# Housestaff Manual

July 2025 - June 2026

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*Editors*
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It is an honor to present the **29th 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.

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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 ENT, General Surgery, OBGYN, Ophthalmology, and Urology 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 to have lived up to their example.

| | | | |
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None of this would be possible without the support of the Department of Medicine. We extend special thanks to Gabby Mills, Libby Cunningham, Rachel Bukis, and Paula Prout. We also thank our Chief Residents – Kelly Buchanan, Mike Kelly, Sarah (SK) Kler, and Karina Ruiz-Esteves – as well as William Kormos and Jose Florez for their devotion to the housestaff and our education.

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 2025

*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, when possible. We hope to provide guidance in the form of peer education and a forum for future experts to share their knowledge 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 launchpad for personal exploration. Although we have reviewed every page, errors may exist (as it is human to err). Please inform next year's editors here to ensure these errors are corrected.*

# MGH Housestaff Manual

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# Cardiology — ACLS: Cardiac Arrest & TTM

**UNRESPONSIVE PATIENT**
*Check circulation (pulse), airway and breathing (C-A-B)*
*No definite pulse within 10 sec.*

→ **START CARDIOPULMONARY RESUSCITATION**
*start compressions*

**Maternal Code Blue Algorithm**: AHA 2020
AHA 2023 Guideline (Circ 2024;149:e254)
ILCOR 2023 Guidelines (Circ 2023;148:e187)

Call **CODE BLUE** (x6-3333, blue button on wall)
Call for defibrillator, backboard, ambu bag
Monitoring: tele, defib pads, cont O2, BP cuff

Compress 2-2.4" deep, 100-120BPM,
minimize interruptions & allow full recoil
Without ETT: 30:2 compressions to mask vent
With ETT: Δ compressors q2min, breaths q6-8s

**Rhythm check as soon as pads are on**
Initial Defib if shockable, Epi if non-shockable

## MGH CODE ROLES

- **Code leader**: Senior On
- **Code Whisperer**:
  AM = Consult SAR
  PM = Units NT
- **Pulse**: SDU JAR
- **Compressions**: Interns
- **Bring LUCAS and ultrasound**: MICU Intern

## CODE TASKS

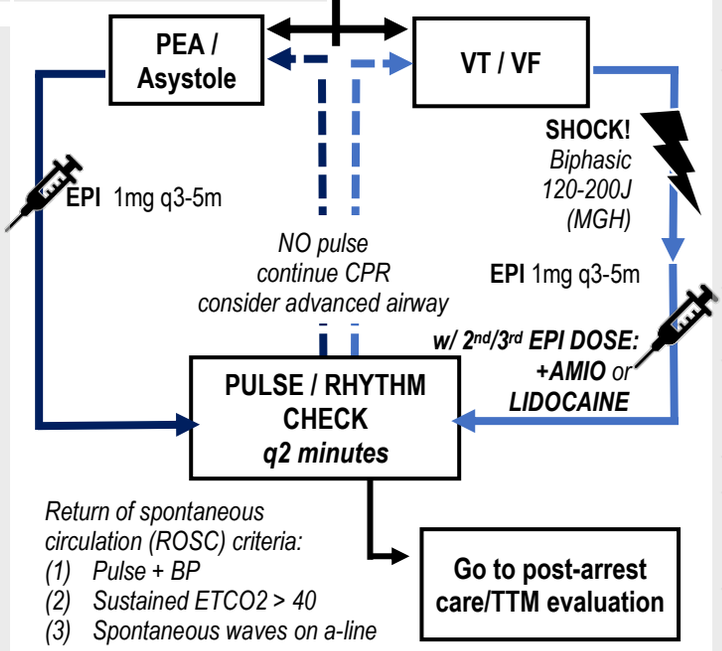
- **A**ccess (IV>>IO), **A**irway
- **B**ackboard
- **C**ompression quality / **C**ode status (always confirm)
- **D**efibrillator, **D**rips
- **E**CMO/**E**mbolus **E**arly:
  - page <10min of coding
  - Consider Tenecteplase
- **F**amily (call HCP)

## REVERSIBLE CAUSES (H&Ts)

- **H**ypovolemia
- **H**emorrhage
- **H**ypoxia
- **H+** ion (acidosis)
- **H**ypokalemia, **h**yperkalemia
- **H**ypothermia

- **T**hrombosis, coronary (ACS) & pulmonary (PE)
- **T**ension pneumothorax
- **T**amponade (cardiac)
- **T**oxins (drugs, accidents)

**MATERNAL CODE: ABCDEFGH**




## QUICK GUIDE: DOSING

- **DEFIB**: Biphasic (MGH) vs. Mono (360J), *if unknown, use max setting. repeat shocks @ same or ↑dose.* ***If no ROSC w/ 3 shocks consider AP pad placement and double sequential defib***
- **AMIODARONE**: 1st dose = 300 mg, 2nd dose = 150 mg
- **LIDOCAINE**: 1st dose: 1-1.5 mg/kg, 2nd dose: 0.5-0.75mg/kg
- **MGSO4**: if TdP give 2g IV
- **HYPERKALEMIA**: 1g $CaCl_2$, bicarb 1-2 amp IV, D50W 1-2 amp, insulin 10u IV
- **NALOXONE**: minimum 2 mg IV if pulseless, if apneic but has pulse, 0.2-1 mg IV

Code Cart Medications

## 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)
- **STAT LABS**: ABG plus, CBC, BMP, LFTs, lactate, T&S, coags, fibrinogen, troponin
- **MONITORING**: recommend wave capnography during CPR, keep ETCO2 at least >10mm H20, **ideally >20**
- **PROGNOSTICATION**: ETCO2 <10 mmHg in intubated pts after 20min CPR ~90% sensitive for no ROSC
- **PREGNANT WOMEN**: Apply left lateral uterine displacement, IVs above diaphragm, if receiving IV Mg, stop and give CaCl, resuscitative hysterotomy if no ROSC within 5min, TTM should still be considered with ROSC

## Thrombolysis for Known/Suspected PE During Code

- **Tenecteplase (TNK - preferred over tPA in PE Code) Given as IV push over 5 seconds**
  - <60 kg: 30 mg
  - ≥60 to <70 kg: 35 mg
  - ≥70 to <80 kg: 40 mg
  - ≥80 to <90 kg: 45 mg
  - ≥90 kg: 50 mg
- If TNK is not available: Alteplase (tPA) 50mg IV over 2 minutes. Can give a second dose in 15min if no ROSC
- **Continue CPR for at least 15 minutes post lysis**
- **Heparin gtt after lysis when PTT falls to <2x normal**
- **Contraindications (absolute):** prior ICH, ischemic stroke, head trauma (3mo), intracranial neoplasm or AVM, suspected aortic dissection, active bleeding

## ECMO for Cardiac Arrest (ECLS, ECPR)

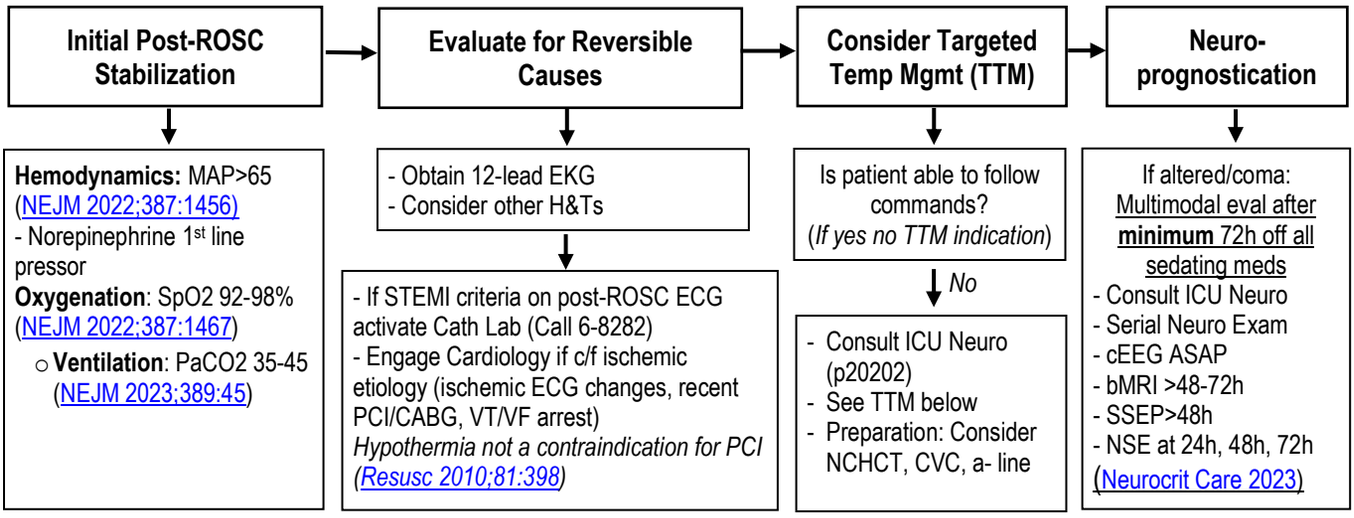
- STAT page "ECMO Consult MGH" or use "MGH STAT" app to call consult and for MGH ECMO guidelines **ideally <10 minutes from code initiation.**
- Indications: Age<75, no ROSC w/in 5 min, EtCO2 >10 mmHg
- Contraindications: BMI>45, EtCO2<10, lactate>18, pH<7.0, PaO2<50 on ABG, severe aortic regurgitation, aortic dissection, uncontrollable hemorrhage.
- Significant medical comorbidity should be discussed with ECMO team
- Favorable if initial shockable rhythm, shorter low-flow time
- Evidence: (Lancet 2020;396:1807; JAMA 2022;327:737, NEJM 2023; 388:299)
- See *ECMO*

