanine (prodrug)	Hepatic necrosis, teratogenic, hepatic vein thrombosis, ↑↑n/v, BM↓↓
Cis/Carbo/Oxaliplatin	Crosslink DNA	N/v, renal tox, ototoxicity, neurotoxicity, BM↓; oxali: rhabdo, ↑QT, PRES
ANTIBIOTICS		
Bleomycin	Binds GC-rich DNA causing DNA breaks	Late pulm fibrosis, dermatographia, hyperpigmentation, Raynaud's
Mitomycin	Crosslinks DNA at N ⁶ of adenine and O ⁶ , N ² of guanine	BM↓, renal/cardiac tox, HUS, interstitial pneumonitis/ARDS, bladder fibrosis
HORMONAL THERAPY		
Tamoxifen/Raloxifene	Selective estrogen receptor modulator (SERM)	Menopausal sx (hot flashes, vaginal atrophy/bleeding), VTE, endometrial cancer (tamoxifen only)
Anas-/Letrozole	Nonsteroidal aromatase inhibitor	Sexual dysfunction, bone/joint pain, osteoporosis, premature menopause
Exemestane	Steroidal aromatase inhibitor, irreversible	
Fulvestrant	Estrogen receptor antagonist	Sexual dysfunction, bone/joint pain, osteoporosis, injection site reactions
Megestrol	Synthetic progestin, appetite stimulant	Teratogenic, ↑weight, hypogonad., VTE, hot flashes, adrenal suppression
Leuprorelin	GnRH receptor agonist	Hypogonadism, edema, depression, bone pain, osteoporosis, transient worsening of prostate CA sx 2/2 brief testost. surge (ppx w/ AR inhibitors), seizure, ↑CVD risk
Goserelin	GnRH analog	
Flutamide/Nilutamide	Nonsteroidal antiandrogen	Hot flashes, gynecomastia, ↓libido, n/v/d, muscle atrophy/pain, liver tox, ILD, visual changes (N), osteoporosis
Bicalutamide	Nonsteroidal antiandrogen	Hypogonadism, sexual dysfunction, depression, fatigue, liver tox, ILD
TOPOISOMERASE INHIBITORS		
Anthracyclines (Dauno/Epi/Doxorubicin)	Topoisomerase II inhibitor (intercalator)	Cardiotoxicity (DCM, myopericarditis), BM↓, IS, 2° malignancies, extravasation , liver/renal tox, typhlitis, "chemo brain"
Mitoxantrone	Topoisomerase II inhibitor (intercalator)	Cardiotoxicity (DCM, myopericarditis), BM↓, IS, n/v
Etoposide	Topoisomerase II inhibitor	BM↓, acute infusion reaction (HoTN), metallic food taste , SJS/TEN
Irinotecan/Topotecan	Topoisomerase I inhibitor	BM↓, diarrhea , late ILD, thrombosis, typhlitis
MITOTIC INHIBITORS		
Pacli/Docetaxel	Microtubule stabilizer; dimer assembly	BM↓, hypersens., infusion reactions, neuropathy, liver tox, fluid retention
Vinblastine	Inhibitor of microtubule formation	Extravasation , BM↓, neuropathy, bronchospasm, stomatitis
Vincristine	Inhibitor of microtubule formation	Neurotoxic (deaf, blind, ataxia, neuropathy, areflexia, ileus), MI, SIADH, extravasation, bronchospasm

Oncology

Chemotherapy & Toxicities

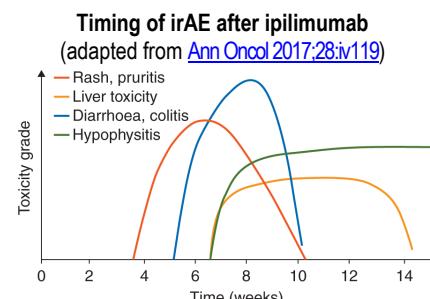
Drug	Mechanism of Action	Toxicities
MONOCLONAL ANTIBODIES (selected)		
Bevacizumab	Anti-VEGF	Perf/bleed (septal, GI), wound dehisc, nec fasc, HTN, endophthalmitis
Brentuximab Vedotin	Anti-CD30+MMAE (Antibody-drug conj.)	PML, peripheral neuropathy, neutropenia, pulm tox, SJS/TEN
Cetuximab	Ant-EGFR	Cardiopulmonary arrest, hypersensitivity , angioedema, ILD
Obinutuzumab	Anti-CD20, glycoengineered	HBV reactivation, PML, BM↓, hypersensitivity, liver tox, URI sx
Rituximab	Anti-CD20	Hypersensitivity, CRS, HBV reactivation, PML, renal tox
Trastuzumab	Anti-HER2	Cardiotoxicity (↓EF), hypersensitivity, pulm tox , headaches, diarrhea, URI sxs, extremity pain, teratogenic
IMMUNOMODULATORS		
Aldesleukin/Denileukin	IL-2 receptor agonist	Capillary leak syndrome, sepsis, cardiopulmonary disease, CNS toxicity, hypersensitivity, renal tox, autoimmune diseases, vision loss (denileukin)
Lena/poma/thalidomide	TNFα, IL-2 modulation	Teratogenicity, BM↓, DVT/PE, MI, stroke, rash, SJS (lena), liver tox, peripheral neuropathy, 2° malignancy
Interferon-alpha	T-cell activation	Flu-like sx, ↑LFTs, fatigue, depression , HLD, anorexia, BM↓
ATRA	Induces differentiation of APL cells	Differentiation synd., hemorrhage, ↑ICP, xerosis, DIC, teratogenicity
Arsenic	Induces apoptosis via DNA frag. Degrades PMR-RAR fusion protein	Differentiation syndrome, ↑QTc, confusion, n/v/d, URI sx
TYROSINE KINASE INHIBITORS (TKIs)		
Imatinib, Dasatinib	Inhibits BCR-ABL	Renal/liver tox, CHF, DRESS/SJS, n/v/d, BM↓, hemorrhage, PAH, ↑QTc
Nilotinib, Bosutinib, Ponatinib	Inhibits BCR-ABL with resistance to imatinib	↑QTc, liver tox, CHF, n/v/d, BM↓, hemorrhage, MI, arterial occlusions and VTE , arrhythmias
Gilteritinib	FLT3 inhibitor	Myalgias, ↑LFTs, n/v/d, rash, stomatitis, differentiation syndrome , FN
Midostaurin	FLT3 inhibitor	N/v/d, edema, BM↓, mucositis, ↑LFTs, renal tox, ↑QTc, pyrexia, fatigue, URI, hyperglycemia, hyperuricemia
Ibrutinib	BTK inhibitor	AF, edema, diarrhea, URIs, bruising/bleeding including SDH/ICH (may want to avoid if on DAPT), fatigue, HTN
Osimertinib, Dacomitinib, Gefitinib, Erlotinib	EGFR inhibitor	Acneiform rash (predictive of response), late ILD/pneumonitis, ↑LFTs, ocular tox, n/v/d, MI, GI perf, liver tox and HRS
Lapatinib	EGFR and HER2/neu inhibitor	ILD/pneumonitis, liver tox, n/v/d, rash
Crizotinib, Brigatinib, Ceritinib	ALK and ROS1 (C)/EGFR (B) inhibitors	↑QTc, bradycardia, pneumonitis, n/v/d, edema, ↑LFTs, visual disturb , neuropathy, ↓K, ↓phos, BM↓, hyperglycemia
Lorlatinib	ALK and ROS1 inhibitor	HLD, edema, hypergly., neuropathy, BM↓, ↑LFTs, ↓alb, n/v/d, myalgias
Vemurafenib/Cobimetinib	BRAF (V600E) inhibitor	N/v/d, skin tox (SCC, rash, hand-foot syndrome, photosensitivity), central serous retinopathy, arthralgias , ↑QT, ↓EF, liver tox, pyrexia
Dabrafenib/Trametinib, Encorafenib/Binimelanib	BRAF (V600E)/MEK inhibitors (dosed in tandem)	HA, pyrexia , skin tox (SCC, rash, hand-foot syndrome, photosensitivity), n/v/d, central serous retinopathy, HTN, CHF, arthralgias
Vandetanib	Multikinase inhibitor (EGFR, VEGF, etc.)	N/v/d, rash, ↑QTc, dry mouth, cerebrovascular ischemia
Neratinib	EGFR/HER2 inhibitor	N/v/d, stomatitis, rash, liver tox, muscle spasm
Sorafenib, Sunitinib, Regorafenib, Lenvatinib	Multikinase inhibitors	Hemorrhage/GI perf , HTN, renal tox/abnl lytes, hand-foot syndrome, palmar-planter erythrodysesthesia (L), CHF/MI/↓EF (So, Su) , neuropathy, liver tox (Su,R) , ↑QT, mucositis (Su), thyroid tox (So), jaw necrosis (Su), TLS, arthralgia/myalgia (L), arterial thrombosis (L)
Cabozantinib	Multikinase inhibitors	Fistula, GI perf, hemorrhage, osteonecrosis, ↑LFTs, cytopenias, hand-foot syndrome, HTN, ↑triglycerides, abnormal electrolytes, PRES
Axitinib, Pazopanib	VEGFR-1,2,3 inhibitors	Liver tox (P) , ↑QT (P), ↓EF (P), n/v/d, HTN, hemorrhage, hypothyroid., dysphonia (A) , BM↓ (P), GI perf (P), arterial thrombosis (A)
Bortezomib	Proteasome inhibitor (26S)	Neuropathy, PRES, PML, ARDS, BM↓, AIN, n/v/d, HoTN, shingles, ↓EF
Larotrectinib	Tropomyosin receptor kinase inhibitor	N/v/d, ↑LFTs, fevers, BM↓, neurotox (dizziness, dysarthria, delirium, enceph.)
Sirolimus/Temsirolimus	mTOR inhibitors	N/v/d, edema, mouth sores, anemia, increased thirst/hunger, pneumonitis , metabolic effects (HLD, hyperglycemia), proteinuria, renal failure, fever
OTHER INHIBITORS (selected)		
Olap/Rucap/Niraparib	Poly (ADP-ribose) polymerase inhibitors	N/v/d, fatigue, BM↓, constipation, pneumonitis (O), HTN (N)
Abema/Palbo/ribociclib	CDK4,6 inhibitors	BM↓, fatigue, diarrhea (A)

IMMUNE CHECKPOINT INHIBITORS (ICIs)

- Mechanism of Action:** *block* receptors that *down-regulate* T cell activation → CTLA-4, PD-1 (on T-cell), or its ligand PD-L1 (on cancer cell) ↑ → antitumor immune response ([Nat Rev Clin Oncol 2016;13:473](#); [NEJM 2018;378:158](#); [NEJM 2016;375:1767](#))
- Indications:** numerous, incl melanoma, NCSLC, and multiple GU tract cancers; see [Solid Organ Malignancies](#) for some specific tumors. PD-1i FDA-approved for **any** microsatellite instability-high (MSI-H) or mismatch-repair deficient cancers (dMMR) ([NEJM 2017;377:1345](#); [NEJM 2018;378:1277](#)). Pre-existing autoimmune dz NOT absolute CI, but can flare ([JCO 2018;36:1905](#); [Ann Oncol 2017;28:368](#))

IMMUNE RELATED ADVERSE EVENTS (irAEs) ([NEJM 2018;378:158](#); [Ann Oncol 2017;28:i119](#); [J Immunother Cancer 2017;5:95](#))

- Definition:** systemic autoimmune/inflammatory event 2/2 immune activation by ICI
- Risk factors:** combination (anti-CTLA-4 + anti-PD-1) a/w earlier, ↑ incidence, and ↑ severity; anti-PD1 < anti-CTLA-4
- Timing:** highly variable, can present weeks-years
- Clinical presentation:** derm tox, hepatitis, thyroiditis, colitis, myocarditis, pneumonitis, DM1, neurotox, arthralgias>arthritis, sicca. See below for details
- Tx:** based on expert consensus (ASCO: [J Oncol Pract 2018;14:247](#)). 1st line prednisone. If refractory: infliximab, MMF, tacrolimus, MTX, ATG, tocilizumab. IVIG/plasmapheresis in autoAb-mediated/neurologic irAEs



SELECTED IRAE DIAGNOSIS, GRADING, AND MANAGEMENT (ASCO: [JCO 2018;36:1714](#); [NCCN Guidelines 2020](#))

Consult SIC (Severe Immunotherapy Complications) Service:

- Inpt questions regarding concern for complications of prior/current immunotherapy: page SIC attending in Amion

Skin toxicity: rash, pruritis, rarely SJS/TEN. Common, up to 30-40% of patients (CTLA-4 > PD-1/L1 blockade). Vitiligo seen in melanoma, rarely in other malignancies, a/w response to tx ([JAMA Dermatol 2016;152:45](#))

- Timing:** early, within the first few weeks of tx initiation
- S/Sx:** four types of skin reactions (1) Inflammatory: psoriasiform or lichenoid reactions; (2) Immunobullous: dermatitis herpetiformis or bullous pemphigoid; (3) Keratinocyte alteration: acantholytic dyskeratosis; (4) Immune reaction mediated by alteration of melanocytes
- Dx:** exam; r/o other etiologies (infection, DRESS, TEN/SJS); grade based on BSA (<10% Gr 1, 10-30% Gr 2, >30% Gr 3)
- Tx:** topical steroids, oral antihistamines for inflammatory/pururitic reaction. If severe, consider systemic steroids + derm consult

Hypophysitis ([JAMA Oncol 2018;4:173](#)): primarily w/ anti-CTLA-4 (3.2%), rarely w/ anti-PD-1/PD-L1 (0.5%). Mechanistically distinct from other irAEs; possibly by direct binding of ipi to CTLA-4 on normal cells of ant. pituitary ([Sci Transl Med 2014;6:230](#)). See [Pituitary Disorders](#)

- Timing:** median onset 8w
- S/Sx:** HA most common (can be severe); fatigue, n/v, dizziness, weight loss, hot flashes, cold intolerance, hyponatremia (anterior hypopituitarism); without central diabetes insipidus (posterior pituitary spared)
- Dx:** MRI brain/pituitary shows diffuse pituitary enlargement (generally resolves by 2mo); test hormonal axes: 8AM serum cortisol + ACTH and/or cort stim; TSH w/ FT4/total T4/T3; PRL; LH/FSH, serum testosterone/SHBG (in men); IGF-1
- Tx:** hormone substitution: **Hypocortisolism**: glucocorticoid replacement (prednisone 3-5mg daily) ([Cancer 2018;124:3706](#); [Oncologist 2016;21:804](#)). **Central hypothyroidism**: levothyroxine. **Hypogonadism**: consider testosterone replacement if persists. **GH deficiency**: GH theoretically contraindicated due to active malignancy, although no evidence

Myocarditis ([JACC 2018;71:1755](#)): rare but serious AE a/w high mortality (46% in severe myocarditis); risk higher with combo tx

- Timing:** generally within 3mo ([Oncologist 2018;23:874](#); [Lancet 2018;391:933](#)); **S/Sx:** heart failure, arrhythmia
- Dx:** EKG/tele; **troponin**, NT-proBNP, TTE; **myocardial Bx**. **Tx:** pulse-dose steroids (1g IV x3d, then PO pred 1mg/kg); 2nd-line consider ATG/IVIG, or infliximab/MMF/tacrol ([Oncologist 2018;23:879](#)); GDMT for HFrEF

Pneumonitis: more common w/ anti-PD-1, serious toxicity rare. Higher risk w/ combination or targeted therapy ([Chest 2017;152:271](#))

- Timing:** highly variable, can be later. **S/Sx:** dyspnea, cough, AIP/ARDS; 1/3 asx ([JCO 2017;35:709](#); [Clin Cancer Res 2016;22:6051](#))
- Dx:** r/o other etiologies, consider BAL, PCP, CT often non-specific. **Tx:** oxygen, glucocorticoids w/ prolonged taper, diuresis

Colitis: more common w/ anti-CTLA-4; grade 3/4 colitis is higher with ipi (<10%) than with anti-PD-1 agents (1-2%)

- Timing:** 6-8w s/p initiation of therapy. **Dx:** lactoferrin/calprotectin; r/o other etiologies: C diff., stool Cx, CMV PCR, CT A/P can show mild diffuse bowel thickening or segmental colitis, EGD/flex sig/colo for Grade 2 sx, path w/ active acute colitis
- Tx:** antidiarrheal agents, budesonide 9mg PO or prednisone PO vs high dose steroids w/ taper, infliximab in refractory cases

irAE	Features	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
Colitis	<ul style="list-style-type: none"> More common with anti-CTLA-4 Grade 3/4 colitis higher with ipilimumab (<10%) than with anti-PD-1 agents (1-2%). Median onset 6-8 wks after treatment initiation 	≤4 stools/ day, or above baseline	4-6 stools/day above baseline	>7 stools/ day above baseline	Life-threatening, requiring urgent intervention
Hepatitis	<ul style="list-style-type: none"> Median onset 6-14 wks after treatment initiation 	Bili: 1-1.5x ULN AST/ALT: 1-3x ULN Albumin: 3g-LLN	Bili: 1.5-3x ULN AST/ALT: 3-5x ULN Albumin: 2-3 g	Bili: 3-10x ULN AST/ALT: 5-20x ULN Albumin: <2g	Bili: >10x ULN AST/ALT: >20x ULN Albumin: ---
Pneumonitis	<ul style="list-style-type: none"> Dyspnea, cough Onset highly variable, later than other irAEs More common with anti-PD-1 Higher risk with combination therapy 	Asymptomatic radiographic changes, confined to one lobe of lung or <25% parenchyma	Symptomatic, 25-50% parenchyma or >1 lobe involved, limits ADLs	Severe symptoms, hospitalization required, involves all lobes of >50% parenchyma	Life-threatening respiratory compromise, intubation required
Endocrinopathies	Hypo-/Hyperthyroidism, adrenalitis, hypophysitis, DMI	Asymptomatic/ mild symptoms	Moderate symptoms, may require thyroid replacement	Severe, requiring hospitalization, may need insulin or hormone replacement	Life-threatening, requiring urgent intervention

irAE Severity	Management
Grade 1	<ul style="list-style-type: none"> Continue checkpoint inhibitor Increased monitoring Supportive care
Grade 2	<ul style="list-style-type: none"> Delay checkpoint inhibitor Oral corticosteroids (0.5-1 mg/kg) as outpatient, taper over 2-4 wks Re-challenge with ICI if returned to grade 1 toxicity Increased monitoring
Grade 3	<ul style="list-style-type: none"> Delay checkpoint inhibitor, consider rechallenge if benefits outweigh risks Oral corticosteroids (1-2 mg/kg) as outpatient, IV if symptoms persist 48-72 hours, taper over 4-6 wks Consider organ specialist consultation (GI, pulm, etc.)
Grade 4	<ul style="list-style-type: none"> Discontinue checkpoint inhibitor (except for endocrinopathies managed with hormone replacement) Hospitalize for IV steroids Consider additional immunosuppressive agents if no response to IV steroids Consult organ specialist

Adapted from [Curr Oncol 2018; 5:342](#)

TUMOR LYSIS SYNDROME ([NEJM 2011;364:1844](#); [JCO 2008;26:2767](#))

- **Pathophys:** tumor lysis (from cytotoxic tx initiation; rarely spontaneous in NHL and acute leukemia) → release of intracellular components (nucleic acids → uric acid, K+, phos); **clinical effects:** renal failure (uric acid precipitates in tubules), seizure, Ca-phos crystal deposition (\uparrow phos → \downarrow Ca); arrhythmias (\uparrow K); **timing:** 1-2d after tx (can occur within hrs)
- **Presentation:** \downarrow UOP, weakness/cramps/tetany, seizure, arrhythmia
- **Risk factors:** high risk: ALL/AML (WBC $\geq 100k$), CLL (on venetoclax & \uparrow uric acid), stage 3/4 Burkitt's/lymphoblastic NHL, bulky DLBCL; intermediate risk: ALL (WBC $< 100k$), AML (WBC 25-100k or $< 25k$ & \uparrow LDH), Burkitt's, DLBCL, CLL (chemo-specific & \uparrow WBC), rare chemo-sens bulky solid tumor; low risk: HL, indolent NHL, CML, CLL (on alkylating tx & WBC $< 50k$), MM
 - High risk substrate: WBC $> 50k$, LDH $> 2x$ ULN, bulky tumor ($> 10\text{cm}$), hypovolemia, uric acid > 7.5 , renal failure
- **Labs/workup:** BMP (electrolytes, Cr, Ca), Mg, phos (calculate Ca-phos product), uric acid, CBC/diff, ECG
- **Diagnosis (Cairo-Bishop criteria):**
 - Laboratory diagnosis: ≥ 2 criteria within 3d before or 7d after cytotoxic therapy: uric acid $\geq 8\text{mg/dL}$, K $\geq 6\text{mEq/L}$, phos $\geq 4.5\text{mg/dL}$, or Ca $\leq 7\text{mg/dL}$. Criteria also satisfied if 25% change from baseline
 - Clinical diagnosis: laboratory dx & ≥ 1 clinical criteria: Cr $1.5x$ ULN, arrhythmia, seizure
- **Prophylaxis and treatment:** while treating, labs q2-4h & telemetry (electrolyte abnormalities)
 - **Hydration:** 2-3L/m² per day. Maintain UOP $\geq 100\text{cc/hr}$ for excretion of uric acid and phos; diuretics PRN
 - **Treat electrolyte abnormalities:** hyperK tx, phos binders, avoid correction of hypocalcemia until phos nml or sx
 - **Allopurinol** (\downarrow uric acid formation): 300-600mg/day, administer 24-48h before chemo, continue until hyperuricemia resolved
 - Renally dose; note reduced clearance of other meds (e.g. cyclophosphamide, MTX, 6-MP, azathioprine, ampicillin)
 - **Rasburicase** (\uparrow uric acid clearance; discuss w/ attending): 0.2mg/kg IV (but 3-6mg IV usually effective), administer if high risk, baseline renal failure, baseline elevated/rising uric acid or Cr despite allopurinol/saline, or cannot hydrate (volume overload)
 - Risk of anaphylaxis, methemoglobinemia. Contraindicated in G6PD def (hemolysis); **check G6PD early**
 - **Renal replacement therapy:** indicated if Ca-phos product $\geq 70\text{mg}^2/\text{dL}^2$ (albumin-corrected Ca × phos)

HYPERVISCOSITY SYNDROME/LEUKOSTASIS ([Blood 2012;119:2205](#); [Blood 2018;132:1379](#))

- **Etiology:** 1) hyperproteinemia from monoclonal gammopathies (mostly commonly Waldenström's macroglobulinemia [IgM], uncommonly MM) 2) hyperleukocytosis/leukostasis seen in **AML** with blasts $> 50k$ (uncommon in ALL/CLL unless very high counts); 3) other diseases such as rheumatoid disease, polycythemia, sickle cell, spherocytosis
- **S/Sx:** most common: pulm (SOB) & CNS (blurry vision 2/2 retinal vein engorgement, HA, dizziness, ataxia, confusion, coma), fever, epistaxis → page **Heme fellow & Clin Path resident for emergency viscosity study**, notify attending to discuss pheresis
- **Diagnosis:** serum viscosity (\uparrow Ostwald tube), SPEP, SFLC, **WBC (often $> 100k$, but can be lower in blast crisis)**
 - Lab artifacts from hyperleukocytosis: **spurious 1K** (use blood gas K), **falsely low arterial pO₂** (use pulse oximeter)
- **Treatment:** always start with plasma volume expansion with **IV NS**
 - **Hyperproteinemia:** **plasmapheresis** (aiming for resolution of symptoms); reduces viscosity by 20-30% per session
 - **Leukostasis:** **leukapheresis**; cytoreduce (**hydroxyurea**); **induction chemo**; avoid RBC & plt transfusion (\uparrow viscosity)

METASTATIC EPIDURAL SPINAL CORD COMPRESSION ([Seminars in Neurology 2010;30:245](#); [Lancet Neurology 2008;7:459](#))

- **Primary CA:** lung $>$ prostate & breast $>$ non-Hodgkin's lymphoma, renal cell, multiple myeloma, lymphoma
- **Location:** T (60%) $>$ L (25%) $>$ C (15%); multiple sites in 30%; ESCC score for spinal level ([JNCCN 2016;14:70](#))
- **S/Sx:** back pain (usually 1st sx; radicular, localized, worse at night/recumbent/Valsalva) → weakness, gait instability → sensory deficits (saddle anesthesia in cauda equina lesions), bowel/bladder dysfunction (urinary retention, incontinence)
- **Exam:** pain precedes other sx by ~7w, weakness/atxia, paresthesia, \uparrow reflexes, \oplus Babinski, \downarrow anal sphincter tone
- **Diagnosis:** STAT vs. urgent FULL spine MRI with cord compression/metastasis protocol, CT myelography if MRI not possible
- **Treatment:** call Spine Surgery & Radiation Oncology ASAP → more effective than chemo (except for heme, germ cell malignancies)
 - Severe deficits: **dexamethasone 96mg x1**, then 24mg IV q6h x3d, then taper x10d
 - Minimal deficits: **dexamethasone 10mg IV x1**, then 4mg IV q6h

BRAIN METASTASES WITH INCREASED INTRACRANIAL PRESSURE ([Ann Palliat Med 2015;4:225](#); [JCO 2015;33:3475](#))

- Intracranial tumors present in ~10-30% of patients with metastatic disease; call Neurosurgery & Radiation Oncology
- **Primary CA:** lung (48%), breast (18%), melanoma, RCC, osteosarcoma, head and neck, thyroid, colorectal
- **S/Sx:** HA (40-50%; "tension", worse w/ Valsalva, n/v), focal neuro deficits (20-40%, hemiparesis most common), cognitive dysfunction (30-35%), new onset seizures (10-20%), stroke (5-10%)
- **Diagnosis:** contrast MRI 1Sn $>$ non-enhanced MRI or CT with contrast
- **Treatment:** control vasogenic edema (**dexamethasone 10mg IV x1, then 8mg BID**), consider AED (usually not recommended for 1° ppx); avoid AC if concern for active hemorrhage; definitive treatment will \downarrow local recurrence: stereotactic radiosurgery $>$ whole-brain XRT (\uparrow neurocognitive impairment; hippocampal sparing helpful) $>$ surgery

SUPERIOR VENA CAVA (SVC) SYNDROME ([NEJM 2007;356:1862](#); [Mayo CP 2017;92:609](#))

- **Etiology:** external compression of SVC from a mediastinal mass (commonly lung CA or NHL) causing \uparrow upper body venous pressure
- **Symptoms:** cerebral edema (HA, confusion, herniation), narrowing of larynx/pharynx (dyspnea, stridor, cough, dysphagia, hoarseness), head/neck swelling (visually striking, often not clinically significant), hemodynamic instability (\downarrow venous return)
- **Diagnosis:** CT chest w/ (venous phase) contrast, obtain/ensure tissue diagnosis to guide tx (extremely important!)
- **Treatment:** secure airway, RT/chemo, intravascular stent (emergent/refractory), steroids (stridor/resp distress only, clear with onc)

DEFINITIONS AND ETIOLOGY ([J Oncol Pract 2019;15:19; NCCN Prevention and Treatment Guidelines](#))

- **Definition:** $T \geq 100.4$ with ANC <500 cells/mL or expected to decrease to <500 over the next 48h
 - Functional neutropenia: defective PMNs, common in leukemia (\downarrow neutrophil function despite ANC>500)
- **Microbiology:** ~30% have infectious source identified; others attributed to translocation of intestinal bacteria
 - When organisms identified: 40% GNPs (E. coli, Klebs > PsA); 60% GPCs (CoNS > MSSA/MRSA, strep, enterococcus/VRE) esp w/ indwelling lines or mucositis; fungal (Candida, Aspergillus) more likely w/ prolonged \downarrow ANC, broad-spectrum abx use, or TPN

EVALUATION

- **H&P:** prior micro data, time since last chemo, recent antibiotic therapy/ppx, major comorbid illness, use of devices
- **Exam:** mouth (mucositis), emphasis on skin, perineum/rectal (**visual inspection, avoid DRE**), indwelling lines (erythema/tenderness)
- **Studies:** BCx x2+ sites (≥ 1 periph, 1 per CVC lumen), UA/UCx, CXR, SCx/GS, resp viral panel/Covid-19 PCR, CMV PCR (SCT)
- **Further site-specific studies to consider:**
 - Diarrhea: stool culture, O&P, C. diff, abdominal pain: CT A/P (may not have abdominal pain, consider imaging)
 - Pulmonary symptoms: CT chest, \pm bronch/BAL (especially if prolonged F&N)
 - HA/sinus pain: CT face/sinus
 - Fungal markers: LDH, β -D-glucan; galactomannan if high risk for Aspergillus (SCT, GVHD, neutropenia >10-14d)
- **Risk stratification:** ([J Oncol Pract 2019;15:19; NCCN Prevention and Treatment Guidelines](#))
 - **MASCC Risk Index score** ([JCO 2000;18:3038](#)): identifies cancer patients with febrile neutropenia at *low* risk of complication
 - **High risk:** anticipated ANC ≤ 100 for ≥ 7 d, inpt status, MASCC<21, co-morbidities/infections (renal/hepatic impairment, PNA, central line infxn), allogeneic HSCT, mucositis grade 3-4, alemtuzumab use within past 2mo \rightarrow inpatient management
 - **Low risk** ([JCO 2018;36:1443](#)): anticipated ANC ≤ 100 for <7d, no co-morbidities, good performance status (ECOG 0-1), strong home social support, MASCC ≥ 21 \rightarrow treated with PO antibiotics after brief inpatient stay versus strictly outpatient

TREATMENT/PROPHYLAXIS ([NCCN Prevention and Treatment Guidelines](#))

- **Empiric abx:** within 1h; up to 70% mortality if delayed abx ([Antimicrob Agents Chemother 2014;58:3799](#))
 - **Gram-negatives (PsA dosing):** broad Gram-negative coverage (including PsA) within 60min of presentation
 - Cefepime 2g q8h (or ceftazidime 2g q8h), pip/tazo 4.5g q6h, or meropenem 1g q8h
 - PCN allergy: confirm allergy; use [Penicillin Hypersensitivity Pathway](#) and test-dose cefepime or meropenem; consider allergy consult. If true allergy, use aztreonam (avoid in ceftazidime allergy) + levofloxacin
 - High-risk ESBL: meropenem 1g q8h (2g q8h if meningitis)
 - Low risk: PO regimen; cipro/levofloxacin + amox-clav vs clinda (if PCN allergy); avoid if prior FQ ppx
 - **Gram-positives:**
 - First line: vanc; VRE: daptomycin (unless pulmonary process, inactivated by surfactant) or linezolid
 - Indications: HoTN/severe sepsis, GPC bacteremia, catheter-related infxn (rigors with infusion), SSTI, PNA on imaging, MRSA colonization (esp in HSCT), severe mucositis + prior FQ ppx + GNR coverage with ceftaz
 - **Vancomycin is NOT part of FN empiric regimen** ([JAC 2005;55:436](#); [Clin Infect Dis 2011;52:56](#)), but consider if suspicion for any of the above
 - **Anaerobes:**
 - Indications: intra-abd source, C. diff, oral ulcer/periodontal infxn, post-obstructive PNA, necrotizing ulceration
 - **Fungal:**
 - Indications: F&N $>4-7$ d despite abx, \oplus fungal biomarkers, \oplus CT chest (circumscribed, air crescent, cavity), \oplus BAL Cx
 - Micafungin 100mg q24h or Amphotericin 3mg/kg (admin after 500cc NS)
- **Modification/duration:** refer to NCCN guidelines for additional modifications
 - **Resolution of fever:**
 - Documented infxn: narrow abx and tx for recommended course, then switch to FQ ppx until ANC >500
 - Culture negative: continue empiric treatment until afebrile & ANC >500 vs narrow to FQ ppx if afebrile x4-5d
 - **Fever continues >4-7d:**
 - Clinically stable: do not broaden abx or add vanc, consider other causes (e.g. engraftment, differentiation, GVHD, TLS, drug fever, thrombophlebitis, hematoma, hepatosplenic candidiasis)
 - Clinically worsening: broaden abx \pm fungal coverage, consider CT chest \pm bronch to evaluate for fungal infxn
 - **Catheter-associated infection:** also see [Bloodstream Infections & Endocarditis](#)
 - Coag-negative staph, non-VRE Enterococcus: can keep line if IV abx + abx lock x2w
 - Staph aureus, PsA, fungi: must remove line. For gram negative, d/w attending; line removal vs lock therapy
 - Complicated infxn: (endocarditis, septic thrombosis, bacteremia/fungemia >72h), remove line, abx x4-6w
- **Prophylaxis:**
 - **Anti-microbial ppx:** refer to NCCN guidelines for more specific indications, also see [Stem Cell Transplantation](#)
 - Antibacterial (FQs): high-risk pts (heme malignancy) and attending discretion for intermediate-risk pts
 - Antifungal (azole vs echinocandin): heme malignancies during neutropenia and 75 days post-allo HSCT
 - PCP (TMP-SMX): if ≥ 20 mg prednisone daily for ≥ 1 mo, purine analog (AZA) use, & allo/auto HSCT
 - HSV/VZV (acyclovir vs famciclovir): sero+ undergoing tx while neutropenic, or 1y post-auto and 2y post-allo HSCT
 - **G-CSF:** ppx reduces incidence and duration of FN when risk >20% but does NOT decrease mortality ([JCO 2006;24:3187](#)); consider adding to FN regimen if critically ill, anticipated prolonged neutropenia, PTLD, or HIV

Oncology

Inpatient Leukemia & Lymphoma Regimens

Regimen*	Protocol	Supportive Care
LEUKEMIA		
Decitabine (5-aza-2'-deoxycytidine, Dacogen) 28d or 42d cycle	MDS/AML: 20mg/m ² IV qd D1-5 AML w/ unfavorable cytogenetics and/or TP53 mutation: 20mg/m ² IV qd D1-10	Pre-Rx: bowel reg/antidiarrheals, IVF ± lytes N/V: min-to-low Neutropenia : mod. Growth Factor : (peg)filgrastim to count recov.
5-Azacytidine (5-Aza, Azacytidine, Vidaza, Azadine) 28d cycle	AML: 300mg PO qd D1-14 MDS: cycle 1: 75mg/m ² /d D1-7; subsequent: 75mg/m ² /d q4w (dose may ↑ to 100mg/m ² /d if no benefit after C2)	Pre-Rx: first 2 PO cycles, antiemetic 30min before each dose; can omit after C2 if no n/v N/V: mod., C1-2 Neutropenia : mod. Growth Factor : (peg)filgrastim to count recov.
HiDAC (High-Dose ara-C) (ara-C, Cytarabine)	Consolidation: HiDAC: 1.5-3g/m ² q12h D1/3/5 -OR- D1-3 x3-4 cycles	Pre-Rx: steroid eye drops throughout N/V: mod. Neutropenia Risk : mod. Growth Factor : (peg)filgrastim to count recov.
Hyper-CVAD <u>Dose-intensive phase:</u> 8 cycles alternating w/ High-Dose MTX & Cytarabine (HD MTX-ara- C) + intrathecal (IT) PPx each cycle for 16 IT treatments <u>Maintenance phase:</u> Depends upon response	Hyperfractionated Cyclophosphamide (CP): 300mg/m ² IV q12h D1-3 + Mesna 600mg/m ² infusion ending 6h after last dose Vincristine: 2mg IV D4/11 Doxorubicin: 50mg/m ² IV D4 Dexamethasone: 40mg daily D1-4; 11-14 HD MTX-ara-C: MTX: 200mg/m ² IV → 800mg/m ² IV D1; leucovorin rescue 24h after completion MTX; dose to MTX level ara-C: 3g/m ² q12h x4 D2-3 Methylprednisolone: 50mg IV q12h D1-3 CNS PPx: Alternating IT: MTX: 12mg IT D2; ara-C: 100mg IT D8	Pre-Rx: NS 100mL/h prior & through CYC N/V: D1-5, high Neutropenia : high; median granulocyte & platelet recovery = 18d & 21d Growth Factor : (peg)filgrastim D5 (24h after chemotherapy)
ATRA/ATO (All-Trans Retinoic Acid/Arsenic trioxide) <u>Induction:</u> until CR. Restage w/ BM D28	Induction: ATRA: 45mg/m ² /d. Start upon first suspicion of APL ATO: 0.15mg/kg IV qd after cytogenetics confirmation Consolidation: ATRA: 45mg/m ² /d for 2w q4w, total 7 cycles ATO: 0.15mg/kg IV 5d/w for 4w q8w, total 4 cycles	Pre-Rx: none N/V: mod. Neutropenia : high Differentiation Syndrome : steroids, supportive, see Acute Leukemia Growth Factor : not during induction, consider if life-threatening infection, sepsis, etc.
Hydroxyurea (Hydrea; HU)	HU: 500mg BID or 1g qd; dose adjusted to ANC 500-1000; cytoreduction/WBC goal based on dz & tx regimen	Premedication: none N/V Risk: min-to-low Neutropenia : mod. Growth Factor : none
LYMPHOMA		
Rituximab (R)	375mg/m ² IV D1	Pre-Rx: diphenhydramine & acetaminophen
High-dose Methotrexate (MTX) Depends on regimen & count recovery, 1-8 cycles	CNS PPx: MTX: 3,000-3,500mg/m ² D1 on alternate days of regimen Leucovorin: 25mg IV or PO D2 starting 24h from initiation of MTX & q6h until MTX <0.05 μM	Hydration: D5NaHCO ₃ 100 mEq/L at 150cc/h 4h prior until 72h after MTX N/V: mod. on days of MTX Neutropenia : high Growth Factor : (peg)filgrastim D4 or 3-4d after completion to count recov.
R-CHOP 14d cycle, restage after C2-4, total 3-6 cycles ± radiation	Cyclophosphamide: 750mg/m ² IV D1 + 2-3L PO/IV fluid Doxorubicin: 50mg/m ² IV D1 Vincristine: 1.4mg/m ² (max 2mg) IV D1 Prednisone: 100mg PO D1-5 CNS PPx: IT MTX x4-8 and/or ara-C or high-dose MTX	N/V: D1, high Neutropenia : high Growth Factor : (peg)filgrastim D6 or 3-4d after completion to count recov.
Dose-Adjusted R-EPOCH 21d cycle, 6 cycles	Etoposide: 50mg/m ² infusion qd D1-4 Doxorubicin: 10mg/m ² /d continuous infusion D1-4 Vincristine: 0.4mg/m ² /d continuous infusion D1-4 Cyclophosphamide: 750mg/m ² IV D5 + 2-3L PO/IV fluid Prednisone: 60mg PO BID D1-5 CNS PPx: IT MTX x4-8 and/or ara-C or high-dose MTX	N/V: D1-5, high Neutropenia : high Growth Factor : (peg)filgrastim after completion to count recov.
(R)-ICE 14d cycle, 3 cycles	Ifosfamide/Mesna: 5,000mg/m ² infusions D2 + NS Carboplatin: dose ~ AUC 5 IV D2 Etoposide: 100mg/m ² qd D1-3	N/V: D1/3 low; D2 high Neutropenia : high Growth Factor : (peg)filgrastim D4 or 3-4d after completion to count recov.
R-DHAoX 21d cycle	Dexamethasone: 40mg PO qd D1-4 Cytarabine: 2,000mg/m ² IV D2 (2 doses) Oxaliplatin: 130mg/m ² IV D1	N/V: mod. Neutropenia : high Growth Factor : (peg)filgrastim D5 or 3-4d after completion to count recov.
R-Bendamustine 28d cycle, 6 cycles	Bendamustine: 90mg/m ² IV qd D1-2, CVC recommended	N/V: mod. D1-2 Neutropenia : high

*Chemo regimens may be modified based on genetics, risk stratification level, cardiac history, QTc prolongation. For further details on stratification and protocol details see [NCCN.org](#)

Geriatrics & Palliative Care

Pain Management

GENERAL APPROACH TO PAIN MANAGEMENT ([NEJM 2015;373:2549](#); [Lancet 2011;377:2236](#))

- Pain history and etiology can help guide therapy. Goal is to maximize level of functioning and quality of life
 - Ask about time course, location, radiation, quality, severity, exacerbating/relieving factors, associated symptoms, side effects from prior analgesics, functionality (e.g., ADLs, ambulation)
 - Use adjuvant medications and non-pharmacologics: PT/exercise/activity, heat or ice, CBT, treating comorbid psych dx, addressing existential issues, massage, acupuncture or other integrative therapies
- Step-wise approach to pain management: ([WHO Guidelines](#); [CDC guidelines](#); [DFCI Pink Book](#))
 - Mild to moderate pain: non-opioids and adjuvants
 - Acetaminophen: max dose 3g daily, 2-3g safe in liver disease ([Br J Clin Pharmacol. 2016;81:210](#))
 - NSAIDs: celecoxib best if 1GIB risk, ketorolac if severe pain, use with caution in known CVD and renal disease
 - Moderate to severe pain: schedule non-opioid options, try topicals, then consider short-acting opioids PRN
 - Severe pain: requiring around the clock opioids. Discuss w/ attending, consider adding extended release (ER) meds
 - Avoid ER opioids if pain source expected to resolve (e.g., bone fracture, hematoma)

PAIN ARCHETYPES AND USEFUL ADJUVANT ANALGESICS

- Somatic/musculoskeletal: easily localized, sharp, aching, gnawing
 - Bony pain: high dose NSAIDs or steroids*. Consider palliative XRT (if cancer-related) or surgery
 - Muscle spasm: topical lidocaine, capsaicin, methyl salicylate-menthol ointment; muscle relaxants such as cyclobenzaprine, baclofen, tizanidine (*watch for sedation & delirium*)
- Visceral: deep tissues and internal organs, vague, referred or difficult to localize
 - Visceral distension (e.g., hepatic capsular stretch from liver mets, malignant bowel obstruction): depends on etiology but steroids* can be helpful. Can consider plexus block with Chronic Pain
- Inflammatory: associated with other signs of inflammation (swelling, erythema, warmth)
 - NSAIDs, steroids*
- Neuropathic: burning, stinging, allodynia (perceiving innocuous stimuli as painful), hyperalgesia
 - Topical camphor/menthol, lidocaine, diclofenac gel (*NB: short-term benefit, available OTC*)
 - Pregabalin, gabapentin, clonidine, SNRIs (duloxetine, venlafaxine), TCAs (amitriptyline, nortriptyline, desipramine)

*considerations with steroids: in cancer patients, may interfere with treatment (e.g immunotherapy) and/or diagnostics. If prolonged course, will need GI and PJP ppx; determine who will manage taper plan at discharge

OPIOIDS

- Opioid-tolerant defined as total daily dose (TDD) x7d: morphine 60mg/oxycodone 30mg/hydromorphone 8mg/fentanyl 25mcg/h
- Patients on suboxone or methadone for OUD → consult ACT for assistance with pain management
- No max dose. Goal is to find minimum dose needed to control sx w/ minimal SE
- Avoid using combo pills (limits titration flexibility)
- Treat constipation prophylactically
- Rotate opioids if side effects, dose reduce by 25-50%

Opioid Equianalgesic Doses		
Drug	PO (mg)	IV (mg)
Morphine	30	10
OxyCODONE	20	n/a
HYDROcodone	20	n/a
HYDROMorphone	7.5	1.5
FentaNYL*	n/a	0.1 (100 mcg)
Fentanyl patch (mcg/hr)	Morphine PO (mg/day)	
25	50	

*Use caution converting to fentanyl (short duration of action)

CONVERTING OPIOIDS

Ex: Pt takes morphine ER 60mg PO q12h and uses two morphine IR 15mg PO breakthrough doses per day

Step 1) Calculate total daily opioid requirement

$$\text{TDD} = (60\text{mg} \times 2 \text{ doses}) + (15\text{mg} \times 2 \text{ doses}) = 150\text{mg morphine}$$

Step 2) Convert TDD to equivalent dose of new opioid

$$\frac{30\text{mg morphine}}{20\text{mg oxycodone}} = \frac{150\text{mg morphine}}{x} = 100\text{mg oxycodone}$$

Reduce dose by 25-50% to account for incomplete cross-tolerance
→ ~60mg oxycodone total daily dose

Step 3) Divide TDD by number of doses per day

- If initiating or converting to long-acting opioid, divide TDD into ER doses and add breakthrough dose (10-20% of TDD of ER opioid)

Final dose: oxycodone ER 30 mg q12h with 10 mg oxycodone q4h prn breakthrough

METHADONE AND FENTANYL: initiate with assistance of Palliative Care or Pain consult

- Methadone: both a mu agonist and NMDA antagonist
 - Beneficial in neuropathic pain
 - Cannot be converted linearly from other opioids
 - Safety concerns: bimodal short and long half-life (up to 150 hours), QTc prolongation (monitor K, Mg)
 - TID dosing for pain vs daily for OUD
 - Takes several days to reach steady state. Would not titrate more frequently than every 4-5 days

- Fentanyl:
 - Safer in both liver and renal dysfunction
 - Safety concerns: must remove patch if febrile (cutaneous vasodilation → faster transdermal absorption)
 - Requires 18-24h to reach therapeutic level (patch)

Geriatrics & Palliative Care

Pain Management

OPIOID PHARMACOKINETICS CHART

	Route	Sample Initial PRN Doses* (dose reduce ~50% for elderly)	Onset (min)	Peak Effect (min)	Duration of Effect (hr)	Clearance/Metabolites**
Morphine	IV	2-4mg q2-3h prn	5-10	10-30	3-5	AVOID in renal disease
	PO	7.5-15mg q3-4h prn	15-60	90-120	4	
HYDROmorphine	IV	0.2-0.4mg q2-3h prn	5-20	15-30	3-4	Safer in renal and liver disease
	PO	2-4mg q3-4h prn	15-30	90-120	4-6	
OxyCODONE	PO	5-10mg q3-4h prn	15-30	30-60	4-6	2 nd line for renal disease
FentaNYL	IV	25-50mcg q15-30m prn	<1	5-7	45m to 2+ hr	Safer in renal and liver disease
Methadone	IV	Consult pain and/or pall care	10-20	60-120	4-6	Safer in renal and liver disease
	PO		30-60	90-120	4-12	

* For opioid naïve patients in moderate or severe pain. If opioid tolerant, consider home PO breakthrough dose or 10-20% ER dose

**If concern for hepatic or renal metabolism, would use wider dosing intervals and be more cautious with uptitration

PAIN CRISIS MANAGEMENT

Severe worsening of pain; while treating, pursue reasonable diagnostic workup for etiology (e.g., bowel perforation/peritonitis, procedural complication, bleeding). **Goal is reduction in pain score by >50%**

- 1) Opioid-naïve: give morphine IV 2-5mg or hydromorphone IV 0.2-0.4mg bolus dose
Opioid-tolerant: convert usual breakthrough PO dose or 10-20% of total daily ER dose to IV and administer
- 2) Assess for response after 15min:
 - o No pain relief and no side effects → increase dose by 50-100%
 - o Minimal relief and no side effects (<50% reduction in pain score) → repeat the same dose
 - o Pain reduced >50% and no side effects → reassess in 2-3h, use this dose as new breakthrough dose
 - o Side effects with no pain relief → rotate to different IV opioid (no dose reduction if uncontrolled pain)

UPTITRATION

- If pain only moderately controlled with scheduled doses (not in pain crisis), ↑ total daily dose by 30-50%
- If taking ER opioid and needing >3-4 rescue doses daily, ↑ ER dose by 50-100% of total rescue dose used in past 24h

PATIENT-CONTROLLED ANALGESIA (PCA)

- Appropriate for patients who are alert & oriented and able to use equipment. Families may NOT use PCA by proxy at MGH
- Quickest relief if episodes sudden and severe (pain onset to drug administration; do not have to call/wait for RN to pull medication)
- PCA and/or continuous infusion, when implemented safely, reduce burden on nursing for patients who need frequent administration of pain medications (generally q1-2h is the most frequent a PRN can be ordered on the floor)
- Medicine residents can order “General PCA” (for opioid-naïve patients) or “High Risk PCA” (BMI >40, hx OSA, RAAS -2 to -5, age >65). If opioid-tolerant, requiring continuous infusion, or pain difficult to control, consult Palliative Care or Pain

General Opioid-Naïve PCA Dosing		
	Morphine	Hydromorphone
Patient Administered (PCA) Dose	1.5mg	0.2mg
Lockout Interval (in minutes)	10-15min	10-15min
One-Hour Dose Limit	6mg	1.4mg
RN/Clinician Bolus Dose (for breakthrough)	2mg q30min PRN	0.3mg q20min PRN
Continuous Infusion Rate	0mg/hr	0mg/hr

ADVERSE EFFECTS OF OPIOIDS AND MANAGEMENT

- Respiratory depression: hold opioid, consider low doses of naloxone but CAUTION if on high dose ER opioids
 - o Dilute 0.4mg naloxone (1ml) in 9ml saline, give 1-2ml q2min until ↑RR or mental status improves
 - o Naloxone half life is shorter than many opioids, watch for **recurrence** of resp depression and consider naloxone ggt
 - o All patients being discharged on opioids should also be given a naloxone prescription
- Constipation: ALWAYS start **standing Senna and/or Miralax** when initiating opioids; use other laxatives if needed; methylnaltrexone QOD if failed laxative therapy (but can cause severe nausea and cramping; avoid if concern for GI obstruction)
 - Can titrate Senna up to 4 tabs BID as tolerated and Miralax up to 34 grams BID as tolerated
- Myoclonus: reduce dose or rotate opioid, increase hydration/IVF; can give low dose BZD, baclofen or gabapentin
- Nausea/vomiting: prochlorperazine, metoclopramide, haloperidol; **avoid ondansetron** (constipating)
- Pruritus: pruritus mediated by mu receptor (not histamine - Benadryl ineffective, unless rash/allergic reaction); consider opioid rotation or nalbuphine 5mg IV q6h
- Sedation: consider CNS stimulants (dextroamphetamine, methylphenidate)
- Delirium: reduce dose or rotate opioid; Haldol 0.5-1 BID-QID or Zyprexa 2.5-5 mg PO QD-BID

Geriatrics & Palliative Care

Adv Care Planning & Code Status

SERIOUS ILLNESS CONVERSATIONS

When? Preferred early in disease course as outpatient; however, in the inpatient setting can come up organically or can be brought up by providers in certain scenarios:

- New or progressive serious medical illness such as advanced cancer, ESRD, ESLD, HF, COPD
- Prognosis trigger: "Would I be surprised if this patient died in the next year?" ([J Palliat Med 2010;13:837](#))
- Indicator of life expectancy <6mo ([calculator, J Palliat Med 2012;15:175](#))
- Age >80 and hospitalized; see [Geriatrics: Frailty](#)

Why? Ascertain how the patient wants to **live**, what they **value**; more than just end of life care preferences

How? Conversations can be planned or may happen spontaneously in any setting ([NEJM 2014;370:2506](#))

Preparation for planned meetings:

- Identify time and location to accommodate all meeting participants in an appropriate manner
- Include patient and their preferred participants, primary team, RN, SW, and other providers as appropriate
- If complex decisions/psychosocial issues/family conflict, consider palliative care consult
- Pre-meet with team, including subspecialty consultants, to discuss: goals, unified assessment of clinical scenario, if a clinical decision needs to be made urgently, and if so, what are treatment options and team recommendations

Serious Illness Conversation (SIC): suggested outline/prompts

Step	Suggested Prompts
Open the conversation	"I'd like to talk about what is ahead with your illness. Would that be ok?"
Assess illness understanding and prognostic awareness	"What is your understanding of your illness?" "Looking to the future, what are your hopes about your health?" "What are your worries?"
Share hope and concerns	"Would it be ok if we talked more about what lies ahead?" "I hear you're hoping for _____ and I'm worried the decline we've seen will continue" or "I hope that this is not the case and I'm worried something serious may happen in the next (time window: weeks, months, years)"
Align	"I wish we didn't have to worry about this"
Explore what's important	"If your health worsens, what is most important to you?" "How much do your family or friends know about your priorities and wishes?"
Close the conversation	"It sounds like _____ is very important to you" "Given what's important to you, I would recommend _____"

**Note: some patients may respond better to being asked about their "health" rather than their illness, especially those who are semi-stable in clinic but have frailty or multiple comorbidities

Next Steps:

- Debrief with team: "How did that feel? What went well? What could have gone better?"
- Document Serious Illness Conversation in Epic:
 - Patient ID banner (top left of storyboard): click "Code: _____" → "Advance Care Planning Activity" → "Serious Illness Conversation" in left tab; fill out SIC form → "Close"
 - Open a note with type "Advance Care Planning" and use the dot phrase to insert the SIC → type .seriousillnesslast

ADVANCE CARE PLANNING FORMS

- **Health Care Proxy (HCP)**/medical power of attorney: an advance directive document that designates a healthcare agent to make future medical decisions if patient loses capacity. Expressly authorized in MA by statute
 - *If no HCP:* surrogate hierarchy: see Section 3, bullet 6 of [MA: An Act Improving Medical Decision Making](#)
- **Living Will:** an advance directive document in which a competent person specifies future medical treatments in the event of incapacity, usually at end-of-life or if in a persistent vegetative state. Can be used as evidence of a person's wishes, but not considered to have legal authority (no MA statute that expressly authorizes)
- **MOLST** (MA Medical Orders for Life-Sustaining Treatment; hot-pink form available on all medical units): medical orders for patients with advanced age or serious illness that documents preferences for CPR, intubation, hospital transfer, artificial nutrition, dialysis, and more
 - Transferrable to outside facilities; must complete MOLST prior to discharge to rehab/SNF if patient DNR/DNI
 - Remember that you **do not** have to fill out or discuss everything on the back page (clinical discretion)
 - As a PCP/outpatient provider, can fill out a MOLST with longitudinal patients. Provide patients with a copy and scan into Epic for future documentation
- **Links to MOLST/HCP forms** are found in [Advance Care Planning Activity tab](#) or scanned into the [Media tab](#)

CODE STATUS DISCUSSIONS

General Considerations

- Epic prompts to confirm code status at time of admission; can “defer discussion” if necessary
- Confirm directly with the patient/HCP, MOLST, and/or prior documentation by outpatient providers
- Readdress if a patient’s clinical status changes, or if code status is deemed inappropriate for the clinical setting, but do *not* need to routinely readdress on admission if has been recently addressed by outpatient providers
- Code status should reflect a patient’s values and preferences and is not equivalent to ACP (it is a specific medical procedure for which harms/benefits should be weighed given clinical context)

Survival Outcomes ([Circulation 2019;139:e56](#))

- *Out-of-hospital cardiac arrest:* survival to hospital discharge 10.4%; survival with good neurologic function 9.9%
- *In-hospital cardiac arrest:* survival to discharge 25.6%; survival with good neurologic function 22%
 - Favorable prognostic factors: ACS, drug overdose, drug reaction (up to 40% survival)
 - Unfavorable factors: age >80 (<10% survival), multi-organ failure, sepsis, advanced cancer, ESRD, ESLD, dementia
 - Post-arrest complications: hypoxic-ischemic brain injury, rib fractures, pulmonary contusion, prolonged ICU care

Conducting Code Status Discussions ([JAMA 2012;307:917](#))

- **Initial tips:**
 - Suggested framing of CPR and intubation for patients: “CPR is a medical procedure we would perform if you were to die, that is, if your heart were to stop and you were to stop breathing. CPR includes pressing on your chest to pump the heart and inserting a breathing tube into your mouth and the use of a breathing machine to help you breathe.”
 - Do not offer DNI alone, as resuscitation almost always requires intubation. Can offer DNR/OK to intubate if this is in line with patient’s goals
- **Three common goals** for conversations about CPR and intubation ([NEJM 2020;382:2450](#))

Goal for the conversation	Indication
Information gathering	The patient has a stable condition and is likely to benefit from CPR and intubation The patient already has a preference to limit CPR and intubation that needs confirmation It is the wrong time for a more in-depth conversation.
Shared decision making	The patient has an advancing illness, and it is unclear whether the benefits of CPR and intubation would outweigh the burdens because at this point the decision depends heavily on the patient’s values and goals
Informed consent	The patient is at risk for decompensation/death, unlikely to benefit from CPR and intubation

Information gathering conversation (when a patient has a stable condition and is likely to benefit)

Aim: make sure the patient does not strongly prefer to avoid these medical interventions

- “Have you ever discussed CPR and intubation with your medical team?” “What are your thoughts about it?” “Right now, if your heart were to stop, you would receive CPR. Is this consistent with your goals?”

Information gathering conversation (when a patient has an established preference to limit CPR and intubation)

Aim: confirm an already established preference

- “Your records show that you made an emergency plan with our outpatient doctor to focus on comfort and allow for a natural death. This means that we would not use chest compressions to start your heart or a use a breathing machine. Based on my medical assessment, I think we should continue this plan now. Does that sound right to you? We will do everything else we can to help you get through this.”

Informed consent conversation

Step	Suggested Prompts
Introduce/assess	See SIC table for prompts. If urgent: “I wish we were meeting under different circumstances.”
Share information	“Unfortunately, we are in a different place now.” (Discuss medical situation, share concerns using hope/concern statements)
Explore goals	“Given where we are, what is most important to you?”
Make a recommendation	“I recommend we make a plan to help you meet your goals and avoid treatments that are unlikely to help.” “Our plan to help you meet your goals is...” “I recommend that if your heart and lungs were to stop working, we focus on your comfort. This means having treatments such as oxygen and medication. This also means we would not use CPR or a breathing machine. Does this plan sound OK to you?”

PRIOR TO DEATH

- Involve family ± chaplaincy (available 24/7), longitudinal care team members (e.g. PCP). Ask about religious/cultural traditions
- When passing off patient who may pass away, prep the “Report of Death” form (at min, cause of death section); form available w/ OA
- Consider whether you will need to notify medical examiner. Common reasons:
 - Any acute or chronic alcohol-associated death, including due to alcohol-related cirrhosis
 - Death associated with diagnostic or therapeutic procedures
 - Death by accidental/unintentional injury (including falls), criminal violence, or suicide

WITHDRAWING VENTILATORY SUPPORT (palliative extubation, discontinuation of NIPPV)

- Prior to extubation, refer to MGH MICU Policy and ATS Guidelines ([AJRCCM 2008;177:912](#)). Review plan with the following people:
 - Family: Ask if they want to spend time privately with patient prior to extubation. As appropriate, review expected signs of dying process (agonal breathing/rattle' of pooled secretions, mottled extremities), expected timeline [usually minutes to hours ([Chest 2010;138:289](#))] and plan for symptom control
 - RN: Ensure adequate PRNs for air hunger/pain (IV opioids), anxiety (IV haldol, IV benzo), and secretions (glycopyrrolate) at bedside (see [Comfort Focused Care](#)). May need continuous infusions depending on requirements. Stop paralytics
 - RT: Determine plan for immediate withdrawal vs down-titration of vent support
- Do not withhold appropriate sx management because of concern for hastening death
 - “*The Rule of Double Effect*” ([NEJM 1998;338:1389](#)): focus on managing sx, including palliative sedation if no other reasonable options. If in doubt, ask for help

ORGAN DONATION

- Eligibility: after family and medical team decide to discontinue medical support, medical team notifies New England Organ Bank (NEOB), (800) 446-6362, who coordinates consent and donation. This process can take up to 24h. DO NOT broach topic of potential organ donation with family; NEOB is specifically trained to do this
- Care prior to donation: maintaining organ viability during severe autonomic/inflammatory responses following severe neurologic injury. Key goals: MAP 60-110, normothermia, UOP 0.5-1.0cc/kg/hr, LTVV ([CCM 2015;43:1291](#); [NEJM 2004;351:2730](#); [JAMA Surg 2014;149:969](#))
- OR Preparation: Death paperwork must be signed in OR by declaring MD (prepare in advance). After ventilatory withdrawal (usually extubation in OR), MD/RN coordinate symptom management until time of death, declare death based on irreversible cessation of circulatory/respiratory function

DEATH PRONOUNCEMENT

PRONOUNCEMENT. Introduce yourself to the family, explain what you are doing, express condolences

- FEEL for pulse, LISTEN for heart sounds/breath sounds (> 60 sec), SHINE light to determine absence of pupillary light reflex, and NOTE time at the end of your exam, which becomes the time of death

QUESTIONS FOR NEXT OF KIN (Not HCP, but **Next of Kin (NOK)**): Husband/Wife > Children > Other Family

- If no NOK in room, call NOK to notify of patient's death
- Ask the family if they would like to see a chaplain or social worker
- Ask if family would want an autopsy
- If family accepts autopsy, ask about disposition of organs. Consider recommending the option of MGH retaining organs for further testing, education, research
- Are there other family members they would like you to inform?
- Will anyone else be coming to view the body prior to transport to morgue?
- **What you can tell family**: body is kept at MGH until the funeral home calls MGH and arranges for pick-up. Ask family if they plan to contact funeral home or if they have a preferred funeral home they want notified

AUTOPSIES are **free** and do not delay funerals (can still have open casket). In addition to helping determine cause of death, they can be instrumental in advancing research

ONCE YOU LEAVE THE ROOM:

- **Notify ATTENDING and PCP**. Email acceptable if death was expected
- **Obtain “Report of Death” form** from OA. Fill out in **BLACK** ink. If any mistakes, you will need to START OVER
 - Log into Epic before calling the numbers listed on the form
 - Call the Medical Examiner if necessary or in doubt (see above “prior to death”, most cases not necessary). Document the first name of the staff member
 - Call New England Organ Bank: 800-446-6362: will need patient's demographics, cause of death. May require history of cancer, recent infections, recent labs, hx dementia, other PMHx
 - Call the Admitting Office (x6-3393) to inform them of the death. They will ask cause/time of death, Med Examiner, NEOB
 - The “Report of Death” goes to admitting with the chart. Chart/patient cannot leave the floor until the Report of Death is completed
- **Document a brief “note of patient death”**: SmartPhrase “.MGHDOMDEATHNOTE”
- Complete short **discharge summary** using “Deceased Patient” portion of the Discharge tab in Epic

Geriatrics & Palliative Care

Comfort Focused Care & Hospice

CMO GENERAL PRINCIPLES

- CMO: "Comfort Measures Only;" a care approach focused on patient comfort rather than reversing underlying medical issue. Does not mean all treatments need to be stopped, but instead it means **tailoring care** to maximize comfort
- Reflects pt's goals rather than current medical state. Pts at EOL (a medical state) are not always CMO (goals/values)
- Goals: maximize comfort (treating pain, anxiety, dyspnea, N/V, delirium), enable loved ones' time with patient, and facilitate end of life rituals as feasible. **Offer chaplaincy and social work services**
- Communicate expected signs of dying and time course to loved ones. Offer to call additional family members
- Prepare paperwork and logistical planning as feasible prior to death (see [End of Life and Pronouncement](#))

PRACTICAL TIPS FOR CMO: DISCONTINUING NON-BENEFICIAL CARE

- Lines/tubes: maintain IV access as possible, d/c central line as feasible
- Foley: can maintain for comfort; discuss w/ RN
- Stop labs, routine VS. Okay to monitor RR and temperature for symptom management
- Medications: continue meds contributing to patient comfort, those that will prevent uncomfortable events (e.g. maintain rate control to avoid AFRVR, AEDs for seizure control), or that have a withdrawal syndrome (e.g. SSRIs)
- Tube feeds, TPN/PPN: generally avoid; may cause volume overload without meaningful benefit ([JCO 2013;31:111](#))

Example PRN Orders: if questions or concerns, consult Palliative Care for support

*Always treat acute symptoms with boluses rather than changing drip rate. Drips take hours to reach steady state

**If ongoing uncontrolled acute symptoms despite IV bolus, can repeat after 20-30min at same dose or doubled dose and change PRN bolus dose to reflect effective dose for symptom benefit

	Floor (IV access)	Floor (no IV access)	ICU
Analgesia/dyspnea	Opioids: see example in Pain Management . Can uptitrate dose q30min PRN for air hunger/discomfort		
Secretions	Glycopyrrolate 0.2-0.4mg IV q6h PRN	Glycopyrrolate 1mg PO q6h PRN	Glycopyrrolate 0.2-0.4mg IV q6h PRN
Delirium, Nausea, Restlessness, Anxiolysis	Haldol 0.5-1mg IV q6h PRN	Olanzapine 2.5-5mg SL q6h PRN	Haldol 0.5-1mg IV q6h PRN
Anxiolysis associated with dyspnea	Lorazepam 0.5-1mg IV q4-6h PRN (increase as needed)	Lorazepam 2-4mg PO q4-6h PRN (increase as needed)	Midazolam 2-4mg IV bolus, 2-4mg gtt, OR lorazepam 2.5-10mg q15min PRN

Resources: Palliative Care Network of Wisconsin [fast facts and concepts](#) for disease specific resources; DFCI resources: [Pink Book](#) for pain, [Green Book](#) for nausea/vomiting

HOSPICE OVERVIEW

- **Hospice**: multidisciplinary care for patients with advanced illness and life expectancy <6mo with goal of providing comfort rather than reversing underlying disease. Paid through Hospice Insurance Benefit (most often through Medicare)
- **Can be provided in multiple locations**, including home (most common), SNF, residential facility, or acute care hospital depending on patient's care needs and caregiver support
- Services include: intermittent nursing care (~1-2 visits/w with 24/7 on-call emergency support), social work, chaplaincy, all medications and supplies related to terminal illness or comfort, equipment (bed, commode, wheelchair etc.), home health aide (avg 1 h/d), bereavement support, short-term respite care (provides relief for caregivers), and short-term inpatient care for symptoms that cannot be managed at home. **Caregiving most often provided by family and friends**
- **DOES NOT** cover room/board at facilities or 24/7 nursing care
- Hospice sometimes covers treatments like abx, IVF if it will contribute to pt's comfort. Determined on case-by-case basis

GENERAL INPATIENT HOSPICE (GIP)

- GIP Hospice: level of care for hospice patients who have symptoms that cannot be managed in home setting (e.g. high flow O2, uncontrolled sx requiring IV medications, high RN needs for wound care/suctioning)
- Can occur at "Hospice Houses" or at MGH
- Hospice houses have more "home-like" feel compared to MGH. Consider if pt not actively/imminently dying, has prognosis on scale of days to weeks, and stable enough for transport
- Consider GIP at MGH for pts who are actively or imminently dying and/or cannot safely transport
- Discuss w/ floor CM team (for insurance benefit screen and coordinate w/ hospice liaison) and Pall Care if pt is appropriate for GIP Hospice and if so, which location
- If admitted to GIP at MGH, pt transitions off Housestaff team and Pall Care becomes primary team

Geriatrics & Palliative Care

Frailty & Polypharmacy

FRAILTY

Screening: consider for all admissions: >70yo, frequent falls/admissions, “failure to thrive” or “possible placement”

- Reframe “failure to thrive” as frailty, which has evidence-based assessment criteria and diagnostic approach
- **Definition:** “medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death” ([JAMDA 2013;14:392](#)). Older age is a risk factor but is not necessary or sufficient for the diagnosis
- Most cited tool is [Phenotype of Frailty \(J Geront 2001;56:M146; BMC Geriatr 2013;13:64\)](#) but can use quick screen below
- **FRAIL screen:** **frail** = 3 or more \oplus answers; **pre-frail** = 1-2 \oplus answers ([J Nutr Health Aging 2012;16:601](#))
 - **Fatigue:** “In the past four weeks, do you feel tired all or most of the time?”
 - **Resistance:** “By yourself, do you have any difficulty walking up 10 steps without resting?”
 - **Ambulation:** “By yourself, do you have any difficulty walking a city block?”
 - **Illnesses:** Does patient have more than 4 comorbidities?
 - **Loss of weight:** Greater than 5% weight loss over past year?

Inpatient frailty assessment: find the root cause!

- Thorough H&P and workup to evaluate for new/progressive illness and reversible causes
- Assess whether cognitive decline, physiology of aging, or manageable medical pathology is driving the frailty
- **Ddx:** anemia, infxn, cancer, HF, COPD, cirrhosis, CKD, DM, PMR, thyroid dz, nutrition def. (incl vitamin D), depression
- **Physical functioning:** goal is to identify ADL/IADL deficits for targeted intervention
 - Katz ADL Scale (“Does anyone help you with: walking, feeding, dressing, bathing, grooming, toileting?”)
 - Instrumental ADLs (“Does anyone help you with: cooking, cleaning, shopping, driving, medications, finances?”)
- **Cognition and mental health:**
 - Evaluate for delirium with Confusion Assessment Method (see [Delirium](#)) & mental status exam (see [Psychosis](#))
 - If negative, proceed to [Mini-Cog](#) evaluation to screen for dementia; if any deficits, refer for outpatient evaluation
 - Always screen for depression with PHQ-2 (see [Health Screening & Maintenance](#))
- **Social functioning:** how much social support does the patient require? Address advanced directives/HCP/Code Status

Interventions for frailty ([Age Ageing 2017;46:383](#))

- Establish **patient- and family-centered goals** to guide treatment plan
- **Exercise:** PT; exercise programs (e.g. Tai Chi) can reduce fall risk ([JAMA 2018;319:1705; BMC Geriatr 2020;20:108](#))
- **Nutrition:** nutrition consult, particularly for patients with weight loss
- **Cognition training:** inpatient: delirium precautions (limiting overnight VS/interventions, labs, lines/tethers, physical/chemical restraints); outpatient: OT consult (improve short-term memory, info processing, problem-solving)
- Home **environment assessment** and modifications: consider social work consult, OT consult, iCMP referral
- Referral to OP [geriatrics/palliative care](#) for regular review of medications and **reduction in polypharmacy** (see below)

POLYPHARMACY AND INAPPROPRIATE MEDICATIONS

Preadmission Medication List (PAML) on admission: especially important for patients with frailty

- Boston-area 24/7 pharmacies: CVS: 781-894-1600 (dial 2, 2); Walgreens: 617-389-2188 (dial #,0)
- **Coordinate discharge Rx planning** and education with patient, pharmacy, PCP → lower risk of readmission with intensive pharmacist intervention (med rec and education) and coordination with PCP ([JAMA IM 2018;178:375](#))

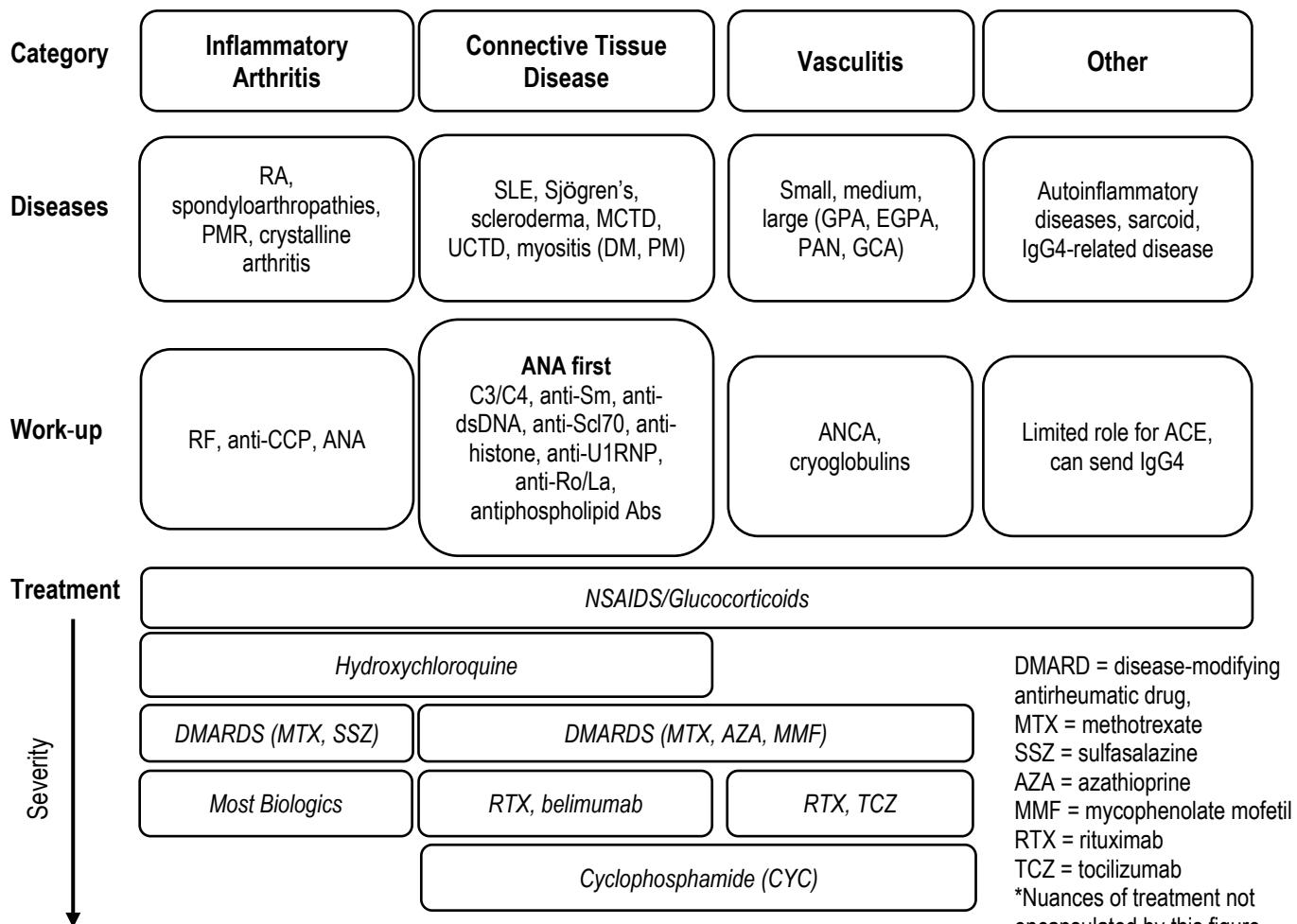
Inappropriate medications for elderly patients ([Medication Appropriateness Index; MedStopper; deprescribing.org](#))

- **Classes to (usually) AVOID in geriatric patients:** See Beer's list ([J Am Geri Soc 2019;67:674](#)) and [STOPP-START](#) for further details on potentially inappropriate meds
 - **Anticholinergics:** delirium, falls, blurred vision, urinary retention, tachycardia. Avoid antihistamines, TCAs, MAOIs, antimuscarinics (oxybutynin), muscle relaxants (cyclobenzaprine), prochlorperazine
 - **Benzodiazepines:** delirium, falls, cognitive impairment, etc. (also risk w/ non-BZD hypnotics)
 - **Antipsychotics:** ↑mortality with antipsychotics in the elderly ([JAMA Psych 2015;72:438](#))
 - **Peripheral alpha blockers and central alpha-agonists:** -zosins and clonidine → risk of orthostasis and falls
 - **Long-acting sulfonylureas and rapid/short acting insulin:** hypoglycemia
 - **PPIs:** C. diff, bone loss/fracture (switch to H2 blockers unless clear indication for PPI)
 - **NSAIDs:** CVD, GI bleed, AKI (especially in elderly patients with decreased CrCl)
 - **Aspirin for primary CVD prevention:** bleeding (use with caution and reevaluate at age >70)
- **Parkinson's disease:** ondansetron is antiemetic of choice. Avoid metoclopramide, prochlorperazine, antipsychotics
- **Dosage adjustments:** ensure appropriate renal and weight-based dose adjustment for anticoagulants (enoxaparin, apixaban, rivaroxaban, dabigatran), antibiotics, etc.
- Ask about OTC meds and herbal/dietary supplements, which can be easily missed culprits of drug-drug interactions

Rheumatology

Approach to Rheumatologic Disease

OVERVIEW: rheumatologic diseases may be roughly separated into 4 categories



RHEUMATOLOGIC ROS

Fever, arthritis, rashes/photosensitivity, alopecia, nail/nailfold abnormalities, sicca symptoms, conjunctivitis, uveitis, episcleritis, scleritis, Raynaud's, acrocyanosis, oral/genital ulcers, polychondritis, enthesitis, serositis sx, thromboses, neuropathy, pregnancy loss

BASIC LABS: CBC/diff, BMP, LFTs, UA, ESR/CRP, TSH

DDx

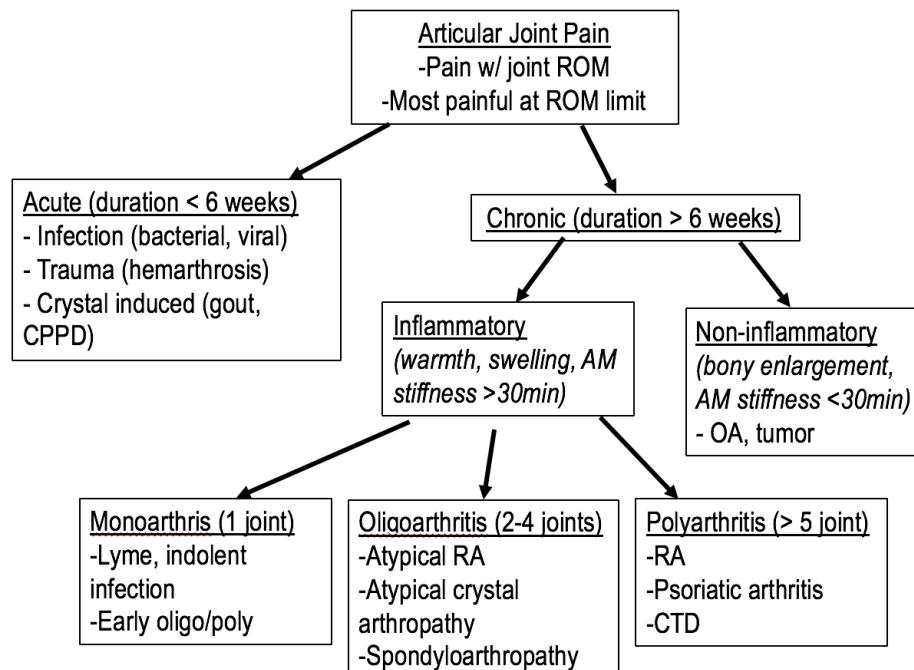
Always consider malignancy and infection as alt. diagnoses prior to initiation of immunosuppressants unless at risk of permanent organ damage (i.e. do not withhold glucocorticoids when suspecting GCA, mononeuritis multiplex, RPGN, etc.)

COMMON INPATIENT RHEUM CONSULT QUESTIONS

1. Inpatient inflammatory arthritis, should this patient have a joint aspiration/injection?
2. Guidance on interpretation/further work-up of positive rheumatologic serologies (i.e. positive ANA (>1:80), +RF, etc.)*
3. Work-up/management of FUO
4. Patient with history of established rheumatological disease and c/f exacerbation or complication (i.e. h/o SLE and c/f flare, nephritis, pericarditis, cytopenia, etc.)
5. Concern for new onset vasculitis including GCA
6. Concern for new onset myositis
7. Work-up/management of new interstitial lung disease
8. Work-up/management of inflammatory eye disease
9. Guidance on immunosuppressive meds for pt w/ established rheumatologic dz & c/f new infection or malignancy

***Important note:** rheumatologic serologies are pieces of data that must be incorporated into the larger clinical picture. A patient with new onset pericarditis and +ANA with no other signs/sx of rheumatologic disease is different from a +ANA in a young F with recurrent pericarditis, inflammatory arthritis, leukopenia, and a history of pregnancy loss. Incorporate history and exam findings when contemplating Rheumatology consult for a positive serology

APPROACH TO THE PATIENT WITH ARTHRITIS



ACUTE ARTHRITIS SYNDROMES

Arthritis	Joint pattern	Presentation	Diagnosis	Treatment
Gout	- Mono>poly - Podagra (1 st sx in 50% pts), hindfoot, fingers, ankle, knee	- Triggers: diuretics, meat, seafood, EtOH, HTN, DM2, CKD - Acute flares → chronic arthropathy (tophi) - Urate nephrolithiasis, chronic nephropathy	- Arthrocentesis: neg birefringent needle-shaped crystals, WBC 10k-100k/uL - Can co-exist with septic arthritis - ACR-EULAR Criteria for Gout can help establish likelihood of dx in absence of synovial fluid crystals	- <u>Acute</u> : colchicine (1.2mg x1, 0.6mg 1h later, 0.6mg 1-2x daily until 2-3d after resolved), pred 40mg QD until resolved then taper, NSAIDs (naproxen 500mg BID or indomethacin 50mg TID for ~5-7d), intra-articular steroids (if 1-2 joints) - <u>Chronic</u> : urate lowering tx if ≥2 attacks/y, CKD, tophi (uric acid goal <6); diet changes; stop diuretics. Do not stop during acute attack
CPPD (pseudo-gout)	- Mono>poly - Knee>wrist, shoulder, ankle	- Can be asymptomatic - Can coexist with gout, OA	- Arthrocentesis: small pos birefringent rhomboid crystals, WBC 10k-100k/uL - chondrocalcinosis	- <u>Acute</u> : if ≤2 joints → intra-articular steroids (1st line) . 2 nd line same as gout (colchicine w/in 24h sx onset) <u>Chronic</u> : HCQ, low-dose pred, MTX
Septic arthritis	- Mono - Knee (50%), >1 joint (20%)	- Hematogenous spread (most common), endocarditis - ↑ risk in RA - Staph>strep>GNRs	- Arthrocentesis: positive GS/Cx, WBC 50k-150k/uL	- Antibiotics for 3-4w - Joint drainage/washout (ortho c/s)
Reactive arthritis	- Oligo > mono > poly (small joints) - Asymmetric - LE > UE	- 1-4w post-infxn*: Conjunctivitis, urethritis, cervicitis, oral ulcers, keratoderma, E nodosum	- Presence of preceding infection* - Arthrocentesis: GS/Cx - Stool cx (if diarrhea) - GC/Chlamydia	- If GU infxn, treat. If GI infxn, may not need to treat - <u>Acute</u> : NSAIDs > intra-articular steroids > prednisone - <u>Chronic</u> : if >6mo, MTX or SSZ

* Causes: Enteric: *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C. diff*; GU: *Chlamydia*, *E. coli*, *Ureaplasma*, *Mycoplasma*

Rheumatology

Arthritis

CHRONIC ARTHRITIS SYNDROMES				
Arthritis	Joint pattern	Presentation	Diagnosis	Treatment
Osteoarthritis	- Poly - Knees, hips, MTP, CMC, PIP, DIP, C-spine, L-spine	- Age >45 - AM stiff <30min, slow progression, no warmth, muscular wasting - <u>Stage 1</u> : pain limits high-impact activity - <u>Stage 2</u> : constant pain, affects ADLs - <u>Stage 3</u> : intense pain	- Clinical dx - Bony swelling, joint deformity, limited ROM	- PT, braces - Topical NSAIDs, PRN NSAIDs - Duloxetine 60-120mg QD - Intra-articular steroids - If severe, refer to ortho - Not recommended: glucosamine, bisphosphonates (ACR Guideline 2019)
Rheumatoid Arthritis	- Mono in early stage, then poly - Small peripheral (MCP, PIP, wrists, MTP) - Symmetric	- F>M, age 35-65 - AM stiff >30min - Joint deformity	- RF, anti-CCP - Joint XR - Exclude other causes	- <u>Acute</u> : prednisone or NSAIDs , initiate DMARD if not on already - <u>Chronic</u> : DMARD (MTX > HCQ > SSZ > leflunomide); 2 nd line combination or transition to biologic (infliximab, abatacept, tocilizumab)
Psoriatic arthritis	- 5 patterns (distal [DIPs], asymm oligo, symm poly, arthritis mutilans, spondyloarthritis [sacroiliitis]) - axial (spine) involvement (42%)	- 70% with psoriasis - <u>Extra-articular</u> : tenosynovitis, enthesitis, dactylitis, nail pits/onycholysis, uveitis	- Clinical dx - ↑ESR/CRP (40%) - HLA-B27 - CASPAR criteria (91% Sn, 99% Sp)	- NSAIDs (1 st line) - If mod/severe, MTX > SSZ, leflunomide - If severe/erosive, TNFα inhibitor (infliximab, adalimumab, golimumab) (ACR Guideline 2018)
Ankylosing spondylitis	- Spine & SI joints	- Gradual onset - AM stiff >30min - Pain in low back, buttock - <u>Extra-axial</u> : synovitis (mono or oligo; ankle or other large joint), TMJ pain, enthesitis, dactylitis, uveitis, psoriasis, IBD	- Sacroiliitis (XR or MRI) - ↓ spine mobility - ↑ESR/CRP, HLA-B27 (90% Sn/Sp but low PPV due to prevalence)	- NSAIDs (1 st line) - No steroids - DMARDs <u>not</u> effective - TNFα inhibitor (2 nd line) (infliximab, etanercept, adalimumab)

SYNOVIAL FLUID ANALYSIS					
	Normal	Non-Inflammatory	Inflammatory	Septic	Hemorrhagic
Clarity	Clear	Clear	Clear-opaque	Opaque	Bloody
Color	Pale yellow	Yellow	Yellow to opalescent	Yellow to green	Red to brown
Viscosity	High	High	Low	Variable	Variable
WBC (per mm ³)	<200	0-2,000	2,000-100K	50-150K	200-2,000
PMNs (%)	<25	<25	≥50	≥75	50-75
Major Ddx		OA, trauma, AVN, mechanical dysfunction	Many: inflammatory and infectious arthropathies, rheumatic diseases, gout/CPPD	Septic arthritis; occasionally, noninfectious: gout, reactive arthritis, RA	Trauma, coagulopathy, iatrogenic, tumors, scurvy

Rheumatology

Connective Tissue Diseases

Disease	Clinical Presentation	Work-up	Treatment	Complications
SLE	<ul style="list-style-type: none"> - F>M, 15-40yo, Afr./LatinX/Asian descent > White - constitutional sx (fever, wt loss, fatigue), malar rash (spares NL fold), discoid lesions, photosens., oral/nasal ulcers (often painless) - arthritis: migratory, polyarticular (knees, carpal joints, PIPs > other), symmetric, nondeforming. Morning stiffness brief - cytopenias, serositis, nephritis, pneumonitis/DAH/ILD, CNS dz (seizure, CVA, neuropsych) 	<ul style="list-style-type: none"> ⊕ ANA (>95%; Sn not Sp) ⊕ anti-dsDNA (~70%, a/w active dz & lupus nephritis) ⊕ anti-Sm (30%, Sp, remains ⊕ in remission) ⊕ anti-RNP (30-50%) ⊕ anti-SS-A/Ro, ⊕ anti-SS-B/La (35%, 15%) ⊕ antiphospholipid Abs (40%) - CBC/diff, BMP, Coomb's, C3/4, ESR/CRP, UA/UPCR <p>(2019 EULAR/ACR Criteria)</p>	<ul style="list-style-type: none"> - All: HCQ (↓ flare rates, thrombosis, mortality), incl. preg. unless CI (Ann Rheum Dis 2010;69:20) - Nephritis: steroids + (MMF or cyclophosph. [CYC]) → MMF or AZA - Skin, joint, serositis: prednisone & HCQ - Other end organ: pred, HCQ, & (MTX, MMF, CYC, biologics) 	<ul style="list-style-type: none"> - CVD (Semin Arthritis Rheum 2013;43:77). - High risk VTE/AE (APLS) - Preg. (neonatal death, pre-eclampsia, premature delivery) - Osteonecrosis (both 2/2 SLE and steroids)
Drug-induced lupus (DIL)	<ul style="list-style-type: none"> - Fever, arthralgias/arthritis, myalgias, rash, serositis - Other SLE complic. less frequent - Months-years exposure (Ann NY Acad Sci 2007;1108:166) - Isolated subacute cutaneous lupus drug-induced in ~1/3 of cases (Br J Dermatol 2012;167:296) - High risk: procainamide (15-20% per y), hydralazine (5-10% per y). Mod: quinidine. Low: penicillamine, carbamazepine, methyldopa, SSZ, mino., chlorpromazine, PTU, INH 	<ul style="list-style-type: none"> *Serologies/clinical features often unique to the offending drug ⊕ ANA (almost all cases) ⊕ Anti-histone (>95% but also ≤80% of idiopathic SLE) ⊖ anti-dsDNA (exc. TNFi, IFN) ⊕ anti-SS-A/Ro (not Sp) 	<ul style="list-style-type: none"> - Withdraw offending agent: resolution may take weeks-months - Occasionally NSAIDs, HCQ, steroids for sx 	
Sjogren's	<ul style="list-style-type: none"> - F>M, 40-60yo - Sicca (dry mouth/eyes), caries, parotid enlargement, vasculitis, interstitial nephritis, neuropathy, cytopenias, RA/SLE a/w 2° SS 	<ul style="list-style-type: none"> ⊕ ANA ⊕ anti-SS-A/Ro, ⊕ anti-SS-B/La - Schirmer test, parotid US, salivary gland bx 	<ul style="list-style-type: none"> - Sicca only: sx mgmt - Systemic: HCQ, MTX, AZA, RTX, CYC, steroids 	<ul style="list-style-type: none"> - 5-10% lifetime risk of NHL, MALT lymphoma
Myositis (poly-, dermat-, inclusion body)	<ul style="list-style-type: none"> - F:M (2:1), 40-50yo - Proximal>distal muscle weakness - <u>Extramuscular</u>: constitutional sx, arthralgias, dysphagia, pulm sx (cough, DOE, ILD), HTN, DM2 - <u>DM skin findings</u>: heliotrope rash, poikiloderma (chest: V-sign; back: shawl sign; thigh: Holster sign), scalp rash, Gottron's papules - clinically amyopathic DM (CADM) a/w severe ILD 	<ul style="list-style-type: none"> ⊕ ANA (50%), ⊕ anti-Jo1 (20%, ILD, mechanic's hands, arthritis), ⊕ anti-Mi2 (15-20%, acute, shawl, good prognosis), ⊕ anti-MDA5 (↑ risk ILD incl. rapid progressive) - CK/aldolase, myositis panel 3, LDH, AST/ALT - Muscle bx: DM: CD4, PM/IBM: CD8 cells 	<ul style="list-style-type: none"> - Induction: pred - Maintenance: AZA, MTX - Resistant/severe: pulse steroids, AZA, MTX, MMF, IVIG, RTX, CYC if ILD 	<ul style="list-style-type: none"> - Occult malignancy in DM (9-32%): ovarian, breast, colon, lung, NHL, nasopharyngeal - ILD in 10% - upper esoph. dz - ↑ risk of MI
MCTD	<ul style="list-style-type: none"> - 80% F - Overlap of SLE, systemic sclerosis, polymyositis; Raynaud's; non-erosive arthritis 	<ul style="list-style-type: none"> ⊕ ANA (often speckled) ⊕ anti-U1 RNP (100%) 	<ul style="list-style-type: none"> - SLE features: steroids, RTX - Scleroderma fts less responsive to steroids 	Main cause of death is PAH
UCTD, Overlap Syn.	- Early Raynaud's, incomplete SLE	- Dx of exclusion; not meeting criteria for dx of specific disease	- According to sx	- According to dominant fts
Systemic Sclerosis (scleroderma, SSc)	<ul style="list-style-type: none"> - F:M 4:1, 30-50yo - Systemic: limited cutaneous (67%, hand/face skin thickening, freq. CREST sx, PAH) or diffuse cutaneous (33%, diffuse skin thickening, multi-organ dz, less freq. CREST sx) - <u>CREST</u>: Calcific nodules, Raynaud's, Esoph dysmot, Sclerodactyly, Telangiectasias - <u>Other systemic sx</u>: renal crisis, ILD (>70%), PAH (10-40%) - SSc sine scleroderma = <u>no skin findings</u> 	<ul style="list-style-type: none"> ⊕ ANA (95%) ⊕ anti-centromere* (a/w limited) ⊕ anti-Scl-70* (a/w diffuse) ⊕ anti-RNA pol III* (a/w diffuse & scleroderma renal crisis) - HRCT, PFT, TTE (ILD, pHTN) <p>*Ab are >99% specific (Arthritis Rheum 2013;11:2737)</p>	<ul style="list-style-type: none"> - Skin: MMF, MTX - GI: PPIs, motility agents - Lung: CCBs, endothelin-1 antag, PDEi, prostacyclin ag - MSK: Low dose pred, HCQ, MTX - Raynaud's: CCBs 	<ul style="list-style-type: none"> - Increased risk of multiple cancers - Scleroderma renal crisis (<20%): AKI, abrupt HTN; a/w anti-RNA-pol III; treat with ACEi (captopril) + avoid steroids

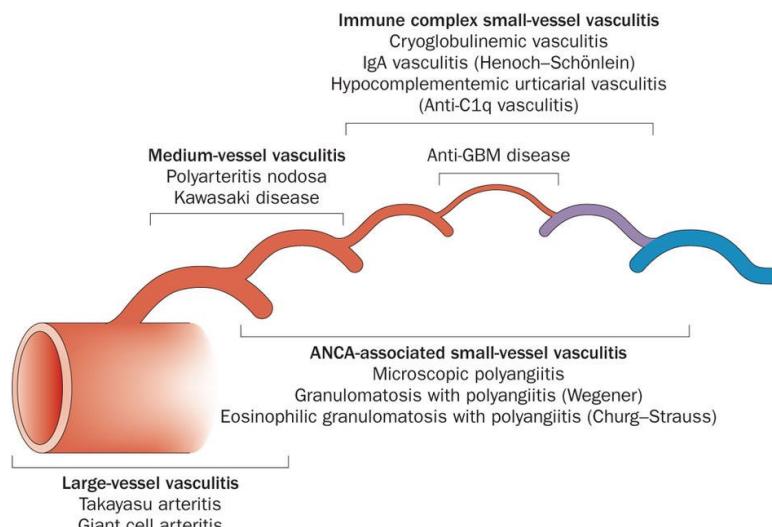
DIAGNOSTIC OVERVIEW ([Arthritis Rheum 2013;65:1](#))

- Classified by size and type of blood vessel involved. Large vessels (aorta and its branches) vs. medium-sized vessels (main visceral arteries = named) vs. small vessels (vessels without names such arterioles, capillaries, venules)
- **Note:** several vasculitides carry eponyms that are intentionally de-emphasized from the lexicon in favor of more descriptive names. The most common of these are noted here to facilitate recognition of clinical syndromes, not to encourage their use**

STEP 1 – SUSPECT VASCULITIS

Overview:

- No “typical” presentation, consider in constitutionally ill pt w/ evidence of multisystem organ involvement & evidence of inflammation
- LARGE** vessel: aorta/branches, e.g. external carotid, temporal, ophthalmic → limb claudication, bruits, asymm. BP, absent pulses, HA, visual loss
- MEDIUM** vessel: renal/hepatic/mesenteric arteries, etc. → cutaneous nodules, “punched out” ulcers, livedo reticularis, digital gangrene, mononeuritis multiplex (e.g. foot/wrist drop), renovascular HTN
- SMALL** vessel: vessels of skin, small airways, glomeruli → petechiae, palpable purpura, glomerulonephritis, alveolar hemorrhage, mononeuritis multiplex, scleritis



General testing:

- Inflammation?** → CBC/diff (ACD, thrombocytosis, neutrophilia, eosinophilia), ESR, CRP
- Organ involvement?** → BMP, LFTs, stool guaiac, CXR, brain MRI (if neurologic symptoms), CTA (if GI/claudication)

Presentation-specific testing (i.e. small-vessel s/sx):

Immune complex? → C3/C4, RF/Cryoglobulins (note ANA/RF not \oplus in 1° vasculitis; \oplus RF may suggest cryoglobulinemia/endocarditis; C3/C4 ↓ in cryoglobulinemia, SLE, 25% of PAN)

ANCA? → send for IIF, will reflex to MPO/PR3 ELISA. If high suspicion for ANCA-associated vasculitis, call lab to expedite test

STEP 2 – RULE OUT MIMICS and assess for SECONDARY CAUSES: based on presentation

- Ddx:** infections (SBE, HIV, HBV, HCV, EBV, *Neisseria*, syphilis), malignancies, IgG4-Related Disease ([NEJM 2012;366:539](#)), hypercoagulable states (APLAS, TTP). If skin necrosis of lower ext., consider cholesterol emboli or calciphylaxis. If renal/internal carotid/vertebral art. involvement, consider fibromuscular dysplasia
- 2° causes: HBV>HCV for PAN, HCV for CTD, HBV/HIV, MGUS/malignancy for cryo, meds/drugs (esp. hydralazine, PTU, levamisole in cocaine; see ANCs in [Autoantibodies](#) and Drug-Induced Lupus in [Connective Tissue Diseases](#))
- Tests:** BCx, HBV, HCV, HIV, syphilis Ab, SPEP/SFLC, tox screen, consider IgG4 level, consider TTE

STEP 3 – CONFIRM DIAGNOSIS

Tissue biopsy: may be required to secure diagnosis

- Sites: Skin, sural nerve and muscle (PAN, EGPA), temporal artery (GCA), kidney (GPA, MPA), lung (GPA, MPA)
- Less common: testicle (PAN), rectum/gut, liver, heart, brain (1° CNS vasculitis), sinus (GPA)

Conventional angiography: particularly if tissue bx infeasible. Celiac/SMA, renal (PAN), chest (Takayasu, GCA), extremities (Buerger's), brain (1° CNS vasculitis)

GENERAL TREATMENT APPROACH

- Remove inciting agents (meds, drugs), treat primary conditions (infections)
- Induction:** often steroids + cyclophosphamide (CYC) or biologic, e.g. rituximab (RTX) for ANCA-associated ([NEJM 2010;363:221](#)), Nephrology at MGH tends to use steroids + CYC + RTX ([Ann Rheum Dis 2015;74:1178](#))
- Maintenance:** typically AZA, MTX, MMF, RTX
- Monitoring:** disease activity & drug toxicity
- Prevention of treatment complications:** PPD, HBV serologies, Pneumovax (and other vaccines), glucocorticoid prophylaxis (consider PPI, TMP-SMX, calcium/vit D)

LARGE-VESSEL VASCULITIS ([NEJM 2003;349:160](#))

GIANT CELL ARTERITIS: inflammation of aorta & extracranial branches (i.e. spares ICA), often temporal artery (TA), most common primary systemic vasculitis. Age >50, 2:1 M:F. Rare <50yo → consider alternative diagnoses

- **Sx:** constitutional (low grade fevers, fatigue, wt loss, anorexia), new/different HA (incl. scalp tenderness), abrupt visual disturbance (amaurosis fugax, blindness, diplopia), jaw claudication (most Sp; fatigue with chewing, NOT PAIN), current or recent PMR
- **Exam:** asymmetric BP/pulse; tender, thickened or pulseless TA; jaw claudication (r/o TMJD)
- **Dx:** combination of 2-3+ s/sx should prompt Doppler US & Rheum c/s. **Gold standard = temporal artery biopsy (Surg c/s).** ↑ESR (usually high but <50 in 10%), ↑CRP, ↑IL-6. **TA biopsy:** start w/ unilateral; if ⊖, consider bilateral (↑yield by 5%); up to 30-45% of bx may be false ⊖ due to "skip areas". If concern for large-vessel GCA: vessel imaging (CTA/MRA)
- **Rx:** pred 1mg/kg/d immediately (≤60mg) if ↑suspicion; NEVER delay Rx for Bx. Steroid-sparing regimen: toci, MTX

POLYMYALGIA RHEUMATICA (PMR): seen in 50% of GCA pts; 10% develop GCA, peak age 70-80

- **Sx:** symmetrical AM stiffness/pain (± weakness) in neck, shoulders/prox arms, hips/prox thighs
- **Rx:** prednisone 12.5-20mg/d w/ slow taper, consider addition of MTX if refractory ([Ann Rheum Dis 2015;74:1799](#))

TAKAYASU ARTERITIS: "pulseless disease," inflammation of thoracoabdominal aorta & branches. Age <40, 8:1 M:F, Asian descent

- **Sx:** inflammation (fever, arthralgias/myalgias, wt loss, night sweats), vessel inflammation (carotidynia, limb claudication), vascular dz (TIA/stroke, HF, CAD, mesenteric ischemia). **Exam:** unequal pulses and BPs (LE>UE), ↓ pulses, bruits, formal eye exam
- **Dx:** MRA or CTA; arteriography will show occlusion, stenosis, aneurysms; consider carotid US/Doppler studies
- **Rx:** prednisone 1mg/kg/d; 50% of patients will need 2nd agent for chronic sx (MTX, tocilizumab, TNFi)

MEDIUM-VESSEL VASCULITIS

POLYARTERITIS NODOSA: kidneys, skin, muscles, nerves, GI, joints (almost always spares lung). Age 40-60, a/w HBV

- **Sx:** mononeuritis multiplex (≤70% of pts), GI distress (mesenteric ischemia), myalgias, AKI (GN suggests alternate etiology), testicular/ovarian pain (>10%), seizures. **Exam:** HTN, skin lesions (erythematous nodules, purpura, livedo reticularis, ulcers, bullous eruption, palpable purpura), neuropathy
- **Dx:** gold standard = biopsy; HBV/HCV serologies, C3/C4, CTA/MRA w/ focal stenosis or microaneurysm (renal/mesenteric vessels)
- **Rx:** prednisone 1mg/kg/d ± CYC 2mg/kg/d PO or IV pulse (if mod-severe or steroid-refractory); antivirals if HBV-related

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE): segmental inflamm. of small-med arteries and veins of extremities; occlusive intravasc. thrombi. Age ≤45, 70-90% ♂, strongly a/w tobacco use, Raynaud's in 40% of pts

- **Dx:** clinical: age + tobacco + distal ischemia + arteriographic findings + r/o autoimmune, thrombophilia, DM, embolism
- **Rx:** smoking cessation! Iloprost (PG analog) for pain, CCB (for Raynaud's), intermittent pneumatic compression (painful ulcers)

ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS (AAV)

c-ANCA = cytoplasmic staining (proteinase 3 [PR3]), p-ANCA = perinuclear staining (myeloperoxidase [MPO])

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S GRANULOMATOSIS): necrotizing vasculitis w/ granulomatous features by sx (sinusitis, mass lesions [orbital pseudotumor, subglottic stenosis, large pulm nodules]) or on path, usually involving upper and lower airways (90%) and kidney (80%), ± cutaneous leukocytoclastic vasculitis (LCV)

- **Dx:** sinus CT (± bone erosions), Bx w/ granulomatous inflammation of vessel walls, ⊕PR3-ANCA 90%
- **Rx:** limited disease: MTX + prednisone; severe disease: IV pulse steroids x3d (with oral taper) + RTX or CYC

MICROSCOPIC POLYANGIITIS (MPA): necrotizing vasculitis of small vessels without granulomas. All ages (mean 50-60), M>F, ↑White; most common cause of pulmonary-renal syndrome ([NEJM 2012;367:214](#))

- **Dx:** ⊕p-ANCA 70%, ⊕c-ANCA rare; BAL; gold standard = skin/renal biopsy; r/o HIV, cryo, HBV, HCV
- **Rx:** similar to GPA → methylprednisolone + CYC or RTX ([NEJM 2010;363:221](#))

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME): necrotizing granulomatous inflammation of vessels in lungs, skin, nerves; strongly associated with asthma/allergic rhinitis (asthma precedes vasculitis)

- **Dx:** ≥4 of following: asthma, >10% peripheral eos, neuropathy, pulm opacities, paranasal sinus dz, consistent Bx. 50% ⊕ p-ANCA
- **Rx:** IV pulse steroids x3d (with oral taper) ± CYC or RTX (if severe disease) or mepolizumab (if not severe). Do not delay Rx if mononeuritis (risk of nerve infarction)

IMMUNE COMPLEX-ASSOCIATED SMALL-VESSEL VASCULITIS

IgA VASCULITIS (HENOCHE-SCHÖNLEIN PURPURA): 70% in children; ♂>♀; preceding URI, in adults, more severe presentation, med related, a/w malignancy

- **Sx:** clinical: classic tetrad of 1) palpable purpura (100%, on LEs/buttocks = dependent areas), 2) colicky abdominal pain (60%), 3) arthritis (75%), 4) renal involvement (40-50%, proteinuria, microscopic hematuria, RPGN)
- **Rx:** children: usually self-limited; adults: may require immunosuppression (steroids, dapsone). NSAIDs if mild GI/arthritis

CRYOGLOBULINEMIA: immunoglobulins that precipitate at low temperatures and re-dissolve on rewarming

- **Type 1:** monoclonal (usually IgM or IgG), a/w Waldenstrom's, MM. S/Sx: peripheral neuropathy, renal impairment, hyperviscosity (Raynaud's, digital ischemia, livedo)
- **Type 2:** "mixed" monoclonal IgM against polyclonal IgG (often IgM with RF activity), a/w HCV, HIV, HBV, EBV
- **Type 3:** "mixed" polyclonal Ig (IgM or IgG) against polyclonal Ig (IgM or IgG), associated with CTDs, lymphoproliferative disorders, HCV. S/Sx: palpable purpura, arthralgias, myalgias, mononeuritis multiplex
- **Rx:** tx underlying cause (e.g. HCV); prednisone ± RTX/CYC; consider plasma exchange in Type 1

Rheumatology

Miscellaneous Rheumatologic Diseases

BEHÇET'S DISEASE

- Autoinflammatory condition characterized by recurrent aphthae and skin/GI/neuro/joint/ocular sx thought to be due to a vasculitis affecting vessels of all sizes, both venous and arterial
- **Epi:** F>M, age 20-40, Turkey, Middle East, and Asian countries
- **Sx:** recurrent painful oral ulcers and ≥ 2 of the following: painful genital ulcers (specific), ocular disease (most commonly uveitis or retinitis), skin lesions (pustules, folliculitis, papules, erythema nodosum)
 - Other manifestations: GI (similar to IBD), neurologic disease (parenchymal, extra-parenchymal), vascular disease (ATE/VTE, **vasculitis**, aneurysms [PA]), arthritis (nonerosive, asymmetric). Less common: kidney, heart, lung dz
- **Dx:** clinical dx only, no specific laboratory tests exist; may have ↑ESR/CRP
- **Rx:** ([Ann Rheum Dis. 2018;77:808](#)); Mild (arthritis, ulcers): colchicine 1-2mg qd, low dose pred. Apremilast for ulcers ([NEJM 2019;381:1918](#)); Severe: pred 1mg/kg/d, ± AZA, TNFi, IFN, CYC, MTX; organ failure (esp ophth.): IV pulse steroids x3d

IGG4-RELATED DISEASE

- Immune-mediated fibro-inflammatory condition, most commonly involving pancreas, biliary tree, salivary/lacrimal glands, retroperitoneum, and orbits ([Arth Rheum 2020;72:7](#))
- **Sx:** **pancreatitis**; sclerosing **cholangitis**; sialadenitis; lacrimal gland hypertrophy; **retroperitoneal fibrosis**; orbital pseudotumor; **masslike** enlargement of lungs, kidneys, or any of the above organs
- **Dx:** tissue **biopsy** (storiform ["strawlike"] fibrosis, lymphoplasmacytic infiltrate, obliterative phlebitis, tissue eosinophilia), ↑serum IgG4 levels (90% Sn, 60% Sp, NPV 96%) ([Ann Rheum Dis. 2015;74:14](#))
- **Rx:** if symptomatic and/or progressive, **glucocorticoids** ± biologics (**rituximab**) to induce remission

SARCOIDOSIS

- Systemic inflammatory disorder characterized by granulomatous inflammation of virtually any tissue, most commonly **hilar lymph nodes**, pulmonary parenchyma, and skin ([Int Emerg Med 2018;13:325](#))
- **Epi:** F>M, young adults. ↓incidence in Northern populations, ↑incidence reported in Black patients
- **Sx:** fever, arthralgias, wt loss, fatigue; dyspnea, cough; rash; HSM, LAD; uveitis; cytopenias due to BM involvement; restrictive CM; neurosarcoidosis (CNopathy, peripheral neuropathy, meningitis, seizures, hypothalamic dysfunction)
- **Dx:** definitive dx usually requires **non-caseating granulomas on bx** (skin, LN, EBUS) in pt w/ compatible clinical findings. No need to bx isolated asymptomatic hilar LAD on CXR. ↑serum ACE 41% Sn, 90% Sp ([Lung 2016;194:91](#))
- **Rx:** if symptomatic, oral **glucocorticoids** ± MTX, azathioprine, leflunomide, MMF

ADULT ONSET STILL'S DISEASE (AOSD)

- Systemic inflammatory disorder characterized by fevers, arthritis, and rash. Can present as single episode (wks-mos), multiple flares, or be persistently active
- **Epi:** F=M, bimodal (15-25yo and 36-46yo)
- **Sx:** fever; arthralgias; evanescent, **salmon-colored maculopapular rash** that coincides w/ recurrent fever, usually on the trunk, may be precipitated by trauma (Koebner phenomenon); pericarditis; pleural effusions; **macrophage activation syndrome (MAS)** (Rheum-associated HLH; see [Pancytopenia & Anemia](#))
- **Dx:** **Yamaguchi criteria** requires ≥ 5 features, including ≥ 2 major criteria ([J Rheumatol 1992;19:424](#))
 - Major: fever $\geq 39^{\circ}\text{C}$ for $\geq 1\text{w}$, arthralgias/arthritis $\geq 2\text{w}$, salmon-colored rash, ↑WBC ($\geq 10\text{K} + \geq 80\%$ PMN)
 - Minor: sore throat, LAD, HSM, ↑AST/ALT, ↑LDH, negative ANA/RF
 - Other labs (not part of criteria): ↑ESR/CRP, **ferritin $>3000\text{ ng/mL}$** (if $>10,000$, consider MAS spectrum), ↑plt, ↓Hgb
- **Rx:** Mild: **NSAIDs**. Severe: **pred** 0.5-1mg/kg/d (may not respond). If uncontrolled: MTX, TNFi, anti-IL6R, anti-IL1

FIBROMYALGIA

- Chronic widespread musculoskeletal pain, often w/ fatigue, sleep disturbance, and multiple somatic symptoms
- **Epi:** F>M, 20-55yo. Can coexist with other inflammatory diseases like SLE, RA. Often psychiatric comorbidities
- **Sx:** widespread MSK pain, fatigue, cognitive disturbance (decreased attention & ability to perform complex tasks), psychiatric sx (depression), headache, paresthesias, IBS. Pan-positive ROS not uncommon
- **Dx:** clinical diagnosis, $>3\text{mo}$ duration of sxs, multiple tender points. Newer criteria involve widespread pain index (WPI) and symptom severity (SS) scale ([J Pain 2019;6:611](#)). Labs: normal (ESR, CRP, TSH, CBC, BMP)
- **Rx:**
 - Initial therapy: patient education, **exercise program**, sleep hygiene
 - Pharmacologic therapy: 1st line includes **amitriptyline**, duloxetine, or milnacipran; also may consider cyclobenzaprine, gabapentin, and pregabalin (monotherapy > combo therapy). Avoid narcotics

Rheumatology

Autoantibodies

Antibody	Antigen (ANA Pattern if \oplus)	Disease	Comments
Inflammatory polyarthritis			
RF (IgM)	Fc gamma	RA (50-75%), Sjogren's (30%), Cryoglobulinemia (90%), others	- Not Sp despite name: RA, CTD, cryoglobulinemia, chronic infxn (e.g. HCV, SBE) - \oplus in 10% of healthy patients - RA: "seropositive", a/w erosive & extraarticular manifestations (nodules, scleritis, ILD, pleuritis, rare rheumatoid vasculitis)
CCP	Citrullinated proteins	RA (50-75%)	- Most Sp test for RA, \oplus in 50-75% ("seropositive RA"), a/w erosive dz & extraarticular manifestations. Used for dx only, <u>NOT</u> marker of dz activity
Connective tissue diseases (SLE, Sjogren's, SSc, MCTD, UCTD, DM/PM)			
ANA	<p>When to order: clinical suspicion for SLE or other ANA-\oplusdisease (<u>not</u> a screening test given high prevalence of false \oplus; not to track disease activity). In populations with low prevalence of SLE (e.g. elderly), PPV low given high false \oplus rates</p> <ul style="list-style-type: none"> - ANA = antinuclear antibodies (ENAs ("extractable nuclear antigens") specify Ag). Low titer ANA \leq1:160 often false \oplus. If ANA \oplus, order specific autoantibodies guided by clinical presentation - \oplus ANA: MCTD (100%), SLE (98%), scleroderma (90%), drug-induced lupus (DIL, 90%), Sjogren's (60%), PM/DM (50%) - Ddx for \oplus ANA: <u>Autoimmune</u>: autoimmune hepatitis, PBC, IBD, myasthenia gravis, Graves', Hashimoto's; <u>ID</u>: malaria, SBE, syphilis, HIV, HSV, EBV, HCV, parvo-B19; <u>systemic inflammation</u>: lymphoproliferative disorders, IPF, asbestos 		
dsDNA	ds/mtDNA (homogenous)	SLE (40-60%)	- <u>Sp</u> for SLE, a/w SLE activity (follow titers) & lupus nephritis, consider TNFi DIL
Histone	Histones (homogeneous)	SLE, drug-induced lupus (90%), Felty's	- <u>Sn</u> but not <u>Sp</u> for DIL - Common meds: procainamide, hydralazine, minocycline, phenytoin, lithium, INH, quinidine, terbinafine, TNFi
RNP	U1-snRNP (speckled)	MCTD (100%), SLE (30%)	- <u>MCTD</u> : high-titer anti-U1 RNP. Also seen in systemic sclerosis (20%)
Smith	snRNP (speckled)	SLE (30%)	- <u>Sp</u> for SLE, <u>not</u> indicative of dz activity
SS-A/Ro	Ro52, Ro60 (speckled)	Sjogren's (75%), SLE (40%)	- Can be seen with myositis, PBC, SSc. In SLE, a/w skin dz & congenital heart block. 2% SLE pts have \ominus ANA but \oplus anti-Ro
SS-B/La	La (speckled)	Sjogren's (40%), SLE (10-15%)	- In SLE a/w congenital heart block
ACA	CENP A-F (centromere)	IcSSc (15-40%)	- A/w limited systemic sclerosis, <u>↑ risk of PAH</u> , <u>↓ risk of ILD</u> , esophageal disease
Scl-70	Topo-I (speckled)	dcSSc (10-40%)	- A/w diffuse systemic sclerosis; <u>↑ risk of ILD</u> , scleroderma renal crisis
RNA pol III	RNA pol. III (nucleolar)	dcSSc (4-25%)	- A/w <u>scleroderma renal crisis</u> , rapidly progressive skin disease, cancer
Fibrillarin	U3-RNP (nucleolar)	dcSSc (<5%)	- A/w PAH, pulmonary fibrosis, & myositis, esp. in African-Americans
PM-Scl	Exosome (nucleolar)	SSc (5-10%)	- A/w limited systemic sclerosis, <u>↓ risk of pulm. & renal dz</u> , <u>↑ risk inflamm. myositis</u>
Myositis			
Jo-1*^	tRNA (His) (cytoplasmic)	PM/DM (30%), anti-synthetase syndrome (~20%)	- <u>Antisynthetase syndrome</u> : myositis (DM/PM), ILD (70%), polyarthritis, mechanic's hands, Raynaud's, fever
Mi-2*	Mi-2 (homog., speckled)	DM (15-20%)	- More likely in acute DM, good prognosis
MDA-5*^	MDA-5	DM	- Clinically amyopathic dermatomyositis, rapidly-progressive ILD
TIF1g*	TIF1g (fine speckled)	Juvenile DM	- A/w malignancy in adult DM
SRP*	Signal recog. particle (cytoplasmic)	PM	- Immune-mediated <u>necrotizing myopathy</u> (degenerating, regenerating, and necrotic cells on bx), rapidly progressive disease course
HMGCR	HMG CoA reductase	myositis	- Immune-mediated <u>necrotizing myopathy</u> , 70% with <u>statin</u> exposure (at any time in past), \neq statin myopathy (does not respond to discontinuation of statin), very high CPK, often steroid-refractory, good response to IVIG
Vasculitis			
PR3 (c-ANCA)	Proteinase 3	GPA (90%)	- Poor correlation of titer with disease flare/remission - Antibody frequency lower in GPA <u>without</u> renal involvement
MPO (p-ANCA)	Myeloperoxidase	MPA (70%), EGPA (50%), Renal-Limited, DIV (95%)	- Poor correlation of titer with disease flare/remission - <u>Drug-induced vasculitis (DIV)</u> : high-titer \oplus for MPO (hydral, PTU, minocycline) (Arthritis Rheum 2000;43:405) - Levamisole vasculitis 2/2 cocaine use: MPO or PR3/MPO
Cryo-globulins	Fc gamma	Cryoglobulinemic vasculitis	- HCV > HBV, HIV, CTDs, lymphoproliferative disease - A/w low C4, glomerulonephritis, +RF

* ordered as part of "myositis panel 3"

^ order separately for faster results if desired

Rheumatology

Rheumatologic Medications

	DRUG/CLASS	INDICATIONS	COMMON TOXICITIES/NOTES
TRADITIONAL	Azathioprine (AZA, <i>Imuran</i>); purine synthesis inhibitor	DM/PM, RA, SLE nephritis, vasculitis	-GI, hepatotoxicity; myelosuppression, lymphoproliferative disorders, bruising -TPMT deficiency can ↑ toxicity due to 6-MP accumulation, order test before initiating -Avoid xanthine oxidase inhibitors (e.g. allopurinol)
	Cyclophosphamide (CYC, <i>Cytoxan</i>); DNA alkylation	SLE nephritis, vasculitis (most severe)	Myelosuppression, lymphoma, hemorrhagic cystitis (MESNA for ppx), infertility (cumulative dose, leuprolide ppx), teratogen, <1% pneumonitis
	Hydroxychloroquine (HCQ, <i>Plaquenil</i>)	RA, SLE, Sjogren's	N/V, retinopathy (baseline & q1y retinal exam), dizziness, alopecia, myelosuppr., QTc prolong.
	Leflunomide (<i>Arava</i>)	PsA, RA	N/V, alopecia, rash, diarrhea, HTN, hepatotoxicity , URI, dizziness/H/A, teratogen
	Methotrexate (MTX, <i>Rheumatrex</i>); DHFR inhibitor (antifolate)	RA (first line), PsA	Myelosuppression (add folate), hepatotoxicity , pneumonitis , stomatitis, rash, teratogen
	Mycophenolate (MMF, <i>CellCept</i>); purine synthesis inhibitor	AAV, DM/PM, PsA, Scleroderma, SLE	Cardiac (HTN, edema, CP, ↑HR), diarrhea, HA, insomnia, pain, fever, rash, stomatitis, teratogen
	Sulfasalazine (5-ASA, <i>Azulfidine</i>)	AS, IBD, JRA, Psoriasis, RA	Sore throat, stomatitis, rash, HA, N/V, myelosuppression; check G6PD
	Apremilast (<i>Otezla</i>); PDE4 inhibitor	PsA, severe psoriasis, Behcet's	N/D, URI, depression, wt loss
Non-TNF BIOLIC*	Tofacitinib (<i>Xeljanz</i>); pan-JAK inhibitor Upadacitinib (<i>Rinvoq</i>); JAK1 inhibitor	RA, AS, psoriasis	-Infection, lymphoma, hepatotoxicity, diarrhea, ↑clot -Upadacitinib > abatacept in DMARD-resistant RA (NEJM 2020;383:1511)
	NSAIDs ibuprofen (short acting) naproxen (long acting) celecoxib (COX-2 selective inhibitor) diclofenac (<i>Voltaren</i> , topical)	AS, RA, SSc, SLE, gout, CPPD, OA	- Gastropathy (dose- and age-dependent, use PPI or misoprostol for ppx; celecoxib if high risk) - Kidney injury (AKI, AIN, papillary necrosis) - CV mortality (naproxen may have lower risk, celecoxib noninferior NEJM 2016;375:2519) -Anti-inflammatory effects require ↑dose & duration (2w+) leading to ↑risk of toxicities. Used ± glucocorticoids until effective DMARD therapy
	Abatacept (<i>Orencia</i>); soluble CTLA4	PsA, RA	Infection, HA, nausea, dizziness, HTN, dyspepsia
	Anakinra (<i>Kineret</i>); anti-IL-1R	AOSD/MAS, gout	Myelosuppression (neutropenia), rash/inj. rxns, HA, arthralgia, fever
	Belimumab (<i>Benlysta</i>); anti-BAFF	SLE	Depression , HA, infusion reaction, PML, GI
	Rituximab (<i>Rituxan</i>); anti-CD20	APLAS, AAV, IgG4-RD, Scl-ILD, SLE	Infection, HTN, infusion reaction (use premeds) , TLS, PML, fever, rash/pruritus, LE edema
	Tocilizumab (<i>Actemra</i>); anti-IL-6R	GCA, RA	Infection, hepatotoxicity , HLD, GI perforation
	Secukinumab (<i>Cosentyx</i>); anti-IL17A	AS, Ps/PsA	Infection, IBD flare
TNF BIOL*	Ustekinumab (<i>Stelara</i>); anti-IL-12/23	Ps/PsA	Infection, RPLS, seizures
	IVIG	APLAS, DM/PM, IBM, IMNM, Kawasaki's	Transfusion reactions/anaphylaxis, aseptic meningitis, thromboembolism, HA
	Adalimumab (<i>Humira</i>); anti-TNF	AS, IBD, Ps/PsA, RA	
	Infliximab (<i>Remicade</i>); anti-TNF	AS, IBD, Ps/PsA, RA	- Myocardial toxicity (contraindicated in HF), HA, nausea, rash, infection, drug-induced lupus (DIL) -NB: TNFα inhibitors are <u>safe</u> in HCV infection and may be beneficial (Expert Opin Biol Ther 2012;12:193)
	Golimumab (<i>Simponi</i>); anti-TNF	AS, IBD, PsA, RA	
	Certolizumab (<i>Cimzia</i>); anti-TNF	AS (axial), IBD, RA	
	Etanercept (<i>Enbrel</i>); sol. TNF-R	AS, Ps/PsA, RA	

*Can cause HBV/TB reactivation (check hepatitis serologies + IGRA or PPD prior to starting). If positive, discuss prophylaxis/treatment with ID/Rheum

Endocrinology

Outpatient Type 2 Diabetes Mellitus

SCREENING

- Begin at age ≥ 45 years OR after gestational DM (GDM) OR if BMI ≥ 25 (≥ 23 in Asian-Americans) + RF (1st degree relative with DM, nonwhite, history of CVD, HTN, HDL < 35, triglycerides > 250, PCOS, sedentary lifestyle); screen q3y if normal ([Diab Care 2021:44:S15](#))

PRE-DIABETES ([Diab Care 2021:44:S15](#))

- Diagnosis: A1c 5.7-6.4%; fasting plasma glucose (FPG) 100-125; or 75g OGTT w/ 2h glucose 140-199
- Monitoring: A1c at least q1y; if A1c 6-6.4%, screen q6mo (25-50% 5-year risk of progression to diabetes if A1c 6-6.5%)
- Treatment: **lifestyle interventions** most effective; **metformin** also effective, esp. if BMI ≥ 35 , age < 60 , or GDM hx ([Cochrane Rev 2019](#))

DIABETES ([Diab Care 2021:44:S15](#))

- Diagnosis: A1c $\geq 6.5\%$; FPG ≥ 126 ; 75g OGTT with 2h glucose ≥ 200 ; or random BG ≥ 200 & symptoms. Unless diagnosis is made by symptoms & random glucose > 200 , **confirm with repeat or additional test**. For T1DM, check TSH, celiac screen at diagnosis. Use plasma blood glucose criteria and not A1C if high RBC turnover: sickle cell disease, 2nd/3rd trimester of pregnancy, ↓ G6PD, HD, recent blood loss/transfusion, EPO tx. A1c less reliable post-partum, with certain HIV drugs, and Fe-deficient anemia.
- Treatment: goal A1c $< 7\%$; liberalize to $< 8-8.5\%$ if life expectancy ≤ 10 years or high risk for hypoglycemia

Healthcare Maintenance for Diabetic Patients	
Every visit	<ul style="list-style-type: none">Review blood sugar log: goal AM FPG 80-130, postprandial (1-2h) < 180; screen for hypoglycemia awarenessReview medication regimen and medication-taking behaviorBlood pressure: goal < 140/90; ACEi/ARB first lineWeight, BMI: weight center referral if BMI ≥ 40 or ≥ 35 with poor control; nutrition referral for all patientsFoot exam (inspect skin, joints, pulses, sensation) esp. if known neuropathy or PVD; ABIs/vascular referral if PVDScreen for tobacco, alcohol, and substance use and provide appropriate counseling
Q3-6mo	<ul style="list-style-type: none">A1c q6mo if controlled; q3-6mo if A1c above target
Annually	<ul style="list-style-type: none">Lipids: moderate-intensity statin if age 40-75; high-intensity if CVD, risk factors, LDL ≥ 190, or 10y ASCVD $> 20\%$Urine mAlb/Cr, BMP; ACEi/ARB if hypertensive w/ proteinuria <u>or</u> GFR < 60; refer to renal if GFR < 30Neuropathy exam: 10g monofilament (+ if no sensation at 4/10 sites, see PCOI); pinprick, vibration, or reflexesRetinopathy screen w/ dilated eye exam or retinal photography; can consider q2-3y if normal exam(s)LFTs: consider elastography and/or hepatology referral if elevated to evaluate for NASH
Vaccines	<ul style="list-style-type: none">Influenza annuallyHepatitis B series if age < 60 and not immunePPSV23 x1 age < 65; re-dose x1 ≥ 65 with at least 5 years between doses; PCV13 x1 age ≥ 65

Basal Insulin Management	
Criteria for initiation	<ul style="list-style-type: none">Consider if A1c $\geq 9\%$, random BG ≥ 300, fasting BG ≥ 250, or symptomatic; suspicion for T1DM; < 65yo on two agents with A1c $> 8\%$ (or ≥ 65yo and A1c $> 8.5\%$) on two occasions > 3mo apart; or A1c rising quicklyAble to perform self-monitoring with glucometer; consider referral to DM educator
Initial dose	<ul style="list-style-type: none">Starting dose: 0.1-0.2U/kg/d or 10U/d (if weight > 80kg, may consider starting at 20U/d)Choice of agent: choose long-acting (glargine, detemir qd) or intermediate-acting (NPH BID \rightarrow cheaper)Route: pen (easier to use, more expensive) vs needle/syringe
Titration	<ul style="list-style-type: none">Increase by 2-4U or 10-15% q3d until AM fasting BS is 80-130 without hypoglycemia; savvy patients can self-titrateIf hypoglycemia occurs or FPG < 80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater

Prandial Insulin Management	
Criteria	<ul style="list-style-type: none">Consider if A1c still not at goal with basal insulin > 0.5U/kg/d and fasting glucose within target range (80-130)
Initial dose	<ul style="list-style-type: none">Strategy 1: add 1 rapid-acting insulin before largest meal \rightarrow start w/ 4U or 0.1U/kg or 10% basal doseStrategy 2: change to mixed insulin (e.g. fixed 70/30, NPH + regular) BID (before breakfast and dinner). Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM. Counsel to avoid missing meals to avoid hypoglycemia
Titration	<ul style="list-style-type: none">Increase dose by 1-2U or 10-15% q3d until target glucose reached (pre-prandial: 80-130; 1-2h post-prandial < 180)If A1c still not controlled: add rapid-acting insulin to another meal and titrate as aboveIf hypoglycemia occurs or FPG < 80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater

INSULIN SUPPLIES

- Needles: come as universal pen needles, or attached to syringes, made by many companies. 32G 4mm is less painful (higher gauge = thinner and shorter needle), but obese patients and high insulin doses often require deeper/wider needle
- Syringes: boxes of 100. Long-acting insulin only = 1 box/3mo. Basal/bolus insulin = 4 syringes/d (4 boxes/3mo). Choose smallest syringe that will hold the dose (smaller barrel \rightarrow clearer scale markings)
- Alcohol swabs (or patients can wash hands/skin with soap and water)
- Glucometer & test strips: Many choices (insurance dependent), each with own strip brand. Most test strips come in boxes of 50-100
- ** All durable medical equipment including test strips and glucometers requires an ICD-10 code on the script itself ****

Use this barrel size...	With this dose range...
3/10mL	30U or less
1/2mL	31-50U
1mL	51-100U

Endocrinology

Outpatient Type 2 Diabetes Mellitus

NON-INSULIN AGENTS				
Drug/Dose Range	% ↓ A1c	Indications/Benefits	Contraindications	Side Effects/Considerations
Metformin: 1 st line anti-diabetic medication; many effects, primary mechanism is decreasing hepatic glucose production				
Metformin (Glucophage) 500-1000mg BID	1-2	- First line therapy - Weight loss - Improvement in lipids	GFR cutoffs: - <45mL/min don't initiate - <30mL/min discontinue - Metabolic acidosis	- Nausea, bloating, diarrhea - B12 deficiency - Lactic acidosis in severe liver/renal disease or hypoperfusion state
Metformin pearls: to increase adherence, warn patients about GI side effects but remind that side effects usually go away with time. Can be minimized by uptitrating SLOWLY (250-500mg/w), taking WITH food, or switching to ER formulation. Benefits and side-effects are dose-dependent – <i>maintain highest dose tolerated</i> . Can also take a break (e.g. with antibiotics) and re-introduce later.				
SGLT-2 Inhibitors: block renal glucose reabsorption, increase glucosuria				
Canagliflozin (Invokana) 100-300mg qd Empagliflozin (Jardiance) 10-25mg qd Dapagliflozin (Farxiga) 5-10mg qd	0.8-0.9	- ↓CV events, ASCVD mortality, CHF hospitalization, and CKD progression (NEJM 2019;380:2295) - Weight loss - ↓ risk of hypoglycemia - ↓ BP 3-5mmHg	GFR cutoffs: - <45mL/min new data suggests ok to initiate <30mL/min discontinue - Prior DKA	- UTI & GU fungal infections - Small risk of euglycemic DKA - Risk of dehydration/HoTN - Risk of fracture (canagliflozin) - May ↑LDL cholesterol
SGLT2i pearls: counsel patients on diuretic effect and to replace water losses to avoid euglycemic DKA. Uptitrate to effective dose after 1 month at low dose. For potency, empagliflozin > canagliflozin > dapagliflozin. Benefit is probably not a function of A1c lowering.				
GLP-1 Receptor Agonists: stimulate glucose-dependent insulin release from beta cells				
Liraglutide (Victoza) 0.6-1.8mg qd Dulaglutide (Trulicity) 0.75-1.5mg qw Semaglutide (Ozempic) 0.25-1mg qw	0.5-1.1	- ↓CV events, ASCVD - Weight loss - Alternative to basal insulin as initial injectable option - ↓ risk of hypoglycemia	- FDA Black Box Warning: ↑risk thyroid C-cell tumors. Avoid if hx thyroid ca/MEN2 - GFR 30-45: avoid exenatide	- GI: n/v, diarrhea - Injection site reactions - Delayed gastric emptying - ↑ risk of pancreatitis
GLP-1 RA pearls: for weight loss, semaglutide > dulaglutide > liraglutide > others. Uptitrate to effective dose in 1mo intervals				
DPP-4 Inhibitors: inhibit degradation of DPP4, increasing glucose-dependent insulin secretion and decreasing glucagon secretion				
Sitagliptin (Januvia) 25mg-100mg qd Linagliptin (Tradjenta) 5mg qd	0.5-0.8	- Safe in CKD/ESRD (w/ dose reduction) - ↓ risk of hypoglycemia - Weight neutral	- No contraindications, but very weak	- Saxagliptin, alogliptin 1 hospitalizations for CHF - Joint pain
Insulin Secretagogues: stimulate release of insulin from pancreatic beta cells, thus only effective in pts who still have beta cell function				
Sulfonylureas: Glipizide 2.5-20mg qd Glimepiride 1-8mg qd	1-2	- Affordable	- T1DM, DKA - low cross-reactivity in pts with sulfa allergy	- Weight gain - Hypoglycemia (esp glyburide) - Possible ↑CV mortality
Meglitinides: Repaglinide (Prandin) 0.5-4mg qAC	0.5-0.7	- Use like bolus insulin (short-acting) - CKD - ↓ nocturnal hypoglycemia	- Severe liver disease - Concurrent gemfibrozil therapy	- Weight gain - Hypoglycemia - ↑ serum conc. w/ clopidogrel - TID dosing
Thiazolidinediones: increase insulin sensitivity by acting on adipose, muscle, and liver to ↑ glucose uptake, ↓ ectopic lipid deposition				
Pioglitazone (Actos) 15-30mg qd	1-1.6	- ↓ risk of hypoglycemia - Possible benefit in NASH	- Avoid if hx bladder cancer - NYHA Class III/IV HF	- FDA Black Box Warning: ↑ risk of CHF - Weight gain - ↑ risk of fracture

ALGORITHM FOR ORAL ANTI-DIABETIC THERAPY ([Diab Care 2021;44:S111](#))

1. A1c ≥6.5: lifestyle changes ± metformin. Counsel for whole foods, carbohydrate restriction, and time-restricted eating
2. Regardless of A1c:
 - a. If **ASCVD** or high risk: add GLP-1RA and/or SGLT2i (↓CV events)
 - b. If **HF** (esp. HFrEF) or CKD (eGFR >30 or mAlb/Cr >30): add SGLT2i, avoid TZD
3. If A1c targets not met with above therapy:
 - a. If **weight loss/neutrality desired**: add GLP1RA and/or SGLT2i > DPP4i, avoid sulfonylurea, TZD
 - b. If **cost** is a major concern: add sulfonylurea or TZD

INSULIN NOMENCLATURE

Type (Onset)	Formulation	Peak	Duration
Rapid (10min)	lispro (Humalog) aspart (Novolog) glulisine (Apidra)	0.5-2.5h	<5h
Short (30min)	regular (Humulin R, Novolin R)	2.5-5h	4-12h
Intermediate (1-2h)	NPH (Humulin N, Novolin N)	4-12h	12-18h
Long (3-4h)	glargine (Lantus) qd detemir (Levemir) BID degludec (Tresiba) qd	none	24h

Basal insulin: fixed intermediate/long-acting for basic metabolic requirements

Prandial insulin: fixed rapid/short-acting to cover meals

Correctional insulin: sliding scale rapid/short-acting to correct hyperglycemia (**not intended to cover meals**)

Pre-Mix (avoid in hospital, but consider for transition to outpatient regimen): combine basal and prandial insulin into one injection

Insulin gtt: use in ICU if BG >180 x2 and anticipated ICU LOS >3 days; reference [MICU Insulin Protocol](#) in Partners Handbook. Ensure an active source of dextrose (e.g. D10W @ 30cc/h). Always overlap with SC insulin by 2-3h before stopping insulin gtt

INPATIENT MANAGEMENT ([Diabetes Care 2021;44:S211](#))

- Glycemic targets: **Floor:** fasting 100-140mg/dL, random <180mg/dL. **ICU:** 140-180mg/dL (NOT stricter) ([NEJM 2009;360:1283](#))
- Check **FSBG AC & QHS** (at least for 24-48h) in (1) known diabetics, (2) non-diabetics with BG >140mg/dL, (3) those receiving therapies a/w hyperglycemia (corticosteroids, octreotide). Check FSBG q6h if NPO or on continuous TF or TPN.

Note: FSBGs inaccurate in hypotension (esp. on pressors) and hypothermia due to altered blood flow to skin. Confirm w/ serum glucose

Admission Orders ([NEJM 2006;355:1903](#))

- Hold home oral antihyperglycemic agents when patients are acutely ill (**NEVER hold basal insulin for T1DM**)
- Check A1c** in all patients with hyperglycemia if not done in last 3 months
- Continue home insulin regimen with dose reduction (~25-50% reduction) given expected change in diet while hospitalized
- If **not** on home insulin:
 - Well-controlled: reasonable to start with ISS and soon change to basal-bolus once TDD established. Prolonged use of ISS regimen as only anti-hyperglycemic treatment is **discouraged** ([J Hosp Med 2019;2:114; Rabbit2; Basal Plus](#))
 - Not well-controlled: start w/ **basal (0.25U/kg)**, use 0.15U/kg in pts with ESRD, elderly, and low BMI
 - Add prandial insulin (0.05-0.1U/kg) qAC PLUS correctional insulin qAC
- If NPO:** 50% dose reduction or 0.1U/kg/day for basal. Hold prandial & change correctional ISS and FSBG from TID AC to q6h
- Correctional insulin sliding scale:** use low-dose if insulin-sensitive/ESRD/ESLD/frail, otherwise moderate-dose for most T2DM

Adjusting Insulin Dosing: in general, adjust insulin requirement by no more than 20%

Fasting or AM BG high (w/ other BGs in range)	→	↑ basal insulin dose*
Fasting BG high + HS BG high (w/ other BGs in range)	→	↑ pre-dinner prandial insulin dose
Pre-lunch or dinner BG high (w/ other BGs in range)	→	↑ prandial insulin dose of preceding meal
BG rising steadily over course of day	→	↑ prandial insulin dose at each meal

*Avoid titrating basal insulin more than q2-3d (d/t long half life, requires time to reach steady state) to avoid "stacking" and hypoglycemia

Special Situations:

- Glucocorticoids:** NPH 0.1U/kg/d for every 10mg pred, up to 0.4U/kg/d (dosed BID); if dexamethasone, use glargin qd instead
- Tube feeds:** if not on insulin already, start with regular ISS q6h. Convert to NPH BID based on needs. **If on insulin**, use ½ basal (NPH BID) + ½ bolus (regular insulin q6h) + ISS. **If TF stopped**, give D5W at TF rate until next NPH dose, and ↓NPH dose by 50% or more based on pre-TF insulin requirements. **TPN:** regular insulin can be added to TPN (discuss w/ nutrition), does not cover basal!
- Insulin pumps:** continuous SQ infusion of rapid-acting insulin. Consists of basal rate (units/kg/h), carb ratio (units insulin:gram carbs), sensitivity factor (units insulin:mg/dL above target), & insulin action time. Complications: site infection, system failure interrupting infusion. Back-up insulin: give 3-4x hourly rate of rapid-acting q3-4h or give TDD as NPH BID or glargin qd. Hospitalized patients must sign a waiver to use their own device. **Endocrine consult required** and will develop a contingency plan in case of pump failure.

Discharge: if new home insulin → nutrition c/s + floor RN teaching and arrange outpatient f/u. Using discharge order set, send rx for glucometer, test strips, lancets, syringes/vials or pens/needles to MGH outpatient pharmacy and bring up to floor for RN teaching

INPATIENT HYPOGLYCEMIA

↑Risk: T1DM, malnutrition, emesis, ↓body weight, ↓PO intake, ↓steroid dose, AKI (↓insulin clearance), CKD (esp. dialysis)

Beware of hypoglycemia unawareness in T1DM and longstanding T2DM

Manifestations: <70: shakiness, anxiety, diaphoresis, visual Δ, HA, AMS. <55: seizure, coma

Treatment: PO (15g gel, tabs, juice) > IV (12.5-25g D50) > IM/SQ (1mg glucagon); recheck in 15min, chase with PO if due to insulin OD

If sulfonylurea OD: 50-75mcg octreotide SQ. **Review and adjust insulin regimen**

Ddx: If ill/medicated: drugs (insulin [secretagogues], EtOH), sepsis, ESLD, ESRD, HF, adrenal insufficiency, nonislet cell tumor

If well-appearing: insulinoma, post-gastric bypass (late dumping), insulin or insulin receptor antibodies, insulin (secretagogues)

Workup: must meet **Whipple's Triad** to merit eval: sx c/w ↓BG, reliable ↓BG while sx present, sx relief once BG corrected

- Mixed-meal with postprandial eval (q30min labs for 5h post-meal), or fasting eval with admission for 72h fast if no episodes (labs if sx and FSBG <60)
- Check: serum glucose, insulin level, C-peptide, βHB, proinsulin, sulfonylurea, meglitinide screen

Insulin	Pro-Insulin	C-Peptide	Ddx
↑	↑	↑	Insulinoma, oral hypoglycemic, autoimmune
↑	↓	↓	Exogenous insulin administration
nl	nl	nl	Nonislet cell tumor

DIABETIC KETOACIDOSIS (DKA)

Pathophysiology: think about each element of Diabetic Keto-Acidosis

- Diabetes: ↓insulin & ↑opposing hormones (glucagon, catechols, cortisol) → hyperglycemia → osmotic diuresis → hypovolemia
- Ketones: ↓insulin → ↑lipolysis → ↑free fatty acids → ↑ketones (acetooacetate, β-hydroxybutyrate, acetone)
- Acidosis: ↑β-hydroxybutyrate and acetooacetate, and contraction alkalosis with total body HCO₃ deficit ([NEJM 2015;372:546](#))

Precipitants (the “I’s”): infection (30-40% of cases, commonly PNA or UTI), initial presentation of DM (20-25% of cases), insulin non-adherence, inflammation (pancreatitis – but can see ↑amylase/lipase in DKA even w/o this), infarction (MI, CVA, gut), intoxication (EtOH, cocaine), iatrogenesis (e.g. SGLT2 inhibitors, steroids, thiazides, dobutamine/terbutaline, atypical anti-psychotics), infant (pregnancy)

Presentation: dehydration, polyuria/polydipsia, weight loss, n/v/abd pain, AMS, Kussmaul's respirations, fruity breath (acetone)

Dx: BG 250-800, pH <7.3, AG >10, ketonemia. Consider euglycemic DKA in pt on SGLT2i, EtOH liver dz, pregnancy

- Check BMP, CBC/diff, UA, SOsm, serum β-hydroxybutyrate, ABG/VBG. Consider hs-trop, EKG, BCx/UCx, CXR, lipase/amylase
- **Na correction** → use absolute sodium value when calculating anion gap. Use corrected value to assess for underlying hypotonic hypoNa: Corrected Sodium = Measured sodium + 0.02 * (Serum glucose - 100)
- UA ketone **does not** test for β-hydroxybutyrate, which is the predominant ketone in DKA (must measure from **serum**)

Management: prioritize ABCs, volume status, identifying precipitant → THEN electrolytes (especially K+) → THEN glucose

Labs: BMP q2h until AG closes, then q4h until normal K⁺; VBG, β-hydroxybutyrate q2-4h; FSBG q1h while on insulin gtt

Step 1: volume resuscitation (typically 5-8L deficit) ([QJM 2012;105:334](#); [JAMA Netw Open 2020;3:e2024596](#))

- **Bolus LR** 15-20cc/kg/h for initial resuscitation in first 1-2h (unless CHF, ESLD, ESRD, hypoxemia)
- **Corrected Na** → if **low**, start NS/LR±K⁺ at 250-500cc/h; if **normal/high** or hyperCl acidosis, start ½NS/LR±K⁺ at 250-500cc/h
- Add D5 to IVF at 150-200cc/h once BG<200 (DKA) or <300 (HHS)

Step 2: potassium repletion and management

Potassium	Action	K ⁺ may be normal/elevated at presentation, but total body K ⁺ is low. Multifactorial causes: solute drag of K ⁺ into extracellular space, osmotic diuresis, ↓insulin not driving K ⁺ into cells. Aggressive K⁺ repletion is critical: HYPOkalemia will limit your ability to administer the necessary insulin!
K <3.3	Give 20-40mEq KCl IV per hour + hold insulin !	
3.3≤K≤5.3	Add 20mEq K to IVF	
K >5.3	Continue to monitor q2h	

Step 3: insulin therapy, see flow chart ([Diabetes Metab Syndr Obes. 2014;7:255](#))

The #1 goal of insulin therapy in DKA is to stop ketogenesis and close the AG

- **Don't start insulin until you have control of K⁺**
- **Don't stop the insulin gtt** unless true hypoglycemia (<65 mg/dL) or hypokalemia (<3.3 mEq) occurs
- **Initial:** bolus 0.1U/kg regular insulin, then start 0.1U/kg/h IV regular insulin gtt; OR no bolus and start 0.14U/kg/h IV gtt
 - Goal is to ↓BG by 50-75mg/dL each hour
 - For mild DKA, subcutaneous insulin regimens may be used instead of IV ([Cochrane Rev 2016](#))
- **Titrating insulin drip:** MICU insulin gtt protocol is NOT for DKA
 - If BG does not ↓ by 50-75mg/dL in 1st hr, re-bolus (DKA) or double the gtt (HHS), no evidence for hourly titration afterwards
 - If BG >250 and falling: increase gtt by 25% if drop is <40, no change if drop is 40-80, decrease by 50% if drop >80
 - Once BG <200 (DKA) or <300 (HHS), ↓gtt to 0.02-0.05U/kg/h and add D5 to fluids
 - Goal BG is 150-200 (DKA) or 250-300 (HHS)

For BG <150	Δ Insulin gtt and glucose source
BG 91-149	↓gtt by 25% + 1D5 gtt by 50cc/hr
BG 66-90	↓gtt by 50% + ½ amp D50 + continue D5 gtt
BG ≤65	hold insulin + 1 amp D50 + continue D5 gtt

Other electrolytes:

- **HCO₃**: no proven benefit w/ pH > 6.9. If **pH <6.9**, give 2 amps HCO₃ dissolved in 400mL sterile water w/ 20mEq KCl over 2h
- **Phos**: total body deficit but serum phos may be ↑/nl; will ↓ w/ insulin; **only replete if <1.0** to prevent cardiac dysfunction

Transitioning to SQ insulin: start if BG <200 **and** pt is **able to eat and two** of the following are met: **AG <12, HCO₃ ≥15, pH >7.3**.

Start **basal** regimen w/ either: home glargine dose **OR** glargin at 0.25-0.4 U/kg/d **OR** glargin at (# units on IV gtt over past 6h x 4 x 0.7).

Consider NPH 0.25-0.4U/kg/d in pts presenting with newly diagnosed DM for easier titration (split dose as 2/3 AM dose, 1/3 PM dose).