*Brian Huang*



Suggest an Edit

# Cardiology ACLS: Cardiac Arrest & TTM




## Targeted Temperature Management after Cardiac Arrest

**Rationale**: Fever is associated with worse neurological outcomes and neuronal damage due to inflammatory changes and biochemical cascades that develop following ischemia and reperfusion injury associated with cardiac arrest (Arch Intern Med 2001). TTM is a class I recommendation for all patients not following commands post arrest (AHA 2023). **Goal is to avoid fever for neuroprotection and to be aggressive about diagnosing/treating infections.**

**Causes of fever:** Inflammatory response to global ischemia-reperfusion, drug fever, and/or infection

- High infection risk in all post arrest patients from aspiration/pneumonia, global ischemia -> gut ischemia -> bacterial translocation. Pan-culture and consider empiric antibiotic treatment.
- If on temperature control device preventing rise in temperature, potential fevers will present as changes in cooling pattern

***Importantly*: Per** MGH policy**, default strategy is maintenance of normothermia ≤37.5 C/≤99.5 F for at least 72 hours w/central temperature monitoring (bladder preferred) and temperature control device placement for all qualifying patients (eg Arctic Sun)**

**TTM options** if patient is not following commands (patient needs to be stable enough to wean sedation and paralysis for this exam)**:**

- **Normothermia** (≤37.5 C)
  - Allow passive rewarming until patient achieves T 37 C. Once at 37 C, use temp control device
  - Arctic Sun or other temperature control device to maintain T <37.5 C for 72 hr
- **Mild Hypothermia** (T 33-36 C)
  - Individualized patient selection for mild hypothermia (T 33-36 C) decided by primary team and Neurology
  - Temperature control device placed as soon as possible with goal of achieving target temp within 4h of ROSC
  - Maintain mild hypothermia for 24 hr, followed by normothermia for 48hr for total 72 hr
  - For mild hypothermia, re-warming should occur at a target rate of 0.25 °C/h until normothermia achieved.
  - Monitor blood glucose/electrolytes closely
- Relative Contraindications to Mild Hypothermia: **Refractory hypotension,** Recent head trauma, active bleeding, major surgery (<14d)

**Evidence:**
- Targeted hypothermia (T 33 C) did not reduce 6-month mortality or survival with good neurologic outcome compared to targeted normothermia (T<37.5 C) (NEJM 2021;384:2283)
- Whether certain subgroups benefit from targeted hypothermia is uncertain (e.g., initial non-shockable rhythm (NEJM 2019;381:2327))
- Currently insufficient evidence to recommend different therapeutic temperatures for specific cardiac arrest groups (Class 2b, AHA 2023)

**Sedation and Analgesia:**
- Patients should undergo continuous sedation/analgesia if undergoing TTM w/mild hypothermia. Propofol is preferred sedative agent, dilaudid (or fentanyl) is preferred analgesic

**Shivering:**
- Stepwise approach to shivering in pts undergoing TTM (1st line: PR/PO acetaminophen 650q6 → IV, Mg >3, 2nd line: skin counterwarming + dexmedetomidine OR propofol OR hydromorphone boluses, 3rd line: propofol + hydromorphone gtt, consider buspirone 30q8, 4th line: NMBA) (Neurocrit Care 2011;14:389)

**Neuro-prognostication** see Neurology section

# Cardiology — ACLS: Bradycardia

## Bradycardia with Pulse

HR<60 bpm and **symptomatic**

Circ 2020 Evidence Review | ACC/AHA Brady 2018

### ASSESS PATIENT

- **Focused exam** → vitals, mental status, pupils, pulmonary edema, murmurs, warm/cold
- **Review** recent ECG, tele/labs, meds/dose changes
- Obtain 12-Lead **ECG,** have **pacing pads** available, call for atropine to bedside (may take time)
- **IV Access**: BMP, Mg, lactate ± trop
- **Monitor BP** freq., keep **O2** > 92%, maintain airway

### PATIENT UNSTABLE IF:

☑ **Any of the following present**

- **Hypotension**/shock
- **Altered mental status**
- **Ischemic chest discomfort**
- **Acute heart failure**/pulmonary edema

Trial medications

**Low threshold to jump to pacing**

### ATROPINE

**1mg bolus |** q3-5mins (max 3mg); 2hr half-life

*do not give s/p heart transplant*

*avoid with AV block Mobitz II or CHB*

**& ANTIDOTES BY CAUSE**

**DOPAMINE** IV infusion
5-20mcg/kg/min

**OR**

**EPINEPHRINE** IV infusion
2-10mcg/min

Transcutaneous vs venous pacing

### TRANSCUTANEOUS PACING

- Basics: Emergent 2mg lorazepam + 2mg dilaudid OR RICU for fentanyl/midazolam +/- intubate → turn to **PACER** → SET **RATE**: 100 BPM + SET **OUTPUT**: 100 mA → turn output down to minimum needed to capture → adjust rate down based on hemodynamics

### TRANSVENOUS PACING WIRE

- Wire placed by cardiology
- Indications: 1) need for transcutaneous pacing despite meds, 2) unstable rhythm with **no quickly reversible** cause

### IF PATIENT IS STABLE:

**Monitor + Assess for reversible causes**

- **Mobitz II & CHB with wide QRS** → often gets pacing wire even if stable, *call cards + ensure prepared to pace*
- *HOLD nodal blockers/anti-HTN if applicable*

### ATROPINE & AV BLOCKS

**Take-home message:** Atropine will not help in the setting of CHB and Mobitz II

- Ineffective for blocks below AV node (↓response to atropine in pt with *AVB;* Resuscitation 1999;41:47)
- Potential worsening of Mobitz II 2/2 ↑HR (Am J Card 1974;33:333)

## Bradycardia Diagnostic Algorithm

***Bold** = call Cards to consider pacing*

Are P waves present?

- **No** → 1. Sinus arrest w/ junctional escape OR ventricular escape [idioventricular]* 2. A fib/flutter w/ slow/variable conduction
- **Yes** → Regular P-P interval?
  - **No** → 1. Sinus pause/sinus arrhythmia 2. Wandering pacemaker 3. Non-conducting PACs
  - **Yes** → Regular P-R interval?
    - **Yes** → 1. Sinus bradycardia (# of P = # of QRS) 2. Mobitz I w/ 2:1 block 3. **Mobitz II** (# of P > # of QRS)
    - **No** → 1. Mobitz I (# of P > # of QRS) 2. **CHB w/ junctional escape OR ventricular escape if wide QRS** (Ps unrelated to QRS)

### RHYTHM PEARLS

- If grouped beats → look for Mobitz I & II
- In 2nd degree AV block with 2:1 conduction, it is not possible to differentiate Mobitz I vs. Mobitz II
- Always remember to consider hyperkalemia!

### ETIOLOGIES OF SINUS BRADYCARDIA AND/OR CHB

| Primarily SB | Primarily CHB |
|---|---|
| -SSS<br>-Elevated ICP<br>-Hypothermia<br>-Hypothyroidism<br>-Hypoxia<br>-Sleep apnea<br>-Carotid dz + recent stent | -s/p TAVR<br>-s/p septal ablation<br>-Endocarditis |
| **Both** | |
| -Ischemia/ACS (inferior MI commonly)<br>-Increased vagal tone<br>-Meds/toxins (esp in liver/renal disease)<br>-Hyperkalemia | -Degenerative, calcific conduction dz<br>-Infiltrative disease<br>-Lyme myocarditis<br>-Autoimmune myocarditis<br>-Pericarditis |

### SPECIFIC ANTIDOTES BY CAUSE

- **Beta blocker**: glucagon 3-10mg IV (if no response, repeat bolus, if response, infusion at 3-5mg/h)
- **Calcium channel blocker**: glucagon as above, calcium gluconate 3-6g q10-20min or gtt, insulin 1U/kg bolus with 0.5U/kg gtt
- **Digoxin**: dig immune FAB vial, 1 vial binds ~ 0.5mg digoxin, administer over 30min
- **Opioids**: naloxone 0.4-0.8mg IV, consider gtt
- **Organophosphate**: atropine 2-5mg IV (double dose q5min until effect), pralidoxime 1-2g IV over 15-30min

# Cardiology — ACLS: Tachycardia

## Tachycardia with Pulse
HR>120 bpm and **symptomatic**

↓ ACLS Guidelines 2020

### ASSESS PATIENT
- **Focused exam** → vitals, MS, pulmonary edema, murmurs, warm/cold, pupils, other sx
- Review: **most recent ECG**, tele, labs, meds, events
- Obtain: 12-Lead **ECG,** Defib + **pads**
- **IV Access**: BMP, Mg, lactate ± trop if c/f ischemia
  - **Correct all electrolyte abnormalities**
- **Monitor BP** frequently
- **O2**: supplement to >92%, maintain airway

↓

### IS THE PATIENT UNSTABLE?
☑ **Any of the following present:**
- Hypotension / shock
- Altered mental status
- Ischemic chest discomfort / angina
- Acute heart failure / pulmonary edema

**YES** → *Analgesia (1-2mg dilaudid) + sedation (2mg lorazepam)* → **SYNCHRONIZED CARDIOVERSION VS. DEFIBRILLATION**

| Rhythm | Mode | Dose (J) * |
|---|---|---|
| Narrow & Regular | Sync | 50-100 |
| Narrow & Irregular | Sync | 120-200 |
| Wide & Regular | Sync | 100 |
| Wide & Irregular | **Defib** | 120-200 |