Start **bolus** regimen w/ either: 0.25-0.4U/kg/d divided (if T1DM or unknown) **OR** ISS only (if T2DM). **Overlap IV gtt/SQ insulin by 2-4h**

Ketosis-prone diabetes: characterized by DKA w/ hx T2DM or atypical substrate for T1DM (older age, overweight). Patients should be discharged on insulin and see an endocrinologist for antibody (GAD65, IA2) and β-cell function (C-peptide levels) testing to determine diabetes subtype (antibody ±, β-cell function ±). Patients may not require long-term insulin therapy

HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)

Pathophysiology: hyperglycemia → osmotic diuresis → volume depletion; ketogenesis suppressed by low (but present) insulin levels

Precipitants: same as DKA (note: pts w/ T2DM and burnt-out pancreas can also present with DKA)

Presentation: AMS (25-50%), obtundation, seizure, focal neuro def, volume depletion, evolves over days-weeks (vs hours-days in DKA)

Dx: glucose >600mg/dL (frequently >1000), osmolality >320mOsm/kg, pH >7.3, absent or minimal ketones

Management: as above for DKA w/ modifications: more aggressive IVF (~8-10L deficit); **goal glucose 250-300mg/dL** (in DKA, 150-200); transition to SQ insulin when BG <300 **and** mental status improved **and** patient is able to eat. Mortality >> DKA ([Diab Care 2014;37:3124](#))

Endocrinology

Adrenal Insufficiency

Etiology ([Lancet 2014;383:2152](#); [NEJM 2009;360:2328](#))

Primary AI: ↓ adrenal hormone → ↑ ACTH. Lesion localizes to the **adrenal gland**

- Causes: autoimmune (80-90% cases in developed countries; anti-21-hydroxylase Ab in 86%, autoimmune polyglandular syndromes) >> infxn (TB, HIV, CMV, histo, meningococcus), bilateral adrenal hemorrhage (infxn, DIC, APLAS), malignancy (mets), genetic (CAH, adrenal leukodystrophy), meds (keto/fluconazole, etomidate, phenobarb, phenytoin, rifampin, opioids)

Secondary AI: ↓ ACTH → ↓ adrenal hormone. Lesion localizes to **pituitary gland**

- Causes: Meds (chronic glucocorticoids, opioids, medroxyprogesterone, megestrol), pituitary lesions (see [Pituitary Disorders](#))

Clinical Manifestations

Primary AND Secondary:

- Signs/symptoms: weakness, fatigue, anorexia, GI complaints, myalgias, psychiatric sx, wt loss, orthostasis, vasodilatory shock
- Lab abnormalities: hyponatremia, hypoglycemia, hypercalcemia, non-AG acidosis, anemia, eosinophilia, lymphocytosis

Primary only (↓ serum aldosterone): hyperK, salt craving, **hyperpigmentation**; long-term → nausea/vomiting, abdominal pain

Secondary only (RAAS intact): ± hypopituitarism, hypoglycemia (more common than in primary)

Diagnosis

- **Preferred test:** cosyntropin stimulation test (aka "cort stim") ([JCEM 2016;101:364](#)). Can be performed any time of day
 - Check serum cortisol and ACTH → give cosyntropin (ACTH) 250 µg IV → repeat serum cortisol **30-60min later**
 - Normal response: serum cortisol ≥18 µg/dL (note: this rules out all cases of 1° AI + chronic cases of 2° AI)
 - In acute 2° AI, adrenal glands have not had time to atrophy, so cort stim test will be normal!
 - If abnormal cort stim, consult endocrine
- **6-8 AM cortisol:** highly suggestive of AI if ≤3 µg/dL (<5 µg/dL suggestive); rule out AI if ≥18 µg/dL. ↓ is late finding in AI
 - Falsely low: ↓ albumin (e.g. cirrhotics, nephrotic syndrome, critical illness; ↓ bound and total cortisol, but free cortisol may be nl); PM testing (cortisol responses are greatest in morning)
 - Falsely high: pregnancy, estrogen tx (↑ cortisol binding globulin, ↑ bound/total cortisol, free cortisol may ↓)
- **Testing for primary AI:** ↑ ACTH >2x ULN; ↓ aldo, plasma renin, 17-OH-prog, 21-OHase Ab; TB test, VLCFA. Consider CT A/P
- **Testing for secondary AI:** ↓ ACTH, normal aldo

Adrenal Crisis

- Acute-onset AI with distributive shock in s/o major stressor (infxn, trauma, major surgery, critical illness). **Consult endocrine**
- **No known AI ± not taking chronic steroids:** draw ACTH/cortisol but don't delay empiric treatment; defer cort-stim until stable
- **Known AI or taking chronic steroids:** start treatment; diagnosis can be presumed by history; no role for cort stim test

Treatment ([JCEM 2016;101:364](#))

- **Adrenal crisis → stress dose steroids (hydrocortisone 100mg IV or dexamethasone 4mg IV x1) and >2-3L NS.** Follow with hydrocortisone 50mg IV q6h or dexamethasone 4mg IV q24hr ± fludrocortisone 0.1mg QD when off saline infusion if 1° AI
 - May taper once patient's clinical status improves and underlying precipitant is adequately addressed
 - Dexamethasone not detected in cortisol assay; steroid of choice if considering early cort stim dx ([Clin Chem 2004;50:2345](#))
 - Treat AI **BEFORE** treating severe **hypothyroidism**; otherwise can precipitate adrenal crisis
- **Chronic AI → glucocorticoid:** hydrocortisone 15-25mg PO QD (2/3 AM, 1/3 early PM) or prednisone 3-5mg PO QAM
Mineralocorticoid (only in 1° AI): fludrocortisone 0.05-0.1mg PO QD
 - **If minor illness or minor surgery → sick dose:** "3x3 rule" = 3x daily dose for 3 days
 - **If severe illness → stress dose:** hydrocortisone or dexamethasone (as above)
 - Supply patients with medical alert bracelet and glucocorticoid injection kit for emergency use if new diagnosis

Steroid Pearls

- Taper: **not necessary if steroid use <3w (independent of dose)** → low risk of HPA suppression. Patients needing to taper off long-term corticosteroids should do so with endocrinology guidance, may need cort-stim before stopping
- Side effects of supra-physiologic doses: ↑ weight, insomnia, skin thinning, AMS, hyperglycemia, edema, osteoporosis, gastritis
- Prophylaxis: **PJP:** if taking prednisone ≥20mg for ≥4w plus second reason for immunocompromise; **PUD:** if also taking aspirin/NSAIDs; **osteoporosis:** start calcium 1200mg/d + vitamin D 800IU/d if on glucocorticoids (any dose) >3mo (consider bisphosphonates for pts at intermediate/high risk of fracture); **DM2:** monitor glucose/A1C, consider NPH dose (0.1-0.4U/kg/d) with glucocorticoid if BG/A1C high

Steroid	Equivalent Anti-inflammatory Dose (mg)	Relative Anti-inflammatory Activity	Relative Na Retention Activity	Duration (hrs)
Hydrocortisone	20	1	2	8-12
Predniso(lo)ne	5	4	0.8	12-36
Methylprednisolone	4	5	0.5	12-36
Dexamethasone	0.75	30	0	36-72
Fludrocortisone	n/a	10	125	12-36

Endocrinology

Pituitary Disorders

HYPOPITUITARISM

Definition: ↓ pituitary hormone production/release resulting from diseases of pituitary (1°) or hypothalamus/stalk (2°)

Causes:

- Surgery, radiation, infection (TB, fungal, meningitis), infiltration (sarcoid, hemochromatosis), trauma, tumors (1°: pituitary tumors, mets; 2°: external stalk compression [e.g. craniopharyngioma, meningioma, mets]), genetic
- 1° only: Sheehan's (infarction), apoplexy (hemorrhage), meds (DA agonists), autoimmune (classically in 3rd trimester/postpartum)

Clinical Manifestations & Diagnosis:

Hormone Deficiency	Signs/Symptoms	Laboratory Tests
Prolactin	Reduced lactation	PRL
ACTH (2° adrenal insufficiency)	Weight loss, orthostatic dizziness, hypotension	AM cortisol, cort stim test, ACTH
GH	Low energy, central obesity, ↓ bone mineral density	IGF-1, insulin tolerance test
TSH (2° hypothyroidism)	Weight gain, bradycardia, hair loss, dry skin, hyporeflexia	TSH, free T4
LH/FSH	Amenorrhea, decreased libido, ED, infertility	LH, FSH, estradiol, AM testosterone

Treatment: replace deficient hormone ([JCEM 2016;101:3888](#)) & **endocrine consult**. Most sensitive issue is cortisol/thyroid hormone replacement: if concurrent deficiencies **treat AI before hypothyroidism** as can otherwise precipitate adrenal crisis

HYPERPITUITARISM

Definition: excess of any of the hormones secreted by the anterior pituitary gland (PRL, ACTH, GH, TSH, LH/FSH)

Causes: (1) hyperfunctioning pituitary adenoma, (2) elevated prolactin due to disruption of pituitary stalk, medication/toxin

Clinical Manifestations: if pituitary adenoma → headaches, visual field deficits (bitemporal hemianopia)

Hormone Excess	Signs/Symptoms
Prolactin (Prolactinoma)	Infertility, amenorrhea, galactorrhea (F>M), erectile dysfunction
ACTH (Cushing's disease)	Weight gain, fatigue, irritability, anxiety, depression, insomnia, easy bruising, poor wound healing, central obesity, acne, hirsutism, wide violaceous striae, prox muscle weakness, HTN
GH (Acromegaly)	Arthralgias, fatigue, paresthesias (carpal tunnel syndrome), hyperhidrosis, OSA, CHF, enlarged jaw, hands, feet, coarse facial features, deepening of voice, skin tags, hirsutism, HTN
TSH (2° hyperthyroidism)	Goiter, fatigue, exertional intolerance, irritability, palpitations, diarrhea, tachycardia, tremor, hyperreflexia

Diagnosis:

- **Labs:** Targeted based on sx – prolactinoma (PRL), Cushing's disease (overnight 1 mg dexamethasone suppression test, late-night salivary cortisol, or 24h urinary free cortisol excretion), acromegaly (IGF-1, confirm with GH level after glucose tolerance test), 2° hyperthyroidism (TSH, free T4, total T3)
- **Imaging:** MRI brain w/ and w/o contrast, pituitary protocol

Management:

- **Prolactinoma:** if >1cm or symptomatic, first-line treatment is **dopamine agonist** (cabergoline 1st (get TTE before), bromocriptine preferred in preconception setting). If <1cm or asymptomatic, can monitor closely with MRI and prolactin levels ([JCEM 2011;96:273](#))
- For all other hypersecreting pituitary adenomas, treatment is **transsphenoidal pituitary surgery ± radiation therapy**
- For GH secreting adenomas in patients who are poor surgical candidates, can treat with somatostatin analog (octreotide)

DIABETES INSIPIDUS (DI)

Definition: polyuria (>50mL/kg/day in DI) in setting of insufficient amount of (central) or response to (nephrogenic) ADH

Causes: (1) central – trauma, surgery, hemorrhage, infarction, neoplasm, infiltrative (sarcoidosis, histiocytosis), infection, autoimmune, drugs (EtOH, phenytoin); (2) nephrogenic – drugs (lithium, cisplatin), hypoK/hyperCa, infiltrative (sarcoidosis, amyloidosis, MM), sickle cell

Diagnosis:

- **Water deprivation test:** normal physiology: water restriction → ↑SOsm → ↑ADH → ↑UOsm ([JCEM 2012;97:3426](#))
 - Check Na, SOsm, UOsm, UVol q2hr. Urine dipstick for glucose should be negative
 - If UOsm > 800 mEq/kg, stop test due to appropriate vasopressin response (dx: **primary polydipsia**)
 - Once (1) **SOsm > 295 mEq/kg**, (2) **Na > 145 mEq/L** (adequate ADH stimulus) **AND** (3) **UOsm stable** on several checks despite ↑SOsm (ADH response plateaued) → administer **desmopressin 4 mcg IV**, then check UOsm, UVol q30min x 2hr
 - **UOsm < 300 mEq/kg prior to desmopressin suggests complete DI**; **UOsm 300-800 mEq/kg suggests partial DI**
 - > 50% ↑UOsm following desmopressin = **central**
 - < 50% ↑UOsm following desmopressin = **nephrogenic**

Treatment: correct hypernatremia (see [Sodium Disorders](#)). Allow patient to drink to thirst. PO preferred to avoid rapid Δ in serum sodium

- **Central:** **desmopressin** (exogenous ADH) given **intranasally** (5mcg qhs + 5mcg QD-TID), can augment with adjunctive meds
- **Nephrogenic:** if partial, may try desmopressin; if complete, use adjunctive meds
- **Salt/protein restriction:** low solute intake reduces thirst, thereby reducing free water intake
- **Adjunctive meds:** **HCTZ** (volume depletion → increases proximal Na/water reabsorption, decreasing distal Na delivery where ADH acts); **amiloride** (mechanism similar to HCTZ, beneficial in Li-induced nephrogenic DI by blocking entry of Li across ENaC), **NSAIDs** (enhance renal response to ADH), **chlorpropamide** (enhances renal response to ADH)

Endocrinology

Calcium Disorders

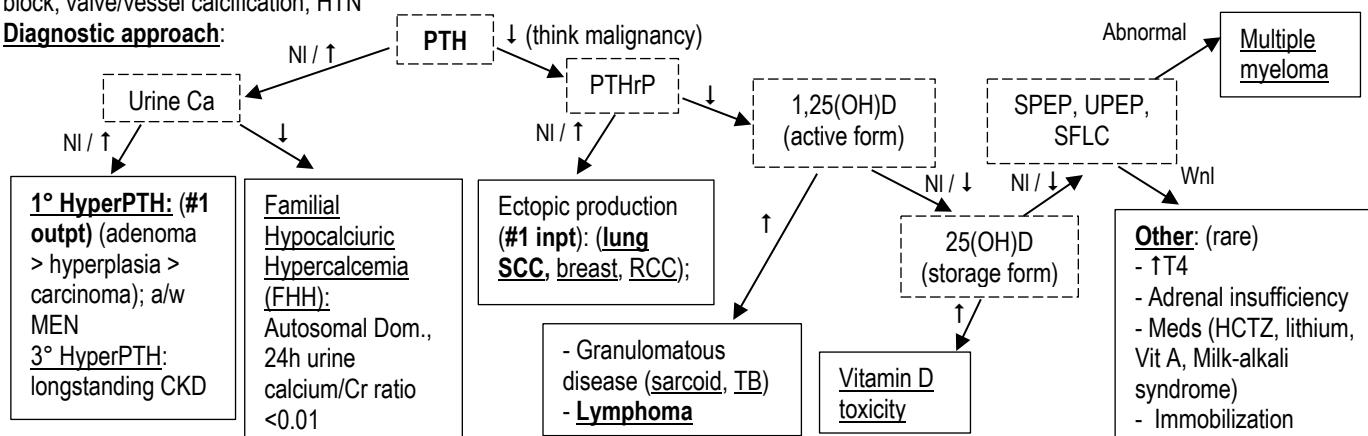
HYPERCALCEMIA

MAKE SURE TO CORRECT CALCIUM FOR ALBUMIN: Corrected Ca = Serum Ca + 0.8 x (4-Alb)

Definition: mild (corrected Ca <12); moderate (corrected Ca 12-14); severe (corrected Ca >14)

Clinical signs/symptoms: MSK ("bones") → osteitis fibrosa cystica (1° hyperPTH), arthralgia, osteoporosis, weakness; renal ("stones") → polydipsia, polyuria, nephrolithiasis, Type 1 RTA, AKI/CKD; GI ("groans") → n/v, anorexia, constipation, ileus, pancreatitis, peptic ulcers; neuropsych ("overtones") → fatigue, depression, anxiety, confusion, stupor, coma; CV → bradycardia, short QTc, AV block, valve/vessel calcification, HTN

Diagnostic approach:



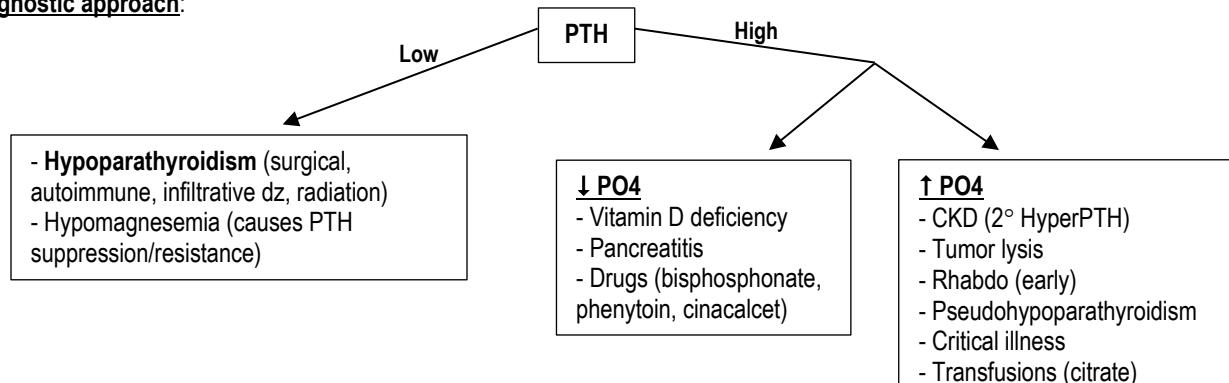
Management:

- In general, asymptomatic mild-moderate hyperCa can be managed conservatively as outpatient; patients with **symptomatic** or severe **hyperCa (>14)** should be **admitted** for treatment and have an endocrine consult
- Conservative measures:** avoid contributory meds; oral hydration; oral PO4 repletion to 2.5-3.0 (IV could lead to hypoCa)
- Volume resuscitation:** patients are typically very dehydrated; bolus NS then gtt @ 200-300cc/h with goal UOP 100-150cc/h
- Loop diuretics:** **ONLY** if concurrent HF, CKD (and only once volume replete), elderly; otherwise avoid as they can worsen dehydration
- Bisphosphonates:** best studied in malignancy; zoledronate >> pamidronate (**except in MM: more ATN**). Takes 2-4d for effect. Side effects: hypoCa (check 25(OH)D & replete prior to admin), flu-like illness. Reduce dose if CKD. Avoid if CrCl <30.
- Denosumab:** monoclonal Ab against RANKL → blocks pre-osteoclast maturation; good option in patients with CKD
- Calcitonin:** 4-8U/kg SC BID for 48 hours (substantial Ca reduction within 12-24 hours). Tachyphylaxis usually occurs within 48-72h.
- Other:** **glucocorticoids** (effective in calcitriol mediated etiologies, takes 2-5 days for effect), **HD** (if refractory or life-threatening)
- Special considerations for 1° hyperPTH:** surgery is curative. Indicated if (1) symptomatic **OR** (2) asymptomatic with Ca >11.5, osteoporosis/vertebral fracture, CCI <60, nephrolithiasis, **or** age <50. If poor surgical candidate, consider **cinaclacet**, bisphosphonate, tamoxifen ([JAMA Surg 2017;152:878](#); [JCEM 2014;99:3607](#))

HYPOCALCEMIA

Clinical signs/symptoms: **neuromuscular** (paresthesias, muscle cramps/spasms, tetany, Trousseau sign [carpal spasm w/ BP cuff inflation 94% Sn, 99% Sp], Chvostek sign [circumoral muscle twitch w/ facial nerve tapping poor Sn, 85% Sp]); **seizures**; **↑QTc**, laryngospasm, bronchospasm, AMS, abdominal pain, dysphagia ([BMJ 2008;336:1298](#))

Diagnostic approach:



Management:

- Replete magnesium** (hypoCa can be hard to correct without first correcting hypoMg → causes PTH resistance and ↓ secretion)
- IV Ca repletion:** if severe (**corrected Ca <7.5, iCa <1**), symptomatic, or prolonged QT
 - 1-2g IV **Ca gluconate** or CaCl₂ (in codes: via central line, risk of skin necrosis if extravasates) over 10-20 min
 - IV therapy ↑ serum levels for **only 2-3h** (chase w/ gtt or PO); can do sliding scale repletion in ICU
 - Telemetry recommended as arrhythmias may occur
- PO Ca repletion:** if Ca >7.5 or asx: 1-2g elemental Ca QD in divided doses (Ca citrate better absorbed vs CaCO₃ esp. if pt on PPI)
- Vitamin D repletion:** 800-1000IU Vit D3 daily (if severely deficient, 50,000 IU Vit D2 or D3 qweek x 6-8w and measure 25(OH)D level in 3-4mo). In patients w/ poor conversion of 25(OH)D (e.g. hypoparathyroidism, CKD) use **calcitriol** (start w/ 0.25mcg PO QD). See [Vitamin D](#)

OSTEOPOROSIS

Definitions:

- **Osteoporosis:** history of fragility fracture or BMD T-score ≤ -2.5 on DXA. **Osteopenia:** T-score -2.4 to -1 .
 - T-score: SD compared to mean for young, healthy adults of same sex and race
 - Fragility fracture: fracture of any bone after fall from \leq standing height with exception of fingers, toes, face and skull

Etiology:

- 1° osteoporosis is the most common. Risk factors: age ≥ 65 , low body weight (<57.6 kg), FHx of hip fracture, smoking, early menopause, excessive EtOH use
- 2° osteoporosis caused by: renal and liver disease, hyperthyroidism, hyperPTH, vit D deficiency, hypogonadism, glucocorticoids (≥ 5 mg prednisone for >3 mo), myeloma, malabsorption (celiac, IBD), RA, SLE, COPD, drugs (PPI, AED, long-term heparin, leuproide, aromatase inhib, MTX, GnRH agonists)

Diagnosis:

- FRAX score can be used to estimate 10 year fracture risk with or without BMD data
- **Indications for DXA:** (1) all women age ≥ 65 (USPSTF) and men ≥ 70 ; younger if RF for 1° or 2° ([Osteoporosis International 2014;25:2359](#); [JCEM 2012;97:1802](#)); (2) fragility fracture of all ages; (3) fracture and age ≥ 50
- **Initial labs for 2° causes:** CBC, BMP, LFTs, 25(OH)D, TSH, PTH, SPEP w/ sFLC

Management:

- **Lifestyle measures:** all patients with \downarrow BMD: weight-bearing exercise 3-4x/w, smoking cessation, \downarrow EtOH intake, calcium 1200mg QD (diet or supplemented). Replete Vit D to goal >30 ng/ml
- **Pharmacologic therapy:** for osteoporosis or osteopenia with FRAX 10y risk $>20\%$ for any fracture, $>3\%$ for hip
 - **Bisphosphonates:** Ca and Vit D replete prior to initiation. Monitor DXA q 1-3y for response ([JCEM 2019;104:1592](#))
 - **PO alendronate** 75mg or **PO risendronate** 35mg weekly. Avoid if GFR <30 . Strict instructions to prevent pill esophagitis: sit upright and take on empty stomach w/ full glass of water 30 min prior to other meds/food
 - **IV zoledronic acid** 5mg annually if esophagitis/GERD with PO treatment or otherwise unable to tolerate PO
 - **SERMs (tamoxifen/raloxifene):** less effective compared to bisphosphonates and reserved for use if unable to tolerate bisphosphonate/denosumab or in postmenopausal women with increased risk of breast cancer. SEs: endometrial ca (tamoxifen only), \uparrow risk DVT/PE, edema, hot flashes, muscle cramps
 - **Referral to Endocrine** for advanced therapies, refractory disease or age < 50 : denosumab (RANKL monoclonal ab, [NEJM 2009;361:756](#)), teriparatide and abaloparatide (recombinant PTH and PTHrP analog respectively, [Lancet 2018;391:230](#))
- **Inpatient** following fragility fracture: assess need for surgical treatment and consult Fracture Liaison Service (p25656). Bisphosphonates decrease mortality post-hip fracture ([NEJM 2007;357:1799](#))

VITAMIN D

Definitions: ([JCEM 2019;104:234](#))

Measured by **25[OH]D (calcidiol)** in serum. No consensus cutoff but majority of groups use the following values:

- Vitamin D Sufficiency: >20 ng/mL; Insufficiency: $12-20$ ng/mL; Deficiency: <12 ng/mL

Diagnosis:

- Population screening not recommended, only screen high-risk patients: ([JCEM 2011;96:1911](#))
 - Rickets, osteomalacia, osteoporosis, hyper-PTH, inadequate oral intake, decreased cutaneous synthesis (lack of sunlight, sun pigmentation, aging), malabsorption (gastrectomy, IBD, CF, celiac, pancreatic/biliary disease), impaired synthesis (ESLD, CKD), increased catabolism (AEDs, steroids, HAART, immunosuppressants)
- If deficient, obtain PTH, electrolytes, BUN, Cr, Ca, Phos, Alk Phos, and TTG

Management: ([NEJM 2007;357:3](#); [J Am Geriatr Soc 2014;62:147](#))

- Supplement with D3 or D2 (D3 slightly more preferred but D2 more readily available); recheck levels in 3-4 months
 - <12 ng/mL: 50,000IU QW x6-8w followed by 800-1000IU QD
 - $12-20$ ng/mL: 1000-2000IU QD
- For patients ≥ 65 y at high fall/fracture risk: Vit D 1000IU + calcium 1000mg QD with goal of >30 ng/mL
- For patients with malabsorption: Up to 10,000 to 50,000IU QD and/or UVB irradiation
- For patients with ESRD, ESLD, or vitamin D-dependent rickets: calcitriol 0.25-1.0 μ g QD
- For patients taking prednisone ≥ 2.5 mg QD for ≥ 3 months: 600-800IU QD with calcium 800-1000mg QD

Endocrinology

Thyroid Disorders & Male Hypogonadism

INPATIENT TFTs

- If thyroïdal illness suspected, TSH alone is inadequate; should also test for FT4 & T3. TSH reflects changes within 4-6 wks
- **Nonthyroidal illness "euthyroid sick"**: alterations in thyroid fxn due to illness, not 1° endocrine disorder; may be adaptive (anti-catabolic); no indication to treat; most likely cause of abnormal TFTs among inpatients ([Lancet Diab Endo 2015;3:816](#))
 - **Typical pattern:** (1) acute illness: ↓↓ T3, ↓T4, ↓/nl FT4, ↓/nl TSH. (2) recovery phase: ↑TSH → recovery of T4, T3
 - Sequential FT4 should ↑ in recovering sick euthyroid but remains low in 1° hypothyroid. rT3 can differentiate central hypothyroidism (↓) from sick euthyroid (↑), but rarely needed. FT3 only helpful to dx hyperthyroidism w/ altered TBG.
 - **Undetectable TSH (<0.01)** suggests true hyperthyroidism, and **TSH >20 + low T4** suggests true hypothyroidism
- Biotin supplementation can interfere with TSH and other assays, ensure pt off biotin x 1wk before testing
- ↓ TSH also seen with glucocorticoids, dopamine, dobutamine, octreotide, ↑β-HCG levels (pregnancy, trophoblastic disease)

HYPOTHYROIDISM

- **Definition:** elevated TSH with low T4 (primary) or low/normal TSH with low T4 (2°/central)
- **Signs/symptoms:** general (fatigue, cold intolerance, constipation, dry skin, myalgias, weight gain), neuro (depression, cognitive dysfxn, carpal tunnel), CV (bradycardia [severe], diastolic HTN) irregular menses
 - Exam: delayed relaxation phase of DTRs, non-pitting edema, lateral eyebrow thinning, macroglossia
- **Labs:** ↑LDL, ↑triglycerides, macrocytic anemia, ↓Na
 - Check other pituitary axes if concern for central hypothyroidism
- **Workup:** TSH with reflex, anti-TPO ab. No role for thyroglobulin or anti-thyroglobulin ab (only useful for monitoring thyroid Ca)
- **Causes:**
 - 1°: **Hashimoto's** (most common, +TPO Ab), infiltrative dz (hemochromatosis, sarcoid), transient thyroiditis (lymphocytic, granulomatous, postpartum), drugs (lithium, amio, TKIs, contrast), iatrogenic (thyroidectomy, radiation), iodine deficiency
 - 2°: see [Pituitary Disorders](#)
 - **↑ T4 requirement:** pregnancy, estrogen (↑THBG), weight gain, malabsorptive states (e.g. celiac disease), nephrotic syndrome (↑excretion), rifampin, phenytoin, carbamazepine, phenobarbital
- **Tx:** levothyroxine (T4) starting dose ~1.6mcg/kg/d PO (use 25-50mcg QD for elderly or comorbidities); IV = 50-75% PO
 - Take on an empty stomach 1h before food/meds; several hrs apart from PPI, aluminum hydroxide, iron, cholestyramine
 - **Check TSH q6 weeks and adjust by 12-25mcg** until normal TSH

	TSH	FT4
Primary	↑	↓
Secondary	↓/normal	↓
Subclinical	↑	Normal

Subclinical hypothyroidism: elevated TSH with normal FT4 (biochemical diagnosis)

- Dx: can check anti-TPO Ab (if +, monitor TFTs regularly because at higher risk for Hashimoto's)
- Treatment: treat if **TSH ≥10**. If TSH <5, consider risk factors (e.g. CV disease, CAD, HLD) to guide tx
- Elderly patients often have higher TSH levels and this can be normal

MYXEDEMA COMA

- Manifestation of severe hypothyroidism, STAT endo consult; mortality >30%, commonly due to hypercarbic respiratory failure
- **Precipitants:** infection, MI, cold exposure, surgery, sedative drugs (esp opioids) in a poorly controlled hypothyroid pt
- **Signs/symptoms:** **AMS** (lethargy/obtundation, not always coma), **hypothermia**, **hypotension**, bradycardia, ventricular arrhythmias, hypercarbic resp failure, seizure. Exam: puffy hands and face, swollen lips, enlarged tongue
- **Labs:** ↓Na (be careful with IVF), ↓Glu, ↓T4
- **Treatment:** do not wait to start tx for lab confirmation
 - **Test and empirically treat adrenal insufficiency:** **hydrocortisone** 50-100mg BEFORE T4 (if concomitant AI, replacing thyroid hormone first will catabolize residual cortisol and cause HoTN/death). Draw serum cortisol before initiating therapy.
 - **Levothyroxine (T4)** 12.5-50mcg IV QD in elderly or at risk for MI, up to 200mcg if sick and young
 - **Liothyronine (T3)** (5-10mcg Q8H) only given if pt is critically ill (T4 conversion to T3 takes several days), give only with endo guidance, can cause rebound hypermetabolism
 - Recheck FT4 in 3-7d; if giving T3, monitor peak levels
 - Patients are **hypometabolic**: use lower drug doses at lower frequency, avoid MS-altering meds

AMIODARONE-INDUCED THYROID DISEASE

Check TSH prior to treatment, q4-6 mo while on amio, and for 1 yr after amio discontinued

- Typical response to amio acutely: ↑TSH (2-3x nl), ↑T4 and FT4, ↓T3, ↑rT3 → levels return to normal in 3-6 months
- May cause **hypothyroidism** (due to Wolff-Chaikoff or destructive thyroiditis) **OR** **hyperthyroidism**
 - **Type 1** (early) → ↑synthesis due to ↑iodine
 - **Type 2** (late) → direct toxicity of drug causing thyroiditis and stored hormone release without increased synthesis

HYPERTHYROIDISM

- **Definition:** low TSH with high T4 (primary) or high/normal TSH with high T4 (secondary/central) ([Thyroid 2016;26:1343](#))
- **Signs/symptoms:** general (\downarrow weight, \uparrow appetite, heat intolerance, tremor, weakness), CV (palpitations, AFib, systolic HTN), hyperdefecation, dyspnea, sweating, anxiety, emotional lability, urinary frequency, abnormal menses, osteoporosis
 - Exam: lid lag, exophthalmos and pretibial myxedema (Graves' only), hyperreflexia, thyroid bruit
 - Apathetic thyrotoxicosis: depression, weakness; seen in elderly
- **Labs:** \uparrow HDL, \downarrow LDL, normocytic anemia, \uparrow Ca, \uparrow AlkP, \uparrow Glu
- **Workup:** 1) TSI and TBII (Graves'), 2) RAIU (not for amio-induced or if recent IV contrast), 3) thyroid US w/ Doppler
- **Causes:**
 - 1°: **Graves' disease** (most common, **T3:T4 ratio >20**), toxic adenoma, toxic multinodular goiter, transient thyroiditis (lymphocytic, granulomatous, postpartum, viral), drugs (amio, iodine, lithium), iatrogenic (radiation, palpation), exogenous T3 or T4 ingestion (low thyroglobulin), HCG-mediated, struma ovarii. 2°: see [Pituitary Disorders](#)
- **Treatment:** β -blocker for adrenergic symptoms (e.g. metoprolol, propranolol)
 - **Graves' disease:** thionamides (methimazole $>$ PTU due to hepatotoxicity), radioiodine (risk of ophthalmopathy), thyroidectomy (watch for hypoparathyroidism). Monitor total T3 and FT4 q6wks.
 - Toxic adenoma or multinodular goiter: radioiodine, surgery, less commonly thionamides

	TSH	FT4	Total T3
Primary	\downarrow	\uparrow	\uparrow
Secondary	\uparrow/nl	\uparrow	\uparrow
Subclinical	\downarrow	nl	nl

THYROID STORM

- Manifestation of severe thyrotoxicosis, STAT endocrine consult. Mortality rate 10-30%, mostly due to cardiovascular collapse
- **Precipitants:** surgery (thyroid or other), trauma, infection, iodine load, irregular use or discontinuation of antithyroid drugs
- **Signs/symptoms:** **AMS** (agitation, delirium, psychosis, coma), **hyperthermia, tachycardia**, atrial arrhythmias, CHF
 - Exam: goiter, tremor, warm/moist skin, exophthalmos (Graves')
- **Labs:** \uparrow T4/T3, \downarrow TSH
- **Dx:** Burch-Wartofsky Point Scale ([BWPS](#)) >44 highly suggestive
- **Treatment:**
 - **β B:** only propranolol decreases T4 \rightarrow T3 conversion, may require high doses (2g/d). Titrate to sx and HR (i.e. <80).
 - **Anti-thyroid meds:** only stop formation of new hormone, not release of stored hormone
 - **Methimazole** (20mg q4h-q6h) is preferred unless pt is critically ill. **PTU** (200mg q4h-q6h) decreases T4 \rightarrow T3 but higher rates of fulminant hepatic necrosis
 - **Iodine** (100-250mg q6h-q8h) blocks release of thyroid hormone, must be given at least 1h after thionamide; can cause Jod-Basedow (iodine-induced hyperthyroid) in toxic adenoma and Wolff-Chaikoff (iodine-induced hypothyroid) in Graves
 - **Hydrocortisone** (300mg loading dose then 100mg q8h) to reduce T4 \rightarrow T3
 - Patients are **hypermetabolic** and will clear drugs quickly

MALE HYPOGONADISM ([J Clin Endocrinol Metab 2018;103:1715](#))

- **Definitions:**
 - Clinical syndrome that results from a failure of the testes to produce physiologic levels of testosterone and/or normal number of spermatozoa due to pathology at the testicular level (1°), hypothalamus/pituitary (2°), or both
 - 1° causes: Klinefelter, cryptorchidism, testicular radiation, orchitis, myotonic dystrophy, HIV
 - 2° causes: hyperprolactinemia, severe obesity, Fe overload, opioids, steroids, GnRH agonists
 - Signs/Symptoms: loss of axillary/pubic body hair, reduced libido, erectile dysfunction, gynecomastia, low sperm count, decreased energy, depressive mood, normocytic anemia, reduced muscle bulk, increased body fat
- **Diagnosis:**
 - Measure morning fasting total testosterone x2 (nl total T range $\sim 300-800$)
 - Measure free testosterone only if there may be alterations in level of SHBG (obesity, nephrotic syndrome, use of steroids, HIV, cirrhosis, thyroid disease)
 - If testosterone level is low on both measurements, measure LH/FSH to determine 1° vs 2° etiology
 - If 2° measure Fe studies, other pituitary hormones, & consider imaging; for 1° consider karyotype
- **Management:**
 - **Testosterone therapy** is the mainstay of treatment to induce and maintain 2° sex characteristics and address sx
 - Formulations: intramuscular (weekly, q2w, and monthly), transdermal gel, patches, tablets
 - Adverse effects: site reactions, acne, oiliness of skin, erythrocytosis, no large RCT to study cardiovascular risk/MACE or VTE; higher risk of adverse outcomes in patients with metastatic prostate cancer, elevated PSA, severe BPH
- **Monitoring:**
 - Evaluate around 3-6mo after initiation to assess response to treatment and measure concentrations, then annually
 - Goal level is mid-normal physiologic range (300-800)
 - Check baseline Hct and 3-6mo after tx, if Hct $>54\%$ stop therapy, reinitiate at reduced dose once Hct reaches safe level
 - If patient chooses to monitor for prostate ca, perform DRE and measure PSA before treatment and 3-12mo after starting

Allergy & Immunology

Drug & Contrast Allergy

ADVERSE DRUG REACTIONS (ADRs): ([JACI 2010;125:S126](#))

- Type A** = predictable (~75-80%): dose-dependent reactions related to drug's known pharmacological action which occur in otherwise healthy patients if given sufficient dose and exposure (e.g. gastritis after NSAIDs)
- Type B** = unpredictable (20-25%): dose-independent, unrelated to pharm action, and occur only in susceptible pts
 - Drug intolerance**: undesirable pharmacologic effect w/o abnormalities of metabolism/excretion/bioavailability of drug (e.g. tinnitus after aspirin)
 - Drug idiosyncrasy**: abnormal effect caused by underlying abnormalities of metabolism/excretion/bioavailability (e.g. hemolysis after antioxidant drug in G6PD deficiency)
 - Pseudo-allergic reaction** (formerly known as anaphylactoid): drug causes direct release of mediators from mast cells/basophils (e.g. flushing during vancomycin infusion, exacerbation of asthma/rhinitis w/ aspirin in AERD)
 - Drug allergy** (5-10% of all ADRs): immunologically-mediated hypersensitivity reactions

HYPERSENSITIVITY REACTIONS (Gell and Coombs Classification): ([Clin All 1998;18:515](#))

Type	Reaction	Mechanism	Presentations
I	Immediate (min-hr)	Ig-E mediated degranulation of mast cells due to antigen binding and cross-linking of IgE	Anaphylaxis, allergic rhinitis, allergic asthma, urticaria, angioedema
II	Antibody	IgM/IgG antigen interactions on target cell surfaces	Drug-induced cytopenia
III	Immune-complex	Immune complex formation and deposition in tissues → complement activation → local/systemic inflammation	Serum sickness, vasculitis, drug induced lupus
IV	Cell-mediated	Ag activates T cells → Ag later binds to activated T cells → cytokine release → macrophage & cytotoxic T cell accumulation	Contact dermatitis, SJS/TEN, DRESS, AGEP

CLINICAL MANIFESTATIONS OF DRUG ALLERGY ([AACI 2018;14:60](#))

	Manifestation	Clinical Features	Timing	Causative Drugs
SKIN	Urticaria, angioedema, drug exanthem, SJS/TEN, AGEP	For information on skin manifestations of drug allergy, see Dermatology: Drug Eruptions		
HEME	Hemolytic anemia, thrombocytopenia, leukopenia	Varies, but in general: -Hemolytic anemia: acute -Drug-induced TMA: acute or subacute		PCN, sulfa drugs, AEDs, cephalosporins, quinine, heparin, thiazides
HEPATIC	Hepatitis, cholestatic jaundice	Variable. Can be acute or chronic		Sulfa drugs, phenothiazines, anti-TB drugs, carbamazepine, erythromycin, allopurinol
RENAL	Interstitial nephritis, glomerulonephritis	Variable. Days to months		PCNs, sulfonamides, allopurinol, PPIs, ACEi
MULTI-ORGAN	Anaphylaxis	Urticaria, angioedema, bronchospasm, GI, hypotension	Immediate (usually within 1 hr)	Abx, NM blockers, anesthetics, contrast
	DRESS	Rash, fever, eos, hepatic dysfxn, LAD	2-8 weeks	AEDs, sulfa drugs, minocycline, allopurinol, mAB (monoclonal Ab)
	Drug induced lupus	Arthralgias, myalgias, fever, malaise	Months to years	Hydralazine, procainamide, INH, quinidine, minocycline, abx, anti-TNF agents
	Serum sickness	Arthralgias, myalgias, fever, malaise	1-2 weeks	Heterologous antibodies, infliximab, allopurinol, thiazides, Abx, bupropion, mABs
	Vasculitis	Cutaneous or visceral vasculitis		Sulfa abx and diuretics, mABs, hydralazine, penicillamine, PTU

EVALUATION

- Key Qs in drug allergy hx:** approximate date, drug, dose and route, doses/days into course, co-administered meds, coincident infections, sx, severity (home/office/ED/hospitalization), how treated, exposures since
- Please document appropriately** in EPIC allergy section. Include rxn, date, intolerance v. reaction, other meds tolerated

Allergy & Immunology

Drug & Contrast Allergy

DIAGNOSIS [Drug Allergy Practice Parameter 2010](#)

- **Labs** (sometimes helpful): CBC w/ diff (eos), tryptase (if anaphylaxis), auto-Abs (e.g. anti-histone in drug induced lupus)
- **Skin testing**: evaluates for drug-specific IgE antibodies for a limited # of meds. NPV of penicillin skin testing = 95%
- **Deliberate re-challenge = graded challenge = test dose procedure**
 - Used when there is a **low suspicion for true allergic reaction** to a medication. Does NOT assess cross-reactivity of structurally-related drugs. Contraindication = severe non-IgE mediated HSR (ex: DRESS, SJS, etc.)
 - **How to order: Antibiotic Test Dose** in Epic order sets (can also type "penicillin" "allergy" "test dose")
 - Automatically orders the rescue medications, nursing communication orders, and fills in doses of desired med (FYI test dose = 1/10 of rx dose for IV meds and 1/4 of rx dose for oral meds)
 - **If negative:** patient is *not* allergic to that agent and can safely receive it, please update allergy list
 - If agent was a related agent (e.g. CTX administered in PCN-allergic pt): update "comments"
 - If agent was same agent as recorded allergy (e.g. PCN administered in PCN-allergic pt): remove allergy
 - **If positive:** Epi 1:1000 IM (0.3 mg), Benadryl 50mg IV/PO, and page allergy fellow

DRUG DESENSITIZATION [JACI 2010:125:S126](#) (used if **true allergy**)

- **Indications:** \oplus skin test, \oplus test dose, or h/o severe type I HSR **AND** no alt. tx. ONLY for Type I (IgE-mediated) rxns
- **Method:** administer drug with increasing doses over hours such that it induces state of **TEMPORARY** tolerance
- At MGH, consult Allergy. Generally, desensitization needs to be done in the ICU but there are exceptions (e.g. Lunder)
- **If patient discontinues medication:** procedure must be performed again if pt stops medication for >2-3 half-lives

PENICILLIN & CEPHALOSPORIN ALLERGY

- Pathway: [Elucid](#)
- 10% of pts report a PCN allergy, but **90%** of patients with a h/o PCN allergy can tolerate PCN ([JACI 2010:125:S126](#))
- Patients w/ PCN allergy have a **<1% cross reactivity to carbapenems** ([CID 2014:59:1113](#)); and **<2% of patients w/ skin test-proven sensitivity to PCN will react to cephalosporins** ([Annals 2004:141:16](#))
- PCN allergy is typically mediated by the β -lactam ring, while cephalosporin allergy is due to the R-group side chain. ↑risk of cross-reactivity w/ β -lactams w/ similar R-group

Groups of common β -lactam antibiotics that share similar R-group side chains			
Amoxicillin	Ceftriaxone	Cefotaxime	Ceftazidime
Ampicillin	Cefpodoxime	Cefepime	Aztreonam
Cephalexin	Cefadroxil		

OTHER COMMON DRUG ALLERGIES

- **Taxanes/platinum-based Chemotherapy**: differentiate *infusion reaction* (SIRS response) from anaphylaxis (type I HSR). 19.5% carboplatin, 30% taxanes ([NEJM 1995:332:1004](#)). ↑freq of infusion rxns with subsequent infusions ([AAAAI 2009:102:179](#))
- **Allopurinol hypersensitivity syndrome (AHS)**: rash, fever, hepatitis, and/or AKI after exposure. Usually occurs after 4-8 wks. In patients of E. Asian descent, unless initiating for TLS, consider sending *HLA-B5801* genotyping (high risk)
- **Aspirin/NSAIDs** ([JACI 2010:125:S126](#)): wide spectrum of drug-induced allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis
 - Management: avoid NSAIDs (COX-1 inhibitors). If NSAIDs are necessary, consult Allergy
 - **Aspirin-Exacerbated Respiratory Disease (AERD)** (aka Samter's Triad): triad of asthma, rhinosinusitis w/ nasal polyps, and ASA/NSAID sensitivity (nasal congestion, bronchospasm). **Tx:** ASA desensitization

IV RADIO CONTRAST MEDIA ([ACR Guidelines 2020](#)): see [Contrast](#) for details on contrast reactions

Type/Path	Epidemiology	Presentation	Clinical pearls	Pre-Treatment (MGH protocol)
Pseudoallergic Direct stimulation of mast cells / basophils	-Mild rxn: 0.5% pts -Severe: 0.04%	Immediate pruritus, urticaria, angioedema, airway obstruction, HoTN, abd pain	Seafood allergy is not a contraindication. Oral contrast is NOT contraindicated in a patient with IV contrast allergy, though rarely can cause a reaction.	Elective (13h protocol) Prednisone 50mg PO at 13, 7, & 1h prior AND Benadryl 50mg PO 1h prior Accelerated (4-5h) Methylprednisolone 40mg IV now & q4h until scan AND Benadryl 50mg IV 1h prior Emergent (no data) (1h): Methylpred 40mg IV AND Benadryl 50mg IV @ 1h prior
Delayed T cell-mediated	2% of patients	>1h - 1 wk. Usually mild, skin eruption.	Tx: Supportive care	

Allergy & Immunology

Angioedema & Anaphylaxis

ANGIOEDEMA ([Allergy 2018;73:1393](#))

- Definition:** localized non-pitting swelling of skin or mucosal tissue due to interstitial edema; may affect face, extremities, genitals, bowels. Often asymmetric. Occurs in min-hrs and resolves within 1-3d
- Common triggers: heat, cold, delayed pressure, solar, vibratory, cholinergic, contact, and aquagenic

Type	Urticaria	Triggers
Histamine	Usually (may have angioedema only)	ASA, NSAID, CCB, platinum-based chemo, β -lactams, metoprolol, siro/everolimus, risperidone, Idiopathic/spontaneous
Bradykinin	Never	ACEi: 0.1-0.7% pts; may occur any time during trtmt and recur 4-6 wks after cessation Hereditary angioedema: autosom dom. C1 esterase deficiency/dysfxn. <u>Screen:</u> ↓C4

- Treatment:** in ALL: **ABCs, secure airway**
 - If urticaria: identify & remove exposure → H1 antihistamines (IV Benadryl vs high-dose PO cetirizine) + steroids
 - If no urticaria:
 - On ACEi → stop ACEi → supportive care (if severe, consider icatibant), add ACEi to allergy list
 - Known hereditary or acquired angioedema → page Allergy for C1-inhibitor, ecallantide, **icatibant**. FFP 2nd line
 - Not on ACE; no known disorder → H1 antihistamines + methylpred → PO pred + H1 antihistamine

ANAPHYLAXIS ([AAAI 2015;115:341](#); WAO: [World Allergy Org J 2011;4:13](#))

- Definition:** acute, life-threatening, multi-system syndrome due to allergy or hypersensitivity

Type	Mechanism	Triggers
Immunologic	IgE mediated	Food (e.g., nuts, shellfish, milk, eggs), insect venom, meds (e.g. NSAIDs, β -lactams, biologics), latex, occupational allergens, aeroallergens, etc.
	Non-IgE mediated	NSAIDs, dextrans (e.g. HMW iron), biologics, contrast
Nonimmunologic	Direct mast cell activation	Physical factors (exercise, heat, cold, UV light, XRT), EtOH, meds (opioids)
Idiopathic	No apparent trigger	Mastocytosis/clonal mast cell disorder, previously unrecognized allergen

- S/Sx:** (1) Cutaneous = angioedema, urticaria, flushing, pruritis; (2) Respiratory = dyspnea, wheeze, upper airway angioedema, rhinitis; (3) GI = nausea, vomiting, diarrhea; (4) Cardiovascular = hypotension
 - Associated with **biphasic reaction** in 4-20% pts → return of symptoms 1-72h (usually <8) after initial symptom resolution despite no further exposure to trigger
- Diagnostic criteria:** 1 of 3 must be met
 - Skin ± mucosal involvement AND either respiratory sx OR hypotension** after **POTENTIAL** allergen exposure
 - Two or more of following after exposure to **LIKELY allergen**: skin/mucosa swelling, respiratory sx, HoTN, GI sx
 - Low BP** (SBP<90 or >30% drop from baseline) after exposure to **KNOWN allergen** for pt
- Labs:** **tryptase** (within 15min-3h of symptom onset and 24h after symptoms resolve to establish baseline). Values $\geq 1.2 \times$ baseline + 2ng/dL = mast cell activation. Normal levels do not rule out anaphylaxis
- Treatment:**
 - Establish and maintain airway, administer oxygen/IVF (1-2L) for hypotension, remove trigger if possible
 - Epinephrine:** 1st line. ONLY medication that reverses airflow obstruction & prevents cardiovascular collapse
 - Dosing:** prefer 0.3-0.5mg IM (1:1000 dilution, 1 mg/mL) in mid-outer thigh. Could also do 0.1-0.3mg IV (1:10,000 dilution, 0.1mg/mL). May repeat q5-15min; if >3 doses required, consider continuous epi gtt (1-10mcg/min)
 - If on beta blockers AND resistant to epinephrine, administer glucagon (1-5mg bolus → gtt @ 5-15mcg/min)
 - Adjunctive agents:**
 - Albuterol** (stacked nebs x 3) PRN wheezing/cough/SOB
 - H1 antihistamines:** PRN for pruritis/urticaria. *Does NOT treat airway obstruction or hypotension!* Benadryl 25-50mg
 - H2 antihistamines:** famotidine 20mg IV
 - Methylprednisolone 1-2 mg/kg qd x2.** No evidence to prevent biphasic rxn. May be beneficial if (1) severe sx requiring hospitalization (2) known asthma (3) significant and persistent bronchospasm
 - Make sure to discharge home with EpiPen & refer to Allergy**
 - If h/o anaphylaxis to stinging insect, refer for skin testing. If +, consider SQ venom immunotherapy, which decreases risk of subsequent anaphylaxis from 50-60% to 2-3% (NNT = 2) ([NEJM 2014;370:1432](#))

MAST CELL BASICS ([NEJM 2015;373:163](#))

- When activated, mast cells degranulate and release **vasoactive & pro-inflammatory** mediators such as histamine, heparin, serotonin, leukotrienes, prostaglandins, proteases (including tryptase), cytokines, etc.
- Signs and symptoms associated w/ mast cell activation are similar to those of allergic & anaphylactic reaction. However, **angioedema, hives and wheezing are uncommon in mastocytosis**
 - Cutaneous: flushing, pruritis, conjunctival hyperemia
 - GI: heartburn & nausea (histamine → hypersecretion of acid from parietal cells), diarrhea, abdominal cramps
 - Cardiovascular: tachycardia, hypotension, presyncope, and syncope
 - Neuro: fatigue
- Triggers for mast cell activation = temperature changes (e.g. hot showers), exercise, ingestion of alcohol or spicy foods, emotional stress, insect stings, certain medications (opioids, NSAIDs, muscle relaxants). *Can also be spontaneous*

MASTOCYTOSIS ([Blood 2017;129:1420](#))

- Heterogenous group of **rare** disorders characterized by excess mast cell proliferation and accumulation.
- Symptoms are primarily related to episodic release of mast cell mediators (lasts 30 min – few hours) and rarely by infiltration of mast cells into tissues

Mastocytosis	
Epidemiology	Primarily presents as systemic mastocytosis Rare presentations of cutaneous mastocytosis (primarily in infants and young children)
Organ systems	Multifocal infiltration of mast cells in various internal organs Bone marrow is involved in virtually <u>all patients</u> Skin more common w/ indolent mastocytosis.
Variants	1. Indolent SM (most common): no end-organ dysfunction 2. Smoldering SM 3. SM a/w non-mast cell hematologic neoplasm 4. Aggressive systemic mastocytosis: + end-organ dysfunction 5. Mast cell leukemia 6. Cutaneous only – Urticaria pigmentosa (UP), Mastocytoma, Diffuse cutaneous mastocytosis
Cutaneous manifestations	-Due to mediator release = flushing, pruritis -Due to mast cell infiltration = urticaria pigmentosa (most common; fixed, salmon/tan lesions; predominate on trunk / limbs), bullous eruptions, mastocytomas, telangiectasias
Systemic manifestations	-GI (50%): nausea / bloating, diarrhea, PUD. If mast cells accumulate in GI tract, can cause malabsorption & hepatic fibrosis -MSK: Fibromyalgia-like pain, osteoporosis (due to prolonged TNF/IL-6), sclerotic/lytic lesions -CV: Episodes of tachycardia, hypotension -Heme (50%): Anemia (most common), thrombocytopenia, eosinophilia, lymphadenopathy, splenomegaly. -Neuro: Anxiety, mood disorder, insomnia -Systemic: fatigue, cachexia
Characteristic clinical presentations	(1) Adult w/ recurrent symptoms of mast cell degranulation (flushing, hypotension, GI sx) (2) Adult w/ urticaria pigmentosa (3) Adult w/ hypotensive anaphylaxis, especially with stinging insects! (4) Adult w/ unexplained osteoporosis (5) Adult w/ suspected hematologic disease
Lab findings	Elevated baseline serum tryptase ($>20\text{ng/mL}$) in non-symptomatic state strongly suggestive of SM. Note: increases $>1.2\times$ baseline value + 2ng/mL are indicative of mast cell activation
Diagnosis	Bone marrow biopsy and aspirate If cutaneous lesions present, skin biopsy See WHO diagnostic criteria

MAST CELL ACTIVATION SYNDROME (MCAS)

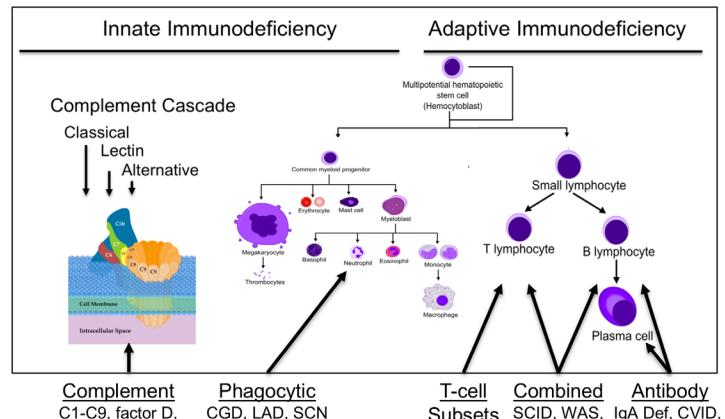
- = Idiopathic mast cell disorder in which mast cell activation occurs but there is no clear trigger and no clonal population
- Clinical syndrome characterized by **episodes of objective signs & symptoms of mast-cell release involving ≥ 2 organ systems** with **corresponding elevations in mast cell mediators (e.g. tryptase)** that **respond to medications** (e.g. anti-histamines, cromolyn, anti-leukotrienes)

Allergy & Immunology

Primary Immunodeficiency

PRIMARY IMMUNODEFICIENCY DISORDERS ([JACI 2015;136:1186, JCI 2015;35:696](#))

- Definition:** inherited deficits of immune system → increased incidence/severity/frequency of infections
- Prevalence:** 1/1200-2000 pts
- Warning signs in adults:** >4 new ear infxn/yr, ≥2 new sinus infxn/yr, recurrent viral infxn (e.g. HSV, VZV), ≥2 PNA/yr x multiple yrs, chronic diarrhea, recurrent deep abscesses, persistent fungal infection, recurrent need for IV abx, infxn w/ benign mycobacteria
- H&P:** dev hx, FH, age at onset, frequency & type of infections, syndromic features
- Need to r/o 2° causes (HIV, immunosuppressants, cancer, cirrhosis)
- General principles of management:** vaccination, abx ppx, immunoglobulin replacement, HSCT



	Disorder (% Total)	Presentation	Infectious Organisms	Advanced Testing (JACI 2010;125:S297)
INNATE	Complement (5%)	Any age - Sinusitis, PNA, meningitis - Lupus-like syndrome - Rheumatoid disorders	Bacteria: encapsulated esp. Neisseria (also strep, H flu)	Complement levels CH50+AH50 (alt pathway)
	Phagocytic (10%)	Infancy/childhood - Oral, lymphadenitis, skin and soft tissue, liver, lung, bone, anorectal - Unusually severe infections - Granulomas, poor wound healing	Bacteria: S aureus, PsA, Serratia, Klebsiella, non-TB mycobacteria Fungi: Candida, Aspergillus	ANC Oxidative burst via DHR/NBT test for CGD
ADAPTIVE	T cell subset defects (5%)	Infancy - Oral thrush	Bacteria: Mycobacteria Viruses: CMV, adenovirus Fungi: Candida, PJP	Flow cytometry Anergy/proliferation tests
	B cell / Antibody (65%)	>6 mos, can present in adulthood - Recurrent sinusitis, PNA, viral URI - Chronic GI malabsorption, diarrhea - Autoimmune disease (29% in CVID) (Blood 2012;119:1650) - Anaphylaxis to blood products (IgA deficiency)	Bacteria: H flu, Strep, Staph, Moraxella cat, PsA, mycoplasma pneumoniae Virus: Enterovirus (esp with IgA deficiency) Parasites: Giardia	SPEP (IgG, IgA, IgM), IgG subclasses, flow cytometry Vaccine response Polysaccharide PPSV23 titers: ≥70% of serotypes ≥1.3 = adequate. If not, give PPSV23 & repeat titers in 4-6 wks Protein: tetanus, diphtheria IgG Conjugated: Hib IgG
	Combined B & T cell (15%)	Infancy - FTT - Oral thrush, viral infections - Chronic diarrhea - Absent thymus - Active disease to live vaccines	Bacteria: Salmonella, Listeria, non-TB mycobacteria Viruses: CMV, EBV, VZV Fungi: Candida, Aspergillus, cryptococcus, histoplasmosis Parasites: PJP, toxoplasmosis, Cryptosporidium	As above for B & T cell deficiencies Avoid live vaccines

IMMUNOGLOBULIN REPLACEMENT ([JACI 2017;139:S1](#))

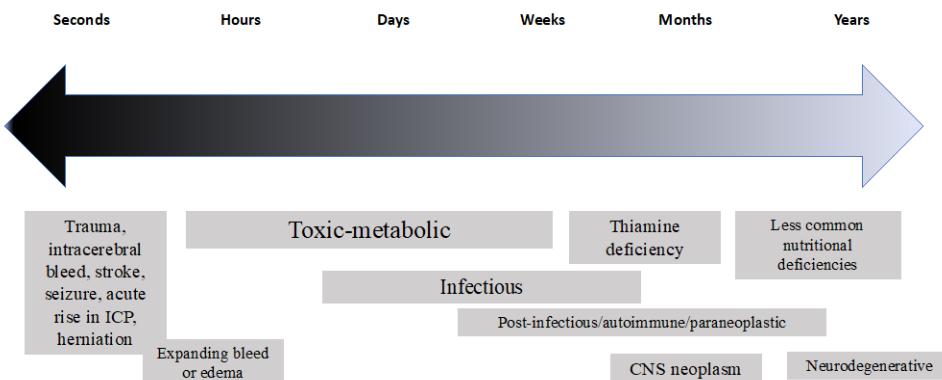
- Manufactured using donor pools of donated human plasma & contains IgG antibodies, administered as IVIG or SQ Ig
- In addition to **antibody replacement**, it also has **anti-inflammatory** and/or **immunomodulatory** effects at higher doses
- Starting doses:** 400-800 mg/kg q3-4 wks for trough level >500-600 mg/dL (higher in pregnancy & bronchiectasis)
- Once on IVIG, cannot check serologies for 3-4 months. Can check PCR instead (e.g. HBV PCR)
- IVIG in infection:** depends on host & infection. If CVID w/ infection, can check SPEP for IgG trough. Beneficial in CMV pneumonitis in solid organ tx recipients, rotaviral enterocolitis & bacterial infections in lymphoproliferative dz (e.g. CLL)

THERAPEUTIC USE OF VACCINES IN PATIENTS WITH PID ([JACI 2018;141:474](#))

- ALL** patients with PID can receive **INACTIVATED** vaccines according to routine schedule. Prioritize yearly influenza vaccine and HPV vaccine. For **LIVE ATTENUATED** vaccine safety/benefit, see [UpToDate Table](#)
- Pts on **IVIG** have adequate titers to measles, mumps, varicella, rubella, pneumococci, Hib, and meningococcus (variable). If exposed to an infection requiring “hyperimmune” Ig (rabies, HBV, tetanus), should still receive pathogen-specific Ig

CAUSES OF AMS

- Major categories include 1) Metabolic, 2) Infectious, 3) Drugs/Toxins/Medications, 4) Primary CNS, 5) Delirium
- Duration: flow diagram (below)
- AEIOU TIPS:** Alcohol (intox, HE, withdrawal, DTs, Wernicke's)/Arrhythmia, Electrolyte/Endocrine (gluc, thyroid, adrenal), Infection, Oxygen (hypoxia, hypercarbia)/Overdose (opiate), Uremia/Urine retention, Trauma/Tumor/TPP/Temp, Iatrogenic (meds - anticholinergics, BZDs, antidopaminergics, etc), Psych/Poison, Seizure (+post-ictal)/Stroke/Syncope



APPROACH TO ACUTE AMS

- ABCs & vitals:** if GCS <8, call **Rapid Response & RICU** for intubation. Include **breathing pattern, FSBG, EKG**
- Hx:** last known well, acuity, time course, previous AMS, recent clinical events, **MAR/toxins** (stopped, started, withdrawal, overdose)
 - MAR:** insulin, benzo, opioid, steroid, anticholinergic, antihistamine, antihypertensive, AED, anti/dopaminergic, digoxin, Li, ASA, OTCs, abx (incl. **cefepime**, other cephalosporins, PCNs, FQs) ([Neurology 2016;86:963](#))
 - Consider catatonia, NMS, serotonin syndrome and see [Catatonia, NMS, & Serotonin Syndrome](#)
- Neuro Exam:**
 - Arousable (**GCS**): commands, attention, cranial nerve or focal weakness, abnormal movements, meningismus, tongue biting
 - Not arousable: coma exam: pupils, doll's eyes, corneals, grimace, cough/gag, withdrawal to pain, posturing ([JNNP 2001;71:i13](#))
 - Other helpful findings: **trauma** (c-spine, hip frx, fat embolus), **asterixis/myoclonus** (toxic, metabolic), **volume status**, **cherry red discoloration** (CO), findings c/f **toxicdromes**, **incontinence** (seizure)
- Dx:**
 - FSBG, CBC/diff, BMP, LFTs, lactate, VBG, UA, CXR, bladder scan
 - Consider based on initial assessment: cultures, toxicology, drug levels, CK, CTH ± CTA H/N, EEG, etc

NEUROLOGIC EXAMINATION		
Arousal/Mentation	Brainstem Functions	Motor Sensory
<u>Arousal level:</u> "AVPU scale"	<u>Pupils</u> (CN 2/3): -Absent light reflex (upper brainstem injury, excessive sedation) -Bilateral fixed, dilated (upper brainstem injury/compression) -Unilateral fixed, dilated (herniation w/ CN III compression) -Pinpoint (opioids, pontine injury) <u>Blink to threat or visual field testing if able</u> (CN 2) <u>Corneal reflexes</u> (CN 5/7): absent (upper brainstem injury, deep sedation), normal, or forceful closure <u>Extraocular eye movements</u> (CN 3/4/6): -Conjugate lateral deviation (destructive or irritative lesions) -Vertical disconjugate ("skew deviation"; structural) -Roving eyes (esp if conjugate suggests metabolic cause) <u>Facial symmetry</u> (CN 7): test at rest and on activation (smile) <u>Oculocephalic reflexes</u> (CN 8): doll's eye movement <u>Cough/gag</u> (CN 9/10): if intubated, suction	<u>Muscle strength:</u> if mental status allows, perform confrontational testing <u>Sensory:</u> compare sensation to light touch
<u>Orientation</u>		
<u>Attention</u> (days of week backwards)		<u>Response to noxious stimuli in each extremity:</u> (localizing > withdrawal > extension)
<u>Language:</u> more detailed exam: comprehension, fluency, repetition, naming		

APPROACH TO SUBACUTE AMS:

consider Neurology consult prior to further extensive work-up

- Hx/Exam similar to above. **DDx** also includes: infection (HIV, Lyme, syphilis), autoimmune (anti-NMDA, sarcoid), metabolic (thyroid, B1, B3, B12, Wilson's), med, HTN encephalopathy, PRES (tacro/cyclosporine), adrenal insufficiency, porphyria (urine PBG)
- Dx:**
 - rEEG:** for non-convulsive status epilepticus (NCSE); **LTM:** for intermittent seizures
 - MRI w/ contrast:** for stroke, malignancy, infxn/inflammatory process, Wernicke's
 - LP (CTH to r/o herniation first):** see [Lumbar Puncture](#), discuss advanced testing with Neuro

TREATMENT OF AMS:

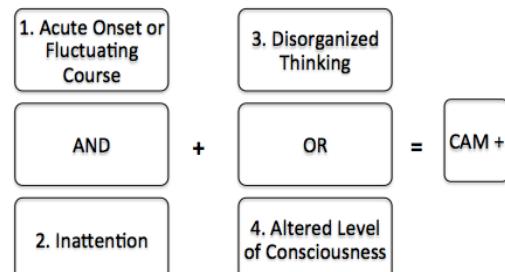
diagnose and treat underlying cause; see disease-specific pages

DELIRIUM: definition per DSM-5

- 1) Impairment in **attention**;
- 2) Δ from baseline, develops over a short period of time (usually hours to days), tends to fluctuate during the course of the day;
- 3) additional disturbance in **cognition** (memory, disorientation, language, visuospatial ability, or perception);
- 4) **not better explained by another preexisting neurocognitive disorder** and does not occur in the context of a severely reduced arousal/coma;
- 5) clinical and/or lab evidence that the disturbance is **caused by a medical condition or substance**

- **RFs:** age >65 (~50% have delirium inpt), Hx delirium/TIA/CVA/dementia, long hospitalization, critical illness, recent surgery (esp orthopedic), EtOH, infxn, visual/hearing impairment, depression, HIV, h/o TBI
- **Exam:** test inattention: reciting **months of the year backwards** (Sn 84%); **days of the week backwards** (Sp 82%) ([JHM 2018;13:551](#))
- **Complications:** a/w ↑ mortality ([JAMA 2010;304:433](#)), ↑ institutionalization ([Lancet 2014;383:911](#)), ↓ cognition ([NEJM 2012;367:30](#))

CAM (Confusion Assessment Method)



Sn 94-100%, Sp 90-95%, high inter-rater reliability ([Annals 1990;113:941](#))

AVOID DELIRIUM BY PREVENTING IT IN VULNERABLE PATIENTS

- **Minimize deliriogenic meds:** anticholinergics, antihistamines, benzodiazepines, opioids (**optimize pain w/ non-opioids**)
- **Precautions:** frequent reorientation, mobilize with PT/OT, OOB to chair, glasses/hearing aids, minimize lines/telemetry/catheters, early volume repletion if c/f dehydration. **Avoid** room changes or physical restraints
- **Anticipate circadian dysfunction:** standing melatonin 3mg q6PM, lights on during day and off at night, schedule meds for earlier in evening, avoid late diuresis, reduce noise

DELIRIUM MANAGEMENT

- Both HYPERactive and HYPOactive delirium warrant treatment
- Behavioral management: implement delirium precautions, modified deliriogenic medications, treat circadian dysfunction
- Identify & treat **UNDERLYING CAUSE** w/ special attention to life-threatening conditions (see [Altered Mental Status](#))
- **Monitor QTc daily** (goal <550ms); daily repletion of K>4 & Mg>2 (in anticipation of pharmacotherapies)
- Reserve pharmacologic agents for **dangerous behavior ONLY** i.e. if **danger to self or others**; no evidence for altering duration of delirium ([NEJM 2018;379:2506](#)), severity, hospital or ICU LOS ([JAGS 2016;64:705](#)) with increased potential for adverse effects (e.g. QTc prolongation and drug interactions)

Medical Management

1:1 sitter (re-orient) >> meds >> restraints (deliriogenic)

- **For HYPERactive delirium/AGITATION → start PRN, escalate to scheduled** ([Nat Rev Neur. 2009;5:210](#))
 - Haloperidol 2-5mg IV q3h PRN vs. 0.5-1mg PO q4h PRN vs. IM q1h PRN (NB: can → EPS, acute dystonias in Parkinsonism)
 - Quetiapine 12.5-50mg PO q6-12h PRN
 - Olanzapine 2.5-10mg SL/PO/IM qd-q4h PRN
- **If continued severe agitation → consider Psych/Geri consult:**
 - Haloperidol PRN: double PRN dose q20 min till effective, ~5-20mg IV, consider standing or gtt (ICU)
 - Quetiapine PRN: standing 25-50 mg TID, extra dose HS
 - Olanzapine PRN: standing 2.5-10 mg BID, extra dose HS
- QTc ↑ severity: haloperidol > quetiapine > olanzapine; Δ tx if QTc ↑ by 25-50%, QTc>500, ⊕U-wave/T-wave flattening
- **Discontinue when able, avoid benzos. Prolonged antipsychotic use in elderly can increase mortality**
- For patients with prolonged QTc or refractory symptoms to medications, consider IV valproic acid (discuss with psychiatry)

WHEN TO CONSIDER PSYCHIATRY/GERI CONSULTATION

- **Escalating/persistent delirium**, Hx agitated delirium, underlying neurodegen. disorder (esp PD), hx TBI
- **Co-morbid EtOH or other substance use disorders**
- Significant co-morbidities (CV disease/critical illness)
- At risk for disinhibition/impulsivity

WHEN TO CONSIDER NEUROLOGY CONSULTATION

- New focal finding suggesting stroke: Stroke p20202
- Other concerning findings (convulsions, meningismus, e/o elevated ICP, abnl spot EEG/LP): General p20702
- **Know the following prior to calling:** last seen well, baseline deficits, anticoagulation

Neurology

Dementia

INITIAL EVALUATION: should almost always be in the outpatient setting, can assess over time without acute illness or delirium

- Obtain **collateral**, determine symptom onset, ADLs/IADLs, assess safety, screen for depression
- Review medications for those with cognitive SEs (e.g. analgesics, anticholinergics, psychotropic medications, sedative-hypnotics)
- Assess cognitive impairment (**MOCA >> MMSE**), track score at subsequent visits
- Labs: CBC, TSH, BMP, B12; consider: tox, syphilis, Lyme, HIV, UA, metals, ESR, LFT, folate, B1, B6 ([AFP 2005;71:1745](#))
- Imaging: NCHCT or **MRI brain (preferred)** to r/o structural lesion (tumor), assess **atrophy pattern** and vascular dementia
- Inpt eval considered for 1) any rapidly progressing dementia syndrome (c/s Neuro to discuss LP → RT-QuIC 14-3-3 in CSF (CJD), ACE [sarcoid], autoimmune encephalitis), or 2) new dementia diagnosis in pts <55yo or w/ new focal deficit (?stroke)
- **Outpatient Neurology referral to Memory/Cognitive clinic** (and formal neuropsychological testing)

DEMENTIA SYNDROMES ([Prog Neurol Psych 2012;16:11](#); [BMJ Neurol Neurosurg Psych 2005;76:v15](#); [Ann Neurol 2008;64:97](#))

Clinical phenotypes often overlap and may require years to differentiate

Syndrome	Presentation	Exam	Imaging	Treatment
Gradually Progressive				
Alzheimer Dementia	<ul style="list-style-type: none"> • Amnesia earliest sx; also language and visuospatial deficits • Apraxia in later stages 	<ul style="list-style-type: none"> • NI neuro exam (excluding MS) • Neuropsych: amnesia w/ short memory span, alexia, agraphia 	Hippocampal (\pm global) volume loss; ?microhemorrhages (CAA)	<ul style="list-style-type: none"> • AChE-inhibitors (mild-severe dz) • NMDA-inhibitors (mod-severe dz)
Lewy Body Dementia	<ul style="list-style-type: none"> • Fluctuations in attention/alertness • Visual hallucinations • REM behavior d/o • Falls/syncope • Neuroleptic intolerance • Memory problems late 	<ul style="list-style-type: none"> • Parkinsonism: resting tremor (can be absent), cogwheel rigidity, bradykinesia, stooped/shuffling gait – named Parkinson's dementia if movement sx present for >1y before dementia • Neuropsych: fluctuations w/ intrusions and confabulation, visuospatial impairment 	Global volume loss	<ul style="list-style-type: none"> • AChE-inhibitors (specifically rivastigmine) for memory sx • Carbidopa/levodopa trial for motor deficits • Sx management of autonomic dysfxn
Frontotemporal Dementia	<p>Behavioral variant most common:</p> <ul style="list-style-type: none"> • Changes in personality (<u>disinhibition, apathy</u>) • Stereotyped behaviors • Lack of insight <p>Primary Progressive Aphasia variant</p>	<ul style="list-style-type: none"> • May have frontal release signs (non-specific) • 15-20% get motor neuron dz • Neuropsych testing: poor impulse control, difficulty in organization 	Atrophy predominantly in frontal and temporal lobes	<ul style="list-style-type: none"> • Management of behavioral sx (consult psych) • AChE-inhibitors not helpful • Avoid NMDA-inhibitors
Stepwise Progressive				
Vascular Dementia	<ul style="list-style-type: none"> • Abrupt focal sx, stepwise progression • Depression common • Hx: CVA, HTN, HLD, AF 	<ul style="list-style-type: none"> • Focal deficits (depends on stroke location), can include: weakness, dysarthria, ataxia, gait changes • Often look older than age 	Cortical or subcortical punctate lesions, white matter disease, and volume-loss	<ul style="list-style-type: none"> • Secondary stroke prevention and risk factor modification • AChE-inhibitor for memory deficits
Rapidly Progressive				
Prion Diseases (Sporadic, Variant Creutzfeldt-Jacob Disease)	<ul style="list-style-type: none"> • Rapidly progressive sx in memory, concentration, judgment • Mean onset age ~60 for sporadic, 28 for variant • Younger pts: more sig psychiatric sx 	<ul style="list-style-type: none"> • Myoclonus, exaggerated startle response • EPS: bradykinesia, nystagmus, ataxia • UMN signs (hyperreflexia, \oplusBabinski, spasticity) • LP: RT-QuIC>>14-3-3 	MRI: cortical ribboning on DWI, subcortical hyperintensity on FLAIR EEG: 1-Hz periodic epileptiform discharges	<ul style="list-style-type: none"> • No tx • Death w/in 1y (median disease duration 6mo)
Limbic Encephalitis (Autoimmune, Paraneoplastic)	<ul style="list-style-type: none"> • Sx evolve days-weeks (more indolent possible) • Short-term memory sx • Psych sx: agitation, delusions, hallucinations • Focal seizures 	<ul style="list-style-type: none"> • Prominent psych features • Dyskinesias, rigidity • Autonomic instability • LP: lymphocytic pleocytosis, oligoclonal bands, autoantibodies (CSF + serum) 	MRI: FLAIR hyperintensity or contrast enhancement (esp in temporal lobe) EEG: extreme delta brush very specific	<ul style="list-style-type: none"> • Immunotherapy: steroids, IVIG, PLEX, rituximab, cyclophosphamide • Tumor resection

TREATMENT: can treat symptoms, but treatment does not slow the progression of disease

- If patient has **Parkinson's dx**, **do NOT stop or change home medications** (NGT if needed). Stopping sinemet **can cause NMS**
- AChE inhibitors: **donepezil** (first line), rivastigmine (patch), galantamine. Small effect on cognition, ADLs. Major side effects: GI (n/v/d); less common bradycardia and heart block (increased vagal tone)
- NMDA inhibitors: **memantine**. Can precipitate agitation and exacerbate neuropsychiatric sx (caution in pts with significant behavioral sx)

Neurology

Headache & Vertigo

HEADACHES

Approach: distinguish **primary HA** (tension, migraine, etc.) from **secondary HA** (tumor, ↑ICP, vessel lesion, etc.)

Tension HA: ~40% population, ♀>♂. **Band-like, radiate forehead to occiput, mild-mod severity, 30min to 7d.** ([JAMA 2002;266:797](#))

- **Abortives:** NSAIDs, Tylenol. Can add antiemetic (metoclopramide, promethazine). Use abortives no more than 2 days/week
- **Preventatives:** TCA, SSRI, treat OSA, smoking cessation

Migraine HA: sx >3/5 "POUND" criteria (Pounding, Photo/phonophobia, Onset 4-72h, Unilat, N/V, Disabling) ([JAMA 2006;296:1274](#))

- **Migraine w/ aura:** 1 reversible sx: **visual** (scintillating scotoma, visual field deficit), **sensory** (tingling, numbness), **speech/lang**, **motor** (weakness, hemiplegic), **basilar** (dysarthria, vertigo, ataxia, diplopia), **vestibular** (vertigo), **retinal** (monocular field deficit). Similar sx spread over min w/ each HA (stroke mimic). Aura w/o migraine HA possible (acephalic migraine)
- **Menstrual migraine:** before/during menstruation → NSAIDs or sumatriptan ([Neurology 2008;70:1555](#)). Consider preventive tx perimenstrually w/ slow triptan (frovatriptan) 2.5mg QD/BID (begin 2d premenstrually, for total 6d/month)
- **Abortives:** tx early; **stepwise (q60min) abortive management** for migraine/tension HA **w/o focal deficits** ([ellucid](#))
 - **Step 1:** a) 1L IVF (adjust PRN); b) 2g Mg; c) APAP 1g PO OR NSAIDs (naproxen, ibuprofen, indomethacin PR; ketorolac IV/IM) ([Headache 2012;52:467](#)); d) sumatriptan 6mg SC
 - **Step 2:** IV antiemetics/antihistamine: chlorpromazine 25mg **OR** prochlorperazine 10mg **OR** metoclopramide 10mg **AND** diphenhydramine 25mg
 - **Step 3:** a) AED: valproate 500mg IV (negative pregnancy test first)
 - b) other neuroleptics: droperidol 2.5-5mg IV/IM; haloperidol 5mg IM can be administered (only if other meds fail)
- **Preventatives:** if >3 d/mo, long aura, or disability ([Neurology 2012;78:1337](#))
 - **BB/CCB:** propranolol 20mg BID, up to 160mg/d; metoprolol 25mg BID, up to 200mg/d; verapamil 80mg TID, ↑ gradually
 - **Antidepressants:** amitriptyline/nortriptyline 10mg qhs, ↑ to 150mg; venlafaxine 37.5mg qd, ↑ to 75-150mg
 - **Anticonvulsants:** topiramate 25mg qd, ↑ gradually to 100mg BID; VPA 500-1500mg qd (avoid both in young ♀)
 - **Supplements:** magnesium 400mg qd, riboflavin 400mg qd, feverfew
 - **Botox:** referral to HA clinic

Red flags for secondary HA evaluation	
Symptoms	Imaging
New >35yo, abn neuro exam, acute, severe, positional, ↑ w/ exertion, immunosuppressed, wakes at night	MRI brain w/ contrast
Vestibular, brainstem, retinal, motor	MRA/CTA H/N

Triptans (max 4x/d, 2x/w)
Nasal: Sumatriptan 5-20mg q2h (max 40mg/d), Zolmitriptan 5mg q2h (max 10mg/d)
SC: Sumatriptan 4-6mg q1h (max 12mg/d; 70-80% pts w/ sx reduction; 35% resolution)
PO: Sumatriptan 25-100mg q2h (max 200mg/d), Zolmitriptan 1.25-2.5mg q2h (max 10mg/d)
C/I: ischemic CAD/PAD (vasoconstriction), liver dz, basilar migraine, MAOIs w/in 2w
*Caution w/ SSRIs 2/2 risk of serotonin syndrome

VERTIGO

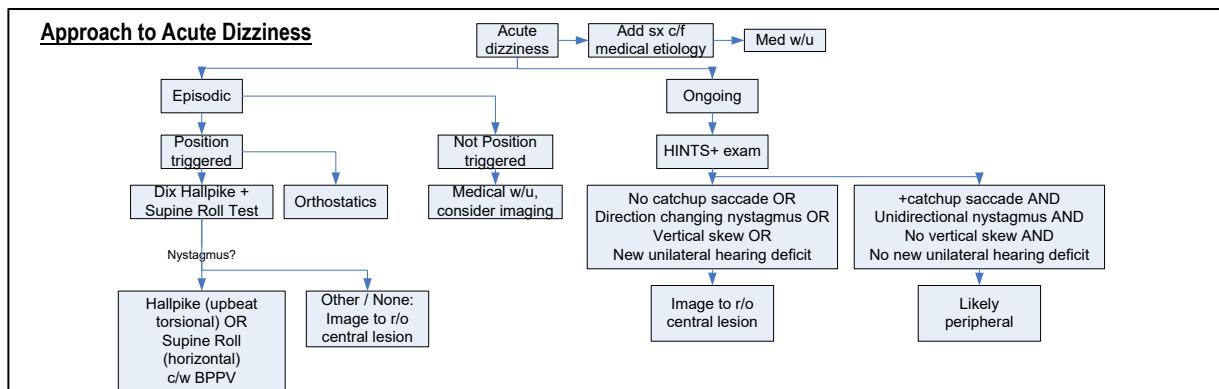
Definition: illusion of motion of self or world 2/2 vestib dysfxn; a/w n/v, postural/gait instability

Approach: distinguish **central vs peripheral** ([JAMA 2017;95:154](#); [ellucid](#))

- **Hx/Exam:** duration of sx, episodic/persistent, triggers (position Δ), prior sx, assoc sx (5D's for brainstem: dysarthria, diplopia, dysphagia, dysphonia, dysmetria). Orthostatics. Dix-Hallpike. [HINTS](#)
- **HINTS exam:** everything *must be c/w peripheral to be reassuring*. In **acute** vertigo, Sn 97%, Sp 85% for stroke (>[MRI](#))
 - **Head Impulse** (pt looks at your nose, passively rotate head. No saccade = ambiguous. Catchup saccade = peripheral)
 - **Nystagmus** (unidirectional e.g. always left-beating = peripheral; direction changing = central, any vertical = central)
 - **Test of Skew** (cover one eye, then other, any vertical skew/correction = central) ([Acad Em Med 2013;20:986](#))

	Symptoms	Ddx	Imaging
Peripheral	Severe nausea, mild imbalance, hearing loss/tinnitus	Benign positional paroxysmal vertigo (BPPV), infxn (labyrinthitis, vestibular neuritis, herpes zoster oticus), Meniere's, vestibular migraine, otosclerosis, trauma (perilymphatic fistula)	If exam reassuring, none
Central	Mild nausea, severe imbalance, rare hearing sx	Vertebrobasilar ischemia/TIA, ICH, toxic, cerebellopontine mass (vestib schwannoma, ependymoma, brainstem glioma, medulloblastoma), NF, MS, vestibular migraine	MRI brain w/o contrast (coronal DWI brainstem cuts), MRA head & neck

- **Tx (peripheral):** metoclopramide, prochlorperazine, meclizine (≤2w, vestib suppression), lorazepam, or diazepam, **AND vestibular PT**



Consider stroke for any sudden-onset focal neurologic symptoms		IV tPA		
ACUTE STROKE ACTIVATION				
1) If high suspicion and onset of sx <u>within past 24h</u> , activate the code pager by calling the operator at 6-3333 . This will notify the stroke resident and fellow. Stroke resident will activate stroke group pager if needed (pharmacy, radiology, NSGY, IR, ICU RN, resource RN)		Inclusion: 1. Measurable deficit (usually NIHSS ≥3 , but can give if lower, depending on sx) 2. Age ≥18 3. Time since last seen well <4.5h		
2) BE AT BEDSIDE. Consider this a code equivalent. Ensure 18g PIV is in place and bed is ready for travel with travel monitor in place	Exclusion: History: stroke/head trauma in last 3mo; recent head/spine surg; prior ICH; intracranial malignancy, AVM, aneurysm; incompressible arterial puncture last 7 days			
3) ABC/V/S , check EKG, telemetry, glucose, keep NPO & HOB >30° . Do not treat HTN unless BP >220/120, ACS, or ICH (see below)	Clinical: BP ≥185/≥110 (treat!) ; BG <50; active internal bleeding; bleeding diathesis			
4) Be ready to provide the following information:	Heme: Plt <100K; current AC (warfarin w/ INR >1.7; therapeutic heparin use w/in 48h w/ ↑PTT; DOAC w/in 48h)			
a) <u>Last seen well (LSW) time</u> (last time patient confirmed to be normal) – this is <u>NOT</u> the time that sx were noticed by you or patient	Head CT: hemorrhage; multilobar infarct >1/3 involvement of cerebral hemisphere			
b) AC or antiplatelets, CrCl, allergies, code status, baseline function	Intra-arterial therapy			
c) Contraindications to tPA - <u>even if present, call an acute stroke (patient may be candidate for thrombectomy)</u>	Inclusion: 1. Clinical: NIHSS ≥6, LSW ≤24h, age 18-85, baseline mRS ≤1, life expectancy >12mo 2. Radiological: ICA or MCA M1/2 occlusion, basilar or dominant vert occlusion, small infarct core volume			
d) Physical exam findings. Most predictive findings: facial paresis, arm drift/weakness, and abnormal speech (JAMA 2005;293:239)	Exclusion: Clinical: BP ≥185/≥110 (treat!) , BG<50 or >400			
e) Premorbid disability (e.g. walks w/ assistance, bedridden)	Heme: Plt <40k, INR >3			
5) Order STAT CTA Head/Neck (only need to order CTA; it includes NCHCT). If unable to receive contrast or LSW ≥6h, stroke team will consider STAT MRI ± MRA				
6) Obtain Labs: BMP, LFTs, CBC, PT/PTT, trop, UA/UCx, tox screen, & AED levels (if appropriate)				
7) Neurology will perform NIHSS at bedside				
ACUTE STROKE INITIAL MANAGEMENT (in-house stroke pathway)				
(Stroke team will provide guidance, but IV tPA may be given by any MD)				

1. ISCHEMIC STROKE

- **IV (intravenous) thrombolysis (tPA):**
 - **LSW 0-3h:** goal to start IV tPA w/in 60min of ED arrival (AHA/ASA: [Stroke 2018;49:e46](#))
 - **LSW 3-4.5h:** IV tPA recommended but w/ relative exclusion criteria including age >80, AC (regardless of INR), NIHSS score >25, ischemia >33% of the MCA territory, h/o both stroke & DM2 ([ECASS III NEJM 2008;359:1317](#)) (note: guidelines actively changing)
 - **Dosing:** 0.9mg/kg; 10% bolus over 1min, remainder infused over 1h
- **Intra-arterial therapy (thrombectomy, thrombolysis):**
 - Patients with disabling deficit & large vessel occlusion with **LSW <6h** ([MR CLEAN NEJM 2015;372:11](#))
 - May extend time to **LSW 6-24h** based on imaging criteria ([DAWN NEJM 2018;378:11](#))
- **BP control:** low SBP (<150) a/w poor outcome ([Arch Intern Med 2003;163:211](#))
 - If tPA candidate: goal BP **≤185/110** prior to tPA (**treat STAT if higher!**); goal BP **≤180/105** after tPA for 24h
 - If no tPA: goal BP **≤220/120** (allow auto-regulation) for 1d; lower SBP <20 per day subsequently
 - If anticoagulated: goal SBP **≤180**
 - If active cardiovascular disease (ACS) & requires tighter BP control, discuss w/ neuro
 - Monitor neuro exam - sx worse at low BP suggests critical stenosis → lay bed flat, give IVF bolus, **STAT page neuro**
- **HEMORRHAGIC STROKE** (see [CNS Emergencies](#))

INPATIENT POST-STROKE CARE

- Frequent **neuro checks** q1-2h x 24h if unstable/ICU; q4h if stable/floor pt, **STAT** head CT if change in exam
- Consult **PT, OT, SLP (NPO until bedside swallow eval)**. Keep **euthermic** (antipyretics), **euglycemic** (FSG<180), **Mg>2**
- If received tPA: **NCHCT 24h post-tPA** → if no e/o hemorrhagic transformation, start antiplatelet + DVT ppx
- If did not receive tPA: **ASA 325mg x1**, followed by long-term antiplatelet or AC (may delay AC for large ischemic strokes). Start DVT ppx if ischemic stroke (unless large hemorrhagic conversion)
- **Antiplatelet long-term 2° prevention**
 - **ASA** 81mg qd (50-325mg/d effective; ≤200mg/d lower risk of major bleed) ([Am J Cardiol 2005;95:1218](#))
 - **Clopidogrel** 75mg qd (may be superior to ASA for atherosclerotic vascular dz) ([CAPRIE Lancet 1996;348:1329](#))
 - **DAPT (ASA + clopidogrel)**
 - **TIA or minor stroke:** consider in patients w/ NIHSS<4 or TIA. ASA+clopidogrel for **3w** followed by clopidogrel (or ASA) alone ([CHANCE NEJM 2013;369:11](#)). Consider clopidogrel load (300-600mg) w/in 24h of symptoms
 - **Symptomatic intracranial stenosis:** consider ASA/clopidogrel for **3mo** ([SAMMPRIS NEJM 2011;365:993](#))
 - **Recurrent stroke on ASA or clopidogrel alone + significant athero:** some use DAPT long-term; no clear evidence & higher bleed risk ([CHARISMA NEJM 2006;354:1706](#); [MATCH Lancet 2004;364:331](#)) – discuss w/ Neurology
- **Anticoagulation long-term 2° prevention** (embolic infarcts from AFib, paradoxical embolus, LV thrombus or hypercoagulable state)
 - **Warfarin or DOAC** for pts w/ AF (hold off x 2-4w if hemorrhagic conversion or large hemispheric stroke)
 - **No need for both antiplatelet & anticoagulation**
- Start **atorvastatin 80mg** w/ LDL goal <70 ([NEJM 2020;382:9](#))

- Work up/secondary prevention: (see below)
 - Labs:** lipids, A1c, TSH, ESR/CRP; if <60yo, tox screen (cocaine), hypercoagulability w/u (if recommended by Neuro)
 - Imaging:** head and neck CTA or MRA (can do TOF if low GFR); carotid U/S as alternative
 - Cardiac workup:** EKG, TTE (with bubble if <60), inpatient tele then 30d MCOT vs LINQ if tele is negative for AF

CARDIOEMBOLIC STROKE	
SUSPECT WHEN: <ul style="list-style-type: none"> ACA/MCA/PCA occlusion w/o sig vascular dz Infarcts in multiple territories or cerebellar stroke Known risk factors (LA/LV thrombus, AF, LVEF<25%, aortic disease, intracardiac shunt) Hypercoagulability/hyperviscosity (solid organ or heme malignancy, HbSS, cryo, clotting d/o) 	DX WORKUP: <ul style="list-style-type: none"> TTE (w/ bubble if <60yo) - if PFO, r/o venous thrombus (LENIs/ MRV pelvis), can consider closure (RESPECT NEJM 2017;377:1022) Inpatient telemetry followed by 30d MCOT vs. LINQ at discharge (unless known AF) ACUTE MANAGEMENT CONCERNS: <ul style="list-style-type: none"> Avoid immediate AC unless known intracardiac thrombus or mechanical valve. Transition to long-term AC in 2-4w
SYMPTOMATIC CAROTID STENOSIS	
SUSPECT WHEN: <ul style="list-style-type: none"> Carotid stenosis present on ipsilateral side H/o amaurosis fugax DIAGNOSTIC WORKUP: <ul style="list-style-type: none"> CTA vs. MRA head & neck usually sufficient Alternatives: carotid US - typically needed prior to carotid endarterectomy (CEA) 	ACUTE MANAGEMENT CONCERNS: <ul style="list-style-type: none"> If >50% carotid stenosis causing stroke/TIA, consider carotid revascularization (stent/angioplasty/endarterectomy) – ideally w/in 2w of sx (NASCET II NEJM 1998;339:1415) Consider temporary anticoagulation (d/w neurology) Consider induced HTN if symptoms fluctuate with BP
INFECTIVE ENDOCARDITIS	
SUSPECT WHEN: <ul style="list-style-type: none"> Unexplained fever w/ stroke or pt with valvular dz DIAGNOSTIC WORKUP: <ul style="list-style-type: none"> Blood cultures, TTE followed by TEE if neg CTA head to identify mycotic aneurysms (↑risk bleeding) If CTA negative, may need conventional angio (CTA not as sensitive for mycotic aneurysms) 	ACUTE MANAGEMENT CONCERNS: <ul style="list-style-type: none"> Immediate antibiotics; caution with tPA Early cardiac surgery if small non-hemorrhagic stroke; delayed cardiac surgery (2-4w) if large or hemorrhagic stroke Avoid anticoagulation or antiplatelet w/o a separate indication
CAROTID AND VERTEBRAL DISSECTIONS	
SUSPECT WHEN: <ul style="list-style-type: none"> <60yo or posterior circulation stroke in pt w/o RFs Neck pain, HA, or Horner's syndrome Trauma (vertebral fx), chiropractor, coughing spells DIAGNOSTIC WORKUP: <ul style="list-style-type: none"> CTA vs. MRA with T1 fat saturation Consider comorbid conditions (Marfan's, FMD) 	ACUTE MANAGEMENT CONCERNS: <ul style="list-style-type: none"> Goal of tx is to prevent stroke: highest risk in first few days Anticoagulation vs antiplatelet. Prefer antiplatelet if: sx onset >3d ago, dissection extends intradurally (no AC due to risk of SAH), large infarct (risk of hemorrhage) (CADISS Lancet Neurol 2015;14:361) High rate of recanalization → tx 3mo then re-image vessel
CEREBRAL VENOUS SINUS THROMBOSIS	
SUSPECT WHEN: <ul style="list-style-type: none"> Positional HA, vomiting, papilledema, vision Δ P/w seizure (common, may be difficult to control) DIAGNOSTIC WORKUP: <ul style="list-style-type: none"> NCHCT: hyperdensity in torcula (dense delta sign) CTV vs. MRV to assess intracranial venous system Consider hypercoagulable workup 	ACUTE MANAGEMENT CONCERNS: <ul style="list-style-type: none"> Immediate anticoagulation even in presence of hemorrhage AEDs if seizures (not indicated for ppx) IV fluids, avoid dehydration, modify risk factors (smoking, OCPs)

TRANSIENT ISCHEMIC ATTACK (TIA)

- Definition:** transient neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia w/o acute infarction
- Causes:** atherothrombotic stenosis (ICA, vertebral, basilar, small vessel), embolic (arterial, aortic, cardiac, paradoxical), dissection (ICA, vertebral) – identification will guide tx (antiplatelet therapy vs. search for underlying arrhythmia ± anticoagulation)
- Imaging:** MRI (w/ DWI/ADC) w/in 24h of sx onset and vessel imaging of head and neck for large vessel occlusive disease (e.g. [MRA head and neck](#) [TOF if low GFR] vs. [CTA head and neck](#) vs. carotid ultrasound)
- Cardiac w/u:** TTE to excl thrombus & PFO (age <60) & [MCOT](#) (monitor) vs. [LINQ](#) monitoring to exclude AF if suspected embolic TIA
- ABCD²** score (Age, BP, Clinical features, Sx Duration, Diabetes): used to identify pts w/ high risk of ischemic stroke w/in 1w of TIA
- Management:** immediate intervention reduces the risk of recurrent stroke (1.5-3.5% risk w/in 48h), see 2° Prevention above

INTRACRANIAL HEMORRHAGE (ICH)

- **Causes:** trauma (all), ruptured aneurysm/AVM (SAH, IPH), IPH also caused by HTN, cerebral amyloid, tumor (most common w/ met breast CA, lung CA, melanoma, RCC, choroid, thyroid CAs), cortical vein thrombosis, venous sinus thrombosis
- **Presentation:** acute focal neuro deficit, ± progressive ↓ consciousness, n/v. **SAH:** thunderclap HA, N/V, meningismus; **EDH/SDH:** s/p trauma, lucid interval with EDH; **IPH:** focal neuro symptoms (may mimic ischemic stroke clinically); often with HA
- **Tests:** STAT imaging (NCHCT for all; +CTA head if SAH/IPH), coags/PLTs; repeat CT head after 6h to assess progression
- **STAT management:**
 - STAT Neurosurg (p21111) if SAH/SDH/EDH; otherwise, Neuro (inpatient: p20202; in ED: p20000)
 - Elevate HOB to 30-45° to reduce ICP and prevent aspiration
 - **BP control:** strict SBP <140 (studied in SAH or ICH due to ruptured aneurysm/AVM), use **IV labetalol** or **nicardipine drip** (avoid hydralazine & nitropaste if possible), place arterial line ([INTERACT Lancet Neurol 2008;7:391](#); [ATACH Crit Care Med 2010;38:637](#))
 - **Correct coags:** warfarin/**INR**>1.5 (vitamin K 10mg IV x1) AND (3-5U FFP or Kcentra); **↓Plt** (transfuse, goal >50); **Uremia/antiplt use** (consider DDAVP 0.3mcg/kg IV); **heparin/LMWH** (protamine); s/p tPA (check fibrinogen, give cryo, ± amicar); **rivaroxaban/apixaban** (andexanet alfa)
 - **Venous sinus thrombosis (VST):** AC w/ LMWH/UFH despite ICH ([Lancet 1991;338:597](#)). Manage ↑ICP and seizures as below
 - Prognosis depends on age, GCS, pre-ICH cognitive impairment, and ICH volume/location ([FUNC Score](#)) ([Stroke 2008;39:2304](#))
 - Typically, acceptable to restart DVT ppx in smaller hemorrhages **after 48h** from last stable NCHCT, confirm w/ Neurology
 - Start levetiracetam 500mg BID x7d for traumatic SDH or SAH (indicated for seizure ppx) ([Neurocrit Care 2010;12:165](#))

ELEVATED INTRACRANIAL PRESSURE (ICP)/HERNIATION

- **Etiologies:** mass (tumor, abscess, hemorrhage), cerebral edema (infarction, inflammation, hyperammonemia, DKA), hydrocephalus (tumor, intraventricular hemorrhage, leptomeningeal disease, meningitis), PRES. High ICP may cause compression/ischemia. Severe local swelling or CSF drainage with large space-occupying lesions causes herniation (displacement and compression of brain).
- **Signs of herniation:** fixed/dilated/asymmetric pupil accompanied by nausea, somnolence/confusion, or limited upgaze; flexor/extensor posturing; ipsilateral hemiparesis (uncal herniation); **Cushing's triad (bradycardia, ↑SBP, irreg. breathing)**
- **Tests:** STAT head CT, blood gas, BMP, CBC
- **Management:**
 - STAT Neurosurgery for ICP monitor/EVD placement/decompressive hemicraniectomy, otherwise page Neurology, patient may require Neuro-ICU level of care
 - Secure ABCs, elevate HOB to 30-45°, keep head midline (to secure venous drainage), treat pain/agitation
 - Hyperventilate to PaCO₂ ~ 30-35 mmHg (if suspect herniation, transiently reduces ICP), only for short-term management
 - Hyperosmolar therapy. **Check BMP, Sosm q6h.** Can use mannitol, or 23% saline, or both 3h apart (discuss with Neuro)
 - IV mannitol therapy 1g/kg q6h (max 100g, use with caution in pts on HD)
 - Hold mannitol if osm gap >15, Na >160, or serum osm >340
 - 23% saline 30cc q6h (requires central line). Better option for patients with AKI/CKD. Use with caution in HF)
 - Hold 23% saline if Na >160
 - **If related to edema from malignancy or bacterial infection,** give 10mg IV dexamethasone x1, then 4-8mg BID
 - **Complications during LP:** if sx of herniation/opening pressures >40cm H₂O with space occupying lesion, consider STAT head CT. Immediately replace stylet into needle, only drain CSF in the manometer, STAT Neurosurgery consult.
 - **Do not** use hypotonic solutions for resuscitation (i.e. LR) as this can worsen edema. Use 0.9% NaCl (NS) instead

HYPERTENSIVE ENCEPHALOPATHY: PRES (posterior reversible encephalopathy syndrome)

- **Typically associated with:** severe HTN, but also relative HTN in setting of preeclampsia/eclampsia, cytotoxic/immunosuppressive drugs (cyclosporine, tacrolimus, cisplatin, bevacizumab), acute/chronic renal failure, uremia, sepsis, vasculitides, TTP → due to impaired cerebral autoregulation and endothelial dysfunction, hypoMg ([NEJM 1996;334:494](#))
- **Symptoms:** HA, confusion, decreased consciousness, visual disturbances, seizures, can result in ICH and ↑ICP
- **Tests:** MRI brain w/ contrast: FLAIR w/ vasogenic edema w/in white matter in the posterior cerebral hemispheres; DWI/ADC nl (but can have strokes also); add'l regions can be affected incl brainstem, cerebellum, basal ganglia, frontal lobes
- **Management:** ICU if severe, strict BP control SBP <140 (reduce 25% daily, if severe use nicardipine or labetalol drip), treat seizures, Mg²⁺ (esp in eclampsia), remove inciting factor
- **Prognosis:** often fully reversible; complications include progressive cerebral edema, ICH, stroke, death

CORD COMPRESSION: high level of suspicion in cancer patients with back pain, urinary sx or LE weakness

- **Etiologies:** subacute (tumor/mets, abscesses) vs acute (disc herniation, trauma, hemorrhage)
- **Symptoms:** back pain, motor weakness, hyperreflexia below lesion if chronic (can be hyporeflexic in acute injury or w/ cauda equina), ⊕Babinski, loss of sensation (assess level), bowel/bladder incontinence OR retention, loss of rectal tone, saddle anesthesia
- **Tests:** **STAT whole spine MRI w/ contrast** (cord compression protocol), call ED (x63050) or inpt MRI (x64226)
- **STAT page** NSGY/Ortho spine ± Rad Onc for possible XRT if tumor related (see [Oncologic Emergencies](#))
- **Dexamethasone** (10mg IV x1 then 8mg IV BID), esp in malignancy

DEFINITIONS ([Epilepsia 2014;55:475](#); [Epilepsia 2015;56:1515](#); [Continuum 2019;25:306](#))

- **Epilepsy:** ≥2 unprovoked seizures (sz) >24h apart or 1 unprovoked sz + recurrence risk ≥60% over the next 10y
- **Status epilepticus:** ≥5min of continuous sz or 2+ sz w/ incomplete recovery of consciousness in between
- **Non-convulsive status epilepticus:** non-convulsive electrographic sz ≥10s or rhythmic EEG responsive to sz tx
- **Tonic:** persistent flexion/extension; **Clonic:** limb jerking; **Atonic:** loss of postural tone; **Myoclonic:** sudden brief muscle contraction
- **Psychogenic Non-Epileptic Seizures (PNES):** distinguish from epileptic events. Common: waxing/waning movements, fluctuating course, long duration, eye closure, ictal crying, gradual onset, asynchronous movements, pelvic thrusting, recall during period of apparent unresponsiveness, and hyperventilation ([Ann Neurol 2011;69:997](#))
- **Classification of Seizure** ([Epilepsia 2017;58:522](#))
 - Focal: unilateral, occurring in one hemisphere ± impaired awareness (formerly simple partial, complex partial)
 - Generalized: occurring in and rapidly engaging b/l distributed networks

ETIOLOGY: provoked vs not?

- **Causes/RFs:** primary epilepsy, vascular (stroke/ischemia/hemorrhage), withdrawal (EtOH/BZDs), masses (tumor, abscess), trauma, metabolic (↓BG, ↑CO₂, ↓O₂, ↓Ca), meds, infxn (systemic, CNS), HTN/HoTN, high fever, eclampsia, PRES
- **Ddx:** syncope, TIA, migraine, PNES (~30% also have epilepsy), myoclonus, dystonia, cataplexy, tremor
- **H&P:** previous sz history, prodrome (palpitation, sweating, N/V, aura), med list (↓sz threshold), triggers (exertion, pain, fatigue, stress, cough, urination, defecation), tongue biting, incontinence, lateralizing signs, EtOH. GET COLLATERAL
- **Labs:** FSBG, UTox & Stox, AED levels, BMP, Mg, Phos, CBC, LFTs, VBG, CK, INR, lactate, b-hcg, prolactin (Sn ~50%)
- **Monitoring:** tele (↑risk for fatal cardiac arrhythmias during ictal/post-ictal period)
- **Neuroimaging:** all w/ unprovoked 1st sz (**MRI w/ contrast**) ([Neuro 2015;84:1705](#)), focal neuro exam, h/o trauma, malignancy, HIV, or **focal seizure** ([Neuro 2007;69:1772](#)). Imaging changes management in ~10% ([Neuro 2007;69:1996](#))
- **LP/BCx:** if febrile, HIV/immunocompromised, or if no clear etiology
- **EEG:** within 24h-48h if not seizing, emergent EEG if seizing: **DO NOT wait** to manage. If emergent, contact EEG fellow (p16834)

TREATMENT

- Seizures that are **NOT status epilepticus:** tx if a) GTC > 2-3min or b) patient has several focal seizures within 24h ("clustering")
 - **Lorazepam 1-2mg IV** (1mg if elderly or low weight), can repeat x1 if needed. Then discuss possible AED load with Neurology
- Treatment of **status epilepticus** (see [MGH status epilepticus treatment protocol](#))
 - **Lorazepam 4mg IV q5min x1-2** → alternative AED load → intubation with propofol/midazolam. **Discuss with Neurology**
 - If no IV access, diazepam 20 mg PR or midaz 10 mg IM/nasal/buccal

SEIZURE PXP

- **No AED in 1st sz unless** previous brain injury OR abnormal EEG OR significant abnormal imaging. Early AED reduces short term recurrence (<2y), not sustained remission (3+y) ([Neuro 2015;84:1705](#))
- **ETOH seizure: ppx not indicated when intoxication or withdrawal** is the cause ([Neuro 2006;67:s45](#))
- **Brain tumor:** no ppx ([Cochrane 2008;CD004424](#)). If szs occur, start AEDs: Keppra > Lacosamide (fewer chemo interactions)
- **Severe TBI:** Keppra 500-750mg BID x7d ([Neurosurg Focus 2008;25:E3](#))
- **ICH:** AED only if clinical sz or traumatic etiology, Keppra 500mg BID x7d ([Stroke 2016;47:2666](#))
- **PNES:** treatment with outpatient Cognitive Behavioral Therapy (CBT), Psychiatry involvement. In acute setting it may be helpful to educate patients about functional neurologic sx, c/s social work
- In MA, no driving for LOC event until 6mo event free. Counsel pt, include in DC summary

AED	Loading	Dosing	Goal Level	Side Effects
Levetiracetam (Keppra)	40-60mg/kg Max 4.5g	1:1 PO:IV	No goal, level to check adherence	Psych sx (irritable, anxiety/depression, sedation, psychosis)
Valproic acid (Depakote)	20-40mg/kg	1:1 PO:IV	50-100mcg/mL (>1h post load)	Teratogenic. Hepatitis, weight gain , hair loss, N/V, encephalopathy (↑NH3), pancreatitis, thrombocytopenia Good for mood disorders
Phenytoin (Dilantin), Fosphenytoin	20 pheny equiv/kg	1:1 PO:IV	10-20mcg/mL, correct for alb, (2h post load)	Teratogenic. Gingival hypertrophy, hair growth, rash, AMS, diplopia, ataxia, slurred speech, hypotension/arrhythmia (if run faster than 50mg/min; fosphenytoin is less cardiotoxic)
Lacosamide (Vimpat)	200-400mg	1:1 PO:IV	10-20mcg/mL	HA, diplopia, dizziness, nausea, hypotension. EKG before & after load (PR prolongation)
Lamotrigine (Lamictal)	No Load	Only PO	3-15mcg/mL	Rash, SJS , nausea, somnolence, dizziness, ataxia. Good in mood disorders
Topiramate (Topamax)	No Load	Only PO	N/A	Weight loss, fatigue, teratogenic. Nephrolithiasis, cognitive decline, anxiety, anorexia, tremor
Carbamazepine (Tegretol)	No Load	Only PO	4-12mcg/mL	SIADH , N/V/D, rash, pruritis, fatigue, blurred vision, diplopia, lethargy. Screen for HLA-B*1502 if Asian descent

Neurology

Weakness & Neuromuscular Disorders

APPROACH TO WEAKNESS

- Ask about **functional issues** (getting out of chair, tripping over curbs/stairs)
- UMN signs:** spasticity, increased tone, hyperreflexia, \oplus Babinski; **LMN signs:** fasciculations, atrophy, decreased tone, hyporeflexia
- Pattern:** UMN (extensors in UEs, flexors in LEs), proximal (many myopathies), bulbar (dysphagia, dysarthria, diplopia)
- Associated sensory sx:** reduced sensation, tingling, burning, allodynia, hyperalgesia, decreased temperature sense, imbalance
- Autonomic sx:** orthostasis, constipation, urinary retention, erectile dysfunction, changes in sweating, hair loss, post-prandial nausea
- EMG/NCS:** can be helpful with localization, determining fiber type involved, determining if disease is axonal vs demyelinating (guides tx), & determining injury extent (guides prognosis). **Often higher yield $\geq 2\text{-}3w$ into illness and as outpatient**

Localization	Associated Signs/Sx	Diagnostics	Important/Common Causes
Brain	Cortical (language, visual field, neglect), cerebellar, UMN	MRI Brain (w/ contrast if c/f cancer, infection, demyelinating disease)	Vascular (hemorrhage or ischemia), tumor, trauma, demyelinating
Spinal Cord	Sensory level, bowel/bladder dysfxn, UMN	MRI Spine (level based on sx, contrast if c/f cancer, infxn, demyelinating dz) CSF if c/f inflammatory or infxn	Transverse myelitis (MS, NMO, CTD), infxn (viral myelitis, HTLV), compression (tumor/disc/abscess), vascular, trauma, paraneoplastic, toxic, $\downarrow B12/Cu$
Anterior Horn Cell	LMN. If motor neuron dz: UMN & LMN	NCS/EMG \pm MRI brain and spine; LP	ALS, SMA, polio
Radiculopathy	Motor/sensory corresponding to nerve root. \oplus Radiating pain	MRI Spine (level based on sx) LP if polyradiculopathy NCS/EMG helpful for localization (Sn imperfect \rightarrow clinical dx)	Nerve root compression (disc herniation, spondylosis) most common; polyradiculopathy: GBS, iatrogenic (post-op, chemo), ischemic, infxn (HIV, Lyme, CMV, EBV), DM (typically thoracic), sarcoid, malig.
Peripheral Neuropathy	Sensory; autonomic dysfxn if small fibers affected. Often symmetric/length dependent. GBS is ascending	Labs: A1c, B12/MMA, SPEP/sFLC Consider: Lyme, syphilis, HIV, B1, B6, vit E, B3, Cu, ANCA, ANA, ESR, CRP, RF, C3/C4, Celiac NCS/EMG: localization & pattern (NB: nl NCS doesn't exclude small fiber dz)	Symmetric/length-dependent: toxic/metabolic/nutritional (DM, chemo, EtOH, $\downarrow B12$, critical illness), paraprotein-related, hereditary (CMT); polyradiculoneuropathy: GBS/CIDP, DM, Lyme; mononeuropathy: compression/trauma; mononeuropathy multiplex: vasculitis, amyloid, sarcoid, HNPP
NMJ	Weakness is fatigable and improves with rest. A/w ptosis, diplopia. No sensory sx	Ice pack test , tensilon (rarely) Labs: myasthenia panel (see below) NCS/EMG: repetitive stimulation, single fiber EMG CT chest if above c/w myasthenia	Myasthenia gravis, Lambert-Eaton, botulism, tick paralysis
Myopathy	Proximal weakness most common. Pain uncommon	Initial labs: CK/aldolase, LDH, LFTs, TSH/FT4, PTH, ESR/CRP EMG: e/o muscle irritability, chronicity May need muscle biopsy	Critical illness, meds (steroids, statins, colchicine, cyclosporine, NRTI), inflammatory myopathies (inclusion body myositis, dermatomyositis, polymyositis)

GUILLAIN-BARRÉ SYNDROME (Acute Inflammatory Demyelinating Polyradiculoneuropathy)

- Symmetric** numbness & weakness, **absent reflexes**, can be a/w facial & oculomotor weakness, autonomic dysfxn, **acute resp failure (30% of pts)** ([Continuum 2017;23:1295](#))
- Causes:** recent infxn (Campylobacter, HIV, CMV, EBV, Zika) or vaccine (rare)
- Dx:** LP w/ albuminocytologic dissociation (\uparrow protein, nl WBC). **NCS/EMG**
- Tx:** IVIG or plasmapheresis; monitor resp w/ NIF/VC (RT)
- Elective intubation 20-30-40 Rule:** VC <20mL/kg, NIF weaker than -30cm H2O, MEF <40cm H2O, **OR $\geq 20\%$ decline in ~24h**
- Casts doubt on the Dx:** persistent asymm. weakness, bowel/bladder dysfxn at onset, >50 PMNs in CSF, sharp sensory level, severe pulm dysfxn w/ little or no limb weakness at onset, fever at onset, slow progression of weakness $>4w$
- Eliminates the Dx:** hexacarbon use, abnl porphyrin metabol. (esp AIP), recent diphtheric infxn, lead exposure, purely sensory

MYASTHENIA GRAVIS/LAMBERT EATON (MG/LEMS)

- Weakness of voluntary muscles, worse w/ exertion & repetitive movements & in the evening. Typically involves ocular (ptosis, diplopia), bulbar, respiratory, neck, proximal>distal limb muscles
- Cause:** auto-Abs against postsynaptic ACh-R in skeletal muscle (MG) or voltage-gated calcium channels (LEMS)
- Exam:** upgaze fatigability – hold sustained upgaze for 1min, look for ptosis. After observing ptosis, place ice on eyes for 1min, weakness will improve (Tensilon test rare, requires atropine at the bedside. Only improves MG not LEMS)
- Dx:** **Ach-R Ab** (80-90% seropositive, Sp); if \ominus check anti-MUSK. **EMG/NCS w/ repetitive stim:** decremental response (MG) or potentiation (LEMS). **Chest CT:** r/o thymoma (in 70-80% MG). Find **underlying malignancy** in LEMS
- Tx:** sx (pyridostigmine); immune: rapid (IVIG, plasmapheresis), chronic (steroids \pm AZA/MMF); thymectomy (thymomatous MG or <65 yo)

MYASTHENIC CRISIS:

- MG exacerbation requiring intubation or delayed extubation post-surgery
- Triggers:** surgery, infxn, IV contrast, preg., meds (abx incl FQs, AGs; AEDs; antipsychotics; β Bs; CCBs; Mg). **AVOID succinylcholine**
 - Respiratory failure:** follow number counting in single breath, assess cough/swallowing. Trend mechanics with RT: NIFs/VC as above (20-30-40 Rule). Aggressive pulm toilet. **HOLD** pyridostigmine if bulbar sx and/or intubated (can \uparrow secretions)

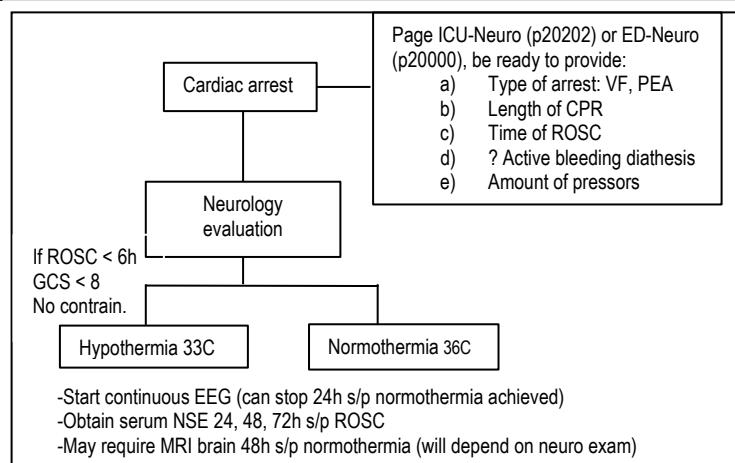
Neurology

Neuroprognostication

Neurological prognostication after cardiac arrest is challenging and uncertain ([Semin Neurol 2017;37:40](#)). The introduction of therapeutic hypothermia alters the timeframe for neurological recovery and the interpretation of prognostic markers

CEREBRAL PERFORMANCE CATEGORY (CPC)

- Good Outcome:
 - CPC 1. Able to work. May have mild neurologic/psychologic deficits
 - CPC 2. Moderate deficits. Capable of independent activities of daily life. Able to work in sheltered environment
- Poor Outcome:
 - CPC 3. Severe deficits. Conscious but dependent on others. Ranges from ambulatory to severe dementia/paralysis
 - CPC 4. Coma (no wakefulness) or vegetative state (wakefulness but unawareness)
 - CPC 5. Brain death: apnea, areflexia, EEG silence, etc



THERAPEUTIC HYPOTHERMIA (TH)

Post-cardiac arrest patients are cooled to 32–34°C within 6h of ROSC, maintained for 24h via surface or endovascular methods ([Nat Rev Neurol 2014;10:190](#)). Targeted temperature management (TTM) to 36°C has equivalent efficacy ([NEJM 2013;369:2197](#)). Pts can be paralyzed w/ neuromuscular blockade to prevent shivering, are commonly sedated (e.g. propofol, midazolam). After 24h of TH, pts rewarming in a controlled fashion over 8-12h, paralytics stopped (if used) once ~36°C (shivering threshold); sedatives weaned only after paralytics stopped ([Therapeutic hypothermia MGH protocol](#), [Therapeutic normothermia for neuroprotection MGH protocol](#))

TIMEFRAME FOR POST-CARDIAC ARREST DIAGNOSTICS

- Day 1-2: therapeutic hypothermia and rewarming
 - Electroencephalography (EEG)
 - Timing: started during TH, continued for 24h post normothermia.
 - Positive prognosis: continuous background pattern and reactivity at day 3 or later
 - Poor prognosis: absence of EEG activity, seizures, burst suppression ([Neurology 2013;80:339](#))
 - Clinical exam
 - Poor prognosis: status myoclonus at <48h post cardiac arrest or normothermia. Defined as spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs, axial musculature. There may be no EEG correlate. **Absent brainstem reflexes** (bilateral pupillary, corneal, and oculocephalic), along with apnea and other criteria (depending on local guidelines), may signify brain death
- Day 3-5:
 - Somatosensory evoked potentials (SSEP) – measurement of brain activity in response to somatosensory stimulation
 - Timing: 48h post cardiac arrest or normothermia
 - Poor prognosis: bilateral absence of N20, which reflects the integrity of thalamocortical projections
 - Neuron specific enolase (NSE) – non-specific marker of neuronal injury (misnomer as it is found in RBC and platelets)
 - Timing: 24-72h post cardiac arrest or normothermia. Check serially at 24, 48, 72h post-ROSC
 - Poor prognosis: >33 ug/l and increasing daily NSE levels ([Neurology 2011;77:623](#)). NSE is prognostic in the pre-therapeutic hypothermia era but is not well validated in patients who received therapeutic hypothermia
 - CT head, 48h post cardiac arrest or normothermia
 - Poor prognosis: widespread hypodensity, loss or reversal of grey-white differentiation
 - Brain MRI, 72h post cardiac arrest or normothermia
 - Poor prognosis: DWI and ADC changes suggestive of ischemic injury ([Ann Neurol 2009;65:394](#)). Quantitative ADC values may correlate with severity. MRI can be insensitive to lesions if not performed during normothermia

COMBINING PROGNOSTIC INDICATORS ([MGH Neuroprognostication Guidelines](#))

- Prognostic value of ≥2 of the following findings (measured after re-warming following TH, between 36-72h post cardiac arrest)
 - Bilaterally absent SSEP
 - Unreactive EEG background
 - Early myoclonus
 - Incomplete recovery of brainstem reflexes
- 79% Sn for in-hospital mortality, 62% Sn for poor 3-6mo neurological outcomes (severe disability/dependency, coma, or death). 100% PPV for both in-hospital mortality and poor neurological outcomes

Psychiatry

Psychosis

MENTAL STATUS: document daily if new AMS or worsening psychiatric sx ([AFP 2009;80:809](#))

APPEARANCE/BEHAVIOR: grooming/hygiene, eye contact, attitude/cooperation, abnormal mvmt (fidgeting, tics, TD)

SPEECH/LANGUAGE: mechanics - rate, volume, prosody, articulation, fluency (pt can place 5 words together), paucity of speech, mutism, echolalia (copying provider's speech), verbigeration (repeating meaningless phrases)

THOUGHT PROCESS: presence of disorganization (including derailing/tangentiality); also note vague use of references (common in psychosis); thought blocking (pt appears unable to produce responses to questions)

MOOD/AFFECT: pt's own description, observed affect, future views, self-attitude (worthlessness, grandiosity)

THOUGHT CONTENT/PERCEPTIONS: SI/HI, delusions, hallucinations, overvalued ideas, obsessions, poverty of content

COGNITION: level of consciousness, orientation, MOCA

INSIGHT/JUDGMENT: use examples - insight (pt recognizes sx as pathological/accepts dx); judgment (pt takes meds)

PSYCHOSIS

- **Characteristics:** delusions, hallucinations (auditory>visual), thought & behavioral disorganization
- **Ddx:** schizophrenia, schizoaffective, mood d/o w/ psychotic fx, substance-induced (stimulants, MJ, bath salts, hallucinogens, EtOH), intellectual disability, dementia, due to another medical condition (**delirium**, epilepsy, porphyria, paraneoplastic limbic encephalitis), less frequently OCD/PTSD/borderline PD, deception syndrome/malingering
 - New onset psychotic disorders in >50yo is fairly rare. Medical cause of psychotic sx in this age group (delirium, CNS pathology, dementia) is more likely unless known psych dx
- **Labs:** CBC, BMP, UA, Utox, VPAIN, serum tox incl EtOH, med levels, delirium w/u (see [Delirium](#))
- **Refer to psych:** outpatient = always, inpatient = if decompensated ± safety concerns (can be associated with fear, agitation, aggression, SI/HI/VI, inability to care for self)

TREATMENT BASICS

- Confirm home antipsychotics/mood stabilizers early in admission & continue only if pt reliably taking; otherwise, dose reduce or hold (clozapine, lamotrigine). Ask if pt on long-acting injectable medication/date of last injection, ask which PRN medications work well for patient. If taking valproate, lithium, clozapine: check levels
- **Antipsychotics:**
 - Avoid multiple antipsychotics in 1 patient. If med list includes >1 standing, confirm before ordering
 - Continue home Cogentin (benztropine) if prescribed to reduce EPS sx (common in 1st gen antipsychotics)
- **Mood stabilizers:** lithium, valproate, lamotrigine, carbamazepine, some antipsychotics
 - Lamotrigine: confirm adherence with lamotrigine given risk of SJS → if has been off for >2-3d, will need to restart titration at 25mg, uptitrated q2w. If any questions, contact pharmacist ± Psychiatry
 - Lithium toxicity: n/v/d, tremor, ataxia, confusion, agitation → seizures, NCSE, encephalopathy. Precipitating factors include dehydration, AKI, new meds (NSAIDs, ACE/ARB, diuretics, CCBs)
- **Extrapyramidal symptoms (EPS):**
 - Pseudoparkinsonism: reversible; tremulousness, rigidity, bradykinesia, masked facies, shuffling gait; **Tx:** anticholinergics (e.g. benztropine, diphenhydramine)
 - Akathisia: subjective feeling of inner restlessness, inability to stay still; **Tx:** low dose BB (e.g. propranolol 20-80mg/d)
 - Dystonia: muscle spasm incl. oculogyric crisis, torticollis, trismus, opisthotonos, laryngospasm; **Tx:** anticholinergics
 - Tardive dyskinesia (TD): occurs w/ long-term antipsychotic use, may not be reversible even with med discontinuation. Includes myoclonic jerks, tics, chorea, & dystonia, often of orofacial region
- **Clozapine:** may cause neutropenia/agranulocytosis; occurs in <1% of pts (84% w/in first 3mo). CBC weekly for first 6mo, every 2w for next 6mo, then monthly. DC if WBC <3 or ANC <1500. Risk for myocarditis. Risk for clozapine-withdrawal catatonia if stopped suddenly. Severe infx can impair metabolism of cloz and ↑levels/toxicity; check levels

ANTIPSYCHOTICS & SIDE EFFECTS ([AFP 2010;81:617](#))

	Anti-cholinergic	Prolonged QTc	EPS	NMS	Prolactin elevation	Postural hypoTN	Sedation	HLD	Weight gain	DM2	Sexual dysfxn
haloperidol	+	+	+++	++	+++	+	+	+	+	+	++
chlorpromazine	+++	++	+	+	++	+++	+++	++	++	+	+++
ariPIPrazole	0	+	+	+	0	+	+	0	0	+	+
olanzapine	+	+	+	+	+	+	++	+++	+++	++	+
quetiapine	+	+	0	+	0	++	++	++	++	+	+
risperidone	0	+	++	+	+++	++	+	+	++	+	++
ziprasidone	0	++	+	+	+	+	+	0	0	+	+
clozapine	+++	+	0	+	0	+++	+++	+++	+++	++	+

AGITATION MANAGEMENT 101

- Goals: 1) Safety of pt & staff, 2) Help pt manage distress & maintain/regain control of behavior, 3) Avoid restraints as able
- General Considerations:
 - Take notice early of anger/fear, yelling, pacing/restlessness, sweating. LISTEN to RN, PCA concerns
 - Address any easily/quickly reversible issues: hunger, thirst, pain, communication breakdowns
 - Offer PO medications early in escalation process. Think about standing medication if it is recurrent
 - If pt requires restraints, should always receive med to help ease/lessen time in restraints. Monitor for ongoing need. Ensure appropriate medical mgmt, as restrained pts are at risk of aspiration, rhabdo/MSK injury, delirium
 - Work-up/treat any other contributors (e.g. delirium—see [Delirium](#), psych d/o, substance intoxication/withdrawal)

APPROACH TO VERBAL DE-ESCALATION: 10 DOMAINS OF DE-ESCALATION ([West J Emerg Med 2012;13:17](#))

Domain	Recommendations	Examples
Respect personal space	Respect your own & pt's space	Maintain 2 arms' length from pt; ensure both have path to exit room, but position yourself closer to door
Do not be provocative	Avoid iatrogenic escalation	Use calm voice/tone, avoid confrontational posturing (e.g. crossed arms, prolonged eye contact, standing directly over)
Establish verbal contact	Only 1 person verbally interacts w/ pt	Can be confusing to have multiple points of contact & may further escalate situation through sense of chaos, intimidation/outnumbered-ness
	Introduce yourself, provide orientation & reassurance	Include your name & role, that you are there to keep them safe and to help them regain a sense of control; ask their name (if unknown)
Be concise	Be concise, keep it simple	Use short sentences, simple vocabulary, give time to process
	Repetition is essential	When upset, pt may need to hear something a few times before it can sink in
Identify wants & feelings	Use "free information" to identify wants & feelings	Gather insight into their goals through what they are saying, body language, prior encounters – allows for empathetic response
Listen closely to pt	Use active listening	Convey that you are paying attention; use clarifying/summarizing statements
	Use Miller's Law	"To understand what another person is saying, you must assume that it is true and try to imagine what it could be true of." Assuming what pt is saying is true will increase your engagement & build alliance
Agree or agree to disagree	Align with pt	Find a way to honestly agree with the pt (an event occurred, in principle, etc.); if nothing else, agree to disagree
Set clear limits	Establish basic working conditions	Pt should be clearly informed of what is acceptable behavior. May refer to hospital policy and your goal to keep caring for them
	Limit set respectfully	State your desire to help without facing abuse; that you will step away if they continue to yell/threaten and return to talk when they are able to speak with you calmly and respectfully. Acknowledge your discomfort
	Coach how to stay in control	Offer gentle instruction: "I'd like you to sit down to talk with me", "I bet you could help me understand if you were to calmly tell me your concerns"
Offer choices & optimism	Offer choices	Can elicit their choice of PRN and/or admin route (within reason)
	Broach meds	Goal is to calm pt so they can participate in care. "You seem overwhelmed by what's going on. What do you think would help? Would you be willing to take medication?" Can be more forceful if is emergency ("I'm going to ask the nurse to give you a medication to help you feel calmer")
	Be optimistic, provide hope	Align with pt goals; provide optimism that things will improve
Debrief pt & staff	Debrief patient	Explain reasoning behind intervention. Let pt explain their perspective. Explore other ways to manage feelings in future
	Debrief staff	Debrief situation with staff & what could be improved

MEDICATION OPTIONS: always offer PO option first if pt able to safely take PO

- PO: **quetiapine** (initial 12.5-25mg q6h, if QTc <550, BP stable). Consider **lorazepam** if stimulant intoxication or catatonia
- IV: **haloperidol** (initial 2.5-5mg, 1-2mg in elderly/frail; watch QTc). Less association with EPS/dystonia than IM/PO. Prefer early Psych consultation for pts requiring higher/more frequent doses
- IM (chemical restraint): use only as a last resort in case of emergencies. Consider Psychiatry consult for pts requiring IMs
 - IM olanzapine or chlorpromazine (Thorazine) should be used cautiously in elderly pts given risk of orthostasis
 - DO NOT** co-administer IM olanzapine with IM benzos/barbiturates due to risk of cardiorespiratory depression
 - IM haloperidol (5mg) should be co-administered with either IM diphenhydramine (25-50mg) or IM benzotropine (0.5-1mg) to reduce risk of dystonia, although these medications may temporarily worsen delirium
 - "5-2-50" IM combo (haloperidol 5mg + lorazepam 2mg + diphenhydramine 50mg) sometimes used for severe agitation not associated with delirium

SPECIAL POPULATIONS

- Antipsychotics carry a black-box warning for increased all-cause mortality in pts with dementia (who commonly present with superimposed delirium) – use only if benefit > risk and with goal of lowest effective dose for shortest time
- AVOID antipsychotics in patients with Parkinsonian syndromes, catatonia, NMS

Psychiatry

Consent & Capacity

THREE ELEMENTS OF VALID INFORMED CONSENT ([Psychosomatics 1997;38:119; NEJM 2007;357:1834](#))

1. Relevant clinical information: at minimum: diagnosis, proposed intervention, its purpose, its risks/benefits, alternatives, and risks/benefits of alternatives (including no intervention)
2. Voluntary decision: the decision must be voluntary and without coercion from hospital staff or family/friends
3. Capacity: confirm patient has the ability to make a decision about the **specific question** being addressed at the time it is being asked

EXCEPTIONS TO INFORMED CONSENT

1. Emergency: imminent risk of death or serious harm without medical intervention. All attempts should be made to find HCP/other surrogate decision-maker. Always discuss with team attending. Document emergent situation, lack of capacity, lack of available surrogate, need for emergent intervention. Consider 2nd opinion/consulting MGH lawyer-on-call
2. Lack of capacity or competency: turn to the appropriate HCP/surrogate decision-maker

CAPACITY ASSESSMENT

- **Capacity**: person's ability to make an informed decision about a **specific question**. It **can change over time**
- **Competence**: legal designation made by a judge. Determines a person's global ability to make decisions in multiple areas of life
- **Any physician can make a determination of capacity**. Psychiatry should be consulted only for complex cases, such as when neuropsychiatric illness may be impairing decision-making or when the pt, family, and medical team disagree. Inform consultant of pt's expressed decision and risks/benefits of each intervention
- **The strictness of the capacity test varies as the risk/benefit ratio of a decision changes**: the more favorable the risk/benefit ratio, the lower the standard for capacity to consent and higher the standard to refuse, and vice versa

CRITERIA FOR DETERMINING CAPACITY (ALL must be met for pt to have capacity) ([NEJM 2007;357:1834; NEJM 1988;319:1635](#))

Criterion	Approach in Physician's Assessment
Communicate a clear and stable choice	Ask patient to indicate a choice. No expression is a presumption of incapacity. Frequent reversals of choice may indicate lack of capacity
Understand relevant information	Ask patient to describe his/her understanding of the information given by the physician (diagnosis, proposed intervention, purpose of intervention, risks/benefits, risks/benefits of alternatives including no intervention)
Appreciate the situation and its consequences	Ask patient to describe views of diagnosis, interventions, and likely outcomes. Is patient aware of her illness? Its seriousness? Consequences?
Be able to manipulate information provided in a rational fashion	Ask patient to compare treatment options, consequences, and reasons for choice. Does the patient weigh the risks and benefits logically?

Documentation: "Based upon my evaluation of the pt, he/she [does/does not] express a consistent preference regarding the proposed treatment, [does/does not] have a factual understanding of the current situation as evidenced by [example], [does/does not] appreciate the risks and benefits of treatment and non-treatment and is [able/unable] to rationally manipulate information to make a decision as evidenced by [example]. Therefore, in my opinion, this pt [has/lacks] capacity to make this medical decision." **If capacity present:** "We should respect the patient's right to make this decision to [details]." **If lacks capacity:** "Surrogate decision-maker needed."

SURROGATE DECISION-MAKERS

- Encourage each pt to sign legal HCP form specifying surrogate. Activated (court procedure) when pt lacks capacity
- Surrogate's job is to make the decision pt would have made for himself/herself if able—not what the surrogate wants. If a pt's wishes cannot be known, the surrogate should make the decision in the best interest of the patient
- HCP may be unconfirmed (most common) or confirmed. **Court-confirmed HCP is required when pt's surrogate is activated & pt actively objects to surrogate's decision.** If HCP confirmation required, contact MGH Guardianship team
- **Guardianship**: legal process by which the MA Probate Court grants a guardian the authority to make decisions on behalf of someone whom a judge has ruled is not competent. **Required when there is no HCP identified & pt is unable to designate a HCP.** Note: a patient may not have capacity to make a certain medical decision **and** still be able to designate a HCP. For help: 'Guardianship Team'
- Emergency guardianship is not required to provide lifesaving treatment & should not delay care. Can consult MGH lawyer-on-call

TEMPORARY INVOLUNTARY (PSYCHIATRIC) HOLD ([Section 12](#) in MA - MGL ch.123 §12): consult Psychiatry for all on 12a

- **Section 12a** (the front of the "pink paper"): MD uses this form to apply for involuntary psych hospitalization of a pt who, based on MD's exam & opinion, requires hospitalization to avoid likelihood of serious harm by reason of mental illness; providers other than MDs can place someone under 12a, including NPs, psych RNs, psychologists, SWs, police officers
- Authorizes pt's transport to psych facility and, if necessary, the use of restraint of the pt to maintain safety
- Issued when likelihood of serious harm to self and/or others is imminent (general rule of thumb is within 24-72h) AND:
 1. Is the result of a "serious mental illness": must be supported in writing with specific evidence. Symptoms caused solely by alcohol or drug intake, organic brain damage, or intellectual disability do not constitute a serious mental illness
 2. Meets ≥1 of the following 3 criteria: (1) substantial risk of **physical self-harm**; (2) substantial risk of **physical harm to others**; (3) very substantial risk of **physical self-impairment or injury** as manifested by evidence that the person's judgment is so affected (i.e., by serious mental illness) that he/she is unable to protect him/herself in the community.
- **Section 12b** (reverse side of the "pink paper," "72h hold"): completed by evaluating MD at receiving psychiatric facility

CIVIL COMMITMENT FOR SUBSTANCE USE DISORDER TREATMENT ([Section 35](#) in MA - MGL ch.123 §35)

- Process by which the court may involuntarily commit someone to inpatient substance use disorder treatment when there is likelihood of serious harm as a result of the disordered substance use; must be pursued via petition filed at courthouse

Psychiatry

Catatonia, NMS, & Serotonin Syndrome

CATATONIA

- Behavioral syndrome that can occur in the context of many psychiatric, neuro, or medical dx; marked by inability to move typically despite full physical capacity; pathophysiology incompletely understood
- Subtypes: stuporous: immobility, mutism, withdrawal; excited: hyperkinesis, stereotypy, disorientation; malignant (medical emergency): sx are accompanied by hyperthermia, autonomic instability, rigidity ([Arch Gen Psych 2009;66:1173](#))

Etiology: ([Schizophr Bull 2010;36:239](#); [Behav Brain Sci 2002;25:555](#))

- Psychiatric: mood disorders (e.g. bipolar d/o) > thought disorders (e.g. schizophrenia, autism) > dissociative disorders
- Neuro/medical: seizures/NCSE, PRES, CNS lesion, infection, TBI, PLE, delirium, anti-NMDAR encephalitis, SLE
- Drug: dopamine-blockers, dopamine withdrawal, sedative/hypnotic withdrawal, hallucinogens, synthetic MJ, opiates

Diagnosis: DSM-V or Bush-Francis Catatonia Rating Scale ([BFCRS](#)), ([Psych Scand 1996;93:129](#))

- Most common signs include: ([World J Psych 2016;6:391](#))
 - >80%: immobility, mutism, withdrawal & refusal to eat, staring
 - >50%: negativism (oppose/no response to instruction), posturing/catalepsy (spontaneous maint of posture), rigidity
 - >10%: waxy flexibility (ability to mold limbs with initial resistance), stereotypy (repetitive, purposeless movements), echophenomena (repetition of examiner's words or movements), verbigeration (repetition of random words)
 - Other signs: automatic obedience, ambitendency (motorically stuck in indecisive movement), grasp reflex
- Exam: observe for 30s outside pt room. Attempt to engage in conversation. Gesture in exaggerated manner (echopraxia). Examine for cogwheeling in arms, alternate force, attempt to reposture. Test for "mitgehen" (movement w/ the slightest touch). Extend hand & say, "Do not shake my hand" (ambitendency, pt will appear stuck). Reach into pocket & say, "Stick out your tongue. I want to put a pin in it" (automatic obedience). Check for grasp reflex
- Ddx: delirium, dementia, stroke, PD, stiff person & locked-in syndromes, NCSE, akinetic & elective mutism, anti-NMDAR encephalitis; If malignant: NMS, malignant hyperthermia, SS, DTs, CNS infection/vasculitis, anticholinergic toxicity

Treatment: ([Schizophr Bull 2010;36:239](#)) — *Always consult psych*

- NO antipsychotics or other D2 blocking meds, e.g. antiemetics (prochlorperazine, promethazine, metoclopramide)
- Trend CK, BMP; q4h VS; supportive care (aspiration precautions, fluids, monitor I/Os, electrolyte/renal fx)
- Lorazepam challenge: 2mg IV x1 (0.5-1mg in frail elderly), repeat [BFCRS](#) in 30min. If response, 2mg IV lorazepam q6-8h, uptitrate as tolerated. Do not hold for sedation (signs of catatonia can be mistaken for sedation → hold for resp depression). If no response, pt may require ECT. Adjunctive 2nd line agents: amantadine, memantine, zolpidem, AEDs

NEUROLEPTIC MALIGNANT SYNDROME: ([Am J Psych 2007;164:870](#))

- Overview: abrupt onset of 1) Δ in mental status 2) rigidity 3) fever 4) autonomic dysfunction (tachy, HTN, diaphoresis) associated with dopamine-blocking agent or withdrawal of pro-dopamine meds (med list: [Neurohospitalist 2011;1:41](#))
- Risk factors: initiation/increase of D-blocking med (typically occurs within hours/days, but can be idiosyncratic), hx of NMS/catatonia, withdrawal from EtOH/sedatives, basal ganglia d/o, exhaustion, dehydration, agitation
- Labs: ↑WBC and CK = most common lab abnormalities. Trend CK and watch for rhabdo/AKI. Low serum iron is 92-100% Sn but not Sp. May see mild elevations in LDH, alk phos, AST, ALT, electrolyte abnormalities
- Ddx: serotonin syndrome, malignant hyperthermia, malignant catatonia (significant overlap), CNS infection, spinal cord injury, seizure, heat stroke, acute dystonia, CNS vasculitis, thyrotoxicosis, drug intoxication/toxicity, withdrawal states
- Staging and Treatment:

Stage	Clinical Presentation	Intervention
Early	Mild rigidity, confusion, T<100.4F, HR <100	<ul style="list-style-type: none">• Stop offending agent & contributors (serotonergics, Li, anticholinergics)• Aggressive fluids/supportive care ± lorazepam 0.5-2mg IV q4-6h
Moderate (may require ECT)	Moderate rigidity, T100.4-104F, HR 100-120	<ul style="list-style-type: none">• Cooling measures ± ICU• Bromocriptine 2.5mg PO q8h <i>or</i> amantadine 100mg PO q12h
Severe (may require ECT)	Severe rigidity, ± coma, T >104F, HR >120	<ul style="list-style-type: none">• ICU level of care (if intubation required, midaz > propofol for sedation)• Dantrolene 1-2.5mg/kg IV q6h x48h

SEROTONIN SYNDROME: ([NEJM 2005;352:1112](#))

- Overview: exposure to serotonergic agent leading to triad of 1) Δ mental status 2) neuromuscular hyperreactivity (tremor, hyperreflexia, clonus) 3) autonomic instability (tachycardia, tachypnea, diaphoresis, mydriasis, hyperthermia, shivering, sialorrhea, urinary incontinence, diarrhea). Note: n/v/d common in SS prodrome but rarely seen in NMS
- Causative agents: amphetamines, bupropion, buspirone, carbamazepine, carbidopa-levodopa, cocaine, cyclobenzaprine, diphenhydramine, fentanyl, linezolid, lithium, LSD, MAOIs, MDMA, meperidine, methadone, methylene blue, metoclopramide, ondansetron, SNRIs, SSRIs, TCAs, tramadol, trazodone, triptans, tryptophan, VPA
- Diagnosis: can use [Hunter's Criteria](#) if unclear ([QJM 2003;96:635](#))
- Treatment: 1) hold offending agent (generally will resolve within 24h), 2) use BZDs if agitation present (**lorazepam** 1-2mg IV, repeat PRN to effect), 3) if unsuccessful, can use **ciproheptadine** 12mg x1 then 2mg q2h until clinical response seen. Very severe cases with hyperthermia may require ICU level of care with cooling, intubation, sedation, and paralysis

MAJOR DEPRESSIVE DISORDER (MDD)

- Epi: common in general population; estimated U.S. prevalence 9% ([CDC MMWR 2010;59:1229](#))
- Screening: USPSTF recommends **universal screening of adult primary care patients** (Grade B)
 - **PHQ-2**: in last month, have you 1) felt down/depressed/hopeless? 2) had little interest/pleasure in doing things?
 - $\geq 1 = \oplus$ screen, 97% Sn, 67% Sp for MDD → **PHQ-9** to grade severity ([AFP 2012;85:139](#))
- DSM-5 criteria: must have depressed mood and/or loss of interest/pleasure + ≥ 4 of following sx: ↑ or ↓ weight/appetite, ↑ or ↓ sleep, psychomotor agitation/slowing, fatigue, worthlessness/guilt, poor concentration, thoughts of death or SI; sx must be present over same **2w period** & cause significant **impairment/distress**
 - Ddx: other psych (e.g. bipolar), drugs/meds, OSA, hypothyroidism, stroke, TBI, delirium, vit def, dementia, MS, HIV
- Tx: meds + therapy > either, but either alone acceptable ([APA 2019](#)). SSRIs generally 1st line: consider **escitalopram & sertraline** (efficacy/acceptability > duloxetine/paroxetine) ([Lancet 2009;373:746](#)). Other common options: bupropion, SNRIs

Side Effect Profiles of Commonly Prescribed Antidepressants

	Drowsiness	Insomnia/Activation	GI upset	Weight gain	Sexual dysfxn	Orthostatic HoTN	QTc Prolongation
SSRIs	--/↑	↑/↑↑ (fluox, sert)	↑/↑↑ (sertraline)	↑/↑↑ (paroxetine)	↑↑↑ (paroxetine)	↑	↑
SNRIs	--/↑	---/↑	↑↑	---/↑	↑/↑↑ (venlafaxine)	---/↑	---/↑
Bupropion*	---	↑↑	↑	---/↓	---	---	↑
Mirtazapine	↑↑↑	---	---	↑↑↑	↑	---	↑

*Bupropion lowers the seizure threshold; contraindicated in pts w/ seizure disorder, anorexia/bulimia nervosa

Dosing of Common Antidepressants

- Start at low dose, titrate q1-2w. Advise pts of initial SEs that they will develop tolerance to (GI upset, headache)
- Adequate trial is 6-12w at full dose; if poor tolerance/response after 4-6w, augment or switch classes
- Stopping requires tapering off over 2-4w to prevent discontinuation syndrome (flu-like sxs, insomnia, hyperarousal)

Refer to Psych: concern for bipolar depression, failure of 2 adequate rx trials, severe MDD w/ SI/HI, psychosis, or catatonia

GENERALIZED ANXIETY DISORDER (GAD)

- Epi: US lifetime prevalence ♀ 7.7% & ♂ 4.6% ([AFP 2015;91:617](#)). 90% will meet criteria for at least 1 co-morbid psych condition in their lifetime (MDD, dysthymia, AUD, simple phobia, social anxiety) ([Arch Gen Psych 1994;51:355](#))
- Excessive worry associated w/ poor CV health, ↑CAD, ↑CV mortality ([Nat Rev 2012;9:360](#))
- Screening: **GAD-7**: score ≥ 5 indicates mild GAD (97% Sn, 57% Sp, LR 2.2); score ≥ 10 indicates moderate GAD (89% Sn, 82% Sp, LR 5.1) ([Arch Intern Med 2006;166:1092](#)). Commonly done annually with PHQ2; no USPSTF recs
- DSM-5 criteria: A) excessive anxiety/worry occurring most days for ≥ 6 mo re: multiple life domains, that is B) difficult to control, & C) associated w/ ≥ 3 sx: restlessness, fatigue, poor concentration, irritability, muscle tension, sleep disturbance. Must also cause D) significant distress/impairment; and E/F) not better explained by drugs/meds/other psych
- Tx: 1st line therapy = **SSRIs/SNRIs** and/or CBT, based on availability/pt preference; no head-to-head trials (meta-analyses have found effect sizes ≈ equivalent). No individual SSRI/SNRI shown more effective; select based on side effects and pt treatment history/preference; titrate & adjust as for MDD above
 - In general, SSRIs have lower risk of insomnia/activation (e.g. restlessness, anxiety) over SNRIs. Citalopram, escitalopram, paroxetine typically thought to cause least; sertraline and fluoxetine cause more

Refer to Psych: failure of 2 adequate next-step trials, severe GAD w/ recurrent panic, SI

POST-TRAUMATIC STRESS DISORDER (PTSD)

- Epi: US lifetime prevalence 8%; trauma-exposed: ♂ 8%, ♀ 20%; combat/severe disaster survivor: higher ([AFP 2013;88:827](#))
- Screening: Primary Care PTSD Screen ([PC-PTSD-5](#)): screens for trauma exposure then for sxs based on DSM criteria; score >2 with 91% Sn, 72% Sp; >3 with 78% Sn, 87% Sp ([Prim Care Psychiatr 2003;9:9](#))
- DSM-5 criteria: A) exposure to trauma, B) intrusive sx (involuntary trauma memories/dreams, dissociative flashbacks, psych distress, marked physiological reactions to trauma reminders), C) avoidance sx (of trauma reminders), D) neg cognition & mood (incl amnesia of trauma, neg beliefs about self/others/world, inappropriate self-blame, neg emotional state), & E) hyperarousal (irritability/anger, reckless/self-destructive behavior, hypervigilance, exaggerated startle, sleep disturbance); lasting **>1mo** & causing significant distress
- Treatment: trauma-focused therapy + SSRIs/SNRIs; tx of psych/SUDs comorbidities; prazosin for sleep disturbance

Refer to Psych: all should be referred for psychotherapy ± Psychiatry (depending on complexity of pharmacology needs)

Psychiatry

Alcohol Use Disorder & Withdrawal

ALCOHOL USE DISORDER (AUD)

Diagnosis and Presentation

- Screen all primary care patients ([USPSTF](#); can use [Audit C](#)) & inpatient admissions about EtOH use. Risky drinking is >4 drinks/occasion for men, >3 for women, OR >14 drinks/w for men & >7 drinks/w for women
- If screens \oplus , ask **5 Cs**: Control, Cravings, health/relationship Consequences, Compulsion to drink, unable to Cut back
- AUD is based on the [DSM-5](#) criteria (11 criteria; 2-3 = mild, 4-5 = moderate, ≥ 6 = severe)
- Chronic use: cytopenia (low Hb, WBC, Plt); low K/Mg/Ca/Phos/VitD – EtOH toxic to renal tubules and \downarrow GI absorp; ketoacidosis – EtOH metab \rightarrow less gluconeogenesis \rightarrow rel hypoglycemia \rightarrow low insulin state \rightarrow FFA to ketones; lactic acidosis – \uparrow ratio of NADH/NAD ([NEJM 2017;377:1368](#))

Treatment for Moderate/Severe AUD: [Boston Area and MGH SUD Resources](#)

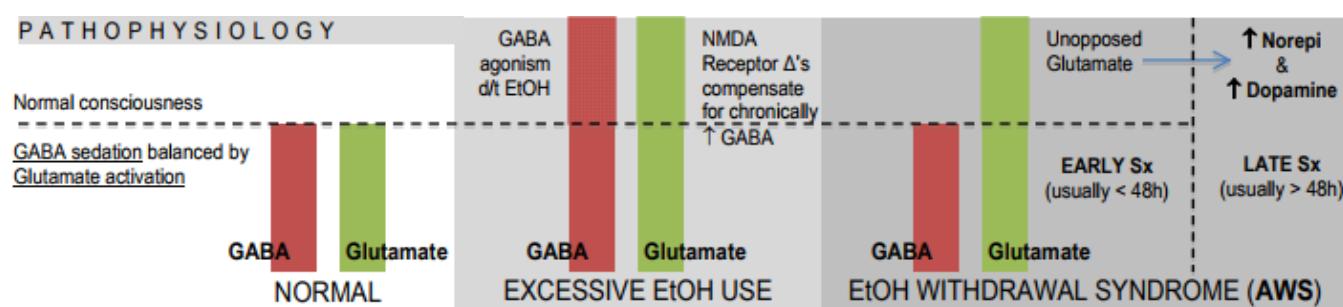
- Counseling**: CBT, recovery coach, mutual help meetings (AA/SMART recovery). AA \uparrow rate of continuous abstinence compared to other counseling methods ([Cochrane Rev 2020](#)). Levels of care (see table below) usually progress from hospitalization/"detox" \rightarrow CSS \rightarrow TSS \rightarrow long-term residential tx \rightarrow "sober" living; PHP and IOP outpatient options
- FDA approved**: naltrexone, acamprosate, disulfiram; data suggests disulfiram efficacy only if dosing is observed
 - Naltrexone (\downarrow reward/cravings) PO 25mg to start \rightarrow 50mg daily or IM (Vivitrol) 380mg q4w (Cl: acute hepatitis/ALF, current opioid use or on bup or methadone). Naltrexone likely $>$ acamprosate ([JAMA 2006;295:2003](#))
 - Acamprosate (\downarrow cravings) 666mg TID (Cl: CrCl<30, pregnancy)
- Non-FDA approved**: topiramate, gabapentin ([Addiction 2019;114:1547](#)), baclofen ([Am J Psych 2018;175:86](#))
- Success can range from reducing heavy drinking days to abstinence. Remember to utilize principles of harm reduction

SUD Levels of Care				
Medically Supervised Withdrawal ("Detox")	Partial Hospitalization Program (PHP)	Intensive Outpatient Program (IOP)	Clinical Stabilization Service (CSS) Transitional Support Service (TSS)	Long-Term Residential Treatment
Medical management of acute withdrawal in a hospital or standalone detox center. Best for patients with risk of severe withdrawal symptoms LOS: 4-6d	Highly structured outpatient treatment 6-8h/d for 5d/w. Intensive group therapy; offers treatment for both SUD and MH concerns LOS: 1-3w	Outpatient and less intensive than PHP; typically ~3h for 3d/w; provides psychoeducation and psychotherapy LOS: 1-3 mo	Inpatient programs to transition from hospital/detox to longer treatment; very structured with counseling. Usually go from CSS \rightarrow TSS LOS: 14d (CSS) 30d (TSS)	"Halfway houses"; covered by insurance, offer groups, counseling and attendance at outside mutual support; few offer meds esp in OUD (JAMA 2020;324:804) LOS: 6-12mo

Wernicke-Korsakoff Syndrome

- Wernicke encephalopathy (acute):
 - Dx: **Caine Criteria** (85% Sn) requires ≥ 2 : (1) dietary deficiency, (2) oculomotor dysfxn, (3) cerebellar dysfxn (LE ataxia), (4) AMS or poor memory. Note: Serum B1 NOT diagnostic ([J Neuro Nsgy Psych 1997;62:51](#))
 - Tx: thiamine IV 500mg TID x5d (**dose 1 before glucose**) \rightarrow IV 250mg qd x3d \rightarrow PO 100mg TID x1-2w \rightarrow 100mg qd
 - Ppx: IV 250mg qd x3-5d \rightarrow 100mg TID x1-2w \rightarrow 100mg qd ([Intern Med J 2014;44:911](#))
- Korsakoff's (chronic): antero+retrograde memory deficits (confabulation), apathy, intact sensorium

ALCOHOL WITHDRAWAL SYNDROME



Pathophysiology: GABA (inhibitory) and glutamate (excitatory) work in balance

- Chronic EtOH use**: high GABA stim \rightarrow glutamate upregulation. After chronic stim, GABA receptors are less sensitive & require more EtOH to balance increased glutamate
- Abrupt Cessation of EtOH**: decreased GABA \rightarrow unbalanced excess glutamate activity \rightarrow noradrenergic surge \rightarrow increased dopamine release \rightarrow complicated withdrawal sxs

Clinical Presentation: symptoms vary by time after last drink: ([Ind Psych 2013;22:100](#))

- **Minor withdrawal:** 6-48h; tremors, sweats, ↑HR, ↑BP, HA, anxiety, intact orientation
- **Withdrawal seizure:** 6-48h; generalized tonic-clonic
- **Alcoholic hallucinosis:** 24h-6d; visual/tactile > auditory (pt typically aware of hallucinations), clear sensorium
- **Delirium Tremens (DTs):** 48h-5d, can last 2w; tremors, sweats, ↑HR, ↑BP, fever, disorientation, inattention, paranoia, hyperalert, hallucinations, agitation. Usually CIWA >20. Death 1-4%

Initial Evaluation

- **H&P:** time of last drink, hx complex withdrawal (sz, ICU/intubation, DTs), hx of patient-initiated discharge, co-ingestions (including BZD), EtOH use history (drinks per day/week, type of alcohol, binge drinking, recent changes in drinking)
- **Labs:** CMP, CBC, serum osm if HCO₃ <15 or AGMA, CPK if found down, tox screen, serum EtOH (clear ~15-35 mg/dL/h, chronic = faster metab, higher tolerance) ([J Forensic Sci 1993;38:104](#))
- **Severe w/d predictors:** age, comorbidities, hx of DT/withdrawal, ↑BP, ↓Na/↓K, BUN >26, Plt <150 ([JAMA 2018;320:825](#))

Management

- **Initial Tx for all EtOH withdrawal:** IV thiamine (if concerned for Wernicke's, see prior page), D5-LR (after thiamine) to fix ketoacidosis, replete lytes, folate 1mg qd, MVI, place on CIWA, offer ACT c/s for AUD treatment
- **Decide BZD protocol vs. phenobarbital:** no difference in outcome or sedation ([Psychosom 2019;60:458](#))
 - Consider **BZD** if: mild-mod w/d sx, no hx complicated w/d, phenobarb contraindicated; generally 1st line
 - Consider **phenobarbital** if: hx DTs, seizures, success w/ phenobarb, prior ICU admissions for w/d; current sx of DTs; not responding to BZD; risk of paradoxical response to BZD (chronic CNS dz)
 - Contraindications: >30mg lorazepam equivalents in 24h; hx SJS/TEN; hx AIP; unstable respiratory status; high likelihood of patient-initiated discharge interrupting therapy (relative contraindication, risk/benefit is unclear)
 - Advantages: auto-taper, long half-life, predictable effect, uniform efficacy, level is accurate if needed, wide therapeutic window, no paradoxical agitation, does not require CIWA evaluation

BENZODIAZEPINE PROTOCOL

Use Epic Alcohol Withdrawal Order Set!