**Biphasic (MGH)*

**NO** ↓ 💉

**MEDICATIONS** → **DETERMINE QRS WIDTH (> or <120 ms) & REGULARITY**

### ACUTE DRUG DOSING
- **Adenosine**: **6mg rapid IV push** (followed by NS flush) + arm raise, can repeat x1 → 12mg if required, **central line = ½ peripheral dose,** relative contraindication in pts s/p heart transplant
- **Amiodarone**: **150mg IV over 10min** (may repeat x1); then infusion at 1mg/min x6h followed by 0.5mg/min x18h (max 2.2g/24h)
- **Diltiazem**: 0.25mg/kg IV bolus over 2min → gtt (avoid if LVEF unknown)
- **Lidocaine**: **1.0-1.5mg/kg IV bolus** (usually 100mg), refractory → repeat 0.5-0.75mg/kg IV push q5-10min PRN, max 3mg/kg → maintenance infusion at 1-4mg/min; preferred agent if ↑QTc
- **Metoprolol:** IV push **2.5-5 mg over 2 min**; repeat q5 min; max dose 15mg; start low and increase; follow with oral after IV rate control
- **Procainamide**: **20-50mg/min or 100mg q5min** until any of the following: arrhythmia terminates, ↓BP, QRS prolongs by 50% from baseline, or total 17mg/kg given → maintenance infusion at 1-4mg/min (adjusted for CrCl), avoid with ↑QTc
- **Sotalol**: **1-1.5mg/kg IV over 5 min**; then maintenance infusion at 10mg/min, contraindicated with ↑QTc & caution in pts w/ ↓EF

### NARROW & REGULAR
Vagal Maneuvers
↓
**Adenosine***
↓
IV BB or Dilt**
Amio/Procainamide

**avoid if heart transplant*
***avoid if HFrEF*

**DDx**: ST, AT, orthodromic AVRT, AVNRT, Aflutter

*If difficult to discern P waves, adenosine can slow rate to differentiate*

### NARROW & IRREGULAR
**Oral vs IV BB or Dilt***
*Consider rate, need for quick effect, c/f hypotension*
*If persists or borderline BP*
↓
**Amiodarone (*rhythm,rate*)****
**Digoxin (*rate*)**
*consider empiric 2g Mg*
**avoid if HFrEF*
***possible cardioversion, consider AC status*

**DDx**: AF + RVR, MAT, Aflutter/AT + variable block, ST + freq PACs

*Consider chronicity/AC status prior to giving rhythm control for Afib/Aflutter*

### WIDE & REGULAR
**Amiodarone**
*(OK for VT or SVT)*
↓
EF >40%: Lidocaine, Sotalol, Procainamide, Metoprolol
EF <40%: Lidocaine

---
Suspect SVT + conduction abnl → can trial vagal + adenosine *(will not worsen VT)*

**DDx**: monomorphic VT, SVT with aberrant conduction, antidromic AVRT, preexcitation, meds & electrolyte abnormality

### WIDE & IRREGULAR
**Lido + 2g Mg** (over 15min) & treat myocardial ischemia

*↑ b/l QTc* → Torsades (TdP): 2-4g Mg & ↑HR (overdrive pacing, isoproterenol)

*nml b/l QTc* → Non-TdP: 2nd line = Amiodarone, procainamide

---
Pre-Excited SVT → **Procainamide** (nodal agents contraindicated)

**DDx**: PMVT (TdP & non-TdP), AFib/Aflutter/AT + pre-excitation vs aberrancy

*Lido generally safe → effective for all PMVT and will not worsen pre-excited rhythms*

### VAGAL MANEUVERS:
- **Unilateral Carotid Massage:** supine with neck extended → steady pressure to carotid sinus (inferior to angle of the mandible at level of thyroid cartilage near carotid pulse), avoid if prior TIA/CVA in past 3mo, and those with carotid bruits; 5%-33% success
- **Modified Valsalva Maneuver:** semi-recumbent → blow forcefully into a 10cc syringe x10-15 seconds → reposition to supine and passively raise legs at 45° for 15 seconds; 43% effective in breaking SVTs vs 17% with standard Valsalva (Lancet 2015;386:1747)
- **Also consider:** cold ice face immersion or ice-water bag to face (diving reflex, more effective in children); 17% success.

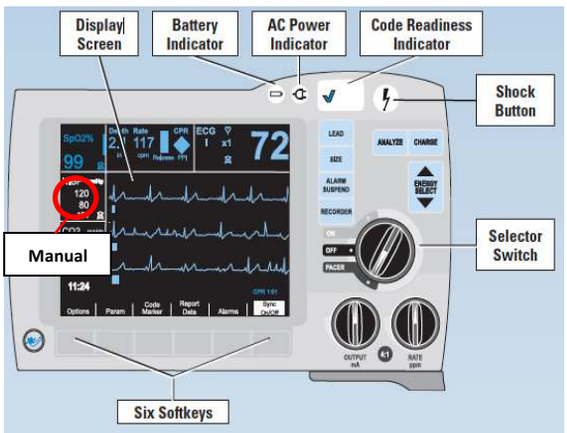
# Cardiology ACLS: Defibrillation/Cardioversion/Pacing

## 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, LUCAS (cardiopulm assist system) **Medications**: use procedural sedation (typically 50mcg **fentanyl** → 2mg **midazolam**) when possible, requires **Cardiac Anesthesia/RICU**. In emergent situations, **Dilaudid** 1-2mg + **lorazepam** 2mg is a reasonable alternative (often readily available).

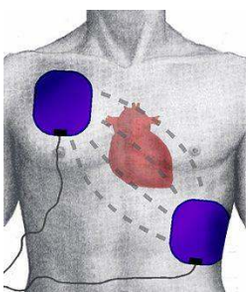
## Display/Operation of Zoll R Series

- **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. Can rip off hair with extra set of pads if razor not readily available in acute situations.
- Attach hands-free therapy electrodes in anteroapical position (pictured) or anteroposterior position for defibrillation. Some evidence that pads should be placed in anteroposterior position for pacing if possible (AHA 2022, Resuscitation 2022)




**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 (avoid bony structures), consider ddx (barrel chest, COPD, hypoxia, tamponade/pericardial effusion, pneumothorax, 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

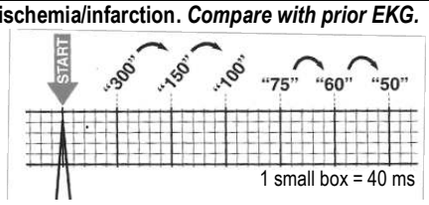


| **FIRST** turn the Selector Switch to **ON**. Then press **Manual** (bottom left soft key) to change to ALS | | |
|---|---|---|
| **Defibrillation** | **Synchronized Cardioversion** | **Transcutaneous Pacing** |
| ***Indications: Pulseless VT or VF*** | ***Indications: Unstable SVT or VT*** | ***Indications: Unstable bradycardia*** |
| 1. Default energy selection is 120 J. Initial dose 120-200 J. Use Energy Select (UP) & (DOWN) arrow keys to change the energy.<br><br>2. If there is a shockable rhythm on the pulse/rhythm check, press **Charge**. Continue CPR while charging.<br><br>3. Once charged, the **red shock button illuminates. Shout "Clear!"** then *press and hold* the illuminated **Shock** button at the top right of the console.<br><br>4. Resume CPR for 2 minutes before the next pulse/rhythm check | 1. Select the desired energy using the up and down arrow keys on the front panel<br>• Narrow, regular: **50-100 J** (atrial flutter often converts with 50 J)<br>• Narrow, irregular: **120-200 J** (atrial fibrillation typically requires 150 J)<br>• Wide, regular: **100 J**<br>• Wide, irregular: **150-200 J** (defib dose)<br><br>2. Press the **Sync On/Off** button<br>• Confirm that a **Sync marker** (↓) appears on the monitor above each detected R-wave to indicate where discharge will occur<br>• If necessary, use the **LEAD** and **SIZE** buttons to establish settings that yield the best display<br><br>3. Press the **CHARGE** button on the front panel. **Ensure patient is "clear"**<br><br>4. *Press and hold* the illuminated **SHOCK** button on the front panel. The defibrillator will discharge with the next detected R wave<br><br>5. If additional shocks are necessary, increase the energy level as needed<br>• Confirm that a Sync marker (↓) appears above each R-wave; you may need to press Sync between shocks<br><br>6. Anticoagulation required for at least four weeks after cardioversion | 1. **PACER** appears as an option on the Selector Switch. Turn to **PACER**<br><br>2. Set the **PACER RATE (BPM)** to a value 20 bpm higher than the patient's intrinsic heart rate. If unknown or absent intrinsic rate, use 100 bpm<br>• Observe the pacing stimulus marker on the display and verify that it is well-positioned in diastole<br><br>3. Increase **PACER OUTPUT (mA)** until the paced beats demonstrate **capture** ("threshold"); the output value is displayed on the screen.<br>• Capture = widened QRS complex + loss of underlying intrinsic rhythm<br>• Confirm mechanical capture with pulse check and/or by observing ventricular contraction w/ US<br><br>4. Set the **PACER OUTPUT** to the lowest setting that maintains consistent capture<br>• Usually ~10% above threshold (typical threshold: ~40-80 mA)<br>• Pressing and holding the 4:1 button temporarily withholds pacing stimuli, thereby allowing you to observe pt's underlying EKG rhythm & morphology<br>• 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)