Route: PO lorazepam if taking POs>IV lorazepam>>diazepam/chlordiazepoxide (↑half-life, delayed toxicity, cleared by liver)

PRN: use CIWA scale (only if patient can **communicate**), NOT ↑HR, ↑BP alone (poor predictors of DTs, [JGIM 1996;11:410](#)). PRN protocol inappropriate if AMS, DTs, or severe w/d. Consider switching to RAAS scoring

Standing: if likely to have severe w/d

Beware paradoxical response, resistance (>6mg lorazepam/h), or BZD toxicity (similar to DTs) w/ escalating dose

Consider switch to phenobarb if CIWA consistently >16 despite aggressive dosing & <30mg lorazepam equivalents

PHENOBARBITAL PROTOCOL

- Phenobarbital (PB) binds GABA-A and glutamate, t_{1/2} = 1-4d
- **NO MORE BZD** after PB started
- Side effects: apnea, hypoventilation, hypotension, bradycardia, laryngeal spasm
- IM load (80% given initially) + PO taper
 - To calculate doses and view modifiers: use Epic Order Set! Dosing based on IBW (height)
 - **↑dose for high-risk withdrawal:** past DTs ± sz AND (EtOH use in <2w OR active w/d sx OR ⊕BAL with labs predictive of severe w/d: ↓plts, ↑MCV, ↓K)
 - **↓dose if sedation carries high risk:** age>65, liver dz (↓excretion/metabolism, consider stopping taper early), head injury, concurrent sedatives/opioids, respiratory compromise
 - Serum level not required. Check 5h after load if considering re-load
- **ED IV PB load:** must stay 1h in ED after IV load. **NO MORE IM** after IV unless re-load (see below). Start PO 8h after IV load, dose per excel sheet
- **Assess frequently!** IM loading dose is split to allow monitoring: 40% 0h, 30% 3h, 30% 6h. Peak plasma concentration 30m-4h post-IM dose & 2-8h post-PO. If uncontrolled sx or developing sedation, call for help from pharmacist to change doses
- **Consider reload:** for breakthrough sx despite IV or IM load. If 5h level <15, OK to reload, Target level 12-15. Consult psych, ACT, and/or pharmacy
 - Options: 1) reload IM, e.g. if serum level 6, give equivalent IM load again to target 12 OR 2) increase taper: ↑PO doses for higher serum target
- **Discharge:** phenobarbital increases receptor sensitivity to BZDs/EtOH; **drinking after** IV/IM load can be **fatal**. Will autotaper over days. If exam/V/S stable, **can d/c patient before all doses complete, no earlier than day 3**. Okay to discontinue PO taper if withdrawal symptoms controlled. No PO doses on d/c

OPIOID USE DISORDER (OUD)

- Chronic, relapsing d/o of opioid use due to dysfunction of brain reward circuits ([J Addict Med 2015;9:358](#))
- Screen all patients with: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" Confirm diagnosis using [DSM-5 Criteria](#) for opioid use disorder. Use ≠ OUD
- Focus on building a **therapeutic alliance** and performing risk assessment ([Med Clin N Am 2018;102:587](#))
 - Assess **risk of withdrawal**: current opioids, frequency of use, last use PTA, g/d or \$ spent/d, recent withdrawal
 - Assess **treatment readiness**: treatment hx (medications, counseling, mutual-aid organizations), social circumstances (housing, food security, legal issues). Understand patient's current goals, including safer use vs abstinence
 - Assess for **high-risk injection practices**: history of bacterial/fungal complications (endocarditis, SSTIs, bone/joint infections), viral complications (HIV, HCV, HBV). If currently injecting, use [PCOI harm reduction conversation guide](#) to review injection practices. Consider PrEP for patients with high-risk injection practices (see [HIV/AIDS](#))
 - Assess **risk of overdose**: h/o OD, ↓ tolerance from recent incarceration or abstinence-based treatment, access to naloxone, high-dose Rx'd opioids and/or other sedatives (check PDMP), injection use ([Addiction 2015;110:996](#))
- Labs: serum/urine tox (must specify fentanyl), LFTs, HIV, HBV/HCV, TB, syphilis, EKG. **NB**: urine fentanyl may take days to result
- **Pain control**: pts w/ OUD and/or chronic opioids likely have developed tolerance and require high doses of opioids to treat pain
 - If using non-prescribed opioids: can initiate methadone for withdrawal & add short-acting opioids titrated to pain
 - If taking methadone: give usual dose once confirmed & add short-acting opioids (e.g. oxycodone) titrated to pain
 - If taking buprenorphine: there are several strategies:
 - For pain of short duration, may continue daily bup & add short-acting opioids (may need high doses, consider PCA)
 - Give TDD of bup divided 3-4x daily (e.g. 4-8mg q6-8h for mod-severe pain)
 - D/c bup & use short-acting opioids to tx acute pain. Blocking effects of bup wear off after 24-72h, so monitor for OD (initial opioid dose is higher than pt will need). After pain resolved, re-start bup ([CMAJ 2016;188:1232](#); [Annals 2006;144:127](#))

ACUTE OPIOID OVERDOSE (OD) ([NEJM 2012;367:1372](#))

- Signs: ↓ mental status, ↓RR, ↓tidal volume, miosis. Normal pupils do not exclude opioid toxicity → co-ingestions may be sympathomimetic/anticholinergic. Rare: hypoxic seizure. Acute toxicity is a clinical diagnosis; +tox screen does NOT confirm toxicity
- Acute stabilization: assess airway (mental status). If apnea and/or stupor, bag valve mask (with O₂). Administer **naloxone**
- **Naloxone**: goal is to improve mental status, SpO₂, and ensure RR>10, **NOT** to achieve normal level of consciousness
 - Dose: 0.04mg IV, if no response increase dose q2 min: → 0.5mg → 2mg → 4mg → 10mg → 15mg. Can administer intranasally or IM
 - Effect lasts 20-40min, but most opioids last longer. **OD can recur** after naloxone wears off so may need to **redose** or start gtt
 - NB: too much naloxone will precipitate opioid withdrawal. Consider diluting 0.4mg in 10cc saline and push 1cc q2-3min
 - If failing to respond, consider **intubation** (STAT RICU consult)
- Post-resuscitation: continuous O₂ monitoring, CXR (post-OD pulmonary edema does NOT respond to diuretics, may evolve to ARDS), APAP level. Examine skin for fentanyl patch. Consider naloxone gtt

ACUTE OPIOID WITHDRAWAL

- **Agonist treatment with buprenorphine or methadone** is first line treatment for opioid withdrawal and OUD. Should be offered to **every patient**. Long-term agonist therapy for OUD decreases **morbidity** and **mortality** ([BMJ 2017;357:j1550](#))
- S/Sx: dysphoria, restlessness, irritability, yawning, piloerection, mydriasis, rhinorrhea, lacrimation, myalgia/arthalgia, n/v/d, abd cramping. Onset: 6-12h after short-acting opioids, 24-48h after last methadone use, variable for fentanyl analogs (long half-lives)
- **Buprenorphine: high affinity partial agonist** with lower risk of respiratory depression/OD than methadone
 - Wait until **Clinical Opioid Withdrawal Scale (COWS)** >10, usually 10-12h after last heroin use/short acting opioids. **Avoid precipitated withdrawal**—rapid, intense withdrawal due to displacement of full agonist by partial agonist
 - First dose: 4mg/1mg (1/2 of an 8mg/2mg bup/nal tablet)
 - Second dose: if continued withdrawal sx, give another 4mg/1mg after 45-60min
 - Third dose: if recurrent withdrawal sx, give another 4mg/1mg after 6-12h
 - Maximum dose for Day #1 is 12mg buprenorphine (unless PDMP documented recent tolerance of higher doses)
 - Prescribe total from Day 1 for Day 2, then reassess later in the day. Can give additional 4mg/1mg for withdrawal symptoms. Max dose for Day #2 is 16mg buprenorphine
 - Microdosing (Bernese Method): start w/ small initial dose of bup (0.5mg) & incrementally increase dose & freq over 7-10d while pts continue other opioids (prescribed or recreational) until therapeutic bup dose (>8mg daily) achieved ([CMAJ 2020;192:E73](#))
- **Methadone: long-acting full agonist**. Check and trend EKG for QTc, use with caution with other QTc-prolonging meds
 - Day 1 initial dose: 10-20mg x1. COWS q2h: If <6 → observe; if 6-12 → 5mg dose x1; if ≥12 → 10mg dose x1. REQUIRED to call ACT if ≥40 mg daily dose
 - Day 2 Stabilization: Day 1 dose if COWS <6, increase by 20% if COWS 6-12
 - If not planning to transition to methadone maintenance, decrease dose by 20% per day
- If unable to initiate suboxone/methadone, offer symptomatic medications and short-acting opioids for pain:
 - Autonomic dysregulation: clonidine 0.1-0.2mg TID PRN (monitor BPs; avoid w/ 1st bup/methadone dose)
 - GI upset: Bentyl 10-20mg q6h PRN abd cramps; promethazine 25-50mg IM PRN N/V; loperamide 2mg PRN diarrhea
 - Anxiety: hydroxyzine 25mg q8h PRN or trazodone 50-100mg q8h PRN
- **Discharge**: ensure pts have **insurance**, **PCP**, **provider** to prescribe bup/nal or methadone, **list of shelters/needle exchanges**, **PrEP**
 - **Last dose letter** for patients on methadone maintenance (includes date/amount of last methadone dose)
 - **Prescribe naloxone and teach** OD response. Emphasize that naloxone reverses OD for ~30min. After OD → **EMS** to the ED
 - **Bridge clinic**: call 617-643-8281 Mon-Fri 8am-4pm to schedule appt or present as walk-in

Psychiatry

Other Substance Use

TOBACCO (USPSTF: [Annals 2015;163:622](#); [JAMA 2021;325:280](#))

- **Screen:** all adults w/ **5A's** framework: Ask about use, Advise to quit, Assess readiness, Assist if ready, Arrange follow up
- **Treatment:** for those ready to quit, combination of counseling and medication is most effective ([Cochrane Rev 2016](#))
 - Set a **quit date**, typically in 2-4w. Abrupt cessation more effective than taper ([Annals 2016;164:585](#))
 - **Counseling:** individual, group, cessation coach, telephone support lines; [smoking cessation resources](#) at MGH
 - **Pharmacotherapy:** start **varenicline** or **buproprion** 1-2w prior to quit date; can continue for duration of 3-6mo; can also monitor tobacco consumption while on pharmacotherapy to see decrease in use (**harm reduction approach**)
 - **Varenicline:** 0.5mg qd x3d → 0.5mg BID x4d → 1mg BID. **SEs:** nausea, insomnia/vivid dreams; avoid if hx PTSD/SI; monitor for signs of neuropsychiatric symptoms (behavior changes, agitation/hostility, depressed mood, SI/SA)
 - **Nicotine Replacement Therapy (NRT):** long acting (patch) + short acting (lozenges/gum); efficacy >6mo not established
 - **Buproprion:** 150mg qd x3d → 150mg BID. **SEs:** insomnia, agitation, HA, dry mouth. **Cl:** seizure disorder/predisposition
 - **E-cigarettes:** evidence to suggest ↑ quit rates > NRT or usual care ([Cochrane Rev 2020](#)). FDA approved therapies should be prioritized; unclear SEs. May be a helpful harm reduction tool if other therapies trialed/refused

CANNABIS

- **Intoxication:** euphoria followed by relaxation; tachycardia; hallucinations (especially w/ high potency THC, e.g. wax/dab)
- **Cannabinoid hyperemesis syndrome:** chronic upreg GI cannabinoid receptors; recurrent n/v, abd pain; **sx relief w/ hot showers;** mild leukocytosis. **Tx:** IVF, antiemetic, THC cessation; consider BZD, antipsychotic, capsaicin ([J Med Toxicol 2017;13:71](#))
- **E-cigarette or Vaping Associated Lung Injury (EVALI):** dx of exclusion in respiratory failure <90d after e-cigarette use. GGOs in b/l lung fields; BAL with lipid laden macrophages. Thought to be due to Vitamin E acetate in THC cartridges ([NEJM 2020;382:903](#))

BENZODIAZEPINES

- **Intoxication:** memory impairment, disinhibition, psychomotor retardation, depression, may be amplified with concurrent EtOH use
- **Withdrawal:** ↑ anxiety, irritability, tremor, HA, nausea, autonomic instability, photo/phonophobia, seizures, paranoia, hallucinations, depersonalization, and delirium. Duration depends on half-life of agent, ranges from 2-10d ([NEJM 2017;376:1147](#))
- **Tx:** manage severe w/d inpatient, use BZD protocol (see [Alcohol Withdrawal](#)); consider taper with same BZD used; abstinence syndrome weeks after cessation: anxiety, tachycardia, restlessness

Commonly Used BZDs	~ Comparative Dosages	~ Half-life (hours)
Alprazolam (Xanax)	0.5mg	6-27 (oral peak 1-2)
Chlordiazepoxide (Librium)	25mg	5-30 (oral peak 0.5-4)
Clonazepam (Klonopin)	0.25mg	18-50 (oral peak 1-2)
Diazepam (Valium)	5mg	20-50 (oral peak 0.5-1)
Lorazepam (Ativan)	1mg	10-20 (oral peak 2-4)
Temazepam (Restoril)	10mg	3-19 (oral peak 1-2)

COCAINE

- **Intoxication:** grandiosity, euphoria, hyperactivity, anorexia, anxiety, psychotic sx (formication, paranoia, AH/VH), fever, mydriasis
- **Withdrawal:** depression, fatigue, nightmares, cravings, ↑ sleep/appetite. **Tx: Acute:** supportive care, BZD for severe sx; **Chronic:** consider topiramate and/or baclofen for cravings/dependence ([consult ACT](#)) ([Psychiatry 2005;2:44](#))
- **Complications:** **Acute:** vasospasm inducing HTN emergency (**Tx:** BZD, phentolamine if refractory, nitroglycerin; avoid βB), ACS (**Tx:** ASA, nitro, BZD), dysrhythmia, ischemic bowel; **Chronic:** LVH, cardiomyopathy ([NEJM 2001;345:351](#))
 - **Snorting:** nasal septum perforation, ulcers, and chronic rhinitis. **Inhalation:** cough, SOB, hemoptysis, and PTX. **"Crack Lung":** syndrome of fever, hemorrhagic alveolitis, respiratory failure, eosinophilic infiltration thought d/t levamisole additive
 - May include other **additives** or **adulterants**, including fentanyl

SYNTHETIC CANNABINOIDS (SPICE/K2/BATH SALTS)

- **Intoxication:** agitation/violence, hallucinations, paranoia, anxiety, tachycardia, arrhythmia, myoclonus, diaphoresis
- **Tx:** low stimulation environment, IVF, consider IV BZD to reduce agitation and prevent seizure ([Curr Psychiatry Rep 2016;18:52](#))

MGH TOX SCREENS: can be clinically useful at admission if hx of use or cause of AMS is unclear

- **Basic serum toxicology screen:** quantitative assays for EtOH, salicylates, acetaminophen; qualitative assay for TCAs
- **Urine toxicology screen:** amphetamines, barbiturates, BZDs, THC, cocaine, opiates, phencyclidine
 - **Urine test characteristics:** refer to tables for [detection times](#) and [cross reactivity](#) ([Mayo Clin Proc 2008;83:66](#))
- **VPAIN ("urine pain panel"):** buprenorphine, oxycodone, methadone, 6-monoacetyl morphine (heroin metabolite)
- **Urine fentanyl:** can take days—send for suspected overdose (e.g. PEA arrest) given prevalence of synthetic fentanyl analogues
- **Oral fluid drug test:** differentiates TYPE of benzo (e.g. lorazepam vs diazepam), opiate (codeine vs heroin), amphetamine
- **Drug screen, prescription/OTC ("full tox"):** send out to Mayo, will take >3d to return
 - **Tests extensive # of medications:** common OTCs, AEDs, propofol, TCAs, SSRI/SNRIs, bupropion, phenothiazines, clozapine, muscle relaxants, sleep meds, lidocaine, trazodone, theophylline, some pesticides (full list: [Mayo Lab Handbook](#))
 - **Limited use for illicit drugs:** benzos, some opiates (incl. codeine, meperidine, methadone, oxycodone, fentanyl), amphetamines
 - **Drugs NOT on screen:** cocaine, lithium, digoxin, ethylene glycol, iron, lead ([order separately and note some are send-outs](#))

Primary Care

Health Screening & Maintenance

GENERAL SCREENING GUIDELINES [Evidence Grade] (^aUSPSTF, ^bADA, ^cAACE, ^dACC/AHA, ^eACCP, ^fACS)

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+														
Cardiovascular Screening/Preventative Health Recommendations																													
CVD Risk	Assess RFs q4-6y [B] ^d (age, sex, Tchol/HDL, HTN, DM, CKD, smoking, FHx)						Estimate risk w/ ASCVD calculator q4-6y [B] ^d If ASCVD risk ≥20% consider high intensity statin* [B] ^a																						
ASA for 1° ppx ^a							Low dose ASA in adults 40-70 with higher ASCVD risk but not higher bleeding risk ^b [A] ^d						Not rec for adults >70 [B] ^d																
DM	If HTN or BMI ≥25 (≥23 Asian) w/ ≥1 DM RF ^a , or GDM [B] ^b						A1c Q3y. ↓ interval if abnl result, ✓ annually in pre-DM ^b																						
HTN	Q3-5y; Q1y if BP >135/90, obese, AA [A] ^a						Q1y [A] ^a																						
HLD	Screen once in age <20	Men 20-45, women 20-55: screen Q5yr, ↑ if RF [C] ^c Q1y in DM [B] ^c						Men >45, women >55 Q1-2y if no RF* [A] ^c , Q1y in DM [B] ^c						Screen Q1y [A] ^c															
Obesity	Annual BMI [C] ^d → refer for or offer comprehensive lifestyle program if ≥25 (overweight) [B] ^d																												
Diet	Intensive behavioral counseling if CVD RF* [B] ^a																												
Exercise	150min/wk moderate-intensity exercise or 75min/wk intense-exercise & 2d of muscle strengthening activity [A] ^d																												
Universal Cancer Screening																													
Colorectal CA	Start 10y prior to age of affected family member at dx**						Colo Q10y, flex sig q5y, FIT q1y [A] ^a						+/-**																
Lung CA							Q1y low-dose CT if 20 pack-yrs & current smoker or quit w/in last 15y [B] ^a																						
Skin CA	Insufficient evidence for routine clinical skin exams [I] ^a																												
Infectious Disease Screening																													
HIV	Screen at least once; repeat based on risk assessment [A] ^a																												
HCV	Screen all 18-79 at least once; repeat based on risk assessment [B] ^a																												
HBV	Born in endemic region, getting HD or immunosuppressed, HIV+, IVDU, MSM, close contact w/ HBV+ person [B] ^a																												
Latent TB	Screen if born or lived in high risk country (see USPSTF recs) or high risk setting (homeless, jail) [B] ^a																												
Psych/SUD/Social Risk Factor Screening																													
Depression	Q1y [B] ^a by PHQ-2: in 2w how often (a) little interest/pleasure doing things & (b) down/depressed/hopeless (JAMA 2020:323:2290)																												
Alcohol	Screen regularly with AUDIT-C [B] ^a																												
Tobacco	Every encounter [A] ^a . Advise to quit, Assist doing so (plan, quit date, QuitWorks, meds), Arrange f/u. Strong evidence to start varenicline (Chantix) over other tx options, despite psych comorbidities or readiness (Am J Respir Crit Care Med. 2020;202:e5)																												
Unhealthy Drug Use	Screening for unhealthy drug use is beneficial when services for accurate diagnosis, effective treatment, and appropriate care can be offered (JAMA 2020:323:2310)																												
IPV	Screen regularly in women of reproductive age [B] ^a . Use HITS tool . Assess immediate safety & consider HAVEN referral						Consider screening for ongoing IPV, elder abuse screening																						
Fall Risk	PT, Vit D [B] ^a																												

*If ASCVD borderline risk (5%-7.5%) or intermediate risk (7.5%-20%) use risk-enhancing factors (FHx, LDL-C ≥160, metabolic syndrome, CKD, S. Asian race/ethnicity, chronic inflammatory disease including HIV, menopause <40y, pre-eclampsia or pre-term delivery, abn biomarkers (e.g. hsCRP, Lp(a), apoB, ABI)) or coronary artery calcium score to guide decision about statin (see [Outpatient CV Health](#))

⁵ History of previous GIB or PUD or bleeding from other sites, thrombocytopenia, coagulopathy, CKD, and concurrent use of other medications that increase bleeding risk (NSAID, steroids, DOACs, Warfarin)

[^]DM RFs: prior abnl testing (A1c≥5.7), FHx, AA/Latinx/Asian/NA ancestry, Hx GDM, PCOS, CVD, HDL<35 or TG>250, physical inactivity

^{**}Age 40: ≥1st degree relative dx<65; Age 45: AA/1st degree relative dx<65; Age 50: expected to live >10y; 75+: based on life expectancy

ADDITIONAL SCREENING GUIDELINES FOR MEN [Evidence grade] (^aUSPSTF, ^fACS, ^gEndo)

Age	18-40	40	45	50	55	60	65	70	75+
AAA								If +tobacco hx [B] ^a	
Prostate CA*		FHx** Q2y ^f	FHx, AA Q2y ^f	Screen all men Q2y if life expectancy ≥ 10-15y ^f			PSA 55-69/y if pt preference [C] ^a ,	recommend against if >70y [D] ^a	
Testicular CA	<i>Recommend against</i> routine screening in all men [D] ^a								
Anal CA	In MSM: Q1y if HIV+; consider Q2-3y >30 if HIV- (Lancet Oncol 2012;12:487)								
Osteoporosis							If RF ^g	DXA ^g	
STIs	In MSM: Q1y, Q3-6mo if multiple/anonymous partners or sex in conjunction w/ drug use								

*All patients should be informed of the uncertainties, risks, and potential harms prior to deciding if they would like to use PSA screening

** >1 first-degree relative with history of prostate cancer

[^]Low body weight, prior fracture, smoking

Primary Care

Health Screening & Maintenance

ADDITIONAL SCREENING GUIDELINES FOR NON-PREGNANT WOMEN [Evidence grade] (eUSPSTF, fACS)

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+
Breast CA*															
Cervical CA**								Q5y 1° HPV testing (preferred if available); if not available, Q5y cytology + HPV co-testing OR Q3y cytology alone ^f		Individualized screen by risk (Gail Model)		Q2y mammogram age 50-74. Stop if <10y life expectancy. [B] ^a			
								Q3y cytology [A] ^a		Q5y 1° HPV testing, Q5y cytology + HPV co-testing, OR Q3y cytology alone [A] ^a			Stop ^Σ		
STIs	≤24: GC/CT annually [B] ^a														Screen based on risk assessment
Contraception															Discuss with everyone (see Women's Health for contraception guidelines). Start folic acid at reproductive age if planning/capable of pregnancy [A] ^a
Osteoporosis															Consider earlier screening based on FRAX assessment [B] ^a DXA [B] ^a

*Considerable discrepancy between societal guidelines created using the same evidence. USPSTF: biannual screening age 50-74 [B]; discussion of risks/benefits age 40-49 [C]; no recommendation for women >75 [I]. ACS: annual mammography age 45-55; discuss transitioning to biennial screening at 55 until life expectancy <10y; discuss initiation of annual screening at age 40. ACOG: offer mammography at 40; start screening at 50; discuss cessation at 75; screen Q1-2 years

^aDiscrepancy between USPSTF and ACS recommendations is likely due to when they were published (2018 and 2020, respectively). ACS explains that recommendations are evolving to eliminate cytology and focus on 1° HPV testing alone

**Important to screen all individuals with a cervix including transgender men. Use [ASCCP Web App](#) for algorithm of next steps

^Σ Stop if 3 consecutive neg paps or 2 consecutive neg co-tests within 10y w/ most recent test within 5y. Continue x20y s/p dx pre-cancerous lesion regardless of age. Do not resume age ≥65 for new sexual partner only

ADDITIONAL SCREENING GUIDELINES FOR TRANSGENDER INDIVIDUALS

Age	18-40	40	45	50	55	60	65	70	75+
CVD Risk									
Osteoporosis									
Breast CA									
Cervical CA									
Prostate CA									

^aCells more likely to be "unsatisfactory" for interpretation on testosterone. On order, note that pt is on testosterone and/or amenorrheic. Self-collected vaginal swabs as sensitive as provider-collected swab ([PLoS 2018:13](#))

VACCINES (CDC)

Immunizations	19-21	22-26	27-49	50-64	≥65
Influenza	1 dose annually (inactivated, recombinant, or live)			1 dose annually (inactivated or recombinant)	
	<i>No live (intranasal) if immunocompromised (or contact), pregnant, asplenia, cochlear implant, CSF leak</i>				
Tdap/Td			1 dose Tdap then Td booster every 10 years. <i>Extra dose of Tdap during each pregnancy</i>		
MMR*		1-2 doses based on indication (if born 1957 or later)			
	<i>1 dose in ♀ of childbearing age; 2 doses if HIV & CD4≥200, healthcare personnel, or college students</i>				
Varicella*			2 doses (if born 1980 or later)		
Zoster*				2 doses (recombinant = RZV) <i>If >60, RZV preferred but can give live = ZVL x1 instead</i>	
HPV**	2-3 doses	With SDM			
PCV13/PPSV23	- CSF leak, cochlear implant, nephrotic syndrome, CKD, HIV, anatomic or functional asplenia, immunocompromised, malignancy, solid organ transplant: PCV13 x1 → PPSV23 8w later → PPSV23 5y later (ø 3rd dose in CSF leak/cochlear implant) - Chronic heart, lung, or liver dz; DM; AUD; or smoking: PPSV23 x1			- If never vaccinated: 1 dose PPSV23. SDM re: PCV13. If both, give 1y apart, PCV13 first - If previously vaccinated: PPSV23 x1 >5y from last dose	
Hep A	Travel to endemic country, HIV, MSM, any drug use (not just IVDU), chronic liver dz, undomiciled, work w/ HAV, close contact to international adoptee, settings for exposure, pregnancy at risk for infxn: 2 doses				
Hep B	Travel to endemic country, HIV, sexual exposure risk, IVDU, chronic liver dz, incarcerated, mucosal or percutaneous blood exposure (incl dialysis, DM <60y, work exposure), pregnancy w/ infxn risk: 2 doses				
Meningococcus** (MenACWY/MenB)	Functional or anatomical asplenia, HIV, ↓ complements (including by meds), travel to endemic country, freshmen in dorms, military recruits: 1-2 doses + Q5Y if risk remains (add MenB for asplenia, ↓ complements + Q2-3Y if risk remains)				
Hib	Functional or anticipated asplenia: 1 dose (if no prior); after HSCT: 3 doses (regardless of vaccination hx)				

*Hold live vaccines in pregnancy, malignancy, and immunocompromised (incl HIV w/ CD4 <200, cochlear implant). Ok if CD4 ≥200

**Wait until after pregnancy

Primary Care

Transgender Health

GENERAL CONSIDERATIONS ([NEJM 2019;381:2451](#))

Gender Terminology

- Gender identity: internal sense of one's gender vs sex assigned at birth: based on DNA, or external (sometimes internal) anatomy
- Transgender/trans: sex assigned at birth and gender are not congruent vs cisgender: sex assigned at birth and gender are congruent
- Non-binary, gender non-conforming, genderqueer: gender identity, role, or expression differs from society's M/F binary

History: use "Sexual Orientation/Gender ID" and "Demographics" activities in EPIC to update patient header w/ chosen name/pronouns

- Gender identity data: chosen name and pronouns, current gender identity + sex listed on original birth certificate (two-step method)
- Organ inventory: guides screening and physical exam. Note natal and surgical anatomy. Confirm patient's preferred terms for organs
 - CA screening: if natal tissue present (even s/p surgery), screen per guidelines for biological sex regardless of hormone tx
 - Include natal organs in ddx: e.g. PID, fibroids, endometriosis in trans ♂ w/ uterus/fallopian tubes; prostatitis in trans ♀
- Sexual history: who are you having sex with? What types of sex are you having? What parts of your anatomy do you use for sex?
 - Trans ♀ may have ↓ penile size after hormone tx making condoms difficult. Encourage condoms after phalloplasty as well
 - PrEP effective in trans ♀ and ♂ when taken as prescribed; no known drug-drug interactions with hormone tx
 - Self-collected rectal and vaginal swabs as sensitive as provider-collected swabs for STIs and HPV ([PLoS 2018;13](#)); can help individuals who may have gender dysphoria regarding genitalia and want to avoid an invasive exam

Physical Exam Considerations

- Skin: acne, hair, irritation/infection 2/2 chest binding or penile/scrotal tucking, tattoos at potential skin flap sites, silicone injections
- Abd: hernial complications from tucking
- GU: pelvic exam in trans ♂ can be traumatizing and painful 2/2 vaginal atrophy on testosterone. Tips: 1-2w vaginal estrogen before exam; start w/ external/digital exam; pediatric speculum; clearly describe every step; consider PO benzos 1h before; self-swab if poss.

GENDER-AFFIRMING CARE ([WPATH Standards of Care](#); [UCSF Center for Excellence in Transgender Health](#); [Fenway Guide](#))

Gender dysphoria: discomfort or distress 2/2 discrepancy between gender identity and sex assigned at birth. May be functionally limiting

- **Affirm gender identity and explore options below for expression of identity and alleviation of gender dysphoria**
 - Psychotherapy: safe space to explore gender expression, confidence in new role, coming out, mental health impact of internalized transphobia, social support, body image, strategies for resilience. Not required to pursue hormone tx or surgery
 - Changes in name and gender marker on identity documents; voice and communication therapy; hair removal; chest binding or padding; genital tucking or penile prostheses; padding of hips or buttocks; hormone tx; surgery

Hormone therapy ([J Clin Endo Metab 2017;102:3869](#)): no RCTs comparing relative efficacy/safety between regimens

- Requires informed consent and well-documented gender dysphoria (not necessarily by a mental health professional)
- Anticipatory guidance: full effects can take 1-5y. Dose titration requires frequent labs and visits in the first year
- Feminization: 17-beta estradiol (PO/SL, transdermal patch, IM) + androgen blocker (spironolactone/leuprolide, to ↓ estrogen dose)
 - +/- 5-alpha reductase inhibitor (MRA intolerance, desire for partial feminization, virilized features after androgen blockade)
- Masculinization: Testosterone (PO, topical gel/transdermal patch, IM/SQ). Progestins/GnRH agonists early on may help stop menses
- Infertility typical: often but not always reversible. Discuss fertility preservation (egg/embryo freezing, sperm banking) before starting tx
- Testosterone ≠ contraception. If gonads present and sexual activities could result in pregnancy, discuss birth control
- When monitoring treatment, indicate hormonal sex in lab requisition and interpret values using ranges for hormonal, not natal, sex
- Reasonable to provide 1-6mo of bridge Rx if patient is already on hormones and then refer to another provider who can prescribe

	Contraindications	Potential Risks	Irreversible changes	Reversible changes	Monitoring
Feminization	- Absolute: estrogen-sensitive neoplasm, ESLD	- VTE* - Gallstones - ↑TG*, liver enzymes - HTN - ↑prolactin (y1) - If RF: CAD, DM - Migraines	- Breast growth - Testicular atrophy - Redistribution of fat mass	- ↓ muscle mass - Weight gain - Hair/skin softens - ↓ sex drive - ↓ libido, erections	- If spironolactone: BP, BUN/Cr/K 0/3/6/12mo, then q1y - total testosterone, estradiol q3-6mo until at goal, then q1y - prolactin PRN if sx
Masculinization	- Absolute: ACS, polycythemia (Hct >55%), pregnancy - Relative: breast cancer or estrogen-sensitive neoplasm	- Erythrocytosis* - HLD*, ↑liver enzyme - Sleep apnea - If RF: HTN, DM, CVD, psych d/o destabilization	- Deepening of voice - Facial and body hair - Clitoromegaly - Breast and vaginal tissue atrophy - Male-pattern baldness**	- Menses cessation - ↑ sex drive - ↑ muscle mass - Possible acne, mood changes	- Before tx: urine HCG, PCOS screen - CBC 3/6/12 mo, then q1y - total testosterone q3-6mo until at goal, then q1y

*Possibly attenuated by transdermal preparation

^Strongly encourage smoking cessation to attenuate risk. Consult [UCSF guide](#) for risk-benefit analysis after VTE

**Treatment with 5-alpha reductase inhibitors may reverse some testosterone effect

Surgery: may require 12mo hormone tx and support letter from a mental health provider

- Feminization: vaginoplasty, mammoplasty, voice feminization surgery, thyroid cartilage reduction, penectomy, orchiectomy
 - Pre-op: no evidence to stop hormone therapy in otherwise low-risk transgender women
 - Post-op considerations: tissue necrosis, fistulae, urethral stenosis, UTIs, urination problems, anorgasmia; regular vaginal dilation/penetrative intercourse to maintain vaginal depth and width
- Masculinization: mastectomy, phalloplasty, metoidioplasty, scrotoplasty, hysterectomy, oophorectomy
 - Post-op considerations: tissue necrosis, urinary tract stenoses/fistulae, flap loss

Primary Care

Women's Health

VULVAR/VAGINAL CONCERNs ([Obstet Gynecol 2020;135:e1](#); [Obstet Gynecol 2020;136:222](#))

	Presentation	Dx	Tx
Vaginitis	Bacterial vaginosis (BV): most common; malodorous discharge, often asx; RF = new/mult partners, smoking, WSW Recurrent: ≥3x/yr	-Amsel criteria (≥3): 1) homogeneous, thin, grey-white discharge ; 2) clue cells ; 3) fishy odor on KOH; 4) pH >4.5 (less reliable if post-menopause) -Wet prep or " Genital culture female " at MGH for GS (collect w/ rayon swab). Nugent score 7-10 = BV	Metronidazole (PO 500mg BID x7d or vaginal 0.75% x5d), clinda (PO 300mg BID x7d or vaginal 2% x7d) Recurrent: Metrogel x10d, followed by 2x/w maintenance for 4-6mo
	Candida: curd-like discharge, no odor, pruritus, vulvar erythema ± edema, dysuria, dyspareunia Complicated: ≥4x/yr, severe sx, non- <i>C. albicans</i> , hx DM or immunosuppr.	-pH <4.5 (normal), KOH microscopy -" Genital culture female " or yeast culture for fungal sensitivity if recurrent	Fluconazole 150mg PO x1, miconazole 2% x7d if pregnant. Complicated/recurrent: fluc 150mg q72h x3; intravaginal boric acid for <i>C. glabrata</i> , azole cream for <i>C. krusei</i>
Other infections: Trichomonas, Gonorrhea, Chlamydia, HSV - see STI			
Pain or Discomfort	Vulvodynia: general or local pain, provoked or unprovoked, >3-6mo	Q-tip test to localize pain, exclude other etiology	TCA, gabapentin, lidocaine 5% before sex, steroid/lidocaine inj., sitz bath
	Genitourinary Syndrome of Menopause: vaginal dryness; pain w/ intercourse; thin, pale mucosa	Vaginal pH >4.5, parabasal cells on wet mount/GS	Topical estrogen (insert, ring), lubricants (prior to intercourse), Replens moisturizer, ospemifene
Vulvar Dermatoses	<ul style="list-style-type: none"> Contact dermatitis: erythema, swelling, fissures, erosions → r/o Candida, remove offending agent Lichen simplex chronicus: intense pruritis + lichenified plaque → antihistamines, topical corticosteroids Lichen sclerosus: onset 50-60s, pruritis, irritation, dysuria, dyspareunia; perianal or vulvar white, atrophic papules lead to skin thinning, labia minora fusion, & clitoral hood phimosis. 5% incidence malignancy → bx to confirm; clobetasol 0.05% taper (qd x4w, qod x4w, 2x/w x4w), vulvar hygiene, monitor for SCC Lichen planus: onset 50-60s, pain/burning, "purple, papular, pruritic," white lacy striae, vaginal involvement, ↑SCC risk → bx to confirm & r/o malignancy; high potency steroids, monitor for SCC 		

URINARY INCONTINENCE

- Very common (25% of young women, 75% of older women); under-reported
- Types:** **stress** (involuntary leakage w/ cough, laugh), **urge** (leakage w/ urge), **mixed** (stress + urge), **overflow** (incomplete emptying, constant dribble), & **functional** (impaired mobility/cognition/neurologic); **DDx:** UTI, vaginal atrophy
- History:** systemic sx (fevers, dysuria, pain), **meds** (anticholinergics, diuretics, etc.), bowel habits, **caffeine/EtOH use**, voiding diary
- Exam:** check for prolapse, cough/valsalva stress test (can be supine, but standing w/ full bladder ↑Sn); rectal exam (fecal impaction, sphincter tone); neuro exam; **Dx:** UA/Cx, **PVR** (abnl >150cc); urodynamic studies not indicated
- Initial tx** (see [PCOI handout](#)): incontinence products, **bladder training** (timed voiding), **lifestyle interventions** (e.g. wt loss, ↓fluid/caffeine intake), **pelvic floor exercises** (e.g. Kegels; pelvic floor PT). **Stress/mixed:** **pessary, vaginal estrogen** (for vaginal atrophy), **surgery**. **Urgency:** **antimuscarinics** (many SE), **β-agonists** (e.g. mirabegron) – monitor for urinary retention
- Refer to Urogyn if:** hx surgery/radiation, c/f mass/pain/prolapse, no response initial tx, abnl PVR, pessary/surgery/intravesicular botox

MENOPAUSE ([J Clin Endo Met 2015;100:3975](#))

- Amenorrhea x12mo w/o alt etiology (no need to ✓ labs, can help s/p hysterectomy), avg onset at 51, suspect 1° ovarian insuff if <40
- Vasomotor sx** (hot flashes): usually resolve in 2-3mo. **First try:** SSRI/SRNLs (paroxetine best), gabapentin. **Systemic hormones** (estrogen + progestin, estrogen mono-Rx if hysterectomy) most effective tx, *only recommended if <60yo, <10y since onset, & <5y duration. Avoid if:* hx or >10% risk CVD, hx/high risk of breast CA/endometrial CA, hx VTE/CVA/TIA, active liver disease, unexplained vag bleeding. **Side effects:** breast tenderness, vag bleeding; ↓CRC, fracture risk; ↑breast CA, CVD, VTE (equivocal if ↑risk attenuated with topical Tx); Ø ↑risk of mortality after 5-7y ([JAMA 2017;318:927](#))
- Vaginal/vulvar sx** (now called **genitourinary syndrome of menopause**): see above; underreported but common, always ask
- Psych sx:** sleep disturbance, poor concentration, new-onset depression. May improve with Rx for vasomotor sx

AMENORRHEA ([AFP 2019;100:39](#))

- In adults, most commonly **2° amenorrhea**: cessation of regular menses for 3mo **or** cessation of irregular menses for 6mo
- Hx:** wt Δ, diet/exercise, hot flashes, galactorrhea, hirsutism, stress, systemic illness; **Initial labs:** HCG, FSH, LH, E2, TSH, PRL
- DDx:** pregnancy, hypothalamic (eating disorder, excess wt loss/exercise, stress, prolonged illness), pituitary (hyperprolactinemia 2/2 adenoma, mass effect, meds, breastfeeding, apoplexy), ovary (1° ovarian insufficiency, PCOS), uterine (prior instrumentation → scar = Asherman Syndrome), other (hypo/hyperthyroidism, DM, celiac, excess androgens [exogenous, Cushing's])
- If nl/low FSH, consider **progesterin challenge**: medroxyprogesterone acetate 10mg x10d. If Ø withdrawal bleed, suggests uterine abnl

POLYCYSTIC OVARY SYNDROME (PCOS) ([J Clin Endo Met 2013;98:4565](#))

- Affects 5-10% of women of reproductive age; often comorbid w/ CVD, DM, HTN, NAFLD, HLD, OSA, depression, and anxiety
- Rotterdam Criteria** (need 2/3): 1) oligo/anovulation, 2) clinical/biochemical hyperandrogenism, 3) polycystic ovaries on pelvic U/S
- Workup:** exclude other dx (hCG, 17-OHP [pre-8AM], prolactin, TSH); DHEAS, total **testosterone**, SHBG to confirm if dx unclear
- Tx:** wt loss, exercise, combined **OCP** (2nd line = oral progesterone or levonorgestrel-IUD), spironolactone, metformin (if insulin resistant), fertility referral if desired

Primary Care

Women's Health

PRECONCEPTION COUNSELING/INFERTILITY ([Fertil Steril 2015;103:e44](#))

- Preconception counseling (PCOI):** avoid tobacco, EtOH, drugs; multivitamin qd w/ 400-800mcg folic acid; review immunizations (Rubella, Varicella, HepB); optimize mgmt of wt, thyroid (TSH goal 0.5-2.5, recheck after conception), HTN (avoid ACEi, check b/l UACR/UPCR & Cr), DM (↑risk birth defects; metformin/insulin first-line), mood (avoid paroxetine; SSRI safety debated, engage psych to weigh risk of relapse w/ risk to fetus), VTE (LMWH preferred), asthma, OUD (methadone & suboxone safe in pregnancy)
- Infertility:** evaluate after **12mo** unprotected intercourse in <35yo, **6mo** in >35, **3mo** in >40; fertility tx covered by insurance in MA
- Hx:** duration, prior OB/GYN hx (menstrual hx, pregnancies, PID, fibroids, abnl Pap, endometriosis, contraceptive use, DTE exposure), sexual hx (timing, frequency, lubrication, dyspareunia), hx chemo/XRT, meds, substance use, FHx. **Ddx:** see amenorrhea above
- Dx: ovarian reserve:** day 3 FSH/E2. **Additional workup:** STI screening, TSH, PRL, pelvic U/S, semen analysis, PCOS w/u
- Tx: fertility awareness** (intercourse qod cycle d9-14, or from 5d before to 2d after ovulation), avoid water-based lubricant, refer to **repro-endo** for other w/u, induction of ovulation, IVF, or donor oocytes

CONTRACEPTION ([CDC USMEC 2016](#), [CDC 2020 Summary](#)) Resource for patients: [bedsider.org](#)

- 45% of pregnancies are unplanned → r/o pregnancy before initiating contraception → **LARCs (IUD, implant) are most effective**
- Hormonal methods (including LARC) take ~1w to take effect → always recommend backup method (condoms) for 7d

Use	1y Failure Rate*	Pros/Cons	Contraindications (A: Abs, R: Rel)
Estrogen-progestin			
Combined Pill	Daily	9% (0.3%)	
Ring (Nuva-Ring)	3w in, 1w out	9% (0.3%)	-Pros: ↓menses, PMS, cramps, acne, endometrial/ovarian CA -Cons: n/v, breast tenderness, can ↑HTN/TGs, ↓libido, spotting for first few months, cannot start if <21d PP (VTE risk), requires pt adherence
Patch (Xulane, Ortho Evra)	Weekly x3w, 1w off; apply to arm, torso, or buttock	9% (0.3%)	A: -Hx VTE, thrombogenic mutation -Active breast or liver CA (or w/in 5y) -Migraine w/ aura, >35 yo & any migraine -Uncontrolled HTN, DM w/ vascular dz, CAD, CVD, valvular dz, ESLD, hx CVA ->35yo & >15 cig/d -Obesity (Xulane patch only)
Progestin-only			
IUD (hormone content Mirena/Liletta > Kyleena > Skyla)	Mirena/Liletta q6y Kyleena q5y Skyla q3y	0.2%	-Pros: effective, long-acting, lighter periods, may reduce cramping/anemia 2/2 menometrorrhagia, discreet -Cons: irregular bleeding , requires removal, physical complications (rare) -Pt preference: amenorrhea (~18%)
Implant (Nexplanon)	q3y to upper arm	0.05%	A (all): active breast CA or w/in last 5y A (IUD): abnl uterine cavity; unexplained vag bld; active STI, PID, endometritis at insertion; endometrial or cervical CA R (all): APLAS, ESLD, liver CA, breast CA >5y ago R (implant): unexplained vag bld R (injection): unexplained vag bld, CV RF, ischemic heart disease, PVD, uncontrolled HTN, DM w/ end-organ damage, CVA R (pill): malabsorption
Injection (Depo-Provera)	q3mo IM/SQ to arm, thigh, or buttock	6% (0.2%)	-Pros: long-acting, discreet -Cons: irregular bleeding ; temporary ↓LBM; prolonged return to fertility (1y); may worsen HA, acne, mood
Pill (Micronor)	Daily	8% (0.3%)	-Pros: no effect on breastfeeding -Cons: irregular bleeding ; must take at same time daily; HA, acne, mood sx
Hormone-free			
Copper IUD (Paragard)	q10y (effective 12-20y in practice)	0.8% (0.6%)	-Pros: effective, long-acting, safe in ESLD, emergency contraceptive -Cons: heavier bleeding, cramping
Male condom	Every encounter	18% (2%)	-Pros: STI prevention -Cons: requires pt adherence
Tubal Ligation / Vasectomy	Permanent	0.5% 0.15%	-Pros: available to men and women -Cons: irreversible

* Typical use – i.e. % women who will have unplanned pregnancy in 1 year on this method (perfect use in parentheses)

Oral Contraceptives (OCPs) ([Quick Start Algorithm](#)): start anytime (exclude preg + 7d backup method if not 1st day period)

- OCP selection:** estrogen (ethinyl estradiol) – 30-35mcg: less breakthrough bleeding. 20mcg: less estrogen SE. Progestin – **2nd gen** (levonorgestrel, norgestrel): ↓VTE risk. **3rd gen** (norgestimate, desogestrel): ↓androgenic SE, ↑VTE risk

Emergency Contraception ([Obstet Gynecol 2015;126:e1](#); PCOI)

- Plan B** (levonorgestrel 1.5mg x1 or 0.75mg q12h x2): OTC, use w/in 72h, less reliable if BMI >25. **Ella** (ulipristal 30mg x1): requires Rx, use w/in 120h, less reliable if BMI >30. **Paragard** (copper IUD): place within 120h (okay up to 160h), **most effective**
- In cases of sexual assault:** refer pt to ED for an exam by a trained SANE RN. If IPV: ask if partner has access to online medical records prior to detailed documentation and prepare safety plan. **MGH HAVEN referral: 617-724-0054**

ABORTION ([Obstet Gynecol 2014;123:676](#); [JGIM 2020;35:2398](#))

- See **PCOI** for list of providers in MA. Avg cost ~\$500, 50% pay out of pocket. Counseling: **1-866-4-EXHALE**
- Workup:** bHCG ± pelvic U/S to confirm intrauterine preg, CBC/Rh; offer STI testing & immediate post-abortion contraception
- Medical abortion** (<10wks gestation, 95-98% effective): PO mifepristone x1 → buccal misoprostol in 24-48h → pt passes pregnancy at home over hrs. May experience cramping and bleeding. Tx with NSAIDs. F/u bHCG or pelvic U/S in 7-14d
- Surgical abortion** (<24wks gestation, 99% effective): same-day office procedure → no f/u unless complications

Primary Care

Postpartum & Sleep Medicine

POSTPARTUM CARE (ACOG Postpartum Toolkit, 2018)

Key Screening Items: proactive questions and anticipatory guidance about nl vs abnl mitigates complications and worry

- **Vaccines:** recommend all contacting baby receive flu & Tdap to protect baby, who cannot be vaccinated; all vaccines safe while breastfeeding except smallpox (give yellow fever and MenB only if benefits > risks)
- **Contraception:** can start progestin-only options (IUD, implant, injection, pills) immediately postpartum & estrogen-containing options 21-28d postpartum (42d if VTE risk factor). Lactation prevents pregnancy only if mom almost fully breastfeeding & amenorrheic
- **Breastfeeding:** see [Lactmed](#) for restarting medications. Challenges: nipple pain (tx lanolin, breast shield), plugged ducts (aspiration if >72h), inadequate milk supply, mastitis (10% breastfeeding mothers; assoc w/ edema, erythema, ± fever/chills; if c/f infection, r/o abscess w/ exam (tx w/ I&D) and Rx dicloxacillin or keflex; encourage continued breastfeeding). Consider referral to lactation consultant. Remind mom federal law requires break time & dedicated space at work for lactation
- **SUDs/Analgesia:** postpartum period high risk for SUDs relapse. Methadone & buprenorphine safe w/ breastfeeding, should be continued. Screen for AUD. Encourage smoking cessation (pt & all household members). Acetaminophen and ibuprofen safe during breast feeding; avoid NSAIDs if HTN. Butorphanol, morphine, hydromorphone are preferred opioids if needed
- **Common sx (often self-resolve):** vaginal soreness & discharge, constipation, hemorrhoids, cramps, breast engorgement, urinary/fecal incontinence, hair loss (w/in 5mo), mood swings ("baby blues")
- **Persistent vaginal bleeding:** normal to have small amount of red-tinged discharge for 1-2w PP (w/ red, heavy discharge for 1-2d); if soaking through pad/tampon in <1h ± pain, fever, tenderness, may be signs of infection, refer to ED
- **Perineal pain, dyspareunia, and sexual dysfunction:** >10% report pain 1y post-vaginal delivery (RF = 3rd/4th degree tears, operative delivery, vaginal atrophy while breastfeeding). Tx: water-based lubricants, topical estrogen, pelvic floor therapy, scar tissue ablation. Decreased libido common and normal (50% at 3mo, 30% at 6mo)
- **Postpartum depression:** w/in 12mo after birth; incidence of 11-20%; screen with [PHQ9](#), Postpartum Depression Scale, or [Edinburgh Postnatal Depression Scale](#); tx with peer counseling, CBT, SSRI

Pregnancy-Related Complications of Cardiovascular Disease and Endocrinopathies

- Postpartum period high risk for: flares of underlying autoimmune disease, peripartum cardiomyopathy
- Excessive gestational weight gain, obesity, preterm birth (<32w) ↑risk for CVD in mom; screen annually for modifiable RF

	Future Risk	Postpartum Screening	Risk Mitigation
Gestational Diabetes/ Diabetes	- ↑risk of recurrent GDM, pre-DM, T1DM, T2DM (7x higher), CVD, & metabolic syndrome (esp w/in 5y) - Uncontrolled DM ↑risk birth defects	- 75g OGTT or fasting BG at 4-12w postpartum (Diab Care 2021;44:S15). If +, screen q1y. If -, q3y for life - If T1DM, TFTs x1 (if never done)	- Encourage breastfeeding - If overt DM: target A1c 6-6.5, consider ASA 81mg qd in future pregnancies to ↓pre-eclampsia risk
Pre-Eclampsia/ HTN	- ↑risk of stroke 48h-10d postpartum - ↑risk of CKD in first 5y - ↑risk of ASCVD (JACC 2019;74:1376)	- Close BP monitoring up to 6w PP - Repeat UACR/UPCR to quantify baseline proteinuria	- Encourage breastfeeding - Early goal BP <160/100, later <120/80 - Add pre-eclampsia as ASCVD risk-enhancer - Consider ASA 81mg qd in future pregnancies to ↓pre-eclampsia risk

SLEEP MEDICINE

Insomnia: 1/3 of population; chronic insomnia **>3mo**. Incl difficulty initiating or maintaining sleep, early awakening, non-restorative ([PCO1](#))

- **Hx:** ask about sleep! Chronicity, effect on fxn/mood, # awakenings and triggers, sleep hygiene; meds, PMH, sleep log for 1w
- **Ddx: medical:** r/o mood d/o, primary medical condition, SUDs, med effect. **Primary sleep d/o:** Insufficient sleep syndrome (<7-8h allotted to sleep), Psychophysiological (inability to sleep due to stress or anxiety about sleep), Paradoxical (no e/o sleep d/o), RLS, Periodic Limb Movements of Sleep (PLMS), OSA, Idiopathic (starting in childhood), Circadian rhythm disorder (delayed sleep phase; advanced sleep phase-common elderly)
- **Tx: sleep hygiene:** regular sleep schedule, exercise, bed for sleep only, no caffeine/EtOH/nicotine <4-6h before bed, **CBT** (through behavioral med, first line with strong evidence), **meds (WEAK evidence):** sleep maintenance (suvorexant, doxepin), sleep onset (zaleplon, triazolam, ramelteon), both (eszopiclone, zolpidem, temazepam). Rx hypnotics for <4w only. No evidence for melatonin, trazodone, or mirtazapine. ([J Clin Sleep Med 2017;13:307](#)) **sleep med referral** for 1^o sleep d/o (except OSA)

Sleep Apnea: obstructive (upper airway occlusion) and/or central (↓resp drive). Affects 10% of adults ([AFP 2016;94:355](#))

- **Presentation:** daytime hypersomnolence (use [Epworth Sleepiness Scale](#)), morning HA, witnessed apnea/gasping, snoring (Sn > Sp), depression, nocturia; RF: obesity, incr age, ♂, post-menopausal, EtOH, FHx. Screen for OSA w/ [STOP-BANG](#) (Sn 85%)
- **Dx: sleep study in-lab** (gold standard) vs **at home** (if high suspicion for at least mod OSA; cannot detect other sleep d/o or central apnea); both quantify apnea-hypopnea index (AHI) = sum of events/h (mild 5-15, mod 16-30, severe >30)
- **Tx: behavioral:** weight loss, avoid ETOH/sedatives, position (avoid supine sleep, elevate HOB); **Positive Airway Pressure:** CPAP, BiPAP, ASV (for central); **other:** Oral device (dentist referral), surgery, modafinil (for daytime sleepiness refractory to CPAP)

Restless Leg Syndrome ([PCO1](#))

- **Presentation:** URGE: Urge to move legs, Rest induces symptoms, Getting active brings relief, Evening/night makes symptoms worse
 - Common triggers: caffeine, nicotine, ETOH, dopamine antag, SSRI, antihistamines
 - Assoc conditions: iron deficiency, CKD, pregnancy, essential tremor, Parkinson's, MS, movement disorders, OSA
- **DDx:** myalgia, neuropathy, venous stasis, PVD, arthritis, nocturnal leg cramps, positional discomfort, habitual foot tapping
- **Dx:** ferritin, Iron sat, CBC, BMP, consider polysomnography; assess for assoc conditions and mimics w/ hx and exam
- **Tx:** avoid triggers, iron supplement to ferritin >75; **dopamine agonists** (take 1-1.5h before trigger or qhs) - pramipexole, ropinirole, carbidopa/levodopa (<3x/w, high risk rebound), rotigotine patch; **a-2-d-ligands** - pregabalin, gabapentin

Primary Care

HEENT Concerns

CHRONIC COUGH (AFP 2017;96:575; NEJM 2016;375:1544)

- Acute ($\leq 3w$) vs. subacute (3-8w) vs. chronic ($>8w$)
- Most common causes: **upper airway cough syndrome (UACS), asthma, GERD;** 18-62% pts have combo
 - Other causes: post-infxn (self-limited; can last 3+ months, treat sx), COPD, OSA, nonasthmatic eosinophilic bronchitis, chemical irritant (eg cigarette smoke), laryngopharyngeal bronchitis, psychogenic/habitual cough, bronchiectasis, CA, TB, sarcoid
 - Normal CXR usually excludes bronchiectasis, persistent PNA, sarcoidosis, TB
- General approach: 1) history (smoking status, URI, ACEi use); consider CXR if no ACEi or irritant exposure (except smoking) and ↓ suspicion for UACS/asthma/GERD; consider spirometry; 2) remove possible offending agent; 3) start empiric tx for UACS/asthma/GERD sequentially until resolution → tx should be added to initial regimen; 4) consider PFTs, esophageal pH monitoring, chest CT, sputum tests, cardiac studies if sx persist despite treatment of usual causes

Etiology	Characteristics	Treatment
Upper Airway Cough Syndrome (UACS)	Formerly <i>post-nasal drip syndrome</i> . <u>Most common</u> cause of subacute/chronic cough. Cough may be only sx. <u>Exam:</u> throat/nose may reveal cobblestoning. Common causes: allergic/non-allergic rhinitis, sinusitis	Avoid environmental triggers of allergic rhinitis. Intranasal steroids, antihistamine nasal spray, oral antihistamine, oral decongestants, or saline nasal rinse for symptom relief
Asthma	Typically w/ episodic wheezing & dyspnea. Cough variant asthma p/w only cough. Pt may have h/o atopy. <u>Exam:</u> may have nasal polyps. Need spirometry w/ bronchodilator response & bronchoprovocation (e.g. methacholine challenge) for dx	PRN bronchodilators ± inhaled corticosteroids. Some pts may use only seasonally. See <u>Asthma</u> for stepwise therapy
GERD	30-40% of chronic cough. Epigastric burning sensation, sour taste in mouth (although sx absent in >40% of patients)	Lifestyle modifications, moderate dose PPI/H2 blocker. Consider <i>H. pylori</i> testing
Respiratory tract infection	H/o recent viral illness. 2/2 postnasal drip/UACS or direct effect of virus on bronchial reactivity/cough receptors. Pts have been shown to experience transient bronchial hyperreactivity as well	UACS tx as above. 2 nd gen (cetirizine) or 3 rd gen (fexofenadine) antihistamine. If bronchial hyperreactivity, tx w/ usual asthma care
ACE Inhibitor	Produces cough in 3-20% of pts. 2/2 ACEi-mediated increase in bradykinin. Sx can occur 1w to 6mo after starting	Withdraw ACEi (resolves within 1-4w), change to ARB (not associated with cough)

RHINOSINUSITIS (Otolaryngol Head Neck Surg 2015;152:598; NEJM 2016;375:962)

- Acute (<1mo) vs. subacute (1-3mo) vs. chronic (>3mo, usually w/ anaerobes); recurrent (4 or more annual episodes)
- Dx: rhinorrhea (viral=clear, bact=purulent) + nasal obstruction or facial pressure/pain/fullness. A/w anosmia, ear fullness, cough, HA
- Acute rhinosinusitis is *infectious* while chronic is *inflammatory* (atopy, asthma, granulomatous disease, immunodeficiency, CF)

Etiology	Time Frame	Treatment
Bacterial: only 0.5-2% of acute rhinosinusitis. S. <i>pneumo</i> (41%), H. <i>flu</i> (35%)	>10d, or worsening w/in 10d after initial improvement	Watchful waiting in pts w/ follow-up vs. amox-clav 875mg BID** or doxy 100mg BID x5-7d
Viral: most common cause	7-10d	Symptom control, oral decongestant
Fungal: mucor (invasive) in DM, immunocompromised	Acute (invasive) to more chronic (>3mo)	Surgical removal of fungal mucin or "fungal ball" (mycetoma). ENT emergency if invasive (destruction of sinus, erosion into orbit or brain)

** Higher dose Augmentin (2g BID or 90 mg/kg/d BID) in pts w/ RFs for resistance: regional resistance pattern, age 65+, hospitalized in last 5d, abx use in last month, immunocompromised, DM/cardiac/renal/hepatic disease, severe infxn (fever >102F, suppurative complication)

- Chronic rhinosinusitis: confirm diagnosis w/ CT or endoscopy; treatment varies by presence or absence of nasal polyps
 - W/o polyps → trial saline irrigation/intranasal steroid; ⊕ polyps → add short course of PO steroid ± ASA desens. (if concern for ASA-exacerbated respiratory disease)
- Complications: meningitis, periorbital/orbital cellulitis (pain, edema, proptosis, painful eye movement, diplopia), subperiosteal/intracranial/epidural abscess, osteomyelitis of the sinus bones, septic cavernous sinus thrombosis
- Alarm symptoms: persistent fevers >102F; periorbital edema, inflammation, or erythema; CN palsies; abnormal extraocular movements; proptosis; vision changes (diplopia, impaired vision); severe HA; AMS; meningeal signs

PHARYNGITIS (JAMA 2012;308:1307; NEJM 2011;364:648; CID 2012;55:e86)

- Most cases are **viral** (suspect if +conjunctivitis, coryza, cough, diarrhea, hoarseness, discrete ulcerative stomatitis, viral exanthema). Only 5-15% of adult sore throat visits are Group A Strep (GAS)
- **Exclude dangerous etiologies:** epiglottitis, peritonsillar abscesses, infxn in submandibular or retropharyngeal space, acute HIV
- **Identify & treat GAS** to ↓ risk of suppurative complications (peritonsillar abscess, cervical lymphadenitis, mastoiditis), prevent rheumatic fever (lower risk in adults), ↓ transmission, & improve sx. ASO titers useful only in dx of non-suppurative sequelae of GAS
 - Centor Criteria: 1 point for each - tonsillar exudates, tender ant. cervical LAD, fever, Ø cough; (-1pt if age ≥ 45)
 - 0-2: no testing, treat sx. 3-4: send Rapid Strep antigen detection test (Sn 70-90%, Sp 95%) ± throat Cx (if neg rapid but ↑ clinical suspicion; not indicated for routine use in adults w/ neg rapid)
 - Tx: PO penicillin V 250mg QID vs 500mg BID x10d; amoxicillin 500mg BID x10d; IM benzathine penicillin G 1.2milliU x1
 - PCN-allergic: cephalixin 500mg BID x10d
 - β-lactam sensitivity: clinda 300mg TID x10d; azithromycin 500mg QD x1d, then 250mg QD x4d
- Symptomatic tx: OTC lozenges (e.g. Sucrets, Cepacol), throat sprays, NSAIDs/Tylenol for pain relief. No PO steroids
- Follow up: if no improvement in sx in 5-7 days, evaluate for other infectious causes (e.g. mono, HIV, GC/chlamydia) or suppurative complications such as tonsillopharyngeal cellulitis, abscess, or acute otitis media

Primary Care

HEENT Concerns

EYE

General Evaluation: see [Ophthalmology](#)

- Physical Exam: visual acuity (Snellen chart, w/ glasses if worn), pupils (reactivity, APD), visual fields, EOM, intraocular pressure (palpate for firmness), color vision (Ishihara cards)
- Red Flags (urgent ophtho eval):** severe pain, HA/nausea, photophobia, severely decreased vision, abnormal pupil exam, corneal opacities, chemical injury, recent eye surgery or trauma

Vision Loss

- Acute, Painless (ED): GCA; non-arteritic ischemic optic neuropathy (~60y, +APD); central retinal artery occlusion (vasculopathy, +APD, +/- amaurosis fugax); central retinal vein occlusion (DM, HTN, hypercoag, glaucoma, OCPs, hyperviscosity, ± RAPD); vitreous hemorrhage (DM, retinal detachment/tear); retinal detachment (flashes of light, floaters, ± abnl red reflex); pseudosudden vision loss (gradual monocular loss misperceived as sudden if other eye occluded)
- Acute, Painful (ophtho w/in 24h): optic neuritis (unilateral, <50y, blurry vision, flashes of light, +APD)
- Gradual, Painless (routine referral): refractive error, cataracts (glare, halos, trouble night driving), open-angle glaucoma (peripheral, RF: age, FHx, AA/Hispanic), diabetic retinopathy (c/b macular edema, vitreous hemorrhage, macular ischemia, tractional retinal detachment), age-related macular degeneration (central, RF: tobacco, poor diet, age, FHx), meds, idiopathic intracranial HTN (RF: ♀, obesity, steroids, OCPs, high-dose VitaA, tetracyclines), mild amblyopia

Red Eye ([AFP 2010;81:137](#)): for tx see [Ophthalmology](#)

- Painless: subconjunctival hemorrhage (unilateral, no vision Δ), episcleritis (painless w/o vision Δ or d/c, unilateral focal erythema, self-limited), dry eye syndrome (bl itching, burning, photophobia, FB sensation, diffuse hyperemia), blepharitis/Meibomian gland dysfunction (bl lid margin burning, itching, AM crusting)
- Painful: conjunctivitis (itching, burning, FB sensation), keratitis (photophobia, tearing, hyperemia; 2/2 corneal ulcer or VZV/HSV), severe tear deficiency (Sjogren's, GVHD), iritis/uveitis (unilateral, photophobia, tearing, sluggish pupils; autoimmune), scleritis (HA, boggy red/pink sclera, tender globe, pain with EOM, no vision Δ), endophthalmitis (floaters, vision Δ, fixed dilated pupil, hypopyon; c/f fungemia), acute angle closure glaucoma (unilateral, HA, halos, n/v, vision Δ, fixed dilated pupil, globe firmness)
- Swollen eyelid ([AFP 2015;92:106](#)): hordeolum = stye (tender nodule 2/2 occluded Meibomian gland), chalazion (painless nodule 2/2 chronic granulomas), contact dermatitis (caution w/ topical steroids), preseptal or orbital cellulitis (see [Orbital and Preseptal Cellulitis](#))

Conjunctivitis ([JAMA 2013;310:1721](#))

- Viral and bacterial very contagious. Strict hand hygiene, avoid contacts until d/c resolves
- PCR, GS, or Cx rarely needed – consider if severe purulence, refractory to tx, recurrent, immunocompromised, c/f GC/CT
- Avoid contact lenses, topical corticosteroids, OTC vasoconstrictors (rebound hyperemia)

Etiology	Presentation	Dx	Tx
Viral (most common)	<u>History:</u> sick contact, URI sx, watery d/c, gritty sensation, itching. <u>Exam:</u> intense hyperemia, ± periocular swelling, preauricular LAD	Typically adenovirus	Cool compresses, artificial tears. If c/f HSV/VZV: topical/PO tx + ophtho
Bacterial	<u>History:</u> mucopurulent d/c, pain/stinging. <u>Exam:</u> crusting, intense hyperemia, LAD rare	Typically <i>S.pneumo</i> , <i>S.aureus</i> , or <i>H.flu</i> ; consider GC/CT if RF	Erythromycin ointment 0.5% QID x7d (mild) or Polytrim 1-2 drops QID x7d (mod-severe, ↓ time to recovery). GC: PO abx + ophtho
Allergic	<u>History:</u> intense itching, painless tearing, hx atopy, allergic rhinitis. <u>Exam:</u> bilateral, mild hyperemia	Chronic or seasonal	Avoid allergens. Cool compresses, artificial tears. OTC anti-histamine/mast-cell stabilizer drops (eg ketotifen BID) ± PO anti-H1

EAR ([AFP 2018;97:20](#))

Ear Pain

- Primary (otitis externa/media, foreign body, Eustachian tube dysfunction, barotrauma, cellulitis, cholesteatoma, mastoiditis, Ramsay Hunt Syndrome 2/2 VZV) vs Secondary (TMJ, Bell's Palsy, sinusitis, dental work, GERD, tumor, GCA, MI, thoracic aneurysm)
- Red Flags:** signs of malignant otitis externa (HA/pain out of proportion to exam, fever, immunosuppressed, granulation tissue in floor of ear canal) or otitis media spread (mastoid pain/swelling, bloody otorrhea, facial weakness, vertigo, nystagmus, photophobia)

Etiology	Presentation	Dx	Tx
Otitis Externa	<u>History:</u> otalgia, itching. DM, water exposure, cerumen. <u>Exam:</u> tragus/pinna pain, ear canal edema/erythema, ± otorrhea/LAD/TM perf	Typically <i>PsA</i> or <i>S.aureus</i> . Assess for other skin conditions	Clean w/ hydrogen peroxide. Keep ear dry. PO pain meds (not topical). <u>Topical:</u> acetic acid, steroid, or abx (FQ) drops (no diff for empiric tx)
Otitis Media	<u>History:</u> recent URI, smoking, hx Eustachian tube dysfunction. <u>Exam:</u> TM bulging ± immobile w/ erythema, conductive hearing loss	Viral > bacterial (<i>S.pneumo</i> , <i>H.flu</i> , <i>M.catarrhalis</i>)	If mild-mod, consider Rx if no improvement at 2-3d. Amox-clav BID x5-10d (or amox 500 TID). ENT if ruptured TM does not close in 6w

Tinnitus: false perception of sound in the absence of acoustic stimulus ([NEJM 2018;378:1224](#); [AFP 2014;89:106](#))

- History: dizziness/vertigo (consider Meniere's), hearing loss, laterality (c/f schwannoma), meds (ASA, loops, abx), trauma, CVA, HA, depression/anxiety. Red flags: persistent + pulsatile, unilateral + hearing loss, vertigo, focal neuro deficits – consider audiology referral, imaging w/ CTA or MRA/MRV
- Tx: r/o underlying etiology. 20-50% have resolution spontaneously. If bothersome: CBT, sound therapy, tinnitus retraining therapy

Hearing Loss: RF - age, ♂, Caucasian, HTN, DM, CKD, immunosuppressed

- Conductive (mechanical): cerumen impaction, otitis externa/media, otosclerosis, ruptured TM, cholesteatoma (middle ear cyst)
- Sensorineural (neuro): presbycusis (age-related, gradual, symmetric, high frequency), noise-induced, Meniere's (asymmetric, +tinnitus, +vertigo), sudden sensorineural (acute, asymmetric, +tinnitus, **urgent eval**), barotrauma, tumor, meds, infxn

Primary Care

Nodules

ADRENAL NODULES (>1 CM) ([Endocr Rev 2020;41:775](#))

- Is it malignant? (<5% primary, <2.5% mets) ↑risk: diameter >4 cm, >10 HU, heterogeneous, irregular shape, calcification, ↑T2 signal on MRI, delayed contrast washout
- Is it functionally active? (10-15%): exam & lab testing for all nodules >1cm (unless obvious myelolipoma) to r/o pheo & Cushing's (see table). Also test for hyperaldo if HTN, hypokalemia. Only test for production of excess sex hormones if clinical stigmata. AVOID testing inpatients due to high false + rates

Diagnosis	Suggestive Clinical Features	Laboratory Tests
Cushing's syndrome (~6-10%)	- HTN, metabolic syndrome, CVD, central obesity, prox muscle weakness, facial plethora - Glucose intolerance, DM - Decreased, normal, or increased bone formation	1mg o/n dex suppression test (if + send 24h urine free cortisol, then confirmatory 8mg o/n DST)
Pheochromocytoma (~3-5%)	- HTN (5-15% don't have), palpitations, HA, diaphoresis, tremors - CT: ≥10 HU, vascularity, cystic changes - Cardiomyopathy - "Pheo crisis": HTN/HoTN, psych d/o, multiorgan failure, hyperthermia	Plasma free (after 30m supine) or 24h urine fractionated metanephrenes
Hyperaldosteronism (~1%)	- HTN, hypokalemia - ↑risk stroke, CAD, afib, HF - ↑mortality (compared to matched population with essential HTN)	Plasma aldo & renin activity (correct hypoK and d/c aldo antagonists before testing). May need adrenal venous sampling
Hyperandrogenism	- ♀: virilization, hirsutism, acne, irregular periods - ♂: decreased libido, testicular atrophy, gynecomastia	DHEAS, total testosterone, 17-OHP

- Consider adrenalectomy: if ↑risk characteristics, >4cm, malignant, or hormonally active; surgery after hormonal eval
- Consider FNA: if c/f adrenal met from another primary without known metastatic disease (**only** after excluding pheo)
- Follow up: repeat CT in 12mo. Consider annual DHEAS/1mg DST x4-5y (unknown effectiveness, guidelines do not recommend). Adrenalectomy if nodule grows >1 cm, reaches 4cm, or becomes functional

THYROID NODULES ([Thyroid 2016;26:1](#); [Endocr Pract 2016;22:622](#))

- Is it malignant? ↑risk: h/o irradiation to head/neck, +family hx, h/o thyroid cancer syndromes (i.e. MEN 2), age <30

Workup: Thyroid Ultrasound, TSH	
TSH normal or high	TSH low
↓	↓
R/o hypothyroid (FT4/TPO Ab)	FT4/T3, Thyroid radionuclide (¹²³ I) scan
↓	↓
"Cold nodule"	"Hot nodule"
↓	↓
U/S-guided FNA if criteria met	Consider tx for hyperthyroidism if sx

- FNA: any nodule w/ extrathyroidal extension, extrusion through rim calcs, abnormal cervical LNs, adjacent to laryngeal nerve/trachea OR >1cm + solid/hypoechoic w/ irregular margins, microcalcs, rim calc, or taller than wide shape. No FNA for pure cystic nodules. ACR uses **TIRADS**
- Follow up (benign): based on U/S characteristics. If highly suspicious U/S findings, repeat US & FNA w/in 12mo. If low-moderate suspicious U/S findings, repeat U/S 12-24mo, consider FNA if >1-2cm change. Stop f/u after 2 neg FNAs

INCIDENTAL PULMONARY NODULES (<3 CM) ([Radiology 2017;284:228](#); [Chest 2013;143:e93S](#); [Thorax 2015;70 Suppl 2:i1](#))

NB: these guidelines are for **incidental findings**; recommendations for f/u of nodules found on LDCT for lung cancer screening are different as that population is high risk (see [Lung-RADS classification](#))

- Ddx: malignant (primary, met, carcinoid) or benign (majority; infectious granuloma, hamartoma, AVM, inflammatory)
- Is it malignant? Pt characteristics: ↑risk w/ **h/o smoking**, emphysema, pulmonary fibrosis, extra-thoracic cancer, asbestos exposure, age. Nodule characteristics: density (part-solid/ground glass>solid), larger size, faster rate of growth (increase >2mm on repeat CT), borders (irregular/spiculated>smooth), location (upper>lower lobe)
- Is it benign? Demonstrates fat (pulmonary hamartoma) or characteristic calcification pattern (granuloma, hamartoma) or stability on CT for a defined period of time (>2y for solid and >5y for subsolid nodules)
- Follow up: tailored to patient and type of nodule. **Subsolid** (entirely ground glass): if <6 mm, no routine f/u. If >6 mm, CT at 6-12mo, then CT every 2y until 5y. **Part solid**: if <6mm, no routine f/u. If >6 mm, CT at 3-6mo, then annual CT for 5y if unchanged and solid component <6 mm. **Solid nodules**: see below
- Consider referral to the Pulmonary Nodule Clinic: refer in Epic or call x38728 for appointment

Nodule type	< 6 mm	6-8 mm	> 8 mm
Single solid nodule			
Low risk	No routine follow up	CT at 6-12mo, then cons. CT at 18-24mo	Cons. CT at 3mo, PET/CT, or tissue sampling
High risk	Optional CT at 12mo	CT at 6-12mo, then CT at 18-24mo	Cons. CT at 3mo, PET/CT, or tissue sampling
Multiple solid nodules			
Low risk	No routine follow up	CT at 3-6mo, then cons. CT at 18-24mo	CT at 3-6mo, then consider CT at 18-24mo
High risk	Optional CT at 12mo	CT at 3-6mo, then at 18-24mo	CT at 3-6mo, then at 18-24mo

Primary Care

Musculoskeletal Pain

KNEE PAIN

- History:** trauma, acute vs chronic, association with activity, constitutional sx, swelling, stiffness, instability, popping or catching sensation, sensory/motor changes, BMI, orthopedic or rheumatologic hx. Have pt point to area of pain with one finger

Knee Exam		
Test	Maneuver	Positive in
Lachman (sim. to anterior drawer)	Pt supine with knee flexed to 20-30°. One hand on pt's femur, just above knee. Other hand on pt's tibia. Apply slight flexion and pull sharply towards your abdomen. If tibia feels less restrained, \oplus test	ACL injury
Posterior drawer	Pt supine with knee flexed, can stabilize foot by sitting on it. Place hands around tibia, apply pressure backward in place parallel to femur. If less restrained motion, \oplus test	PCL injury
McMurray	One hand over medial joint line with knee fully flexed. Externally rotate foot/tibia, apply valgus stress, and gently flex/extend knee. If clicking around medial joint line, \oplus test	Meniscal injury

Location	Traumatic	Related to Activity	Atraumatic
Anterior	Quadriceps or patellar injury	Patellofemoral syndrome*, Osgood-Schlatter, bursitis, quadriceps/patellar tendinopathy	RA, gout, pseudogout, septic joint
Lateral	Lateral meniscal tear, LCL injury	Iliotibial band syndrome	Lateral OA
Medial	Medial meniscal tear, MCL injury, tibial plateau fracture	Anserine bursitis	Medial OA, saphenous nerve entrapment
Popliteal	PCL injury	Popliteal artery entrapment, Baker cyst	Popliteal artery aneurysm, DVT

*Most common etiology in patients <45 yo (pain with patellofemoral joint palpation and compression of patella against femur)

- XR imaging:** if trauma <1w, XR indications per [Ottawa Knee Rule](#) - Sn 98%, Sp 49% ([Annals 2004;140:121](#))
 - If eval of chronic OA, get weightbearing views of both knees; patellar view for patellar problems
- MRI imaging:** if suspecting fracture, infection, or internal derangement (e.g. ACL, meniscal tear in younger patients) or pain refractory to 4w conservative care. *Asymptomatic meniscal tears:* 13% <45 yo, 36% >45 yo ([Clin Ortho Rel Res 1992;282:177](#))
- Tx:** all benefit from rest, ice, NSAIDs \pm APAP, compression, PT, wt loss. For mod-sev OA, young ACL tear, or any pain refractory to conservative tx, consider surgery. For bursitis, popliteal cyst, or IT band, consider steroid injection

SHOULDER PAIN

- General approach:** r/o shoulder mimics, then rotator cuff pathology, then bursitis, impingement, OA or tendinopathy

Etiology	History Findings	Physical exam
Shoulder Mimics	Consider cervical/neck pain, biceps pathology, cardiac or GI radiation	
Rotator Cuff	- Acute = trauma - Chronic = age, acromial spurring, overuse - Tendinopathy, partial or full thickness tears - Pain & weakness, often with overhead arm use - Ortho referral often needed	- \downarrow ROM. Painful arc, impingement - Internal lag test: bring dorsum of patient's hand against lumbar region of back. Take forearm and hand away from the back (~20°). Ask pt to maintain position while supporting elbow. \oplus if not maintained - External lag test: externally rotate shoulder 90°, flex elbow 90°. Ask pt to maintain position. \oplus if not maintained - Drop arm: abduct arm to 90°. \oplus if cannot smoothly adduct shoulder to waist-level - Neer: pronate forearm (thumbs point backwards), bring shoulder to full forward flexion. \oplus if pain - Hawkins: flex shoulder to 90°, flex elbow to 90°, and internally rotate the shoulder. \oplus if pain - Ext rotation (teres minor, infraspin): flex elbow 90°, externally rotate shoulder against resistance. \oplus if pain - Empty can (supraspin): flex shoulder to 90°, internally rotate forearm. \oplus if pain w/ resistance of downward push
Subacromial Bursitis	- Referred pain to deltoid - Overuse, heavy lifting	- Pain w/ arc 60°-120° abduction \pm impingement - \oplus Neer & Hawkins
Glenohumeral OA/ Adhesive Capsulitis	- OA: aching, stiff; age >60 - Capsulitis: ↑risk w/ DM, thyroid disease, immobilization; age 40-60	- OA: crepitus - Capsulitis: loss of active/passive ROM in all planes
AC Joint Pain	- Young: traumatic sprain, fall with separation - Older: AC evolves into OA & impingement	- Pain, tenderness, swelling over AC joint - \oplus cross arm test

- Imaging:** none for bursitis. **XR** if h/o trauma c/f fracture or dislocation, gross deformity, exam concerning for OA, RTC tear or joint involvement. Get true AP of glenohumeral joint, axillary lateral, & "Y view" of AC joint w/ stress views for trauma. **MRI w/o contrast** in pts w/ \oplus internal/external lag tests, r/o full thickness RTC tear, previous abnl XR, persistent pain despite 2-3mo of conservative tx
- Tx:** **conservative tx** w/ activity avoidance, NSAIDs, PT/home exercises \pm short-term steroid injections; **surgery** for refractory instability, labral/full RC tear, AC joint separation

Primary Care

Musculoskeletal Pain

Low BACK PAIN

- Incidence/Prognosis: 84% lifetime acute back pain, 50% sciatica ([Mayo Clin Proc 2015;90:1699](#)); 75-90% improve over 4w
- Exam: palpation of midline & paraspinal muscles, ROM spine/hip, LE strength/reflexes (L4-5 = foot dorsiflex; L5-S1 = foot plantarflex, ankle reflex), rectal tone (if c/f cauda equina), SLR/crossed SLR (pain radiates below knee, often to heel, when straight leg raised while supine; crossed SLR is radicular pain in opposite leg, ↑Sp)

	Origin	Signs and Symptoms
Nonspecific MSK (85%)	Paraspinal muscles, ligaments, discs, facets	<u>Muscle spasm:</u> paraspinal muscle tenderness w/ acute onset, usually unilateral. <u>Disc:</u> young, ↑ w/ spine loading (i.e. sitting). <u>Facet:</u> >40 yo, ↑ w/ extension, ↓ w/ sitting
Radicular/Spinal stenosis (7%)	Disc herniation w/ nerve compression (90% L4-S1), spinal stenosis	<u>Sciatica</u> 95% Sn, 88% Sp for herniation: leg > back pain w/ dermatomal distribution of lancinating/burning pain, SLR ⊕. <u>Spinal stenosis</u> causes neurogenic claudication: leg pain worse with walking (esp downhill) better with sitting/leaning forward
Specific spinal disorder (8%)	Vertebrae, discs, endplates, SI joints, facet joints	<u>Compression fx:</u> older, trauma, osteopenia, steroids. <u>SI pain:</u> MVA/falls, rheum. <u>Inflammatory:</u> AM stiffness, night pain. <u>Cancer:</u> PMH, weight loss, night pain. <u>Infection:</u> fever, night sweats, IVDU, immunosuppression

- Imaging: early MRI or XR if **RED FLAGS** – focal severe/progressive neuro deficits, cauda equina sx (b/l weakness, urinary retention/incontinence, saddle anesthesia); trauma; c/f fracture, osteopenia risk (age >50 or <20, PMH, steroids); c/f CA or infxn
 - Otherwise, defer imaging until after initial 4-6w tx ([Annals 2007;147:478](#); [Choosing Wisely](#)) as herniation, disc bulging, DJD common findings ([Am J Neuroradiol 2015;36:811](#)). See [STarT Back Screening tool](#) for further guidance
- Possibly effective and lower-risk therapies
 - Avoid bed rest.** Explore social/psychological stressors, psych comorbidities, coping mechanisms
 - Non-pharmacologic:** acute: heat/cold, massage, acupuncture; chronic: yoga, CBT, mindfulness, rehab ([Annals 2017;166:514](#)); **PT & exercise** (demonstrated benefit in sciatica ([Annals 2021;174:8](#)), though not other acute LBP)
 - NSAIDs** (ibuprofen 400-800mg TID or naproxen 220-440mg BID) are first line for limited duration if no contraindication
 - Muscle relaxants:** can add for acute pain if NSAIDs alone ineffective ([JAMA 2015;314:1572](#))
 - Duloxetine and TCAs** for **chronic LBP**; second line after NSAIDs ([Annals 2017;166:480](#))
 - Epidural steroids** (Pain Med/PM&R): for radicular pain refractory to 6w tx - limited evidence, benefits likely limited, short-term
- Therapies with questionable evidence and/or higher risk of harm
 - Acetaminophen:** if NSAIDs contraindicated; but little e/o effectiveness ([Lancet 2014;384:1586](#)). **Oral prednisone taper** for acute sciatica: inconclusive evidence ([Annals 2017;166:480](#)). **Gabapentin, pregabalin:** option for sciatica though efficacy inconclusive ([NEJM 2017;376:1111](#)). **Opioids** (see below): limited evidence of effectiveness & ↑ risk of harm ([JAMA 2018;319:872](#)). **Surgery:** short-term sx relief in disc herniation w/o clear long-term benefit, ↑ side effects in spinal stenosis w/o e/o improved fxn

FOOT AND ANKLE PAIN

Etiology	History and Physical	Dx and Tx
Ankle sprain	- Trauma history - Pain/instability/swelling, bruising, focal tenderness over ligament (ATFL most common); squeeze test to r/o syndesmotic sprain	- Imaging: use Ottawa Ankle Rule - Ice, elevation, rest followed by exercise (consider PT) - Grade I (stretch, no tear): elastic wrap; grade II (partial tear, swelling, bruising): aircast or other splint; grade III (complete tear, unstable): casting, sports med/ortho c/s
Achilles tendinopathy	- Overuse or change in activity common - Pain & thickening at insertion or 2-6cm proximally; calf squeeze to r/o complete rupture	- MRI only if uncertain - Rest, ice, tendon support, PT - Surgical c/s for complete tear
Stress fracture	- Overuse; more common in ♀ esp if amenorrheic, underwt (rel caloric deficiency/overtraining syndrome) - Insidious onset of pain after exercising, ± focal tenderness on exam (tibia > tarsal > metatarsal)	- XR insensitive esp early in course; if ⊖ MRI may be req - Rest/non-wt-bearing 2-6w - Consider ortho c/s if high risk for nonunion (anterior tibia, navicular, talus, 1 st or 5 th metatarsal)
Plantar fasciitis	- Assoc w/ overuse, pes planus, overweight - Sharp anteromedial heel pain with activity after rest	- If uncertain, US may show thickening - Ice, stretching, NSAIDs, heel cups/OTC orthotics

- Ddx:** tarsal tunnel, **Charcot foot** (>40yo, obesity/neuropathy, swelling w/ minimal pain), hallux valgus ("bunion"), hallux rigidus (OA of 1st MTP), interdigital neuroma, non-Achilles tendinopathy, arthritis, gout/CPPD, derm (corns, calluses, warts, paronychia)

LONG-TERM OPIOIDS FOR MUSCULOSKELETAL PAIN

- Before prescribing longer-term opioids: (NB limited evidence; high risks of hyperalgesia, tolerance, dependence, addiction)
 - Exhaust non-opioid options. Avoid BDZ, hypnotics. Screen for OSA, SUD, mental health. Stress **complete pain relief is unlikely**. Set functional goals. Perform **risk assessment** ([SOAPP-R](#)). ✓ **PDMP**. Obtain prior records, speak to prior prescribers
 - Pain agreement (PCoI form)** is required. MA law: *Must check PDMP and limit 7 days for initial opioid prescription*. Discuss **6-8w initial trial** & safe use, storage, & disposal of opioids. Educate that random UTox and pill counts are for pt safety. Agree that single prescriber will Rx. Rx on 28d cycle ending on weekday to facilitate refills. **Rx naloxone**
- Follow-up for longer-term opioids:
 - Discontinue opioids if no significant benefit at 6-8w:** significant side effects, risk > benefit, non-adherence
 - Caution prescribing >50mg/d morphine equivalents (MME), avoid >90 MME (c/s pain)**
 - See at least q1-3mo to review pain/function, side effects, adherence
 - Early refill requests should trigger appointment to assess reason, obtain tox screen, discuss use

Primary Care

Immigrant & Refugee Health

MEDICAL EXAMINATION ([CDC checklist](#))

Interpreter Services: In person - x66966, pager 27403 (M-F 6a-8p; S/Su 8a-6:30p) or by phone - 617-643-3344 Pin #1050

History: obtain prior medical records if possible

- **Social history:** country of origin, travel hx, transit countries, residence in refugee camps or detention centers, time living in US, family structure/hx of separation, food security, housing stability, home/neighborhood safety, education, occupational hx
- **PMH:** chronic diseases, meds (incl traditional/herbal remedies), tobacco/substance use (incl those legal in country of origin; inform of legality in US), chronic pain, prior cancer screening, menstrual hx/contraception
- **Mental health:** screen for [PTSD](#), anxiety, depression (2nd visit to ↓ re-traumatization). Can use single screening tool [RHS-15](#)
- **ROS:** fever, wt loss, night sweats, respiratory concerns, diarrhea, abdominal discomfort, pruritis, skin rashes/lesions

Physical Exam: reassure patients this exam is for their health and not regulatory purposes

- Vision, dental, hearing, BMI, BP screening. Eval for murmurs, HSM, LAD, skin lesions (rashes, trauma, micronutrient deficiency)
- See [PCOI](#) for low-cost referral options for dental and eye care: → “Health Care Access”

Vaccinations: if no documentation ([translation guide](#)), assume not vaccinated (see [Health Screening & Maintenance](#))

- Can check titers for VZV. Incomplete HBV vaccination may result in transiently elevated titers

Screening and Labs: ([CDC regional profiles](#))

- **General:** CBC/diff (eos, anemia), U/A (hematuria), BMP (glucose, renal dz), ♀ hCG, lead screening if pregnant or lactating ♀; other age-appropriate screening (lipids, HIV, HCV, etc)
- **STIs (see [STI](#)):** syphilis, HIV, GC/CT if ♀≤24+sexually active or ♀>24+RF
- **HBV serologies:** if from high [prevalence](#) country
- **Tuberculosis:** ask every year about sx, recent travel, sick contacts; retest PRN; (see [Tuberculosis](#))
- **Malaria:** tx if from Sub-Saharan Africa w/o pre-departure tx or from endemic country w/ sx. If pregnant or breastfeeding, test first (do not tx empirically). Obtain thick/thin blood smears or PCR (↑Sn if no sx)
- **Intestinal/tissue invasive parasites:** varies by country & pre-departure tx. See [CDC guideline](#). No empiric ivermectin if from [Loa loa-endemic country](#)
- **Micronutrients** (Fe, D, B12, etc): if malnutrition, anemia, h/o food insecurity

Infection	Signs and Symptoms
Strongyloidiasis, filariasis, schistosomiasis	Peripheral eosinophilia
Schistosomiasis	Hematuria, ♀ infertility, chronic pelvic pain
Malaria, schistosomiasis	Splenomegaly
Mycetoma, onchocerciasis, other filarial diseases	Chronic rash or itching
Chagas disease	Esoph. dysmotility, HF, conduction dz
Neurocysticercosis	Seizures, CNS sx

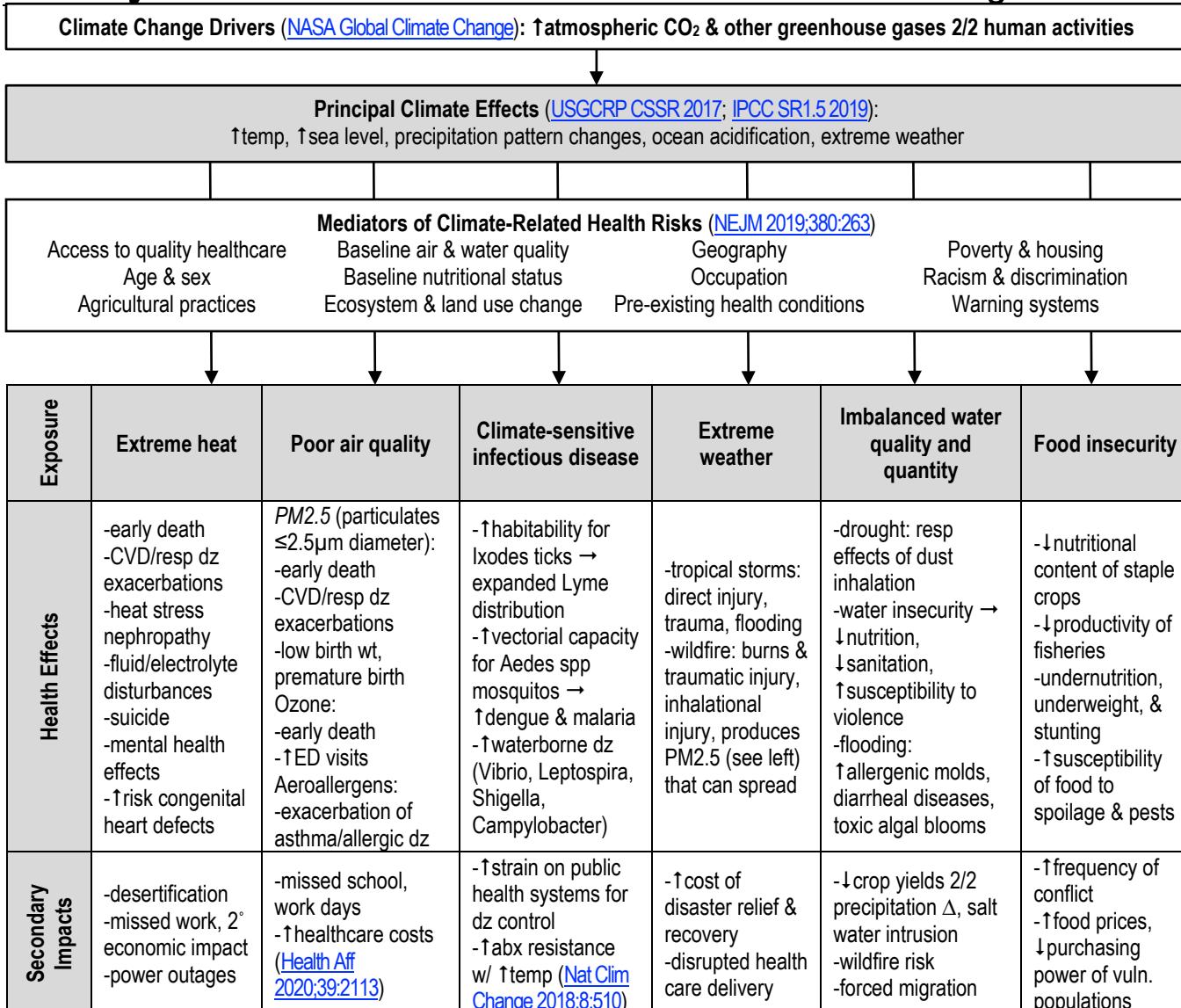
LEGAL CONSIDERATIONS (Boston-area [legal services](#) or MGH Chelsea LINC referral if pt at MGH Chelsea Healthcare Center)

- **Do not** document immigration status in EMR
- MassHealth eligibility is NOT contingent on immigration status. Refer all pts to [PFS](#). [Multilingual videos](#) for pts on the ACA
- **Know your Rights** re: ICE: multilingual infographics from [Immigrant Defense Project](#) & [Immigrant Legal Resource Center](#)
- For the latest on public charge: [Protecting Immigrant Families](#)
- **Asylum screening questions** (yes/no answers sufficient; obtain only as much detail as necessary to refer for legal support; re-telling or re-living experiences can be re-traumatizing and asylum seekers will have to tell their whole story to lawyers/doctors in the future)
 - What led you to leave your home country?
 - Were you ever a victim of violence or (verbal, sexual, physical) abuse there?
 - If so, was it due to your religion, race, political beliefs, nationality, or particular social group (gender, sexual identity)?
 - If so, did you face violence from anyone working for the government, military, or police?
 - If yes → refer to legal organization above, [PAIR](#), or the MGH asylum clinic (mgarland1@partners.org)
- [Resources](#) on conducting asylum evaluations and working with asylum seekers

Type	Details
Lawful Permanent Resident (LPR)	Green card recipient; pathway to citizenship. Family can get green card through “family based” immigration
U-Visa, T-Visa VAWA	Eligible if victim of human trafficking (T) or victim of certain types of crime (U). Violence Against Women Act: eligible if abused by spouse, child, or parent who is LPR/citizen
Temporary Protected Status (TPS)	Short list of countries where conditions preclude safe return. Cannot be deported while country of origin listed
Cancellation of Removal	Based on exceptional hardship anticipated to self or LPR/citizen spouse, parent, child if deported; ineligible with certain criminal convictions
Asylum	Well-founded fear of persecution based on race, religion, nationality, membership in social group, or political opinion. Application due w/in 1y of date of entry. If granted, may apply to spouse/children if they are in US
Refugee	Same legal standard as asylum, based on persecution or well-founded fear, but granted prior to arrival in US. Maximum set annually by President (no limit to asylum)
Medical Deferred Action	Temporary reprieve from deportation for immigrants facing life-threatening medical conditions and other humanitarian circumstances
Withholding of Removal	Asylum/CAT/Withholding all part of same application. No 1y rule. Ineligible with certain criminal convictions. No path to citizenship
CAT	Convention Against Torture: similar to Withholding, but still eligible with criminal convictions
Undocumented	Patients should seek legal counsel to check for options to apply for alternative statuses

Primary Care

Climate Change & Health



TREATMENT

Counsel Patients on Climate & Health Co-Benefits	
Patient-Centered Actions	<ul style="list-style-type: none"> Co-Benefits: actions that both improve health & mitigate emissions that drive climate change. Examples: <ul style="list-style-type: none"> ↓Red meat consumption → improved CV/renal health, ↓emissions (in 2017, excess red meat consumption contributed to 990,000 deaths worldwide, & emissions from beef were >400kg CO₂e/person) Active transportation → improved CV health, ↓transport-related pollution & emissions (BMJ 2020; 368:i6758)
Improve Health Care Delivery in a Changing Climate	
Institutional Actions	<ul style="list-style-type: none"> Improve resilience: 2019 global survey of climate vulnerability revealed that 67% of surveyed cities reported that climate change would seriously compromise their health infrastructure (Lancet 2021;397:129) <ul style="list-style-type: none"> U.S. Climate Resilience Toolkit: best practices for US health care facilities to withstand climate impacts, published by the U.S. Dept of HHS Deliver climate-smart healthcare: US healthcare-associated pollution comprised ~8.5% domestic greenhouse gas emissions & drove comparable burden of disease as deaths from preventable medical errors (Health Aff 2020;39:2071) <ul style="list-style-type: none"> Health Care Without Harm & Practice Greenhealth (free membership for MGH residents): resources to improve resource stewardship, decarbonize energy sources, & procure food & materials sustainably – all examples of health sector imperatives to reduce harm from healthcare-associated pollution and emissions
Example Advocacy Topics in Climate and Health	
Policy & Advocacy Actions	<ul style="list-style-type: none"> <i>Paris Agreement.</i> International compact in 2015 to limit warming to 2°C above pre-industrial levels, with further goal to limit to 1.5°C in recognition that 2°C would be catastrophic for certain populations (IPCC SR1.5 2019). U.S. rejoined on January 20, 2021. At start of 2021, we are on track to exceed 3°C warming by 2100 (UNEP EGR 2020) <i>Equity.</i> Imperative to focus on equity in climate planning, as countries least responsible stand to suffer most (Health Aff 2020;39:2056). Locally, Black and Latinx Americans inhale disproportionately more PM2.5 than is caused by their consumption (“pollution inequity”) (PNAS 2019;116:6001)

Read [NEJM 2019;380:209](#) for further resources for physicians, patients, and policymakers

Consultants

Calling Consults

TIPS FOR CALLING CONSULTS

- To do BEFORE you call:
 - Place order in Epic for consult
 - Know your patient: Review the H&P/chart and briefly see/examine the patient if you have not done so previously.
 - GI: melena/hematochezia, current/prior Hct, plts, coags, transfusions, past EGD/colo, vitals, IV access, NSAID/ASA use
 - Cards: EKG/tele, prior stress/echo/cath (know anatomy), dry weight, biomarkers, current cardiac meds, outpt cardiologist
 - Renal: baseline Cr, CKD stage, on/off HD, dialysis access, electrolyte mgmt, current UOP, nephrotoxins, outpt nephrologist
 - Onc: known cancers w/ stage/tx history, biopsy results (for new dx), current anticoagulants, special slide, outpt oncologist
 - ID: current/past micro data, possible sources, current/prior abx (incl # of days), fever curve, hardware, travel, exposures
 - Know your question – Bigelow JAR should specify consult question in task list. If not there, ASK. It is always OK to clarify
- To do DURING the page/call:
 - Call as early in the day as possible (ideally before noon), find out how to page using the paging directory
 - In your page to consulting team, include: pt name, MRN, location, call back #, brief consult question +/- level of urgency
 - Avoid “curbside” questions. If there is a specific question about management, call a formal consult
 - Tell the consultant a brief HPI, a clear explanation of the team's thinking, and a clear and specific question
- To do AFTER the call:
 - Invite the consultant to find you to relay their recommendations or tell them who will be covering for you

CALLING EMERGENT CONSULTS

- Surgery: STAT = imminently life-threatening emergency (e.g. lost airway, hypotensive from hemorrhage); URGENT = high concern for urgent surgical question (e.g. acute abdomen, perforated bowel, etc.)
 - Page "Senior Resident on call" under Emergency Surgery/Trauma (Churchill) Team
- Psychiatry (e.g. pt actively trying to leave AMA w/ unclear capacity; security concerns, major behavioral issues)
 - 8am-6pm: p33061 (Emergency Consult Resident). If weekend/Holiday: p17911 (weekend rounding psychiatrist)
 - 6pm-8am: Call APS (6-2994) or page APS resident at 27792
- Toxicology (ingestions/overdoses/exposures/interactions): call Poison Control Massachusetts (617-355-6607 or 800-222-1222).
- Cardiac Surgery: call "In-House fellow"

CALLING SURGICAL CONSULTS AT MGH

- In the ED: ED surgery "pit team." They typically sit in Acute bay across from room #5
 - For patients in the Acute bay → pit senior (x44169; p13115)
 - For patients anywhere else in the ED → pit junior (x44187; p20491)
 - Once the patient is on the floor, page PGY1 on the consulting team (identified in the consult note)
- New surgery consult (floor or ICU): page the senior resident of the appropriate surgical service
 - If patient known to an MGH surgeon, consult senior resident on call for that team to discuss
 - If patient not known to a surgeon, do your best to elucidate the appropriate team based on disease state (Baker surgery teams). When in doubt, contact the senior resident of the most appropriate team to further triage
- Follow up on GENERAL surgery consults: page the PGY1 covering the consulted service
- Cardiac Surgery consult → if non-emergent (8:30am-5pm) place order and call referral coordinator 617-724-4833. Can page NP at 30010. All other times (5pm-8:30am, weekends) call "In-House fellow"
- Ortho consult → page "Floor resident" at 20296 under "Orthopedics" or if ED consult, page 22566
- Transplant Surgery consult → page "Intern" (6a-6p) or "House officer on call" (6p-6a) under "Transplant Surgery"

CALLING OTHER SUBSPECIALTY CONSULTS

- ACT (Addiction Consult Team): place consult in Epic (no need to call), for EtOH or other substance use disorders, Suboxone, etc.
- AMS (Anticoagulation Management Service): for established pts: p30104, or click AMS icon in Epic to determine existing AMS RN. For discharge – place Epic consult; if urgent or questions, page Discharge Pathway Service: p30103
- Cardiology: login to Amion under "mghcardiology" to identify appropriate fellow (link also in paging directory)
- Chronic pain service for cancer pain, pain in addiction. Acute pain service for epidurals, periop pain
- Diabetes nurse educator: service NP p20737; MD p14364
- ENT: page 22220. Backup/emergency number is 617-523-7900 (MEEI operator) and ask them to page ENT resident on call
- Optimum Care Committee ("OCC," Ethics): page ethics support pager: p32097 (Mon-Fri, 8am-4pm, except holidays)
- Ophtho: for all consults p21004. Backup/emergency number is 617-573-4063 (MEEI ED back desk). Determine whether patient can travel to MEEI for an exam and if ok to dilate prior to calling consult
- Psychiatry: for non-emergent floor consult: order psych consult in Epic
 - Weekday, Weekend Night, Holiday Night: Call CL coordinators (6-2984). These consults will be seen within 24 hours.
 - Weekend or Holiday 8am-5pm: p17911 (weekend rounding psychiatrist)
- Transfusion reactions: page blood bank resident at 21829

Consultants

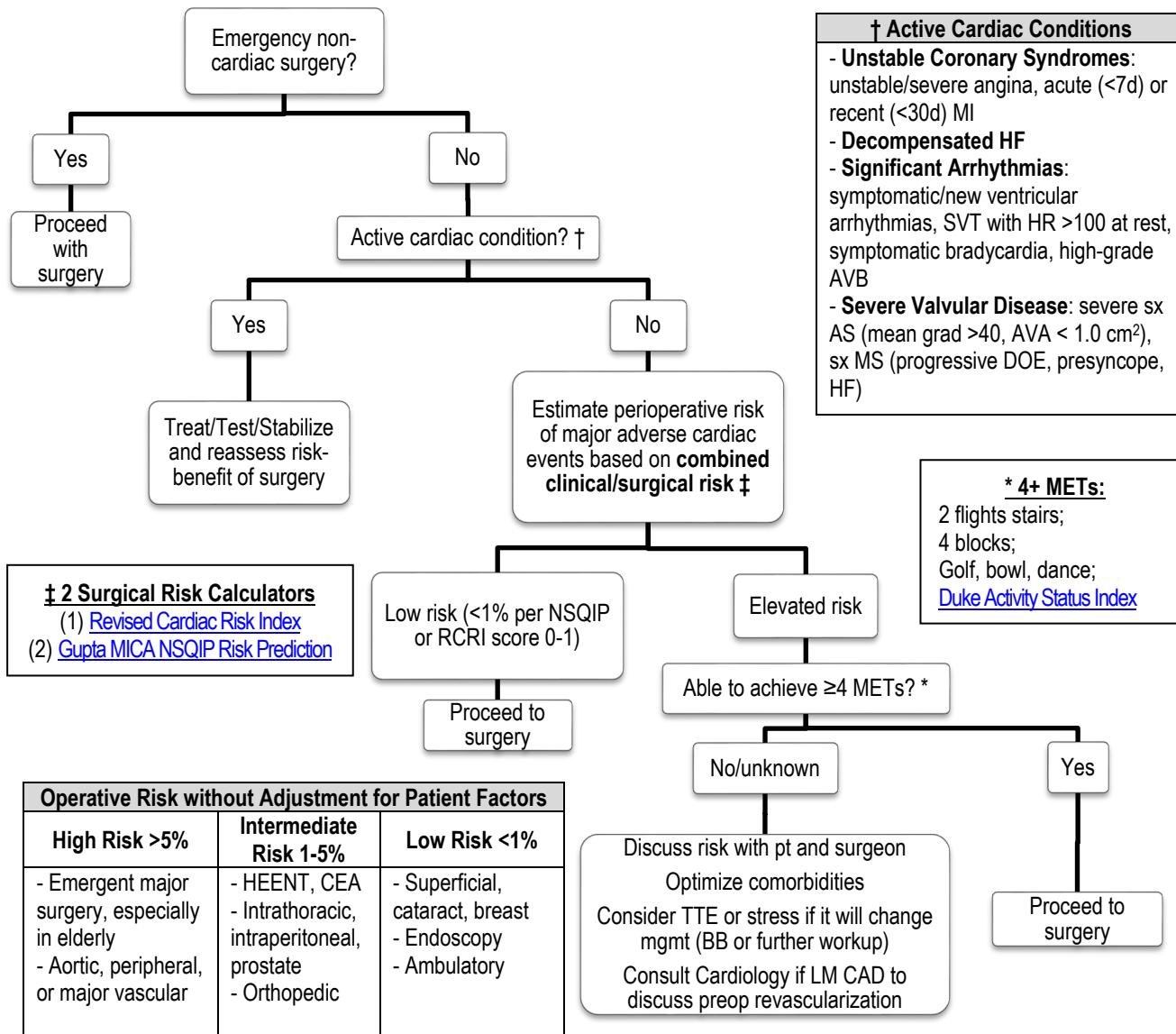
Perioperative Medicine

PERI-OPERATIVE CARDIAC RISK STRATIFICATION AND RISK REDUCTION

GOAL: to estimate and **optimize risk** of peri-operative cardiac events, **NOT to "clear for surgery"**

- Peri-op cardiac events: **MI** (usually clinically silent, NSTEMI>STEMI, POD#0-3, not intraop), **CHF**, **VT/VF**, **cardiac arrest**, **death**
 - Major determinants include: (1) condition of patient (2) risk of procedure (3) functional capacity
- Emphasis on risk stratification. **Very few patients need non-invasive/invasive testing**, only if testing would change management in the absence of surgery

PERI-OPERATIVE CARDIOVASCULAR EVALUATION FOR NON-CARDIAC SURGERY (adapted [JACC 2014;64:e77](#))



REVISED CARDIAC RISK INDEX (RCRI, GOLDMAN) ([Circ 1999;100:1043](#); [Can J Cardiol 2017;33:17](#))

- **Six independent predictors (risk factors) of major cardiac complications**
 1. High-risk noncardiac surgery (not a clinical RF but incorporated elsewhere in algorithm): OR 2.6
 2. CAD (MI, PCI, CABG, angina, nitrate use, EKG with pathologic Q waves, or + exercise stress test): OR 3.8
 3. HF (CHF, pulm edema, bilateral rales, or S3): OR 4.3
 4. Cerebrovascular disease (stroke or TIA): OR 3.0
 5. Diabetes mellitus with preop insulin therapy: OR 1.0
 6. Renal insufficiency with preop Cr >2.0 mg/dL: OR 0.9
- RCRI event rates were re-calculated (and partially validated) in 2017 after multiple trials included troponins ± emergent surgeries

Rate of cardiac death, MI, pulm edema, CHB, cardiac arrest/VF		
RCRI	1999 Event Rates (95% CI)	2017 Event Rates (95% CI)
0	0.4-0.5% (0.05-1.5) → ~0.5%	3.9% (2.8-5.4) → ~4%
1	0.9-1.3% (0.3-2.1) → ~1%	6.0% (4.9-7.4) → ~6%
2	3.6-6.6% (2.1-10.3) → ~5%	10.1% (8.1-12.6) → ~10%
≥3	9.1-11.0% (5.5-18.4) → ~10%	15.0% (11.1-20.0) → ~15%

Consultants

Perioperative Medicine

ALTERNATIVE CARDIAC RISK ASSESSMENT ([MICA](#), [GUPTA](#)) ([Circ 2011;124:381](#))

- Identified 5 risk factors predictive of *risk of STEMI or cardiac arrest* w/in 30 days of surgery:
1) Type of surgery/procedure, 2) preoperative functional status, 3) serum Cr >1.5, 4) ASA class, 5) increasing age
- Compared to RCRI, **better** discriminative predictive value
- Limitations:** likely underestimates actual risk because MI was defined in the study based on only ECG changes: STEMI or new LBBB; biomarkers were NOT monitored post-op, which is necessary to detect more than 50% of perioperative MIs

PREOPERATIVE CORONARY REVASCULARIZATION ([NEJM 2004;351:2795](#))

- CARP:** multicenter RCT of 510 high-risk vascular surgery patients, showed prophylactic revascularization w/ BMS/CABG conferred no survival benefit; data extrapolated to lower risk non-vascular/non-cardiac surgeries.
 - Exclusion criteria: EF < 20%, unstable angina, LMCA disease > 50%, severe AS

PERI-OPERATIVE β -BLOCKADE AND OTHER CARDIAC DRUGS

- Evaluate for peri-operative β -blockade ([Circ 2014;130:278](#))
 - Continue β -blocker: if already taking for other indication (e.g. CAD, arrhythmia, HTN) for goal HR 55-65 (Class I, LOE C)
 - Consider initiating β -blocker: ≥ 3 RCRI RFs or intermediate/high risk preop test (Class IIb, LOE B)
 - Do not start a β -blocker within 24 hours of surgery!** ([Lancet 2008;371:1839](#); [JACC 2014;64:2406](#))
 - Uncertain role of β -blocker: if \oplus stress test or long-term indication without other RCRI risk factors
- Anti-platelet:** ([NEJM 2014;370:1494](#); [Anesth Analg 2015;120:570](#))
 - 1° prevention: can generally be held prior to surgery
 - 2° prevention: continue ASA 81mg unless high risk of bleeding (intramedullary spine, intracranial, hip, knee, possibly prostate)
 - DAPT post-PCI: POBA <14d, BMS <30d, DES <6-12mo → discuss with Cardiology
- ACEi/ARB:** pts have more transient peri- and post-op episodes of HoTN; **no diff** in death, post-op MI, stroke; ↑ or ↓ AKI unclear
 - Discontinue ACEi/ARB night before surgery (unless used for HF and BP ok). At MGH hold prior to cardiac surgery
 - Failure to restart ARB within 48h ↑ 130d mortality ([Anesthes 2015;123:288](#))
- Other:** consider holding diuretics, other anti-hypertensives should be continued perioperatively to goal BP <180/100 to avoid bleeding
- Anticoagulation and bridging:** see [Anticoagulation Management](#)

VTE PROPHYLAXIS ([Mayo Clin Proc 2014;89:394](#))

- Postop VTE risk assessment: [Caparini Score](#)
- Non-orthopedic surgeries: those undergoing **general or abdominal/pelvic surgery** are at highest risk
- Orthopedic surgeries: **all pts at high VTE risk** 2/2 tourniquet time + immobilization; minimum duration 10-14d (35d if higher risk)

PERI-OPERATIVE MONITORING AND CONSIDERATIONS ([NEJM 2015;373:2258](#))

- ACS:** most MIs occur w/in 48h while patients are on analgesics that mask pain → some data show benefit of troponin monitoring ([JAMA 2012;307:2295](#)). Elevated post-op NT-proBNP can be used as a predictor of post-op MI and death ([JACC 2014;63:170](#))
- AF:** may be a more important risk factor than CAD for 30d post-op mortality ([Circ 2011;124:289](#)). Associated with higher preop # of preexisting comorbidities and increased postop LOS, cost, and mortality ([Am Heart J 2012;164:918](#)), as well as similar thromboembolism and death risk to pre-existing NVAF ([JACC 2018;72:2027](#))
 - If multiple episodes or lasts > 48h, recommend OAC and close follow up for further decision-making
- Pulmonary Disease:** numerous risk factors for postoperative pulmonary complications, including COPD, OSA, pHTN, low albumin. Multiple risk calculators for different outcomes, including [ARISCAT](#) ([Anesthes 2010;113:1338](#)), [Gupta](#) (for resp failure), and [Gupta](#) (for PNA). Strategies for mitigating risk are usually supportive, including incentive spirometry and smoking cessation. Consider Pulmonology consult
- Post-operative PNA:** ~20% mortality; pre-op CXR or PFTs not recommended because rarely change management
 - Risk factors: COPD, age >60, ASA class \geq II, albumin <3.5, poor functional dependence, weight loss >10% over previous 6 months ([Annals 2006;144:575](#))
- Renal dysfunction:** increased risk of complications in ESRD; AKI also a/w high morbidity and mortality ([Ann Surg 2009;249:851](#))
- ESLD:** increasing risk of perioperative mortality with increasing [MELD](#) & [Child-Pugh](#) scores. If Child-Pugh B, optimize VIBES & consider TIPS for refractory ascites. If Child-Pugh C, optimize, consider transplant, & discuss risk/benefit nonsurgical options. ([J Gastroenterol Hepatol 2012;27:1569](#); [Clin Gastroenterol Hepatol 2020;18:2398](#))
- Low albumin:** independent predictor of 30d post-op morbidity and mortality ([Arch Surg 1999;134:36](#))

Consultants

Dermatology

Before Consulting Dermatology: **upload photo of rash** (ideally pretreatment) to media tab of EPIC using Haiku

- If consulting for drug rash, note exact timing of rash development and administration of suspect medications

Quick Steroid Guide	
• Face/intertriginous areas:	hydrocort. 2.5% cream, hydrocort. valerate 0.2% cream
• Body:	fluocinolone 0.025% cream if mild, clobetasol 0.05% ointment if severe → mid strength to super potent depending on severity
• Scalp:	0.01% fluocinolone scalp solution or oil (dermasmooth); oil better for dry scalp
Counsel patients:	Use daily x2 wks then 1 wk "off", avoid face (risk = skin thinning)

MGH topical steroid formulary by level of potency	
Super-potent	clobetasol 0.05%, betamethasone dipropionate 0.05%
Potent	fluocinonide-emollient 0.05%
Upper-mid strength	betamethasone valerate ointment 0.1%
Mid-strength	fluocinolone ointment 0.025%
Lower mid-strength	fluocinolone cream 0.025%, betamethasone valerate cream 0.1%
Mild	hydrocortisone valerate 0.2%, fluocinolone scalp oil 0.01%
Least potent	hydrocortisone 2.5%, hydrocortisone ointment 1.0%
Over the counter	hydrocortisone cream 0.5%, 1.0%

COMMON DERMATOLOGIC CONDITIONS

- **Allergic contact dermatitis:** localized, but may generalize 2/2 autoeczematization (a.k.a. "id reaction", may also occur 2/2 tinea anywhere on the body). Identify and remove suspected trigger. Tx w/ high potency topical steroid for limited BSA (low to mid potency for face). Pred taper (>1wk) for more extensive BSA involvement
- **Eczema/atopic dermatitis:** tx depends on severity. Intense BID/TID moisturization (plain hydrated petrolatum, Cetaphil®, CeraVe®). For affected areas, use mid-strength to super-potent topical steroids BID x 2wks. For face, use least potent to lower mid-strength steroids BID x 1-2wks. Scalp: mid- to high-potency steroid in solution, foam, or oil vehicles. Erosions/fissures: petrolatum or mupirocin ointment BID x 1-2wks
- **Cellulitis:** consider **derm consult if not improved in 48h** to distinguish cellulitis mimickers (30% of cases).
 - Calculate ALT-70. 5-7 = 82.2% likely cellulitis; 3-4 = consider derm c/s if no improvement by 48h with abx. Consult reduces abx use + duration ([JAAD 2017;76:618](#), [JAMA Dem 2018;154:529](#)). Bilateral LE cellulitis is rare.
- **Pressure injury/ulcers:** document in H&P with Haiku pics.
 - NPUAP Staging: 1) non blanchable erythema of intact skin, 2) partial thickness skin loss with exposed dermis, 3) full thickness skin loss, 4) full thickness skin and tissue loss. Can be unstageable due to eschar/necrosis
 - **Wound Nurse consult** for: stage 3-4 pressure injury, device related injuries, moisture associated skin damage, edema drainage management, special bed surfaces (i.e. clinifltron, bariatric). **Wound Service consult** (Plastics/Vascular collab) for: acute wound issues such as limb ischemia, wet gangrene, any wound requiring OR debridement. Consider derm c/s to confirm etiology.

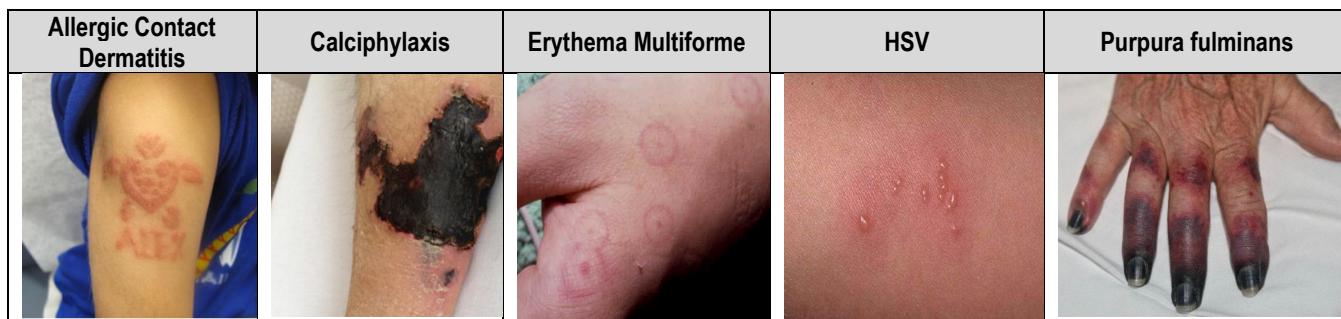
OTHER DERMATOLOGIC CONDITIONS

- **Calciphylaxis:** extreme pain (may precede lesion), violaceous retiform patch/plaque → necrosis, ulcer, eschar.
 - **Risk Factors:** ESRD on dialysis (most common), warfarin, 1° hyperPTH, malignancy.
 - **Dx:** skin biopsy (gold standard, not always needed); Ca²⁺ x phos product, PTH; bone scan w/ increased uptake
 - **Tx:** Normalize serum Ca²⁺, phos, PTH via non-calcium based phos binders (i.e. sevelamer) and cinacalcet; IV sodium thiosulfate; treat 2° infections (death from sepsis) and consider hyperbaric O₂ (consult MEEI Hyperbaric Medicine), pain control, wound care (Medihoney). D/c warfarin if possible; consider AC if appropriate. Calciphylaxis = indication for HD in CKD pts
- **Cutaneous GVHD:** skin pain/pruritus can precede eruption, acral → central; acute vs. chronic based on morphology, *not* time course.
 - **Acute:** follicular erythematous papules. **Chronic:** morphology varies, can be dry and scaly (asteatotic), pruritic and erythematous (eczematous), thickened and raised (lichenoid), tight and thick (sclerodermod), pigment changes and atrophy (poikilodermatous)
 - **Stage 1:** <25% BSA, **stage 2:** 25-50% BSA, **stage 3:** >50% BSA, **stage 4:** erythroderma w/ bullae (TEN-like).
 - **Tx:** immunosuppression with corticosteroids +/- cyclosporine or tacrolimus, supportive care
- **Herpes simplex virus 1/2:** always confirm w/ DFA or PCR from vesicle base; cx possible but takes long to result
 - **Uncomplicated orolabial:** primary is usually gingivostomatitis → acyclovir 400mg TID x7-10d; if recurrent → valacyclovir 2000 mg PO q12h x 1d or famciclovir 1500mg PO x1 at sx onset; periocular skin involvement warrants ophto c/s to r/o herpetic keratitis
 - **Uncomplicated genital (immunocompetent):** 1° episode (<72 hr after onset) → valacyclovir 1000mg PO BID x 10d, acyclovir 400mg PO TID x10d, or famciclovir 250mg TID; recurrent episodes (<24hr onset) → valacyclovir 500mg PO BID x 3-5d or acyclovir 400mg PO TID x 5d.
 - **Complications:** sacral radiculitis (acute urinary retention), proctitis (MSM).
 - **Prophylaxis for immunosuppressed patients:** Acutely immunosuppressed, e.g. transplant patients or patients with hematologic malignancies undergoing induction chemotherapy, HSV seropositive: acyclovir 5 mg/kg IV q8h X 7d → acyclovir 200-400 mg PO 3-5x daily x 1-3 mos; for prevention of recurrence in people living with HIV (NOT primary prevention): acyclovir 400-800 mg PO BID/TID or valacyclovir 500 mg daily or famciclovir 500 mg BID
 - Consider high lysine, low arginine diet to prevent HSV recurrence

Consultants

Dermatology

- **Herpes zoster (shingles):**
 - Uncomplicated, <72 hr (immunocompetent): valacyclovir 1000mg PO Q8H x7d or acyclovir 800 mg PO 5x/d x7-10d.
 - Disseminated: >20 vesicles outside two 1° (non-adjacent) dermatomes; acyclovir 10mg/kg IV q8h; consider immunodeficiency w/u; droplet precautions.
 - Immunosuppressed: acyclovir 10 mg/kg IV q8h; IVFs if hypovolemic/CKD to decrease risk of crystalline nephropathy; obtain DFA/viral culture; monitor for complications (PNA, encephalitis, aseptic meningitis, hepatitis).
 - Zoster ophthalmicus: urgent ophtho consult if c/f ocular involvement ("Hutchinson sign" = vesicle on nasal tip).
 - Post-herpetic neuralgia: risk ↓ w/ early antiviral treatment (<72 hr); if higher risk (≥ 50 yo w/ mod-to-severe acute pain) consider preventive tx w/ gabapentin 300mg PO QD, titrate up to 3600mg QD, divided TID as tolerated.
 - Consider post-episode vaccination
- **Erythema multiforme**: target lesions (well-defined, circular erythematous macules/papules w/ 3 distinct color zones + central bulla or crust) on palms/soles +/- mucosal involvement occurs within 24-72 hours; persist for 2wks;
 - 90% triggered by infection (HSV, mycoplasma, GAS, EBV); less commonly drug rxn
 - Tx: treat underlying infxn, NSAIDs, cool compresses, topical steroids, antihistamines; systemic steroids only if severe
- **Erythroderma**: diffuse redness >90% BSA.
 - Causes: psoriasis, atopic dermat, cutaneous T-cell lymphoma (incl. Sezary), pityriasis rubra pilaris (islands of sparing), drugs
 - Work-up: detailed med rec, +/- HIV. Tx: derm c/s; liberal emollients, mid-potency topical steroids, antihistamines; fluids/lytes; monitor for 2° infections; d/c offending meds.
- **Purpura fulminans**: "**DIC in skin**" = **true emergency**; consult Hematology for possible factor replacement;
 - Microvascular skin occlusion w/ platelet-fibrin thrombi → retiform purpura
 - Causes: infection (Strep, Staph, H. flu, N. meningitidis, Capnocytophaga, VZV, CMV, Babesia); catastrophic APLAS, CTD, malignancy, protein C/S deficiency
 - Work-up: DIC labs, blood cultures, skin bx w/ GS and culture. Tx: broad-spectrum abx + supportive care.
- **Stasis dermatitis**: LE compression (ACE wraps, stockings) with elevation; mid-strength to super potent corticosteroid ointment BID x 1-2wks +/- occlusion with plastic wrap; mupirocin ointment BID x1-2wks to erosions; intensive moisturization (hydrated petrolatum); for hyperkeratosis can liberally apply ammonium lactate BID until improvement
- **Psoriasis**: depends on severity; Short-term tx includes topical steroids, calcipotriene, intense moisturization +/- occlusion w/ plastic wrap; Long-term tx includes phototherapy, acitretin, MTX, biologics w/ outpt derm f/u ([JAAD 2011;65:137](#))
- **Seborrheic dermatitis**: Face: least potent to lower mid-strength topical steroid BID x 1wk and/or ketoconazole 2% cream BID x4wks, then 1-2x/wk; Alternative: pimecrolimus cream, tacrolimus 0.03 or 0.1% ointment. Scalp: ketoconazole 2% shampoo QHS
- **Tinea pedis**: "moccasin distribution"; apply topical imidazole (econazole 1% cream QD or clotrimazole 1% cream BID x 2-4 wks) or allylamine (terbinafine 1% cream BID x 2 wks) to entire foot and webbed spaces between toes. Predisposes to LE cellulitis



DRUG ERUPTIONS

- Step 1: Make timeline to determine time course of drug initiation and development of rash
- Step 2: Discontinue offending agent. Common drugs for each eruption listed, but any drug can be a culprit at any time

	Time Course	Rash	Signs/Sx	Common Drugs	Treatment
Urticaria/ Anaphylaxis	Immediate (min-hr) – delayed (days)		Pruritic, well-circumscribed, erythematous papules/plaques with central pallor. Transient lesions (circle and observe) +/- angioedema, wheezing, GI sx, tachycardia, HoTN	Any	- Antihistamines (benadryl + H2) + steroids if severe + IM epi if s/s anaphylaxis - Allergy c/s

Consultants

Dermatology

Fixed Drug Eruption	Minutes-hours		Solitary sharply demarcated round red-brown patch or edematous plaque recurring in <u>same location</u> each time drug ingested. Can evolve to bullae/become disseminated. Oral/anogenital mucosa commonly, can be anywhere. Usually ax.	Abx (sulfa, TMP, FQs, TCNs), NSAIDs, barbiturates	-Topical steroids if symptomatic
Acute Generalized Exanthematous Pustulosis (AGEP)	2-14 days		Small non-follic. pustules on erythema./edematous plaques, begin on face or intertriginous areas then widespread. Usually w/in 24-48hrs of med exposure. Burning, pruritus common. Fever, marked neutrophilia +/- oral mucosal erosions, facial edema	Abx (PCN, macrolides)	-Anti-pyretic -Topical steroids
Exanthematous/ Morbilliform	4-14d (if prev. exposed to the drug, could be sooner)		"Classic" drug rash. Pruritic, erythematous macules/papules. Start on trunk, spread centrifugally to symmetric extremities. May lead to erythroderma. ± low grade fever	Abx (PCN, sulfa), allopurinol, phenytoin	-Topical steroids, antihistamines (Note: may take 7-14d after stopping drug to resolve)
SJS/TEN	4-21 days		Fevers, malaise, myalgias, arthralgias. Pruritic atypical targetoid (amorphous, 2 color zones) macules → bullae → desquamation; <10% = SJS, 10-30% = SJS/TEN overlap, >30% = TEN. Mucosal bullae, erosions & crusting, conjunctivitis. + Nikolsky. Complications: 2° infection, resp. compromise, GIB, visual impairment	Abx (esp. sulfa), AEDs, NSAIDs, allopurinol, phenobarb.	-Cyclosporine (preferred at MGH) -Steroids possible mortality benefit (JAMA Derm 2017;153:514) but controversial -IVIG, anti-TNF -Burn level care if >30% BSA
DRESS	3-6 wks		Morbilliform; spreads down symmetric. from face; can see SJS/TEN-like lesions & mucosal involv. Face often swollen/painful (can help diff. from morbilliform drug) Fever, arthralgias, eos, internal organ involv. (liver, kidney; rarely lung, heart), LAD	Abx, AEDs, carbamazepine, ARTs (nevirapine, abacavir)	-Dx: obtain CMP, CBC w/ diff, TSH, consider TTE -Supportive care -IV Solumedrol (decreased risk of bowel edema vs. PO), SLOW taper (3-6 wks)

See [Calling Consults](#) for details on how to call the appropriate surgical service

SMALL BOWEL OBSTRUCTION ([J Trauma Acute Care Surg 2015;79:661](#))

- **Causes:** adhesions from any previous abd surgery, hernias, cancer >> intussusception, volvulus, foreign bodies, stricture
- **Dx:** abd distension, vomiting, obstipation. Labs normal or hypok/hypoCl metabolic alkalosis from repeated emesis. Examine for evidence of hernias and **prior abdominal scars**. If severe pain, consider ischemia from strangulation (lactate, leukocytosis)
- **Imaging:** KUB - air-fluid levels; **CT A/P + IV contrast + PO contrast** (if able to tolerate) - dilated bowel proximal to & decompressed bowel distal to obstruction
- **Tx:** **NPO**, large bore **NGT** (18Fr) to continuous low wall suction; consider surgical exploration if signs of strangulation/bowel ischemia, s/p gastric bypass (high risk of internal hernia), closed loop obstructions, or if no improvement in 72 hours

NECROTIZING SOFT TISSUE INFECTION ([CID 2007;44:705](#); [Front Surg 2014;1:36](#))

- **Definition:** progressive, rapidly spreading infection in deep fascia with secondary necrosis of skin and subcutaneous tissues
- **Microbiology:** Majority of cases, esp in patients with co-morbidities are polymicrobial (anaerobes, group A strep, *S. Aureus*, *Clostridium*, *Peptostreptococcus*, *Enterobacteriaceae*, *Proteus*, *Pseudomonas*, *Klebsiella*), less commonly mono-microbial
- **Clinical signs:** **rapidly spreading erythema** (hrs to days) → evidence of soft tissue necrosis; pain disproportionate to exam
 - Suggestive features: rapid expansion of erythema on serial exams, pain extending beyond border(s) of erythema, dusky/violaceous skin, undermining of skin and subcutaneous tissues, turbid ("dishwater") discharge, palpable crepitus
- **Dx:** CT w/ contrast, has a ~95-100% NPV. Labs for **LRINEC** score (CRP, WBC, Hg, Na, Cr, Gluc) – score ≥6 has a 96% NPV
- **Tx:** **IV abx** ([Vanc or Linezolid] + [Pip/Tazo or meropenem] + Clinda to inhibit toxin production) + **urgent surgical consultation**

ACUTE LIMB ISCHEMIA ([NEJM 2012;366:2198](#))

- **6 P's** Pain, Poikilothermia (cool), Paresthesia, Pallor, Pulselessness, Paralysis suggest arterial thrombotic/embolic occlusion

Stage	Description	Sensory Loss	Motor Loss	Arterial Doppler	Venous Doppler
I	Viable	None	None	Audible	Audible
II (a/b)	Threatened	Minimal, painful	None or Mild	Variably inaudible	Audible
III	Irreversible	Profound	Profound	Inaudible	Inaudible

- **Dx:** check and document pulses AND Doppler signals in the entirety of the extremity and the contralateral extremity for comparison. Obtain ankle-brachial indices
 - **Acute Limb Ischemia**, due to thrombotic or embolic causes, represents an acute change in the blood supply to the limb, warranting **urgent surgical evaluation** to prevent acute ischemia
 - **Chronic limb ischemia** represents chronic vascular disease from atherosclerotic changes. Exam usually demonstrates cool, hairless extremities with limited/no pulse that is not acutely painful. **Non-urgent** surgical eval
- **Tx:** if ACUTE limb ischemia, consider IV heparin (unless AC contraindicated); **consult Vascular Surgery immediately**

COMPARTMENT SYNDROME (EXTREMITY) ([Lancet 2015;386:1299](#); [Musc Lig Tend J 2015;5:18](#))

- **Definition:** excessive pressure within a muscle compartment, impairing perfusion
- **Etiology:** crush injury, ischemia → edema, bleed, etc.
- **Clinical signs:** tight, tender skin; pain out of proportion to known injuries; **pain with passive ROM**; ↑lactate or CPK
- **Dx:** measurement of compartment pressures at bedside using Stryker transducer needle (call Churchill Service for assistance)
 - Arterial flow diminished once compartment pressure within 30mmHg of DBP, 20mmHg in hypotensive patients
 - Nevertheless, compartment syndrome is a **clinical diagnosis**, regardless of measured compartment pressure(s)
- **Tx:** surgical emergency (fasciotomy/decompression); **consult Churchill Surgery immediately**

ABDOMINAL COMPARTMENT SYNDROME ([ICM 2013;39:1190](#))

- **Definition:** **IAH = IAP >12**. **Abdominal Compartment Syndrome = IAP >20 AND clinical evidence of organ dysfunction** (e.g. ↑airway pressures, ↓venous return, ↑CVP/PCWP, ↓UOP/AKI, ↑lactate, acidemia). IAP measured via bladder pressure (most reliable if paralyzed, only done in ICU)
- Typically occurs after massive resuscitation in ICU patients with trauma, burns, s/p liver tx, severe ascites, pancreatitis, sepsis
- **Tx:** **True Abdominal Compartment Syndrome** (IAP >20, organ dysfunction despite medical management): **surgical decompression** (i.e. laparotomy incision and vac placement) provides definitive management
 - If IAP 12-20 w/o clinical instability:
 - Evacuate luminal contents (NGT/rectal tube/enema)
 - Increase pain control/sedation (to level of paralysis if necessary)
 - Head of bed tilted up
 - LVP if ascites
 - Decrease tidal volume, permissive hypercapnia
 - Avoid over-resuscitation

Consultants

Urology

Who to call: page 11300 for emergencies, Foleys, SPTs, & urgent hematuria; page 10300 for other non-urgent inpatient consults

Consults: note urine color (if appropriate) before consulting Urology, place urine samples at bedside

URETERAL OBSTRUCTION (OFTEN DUE TO KIDNEY STONES)

- **Evaluation/management:**
 - **Imaging:** stone-protocol CT scan (I-, O-): evaluates position, hints at composition, & presence of hydronephrosis
 - Alternative is MRI vs combined KUB+US, but less diagnostic than stone-protocol CT
 - **Vitals, CBC, UA/UCx:** if UTI, decompress urgently with stent by urology or percutaneous nephrostomy (PCN) by IR
 - **Rehydration:** patients often dehydrated, bolus as tolerated and increase maintenance IV fluids → ↑ ureteral peristalsis
 - **Alpha-Blockers:** **tamsulosin** 0.4mg PO qd (hold for SBP <90) → ureteral relaxation, some evidence of increased passage
 - **Analgesia:** Tylenol, NSAIDs if Cr <1.5, add IV opioids if inadequate pain control
 - **Preoperative workup:** NPO preop, BMP/CBC, continue AC if Urology stent, usually hold AC & obtain coags for IR PCN
- **Urgent urology consults:** solitary or transplanted kidney with worsening AKI, UTI, urosepsis in setting of obstruction
- **Obstruction + sepsis:** image ASAP, BCx/UCx, urgent Urology consult; broad IV abx to cover GNRs + enterococcus
- **Non-stone hydronephrosis:** often stricture or malignancy, can require decompression for renoprotection or need for nephrotoxic chemo. Same options (stent vs PCN), same indications of urgent/emergent consult. Urology can help determine stent vs PCN
- **Clinical Pearl:** patients with an acute abdomen lie still, patients with renal colic can find no comfortable position
- **Relevant History:** renal colic is unilateral pain from CVA wrapping around flank radiating towards ipsilateral scrotum/labium

HEMATURIA

- **DDx:** BPH, UTI, INR>3, traumatic catheter placement, bladder CA (5th most common neoplasm), upper urinary tract CA, prostate CA
- **Acute Management:** manual irrigation & serial flush/aspiration → 3-way catheter → CBI with NS, titrate to fruit punch or lighter
 - **DO NOT start CBI if active clot burden. If 3-way clots off, stop CBI and manually irrigate through 3-way until clear**
 - Manual irrigation removes clots that already exist, CBI prevents new clots from forming by flushing active bleeding
- **Diagnostic Workup:** “3 Cs”: 1) in-house hematuria protocol **CT** (3-phase: non-con, nephrogenic phase, delays to assess ureters); 2) urine **cytology** once hematuria clears (blood interferes with test); 3) outpatient **cystoscopy**

OBSTRUCTED CATHETER VS BLADDER SPASM/URGENCY FROM CATHETER

- **Obstructed Catheters:** bladder feels full, urine spasms around catheter, minimal/no urine through catheter, bladder scan is high
 - Tx: disconnect tube from drainage port, gently flush and aspirate with catheter-tip syringe and reconnect
- **Bladder Spasm:** bladder feels full, urine spasms around catheter but continued flow through catheter, bladder scan is low
 - Tx: antispasmodic agents – restart home meds if they have them normally, otherwise can start **tolterodine** (anticholinergic with fewer side effects than oxybutynin) and/or **belladonna-opium suppository** (local anticholinergic)
- Note: bladder scans are inaccurate when patients have ascites because they inappropriately detect the fluid around the bladder

URINARY RETENTION

- **Etiology:** BPH, UTI, constipation, neurogenic (MS, cord injury), DM, immobility, anticholinergics, opioids, benzos, pelvic surgery
- **Treatment:** **bowel regimen**, treat UTI, **minimize opioids/anticholinergics**, encourage **ambulation**, (re)start **tamsulosin** or other α-blocker. Catheterize as necessary – clean intermittent “**straight cath**”, preferred long-term to Foley/SPT if possible

URINARY INCONTINENCE

- **Classifications:** stress (Valsalva), urge (preceded by urgency), mixed (most common), overflow (PVR >150), functional (neurologic)
- **Treatment:** lifestyle interventions, bladder training (timed voiding), Kegel pelvic floor exercises for all types
 - Stress: vaginal estrogen (post-menopausal women w/ vaginal atrophy), pessaries (mixed data), surgery (urethral bulking, slings)
 - Urge: antichol (oxybutynin, tolterodine, beware side effects), β3-agonists (mirabegron, avoid w/ HTN, ESRD, ESLD), Botox
- Note: workup of “voiding dysfunction” (retention, incontinence) usually takes weeks/months of outpatient observation ± urodynamics.

TUBES AND DRAINS: see [Tube Management](#) for placement and management

- **Foley catheter:** *externally placed tube which travels through urethra and into bladder*
 - Considerations: BPH, men >50yo → 16-18Fr Coudé (gentle curve directs catheter tip through curve of prostate), **all RNs are allowed to place coudes – the tip (and balloon port) point “up” towards sky**; stricture → 12-14Fr (can still use Coudé)
 - *Pro-tip:* use 8-10cc lubricant instilled into the urethra for easier catheter placement in men
 - Urethral trauma: leave catheter in 3-5 days to allow for urethral healing (make sure balloon is in bladder & not urethra though)
- **Suprapubic tubes (SPT):** *externally placed tube travels percutaneously through pelvic wall into bladder*
 - Placed by IR, first exchange done by IR, change q6-12w similar to Foley, **RNs do routine exchange, Urology assists PRN**
- **Percutaneous nephrostomy tube (PCN):** *externally placed tube travels percutaneously through flank wall into renal pelvis*
 - Placed by IR under local vs general anesthesia. Cannot be coagulopathic, thrombocytopenic, or on ASA/P2Y12
 - Urine collects in external bag. If low UOP into bags, passage of blood or concern for malposition - obtain US vs CT A/P, call IR
- **Ureteral stent:** *internally placed tube travels from renal pelvis to bladder inside ureter to drain kidney into bladder*
 - Placed by Urology in OR with general anesthesia, requires change every 3-6mo. May cause urinary urgency. Is NOT changed in setting of infection unless stent has failed (which becomes a ureteral obstruction c/b UTI, tx usually = PCN with IR)
- Note: if stents/PCNs/chronic catheter or SPT/ileal conduit or neobladder – UTIs diagnosed on fever, WBC, symptoms, NOT UA/UCx
- Note: there are no good data that Foley/SPT exchange in UTI is helpful because the new tube goes into the same (infected) tract

Consultants

ENT

To call an ENT consult: page the ENT consult resident p22220. To transfer a patient to MEEI: call MEEI ED at 617-573-3431

EPISTAXIS (NOSEBLEED)

- **Acute management:** ([UpToDate Epistaxis](#))
 1. Have pt lean forward, pinch nostrils, hold pressure for 20 min
 - Do not lean head back or hold bony part of nose
 - Hold over basin, measure blood loss as possible
 - **Do NOT “peek”** – hold continuous pressure for 20 min
 - Patient may not hold pinch – best for RN/MD to do
 2. **Afrin (oxymetazoline 0.025%) nasal spray** (after gently clearing clots)
 - **GENEROUSLY SPRAY (5-10 sprays) on both sides then hold pressure again.** Should not cause rebound congestion.
 3. Control SBP (goal < 120) if much greater than baseline
 4. Correct coagulopathy if present and able to
 5. **Consult ENT if continued bleed**
 - Treatment: silver nitrate cauterization, absorbable nasal packing, non-absorbable nasal packing, Neuro IR embolization
 - Non-absorbable nasal packing: risk of Toxic Shock very low; put patient on prophylactic cephalexin or clindamycin; packing typically removed after 5-7d (whether inpt or outpt – can be removed by anyone by pulling on string)
- Location: most are anterior bleeds; **posterior bleeds are more rare/serious/difficult to manage**
- Useful Hx: side, duration, EBL, prior episodes (and txs), trauma (fingers, fists, foreign body, etc), **prior nasal surgery**, nasal trauma hx, FHx or PMhx coagulopathy, nasal tumors, HTN, **anticoagulation**
- Exam: rapidity of bleeding, inspect nasal septum and oropharynx for originating site; **suction clots from OP to protect airway**
- Tests: CBC, PT, PTT, T&S; crossmatch pRBC if brisk bleed
- Epistaxis prevention: after resolution, x 2 weeks: **petroleum jelly** (or bactroban if cautery used) inside rims; **no nose blowing/touching**, no exercise, keep head higher than heart (use pillows), sneeze with mouth open, use humidification (**saline nasal spray BID**), **oxymetazoline spray PRN** if re-bleeding

STRIDOR

- **Acute management:**
 - **IV access, 100% O₂ by non-rebreather**
 - **Racemic epinephrine neb x1 STAT (lasts ~2h), 10 mg dexamethasone IV x1 STAT (re-dose q8h)**
 - Consider IM/IV epinephrine and Benadryl if allergy suspected (see [Angioedema & Anaphylaxis](#)), consider Heliox
 - **If unstable → Call RICU & trauma surgery (x6-3333) for possible surgical airway**
 - **If stable → Call ENT for airway evaluation**
- Epinephrine dosing: if allergic reaction suspected: **0.3mg IM (1:1000 solution)** or 0.1mg IV (1:10,000 solution)
- Hx: timing/evolution, inspiratory/expiratory/biphasic, inciting events, prior episodes, evidence of infection, allergy, hx EtOH/tobacco (cancer risks), hx subglottic stenosis, **hx of known cancer of head and neck or radiation**
- DDx (in adults): iatrogenic/post-intubation (laryngeal/vocal cord edema/praxis of the recurrent laryngeal nerve from ET tube); infectious (epiglottitis, laryngitis, laryngotracheitis [croup], bacterial tracheitis, Ludwig's angina); allergic; tumor/mass of larynx or trachea; neurological (vocal cord spasm or immobility); foreign body/trauma
- Imaging: if stable, **CT with contrast of head/neck/chest** to localize source

ACUTE SINUSITIS ([Otolaryngol Head Neck Surg 2007;137:S1](#)) – see [HEENT Concerns](#) for outpatient management

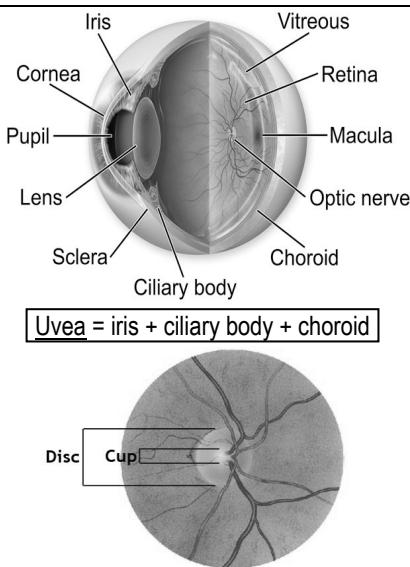
- Primarily a **clinical diagnosis**: CT usually not necessary, and CT findings alone (usually) not sufficient as 40% of asymptomatic people have CT abnormalities of sinuses ([Otolaryngol Head Neck Surg 1991;104:480](#))
- Signs/symptoms:
 - **Uncomplicated** (confined to sinuses): **Major Sx**: facial pressure/pain, purulent nasal discharge, nasal obstruction; **Minor Sx**: fever, cough, malaise, anosmia, dental pain, ear fullness
 - **Complicated** (extra-sinus extension): vision changes, proptosis, mental status changes, severe HA, facial soft tissue changes. In immunocompromised/critically ill, consider **invasive fungal sinusitis, a surgical emergency** (see [Invasive Fungal Infections](#))
- Workup: uncomplicated → no testing required; complicated → CT w/ contrast ± nasal endoscopy to look for evidence of purulence
 - If needing to rule out invasive fungal sinusitis, nasal biopsy with STAT pathology required
- Inpatient treatment:
 - If requires hospitalization, use levofloxacin or **amp/sulbactam IV ± surgery** if complicated/drainable extra-sinus collection
 - Invasive fungal sinusitis: **liposomal amphotericin**, surgical debridement, ID consultation

SUDDEN HEARING LOSS ([Otolaryngol Head Neck Surg 2019;161:S1](#))

- MUST determine conductive hearing loss vs sensorineural hearing loss – obtain audiogram, call 617-573-3266 at MEE to schedule
- If sensorineural hearing loss – initiation of either high dose oral corticosteroids or referral to ENT for intra-tympanic steroids if contraindication to systemic steroids. Must start steroids within 2 weeks of symptom onset

Consultants

Ophthalmology



Basic Eye Exam: "Ocular Vital Signs"

- Visual Acuity (e.g. 20/200, CF)
- Pupils (4mm → 2mm OD, No APD)
- Confrontational visual fields
- Extra-ocular movements
- Intraocular pressure
- Color vision testing (Ishihara cards)

Common Abbreviations:

APD	Afferent pupillary defect	NLP	No light perception (VA)
AT	Artificial tears	NPDR	Non-prolif. diabetic retinopathy
cc/sc	With/without refractive corr.	NS	Nuclear sclerosis (i.e. cataract)
CE	Cataract extraction	OD/OS	Right eye, left eye
CF	Count fingers (VA)	OU	Both eyes
CWS	Cotton wool spot	PDR	Prolif. diabetic retinopathy
DES	Dry eye syndrome	PF	Pred Forte gtt (prednisolone)
EOM	Extraocular movement	PFAT	Preservative-free artificial tears
HM	Hand motion (VA)	PVD	Posterior vitreous detachment
IOL	Intraocular lens	RD	Retinal detachment
IOP	Intraocular pressure	SLE	Slit lamp exam
LP	Light perception (VA)	SPK	Superficial punctate keratitis/dry eye
MGD	Meibomian gland dysfunction	VA, VF	Visual acuity, fields

To call an Ophtho consult: check vision using vision card and pupils prior to calling consult!