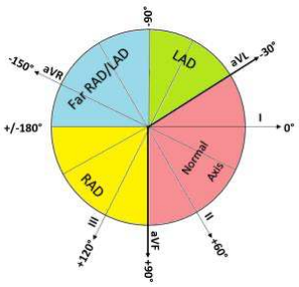

- If regular, 300 / #large boxes between each QRS (60,000/rate = R-R interval in ms)
- If irregular, count # of QRSs on EKG and multiply by 6 (printout = 10 sec)
- Normal atrial rate 60-100bpm; <60 = bradycardia, >100 = tachycardia
  - 100-180: sinus tachycardia; 140-220: atrial tachycardias, AVNRT/AVRT; 260-320: flutter

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

- **Sinus rhythm** = P before every QRS and QRS following every P, regular w/ rate 60-100, normal P wave axis
- P wave morphology: Is **P wave** present (best leads to visualize P wave are II and V1) and **P wave axis** (Normal: upright in I/II, biphasic in V1)
- QRS morphology: narrow (<120 ms) = supraventricular origin; wide (>120 ms) = aberrant supraventricular conduction or ventricular origin
- P wave/QRS complex association: if not 1:1: see if **P>QRS** (AV block) or **P<QRS** (AV node, His-Purkinje, 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/complete heart block (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, pacing |
| Rightward (+90 to +180°) | - | ⊕ | ⊕ | Normal variant, mechanical shifts, RV strain, 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 |

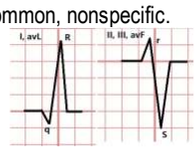



- Clockwise/counterclockwise rotation ("R wave progression"): R wave amplitude typically increases from V1 to V5, amplitude of R becomes greater than S at V3 or V4. Early or late R wave progression is nonspecific and can be normal (Am Heart J 2004;148:80)
  - CCW ("early R wave progression"): R>S prior to V3. Causes: RVH, WPW, LAFB, posterior MI.
  - CW ("late R wave progression"): R>S after V4. Causes: cardiomyopathy, LVH, LBBB, anterior MI.
- **Low voltage**: average QRS amplitude <5 mm in I, II, III *and* <10 mm in precordial leads
  - DDx: obesity, pericardial effusion, PTX, COPD, PE, restrictive or infiltrative CM (particularly amyloidosis), severe hypothyroidism, or anasarca

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

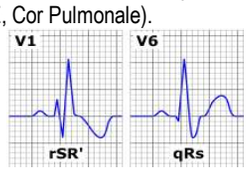
- P wave: right and left atrial depolarization. Normal: duration <120ms, voltage ≥ 0.1mV in I, area (1/2 duration x voltage in II) ≤ 4 (Circ Arrhythm Electrophysiol. 2022; e010435)
- PR interval: atrial depolarization, AV node and His-Purkinje conduction. Normally 140-200ms, changes with rate (shortened 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 unless RBBB, qR in I, aVL and rS in II, III, aVF. Common, nonspecific.



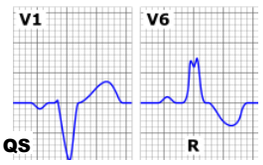

**LPFB**: right axis deviation, QRS <120 unless RBBB, rS in I, aVL and qR in II, III, aVF. Rare in isolation, usually w/ RBBB.

**RBBB**: QRS >120, rSR' in V1 or V2, wide qRS in V6, S>R duration in I, V6. Causes: infection (myocarditis), infarction, increased RV pressure (PE, Cor Pulmonale).




**Bifascicular**: RBBB + LAFB or LPFB

**LBBB**: QRS >120, wide negative QS in V1, wide tall R in I, aVL, V5, V6. Causes: primarily dilated cardiomyopathy (ischemia, infection, valvular, infiltrative).




- ST segment: normally isoelectic plateau of ventricular potentials
- 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: If present, will be right after and in same direction as T wave, 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: P wave duration ≥120ms (>2.5mm), widely notched P (≥40ms), negative component of P in V1 >1mm wide and deep

- RAE: P wave height >2.5mm in II ("P-pulmonae"), initial positive P wave in V1/V2 ≥1.5mm

## ST Segment and T wave changes (JACC 2009;53:1003)

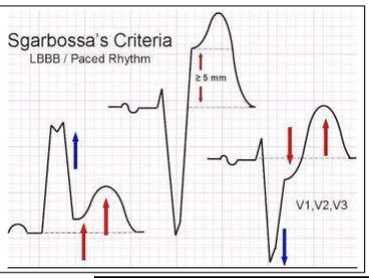
- Analyze abnormalities along the vectors of ventricular depolarization and repolarization (QRS-ST-T)
- **T wave abnormalities**: hyperacute, symmetric T waves can be found within minutes of ischemia, followed by T wave inversions (≥1mm in 2 contiguous leads). TWI normal if only in aVR, V1 or III. Isolated 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, ↑Sp/↓Sn: S1Q3T3, TWI III+V1 high PPV for PE > ACS (Am J Card 2007;99:817)), apical HCM (TWI V1-V6), arrhythmogenic right ventricular cardiomyopathy (TWI V1-3), intracranial pathology ("cerebral T waves", asymmetric), myocarditis, pericarditis, BBB pattern, V-paced, LVH with "strain", normal variant, digoxin effect (biphasic w/ initial neg. predominance), Type 1 Brugada (TWI V1-V2), athlete's heart. (World J Cardiol. 2015; 7(2): 86-100).
  - De Winter's T waves: 2% of STEMIs present with tall, symmetric T waves + >1mm 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, ≥0.5mm below the baseline (TP segment), measured 80ms after the J point in 2 contiguous leads
  - Downsloping or horizontal = more ominous. STD in isolation do not localize ischemia to a specific territory (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, ≥1mm in leads except for leads V2-V3 (≥2mm in M ≥40y, ≥2.5mm in M ≤40y, ≥1.5mm in F), measured at the J point, use TP segment (isoelectric interval) as baseline (Circ 2018: e618-e651). **Differential diagnosis**:

| Diagnosis w/ STE | Characteristic ECG Findings (NEJM 2003;349:2128; Annals 2004;141:858; NEJM 2004;351:2195) |
|---|---|
| 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 <5mm), 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 |
| 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 ≥1mm in 2 contiguous leads (esp V4), amplitude of STE:T wave (in mm) <0.25 |
| 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 |
| Cardioversion | Marked (often >10mm) and transient following DCCV |

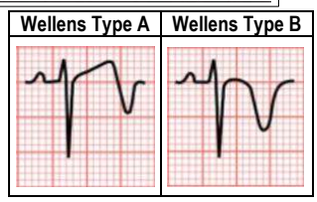
**Coronary Distribution**

| 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 >1mm in any lead = 5 points
- Discordant STE >5mm in any lead = 2 points
- STD >1mm in V1-V3 = 3 points

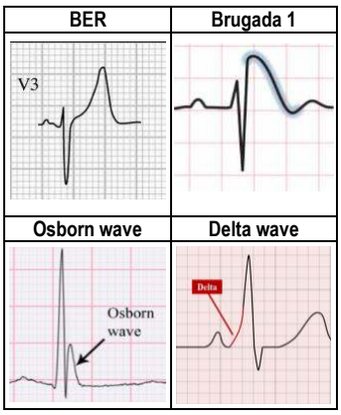



- **Q wave**: usually a marker of scar, pathologic Q waves must be deep (>1mm), 25% height of QRS, and 40ms long. More likely 2/2 prior MI if inverted T wave in same lead. Small "septal" Q physiologic in V5, V6, I, aVL
- **Wellens Syndrome**: sign of **critical proximal LM or LAD lesion**, 75% MI in <2w. 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 (<1mm) ST segment. No precordial Q waves (Am J 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.
  - Benign early repolarization (BER): upsloping STE in young (<50), asymptomatic, healthy patients; commonly w/ notched J joint. Has some associations with adverse outcomes but not well understood.
    - Suspicious features: FH sudden cardiac arrest or early unexplained death, workup c/f channelopathy, unheralded syncope c/f arrhythmogenic pathogenesis (Circ 2016;133:1520)
  - Brugada Pattern: 3 different classic patterns (Brugada 1-3), brugada syndrome only if symptomatic. Autosomal dominant SCN5A loss of function in 10-30%, M>F, nocturnal cardiac arrest common, p/w VT/VF or sudden cardiac death (Circ Arrhythm Electrophys 2012;5:606)
- Osborn wave: hypothermia T<93ºF, occurs before J point, can cause elevation of J point height ~ proportional to degree of hypothermia in II, V2-6. More dome-shaped than Epsilon wave.
- Delta wave: slurred upstroke of QRS indicative of pre-excitation. Found in Wolff Parkinson's White syndrome with a short PR interval and a prolonged QRS complex
- Epsilon wave: Low frequency, positive terminal deflection in V1-V3. Found in arrhythmogenic right ventricular cardiomyopathy (ARVC) (Circ 2005;112:3823), most Sp in V1 (30% with ARVC)
- Electrolyte Abnormalities:




| Abnormality | Characteristic ECG Findings |
|---|---|
| Hypokalemia | Prolonged QT, ST depression, flattened T wave, prominent U wave, higher amplitude P wave, prolonged PR |
| Hyperkalemia | Peaked, *symmetric* T wave → flat P → prolonged PR ± AVB → widened QRS ± BBB (severe) → sinusoidal |
| Hypocalcemia | Prolonged QT, unchanged T wave |
| Hypercalcemia | Shortened QT (if severe, T-wave can merge with QRS and mimic STE) |

# Cardiology — Narrow Complex Tachycardia

## NARROW COMPLEX TACHYCARDIA (QRS <120MS)

**General Principles – diagnostic:**

1. Determine width of the QRS complex
2. Determine if the rhythm is regular or irregular
3. Assess the RP length (Normal: RP > PR or Short: RP < PR) and presence and morphology of P waves
   a. Short RP is indicative of retrograde P waves
4. Compare to baseline EKG & review telemetry for tempo

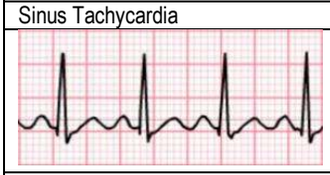
**General Principles – therapeutic:** (see ACLS: Tachycardia and Atrial Fibrillation/Flutter pages)

1. If sinus tachycardia: treat underlying cause
2. If unstable tachyarrhythmia: synchronized cardioversion
3. If stable/peri-stable tachyarrhythmia: rhythm specific treatment

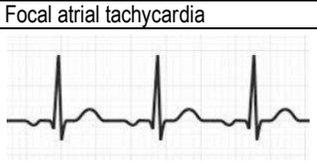
| Rhythm | Regularity | RP Interval | Typical rate | Etiology | P wave morphology | Clinical notes |
|---|---|---|---|---|---|---|
| Sinus tachycardia | Regular | Normal (RP > PR) | > 100 | Determine underlying cause: hypovolemia, hemorrhage, withdrawal (EtOH, BZD, opiate, BB), intoxication, fever/infection, pain, hypoxemia, PE, anemia, tamponade, dissection, endo (hyperthyroidism, adrenal insufficiency, pheochromocytoma) | Sinus P wave morphology | Gradual onset (PE common exception) |
| Focal atrial tachycardia | | | 110-250 | Abnormal automaticity at a single atrial focus other than the SA node | Most often abnormal morphology, but can be hard to distinguish from sinus morphology | -Classic digoxin toxicity is AT w/ variable AVB<br>-Usually seen in otherwise normal hearts<br>-Faster onset/offset than sinus tachycardia<br>-Some focal AT can have short RP such as a sinus node re-entry tachycardia |
| Junctional tachycardia | | Short (RP < PR) | > 100 | Increased automaticity within the AV node | P waves may be absent (QRS buried), inverted and/or retrograde | -Can be challenging to distinguish from AVRT/AVNRT |
| Atrioventricular nodal reentrant tachycardia (AVNRT) | | | 120-220 | Reentrant circuit at the AV node involving two distinct pathways: slow pathway (allows initiation of reentrant circuit, anterograde) and fast pathway (retrograde limb) | Retrograde P waves may either be before, buried or after QRS<br>- RP interval is shorter/none compared to AVRT | -Young adults, F>M, usually arises within structurally normal hearts.<br>-Most common form of regular, sustained paroxysmal SVT |
| Orthodromic atrioventricular reentrant tachycardia (AVRT) | | | 150-250 | Reentry circuit involving accessory pathway and AV node. Narrow complex since depolarization happens via AV node | Retrograde P waves may be present (if so, they appear later than those seen in AVNRT / longer RP interval) | -Antidromic AVRT more rare: ventricular depolarization through bypass tract instead causing wide complex tachycardia |
| Atrial fibrillation (AF) | Irregular | NA | Variable | Numerous re-entrant tracts in atria or pulmonary veins -> fibrillatory waves without coordinated atrial activity | Absent | |
| Multifocal atrial tachycardia (MAT) | | NA | >100 | Either from multiple atrial pacemaker sites or single focus with different conduction properties | At least 3 discrete morphologies, with different PR intervals | -Associated with COPD, pHTN, CAD, electrolyte disarray, aminophylline/theophylline use |
| Atrial flutter (AFL) | Regular (fixed conduction)<br>Irregular (variable conduction) | NA | Classically 2:1 block w/ fixed ventricular rate of 150 | "Typical": (circuit involves cavotricuspid isthmus) "Atypical": (reentry not involving isthmus)<br><br>In both: rapid regular atrial depolarizations without isoelectric baseline | Absent | -Typical presentation is atrial rate of 300 w/ ventricular rate of 150, but other conduction blocks/rates possible |

**Classic Tracings**

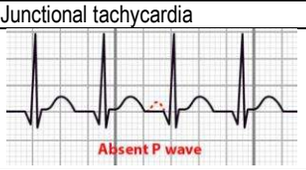
Sinus Tachycardia



Focal atrial tachycardia



Junctional tachycardia

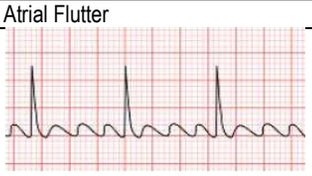



AVNRT

Atrial fibrillation

MAT

Atrial Flutter



AVRT

# Cardiology — Wide Complex Tachycardia

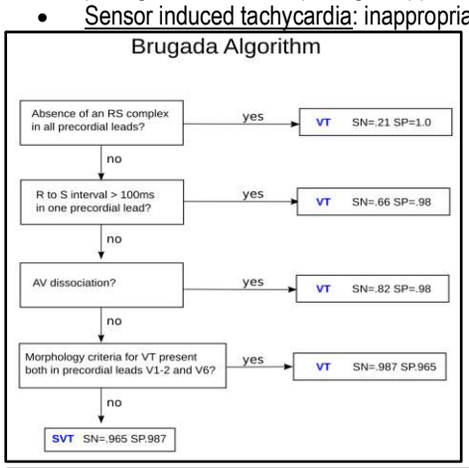
## Wide Complex Tachycardia (QRS ≥120ms)

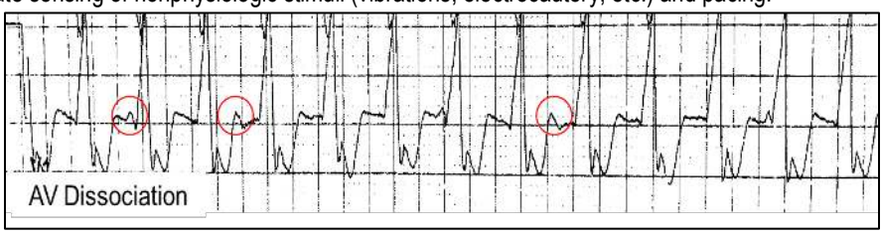
**DDx = VT** (80%), **SVT with aberrant conduction**, **pre-excitation syndrome**, or pacemaker-mediated tachycardia

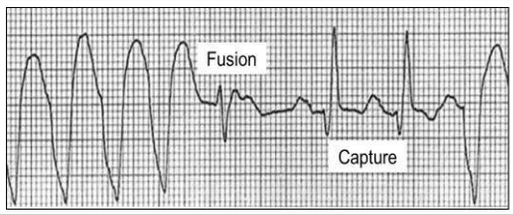
| **Features that Favor VT** (note: absence does NOT rule out VT) | **Features that Favor SVT with Aberrancy** |
|---|---|
| • **History of structural heart disease, prior MI, ICD**<br>• **Very wide QRS** (>160 ms), **Rate > 120** (if <120, consider Na channel toxicity or VT in someone already on significant antiarrhythmics)<br>• **New northwest (aka extreme)** axis (leads I and II negative)<br>• **AV dissociation** (often V rate > A rate): *pathognomonic for VT*<br>• **Concordance**: all QRS in V1-6 are completely (+) or completely (-)<br>• Partial (**fusion beat**) or complete (**capture beat**) depolarization of His-Purkinje by a competing supraventricular (atrial / junctional) rhythm<br>• **Basel algorithm** = VT likely if ≥2 of 3 present: (1) high risk substrate (prior MI, EF<35, prior VT/has ICD), (2) lead II time to first peak >40ms (1 small box), (3) aVR time to first peak >40ms (1 small box).<br>▪ Very effective: 93% sensitive & 90% specific (JACC 2022;7:831).<br>• **Brugada algorithm** also commonly utilized – see below. | • **Known BBB:** ventricular conduction delay (RBBB, LBBB, IVCD) with similar morphology and axis as seen on prior / baseline ECG<br>• **Evidence of His conduction**: QRS has sharp initial deflection (suggests initial use of His-Purkinje system followed by aberrancy)<br>• **Pre-excitation** on baseline ECG → supports antidromic AVRT or pre-excited atrial fibrillation<br>• **R wave peak time < 40msec** (measured in lead II and aVR) |

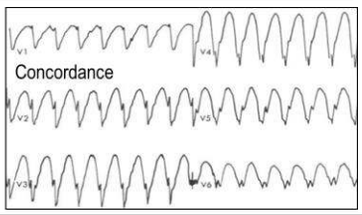
**Other important considerations**:

- 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.