General inpatient consult: check paging directory and page/call listed number; can also call MEEI ED back desk 617-573-4063

HIGH-YIELD PEARLS FOR THE WARDS

- **Vision loss:** acute (requires urgent evaluation) vs chronic (outpt referral) – assess patient with their glasses on!!
- **Glaucoma drops:** prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, or alpha 2 agonists – all lower IOP
 - If brand-name drops unavailable: fractionate combo meds, ask pharm for substitution advice, or have pt bring in home meds
- **Dilating drops:** 0.5% tropicamide (parasympathetic antagonist), 1-2 drops placed 15-20 minutes before exam; light-sensitive 4 hours
- **Finding the retina:** dilate the eye and use the ophthalmoscope as in <http://stanfordmedicine25.stanford.edu/the25/fundoscopic.html>

COMMON EYE PATHOLOGY

- **Red Eye:** typically benign; refer to ophtho if no improvement or any “ocular vital sign” changes (see above)
 - **Viral conjunctivitis:** eyes “stuck shut” in AM, itchy, crusty discharge, ± URI symptoms, ± pre-auricular nodes, winter time
 - Tx: supportive/isolation (typically adenovirus, highly infectious). Wash hands thoroughly if you suspect this!
 - **Allergic conjunctivitis:** olopatadine 0.1% gtt bid x 5d. Clear Eyes/Visine not rec'd (rebound redness 2/2 alpha agonism)
 - **Anterior uveitis:** pain and true photophobia **must** be present ± eye injection. Refer to MEEI ED
 - **Contact lens keratitis:** have patients remove contact lens when admitted! Use glasses. P/w red/uncomfortable eye; infection until proven otherwise. Refer to MEEI ED
- **Blepharitis** (inflammation of eyelids): p/w crusting/red eye/gritty feeling
 - Tx: baby shampoo, warm compresses, abx ointments x 2 weeks, then daily lid hygiene. Tx for **hordeolum ("stye")** is same
- **Dry Eye Syndrome (DES):** p/w eye pain or “grit”/paradoxical tearing ± vague “blurriness”
 - Tx: artificial tears q1h prn first line tx, refer if no improvement
- **Corneal abrasion/exposure keratopathy:** unilateral, redness, mild light sensitivity, common after sedation
 - PPx: intubated patients require lubrication regimen (ophthalmic lubricating ointment QID) ± tape eyelids shut if partially open
 - Dx: apply fluorescein (order in Epic) to the affected eye, illuminate with a blue light (e.g. ophthalmoscope, smartphone screen with Eye Handbook App). Abrasion will light up green; keratopathy will look like “sandpaper” instead of smooth glass
 - Tx: abx ointment (Erythromycin 0.5%/bacitracin ophthalmic QID) + Lacrilube qhs. Consult if no improvement after 24h
- **Anisocoria (unequal pupils):** old (20% population has at baseline) vs. new (can be trivial 2/2 anticholinergic vs. catastrophic from herniation). Always ask for **h/o ocular surgery** as surgical pupil is a common benign cause

Miosis (Constricted Pupil)	Mydriasis (Dilated Pupil)
↑ Cholinergic (e.g. morphine, pilocarpine)	↑ Sympathetic (e.g. atropine, CNIII paralysis)
↓ Sympathetic (e.g. Horner's)	↓ Cholinergic (e.g. epinephrine, cocaine)

- If clinical suspicion for herniation (known bleed, CN3 palsy, obtundation, hemiparesis) → **STAT head CT**
- **Horner's Syndrome:** ptosis, miosis, ± anhidrosis. Wide ddx along pathway from posterior hypothalamus → C8-T2 → superior cervical ganglion → up sympathetic chain along internal carotid and into orbit. Requires head and neck angiographic imaging to r/o potential carotid dissection
- **Retinal detachment:** presents with flashes/floater/curtain coming over vision. Risk factors: myopia (near-sighted), trauma, diabetic retinopathy, prior eye surgery
 - Tx: Refer to MEEI ED. Will likely require vitreoretinal surgery
- **Subconjunctival hemorrhage:** blood between conjunctiva and sclera from ruptured vessel. No vision changes, not painful. Can be 2/2 associated blood dyscrasia, valsalva, trauma, spontaneous. Will resolve spontaneously. No need to consult ophtho
- **Endophthalmitis:** infection within globe. Can be 2/2 trauma, surgery, or endogenous source (bacteremia/fungemia)
 - Tx: Ophtho c/s, antibiotics/antifungals that will penetrate blood-brain barrier. May require vitrectomy (surgery)

Consultants

OB/GYN

HOW TO CONSULT

- Obstetrics:** if pt has pregnancy >20w or has established MGH OB provider
- GYN Onc:** if pt has biopsy confirmed GYN malignancy or established GYN onc provider
- GYN:** everyone else (e.g. pregnancy <20w, undifferentiated ovarian mass). Obtain **pelvic U/S**. If hCG+ but no confirmed intrauterine pregnancy, should be followed on **ectopic list**

ABNORMAL UTERINE BLEEDING

- Postmenopausal bleeding is never normal. If premenopausal, rule out pregnancy and its complications
- History:** verify source of bleeding is vaginal, duration and quantity (#soaked pads), associated sx (pain, dizziness), triggers (e.g. postcoital), trauma hx; Other hx: estrogen contraindications (smoking, BMI, h/o coagulopathy), LMP/menstrual hx, full pregnancy hx, known GYN conditions (e.g. fibroids), meds (hormones, AC)
 - Heavy bleeding = soaking through 1 pad per hour**, symptomatic, Δ VS, ↓ Hgb
- Exam:** external vulvar exam, speculum exam (note how many scropettes required to clear bleeding, volume of blood in vault, cervical lacerations, blood actively coming from cervix). Do NOT do digital exam if pregnant

Differential Diagnosis for Abnormal Uterine Bleeding	
Pregnant	Ectopic pregnancy, miscarriage, implantation of pregnancy, subchorionic hematoma, placental abruption, placenta previa/accreta, vasa previa, trophoblastic disease, cervical/vaginal/uterine pathology (e.g. polyp)
Not pregnant	Endometrial/cervical polyp, adenomyosis, fibroids, endometrial hyperplasia/cancer, coagulopathy, ovulatory dysfunction, cervical cancer, thyroid disease, vaginal/vulvar etiologies (e.g. laceration, atrophy)

- Workup:** CBC, T&S, coags, pad count (Epic order, monitors bleeding quantity)
 - If premenopausal, first step is **urine hCG**
 - If +, obtain **serum quant hCG** (more sensitive for early pregnancy) and **pelvic U/S** (must rule out ectopic pregnancy in all pregnant women with bleeding)
 - If intrauterine pregnancy not confirmed on U/S, measure serial **serum hCG q48h** (should increase 35-50% in 48h) and repeat pelvic U/S. Ectopic risk factors: IVF pregnancy, h/o STIs, prior ectopic, h/o tubal surgery
 - If postmenopausal, **endometrial biopsy** (difficult to do inpatient) or **pelvic U/S** (biopsy if endometrial lining >4mm)

PREGNANCY AND ITS COMPLICATIONS

- Gravida/para (GP), G= #pregnancies, P= #births; TPAL (T=term births, P=preterm births, A=abortions, L=living children)
- References: Normal lab values by trimester ([UTD](#)). Guide to OTC med use/symptom tx during pregnancy: ([AFP 2014;90:548](#))

	Differential and Presentation	W/u and Tx	Complications
Hypertension (>140/>90)	Pre-eclampsia (PEC): new onset HTN + proteinuria (pr/cr >0.3) OR significant end-organ dysfunction after 20w gestation (to 2d-6w postpartum) (ObGyn 2020;135: e237) PEC with severe features: BP >160/110 OR BP >140/90 + ≥1: 1) new onset cerebral/visual sx (photophobia, severe HA, AMS), 2) RUQ/epigastric pain or LFTs >2x nl, 3) plt <100k, 4) Cr >1.1, 5) pulm edema HELLP (see below)	Labs: BMP, LFTs, CBC/diff, LDH, smear, urine protein/Cr ratio or 24h urine protein Tx: delivery, MgSO ₄ , IV labetalol, hydral (if BP >160/>110)	-Stroke (Most commonly hemorrhagic) -Eclampsia (grand mal seizures)
	Gestational Hypertension: new onset HTN after 20w gestation without proteinuria, end-organ damage	If >160/>110; mgmt same as PEC + severe features	High risk progression to PEC
	Chronic Hypertension: HTN present before 20w pregnancy or persists 12w postpartum	Labetalol, nifedipine, methyldopa preferred	
Thrombocytopenia (Plt <150k)	HELLP: rapid onset abdominal pain (epigastric, RUQ), n/v, HA in pt >28w gestation; hemolysis (≥2: smear w/ schistos & burr cells, bilirubin >1.2, low hapt or ↑LDH 2x ULN, severe anemia not related to blood loss), elevated liver enzymes (AST or ALT >2x ULN), low platelets (<100k) Pre-eclampsia (see above)	Labs: BMP, LFTs, CBC/diff, LDH, haptoglobin, smear, urine prot/Cr, coags Tx: delivery, MgSO ₄ , Plt/RBC transfusion if bleeding	Bleeding, DIC, renal failure, pulm edema, liver hematoma
	Gestational thrombocytopenia: Plt >100k, no sx, no anemia Other ddx unrelated to pregnancy: ITP (esp if plt <80k), APS, DIC, TTP, malignancy, drug, infection	No tx or w/u needed	Self-resolves

X-RAY

5 Radiographic Densities				
Air	Fat	Soft Tissue	Bone	Metal

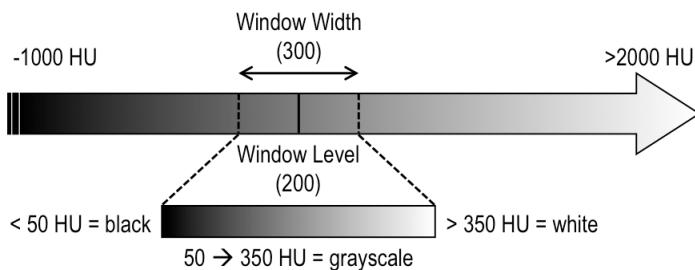
Silhouette Sign: loss of the margin between two opposing structures of the same radiographic density

- RUL – right paratracheal stripe
- RML – right heart border
- RLL – right hemidiaphragm
- LUL – aortic arch
- Lingula – left heart border
- LLL – left hemidiaphragm

COMPUTED TOMOGRAPHY (CT)

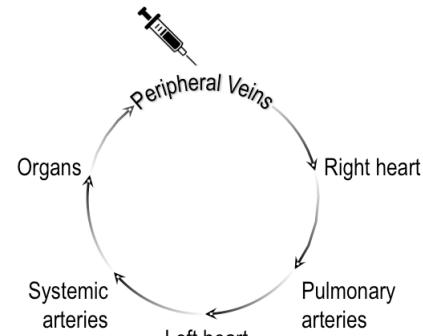
- Hounsfield Units (HU): measurement of CT attenuation
- Windowing and leveling: adjusting contrast and brightness to highlight structures
 - Window (contrast): range of Hounsfield units displayed across the grayscale
 - Wide window – best for large differences in attenuation
 - Narrow window – best for subtle differences in attenuation
 - Level (brightness): HU that corresponds to mid-gray
 - High level – best for structures with high attenuation
 - Low level – best for structures with low attenuation

Substance	HU
Air	-1000
Fat	-100
Water	0
Blood	50
Soft tissue	100
Bone	1000
Metal	>2000



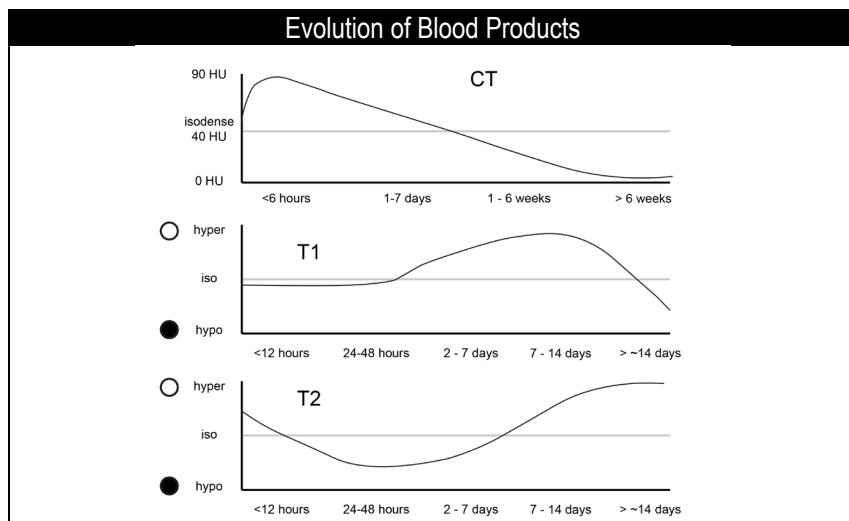
- Phases of contrast:

Phase	Time After Injection	Structures Evaluated
CTPE	15 s	Pulmonary arteries
Arterial (CTA)	30 s	Aorta, systemic arteries, renal cortices
Late arterial	60 s	Routine chest
Portal Venous	70 s	Routine abdomen
Nephrographic	100 s	Renal medulla
Venous	120 s	Peripheral veins
Delayed (Urogram)	10-15 min	Ureters, bladder



MAGNETIC RESONANCE IMAGING (MRI)

	T1	T2
Blood	●	●
Protein	●	●
Air	●	●
Calcium	●	●
Fat	○	○
Fluid	●	○
Gadolinium	○	



- MRI safety
 - Device compatibility: mrисafety.com

Radiology

Contrast

INDICATIONS FOR CONTRAST ADMINISTRATION

- **IV (I+)**: whenever possible, particularly for **infection, tumors, and vessel imaging**
- **PO positive (O+; hyperdense)**: bowel obstruction, bowel wall pathology, differentiate bowel from other abd. structures
- **PO negative (O-; hypodense)**: inflammatory bowel disease, GI bleed, mesenteric ischemia
- **Rectal (R+)**: appendicitis, penetrating abdominal trauma

PREGNANCY AND BREASTFEEDING ([ACR 2020](#))

- **Pregnancy**:
 - *Iodinated*: no need to withhold contrast (no data to suggest potential harm to fetus)
 - *Gadolinium*: unknown risk to fetus → consider noncontrast or alternative study
- **Breastfeeding**: mother's informed decision to "pump and dump" for 12-24h after scan

RENAL FUNCTION ([ACR 2020](#); [MGPO 2020 \(CIN\)](#); [MGPO 2020 \(NSF\)](#); [JAMA IM 2020;2:223](#))

	Contrast Induced Nephropathy	Nephrogenic Systemic Fibrosis
Risk factors	Age >60 years, dialysis, kidney transplant, single kidney, renal cancer, renal surgery, HTN on medication, DM, metformin	Group I and III Gadolinium-Based Contrast Agents (GBCAs) (e.g. Eovist) in patients with kidney disease (acute or chronic) and/or DM. NSF risk "sufficiently low or possibly non-existent" w/ default (group II) GBCAs (Dotarem, Multihance)
Screening (At risk only)	Outpatient: GFR within 30d Inpatient: GFR within 24h	Not necessary for vast majority of scans Obtain GFR within 2d for Eovist if RFs present
Prevention	GFR ≥30: contrast per protocol (NO PREHYDRATION RECOMMENDED) GFR <30: ppx, non-contrast, or alternative study <ul style="list-style-type: none">• If necessary → consult radiology	Group II GBCA: per protocol regardless of GFR Group I or III GBCA: consult radiology if GFR <30
Dialysis pts	HD within 72h after scan	Prompt post-scan HD suggested (PD inadequate)
Repeat studies	Decision is clinical and subjective Insufficient evidence to hold contrast for 24h	No risk factors: proceed At risk pts: consult radiology
Metformin	GFR ≥30: continue metformin GFR <30 or AKI: hold for 48h after scan	No need to hold metformin

• MGH prehydration protocol: ([MGPO 2020](#))

- **Prophylaxis indications**: eGFR <30 (not on chronic HD), AKI, consider with eGFR 30-44 and multiple RFs above
- **PO (preferred)**: 1-2L PO non-caffeinated beverage 12-24h prior to scan
- **IV (outpatient)**: NS 250mL IV bolus @ 1h prior to scan
- **IV (inpatient)**: NS 100mL/h IV 6-12h before and 4-12h after scan ([ACR 2020](#))

CONTRAST REACTIONS ([ACR 2020](#))

	Allergic	Physiologic	Indications for Premedication
Mild	Limited urticaria Itchy throat Nasal congestion URI symptoms	N/V, flushing/warmth HA/dizziness Mild HTN Transient vasovagal reaction	<ul style="list-style-type: none">• Prior mild-moderate allergic reaction• None for prior physiologic reactions• None for shellfish allergies• No cross-reactivity between iodinated contrast and gadolinium
Moderate	Diffuse urticaria Facial/laryngeal edema w/o dyspnea or hoarseness Bronchospasm w/o hypoxia	Protracted N/V HTN urgency Isolated CP Vasovagal reaction requiring tx	
Severe	Anaphylaxis Facial/laryngeal edema w/ dyspnea or hoarseness Bronchospasm w/ hypoxemia	HTN emergency Arrhythmia Seizure Protracted vasovagal reaction	

- See [Drugs and Contrast](#) section on pre-medication prior to scan

ORDERING STUDIES

- All cross-sectional studies are protocolled by radiology – simply provide the necessary information:
 - Body part and modality
 - Indication: clinical history relevant to the study (**GOOD HISTORIES IMPROVE INTERPRETATIONS**)
 - Contrast: “per radiology discretion” unless specific reason otherwise (I+ IV; O+ oral, R+ rectal)
 - Contraindications for contrast: kidney injury or prior allergic reaction (see *Contrast*)
 - Questions: call the appropriate division or page the appropriate on-call radiologist (see *MGH Directory*)
- Level of Urgency:
 - Routine: order of interpretation depends on acquisition time
 - Urgent: takes priority over routine studies
 - STAT: means NOW, high acuity/life threatening emergencies
 - Patient must be ready for immediate transport
 - Patient must be accompanied by a responding clinician capable of providing emergency care
 - Responding clinician must be present for the entire exam
 - Radiology will provide preliminary read: phone call for XR/US, at the scanner for cross-sectionals

OVERNIGHT READS

- Studies with full interpretations overnight: all ED studies, STAT studies, and acute CT PEs
- Verbal preliminary reads:
 - Typically done for **ICU studies only**
 - Inpatient studies are only reviewed overnight if there is an **urgent clinical question** (i.e. one that would alter overnight management). Consider face-to-face consult in ED
 - After communication w/ the primary team, all verbalized prelim reads will be documented in the chart
 - A full interpretation will be generated the following morning for all prelim reads

ED PROTOCOLS

- Trauma: I+ (IV contrast), single phase (arterial for chest, portal venous for abdomen/pelvis – images checked at the scanner by radiology for possible delays)
 - Blunt trauma: includes bone kernel reformats for improved visualization of bones
 - Penetrating trauma: O+R+ (Oral contrast, rectal contrast) for increased sensitivity of bowel injury
- Cervical spine: I-, need for CTA determined by radiology, bone kernel reformats in all 3 planes
 - Images checked at the scanner by radiology only if IV contrast is required for another body part
- Appendicitis: I+ and O+/R+ (please specify PO or PR), kidneys through pelvis only
- Neuro ED: call reading desk @ x68188

GI/GU PROTOCOLS

- Stone protocol: I-O-, low dose
 - Order contrast-enhanced CT if there is concern for ANYTHING else (stones may still be visualized)
- Routine abdomen/pelvis vs renal mass vs bladder cancer vs hematuria:
 - Routine abdomen/pelvis: I+O+, single phase (portal venous) → workhorse protocol
 - Renal mass: I+O+, two phases (noncontrast, nephrographic), abdomen only → renal masses or cysts
 - Bladder cancer: I+O+, two phases (portal venous, delayed) → workup or monitoring of GU malignancy
 - Hematuria: I+O-, “three” phases (noncontrast, nephrographic, urogram) → hematuria, hydronephrosis
- CT urogram vs CT cystogram:
 - Urogram: antegrade filling of ureters and bladder with IV contrast (delayed phase)
 - Cystogram: retrograde filling of bladder with contrast via Foley catheter → evaluation of bladder rupture
- Arterially-enhancing tumors:
 - MR CHIT: Melanoma, RCC, Choriocarcinoma, HCC, Islet cell (neuroendocrine) tumors, Thyroid
- Does my patient need to be NPO?
 - IV contrast CT: 2h Abdomen/pelvis CT: 8h Non-contrast CT: no NPO
- Fluoroscopy protocols:
 - Requisition: specify indication, h/o surgery or aspiration
 - Barium swallow vs modified barium swallow vs UGI series vs SB follow-through:
 - Barium swallow: esophagus, GE junction, proximal stomach → dysphagia, GERD
 - Modified barium swallow: mouth, pharynx, upper esophagus → dysphagia, aspiration
 - UGI series: barium swallow plus stomach, pylorus, and duodenal bulb → bariatric surgery
 - SB follow-through: small bowel, terminal ileum, and proximal LB ± UGI series beforehand

CARDIOVASCULAR PROTOCOLS

- DVT imaging: U/S (LENI) is initial test of choice ([Cardiovascular Diagnosis and Therapy 2016;6:493](#))
 - CTV/MRV: primarily used for central venous thrombosis when initial U/S is equivocal or non-diagnostic
- Arterial imaging:
 - CTA: three phases (noncontrast, arterial, delays) → stenosis, dissection, aneurysm
 - Requisition: specify vessel of interest, field of view, and indication
- Coronary CTA:
 - ECG-gated study of the heart → only performed by CV CT on-call radiologist during normal hours
 - Specify if body parts other than the heart should be imaged (thoracic aorta, CABG grafts, etc.)
- Other EKG-gated CTAs:
 - Indications: any evaluation of the heart or ascending aorta
 - EKG-gating is unnecessary for the descending thoracic aorta, abdominal aorta, and pulmonary arteries
- Noncontrast vascular studies:
 - RP hematoma, pre-op aortic calcifications, coronary calcium score, follow-up aortic size

THORACIC PROTOCOLS

- All chest CTs are high resolution – traditional “high res chest CT” is now the diffuse lung disease CT (see below)
- Routine chest vs CT PE vs CTA chest:
 - Routine chest: single phase (late arterial) → workhorse protocol
 - CT PE: single phase (pulmonary arterial) → pulmonary arteries
 - CTA chest: three phases (noncontrast, arterial, delays) → systemic arteries
- Double rule out studies:
 - Clinical concern for PE and aortic dissection
 - Contrast can only be optimized for one (must pick CT PE or CTA)
- Diffuse lung disease (a.k.a. misnomer “high res CT”):
 - Indications: ILD, lung transplant, air trapping
 - Inspiratory and expiratory images, plus prone images to differentiate between atelectasis and fibrosis
- Nodule follow-up: ([Radiology 2017;284:228](#))
 - Indications: incidental nodule on prior CT, age >35y, AND no history of malignancy or recent infection

NEURORADIOLOGY PROTOCOLS

- Inpatients: page Neuro IP on-call radiologist at p32535
- Acute stroke:
 - Inpatients/ICU: call x6-3333 or page acute stroke consult fellow at p21723
 - ED: activate ED2CT via the group pager
- Head CT: typically noncontrast
 - Indications for contrast-enhanced head CT: infection and/or tumor AND contraindication for brain MRI
- Spine MRI: for more than one segment, please order total spine and specify indication
 - Separate MRIs should not be ordered prior to neurology/NSGY consult
- Fluoroscopy-guided LPs: performed by neuroradiology fellows, NOT neuro IR
 - Indications: difficult anatomy, and only after LP is attempted on floor
 - Typically performed without conscious sedation, although this can be arranged if required for patient safety

NUCLEAR MEDICINE PROTOCOLS

- Overnight studies:
 - Tagged RBC study: BRBPR (NOT guaiac positive stools, melena, or massive bleeding)
 - Requirements: consult IR first for possible angiogram if study is positive
 - VQ scan: acute PE (NOT chronic PE), ONLY if results will alter management (i.e. AC tonight)
 - Requirements: CXR within 24h, patient stable for duration of scan (~4h)
 - HIDA scan: acute cholecystitis, ONLY if results will alter management (i.e. OR tonight)
 - Requirements: NPO 4-24h prior to study, no opiates 12-24h prior to study, bilirubin <10
- PET:
 - Fasting: hold everything but meds and water
 - Overnight is ideal, but at least 6h for non-DM patients
 - At least 4h for DM patients
 - Continue long-acting insulin, hold short-acting insulin 4h prior to scan
 - Blood sugar thresholds: FDG-PET brain < 175 mg/dL, FDG-PET whole body <250mg/dL

MUSCULOSKELETAL PROTOCOLS

: if questions: page MSK IR on-call radiologist at p36321

CHEST X-RAY

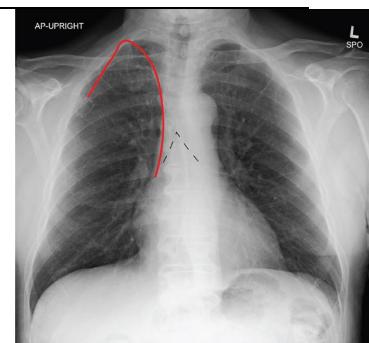
1. Line placement:

- SVC: between right tracheobronchial angle and right heart border ([Chest 1998;114:820](#))
- Cavoatrial junction: two vertebral bodies below the carina ([JVIR 2008;19:359](#))
- Line positioning:
 - Central line: tip in the SVC or at the cavoatrial junction
 - HD catheter: tip in the right atrium
- Post placement: check for pneumothorax (see below)

2. Pneumothorax:

- Sensitivities:

Imaging Position	Detectable PTX Size	Imaging Findings
Supine/Portable	500 cc	Deep sulcus sign, lucency along mediastinal border
Upright	50 cc	Sharp visceral pleural line, absence of distal lung vessels
Lateral decubitus	5 cc	Nondependent collection of air



- Tension: contralateral mediastinal shift, collapse of ipsilateral lung, flattening of ipsilateral hemidiaphragm, widening of ipsilateral rib spaces
- Artifacts that mimic visceral pleural lines: ([BMJ 2005;330:1493](#))
 - Medial border of scapula: in continuity with rest of bone
 - Skin folds: form an interface (not a line), extension beyond rib cage, presence of distal lung vessels

3. Pulmonary edema:

- Vascular redistribution (first sign): increased caliber of pulmonary vessels in upper lobes (cephalization)
- Interstitial edema: increased interstitial opacities, indistinctness of pulmonary vasculature, Kerley B lines, peribronchial cuffing
- Alveolar edema: perihilar/central opacities, pleural effusions, cardiomegaly
- Pearls: typically bilateral and symmetric, rapid appearance/resolution of findings
- Pitfalls: low lung volumes can mimic increased interstitial opacities



ABDOMINAL X-RAY (KUB)

1. Line placement:

- Decompression: gastric fundus or dependent portion of stomach
- Feeding: distal duodenum or proximal jejunum; C-loop of duodenum is only reliable indicator of post-pyloric placement
- Post placement: check for endobronchial placement. G-tube should descend vertically in the midline, pass the diaphragm and tip should be visualized



2. Small bowel obstruction: ([RadioGraphics 2009;29:423](#))

- KUB: preferred initial examination
 - Assess for: small bowel dilatation >3 cm, air-fluid levels, stacked loops of bowel, transition point
- CT: equivocal cases or for further evaluation
 - Assess for: SB dilatation, collapse of distal bowel loops, transition point
 - Severity:
 - Partial: passage or air or contrast beyond the obstruction
 - High grade partial: 50% difference in caliber between dilated and collapsed SB loops
 - Complete: no passage of air or contrast beyond the obstruction
 - Transition point: look for small-bowel feces sign (fecal material mixed with gas bubbles in small bowel)
 - Cause: adhesions, Crohn's, malignancy, hernias
 - Complicated SBO:
 - Closed loop obstruction: radially oriented bowel loops, engorged mesentery, whirl sign
 - Strangulation: bowel wall thickening, lack of bowel wall enhancement, pneumatosus intestinalis, portal venous gas



3. Pneumoperitoneum: ([AJEM 2009;27:320](#))

- Upright: air beneath the diaphragm
- Left lateral decubitus: air over the liver
- Supine (insensitive):
 - Anterior superior oval sign: gas bubbles projecting over liver
 - Hyperlucent liver sign: free air overlying liver
 - Rigler's sign: air on both sides of the bowel wall
 - Falciform ligament sign: linear density projecting over liver



ULTRASOUND

1. Cholecystitis: ([AJR 2011;196:W367](#))

- U/S is preferred initial examination
- Gallstones: echogenic foci with posterior shadowing
- Common findings: gallbladder wall thickening >3 mm, gallbladder distension >40 mm, peri-cholecystic fluid
- Sonographic Murphy's sign: 92% sensitivity (analgesics reduce sensitivity)
- Gallstones and gallbladder wall thickening: 95% positive predictive value for acute cholecystitis

2. Deep venous thrombosis: ([Cardiovascular Diagnosis and Therapy 2016;6:493](#))

- Compression U/S: noncompressibility of vein, echogenic thrombus within vein, venous distension
- Venous duplex U/S: absence of: color Doppler signal, flow phasicity, response to augmentation maneuvers
- CT venogram:
 - Alternative to U/S in critically ill patients who have undergone CT PE
 - Pros: evaluation of pelvic veins and IVC, which are difficult to assess on U/S
 - Cons: invasive, requires contrast, radiation, possible streak or mixing artifacts

CROSS SECTIONAL IMAGING

Excellent resources for anatomy, image interpretation, and sample cases:

[www.radiopedia.org](#); [http://www.radiologyassistant.nl/](#); [https://www.med-ed.virginia.edu/courses/rad/](#); [https://www.learnabdominal.com/](#) (GI/GU); [https://headneckbrainspine.com/](#) (Neuro); [http://xrayhead.com/](#) (MSK)

CT Head
1. Brain parenchyma
a. Mass lesion: brain windows
b. Intracranial hemorrhage: brain and subdural windows
c. Infarction: stroke windows
2. Vessels
3. CSF spaces: ventricles, sulci, cisterns
4. Midline shift or herniation
5. Soft tissues (great place to start for trauma head CTs)
6. Bones/sinuses

MRI Brain
1. Brain parenchyma
a. Mass lesion: T1, T2, FLAIR
b. Intracranial hemorrhage: SWI, T1, T2
c. Infarction: DWI, ADC
2. Vessels: T2 for flow voids, T1 post-contrast, TOF if noncontrast MRA
3. CSF spaces: T2
4. Midline shift or herniation: coronals helpful
5. Soft tissues
6. Bones/sinuses

CT Chest
1. Lines and tubes (scout can be very helpful)
2. Abdomen
3. Soft tissues
4. Bones
5. Heart and mediastinum: thyroid, lymph nodes, heart and pericardium, major vessels, esophagus
6. Pleura: pleural effusion, pneumothorax
7. Lungs: pathology manifests as changes to the secondary pulmonary lobule (see links)
a. Radiology Assistant → Lung HRCT Basics
b. Radiopedia → Lobule Basics

CT Abdomen/Pelvis
1. Lung bases
2. Liver/gallbladder: focal lesions, biliary dilatation
3. Spleen
4. Pancreas: focal lesions, pancreatic ductal dilatation
5. Adrenals
6. Kidneys/ureters: hydronephrosis, stones, focal lesions
7. Bladder/pelvic organs
8. Peritoneum: free air or fluid
9. Lymph nodes
10. Vessels
11. GI tract: bowel distension, bowel wall thickening
12. Soft tissues
13. Bones

Procedures

Ultrasound Basics

REMINDER: do not base clinical decisions on POCUS exams unless the exam and decisions are supported by a supervising provider. Additionally, POCUS should be used in the setting of *limited and targeted clinical questions*

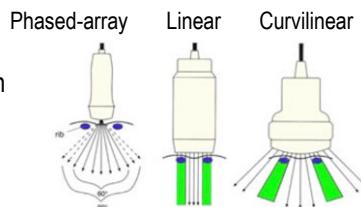
EQUIPMENT ([NEJM 2011;364:749](#))

Basic Terminology:

- Frequency: 1Hz = 1 cycle/sec; medical US typically between 2-15MHz
 - High frequency (>5MHz): ↑resolution, shallow tissue penetration, ideal for **vascular, skin, breast, thyroid**
 - Low frequency (2-5MHz): ↓resolution, deeper tissue penetration, ideal for **abdominal, OB/GYN, cardiac**
- Gain: signal amplification; similar to brightness control. Higher gain = brighter image; lower gain = dimmer image
- Depth: depth of field of view (FOV). Excessively large FOV = ↓spatial resolution; tight FOV limits view of nearby structures
- Attenuation: reduced signal transduction through a medium = ↓signal intensity behind it (bone/air have high attenuation)

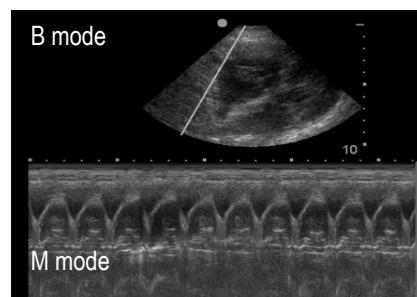
Transducer (probe): converts electricity into sound waves → transmits sound wave into tissue → receives sound waves echoed back from tissue. Indicator (denoted by dot or notch on probe) displays on **left of the screen**. Exception: echocardiography → indicator displays on **right side**. For most indications, position probe with indicator to patient right or cranially

- PHASED-ARRAY (cardiac) probe: good for looking in small windows (i.e. between intercostal spaces for cardiac or pulm imaging); low resolution, fan-like image
- LINEAR (vascular) probe: good for shallow structures (i.e. vascular, soft tissue). Uses high frequency with good resolution, produces rectangular image
- CURVILINEAR (abdominal) probe: good for deeper structures (i.e. intra-abdominal). Uses lower frequency; combines linear and sector probe image qualities



COMMONLY USED MODES

- B-mode (brightness mode): standard 2D gray-scale image
- D-mode (doppler mode): detects flow to or away from transducer. Useful to find and define vessels, or flow across valve
 - Color → direction and velocity are color coded and superimposed on B-mode image. "BART" (Blue is Away from probe, Red is Towards)
 - Power → detects very low flow but not direction, useful in vascular compromise
 - Spectral → velocity presented graphically on a timeline
- M-mode (motion mode): takes a slice of a B-mode image over time. Often used in TTE. Useful to assess lung sliding for pneumothorax



GENERAL IMAGING CONCEPTS

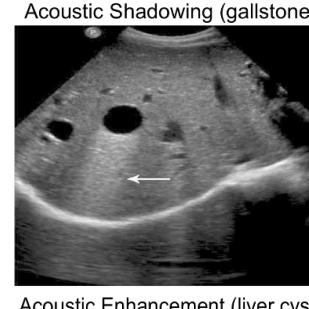
Typical Appearance of Normal Tissue:

- Skin and pleura are smooth and brighter than surrounding tissue (hyperechoic)
- Fat and muscle are darker (hypoechoic), though varies depending on the tissue
- Fluid (e.g. blood, effusion) appears black on US (anechoic), though thick fluids (e.g. pus) can be brighter than typical fluid
- Tendons and nerves are bright (hyperechoic) when perpendicular to probe, but dark (hypoechoic) when angle is changed (anisotropy)
- Bone has a hyperechoic rim (due to reflection) with dark shadow beyond it



Artifacts: elements seen on ultrasound image that do not exist in reality

- Reflection: proportional to the difference in acoustic impedance between two tissues (↑difference = ↑reflection)
- Relative acoustic impedance: bone > solid organ > fat > lung > air
- Shadowing: signal beyond strongly attenuating/reflecting structure (e.g. stones, bone)
- Enhancement: signal posterior to weakly attenuating (hypo or anechoic) structure (e.g., cysts)
- Mirror image: structures in front of strong reflector (e.g. diaphragm) appear to lie behind it as well
- Reverberation: evenly spaced lines at various depths beyond a strong reflector (e.g. A lines beyond pleura)
- Comet tail: tiny, narrow reverberations beyond very strong reflector (e.g. metal pellet) blending into a line



Procedures

Ultrasound Basics

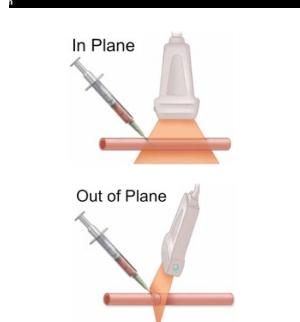
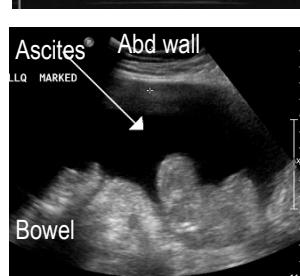
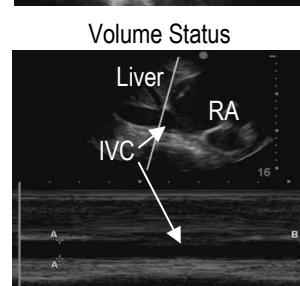
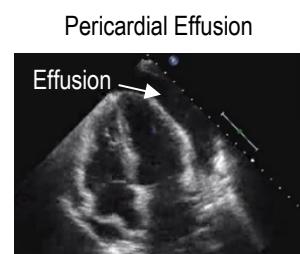
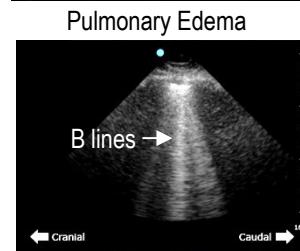
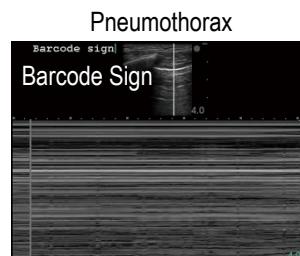
IMAGING AND TIPS (see [The POCUS Atlas](#) for reference)

Diagnostic Use:

- **Pneumothorax:** use LINEAR (vascular) probe. With pt lying supine, look in 3rd intercostal space on anterior chest, pointing indicator cranially. Identify hyperechoic rims of the ribs with posterior shadowing. Identify hyperechoic stripe that is the pleura within the intercostal space. Normal lung will slide along the pleural line with respiration, while pneumothorax will not. If ambiguous, use M mode to confirm. A lack of lung sliding will change the normal 'seashore' sign to a static 'barcode' sign. Sn 91%, Sp 98%, superior to CXR. Can also look for "lung point" (100% specific) ([J Emerg Trauma Shock 2012;5:76](#); [Annals EM 2013;61:207](#))
- **Pulmonary embolism:** use PHASED-ARRAY (cardiac) probe. Bedside US can be used to identify right heart strain. Look for RV size \geq LV size, septal bowing, note Sn 53%, Sp 83% for PE. RV/LV ratio most easily visualized in apical 4 chamber view, can be misleading based upon slight changes in plane. Assess the cardiac septum vertical and in line with midpoint of probe. Combine with parasternal axes for better reliability ([J Am Soc Echocardiogr 2017;30:714](#))
- **Pulmonary edema:** use PHASED-ARRAY (cardiac) or CURVED (abdominal) probe. Evaluate the lung between rib spaces and across multiple lung fields similar to auscultation. Look for B-lines: comet like artifacts that shine perpendicular from the pleural line and obliterate A-lines. ≥ 3 in one interspace is consistent with interstitial fluid, and bilaterally suggests pulmonary edema. Operator dependent but can outperform CXR ([Am J Emerg Med 2015;33:620](#))
- **Pericardial effusion:** use PHASED-ARRAY (cardiac) probe. Look for an anechoic stripe between the heart and the hyperechoic pericardium. Hemorrhagic or purulent effusions may appear more complex. On parasternal long axis, pericardial effusion will be anterior to the descending aorta while a pleural effusion will be posterior. All four views are important but subxiphoid often used in emergencies. Look for chamber collapse indicating tamponade: RA is more sensitive; RV is more specific ([Resuscitation 2011;82:671](#))
- **Volume status:** use the PHASED-ARRAY (cardiac) probe. IVC collapsibility has been proposed as a proxy for CVP and fluid responsiveness, though data is mixed. There are no consensus guidelines. Start with subcostal view of RA/RV, then rotate probe to the sagittal plane to find the IVC draining into RA and abutting the liver. Look at IVC 2cm from RA: fluid responsiveness or an underfilled IVC is suggested by 1) IVC diameter ≤ 1.5 cm and 2) IVC collapses $\geq \frac{1}{2}$ its diameter. Can use M mode to assess collapsibility. Pair IVC POCUS w/ lung US for volume status evaluation. ([Crit Care 2012;16:R188](#); [CCM 2013;41:833](#); [Shock 2017;47:550](#))

Procedural Use: refer to pages on specific procedures for more details

- **Paracentesis:** use CURVED (abdominal) probe. Locate largest fluid collection, often in LLQ. Try rolling patient to side to increase pocket size. LINEAR (vascular) probe can help identify any overlying vessels (particularly inferior epigastric vessels). Bowel appears as hyperechoic finger-like projections within the anechoic ascites. Measure the depth of the abdominal wall and compare to your needle to determine when to expect flash
- **Central venous access:** use LINEAR (vascular) probe. Reduces complications and quality of placement compared to landmark approach ([Crit Care 2017;21:225](#))
 - In-plane (longitudinal): can view entire tip, but harder to keep needle in view
 - Out-of-plane (cross sectional): easier to center needle, may underestimate depth
- **Peripheral IV:** use LINEAR (vascular) probe. Most of your time should be spent finding the best vein to go for. Evaluate anterior forearm prior to assessing the cephalic in upper arm. Track along vessel length to determine trajectory, look for large, superficial, compressible vessels that are not immediately adjacent to pulsatile, non-compressible arterial vessels



Procedures

Ultrasound-Guided Peripheral IV

GENERAL CONSIDERATIONS

Indications: non-emergent access in a patient with difficult access. If emergent obtain IO or central access

Locations: forearm first; then AC, cephalic, basilic, brachial; larger veins offer higher chance of success than smaller veins (see figure)

Contraindications: relative: sensory/motor deficits (clot risk), HD fistula, hx of LN dissection

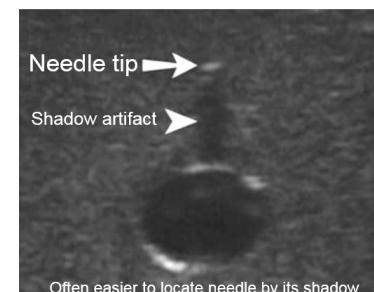
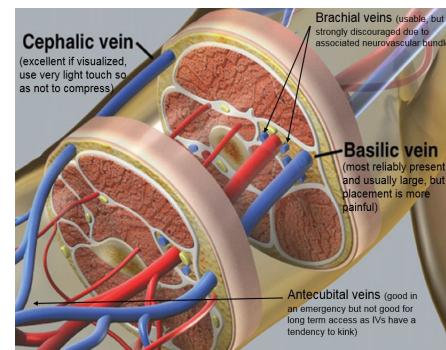
Materials: angiocath (18 or 20G best; small IVs not well visualized on US), vascular probe, gel/sterile lubricant, tourniquet, alcohol wipe/chlorhexidine, tegaderm, extension tubing, saline flush, ± vacutainer adapter and tubes (if labs needed)

- **Angiocath selection:** standard length (30mm) good for vein <0.8cm deep; long needle (48mm) preferred for ≥0.8cm deep (48mm 18G [green] stocked in most supply rooms, but 48mm 20G [pink] more difficult to find. Can try back of AMPS US cart as last resort)

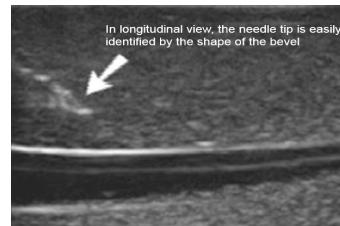
TRANSVERSE TECHNIQUE

[NEJM 2012;366:e38](#): choosing a vein (8:45), transverse (10:05), longitudinal (12:28)

- 1) **Setup:** positioning is very important. Place US on opposite side of pts bed, adjust bed to appropriate height, obtain seat if needed, abduct & externally rotate pts arm
- 2) **Place tourniquet:** place tourniquet proximal, near axilla if possible. Can stack two tourniquets for extra compression
- 3) **Confirm anatomy:** use the vascular probe at minimum depth to locate adequate superficial veins
 - **Find vessels:** start at AC and move proximal first, then distal. Key is to find LARGE vessels (>0.4cm diameter) that are CLOSE to the surface (depth between 0.3cm – 1.5cm) ([J Emerg Med 2010;39:70](#)). Common veins: basilic, cephalic > deep brachial (see figure)
 - **Confirm venous circulation:** gentle pressure differentiates veins (fully compressible, non-pulsatile) and arteries (non-compressible, pulsatile); color doppler can confirm
 - **Trace vessel course:** follow the vessel course proximally and distally; recognize and avoid branch points, diving veins, and irregular coursing veins → identify the trajectory along which the ultrasound probe travels to maintain centered vessel
- 4) **Sterility:** use alcohol pad or chlorhexidine swabs to sterilize proposed venipuncture site; clean US probe, then cover with tegaderm; use sterile lubrication (or sterile US gel) as conduction medium for probe (can also put gel under tegaderm)
- 5) **Orient ultrasound:** center target vein on US screen, confirm with compression, confirm vein course is in line with proposed needle course, stabilize probe by anchoring hand on patient
- 6) **Insert angiocath:** with *bevel up*, puncture skin and advance angiocath 2-3 mm at a 45° angle
 - Angiocath needle tip should be *centered on US probe* – this will be directly over the vein if vein is centered on screen
 - Insertion site at skin is *distal* to the planned site of insertion into vein
 - At insertion, eyes should be on the *site of venipuncture*, not on the US screen, though after puncture, should be watching screen and not hand
- 7) **Find tip and advance:** needle tip (and shadow) should appear on screen → advance PROBE until you lose needle tip → advance NEEDLE tip until it reappears on US screen; continue to advance until tip is “tenting” the roof of the vein
- 8) **Enter vein:** a quick short jab will allow you to enter vein; visualize needle tip as “target sign”
- 9) **Drop angle and advance:** drop your hand to flatten needle angle; continue to advance as above, keep needle in center of vein (always aim to get “target sign” with each probe then needle advancement) until angiocath is hubbed to skin, then retract needle
- 10) **Alternative: Slide off catheter:** once 3-5mm into vein, can slide catheter off needle into vein and hub, and retract needle
- 11) **Flush:** attach extension tubing, REMOVE Tourniquet, pull back on saline flush (ensure drawback), THEN FLUSH with saline → can also confirm lack of extravasation of saline under US visualization
- 12) **Secure:** secure catheter and tubing with tegaderm; nurses may redress IV



Often easier to locate needle by its shadow



In longitudinal view, the needle tip is easily identified by the shape of the bevel

LONGITUDINAL TECHNIQUE: use the following adjustments to the above technique

- 1) Identify target vein in the transverse view
- 2) **Rotate the probe to obtain a longitudinal view with the indicator towards your needle**
- 3) Align needle in the plane of the probe; puncture skin at 45 degrees, visualize needle tip
- 4) Advance needle until you can see that the tip of the catheter itself is fully within the vein
- 5) Do not go through the back wall. Advance the catheter under direct visualization

Technique	Pros	Cons
Transverse (short axis)	- Faster, requires less finesse with US probe - Allows visualization of adjacent structures	- Harder to visualize the needle tip - Risk of “through and through”
Longitudinal (long axis)	- Improved visualization of the needle tip - Can advance catheter under direct visualization	- Challenging to maintain probe/vein/needle in plane - Cannot see adjacent structures

TROUBLESHOOTING ([Transverse Video](#); [Longitudinal Video](#); written guide: [West J Emerg Med 2017;18:1047](#))

- **Can't see needle:** **gently bounce the needle tip** to generate artifact
- **Too much loose tissue:** use tape or have someone assist by **putting tension on the tissue** w/o applying pressure over target vein
- **Vein rolls:** **reposition** directly over the middle of vein, use a slightly **steeper angle** to take advantage of the sharp edge of the needle
- **Trouble finding any veins:** try using a **blood pressure cuff** high in the axilla instead of a tourniquet, but give the patient frequent breaks

Procedures

Central Line

GENERAL CONSIDERATIONS

Indications: hemodynamic monitoring (CVP, CVO₂); admin. of noxious meds (pressors, chemo, hypertonic solution, TPN); rapid large volume resuscitation; inadequate peripheral access; HD/CVVH/pheresis); to introduce other devices (PA line, temp wire)

Contraindications: vein thrombosis or stenosis should prompt another site. Coagulopathy/thrombocytopenia are relative contraindications, if severe coagulopathy, avoid subclavian (not a compressible site & difficult to effectively monitor for bleed)

Site selection: general preference at MGH is RIJ > LIJ > subclavian/femoral due to historical concern for infection. However, more recent data suggests no difference between these sites with proper attention to sterile technique ([NEJM 2015;373:1220](#))

Catheter selection: select based on number of lumens and speed of infusion; if rapid infusion required → large bore, short length Cordis. Right IJ catheter length: 16cm. Left IJ catheter length: 20cm

Alternatives: PICC (if no concern for bacteremia) or IO (if emergent, should not be used for >24h)

Infection control: scheduled exchange of catheters without evidence of infection is NOT indicated. Cultures drawn from indwelling catheters have ↑false + rate; generally not done aside from time of sterile placement ([NEJM 2003;348:1123](#))

INTERNAL JUGULAR VEIN ([Video: NEJM 2010;362:e57](#))

Advantages	Disadvantages
Compressible vein	Carotid artery puncture 2-10%
Lower risk of pneumothorax (< 1%) than subclavian	Less patient comfort
Ability to use real-time ultrasound	Anatomy not as consistent as subclavian

All IJ CVCs placed with real-time US guidance @ MGH: ↓first attempt failure, procedure time, and failure/complication rate

Positioning: supine + Trendelenburg to engorge veins & ↓risk of air embolus. Towel can be used to elevate shoulder to lateralize IJ and make neck flatter/more US-friendly

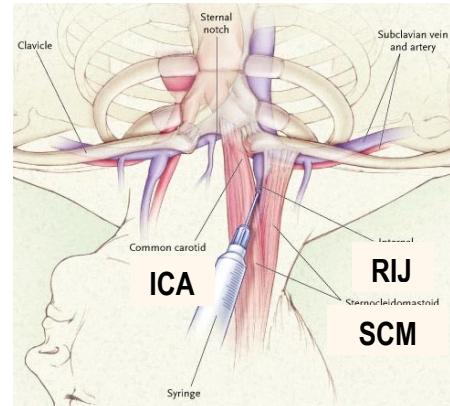
Site selection:

- Locate triangle formed by medial and lateral portions of SCM with the clavicle as base
- Find IJ; typically superficial and lateral to carotid, compressible
- RIJ generally preferred (direct course to SVC), LIJ ↑risk of PTX and thoracic duct injury

Target: aim at ipsilateral nipple, 45 degrees (map out trajectory of vessel using ultrasound)

- Preparation and positioning are essential; ensure someone is always available to help
- Obtain consent; perform TIME-OUT; complete checklist with RN assistance
- Use US to ensure your target anatomy is in good position. Encouraged to assess LIJ & RIJ
- Use 2% chlorhexidine solution to prep (in the kit); drape the entire patient in sterile field
- Place caps on CVC, flush all lines with sterile saline, remove cap from brown port; ensure guide wire advances easily and syringe comes off needle easily
- Locate IJ vein & carotid artery using ultrasound
- Anesthetize with lidocaine; can make wheal & inject along tract (aspirate before injecting!)
- Insert (bevel up) large bore needle at the apex of SCM/clavicle triangle, about 4-5 cm above suprasternal notch. Advance @ 45° towards ipsilateral nipple visualizing tip with US; apply negative pressure throughout. Once flash of blood is obtained → stop advancing the needle, continue to draw back venous flow (dark, non-pulsatile)
 - If arterial flow seen, remove needle and compress ~10 min
 - If air drawn back, suspect PTX → STAT CXR, 100% FiO₂, decompress if tension
- Once flow obtained, stabilize needle with your non-dominant hand, flatten needle angle while drawing back, remove syringe from locator (occlude hub with thumb to minimize risk of air embolism in non-ventilated patients)
- Feed the curved end of the wire into the needle (never feed the opposite end)
NEVER LET GO OF THE WIRE.
 - If any resistance, remove wire, assess for flow w/ syringe; if good blood flow, try twisting wire or flattening angle of needle
 - For RIJ → feed ~25cm of wire (between two and three dark lines)
→ watch for ectopy (suggests wire in RV → withdraw)
- Remove needle
- Confirm wire is in vein using US in transverse and longitudinal planes
- Perform manometry confirmation → advance angiocath from kit over wire, remove wire, connect manometer tubing → leave fluid in manometer and hold vertically to avoid air embolism → venous blood should be non-pulsatile, dark, and rise <20cm → disconnect manometer tubing → replace wire through angiocath → remove angiocath
- Extend puncture site with scalpel by inserting along path of wire (face cutting edge away from wire to prevent cutting wire)
- Thread dilator over wire (using twisting motion) until about 1/3 is inserted, then remove; goal is to dilate skin/subcutaneous tissue, NOT the vessel itself (increased bleeding); ensure the wire moves back and forth freely while dilating (may otherwise be kinked)
- Advance catheter over wire (wire comes out brown port, which is why it must be uncapped); remove wire
- Draw back vertically off all ports through caps using saline flush (only small amount of flash needed), flush all lines clean, clamp ports
- Secure with sutures; place Biopatch prior to securing with dressing
- Order CXR (ASAP) to assess position, rule out PTX/hemothorax; **look at the CXR yourself;** catheters should terminate in superior vena cava or cavo-atrial junction; may need to pull back if in RA (→ ectopy). If adequate position, put in order “OK to use.”

Transverse ultrasound view showing RIJ anterior & lateral to carotid artery



Procedures

Central Line

**For subclavian or femoral vein access especially, please discuss with attending and ensure appropriate oversight prior to procedure!

SUBCLAVIAN VEIN (Video: NEJM 2007;357:e26)

Advantages	Disadvantages
Anatomy more reproducible, incl obesity, w/ bony landmarks	Risk of PTX (1-8%), L side slightly > R, higher dome of L pleura
Improved patient comfort; easier to dress and maintain	Not easily compressible ; more risk a/w bleed if coagulopathic
	Risk of subclavian artery puncture/hemothorax (0.5-1%)

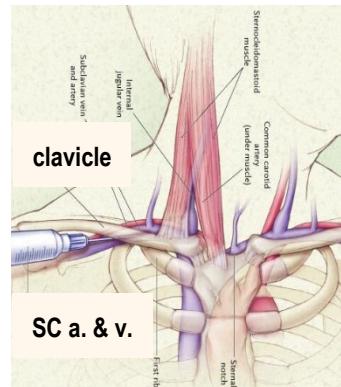
Positioning: place in Trendelenburg to engorge vein and consider placing a roll of towels between the scapula to expose subclavicular area (may distort anatomy for some)

Entry: @ MGH → infraclavicular approach (as opposed to supraclavicular); puncture skin 1cm caudal to junction of medial 1/3 and middle 1/3 of clavicle (where vein flows just under the bone)

Target: bevel up and aim toward sternal notch, 30° to the skin; needle should advance just on the underside of the clavicle (~3-5cm depending on anatomy); some people “walk down” the clavicle to ensure this, but may lead to dulling or bending of needle as well as periosteal pain

Pearls:

- Turning head to ipsilateral side will kink IJ and facilitate wire going down the SVC
- Rotate bevel 90° caudal after needle is in the vein to help direct wire into the SVC
- Ultrasound not always helpful (given acoustic shadowing from bone)
- Subclavian vessels may be compressed with two fingers squeezing around the clavicle
- Guidewire usually only needs to advance 20cm (two dark lines)



FEMORAL VEIN (Video: NEJM 2008;358:e30)

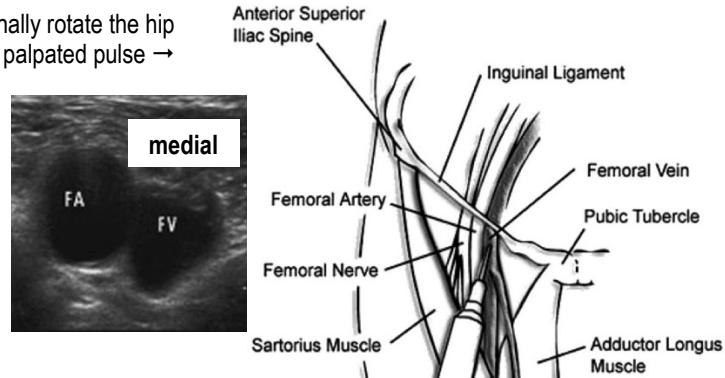
Advantages	Disadvantages
Compressible	Femoral artery puncture 5-10%
No risk of PTX	Risk of development of DVT
Can be cannulated more easily during CPR	Less patient comfort in hip flexion, requires immobility
Large caliber vein technically easier to cannulate	May occlude flow if patient has obesity
	Caution in patients with inferior vena cava filters

Positioning: head of bed flat; abduct lower extremity and externally rotate the hip

Entry: bevel up, 2-3 cm below inguinal ligament, 1cm medial to palpated pulse → femoral vein lies medial & inferior to the femoral artery

- If non-urgent use US to visualize
- **“NAVEL toward the NABEL”** → Nerve, Artery, Vein, Empty, Lymphatics (alternative: venous → penis)
- Two fingerbreadths lateral to pubic tubercle if pulse not palpable
- DO NOT approach vein above inguinal ligament → risk for RP bleed & peritoneal perforation

Target: directly superior at 30-45°



CORDIS (AKA VENOUS INTRODUCER SHEATH)

Combined dilator and sheath w/ side port for IV access

Indications:

- Rapid resuscitation (shorter length, wider diameter)
- Introducer sheath for PA catheter
- Introducer for temp wire placement

Sites: IJ (R preferred for PA line), subclavian vein, femoral vein

Placement technique: uses Seldinger technique (advance catheter over a wire) but dilator and sheath are advanced over wire together as unit; dilator and wire then removed together; side port aspirated and irrigated prior to use

CVC COMPLICATIONS

Arterial puncture: hold pressure x10min; compress 1inch inferior (IJ) or 2 inches superior (femoral) to puncture mark

Dilation/line placement in an artery: consult vascular surgery BEFORE removing line; consider CT if pt stable

Pneumothorax (IJ & subclavian): suspect if hypoxemia, hypoTN, difficult stick; obtain STAT CXR → consult thoracic surgery if PTX or hemoTX; if tension physiology (shock) → immediate decompression with 16G angiocath @ 5th ICS, mid-axillary line (enter above the rib)

Retroperitoneal bleed (femoral): suspect if hematoma or hypotension; STAT CT → consult vascular medicine

Loss of wire or wire stuck in vessel: DO NOT use excessive force to pull out wire if it is stuck → leave in place, hold pressure to prevent exsanguination → STAT KUB/CXR if wire loss → consult vascular medicine

Procedures

Arterial Line

GENERAL CONSIDERATIONS

Indications: real-time BP monitoring (pressors, HTN emergency, CVA); frequent ABGs, lab draws (≥ 3 per day)

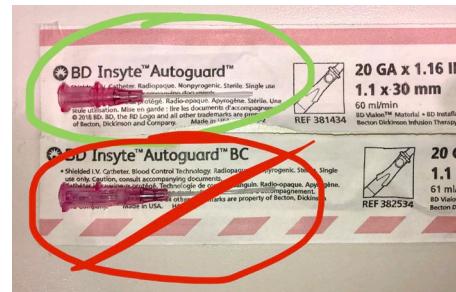
Locations: radial > femoral > dorsalis pedis > axillary; brachial not recommended given lack of collaterals unless placed by anesthesia

Contraindications: lack of collaterals (abnormal Allen test), h/o arterial grafts/stents, Raynaud's/scleroderma

Risks: pain, infection, bleeding, ischemia, vasospasm, arterial dissection, embolization, necrosis, loss of limb

Materials: arm board, tape, Chux, chlorhex prep, 4 x 4 sterile gauze, pack of sterile towels, sterile gloves, mask, eye protection, bouffant, 20G angiocaths, guide wire, Tegaderm, US probe cover (if needed)

- If pt awake → consider lidocaine w/o epi (small syringe and 25G needle)
- **Use PINK SOLID STRIPE angiocath:** do NOT use pink interrupted stripes, which has a one-way valve so can't pass wire
- Alt: use Arrow arterial line kit; the kit's longer catheter is preferable for femoral site

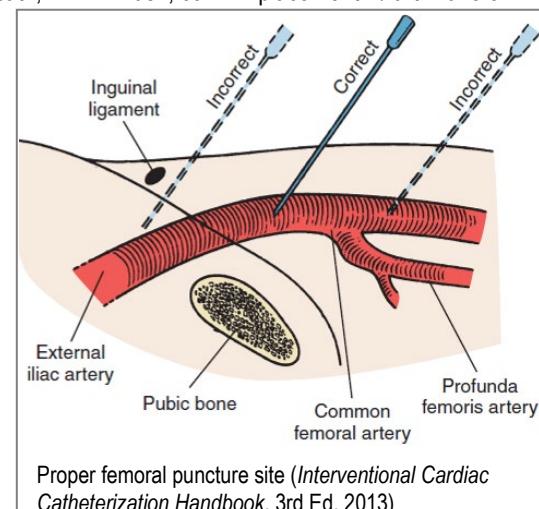


RADIAL TECHNIQUE (Video: NEJM 2006;354:e13)

- 1) Obtain consent and perform TIME OUT; ask RN to prepare for A line
- 2) Confirm anatomy by palpating pulses or with US. Test for collateral circulation of the hand:
 - **Allen test:** make fist for ~30sec, then occlude ulnar & radial arteries; pt opens hand (palm should be blanched); then release pressure from ulnar artery → palm should regain color within ~5-10 sec
 - **Modified Allen test:** place pulse oximeter on index finger or thumb; occlude radial and ulnar arteries until wave form lost; release ulnar artery → should get arterial tracing if good collateral flow
- 3) Proper positioning: adjust bed to appropriate height for operator comfort
 - Put Chux under wrist; extend pt's wrist; secure arm board (bendable arm boards in CCU and MICU)
 - Consider taping hand to bed/table to stabilize; note the course the artery travels
- 4) Sterilize wrist widely with 2% chlorhexidine swabs for ~30 seconds; open towel packet to create sterile field
- 5) Prepare field: drop angiocath & guide wire (and sterile US supplies) on sterile field; don sterile gloves and drape widely w/ sterile towels. Prepare US with gel and probe cover, if utilizing. Leave on sterile field
- 6) Prepare angiocath/guidewire: check angiocath to ensure catheter slides easily off needle; pull one side of wire *slightly* out of paper
- 7) Pick your target: palpate radial artery or (visualize with US) with non-dominant hand; plan to puncture distal to the pulse you palpate
- 8) Insert angiocath: with *bevel up*, advance angiocath needle at a 45° angle toward pulse until flash is obtained (similar to ABG)
- 9) Once flash obtained, go "*through-and-through*": advance ~0.5cm through artery; hold the top of the plastic catheter with non-dominant hand; push button to retract needle, while steadyng the catheter (**should be no blood flow**)
- 10) Hold guide wire close to head of angiocath w/ dominant hand
- 11) Pull back slowly: lower angiocath as parallel to skin as possible and SLOWLY pull it back until pulsatile blood flow is obtained
- 12) Advance wire: insert the wire into the angiocath; should not feel resistance; if unable to advance wire, DO NOT LET GO OF GUIDE WIRE; TRY SPINNING THE WIRE → avoids side branches of artery (where wire commonly gets caught)
- 13) Advance angiocath into the artery over the wire (Seldinger technique)
- 14) Remove guidewire: apply pressure to radial artery proximal to cath; remove guide wire; occlude opening of the angiocath with finger
- 15) Connect transducer: ask RN for A-line setup and connect transducer to angiocath; RN will flush; confirm placement w/ art. waveform
- 16) Dress the area with a Tegaderm; MICU RNs will often re-dress afterwards, so ask their preference; in ED, suture to the wrist; NWH has snap dressings

ALTERNATIVES AND TROUBLESHOOTING

- If using Doppler, mark out course of artery with marking pen
- If using US, can try advance needle/catheter under US guidance and once firmly in vessel, advance catheter over needle (no guide wire; similar to PIV)
- If unable to thread guide wire after attempting spinning during insertion, consider micropuncture wire (with supervision). May help with atherosclerotic arteries at the risk of ↑ risk of perforation
- After multiple attempts, the artery may spasm. Pursue alternative site
- Femoral artery access can be considered in difficult cases. Use the long catheter in the Arrow arterial line kit. Puncture must occur distal to the inguinal ligament to prevent RP bleed. Too distal, however, and the femoral artery will bifurcate into superficial and deep femoral vessels. The femoral artery usually transverses the inguinal ligament ~1/3 distance from pubic symphysis to the ASIS. Optimal point of skin puncture is 1-2 cm below the inguinal ligament at point where pulse is palpated (see graphic)



Proper femoral puncture site (Interventional Cardiac Catheterization Handbook, 3rd Ed. 2013)

Procedures

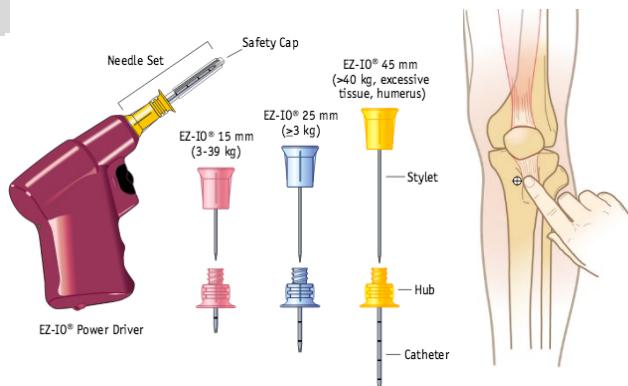
Intraosseous Line

GENERAL CONSIDERATIONS (Video: NEJM 2014;370:e35)

- **Anatomy:** veins that drain medullary sinuses of bones; veins supported by bones do not collapse in patients in shock.
- **Indication:** patients without available IV access with urgent need (arrest, shock, status epilepticus, trauma, etc). Used for delivery of fluids/medications; labs (but tenuous – clots off quickly). Faster access than CVC, low complication risk ([Resuscitation 2012;83:40](#))
- **Contraindications:** fractured or penetrated bone (fluids exit site), local vascular compromise (e.g. trauma or cutdown). Should be avoided in areas of cellulitis, burns, osteomyelitis, bone disease (e.g. osteogenesis imperfecta), R→L intracardiac shunts (TOF, pulm atresia) due to risk of fat emboli, failed IO insertion within 24h at same site
- **Complications:** extravasation, compartment syndrome, fracture, growth plate injury, infection, fat emboli, osteomyelitis (rare)
- **Notes:** infusion rate roughly 160mL/min at tibia or humerus with use of pressure bag, half the rate without. IO samples only accurate for some studies (Hgb, T&S, drugs, Cx). NOT for PaO₂, WBC, K, AST/ALT, iCal, after drug admin

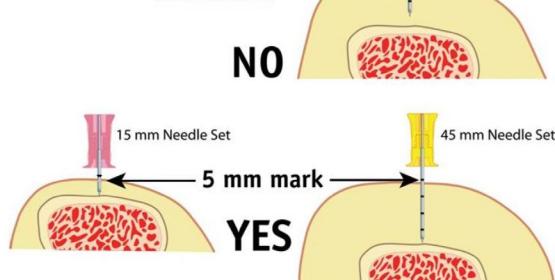
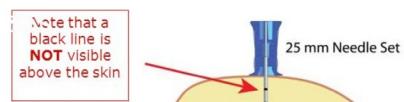
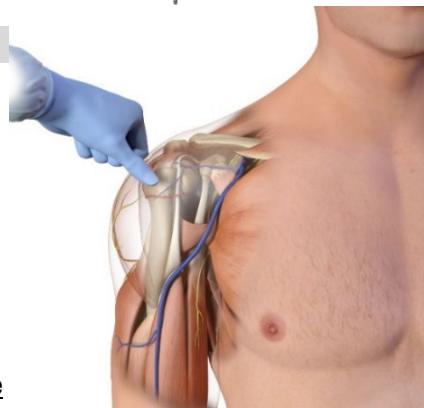
SET-UP

- **Materials:** ALL IN KIT → EZ-IO Power Driver, IO needle-set, connector tubing, 10cc syringe with saline flush, chlorhexidine/povidone iodine, sterile gloves. If awake, 3cc syringe with 1% lidocaine via 25G needle
- **Location:**
 - Proximal tibia (preferred): find the flat surface 2cm below tibial tuberosity, 1-2cm medial along tibia
 - Proximal humerus: position pt palm on abdomen (elbow flexed, shoulder internally rotated), greater tubercle 2cm below acromion process
 - Other sites: distal tibia, distal femur, iliac crest



PROCEDURE (Crit Care 2016; 20:102)

1. Don surgical mask, eye protection, sterile gloves
2. Flush connector tubing with NS or lidocaine if patient is awake
3. Identify injection site
4. Clean injection site with antiseptic (chlorhexidine or iodine)
5. If patient is awake, create wheal with 1% lidocaine
6. Choose proper needle size: generally blue (25mm); yellow (45mm) is for excess tissue or for humerus approach
7. Magnetic pole holds the needle in place; turn the safety cap clockwise for removal
8. Hold drill perpendicular to bone if proximal tibia; Hold 45° to the anterior plane and posterior medial if proximal humerus
9. Manually press the needle through the skin until it touches the bone. Confirm you see one black line on the needle (5mm mark); if not, use a longer needle
10. Apply gentle, steady, downward pressure while holding the trigger; allow drill to do the work
11. Release trigger when decreased resistance felt ("give" or "pop") as you enter into medullary space
12. While holding catheter in place, pull straight up to remove driver
13. Unscrew the needle stylet by rotating counterclockwise (both stylet and needle are encased in colored plastic)
14. Aspirate marrow to confirm placement. Prior to attaching tubing, send labs; blood samples may only be obtained in patients with spontaneous cardiac activity or during initial CPR before drug and fluid infusion through the IO
15. Attach connector tubing and flush IO w/ NS or 1% lidocaine over 45s if the patient is awake (IO infusions are VERY painful); if the patient is unconscious, rapid 10mL NS. Look for superficial swelling and note that no flush means no flow!
16. Apply IO dressing stabilizer – FYI each size needle has a different dressing, will not fit if using dressing for different size needle
17. Administer rapid NS bolus, blood product, pressor, etc. with a pressure bag or syringe
18. Always return the IO kit to unit for resource nurse to refill



REMOVAL

- Remove **within 24 hours** of insertion once other access is obtained, or if signs of erythema, swelling or extravasation

Procedures

Paracentesis

INDICATIONS : (Video: NEJM 2006;355:e21)

- **Diagnostic:** new-onset ascites, unknown etiology of ascites, rule out SBP. Low threshold for inpatients with cirrhosis and often helpful to obtain concurrent RUQUS with Doppler to rule out hepatic or portal vein thrombosis
- **Therapeutic:** large volume paracentesis (>5L) → performed for abdominal pain/discomfort, diuretic-refractory ascites, respiratory compromise, abdominal compartment syndrome, adjunctive treatment of esophageal variceal bleeding (can lower portal pressures)

CONTRAINDICATIONS

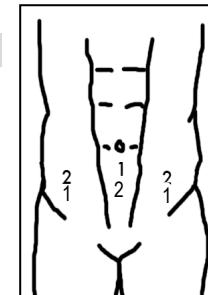
- Overlying cellulitis, inability to demonstrate ascites on US, bowel obstruction/distention, acute abdomen, 2nd or 3rd trimester pregnancy
- ↑INR, ↓plt are **NOT** contraindications (INR in patients with cirrhosis is NOT reflective of the risk of bleeding). There is no need to correct coagulopathy w/ FFP or platelets unless severe DIC ([Hepatology 2013;57:1651](#))

MATERIALS

- Sterile gloves, bouffant, face shield, chlorhexidine, sterile towels, US, 1% lidocaine (10cc syringe, SQ 25G needle, 1.5inch 20-22G needle), two 18G needles, 60cc syringe, diagnostic assay tubes as below, gauze, bandage or Tegaderm dressing
- **Diagnostic:** **20G two-way (pink) angiocath** or 18–22G 1.5inch needle. In obese pts, may use angiocath from femoral art line kit. Purple and green top tube, black top tube (for micro)
- **Therapeutic:** **safe-T-Centesis kit** (preferred, pigtail minimizes perforation risk) or paracentesis kit (straight rigid needle), 1L vacuum bottles, 25% albumin dosed 6-8g per liter of fluid removed if >5L ([Hepatology 2013;57:1651](#))

SITE SELECTION/POSITIONING

- Position patient supine, turned slightly toward the side of the paracentesis, and angled upright at 30°
- Use abdominal probe to **identify fluid pocket ≥2-3cm in all dimensions** by rotating/fanning probe to ensure **absence of bowel loops**
- Avoid superficial veins or prior surgical incisions and **use vascular probe with Doppler to avoid SQ vessels**
- **Approaches:**
 - **LLQ > RLQ (1): most commonly used;** LLQ ↓risk of bowel perf, use caution if pt with splenomegaly; **avoid inferior epigastric vessels** that run along lateral borders of rectus muscles
 - **Infraumbilical (2): midline, 2cm below umbilicus;** **must be certain to differentiate urine in bladder from intra-abdominal free fluid**



Approaches

INSTRUCTIONS

1. Identify best site with abdominal US probe and mark site with pen or round base of needle
2. Open sterile OR towels package. Use light blue covering as sterile field to drop sterile supplies. Don PPE (gloves, mask, bouffant cap) & clean skin vigorously with chlorhexidine. Create sterile field over patient with OR towels or open kit and use dressing provided
3. Anesthetize overlying skin using ~0.5cc lidocaine (SQ 25G needle) to make a wheal. For LVP, use 1.5 inch 20-22G to anesthetize deeper tissues with lidocaine in 10cc syringe. Use **Z-line technique** (below) and aspirate while advancing needle. Once ascitic fluid begins to fill syringe, stop advancing the needle & inject remainder of lidocaine to anesthetize the **highly sensitive parietal peritoneum**

Z-line technique: reduces risk of ascites leak. With non-dominant hand, pull skin ~2cm caudad to deep abdominal wall while para needle is being slowly inserted

Diagnostic paracentesis instructions

- a) Insert **20G two-way (pink) angiocath** through wheal at same angle as US probe and advance until slightly past when flash seen
- b) Advance the catheter without moving the needle
- c) Retract needle, attach 60cc syringe, and fill syringe
- d) Withdraw the catheter and apply pressure with sterile gauze
- e) Apply dressing using folded gauze under Tegaderm
- f) Attach 18G needle to 60cc syringe and fill diagnostic tubes

Therapeutic paracentesis instructions

- a) Prepare Safe-T-Centesis kit: place catheter on needle, attach syringe, and prep tubing
- b) Use scalpel to make small superficial incision (enlarge PRN)
- c) Advance needle/catheter while pulling back on syringe until ascitic fluid return is visualized, then advance 0.5 cm
- d) Advance catheter until hubbed (only with Safe-T Centesis kit!), hold rigid needle in place
- e) Retract needle, attach 60cc syringe for dx sample PRN
- f) Connect tubing to catheter and puncture vacuum bottles
- g) Withdraw catheter and apply gauze/Tegaderm dressing
- h) Give **25% albumin (6-8g/L removed)** if >5L removed

DIAGNOSTIC ASSAYS: (see [Fluid Analysis](#) for interpretation)

Tube	Lab	Tests
Green top	Chem	Fluid albumin (send serum albumin to calculate SAAG), fluid total protein
Purple top	Heme	Fluid cell count
Blood culture bottles	Micro	Can send for aerobic & anaerobic fluid culture, clean top with alcohol and inoculate at bedside for max yield
Black top	Micro	Gram stain and culture plates

Other tests to consider: glucose, amylase, LDH, bilirubin, triglyceride, AFB smear, mycobacterial culture, adenosine deaminase, pH, cytology

COMPLICATIONS

- **Flow stops/slow:** roll patient slightly to side of para, rotate catheter, slightly withdraw catheter, flush catheter, new vacuum container
- **Flash of blood in catheter:** use vascular probe to avoid SQ vessels → withdraw & insert new catheter at different site
- **BRB return:** injury to mesentery or inferior epigastries → stop, assess for hematoma w/ US, IR or surgery consult if HD unstable
- **Hypotension:** likely vasovagal or fluid shift (>1500cc tap) → Trendelenburg, hydrate, and consider 25% albumin
- **Bowel perforation:** may lead to polymicrobial baterascites/sepsis → surgery consult for potential laparotomy
- **Fluid leak:** prevent with Z-line technique → apply pressure dressing, seal w/ Dermabond or single stitch (4-0 non-absorbable suture)

Procedures

Arthrocentesis

INDICATIONS

Diagnostic: evaluation of inflammatory mono/oligoarthritis or uncharacterized joint effusion. A single inflamed joint should always have diagnostic aspiration to differentiate septic arthritis, crystalline arthropathy, inflammatory arthritis, and hemarthrosis

- **Avoid if overlying cellulitis or periarticular infection:** prosthetic joints should prompt Ortho/Rheum consult; safe to perform if on warfarin ([Am J Med 2012;125:265](#)) or DOAC ([Mayo Clin Proc 2017;92:1223](#)) but consider smaller needle
- US may be used to guide needle insertion and can also offer diagnostic information with complexity of fluid
- Hip joint aspiration should be performed by IR

Therapeutic: injection of corticosteroid/anesthetic in autoimmune arthritis (RA/JIA, spondyloarthropathies) or single-joint gout flare (especially when systemic therapy is contraindicated); drainage of large effusion, pus, or blood

- Avoid if overlying cellulitis, periarticular infection, septic arthritis, periarticular fracture, joint instability
- Use of intra-articular steroids in OA is falling out of favor due to progressive cartilage damage ([JAMA 2017;317:1967](#))

COMPLICATIONS

Iatrogenic infection (1/3500, >48h after procedure, may see systemic signs of infection), post-injection flare (mirrors infection and occurs within 24-48h of procedure), hemarthrosis, leakage of joint fluid, local or systemic steroid effects

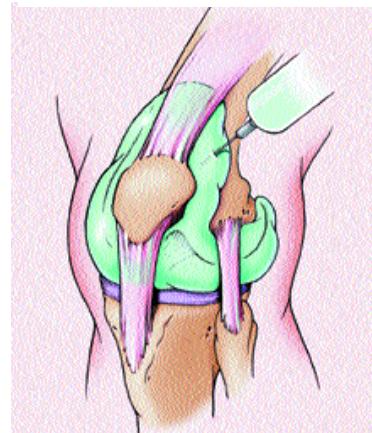
TECHNIQUE: KNEE (Video: [NEJM 2006;354:e19](#))

Materials: sterile gloves, chlorhexidine/iodine, 5cc 1-2% lidocaine w/o Epi (25G needle, 5cc syringe) or ethyl chloride spray, 18-22G needle, 20-60cc syringe, diagnostic tubes (purple/green top, aerobic/anaerobic bottles), sterile towels/sheet, bandage

Positioning/Approach: position the knee in extension or 15-20° flexion. Approaches described below:

- **Lateral** (see image): 1cm lateral and 1cm superior to the superior 1/3 of the lateral patella. Angle the needle approximately 45° toward the feet and insert behind the patella at a 45° angle to the skin. **More likely to yield fluid in difficult cases**
- **Medial:** 1cm medial to the superior 1/3 of the medial patella. Angle the needle perpendicular to the leg and at a 45° angle to the skin

Lateral Approach



Protocol:

- Identify landmarks as above and mark point of entry with the base of a needle cap or pen. Sterilize the site. A sterile field is not technically required but may drape the area w/ a sterile sheet or towels. Prep needles and syringes
- Anesthetize overlying skin using ~0.5cc lidocaine (SQ 25G needle, 5cc syringe) to make a wheal. May use remaining lidocaine along procedure tract
- Attach 18-20G needle to 30cc syringe and position needle according to approach. Advance needle slowly (avg 1-1.5in) and aspirate while advancing
- Once fluid is visualized, aspirate joint fluid to fill syringe. May attach a 2nd 30cc syringe to drain additional fluid for sx relief pending size of effusion
- Withdraw needle and apply bandage. Fill diagnostic tubes (purple top for cell count/diff and crystal eval, aerobic/anaerobic cx bottles)

DIAGNOSTIC ASSAYS

- Cell count/diff, crystal analysis, gram stain/culture **AND** blood cultures ([AFP 2003;68:1](#))
- **Septic arthritis:** most common locations: knee > hip > shoulder > elbow
 - If HDS, **hold abx prior to tap;** 70% Staph, 17% Strep, 8% GNR (*H. flu* child > adult)
 - WBCs usually ~50-150K but can be lower (e.g. <20K in disseminated gonorrhea); ↑WBC = ↑risk of infection
 - **Presence of crystals does NOT rule out septic arthritis** (up to 5% of pts with crystals also have septic joint)
 - Gram stain: Sn 75% for *Staphylococcus*, 50% for GNR, <25% for *Gonococcus*
 - Joint Cx usually ⊕ but only 50% Sn in gonococcal arthritis (swab genitalia & pharynx for diagnosis)
- **Gout:** negatively birefringent needle-shaped urate crystals (yellow) on polarized microscopy (Sn 63-78%, Sp 93-100%)
- **Pseudogout:** positively birefringent CPPD rhomboid crystals (blue) on polarized microscopy (Sn 12-83%, Sp 78-96%)

Procedures

Lumbar Puncture

INDICATIONS

Diagnostic: suspicion for CNS infection (most common), CNS malignancy/mets, SAH, or CNS demyelinating/inflammatory process

Therapeutic: idiopathic intracranial hypertension, NPH, ↑ICP in cryptococcal meningitis, intrathecal meds/chemotherapy/anesthesia

Contraindications: no absolute contraindications; high risk if skin infection over puncture site, epidural abscess, ↑ICP 2/2 mass lesion or obstruction (risk of brain herniation), spinal cord tumor or AVM, thrombocytopenia (<50K) or coagulopathy (INR>1.5)

Preparation:

- **Time frame needed to hold AC prior to LP:** IV heparin (4h, PTT<35), LMWH therapeutic (24h), LMWH ppx (12h), Plavix (5-7d), DOAC (3d), warfarin (3d, goal INR <1.5). OK to proceed if on SQ heparin daily dose <10,000U, ASA, or NSAIDS. If urgent: weigh risks and benefits. For details (including when to restart AC): [ellucid](#)
- **Head CT:** only obtain if ≥1 of the following: age >60, hx CNS disease, seizure <7d, immunocompromised, AMS, aphasia, cranial nerve deficit. If none of these, then 97% NPV for no mass lesion ([NEJM 2001;345:1727](#))

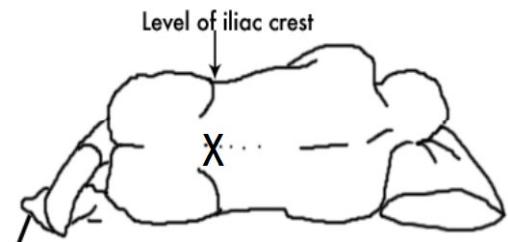
TECHNIQUE (Video: [NEJM 2006;355:e12](#))

Equipment: LP kit, sterile towels, sterile gloves, face shield, pillows to position patient

- LP kit: 1% lidocaine (25G needle, 5cc syringe), sterile drape, iodine/chlorhex, 20-22G needle/stylet, 4 collection tubes, manometer

Positioning: proper positioning is the key to a successful and smooth LP!