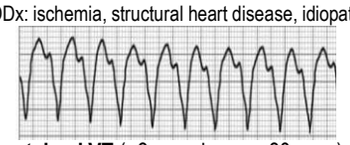




## Management of VT (also see *ACLS*: *Tachycardia*)

- Often no way to confidently distinguish VT vs SVT with aberrancy. If there is any doubt, treat like VT
- **Consider underlying processes**: active ischemia, CAD with scar, electrolyte derangement (low K, low Mg), drug toxicity, indwelling lines, thyrotoxicosis
- Check and replenish electrolytes **(K>4, Mg>2)**
- Review baseline ECG for evidence of long QT or pre-excitation

### Monomorphic VT

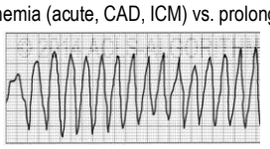
DDx: ischemia, structural heart disease, idiopathic



**Non-sustained VT** (>3 complexes, <30 secs):
**Asymptomatic**: monitor, treat underlying cardiac comorbidities (e.g., CAD, HF)
**Symptomatic or very high burden**: nodal blockade (BB>CCB), then AADs
**Stable and sustained** (>30 seconds): antiarrhythmic agent (e.g. amiodarone, lidocaine, procainamide [WPW])
**Unstable** → synchronized cardioversion (100J) if pulse; defibrillation if pulseless

### Polymorphic VT

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



**Unstable** → defibrillation
Baseline **normal QTc**: emergent eval for revasc (**ischemia** until proven otherwise), AADs (amio, procainamide)
Baseline **prolonged QTc:** magnesium 2-4g over 10-15min, ↑HR (isoproterenol, overdrive pacing), ↓QTc (**lido**), avoid bradycardia (**no** amio, CCB/BB)

### 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)
**Note**: isoproterenol = pure chronotrope will reduce RoT

**VT Storm**: ≥3 sustained episodes of unstable VT within 24 hours

- **Call EP +/- MCS Shock Team**
- **Lido bolus** (preferred if prolonged QTc), **Amio bolus** (careful if long QT), consider co-admin propranolol 40mg q6 (esp. if s/p multiple defibrillations) [JACC 2018;71:1897]
- **Anti-tachycardia pacing** (ATP): overdrive pacing at a faster rate than VT
- Treat / minimize ischemia: **urgent revascularization**, **IABP** to improve coronary perfusion, reduce preload / afterload
- Reduce autonomic tone: **intubation** and **sedation**, stellate ganglion block/cardiac sympathetic denervation
- **Catheter ablation:** In refractory cases, some evidence for ablation first strategy in ischemic CM (VANISH trial, VANISH2 trial)

# Cardiology — Atrial Fibrillation & Flutter

## ATRIAL FIBRILLATION

**Epidemiology** (Lancet Euro 2024; 37:100786))

- RF: age, obesity, HTN, smoking, EtOH, DM, previous MI, HF, OSA
- Recurs in majority of cases due to secondary precipitant (surgery, infection, MI, thyrotoxicosis, acute alcohol, PE)
- Higher incidence in Caucasian and male patients (JACC 2020;76:2982)
- Racial, ethnic, and gender inqeuities persist in AF screening and management (Circ 2024; 149: e1-e156)

| New AF Classification (Circ 2024; 149: e1-e156) | |
|---|---|
| Stage I: At-risk for AF | Presence of modifiable and non-modifiable RFs |
| Stage II: Pre-AF | Structural or electrical findings that predispose to AF (atrial enlargement or ectopy etc.) |
| Stage III: AF Spectrum | Spectrum including paroxysmal (3A, <7d), persistent (3B, >7d), long-standing persistent (3C, >12mo), or s/p successful AF ablation (3D) |
| Stage IV: Permanent AF | Decision is made to no longer pursue rhythm control |

**Clinical Evaluation of New-Onset AF**

- H&P: **presence & timing of sx**, HTN, DM, valve dz, HF, 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, enlarged LA/RA size, valve function, pulmonary HTN, LA thrombus (better visualized with TEE or CT-pulm vein)
- CXR: evaluate for pulmonary parenchymal processes, pulmonary vasculature/edema
- Labs: TFTs, LFTs, BUN/Cr, CBC, NT-proBNP, BMP (K,Mg)
- May also need longer term rhythm monitoring (Holter, Zio patch). Consider stress test if signs/sx of ischemic heart disease.
- Smartwatch notification has PPV 0.84 for AF on subsequent simultaneous EKG in patients > 65 (NEJM 2019; 381:1909-1917)

**Acute Management of AF with Rapid Ventricular Response**

Hemodynamically stable?

| **Stable** (SBP >90) | **Peri-stable** (SBP 80-90) | **Unstable** (SBP<80)<br>See "ACLS: Tachycardia" |
|---|---|---|
| **Rate control** (IV if HR >130 or sx, follow with PO agent once rates controlled)<br>- **Magnesium:** 2-4 g empiric IV Mg + nodal agents ↑ success of rate and rhythm control (J Cardiol 2021;78:375)<br>- **Beta blocker**: metoprolol preferred in most cases<br>- IV: bolus 2.5-5mg over 2min, repeat prn q5min, max dose 15mg<br>- PO: fractionated (tartrate), 6.25mg-50mg q6h<br>- Caution if severe bronchospasm and w/ rapid escalation in pts w/ ADHF<br>**- Calcium channel blocker**: diltiazem<br>- IV: bolus 0.25mg/kg (average dose 10-25 mg) over 2min, repeat prn q10-15min<br>- PO: fractionated, up to 360 mg total daily dose<br>- Reduce dose with hepatic or renal impairment<br>- Avoid in pts with LVEF<40% and in ADHF | If borderline BP, carefully attempt **low dose** BB or CCB (can try concomitant **IVF** if pulm edema not a concern)<br>Consider BP-sparing agents:<br>- **Amiodarone**: 150mg IV over 10 min, can repeat x1 if needed and start gtt at 1mg/min(weigh risk of pharmacologic cardioversion if not on AC)<br>- **Digoxin**: IV 8-12**mcg**/kg IBW divided in 3 doses (50% load then two 25% doses q4-8h or use "Digoxin IV load panel" in Epic) Max 1.5mg in 24hr. Check level 6-24h after load (goal <1.2). Adjust for eGFR, watch for DDIs. C.I. if accessory pathway | Usually HR >150, signs of shock (AMS, cool ext.), refractory pulmonary edema or angina<br><br>**Synchronized cardioversion**: start with 150J (Biphasic)<br><br>If pressors needed: **phenylephrine** is first-line given reflex bradycardia<br><br>Higher HRs (>140) more likely to cause HoTN alone; lower HRs may cause HoTN if systolic or diastolic dysfxn, or decreased preload ("loss of atrial kick") |
| Correct **underlying etiology** whenever possible once stable (e.g. infection, volume, PE, EtOH, PTX, PNA, MI, pericarditis) | | |

**Cardioversion** (ALWAYS consider high risk of embolic stroke if any interruptions in AC for 3 weeks 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),↑energy if NSR not achieved. See *ACLS: Cardioversion*.
- **Chemical Cardioversion**: success rate significantly higher for acute (<7d) compared with longer duration AF
- **Anticoagulation** (applies to BOTH chemical and electrical)
  - Pre-cardioversion: if definitive new onset **<48h**: may proceed without anticoagulation. If Afib onset **>48h or unclear**: anticoagulate for 3w prior to cardioversion *or* obtain **TEE/CT Pulmonary Vein** immediately prior to cardioversion
  - Post-cardioversion: anticoagulate for at least **4 weeks after cardioversion** (risk of myocardial stunning and AF recurrence, but unproven efficacy). Anticoagulation beyond 4 weeks after reversion to NSR is based on $CHA_2DS_2$-VASc and HAS-BLED scores

**Risk Assessment** (Risk scores DON'T account for the complete spectrum of RFs - Individualize AF management)

- **$CHA_2DS_2$-VASc**: 1pt for **C**HF, **H**TN, **A**ge 65-74, **D**M, female **S**ex, **V**ascular disease; 2pt for **A**ge≥75, **S**troke/TIA. $CHA_2DS_2$-VASc > $CHADS_2$ in "truly low risk" subjects (Thromb Haemostasis 2012;107:1172)
  - Score 0 = no AC; Score 1 (2 in women)= no AC vs AC based on clinical judgment, generally lean towards AC initiation; Score ≥2 (≥3 in women) = AC
  - NOT used to guide decision making for HOCM or mitral stenosis (MS) with moderate severity or greater.

- **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/AlkPhos 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
- SPARCtool can aid in risk/benefit assessment and choice of anticoagulation

**Anticoagulation** (AHA/ACC/HRS: Circ 2024; 149: e1-e156 ; Stroke 2010;41:2731)

- Consider AF burden when estimating stroke risk (JAMA Card 2018;601). Subclinical AF is also associated w/ increased stroke/systemic embolism (NEJM 2012;366:120). In these pts, AC reduces the risk of ischemic stroke but increases the risk of major bleeding, thus AC decision should be individualized
- **DOACs vs warfarin**: DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) recommended > warfarin in all except valvular AF, mod-severe mitral stenosis, HOCM, or mechanical valve. Warfarin may be > rivaroxaban in rheumatic heart dz (NEJM 2022;387:978). DOACs: ↓risk of stroke, mortality, & ICH, ↑risk of GIB (Lancet 2014;383:955), apixaban lowest GIB risk (Ann Intern Med 2022;175:1515)
- **Dosing**: see *Anticoagulation Agents* for dosing. Dose-reduce apixaban to 2.5mg BID 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*

**Left Atrial Appendage Occlusion (LAAO) -** LAA is the source of at least 90% of thrombi in pts with CVA and AF

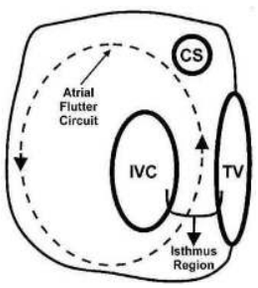
- **Watchman device**: in non-valvular AF, device placement → comparable stroke prevention to warfarin with ↓bleeding risk & improved mortality (JACC 2017;70:2964). Consider if contraindication to long-term AC. AC can be discontinued 6w after LAAO, per MGH protocol.
- **Surgical occlusion**: decreases risk of stroke and systemic embolism. Grade 1A recommendation for pts with $CHA_2DS_2$-VASc ≥2 undergoing cardiac surgery in addition to continued AC (Circ 2024; 149: e1-e156).

**Long-Term Rate vs Rhythm Control**

- Traditionally, rate control considered noninferior to rhythm control for AF sx, CV mortality, & stroke risk (AFFIRM, RACE, PIAF, STAF, HOT CAFÉ, AF-CHF). Latest guidelines shifted with benefit of early rhythm control and reducing AF burden. (Circ 2024; 149: e1-e156)
- **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)
  - 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** > **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 (time to onset 3-6 hrs), ineffective w/ high adrenergic tone
    - Importantly: 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**: no nodal blockade if any 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: flecainide,propafenone, dofetilide, dronedarone, sotalol, amiodarone
    - Structural heart disease: **CAD**: dofetilide, dronedarone, sotalol, amiodarone; **HF or LVH**: amio, dofetilide
  - **"Pill-in-Pocket"**: for patients with recent pAF and infrequent and well-tolerated episodes, ppx may have risk>benefit. PRN flecainide or propafenone + BB or CCB instead at symptom onset is safe and effective (NEJM 2004;351:2384)
  - **Catheter ablation** (pulmonary vein isolation [PVI]): Growing evidence behind PVI as safe & effective initial rhythm control strategy (NEJM 2021;384:305)↓long-term AF recurrence rate vs AADs in both pAF (MANTRA-PAF) & persistent AF (EHJ 2014;35:501). Ablation in pts w/ HF ↓morbidity/mortality (CASTLE-AF) and improves psychological distress. (JAMA 2023;330:925)
  - **AV nodal ablation with PPM**: indicated when pharmacologic rate/rhythm control not achievable (JACC 2014;64:2246)

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

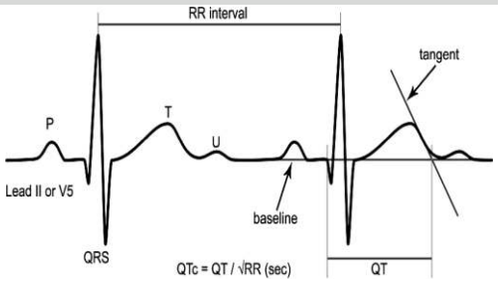
- ECG: "sawtooth" P waves (F waves), atrial rate typically 250-300bpm w/ 2:1 conduction (~V-rate 150), though can be variable block, 3:1, or 4:1. 1:1 conduction can briefly precede VT/VF
  - **Type 1 (typical)**: reentrant loop in RA via cavo-tricuspid isthmus
    - Counterclockwise: more common, inverted flutter waves II, III, aVF + upright flutter waves 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 often faster and refractory to ablation
- **Anticoagulation**: risk of thromboembolism lower than AF (J Stroke Cerebrovasc 2018;27:839) but anticoagulation management is similar to AF (Chest 2012;141:e531S)
- **Rate control**: similar strategies (BB, CCB) to AF, but more difficult to successfully rate-control vs. AF
- **Rhythm control**: **Ablation** > AAD. Cavo-tricuspid isthmus (CTI) ablation for typical flutter >90% effective at 1y (Circ Arrhythmia EP 2009;2:393). However, prophylactic CTI ablation during PVI for AF pts without known AFL does not reduce incidence of AFL or recurrence of AF (Arryth EP Rev 2022; e10).



# Cardiology — QTc Prolongation

## Definition (Circ 2009; 119: e241)

- QT interval correlates with repolarization time of ventricles
- Normal: ≤460ms; Borderline (adult): 460-479ms (female), 450-459ms (male)
- 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; can use ECG or caliper function on telemetry
- QTc is QT corrected for HR; linear (i.e., Hodges/Framingham) formulas are recommended by AHA (J Electrocardiology 2004;37:81)
- Can be **calculated using MDCalc**: **Framingham and Fridericia** provide best rate correction and mortality prediction (JAHA 2016;5:e003264)




## Assessment of QTc with Underlying Wide QRS (Heart Rhythm 2014;11:2273)

- Wide QRS (BBB/V-paced) lengthens QT interval; **calculate using Mayo calculator,** or with rough estimate using QT - (0.5*QRS). Must still account for HR (Heart Rhythm. 2014 Dec;11(12)).

## Congenital Long-QT Syndromes

- Majority of pts are asymptomatic, often discovered on ECG or QTc prolonged more than should be expected by drugs
- Sx: presyncope/syncope, hemodynamic compromise, sudden cardiac death; triggered by exercise, stress
- Tx: beta blocker for all, ICD if previous cardiac arrest and expected survival >1y (Class 1A Recommendation) (Circ 2006;114:e385)
  - BB thought to reduce early after-depolarizations and transmural dispersion of repolarizations, which can trigger arrhythmias

## Drug-Induced Prolonged QT Interval (Heart 2003;89:1363; NEJM 2004;350:1013)

- Drugs inhibit rapid K+ current 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 Pts (Circ 2010;121:1047) | |
|---|---|
| **Demographics** | Elderly, female, congenital long QT syndrome, anorexia/starvation, hypothermia |
| **Comorbidities** | Renal failure, hepatic dysfunction, drug-drug interactions, HF, MI, LVH, hypothyroidism, stress cardiomyopathy |
| **Rhythm-related** | **QTc >500ms,** bradycardia (sinus, AV block, ectopy causing pauses), **PVCs** |
| **Electrolytes** | **Hypomagnesemia**, hypokalemia, hypocalcemia |
| **Medication-related** | QT-prolonging drugs (esp. IV infusions, >1 concurrently), diuretic use, beta blocker use |

| Class of Drug | QT-Prolonging Drugs [**common**, *high-risk*, (low-risk)]: (Br J Clin Pharm 2010;70:16; Circ 2020:142:e214) |
|---|---|
| **Antiarrhythmics** | CLASS IA/C: *quinidine*, *disopyramide*, *procainamide*, flecainide, propafenone<br>CLASS III: ***sotalol***, ***dofetilide***, *ibutilide*, *dronedarone*, ***amiodarone*** - oral amiodarone rarely associated w/ TdP due to uniform delay in repolarization across myocardium |
| **Antimicrobials** | ANTIBIOTIC: **azithromycin**, erythromycin, clarithromycin, **levofloxacin**, moxifloxacin, (**ciprofloxacin**), (**metronidazole**)<br>ANTIFUNGAL: **fluconazole**, voriconazole, (**ketoconazole**)<br>ANTI-MALARIAL: *quinine*, *quinidine*, chloroquine, (also hydroxychloroquine) |
| **Antipsychotics** | ***haloperidol IV***, *thioridazine*, *chlorpromazine*, *ziprasidone*, **quetiapine**, **risperidone**, **olanzapine**, haloperidol oral, clozapine |
| **Antidepressants** | Clomipramine, imipramine, **citalopram, escitalopram,** (**fluoxetine**), (**sertraline**), (**trazodone**), (mirtazapine) |
| **Anti-emetics** | **ondansetron IV>oral**, droperidol, (**metoclopramide**) |
| **Others** | ***Methadone***, **propofol**, **hydroxyzine**, (**loperamide**), (**albuterol**), (donepezil) |

## Monitoring for QT/QTc Prolongation

- 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 bradyarrhythmia
  - Severe hypokalemia or hypomagnesemia