- **Use L4–L5 (level of iliac crests), L5–S1, or L3–L4 interspaces (conus medullaris at L1–L2)**
- **Lateral** (if opening pressure needed): place pt in fetal position (maximize neck and hip flexion), no hip/shoulder rotation; keep back parallel to edge of bed
- **Upright** (easier): sit on bed, head/arms rest on table, spine flexed
- To identify target: place a hand on each iliac crest, mark where thumbs meet at midline or draw line between iliac crests. Before inserting needle, place thumb & pointer finger on either side of spine, ensure needle is midline
- Sitting while performing LP is often easier than standing, as the needle is in your line of sight



Protocol: ([JAMA 2006;296:2012](#))

- 1) **Prep:** sterilize and drape widely. Re-identify target. Make lidocaine wheal w/ 25G, then inject track (aspiration before injecting, goal is **not** spinal anesthesia). Keep CSF collection tubes in order nearby. If checking pressure, have manometer connected and ready
- 2) **Tap:** check needle/stylet mobility. Bevel should face ceiling when pt is lateral. Needle angles slightly toward the head (as if aiming to umbilicus), straight at the back. Stabilize with your hand against the skin and advance with your dominant hand. Remove stylet frequently to check for CSF flow but **always keep stylet in place when advancing**
- 3) **Troubleshoot:** if hitting bone, partially withdraw, adjust angle, and re-advance. Try another space below if no luck. If patient has pain, DO NOT withdraw → ASK "where?" If pain is shooting down the left side, withdraw slightly and go slightly more to the right. If hitting bone early, more likely to be superior or inferior; if hitting bone late, more likely to be too lateral
- 4) **Measure opening pressure:** once flow is established, remove stylet and connect manometer to measure opening pressure (must be in lateral decubitus position). Pt must **extend legs** to obtain accurate pressure. If performing therapeutic LP, drain until pressure normal
- 5) **Collect:** collect CSF tubes 1 to 4; if flow slows, try rotating needle or minimally advancing or withdrawing with stylet in place
- 6) **Finish:** re-insert stylet prior to needle removal (associated w/ ↓ post-LP headache)

If unable to obtain LP (ie overnight) and suspicion for meningitis is high, empirically treat while awaiting diagnostic study

DIAGNOSTIC ASSAYS (see Fluid Analysis)		
Tube	Lab	Tests
1 (1mL)	Heme	CSF cell count
2 (1mL)	Chem	Total protein, glucose
3 (3-5+ mL, depending on # of tests)	Micro	Gram stain/Cx. Consider: HSV PCR, VZV PCR, CrAg, viral Cx, AFB stain, VDRL. Ask lab to <u>save extra CSF</u> . If you need flow cytometry, DO NOT FREEZE CSF!
4 (1mL)	Heme	CSF cell count (should have fewer RBCs than tube 1 unless hemorrhage)

Additional tests: cytology & flow cytometry (meningeal carcinomatosis), oligoclonal bands (MS), paraneoplastic Abs, 14-3-3 & RT-QuIC (prion dz); **can collect extra black top tubes** for these purposes; if c/f prion dz: contact materials management for instruction on special disposal of materials (highly contagious!)

COMPLICATIONS	
Cerebral herniation (acute AMS, fixed pupils, ↑BP, brady, arrest)	Immediately replace stylet and do not drain more CSF beyond what is in manometer. STAT consult NSGY and treat with ICP-lowering agents (e.g. mannitol)
Nerve root injury	Shooting pains during procedure usually transient. Withdraw slightly and adjust position away from direction of pain. Consider dexamethasone if pain is persistent
Post-LP headache (10-30% incidence; likely 2/2 dural leak)	Onset 72h, lasts 3-14d. Give pain meds that do not affect PLT. No evidence for bed rest. If persistent, c/s anesthesia for epidural blood patch (65-98% success, usually immediate relief)
Spinal hematoma	Suspect if on AC w/ persistent back pain or neuro sx → urgent MRI → IV dex + NSGY c/s

Procedures

Thoracentesis

INDICATIONS

Diagnostic: to establish etiology of $\geq 1\text{cm}$ pleural effusion visualized by US (not necessary for small effusions w/ probable alternative dx)

- NB: pleural effusions are visible on CXR when $>200\text{mL}$ of fluid is present

Therapeutic: large effusions \rightarrow resp compromise or sx (e.g., dyspnea), hemothorax, empyema, complicated parapneumonic effusion

Relative Contraindications: no absolute ([Chest 2013;144:456](#))

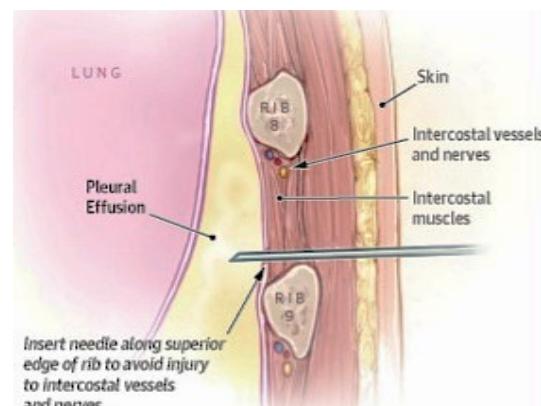
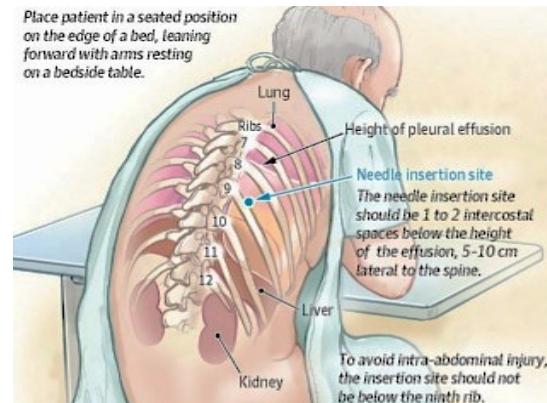
- Consider reversing coagulopathy (INR >1.5 , recent LMWH) or thrombocytopenia (plt $<50\text{k}$), but no data to support
- Skin infection (cellulitis or herpes zoster) over site of entry ↑ risk of pleural space infection
- Positive pressure ventilation ↑ risk of PTX by 1-7% ([Crit Care 2011;15:R46](#))

PREPARATION

- **Materials:** skin cleansing agent, gauze, sterile gloves/drape, hemostat, 1-2% lidocaine, 10cc syringe with 22 & 25G needle, thoracentesis kit with 18-20G over-the-needle catheter, 60cc syringe, 3-way stopcock, drainage tubing, specimen tube, evacuation container, occlusive dressing
- **At MGH:** IP (p23710), Pulm, or IR perform thoracentesis (not AMPS). Attending **MUST** be present for bedside thoracentesis

TECHNIQUE (Video: [NEJM 2006;355:e16](#))

- **Position:** patient at edge of bed, leaning forward with arms resting on table
- **Identify:** height of effusion determined by auscultation & percussion of chest wall. Use **US** to confirm location of effusion
 - Mark 5-10cm lateral to spine & 1-2 ICS below effusion. **Lowest level recommended is 8th ICS** (above diaphragm)
 - In patients who cannot sit upright \rightarrow mid-axillary approach (patient supine) or posterior axillary with patient lateral decubitus
- **Prep & drape:** set up thoracentesis kit, put on sterile gown and gloves, sterilize patient w/ chlorhexidine, then drape
- Using 25G needle, place wheal 1% lidocaine over superior edge of the rib
- Using 22G needle, walk needle over superior aspect of the rib while intermittently aspirating and injecting perpendicular to the pleural space
- When pleural fluid aspirated, withdraw slightly then anesthetize the parietal pleura (highly sensitive) w/ 2-3cc of lidocaine. **Note penetration depth**
- Attach 18G over-the-needle catheter to syringe & advance over superior aspect of the rib, pulling back while advancing
- When fluid aspirated, stop advancing & guide plastic catheter over needle. **Catheter has valve preventing fluid or air from entering the pleural space, so may use both hands to prepare for your next step**
- Attach 60cc syringe to 3-way stopcock connected to catheter, withdraw full syringe of fluid, and put in appropriate tubes for lab & micro studies
- Attach tubing to 3-way stopcock, affixing longer tube to large evacuation container & shorter tube to the syringe. Tubing is all one-way
- Aspirate fluid slowly into the syringe and inject back into bag, never fully empty the syringe as it can lead to difficulty on repeat aspiration. **Stop if: patient experiences chest pain, dyspnea, cough.** Do not remove more than 1.5L fluid as ↑ risk of post-expansion pulm edema
- When done, withdraw catheter **while patient is humming** (to avoid air entry into pleural space); cover site with occlusive dressing
- Obtain **post-procedure CXR** to assess for pneumothorax or hemothorax



DIAGNOSTIC ASSAYS (see [Fluid Analysis](#) for interpretation)

- **Send fluid for:** TP, LDH, chol, glucose, pH, cell count, Gram stain/Cx, anaerobic Cx, fungal wet prep w/ Cx
- **Consider:** TG (chylothorax), Cr (urinotorax), amylase (pancreatitis, esophageal rupture), ADA (TB), AFB Cx, modified AFB Cx, cytology

COMPLICATIONS

1. **Hemothorax/intercostal vessel injury:** ↑ risk if inferior approach to rib or elderly (tortuous vessels). CXR, H&H. Consider chest tube
2. **PTX:** 5-20% risk; most can be monitored with serial CXR; **monitor for signs of tension PTX** and obtain STAT expiratory CXR; if PTX is large or patient is symptomatic and/or in distress \rightarrow STAT page IP for bedside needle decompression with 16G angiocath at **5th ICS mid-axillary line** (always above nipple). A chest tube is indicated in 20% of cases \rightarrow **consult IP or thoracic surgery**
3. **Vasovagal syncope/pleural shock:** caused by needle penetrating parietal pleura. Tx: Supportive care
4. **Re-expansion pulmonary edema:** to avoid, stop thoracentesis if cough, CP, or dyspnea occurs. Limit volume removal to $<1.5\text{L}$. Do not attach to vacuum. Remove fluid slowly without excessive negative pressure. Tx: O2, diuretics, and/or BiPAP

Procedures

Pericardial Drain

INDICATIONS

- Pericardial effusion with tamponade physiology (or if at high risk for development of tamponade physiology)
- Diagnostic or palliative drain of stable pericardial effusion

RELATIVE CONTRAINDICATIONS: no absolute contraindications

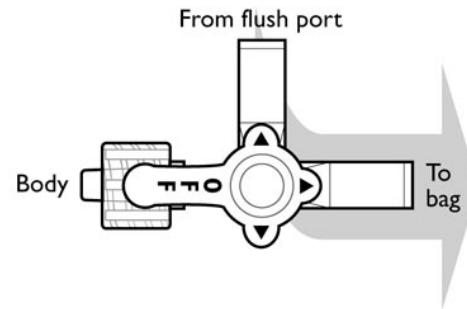
- Coagulopathy: INR>1.7, platelets<20, PTT>60 or on heparin gtt. Consider FFP/platelets when on call for procedure
- Effusion associated with aortic dissection or myocardial rupture, as decompression could lead to extension of injury
- Effusion associated with severe pHTN (controversial), as decompression could lead to RV dilation and acute RV failure ([Pulm Circ 2013;3:467](#))

MANAGEMENT OVERVIEW: if in doubt about management, page the Cardiology team that placed the drain

- Pericardiocentesis does not completely evacuate a pericardial effusion. A pericardial pigtail catheter is often left in for 24-72h to allow for serial drainage, preventing re-accumulation and repeated procedures
- Frequency of drainage depends on chronicity and size of the effusion, usually q6-q12h. Recommendations are often found in the report from the cath lab when the drain was initially placed
- **Post-procedural antibiotic prophylaxis not indicated per MGH guidelines** ([MGH peri-procedural abx guidelines](#))
- Monitor effusion resolution and recurrent tamponade. Check serial hemodynamics/pulsus paradoxus
- If >100cc output/d for 3d s/p placement, aggressive tx may be indicated (e.g. pericardial window, sclerosing agents, etc.)
- Consider removal of pericardial drain if <50cc output over 24h. Remove with cardiology fellow/attending present

MATERIALS

- Sterile technique: sterile gloves, mask, hat
- Sterile towels
- Chlorhexidine swabs (at least 3)
- 60cc Luer lock (screw-on) syringe (x2-3 if high output)
- New blue cap for 3-way stopcock
- Heparin (10U/mL) pre-mixed syringe (in MICU/CCU/SDU med rooms)



TECHNIQUE: mask and hat required (gown is optional)

1. Open sterile towel wrap carefully. Open supplies onto sterile field. Don sterile gloves
2. Ask assistant to lift the catheter off the skin. Place sterile towels around and underneath pericardial drain. Sterilize distal exposed catheter and stopcock with chlorhex swab. Holding the sterilized area, take catheter from assistant and sterilize remaining portion. Once fully sterilized, lay the catheter down on the sterile field
3. **Ensure the stopcock is turned towards the catheter/patient.** This means the catheter line is closed
4. Remove and throw away one blue cap (does not matter which)
5. Sterilize open stopcock tip with iodine or chlorhex swab
6. Hold up flush port for the assistant to connect heparin syringe (syringe itself is not sterile) to open/sterilized tip. **Turn stopcock toward the remaining capped valve** (opens flush port/catheter), and assistant will infuse 2cc heparin
7. **Turn stopcock back towards catheter**, remove (do not discard) heparin syringe, and connect 60cc Luer lock syringe
8. **Turn stopcock to the remaining capped valve** and slowly withdraw pericardial fluid. This may require significant negative pressure. Consider different patient positions (Trendelenberg, lateral decubitus, etc.) to mobilize pericardial effusion. Patient may experience chest discomfort. Monitor hemodynamics and telemetry throughout drainage
9. Can stop draining once fluid flow diminishes/ceases. **Turn stopcock back towards catheter** then remove syringe
10. Save/transfer pericardial fluid if needed for analysis. Otherwise discard
11. Repeat step 6 (flush port with another 2cc heparin). Close stopcock to the patient
12. Remove heparin syringe and attach new sterile blue cap to open flush port
13. Consider re-sterilizing distal exposed catheter and stopcock with chlorhex swab
14. Write a procedure note. **Be sure to deduct the 4cc infused heparin** (2cc from prior drainage, 2cc from current drainage) when calculating amount of fluid removed

FLUID STUDIES

- Gram stain and bacterial/fungal culture
- Specific viral studies/PCR
- Cytology
- AFB stain, mycobacterial culture, adenosine deaminase, IFN-gamma, or lysozyme (if considering TB pericarditis)
- Protein, LDH, glucose, red/white cell count are **not** helpful for fluid characterization

Procedures

Fluid Analysis

LUMBAR PUNCTURE INTERPRETATION						
Condition	Pressure (cm H ₂ O)	WBC/mL	Predominant cell type	Glucose (mg/dL)	Protein (mg/dL)	Further CSF Testing
Normal	9–18	0–5	Lymph	50–75	15–40	N/A
Bacterial meningitis	20–50	<100 to >10k	>80% PMN	<40	100–1000	Cx, Gram stain
Viral meningitis (Enteroviruses, HSV, VZV, arboviruses)	9–20	50–1000	Lymph; early echovirus/HSV can have 80% PMN	>45; low in LCM and mumps	<200	HSV/VZV PCR, consider further viral PCR or Ab if clinical suspicion; d/w ID
Lyme meningitis	9–20	10–300	Lymph	Normal	50–100	Ab testing paired with serum ab (though poor sensitivity)
TB meningitis	18–30	50–300	Lymph	<50	50–300 >2000 if subarachnoid block	MTb Cx <60% Sn, NAAT not approved by FDA, discuss w/ ID
Fungal meningitis	18–30	< 300	Lymph	<50	40–300	Fungal wet prep + Cx, d/w ID
Cryptococcal meningitis	18–30+	5–500	Lymph	<40	>45	Fungal wet prep + Cx, CrAg; d/w ID need for India ink stain
Epidural/Brain abscess	18–30	10–300	Lymph	Normal	50–400	Gram stain not sensitive
WBC correction for RBCs (i.e. traumatic tap) = measured WBC – (measured RBC / 500)						

PARACENTESIS INTERPRETATION (SEE ASCITES)		
	⊕ Ascites culture	⊖ Ascites culture
PMN ≥250/ μ L	Spontaneous Bacterial Peritonitis (SBP) (Secondary Peritonitis → polymicrobial)	Culture Negative Neutrocytic Ascites (CNNA)
PMN <250/ μ L	Non-neutrocytic Bacterascites (NNBA)	Normal
CNNA: has similar clinical presentation and prognosis as SBP, thus treat for suspected SBP after diagnostic PMN count without waiting for Cx (ddx: peritoneal carcinomatosis, tuberculosis, pancreatitis)		
Calculations: # of PMNs = Total nucleated cells x % of PMNs Correction for RBCs (RBC count >50,000/mm ³ , seen in "traumatic tap") = measured PMN – (measured RBC / 250)		
Clues in Fluid Analysis for SBP vs. Secondary Peritonitis:		
- Runyon's Criteria: If ≥2 present, ↑ suspicion for secondary peritonitis: 1) ascitic total protein >1; 2) ascitic glucose <50; 3) ascitic LDH > ULN		
- Fluid CEA >5 or Alk Phos >240 (92% Sn, 88% Sp for secondary peritonitis) (J Hepatol 2001;34:215)		
- Consider repeat paracentesis after 48h of antibiotic treatment: if PMN ↓ and only 1 org. on prior culture, likely SBP; if PMN ↑ and polymicrobial growth on prior culture, then likely secondary peritonitis. Higher risk for secondary peritonitis if recent operation, trauma, or perforation		
	SAAG ≥1.1g/dL (etiology related to portal HTN)	SAAG <1.1g/dL (etiology NOT related to portal HTN)
Fluid total protein < 2.5 g/dL	Cirrhosis	Nephrotic syndrome
Fluid total protein ≥ 2.5 g/dL	Heart failure Budd-Chiari syndrome	Pancreatitis Peritoneal carcinomatosis TB
SAAG = Serum Albumin – Ascites Albumin (from samples obtained on the same day)		

PLEURAL FLUID INTERPRETATION	
Transudate (due to Starling forces) vs. Exudate (due to increased capillary leak) (NEJM 2002;346:1971)	
<u>Light's Criteria</u> : exudate if ≥1 criteria present (98% Sn, 83% Sp)* 1. Pleural fluid protein / serum protein >0.5 2. Pleural fluid LDH / serum LDH >0.6 3. Pleural fluid LDH >2/3 ULN of serum LDH (i.e. >140) *Diuretics cause ~25% of transudates to be misclassified as exudates	If ≥ 1 of these, fluid is exudate with 98% Sn, 70% Sp: ▪ Pleural fluid protein >2.9, LDH >95, cholesterol >45 <u>More specific criteria for confirming exudate</u> : ▪ Pleural fluid cholesterol >60 (54% Sn, 92% Sp) ▪ Serum albumin – pleural albumin ≤1.2 (87% Sn, 92% Sp) ▪ Pleural NT-proBNP <2,300pg/mL (>80% Sn, >70% Sp)
• Other tests: adenosine deaminase, amylase, triglyceride, cholesterol, Gram stain/Cx, cell count, IFN-γ, NT-proBNP, pH, tumor markers	
• Complicated parapneumonic effusion/empyema = ⊕ Gram stain/Cx/purulent OR pH <7.2 OR glu <60 → drainage w/ chest tube	

NASOGASTRIC TUBES

Indications:

- Decompression of SBO or minimize vomiting in ileus
- Enteral feeding/med administration; charcoal admin (OD), oral contrast or colonoscopy prep
- Lactulose (hepatic encephalopathy)

Contraindications:

- Head/maxillofacial trauma, basilar skull fracture, or recent neurosurgical intervention
- Esophageal stricture or ≥grade 2 varices/recent banding (discuss w/ GI if uncertainty regarding varices/banding)

Supplies:

- NGT, lubricant/viscous lidocaine ("UroJet"), Chux, emesis basin, cup of water with ice and straw, 60mL syringe, tape
- If NGT needed for decompression: use 14 to 16 Fr Salem sump NGT (larger diameter, ↓ clogging)

NGT Placement:

- Assess patency & symmetry of nares by direct visualization
- Consider topical anesthetic (e.g. 4% lidocaine) pre-treatment
- Position patient in upright "sniffing" position with neck flexed & chin to chest
- Estimate distance of NGT insertion by measuring from xiphoid process→earlobe→nose tip
- Apply lubricant/ice to tip of NGT and/or apply viscous lidocaine directly into the nares
- Insert NGT into nares along floor & apply pressure posterior & slightly inferomedial, not upward
- After passage of NGT into oropharynx (will feel curve & ↓ resistance), have patient swallow water via straw while advancing rapidly
 - If patient excessively coughs, gags, has change in voice or dyspnea, or increased resistance, **STOP** (never force), suspect improper location (in airway or coiled), & immediately withdraw. Look in posterior oropharynx for coiling
- Advance to predetermined depth. Can insufflate air w/ 60cc syringe while auscultating over stomach for rush of air. May also see return of gastric contents. Inspect oropharynx to ensure no coiling before securing tube w/ tape or bridle if ↑ risk removal (AMS)
- Confirming position: **MUST confirm placement with KUB prior to feeding/meds given risk of placement in trachea/lungs.** KUB will show NGT sideport below diaphragm. Optional for KUB if bilious return when NGT for decompression (bile = stomach)

TYPES OF NGTs & USES

- Dobhoff: PO formula, meds
- 14, 16 Fr: decompression

Dobhoff tube/Enteroflex: thinner, more flexible; more comfortable but ↑ risk of placement into lung

- Requires 2-step 2-CXR placement method
 1. Measure from nose to earlobe to mid-sternum → insert tube this distance → secure → obtain CXR
 2. If CXR shows tip (1) past carina & (2) midline → advance into stomach → repeat CXR → remove stylette once confirmed

General Troubleshooting:

- If tube coiling repeatedly in oropharynx on insertion, soak tip in ice water to make tube more rigid prior to insertion
- NGT to suction should "sump" – air should audibly enter blue port and exit main port; if not: (1) flush blue port with air (never fluids), (2) flush main port with water (not NS, does not need to be sterile), (3) aspirate from main port → if not able to withdraw flush, NGT needs to be advanced vs. withdrawn (KUB can guide)
- To prevent clogging or adherence to gastric wall, NGTs should be flushed with 30cc water & air q8h. If clogged, can try methods to unclog tube as below in "Gastrostomy Tubes"

Complications (↑ with longer duration):

- GI: malposition, coiling, knotting anywhere along course of tube, nasal/GI tract perforation. ↑ risk acid/stomach content reflux and aspiration → consider PPI. Chronic suction → gastritis/pressure necrosis: consider removal if grossly bloody
- Pulm: intubation of lung → inadvertent med, contrast, TF administration → PNA, pulm abscess, tracheal perforation, PTX, death
- HEENT: nasal irritation, epistaxis, intracranial placement, skin erosion, sinusitis, alar necrosis, tracheoesophageal fistula/perf

Removal:

- If for ileus/SBO, consider removal when passing flatus or resolved n/v. Alternatively, may remove when NGT output <1L over 24h. Consider clamp trial before removing (clamp 4h, then check residual. Remove if <150cc)
- Remove tape. Flush tube w/ 10mL air or NS. Turn OFF suction & clamp. Fold Chux around tube insertion site. Gently remove tube

Procedures

Tube Management

GASTROSTOMY TUBES

Description:

- Clear, soft, graduated tubing held in place w/ plastic mushroom-shaped ring/balloon in stomach (~3cm deeper in obese pts)
- May be replaced at bedside after epithelialized track forms (~2-4w; delayed by malnutrition, steroids, immunosuppression)
- Gastrojejunostomy (GJ) tubes have 3 access ports: G tube port, J tube port, & balloon port
- Secured with vertical Hollister device
- Venting means access port is attached to a foley bag so contents/gas can flow out as needed

Troubleshooting:

- **Clogging:** only tube feeds & elixir meds should be given through J tube
 - Attach 3cc syringe w/ warm H₂O to female Luer adaptor. Pulse plunger to force through debris. Flush w/ 30cc warm H₂O to ensure not clogged
 - Can also try Seltzer, ginger ale, Coca-Cola. If persistent, can try pancrelipase (Viokase) with sodium bicarb
- **Leaking:** retract balloon or mushroom back to skin level; do NOT insert larger size tube (can cause stoma to enlarge); call service who placed G tube if persistent
- **Migration:** can cause n/v (w/ or w/o feeds), dumping syndrome. Confirm placement w/ *tube injection study* (30-60mL gastrograffin f/b KUB)
- **Falling out:** replace w/ similar-sized Foley or feeding tube. Obtain tube study
- **Local site infection:** try topical abx ± antifungal before PO (cephalexin, clinda)
- **Granulation tissue:** check tube size (not too long or short); tx w/ warm compresses & silver nitrate (w/ barrier cream on surrounding normal skin)

FOLEY CATHETER

Choosing Catheter:

- (order from Central Supply, ED, or Ellison 6 if not on floor)
- **Many contain latex**, use silicone if allergy; silicone also ↓ risk CAUTI
 - **2-way Foleys** (drainage & balloon ports):
16F (stock), 12F if stricture, use an ~18Fr **coudé if BPH or men >50yo** → insert curve up toward umbilicus (balloon port points towards sky) –MGH RNs can place coudes
 - **3-way Foleys** (drainage, balloon, irrigation ports): 20F/22F used for **continuous bladder irrigation (CBI) in gross hematuria**

Special Circumstances:

Required urology catheter consults: any patient with an artificial urinary sphincter (AUS – prosthetic sphincter for men with incontinence), prostatectomy or other prostate/urethral surgery w/in past 3-4mo, known urethral stricture. See *hospital policy below for full details*

Placement:

1. Lay patient flat, prep, hold penis upright (keep on stretch while advancing)
2. Instill 10cc viscous lidocaine ("UroJet") or other lubricant syringe into urethra (men)
3. In men, insert catheter to the hub. In women, insert until urine return + 5cm more
4. Fill balloon w/ 10cc sterile H₂O only if catheter hubbed (in men) and urine return.
5. If no urine when inserted, can verify position by flushing/aspirating the catheter with a 50cc catheter-tip syringe ("GU gun"). Inability to aspirate suggests:
 - a. Bladder empty and catheter sucking against bladder mucosa (instill 50-100 cc if patient does not feel like bladder is full and re-aspirate)
 - b. Catheter in urethra or false passage (instill 50-100 cc – if catheter is in the urethra, what you flush in may come around catheter but you cannot aspirate)
 - c. Catheter outside bladder (undermined bladder neck in pt s/p prostatectomy/TURP – this is rare)
6. If in the bladder, gently withdraw catheter after inflating the balloon until balloon engages the bladder neck
7. Secure the catheter with a little slack to the leg (attach it in the "crotch" between balloon and drainage ports so the catheter can slide down the attachment)
8. Don't forget to reduce foreskin (if not, may cause paraphimosis = **urgent problem**)

Troubleshooting:

- **Difficulty in female patient:** likely poor positioning. Place sheets under hips & place pt in Trendelenburg
- **Urethral trauma:** blood at meatus. Leave catheter usually 3-5 days (ensure balloon is in proper place)
- **Foley is leaking:**
 - Bladder spasms 2/2 infection, mucosal irritation, overactive bladder. Start anticholinergic (tolterodine 4mg qd PRN)
 - Foley obstructed 2/2 sediment, kinked, dome of bladder, clot. Flush catheter & bladder US
 - Urethra patulous (women w/ chronic indwelling catheters)

Continuous Bladder Irrigation (CBI): consult Urology to initiate

- Indications: gross hematuria (when you cannot see your hand through the foley due to presence of blood). DO NOT start CBI if urine has clots without manually irrigating the clots out first
- Titrate flow to "fruit punch" colored urine (should be able to see through)
- When d/c'ing, usually start with clamp trial to ensure resolution before removal

Suprapubic Tubes:

- Many different types although usually a standard Foley catheter
- Know type & size catheter, who exchanges, how exchanged, how frequently
- First exchange performed by IR. Subsequent exchanges should be performed by RNs. Urology available to assist PRN
- If need to reinser, decompress balloon and remove indwelling SPT tube. Use Foley kit, prep area, apply lubricant to new tube, insert through tract (may have to use some force) until urine return, inflate balloon and ensure tube is mobile, attach to Foley bag

Bladder Pressure: only done in the ICU

Indications: concern for intra-abdominal hypertension ($\geq 12\text{mmHg}$) or frank abdominal compartment syndrome ($>20\text{mmHg}$)

1. Ensure patient position correlates between measurements (head position as flat as possible) and pressure transducer set-up is arranged
2. Drain bladder and clamp drainage tube of foley
3. Inject 25cc of NS into drainage port, wait 30-60s (allows detrusor muscle to relax)
4. Connect pressure transducer to aspiration port, measure pressure at end-expiration

Cath policy: <https://hospitalpolicies.ellucid.com/documents/view/1207>

SPT policy: <https://hospitalpolicies.ellucid.com/documents/view/21862>

Procedures

Tube Management

CHEST TUBES

Indications: drainage of air (PTX), blood (hemothorax), pus (empyema), or lymph (chylothorax)

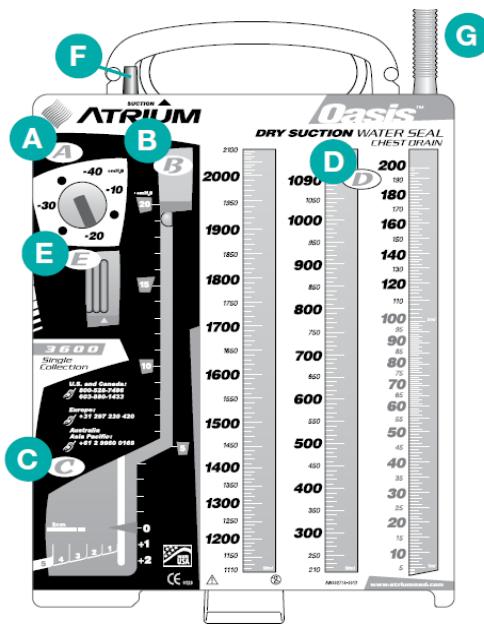
Chest Tube Logistics:

- **Drainage:** measured by gradations in 3 columns; if significant drainage, watch for re-expansion pulmonary edema
- **Suction control:** adjusts negative pressure applied to pleural space
 - Suction determined by setting on the device [A], NOT at the wall; if working properly, suction verification window [E] orange bellows will be at triangle marker
 - “**Suction**” vs “**water seal**”: if disconnected from wall suction, it is on water seal (i.e. “to gravity”) and will allow for one-way flow of air out of chest, [E] orange bellows not expanded

Troubleshooting:

- **Air leaks:** if bubbles present in the water seal chamber [C], indicates air in pleural space. Higher level in chamber, greater leak. Ask patient to cough to assess for leak if bubbles are not continuous
 - **Ddx:** air in pleural space (parenchymal lung injury or bronchopleural fistula) vs leak in chest tube (check tubing and connections to Pleur-evac)
 - **Note:** “Tidaling” (movement w/ respiratory variation in water seal chamber) [C] is normal – i.e. not an air leak
- **Clogging:** look for debris in tube, lack of tidaling, can try “stripping the tube” by compressing it with your fingers while pulling TOWARDS the drainage system, helpful to have an alcohol prep pad for lubrication, might require tPA (alteplase) for clot or Pulmozyme (dornase) for fibrinolysis → involve IP/surgery (whoever placed tube)

- **A** Dry suction control
- **B** Water seal chamber
- **C** Air leak monitor
- **D** Collection chamber
- **E** Suction monitor bellows
- **F** Tube to suction
- **G** Tube from patient



Removal:

- **General criteria:** no active air leak, pt off positive pressure ventilation, <150cc of drainage over 24h
- **Steps to removal:** place on suction (-40mmHg to -10mmHg) → place on water seal → clamp trial (clamp tube with hemostat)
 - With each step, wait 4h, then obtain CXR to ensure stable or improving PTX
- After stable on clamp trial, tube should be removed during exhalation (patient humming). Large chest tubes often require surgical knot to close hole covered by occlusive dressing (xeroform, 4x4 gauze, large tegaderm) for 48h

Procedures

Exposures & Needle Sticks

Please follow the steps below **IMMEDIATELY** in the event of an exposure to bodily fluids while on duty

1. **Stop the procedure**
2. **Immediately clean the affected area**
 - Sharp stick: wash site immediately with soap/water. Alcohol-based agents are also virucidal to HBV, HCV, HIV
 - Splash to open wound: wash site immediately with soap/water
 - Splash to eye(s): irrigate liberally for up to 5 minutes
 - Notify your department supervisor as needed; the charge nurse is often a very helpful resource
3. **Call occupational health (OHS)**
 - Monday-Friday 7am-5pm call 617-726-2217, located at 165 Charles River Plaza (CRP) Suite 404 (4th floor)
 - If outside of normal business hours, page the on-call occupational health provider at p21272 and go to ED
 - **Have the following information available** for the OHS staff member at the time of your call:
 - Source patient: name, MRN, DOB, location, MD, diagnosis, known Hx, exposure to HBV/HCV/HIV, meds
 - Needle: brand, size, gauge, specific device, device manufacturer, safety design type, part of a kit?
4. **Test the patient for HBV, HCV, and HIV**
 - **HBV/HCV: one gold top tube**
 - Order HBsAg and HCV qualitative Ab; if patient known HCV+, also send HCV RNA
 - If using paper form (available from OA), mark with BILLING NUMBER CL00009 so pt not charged
 - **HIV: another gold top tube**
 - Order HIV 1/2 Ag/Ab (4th generation test)
 - **By law in Massachusetts (M.G.L. c. 111, §70F)**, written consent is required to release HIV results to a third party. In the event of an exposure, since HIV status is being released to the exposed individual, written consent is assumed to be required
 - **Send the HIV tube to STAT lab** (results ~60min once received), send HBV/HCV tube to standard core lab

If source patient HAS capacity to consent:	If source patient DOES NOT have capacity to consent:
<ol style="list-style-type: none">1. Obtain a special HIV occupational exposure consent form/lab requisition from the OA2. Write STAT result in the comment section3. <u>Have the patient sign</u>, then sign it yourself4. Ensure form is marked with <u>BILLING NUMBER CL00009</u> so patient is not charged	<ol style="list-style-type: none">1. A valid and invoked health care proxy (you need paperwork!) can sign the occupational exposure consent form OR2. Facility legal staff can assume temporary guardianship <p>If the exposure occurs to a member of the <u>primary team</u>, the implication of the law is unclear, as that person is not technically a third party. Be conservative, obtain written consent anyway. If this is not possible, consider contacting HIV needlesticks fellow (p36222) or the chief residents for guidance</p>

5. **Decide if you will initiate post-exposure prophylaxis (PEP)**

*****Post-exposure prophylaxis is most effective if started within 1-2 hours of exposure*****

- Transmission factors increasing risk: hollow-bore needle, lack of barrier protection/direct skin penetration, depth of needle penetration, increased amount of blood on the needle
- **Starting PEP is recommended if**: patient has known HIV or testing is expected to take >2 hours
 - M-F 7a-5p, PEP can be obtained at the OHS office. At all other times, you must go to the Emergency Department (page the on-call OHS provider at p21272 to be fast-tracked in the ED for treatment)
 - **HIV fellow** can be paged to discuss PEP specifics at p36222

PATHOGEN	TRANSMISSION RISK	POST-EXPOSURE PROPHYLAXIS (PEP)
HIV	Percutaneous (blood): 0.3% Mucocutaneous (blood): 0.09% <i>There has only been 1 confirmed case of occupational transmission since 1999 (CDC)</i>	PEP can vary but usually includes 3 anti-retroviral drugs: <ul style="list-style-type: none">• 2 NRTI tenofovir PLUS emtricitabine AND INSTI raltegravir• 28 days of treatment recommended but optimal length unknown• Regimen usually well-tolerated, side effects include:<ul style="list-style-type: none">○ Common but mild: n/v/d, fatigue, HA○ Rare: hepatitis, hyperglycemia, fevers, rash, pancytopenia• Serial testing at 6w, 12w, and 6mo if patient has HIV
HCV	Percutaneous: 1-2%	No PEP; serial testing at 4w, 12w, and 6mo if patient has HCV
AHBV	Percutaneous: 30%	Positive immune titers usually are an employment requirement Vaccine non-responders should be seen in occupational health

6. **File a safety report**

Logistics

Monitoring & Prophylaxis

CARDIAC MONITORING (MGH Clinical Guidelines for Cardiac Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	- Cardiac monitoring for diagnostic purposes only	- Continuous cardiac monitoring - May be off monitor ONLY in presence of licensed clinical personnel	- Continuous cardiac monitoring
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	- No cardiac monitor - Unaccompanied	- With cardiac monitor - Accompany by MD, PA, NP, or RN	- With cardiac monitor - Accompany by MD, PA, NP, or RN

*Refer to 2017 AHA guidelines on ECG monitoring for more detailed indications and monitoring duration ([Circ 2017;136:e273](#))

- **How to run telemetry:** click on “Patient Data”
 - **Events:** events sorted in reverse chronological order (e.g. runs of NSVT, bradycardia)
 - **FD Strip:** telemetry strip for a **specific moment** in time
 - **FD Page:** global view useful in **identifying abrupt changes** that can be zoomed in on using the FD Strip view
 - **Graphic Trends:** graphic view of **HR trends** over time
 - **Calipers:** interactive calipers used to **calculate intervals** on telemetry strip

O2 SATURATION MONITORING (MGH Clinical Guidelines for O2 Saturation Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	- Spot check O2 sats as frequently as clinically indicated	- Continuous O2 sat monitoring - May be off monitor ONLY in presence of licensed clinical personnel	- Continuous O2 sat monitoring
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	- No O2 sat monitor - Unaccompanied	- With O2 sat monitor - Accompany by MD, PA, NP, RN, or RRT	- With O2 sat monitor - Accompany by MD, PA, NP, RN, or RRT

DVT PROPHYLAXIS

	Low Risk	Moderate Risk	High Risk
Risk factors	- Ambulatory - Estimated LOS <48h - Not meeting moderate- or high-risk criteria	- Major surgery (>45min, not craniotomy, ortho, spine, or for cancer) - Acute illness; immobility w/ est. LOS >48h - H/o VTE, thrombophilia (incl. hormone tx) - Active malignancy	- Major surgery (craniotomy, ortho, spine, or for cancer) - Critical illness in ICU - 2+ moderate risk factors
Prophylaxis	Ambulation	Pharmacologic OR mechanical	Pharmacologic AND mechanical

- **30 / 30 / 30 Rule**
 - **Pharmacologic prophylaxis:** can be administered if platelets **>30K**
 - **Mechanical prophylaxis:** SCD boots should not be off the pt for **>30%** of the day
 - **Ambulation:** pts should ambulate **30min/shift (60min/d)**
- **Pharmacologic prophylaxis options:**
 - **Enoxaparin (Lovenox):** 40mg SC q24h; default in patients with CrCl >30 and BMI <40
 - **Heparin (UFH):** 5,000units SC q8h-q12h; preferred in pts with CrCl <30 or BMI >40; q8h pref. in cancer patients
 - **Fondaparinux:** 2.5mg SC q24h (can be used if concern for HIT)
 - **Alternatives to UFH during shortage:** apixaban 2.5mg PO q12h, rivaroxaban 10mg PO q24h (avoid if CrCl <30)
 - Do not use if critically ill (ICU), trauma/spinal cord injury; avoid if recent/high risk for bleeding, anticipated invasive procedure, GI/GU CA and active intraluminal lesions, Childs B/C cirrhosis or any liver disease w/ coagulopathy

GI PROPHYLAXIS (MGH Stress Ulcer Prophylaxis Guidelines)

- **Indications** ([Crit Care Med 2016;44:1395](#)):
 - Admitted to ICU AND one of the following: 1) mechanically ventilated >48h, 2) coagulopathy (plt <50, INR >1.5, PTT >2x ULN), 3) GI bleed in the last year, 4) TBI, spinal cord injury, or burns, 5) 2+ of the following: sepsis, occult GIB >6d, steroids >60mg prednisone daily, ICU LOS >7d
- **Prophylaxis options (PO unless contraindicated):** **PPI** (omeprazole, esomeprazole, pantoprazole) or **H2 blocker** (famotidine)

Logistics

Peri-Procedural Anticoagulation

GENERAL ANTIPLATELET & ANTICOAGULATION GUIDELINES FOR ELECTIVE PROCEDURES

- ASA: hold for 1 week prior if for primary prevention, continue if for secondary prevention
- P2Y12: hold clopidogrel and ticagrelor 5 days prior; prasugrel 7 days
- Warfarin: hold 5 days prior (see [Anticoagulation Management](#) for indications for and guidance on bridging)
- DOAC: hold 1-3 days prior, depending on agent, renal function, & procedural bleeding risk (see below for guidance for Cath Lab & IR)

CARDIAC CATH LAB ANTICOAGULATION GUIDELINES

Medication	Hold Pre-Procedure*	Resume Post-Procedure
Heparin	Therapeutic (>15k U/d): 1h or on call to lab Prophylactic: continue	4h after sheath removal; no bolus
Enoxaparin (Lovenox)	Therapeutic (1mg/kg): 24h; Prophylactic (<=60mg/d): 12h	Next morning
Bivalirudin	1h or on call to lab	4h after sheath removal; no bolus
Argatroban	1h or on call to lab	4h after sheath removal; no bolus
Dalteparin	Therapeutic: 24h; Prophylactic (<=5000 U/d): 12h	Next morning
Warfarin	5 days or INR ≤1.8	Night of cath
Apixaban, rivaroxaban, edoxaban	CrCl ≥30: ≥2 days; CrCl <30: ≥3 days	Next morning
Dabigatran	CrCl ≥50: ≥2 days; CrCl <50: ≥5 days	Next morning
Fondaparinux	CrCl ≥50: ≥4 days; CrCl <50: ≥7 days	Next morning

*Guidelines for endomyocardial biopsy differ. See [MGH Cardiac Cath Lab Anticoagulation Guidelines](#) (ellucid)

INR Guidelines for Cardiac Catheterization

Planned Access Site	INR
Femoral artery or vein	≤ 1.8
Internal jugular vein	≤ 1.8
Radial artery	≤ 2.0
Subclavian vein	≤ 1.5
Brachial or basilic vein	≤ 2.0
Pericardiocentesis	≤ 1.5

VAD Peri-Procedural Cardiac Catheterization Guidelines

INR goal	1.8-2.5; continue warfarin
PTT goal	≤80; continue UFH pre-, intra-, & post-procedure

Cangrelor and Antiplatelet Agents

- See [ACS](#) for switching/bridging P2Y12 inhibitors
- Generally, prasugrel is held on day -7, clopidogrel/ticagrelor on day -5, & cangrelor is started on day -3. Cangrelor is held 1-6h pre-procedure

IR PROCEDURES

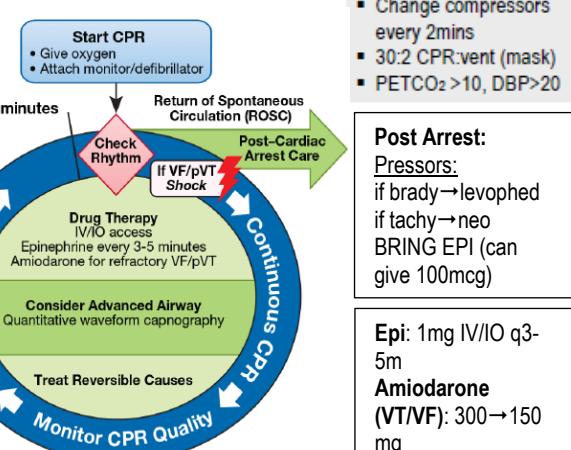
- NPO guidance:** NPO (no solid food; ok to take medications with sip of water) for 8h if will receive sedation (e.g. port placement, biopsies, tube placement) or if a patient-specific need for sedation
- Low bleeding risk procedures:** para, thora, chest tube, PleurX, PICC, non-tunneled central catheter, transjugular liver biopsy, IVC filter placement & simple removal, catheter/tube exchange, dialysis access interventions, superficial bx/aspiration (thyroid, LN, breast, superficial bone), embolization for bleeding control
 - AC goals: INR <3, plt >20k; if cirrhosis: INR <3, plt >20k, fibrinogen >100 (if cirrhosis). **No need to hold AC**
- High bleeding risk procedures:** tunneled central access catheter placement/removal, G- or J-tube placement, nephrostomy tube placement, biliary interventions, TIPS, solid organ/deep tissue biopsies, LP/spine procedures, arterial interventions/angiography, intrathoracic venous interventions (SVC/IVC), portal vein interventions, catheter-directed lysis, complex IVC filter removal
 - AC goals: INR <1.8, plt >50k; if cirrhosis: INR <2.5, plt >30k, fibrinogen >100. AC management per table below

Medication	Hold Pre-Procedure**	Resume Post-Procedure
Heparin	Therapeutic: 4-6h; Prophylactic: 6h	6-8h
Enoxaparin (Lovenox)	Therapeutic: 24h / 2 doses; Prophylactic: 12h / 1 dose	12h
Dalteparin	24h / 1 dose	12h
Fondaparinux	CrCl ≥50: 2-3 days; CrCl <50: 3-5 days	24h
Bivalirudin	2-4h	4-6h
Argatroban	2-4h	4-6h
Warfarin	5 days or INR ≤1.8	Day after procedure; bridge if high-risk
Apixaban, edoxaban	CrCl ≥50: ≥2 days / 4 doses; CrCl <50: ≥3 days / 6 doses	24h
Rivaroxaban	CrCl ≥30: ≥2 days / 2 doses; CrCl <30: ≥3 days / 3 doses	24h
Dabigatran	CrCl ≥50: ≥2 days / 4 doses; CrCl <50: ≥3-4 days / 6-8 doses	24h

**See [MGH Interventional Radiology Periprocedural Management](#) (ellucid)

Logistics

Senior On Encounters

CODES		Code/Rapid Data to Obtain	Bradycardia	Hypotension																								
A-Access	Non-Senior On Tasks: <ul style="list-style-type: none"> Confirm code status Confirm/stop IV infusions Run tele/print strips Check labs, med list Notify attending, family 	[] Preceding events [] Code Status [] Access [] Vitals [] Focused exam [] POCT glucose [] One-liner, PMH [] Recent procedures [] Last TTE [] Run MAR [] Infusions [] EKG [] Tele [] Last labs (Hgb, K, etc) [] ABG/VBG	Conduction disease, R sided MI, vagal, med effect, tICP, hypothyroidism, hypoxemia Atropine 0.5-1mg q3-5m, max 3mg Dopamine 2-20mcg/kg/min Epinephrine 2-10mcg/min Isoproterenol 2-10mcg/min Transcutaneous pacing (midaz/fentanyl or ativan/dilaudid) Transvenous pacing (cards consult)	Cardiogenic: MI, ADHF, BB/CCB toxicity, acute myocarditis, valvular disease (AS) Distributive: <ul style="list-style-type: none"> S-Sepsis A-Anaphylax L-Liver dz T-Toxin Hypovolemic: bleeding, diuresis, removal w/ HD, insensible losses Obstructive: PE, tamponade																								
B-Backboard	LABS TO ORDER (150-200J; tele) Stat ABG with K & Hgb, CBC, BMP, LFTs, lactate, T&S, coags, fibrinogen, cardiac enzymes		Tachycardia Narrow: AVRT/AVNRT, AF/AFlutter, AT, MAT Wide: MMVT, PMVT, SVT w/ aberrancy, pacemaker mediated Synchronized Cardioversion Narrow/regular: 50-100J Narrow/irregular: 120-200J Wide/regular: 100J Wide/irregular: 150-200J	Acute Hypoxemia Aspiration Mucus plug Pneumonia Pulm edema PE Pneumothorax Pleural effusion																								
C-Code Status			Medications Narrow/reg: adenosine (6, 12, 12) Wide/reg: - Amio: 150mg → 1mg/min - Lido: 100mg → 50mg q5 x3 → 1-2 mg/min - Procainamide: 20-50mg/min until hypoTN or QRS ↑50% → 1-4 mg/min - consider adenosine unless WPW Wide/irreg: - PMVT: amio, lido; tx ischemia - Torsades: Mg 2mg, 1HR Isoprot. - AF+WPW: procainamide, ibutilide (1mg) (adenosine, BB/CCB, dig)	Hypercarbia ↓RR: sedatives, central sleep apnea, OHS, brainstem stroke, tumor, infection, hypothyroidism ↓Vt: OSA, pleural effusion/fibrosis, obesity, kyphosis/scoliosis, abd dist, PTX, neuropathy, NMJ disorder, myopathy ↑Vo and/or ↓Vt: COPD, asthma, OSA, ILD, CHF, PNA, PE																								
D-Defib			GIB 2 large bore IV, T&S, IVF, pRBC, IV PPI 40mg. Octreotide 50mcg + CTX if portal HTN. Correct coagulopathy. RICU if hematemesis.	AMS CNS: CVA, ICH, sz, infxn, PRES Metabolic toxins: NH3, CO2, BUN, Na, glucose Exogenous toxins: meds, drugs, w/d Vitals: HTN/HoTN, hypoglycemia, hypoxemia Misc: TTP, AI, hypothyroid																								
E-Drips			PE Intermediate-High risk: PE w/ abnormal VS (tachycardia, hypotension), evidence of R heart strain (TTE, EKG, or +biomarkers), central or saddle PE → PERT x4-7378 Order: TTE, EKG, CBC w diff, PT/PTT, BMP, LFTs, lactate, D-dimer, Trop, NT-proBNP, T&S, LENIs tPA: Pulseless → 50mg/2m, 50mg in 30m Pulse → 100mg/2h Follow w/ heparin gtt Contraindications: prior ICH, ischemic CVA <3mo., active bleeding, CNS surgery/trauma (<2-3mo)																									
F-Epi																												
Electricity (150-200J; tele)																												
F-Fluids																												
F-Family																												
G-Glucose																												
H's and T's:																												
CAUSE		MANAGEMENT																										
Hypoxemia		Intubate, ECMO																										
Hypovolemia		Access, crystalloid, blood																										
H+ (Acidemia)		Bicarb																										
Hypo/hyperK		HyperK tx: (D50W 1-2 amp + insulin 10U IV), CaGlu or CaCl ₂ 1-2g IV																										
Hypothermia		Warming																										
Hypoglycemia		D50																										
Tamponade		Pericardiocentesis																										
Tension PTX		Needle decompression																										
Thrombosis – MI		PCI, ECMO																										
Thrombosis – PE		tPA, ECMO																										
Toxin / Drugs		Stop drugs, give reversal agents																										
Others:																												
CAUSE		MANAGEMENT																										
Septic Shock		Abx, source control																										
Mucus Plug		Suction/Chest PT																										
Auto-PEEP		Disconnect vent																										
Anaphylaxis		Crystalloid, IM/IV epi																										
ACLS																												
Non-shockable rhythm:		Epi as soon as feasible																										
Shockable rhythm (VT/VF):		Epi after initial defib attempts are unsuccessful																										
																												
		High Quality CPR																										
		<ul style="list-style-type: none"> Minimize interruptions Fast: 100-120/min Compress 2-2.4 in deep Allow complete recoil Change compressors every 2mins 30:2 CPR:vent (mask) PETCO₂ > 10, DBP > 20 	Seizure Lorazepam 2-4mg IV x2, diazepam 20mg PR, or leviteracetam 20mg/kg																									
		Post Arrest: Pressors: if brady → levophed if tachy → neo BRING EPI (can give 100mcg)		Anaphylaxis Epi 0.3-0.5 IM (1:1000; 1mg/mL); or 0.1-0.3mg IV (1:10,000; 0.1mg/mL) → repeat q5-15min; start gtt if >3 required <u>Other agents:</u> Benadryl 50mg, methylpred 125mg, albuterol neb, IVF																								
		Epi: 1mg IV/IO q3-5m Amiodarone (VT/VF): 300 → 150 mg		NUMBERS																								
			<table border="1"> <tr> <td>ICU Resource RN</td><td>x6-6718</td><td>p25213</td></tr> <tr> <td>Cardiac Access RN</td><td>x4-2677</td><td>p31951</td></tr> <tr> <td>MICU Intensivist</td><td>c857-331-0741</td><td>p26955</td></tr> <tr> <td>HCICU Intensivist</td><td></td><td>p29151</td></tr> <tr> <td>ECMO</td><td>c857-310-0335</td><td>p29151</td></tr> <tr> <td>STEMI</td><td>x6-8282</td><td></td></tr> <tr> <td>PERT</td><td>x4-7378</td><td></td></tr> <tr> <td>Rapid Response, RICU, Stroke</td><td>x6-3333</td><td></td></tr> </table>	ICU Resource RN	x6-6718	p25213	Cardiac Access RN	x4-2677	p31951	MICU Intensivist	c857-331-0741	p26955	HCICU Intensivist		p29151	ECMO	c857-310-0335	p29151	STEMI	x6-8282		PERT	x4-7378		Rapid Response, RICU, Stroke	x6-3333		**Consider using MGH STAT app (can be found in Partners App Catalog)
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Logistics

Post-Acute Care

POST-ACUTE CARE: post-hospital care of patients

- Largest source of Medicare regional variation. High cost growth ([NEJM 2014;370:689](#)) & risk of readmission ([Health Aff 2010;29:57](#))
- Risk factors for use: living alone, impaired mobility, depression, comorbidity ([JAMA Intern Med 2015;175:296](#))
- Note: do not have capability for rapid diagnostics (CT), procedures, or significant acute issues (hypoxemia, hypotension)
- Rely on Case Management, PT, & OT to help determine who qualifies for each of the below post-discharge destinations

Setting (most to least intensive)	Description	Patients / Diagnoses	Avg LOS	MD	Therapy / Ancillary Services
Long Term Acute Care Hospital (LTAC)	High intensity hospital-level care	- Tracheostomy - Chemotherapy - ≥3d ICU stay required	20+ days	Daily MD visits	- RT - PT/OT PRN - HD
Inpatient Rehabilitation Facility (IRF, "acute rehab")	Intensive therapy for recovery of function	- Post-stroke - Spinal cord injury - Specific dx codes required	7-21 days	2-4x/week MD visits; PM&R presence	- 3+h of therapy/d (pt must be able to participate)
Skilled Nursing Facility (SNF)	"Sub-acute" rehabilitation; looks/feels like nursing home; must have 3-night hospital stay to qualify under Medicare	- CHF, PNA, UTI - Generally older patients with functional decline / unsafe at home	3-21 days	~1x/week MD visits; very limited capacity for management changes	- 1-2h of therapy/d (pt must be able to progress)
Home Health	Home-based services post-hospitalization or via PCP referral	- Wound care - IV antibiotics - Post-hospital functional decline - Home safety eval	N/A	Managed by PCP or prescribing outpatient clinician	- 4-8 PT/OT visits - RN visits as needed

SPECIAL CASES

- Hospice:** see [Comfort Focused Care & Hospice](#)
 - Criteria: pt must have a terminal illness with prognosis of ≤6mo as certified by a physician. Depending on the hospice agency, pt may need to forego curative treatments (i.e., chemo, expensive antibiotics, etc.)
 - Home hospice: fully funded by Medicare. RNs visit, but patients need full-time caregiver support in the home, which can be a barrier to home hospice discharge
 - Inpatient hospice (SNF or dedicated inpatient hospice facility): room & board (~\$400 per day) only covered by MassHealth, but not other insurers
 - GIP (in-hospital hospice care): fully funded by Medicare, patient must qualify
- Long-term care:**
 - Patients residing in nursing homes with stably poor functional status and who require assistance with ADLs/IADLs, but do not require post-acute level care
 - Private pay or covered by MassHealth, but not funded by Medicare
- Alternative programs:** if patient is in Partners ACO, discuss additional home-based care options with case manager

Logistics Microaggressions/Bias, Patient-Directed Discharge, ICE

MANAGING MICROAGGRESSIONS & BIAS

Microaggression: a brief & common indignity (statement, action, or incident) that communicates hostile, derogatory, or negative slights to target a person or group. **Despite the name, 'micro' does not speak to the severity of the impact on the target**

Bias: an attitude projecting favorable/unfavorable dispositions towards people. Bias/microaggressions can be implicit or explicit

Common examples in medicine: questioning of credentials/abilities, assumption of non-physician status, requests to change providers, belittling comments, inquiries into racial/ethnic background, inquiries into relationship status/sexual orientation/gender identity, inquiries into family/pregnancy status, comments on appearance, assumptions of religious affiliation

Upstander: a person who chooses to intervene when witnessing bias/microaggressions

Responding to microaggressions OR bias from patients: ([JGME 2019;11:371](#))

1) Prepare before the encounter:

Within your team, talk explicitly about how leadership should address the situation. For example, team leader: “In our two weeks together, we may encounter a patient who discriminates against one of our team members. It can sometimes feel safer to have the JAR/attending address the behavior, but I want to empower you all to act if you feel comfortable. What do you think?”

2) During the encounter:

- 1) Ensure the patient is stable and assess decision making capacity: if unstable, call for help to provide care. If lacks capacity (see [Consent & Capacity](#)), consider redirection. If stable and has capacity, proceed
- 2) Check your emotions and psychological safety: if you’re not in a space to respond, it is OK to step out, process, ask for support
- 3) If you respond, address the aggression explicitly: “I’m surprised to hear you say ____.” “I’m disappointed you’d say that.” “What do you mean by that?” “That’s frustrating to hear from a patient.”
- 4) Align with the patient: “Our team is here to focus on your health.” “We are all here to treat your ____.”
- 5) Align with your team: “Our team is doing our best to respect you. We ask that you respect Dr. ____/me as well.”
- 6) Set boundaries: varies by aggression. “I’d ask that you refrain from commenting on ____.” “Please call them/me Dr. ____.” “Let’s keep the focus on you.” “We do not accommodate staff changes based on [race/ethnicity/religion/etc], Dr. ____/I will be in charge of your care today.” “Our institution does not tolerate that behavior/language/etc.”
- 7) Give space: if patient or team member is unable to continue the encounter, leave the situation with a defined time to come back. “We are going to give you space for 30 minutes and when we come back, we can focus on your health.”

3) After the encounter:

- 1) Attend to emotion: if you were the target of the aggression, seek support, debrief however feels right to you. If you were a bystander, explicitly acknowledge what you witnessed, offer to support your colleague. Support can range from listening to holding their pager so they can step off the floor to decompress. Ask what they need from you
- 2) Discuss the encounter: once emotions have been attended to, if the target is willing, discuss as a team how the interaction went. What went well? What didn’t? What would you do differently next time? Practice future phrasing together
- 3) Involve others: ensure attending, other providers, and unit-based leadership are aware
- 4) If the behavior continues: reconvene to discuss next steps as a team (attending, residents, other colleagues)

PATIENT-DIRECTED DISCHARGE (HISTORICALLY KNOWN AS AMA)

All patients have the right to discharge from treatment when they have capacity. It is the duty of the physician to obtain informed consent of discharge after discussing the risks and benefits to discharging from care. Common reasons why patients request discharge include: financial concerns, communication issues, insufficient management of pain/cravings/withdrawal, family obligations

Approach to a safe patient-directed discharge: ([JGIM 2013;28:1657](#))

- 1) Is the patient on section 12a or under guardianship? If yes, these patients cannot choose to leave. Involve psychiatry and security as needed to help the patient stay safely. See [Agitation](#). If no, proceed
- 2) Perform a capacity evaluation: see [Consent & Capacity](#). If patient has capacity, proceed
- 3) Determine why the patient is motivated to leave: acknowledge their reasons for leaving, validate their emotions. Use a harm reduction lens, negotiate to meet their needs as able. If time allows, involve SW and CM to help brainstorm solutions
- 4) Discuss risk and benefits of leaving: ask them what they believe are the risks and benefits. Explain your recommendation. Discuss not only the immediate medical impact of their options, but the impact on their longer-term values/goals
- 5) Offer alternatives: if the primary recommendation of staying is rejected, offer other reasonable options. Acknowledge this may require sub-optimal care, for example, admission for IV antibiotics vs PO antibiotics with outpatient follow up or a home visit
- 6) Summarize recommendations, confirm understanding: Example language: “I understand you’d like to leave the hospital today to _____. As we have discussed, remaining in the hospital will _____. That is my primary recommendation for you. Another potential option we discussed is _____. While it is not ideal medically, it is a reasonable option and care should align with your goals.”
- 7) Confirm contact information and give return precautions: coordinate follow up, remind the pt they are always welcome back for care
- 8) Complete paperwork: avoid documenting ‘AMA’ → stigmatizing and has no medicolegal benefit ([JHM 2017;12:843](#))

INFORMATION ON IMMIGRATION AND ICE/DHS

When should a patient's immigrant status be documented in the EHR?

NEVER. EHR can be accessed by law enforcement/immigration officials and used as evidence

What to do if ICE/DHS inquires about a patient?

If an Immigration and Customs Enforcement (ICE) or Department of Homeland Security (DHS) Agent asks for a patient or patient information, **do not provide any information about the patient. Immediately contact your attending and the Partners Office of General Counsel** (available 24/7; during normal business hours, call 857-282-2020. During off hours, call MGH Page Operator)

Main Number	
617-726-2000 (MGH prefix: -724, -726, -643)	
Emergency Numbers	
Senior On (Med Sr)/Bauer Room	3-1388, p22337
ED Triage Sr (ED Sr)	6-2333: x75360
Med Consult Pager (Code Backup)	p13480
RICU Team (intubation), Code Stroke	6-3333
ECMO Consult	857-310-0335, p24252 / p29151
SHOCK Consult	p11511
STEMI Team (CCL activation)	6-8282
PERT (massive PE)	4-7378
IV Nurse (urgent access)	6-3631, p26571
ED Radiology (STAT imaging)	6-3050
RT (on call)	p24225
ICU Nursing Supervisor	6-6718, p25213
Poison Control (ingestion)	617-232-2120
Pharmacy	
Outpatient pharmacy (fax: 6-3789)	4-3100
Outpatient pharmacy (private line)	6-2354
Laboratories	
General lab info	4-LABS
Chemistry/Hematology (Core Lab)/Toxicology	6-2345
STAT Chemistry/Hematology	4-7617
Serology	4-7645
Special coagulation	4-2969
Blood gas / STAT lab – Bigelow 5	6-3856
Blood bank – Bigelow 2	6-3623
Blood bank – Lunder	8-5280
Microbiology – Bigelow 5	6-3613
Micro after hours (blood culture room)	6-7919
Parasitology	6-3861
Virology	6-3820
Surgical Pathology – Blake 3	4-1449
Immunopath (Flow, ANCA, EM)	6-8487
Cytology / Cytopathology – Warren 1	6-3980
Cardiology Studies	
Cath Lab	6-7400
Echo Lab	6-8871
Stress Lab	4-3600
Holter Lab	6-7737
EP Lab	6-5036
Pulmonary Studies	
PFTs – Cox 2	6-1200/3-9680
Sleep Study (inpatient/outpatient)	4-7426
GI Studies	
Endoscopy Lab – Blake 4	6-3732
Neurology Studies	
EEG – Blake 12	6-3640
EMG/NCS – Blake 12	6-3644
Subspecialties	
Anticoagulation (AMS)	6-2768
Boston Healthcare for the Homeless	781-221-6565
Brace Shop (White 10)	6-3248
Mass Eye and Ear Infirmary	
Page Operator	617-523-7900, 0
11th floor (Inpatient)	Above plus x2480
MEEI ED (for ENT transfers)	617-573-3431
Interpreter Services	
In Person	6-6966, p27403
Phone (Pin 1050)	617-643-3344

RADIOLOGY

- **Life Images**

- Upload images to Lifelimage and Epic: Partners Applications → utilities → MGH Upload Image to Radiology (Lifelimage) → Access Lifelimage → find exam on CD/DVD → upload images
- Send images to MGH PACS: upload to MGH → request read
- Retrieve images from The Cloud: <ISDrequests.partners.org> → file urgent ticket or request changes to existing ticket
- Additional information:
 - Urgent reads: contact ISD (**p34188, x30003**)
 - Multiple body parts: interpretations only given for selected body parts
 - Multiple Lifelimages of the same body part: upload all images → request a read only on the most recent
 - Exams will not be read if: requisition was for a different body part than the uploaded images; study >6 months old; a more recent Lifelimage is available; US, fluoroscopy, or mammography

Radiology Reading Rooms

Dodd Reception	44212
Cardiac CT	47132
Cardiac MRI	66947
Chest CT	33899
CXR Inpatient	42051
CXR Outpatient	62197
ED	41533
GI CT	65162
GI Fluoro/KUB	32605
GI MR	49919
IR (GI & VIR)	34723
Mammography	40228
MSK	40516
Neuroradiology	41931
Nuclear Cardiology	43600
Nuclear Medicine	61404
PET	66737
Vascular	47115

Technologists

CT Blake 2	48518
CT ED	66760
ED Radiology	63050
GI Fluoro	44295
Mammography	63092
MRI ED	49867
MRI Inpatient	85692
Nuclear Medicine	68350
PET	64209
Scheduling	4XRAY
US White 2	53074

Logistics

Other Common Formulas

BODY WEIGHTS

Actual Body Weight (ABW): recorded on admission

Ideal Body Weight (IBW):

Male: 50.0kg + 2.3kg for every inch over 5 feet

Female: 45.5kg + 2.3kg per inch over 5 feet

Adjusted Body Weight (AdjBW):

AdjBW = IBW + 0.4 x (ABW - IBW);

use for obese pts (i.e. if ABW > 1.3 x IBW)

CARDIOVASCULAR PHYSIOLOGY

SaO₂ and PaO₂ Correlation:

SaO ₂	99	98	95	90	88	80	73	60	50	40	30
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PaO ₂	149	100	80	60	55	48	40	30	26	23	18
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Arterial Oxygen Content (C_aO₂):

$$C_aO_2 = (1.34 \times Hb \times S_aO_2) + (0.003 \times P_aO_2)$$

Cardiac Output (Fick):

$$CO = VO_2 / (C_aO_2 - C_vO_2)$$

→ VO₂ ≈ 3 x wt (kg) or 125 x BSA (roughly 250 ml/min; use metabolic cart to measure precise value)

Friedewald Formula:

$$LDL = TC - HDL - (TG / 5)$$

PULMONARY PHYSIOLOGY

Shunt Fraction (normal: 3-8%, but 15% for every 100mmHg drop in PaO₂ below 600mmHg):

$$\frac{Q_s}{Q_t} = \frac{0.0031 \times (PAO_2 - PaO_2)}{[0.0031 \times (PAO_2 - PaO_2)] + (C_a - vO_2)}$$

where Q_s = shunt flow, Q_t = total flow, C_{a-v}O₂ assumed 5%.

FiO₂ must be 1.0 in this calculation

R becomes 1.0 after breathing 100% O₂ for 20 minutes because of N₂ wash-out

> 15% = pathologic shunt

Bohr Equation (i.e. dead space fraction) (normal: 0.2 – 0.4):

$$\frac{V_d}{V_t} = \frac{PaCO_2 - PetCO_2}{PaCO_2}$$

NEPHROLOGY

Creatinine Clearance from Timed Urine Collection:

$$CrCl = \frac{UCr \text{ (mg/dL)} \times Uvolume \text{ (ml/min)}}{\text{serum Cr (mg/dL)}}$$

Total Body Water (TBW):

TBW = F x weight; F = 0.6 ♂, 0.5 ♀ (or 0.5 and 0.45 if elderly)

Intracellular fluid (ICF) = 2/3 TBW

Extracellular fluid (ECF) = 1/3 TBW

ECF = 3/4 interstitial, 1/4 intravascular

Urine Osmol Gap:

U_{osm} = 2(U_{Na} + U_K) + U_{urea}/2.8 + U_{glucose}/18 (normal: 10-100)

<150: shows impaired NH₄⁺ excretion (type I/IV RTA)

>400: shows increased NH₄⁺ excretion (type II RTA/diarrhea)