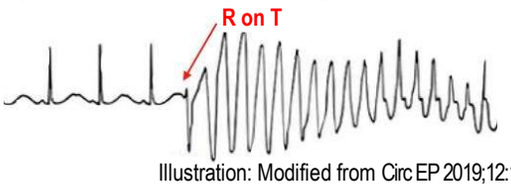



Illustration: Modified from Circ EP 2019;12:12

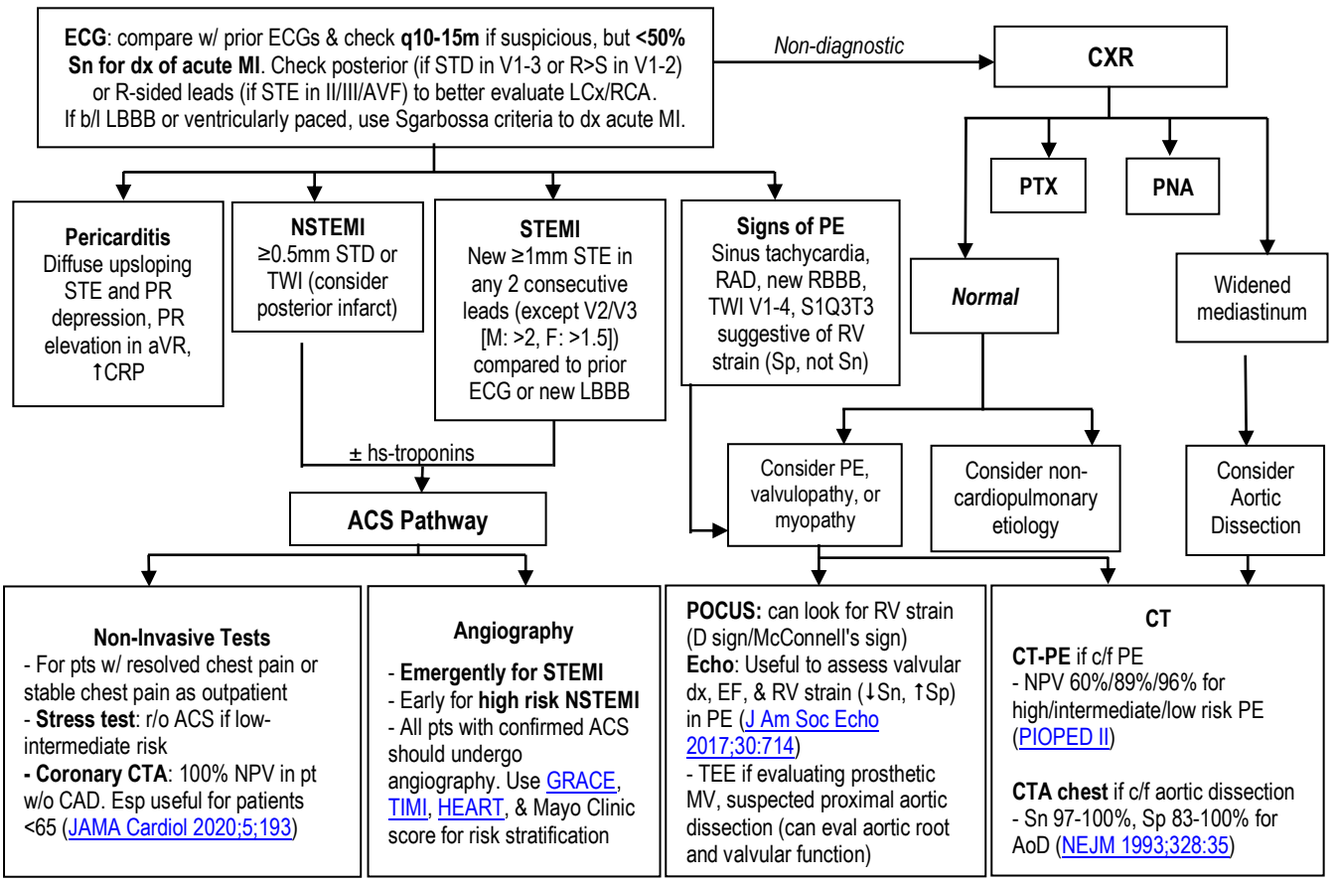
## Management of Acquired Long QT

- **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, above). Stop drugs causing bradycardia.
- Check electrolytes & replenish to supratherapeutic levels (K: 4.5-5, Mg: 2-2.5)
- If patient develops TdP: See ACLS: Wide complex tachycardia page

# Cardiology — Chest Pain

| Etiology | History | Physical Exam |
|---|---|---|
| **Stable Angina/ACS** (Circulation 2021;22;e368)<br><br>*Symptoms are no longer described as atypical/typical, instead use cardiac, possible cardiac, or noncardiac (Circulation 2022;80(17)) | **Assess:** Characteristics/duration of symptoms, associated sx, provoking factors, CVD risk factors<br>**Classic angina triad*:** (1) **substernal** chest pain/pressure, (2) worse w/ **exertion**, and (3) **relieved by rest or nitrate**<br>**Possible anginal Equivalents:** Chest tightness, shoulder/arm/neck/back/upper abdomen/jaw pain, SOB and fatigue, N/V, pre-syncope<br>• **Women**, **elderly** and **pts w/ DM** more likely to have less classic symptoms<br>**Antianginals**: nitrates; avoid if preload sensitive (RV ischemia, HoTN, AS, recent PDEi); BB (careful in ADHF, long PR, 2°/3° AV block); CCB if BB intolerant; ranolazine<br>**Significant racial/ethnic/gender** disparities exist in dx/tx of ACS (Circulation 2023;43:1369)<br><br>Likelihood Ratios for ACS (JAMA 2015;314:1955)<br>**Low Risk**: Pleuritic (0.3); Syncope (0.5)<br>**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)<br>**High Risk**: Similar to prior ischemia (2.2); Pain radiating to both arms (2.6); PAD (2.7); Abnormal prior stress test (3.1) | • Distress, diaphoresis<br>• **New S4**, MR (*ischemia*)<br>• **CHF** (crackles, +S3, ↑JVP, pedal edema)<br>• Carotid, subclavian, & abdominal bruit (indicates vascular disease)<br>• Bilateral femoral and radial pulses (*document pre-cath*)<br>• Exam can be normal<br>• Less likely ACS: **p**leuritic, **p**ositional, re**p**roducible by **p**alpation (LR 0.28) |
| **Acute Aortic Syndromes** | **Abrupt onset** of tearing/sharp thoracic or abdominal pain<br>RF: known aneurysm, Marfan syndrome, CTD, 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, classically improves upon leaning forward<br>May have URI prodrome; rheum history/sx, consider bacterial if high fevers | Friction rub, tamponade (pulsus >10 mmHg) |
| **PE** | Sudden onset, dyspnea/hypoxemia, pleuritic<br>RF: hx of cancer/recent surgery/immobility, hemoptysis, calf/thigh pain/swelling | Tachycardia, tachypnea, hypoxemia, calf/thigh erythema, swelling, tenderness, signs of RV strain |
| **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 a/w fever/↑WBC, productive cough, recent radiation, autoimmune (SLE, RA, drug-induced lupus, collagen vascular diseases) | Bronchial breath sounds, crackles, dull to percussion |
| **Other** | **Cardiac**: HOCM, AS, vasospasm (Prinzmetal's, drug/toxin), Takotsubo; **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

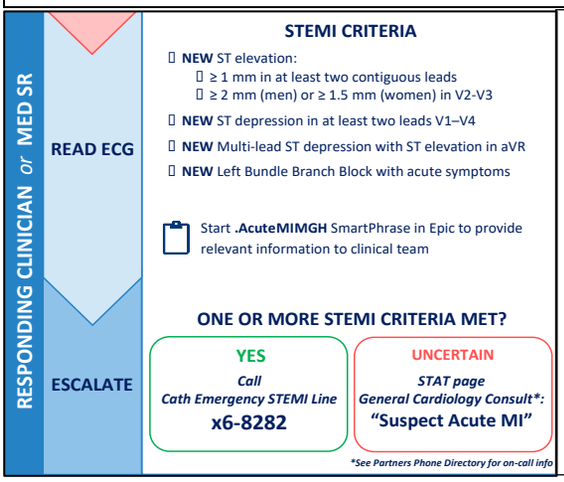
**Myocardial injury**: defined as any patient with troponin >99th percentile without evidence of myocardial ischemia (sx of ischemia, new ischemic ECG changes, new wall-motion abnormalities, and/or acute coronary thrombus on angio). May be acute or chronic.

**Myocardial infarction**: myocardial necrosis (trop >99th percentile + Δ) w/ ischemia (4th universal def. of MI, types 1-5: JACC 2018;72:2231)

- Type 1 MI: spontaneous coronary plaque rupture, erosion → intraluminal thrombus
- Type 2 MI: flow/O2 supply-demand mismatch that is not atherothrombosis – most commonly due to sepsis/infection, arrhythmias, severe anemia, renal failure, surgery, hypertension, and heart failure; other causes include vasospasm, microvascular ischemia (e.g. Takotsubo), thromboembolism (Circulation 2019;140:1661).
  - 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

| 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 3h ΔTn ≥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 | |

| STEMI | NSTEMI | UA |
|---|---|---|
| • 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 ⊕ biomarkers<br>• If baseline LBBB, use Sgarbossa's criteria: ≥1 mm concordant STE, 1 mm STD V1-V3, ≥ 5 mm discordant STE. Though note better Sp and Sn with Smith-Modified Sgarbossa criteria and Barcelona algorithm (JAHA 2020;19:e017119)<br>• Electrically Silent: LCx or RCA lesions. Consider posterior V7-V9 leads → STE>0.5mm is diagnostic. Other changes: large R in V2-V3, STD in anterior leads (mirror image effect) | ⊕ **ECG**: ST depressions, TWI, flattened t-waves, up 1/3 have normal ECG) or hx, ⊕ **biomarkers** | ⊕ ECG or hx, ⊖ **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
- hsTnt peaks within 12-48 hrs, normalizes in 5-14 days

## Revascularization

**STEMI**

- Primary PCI (PPCI) recommended revasc strategy for pts w/STEMI <48h symptom onset (PCI center: aim<60 min to wire crossing)
- PPCI regardless of symptom onset if cardiogenic shock, malignant arrhythmia (recurrent sustained VT/VF), persistent STE and/or CP
- PPCI>48h symptom onset not indicated in stable pts (NEJM 2006;355:2395)
- If PPCI not possible within 120 min first med contact (and <24h symptom onset), fibrinolysis: Aim<10 min to lytic bolus (Tenecteplase preferred) w/ immediate transfer to PCI center. Discuss antithrombotic therapy w/cardiology. Contraindicated in ↑bleeding risk (esp ICH), suspected dissection, ischemic stroke <3 months prior, severe HTN

**NSTE-ACS (NSTEMI/UA)**

- Multiple risk models incl GRACE, TIMI. GRACE score is based on predictors of 6mo mortality (BMJ 2006;333:1091)
- Four subgroups for urgency to revascularization (JACC 2014;64:e139)
  1. **Very high risk** ("immediate invasive," within 2h): **refractory/recurrent angina, hemodynamic or electrical instability, mechanical complications, recurrent dynamic ECG changes suggestive of ischemia**
  2. **High risk** ("early invasive," within 24h): temporal change in troponin, ECG changes (transient STE, STD, TWI), high risk pt (GRACE>140)
     a. 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
  3. **Intermediate risk** ("delayed invasive," within 72h): none of above but risk factors at baseline (e.g. EF <40%, GFR <60)
  4. **Low risk** ("ischemia guided," no cath): no risk factors, GRACE <109, TIMI 0-1 OR not good candidate for angiography

**PCI vs CABG**: Selection of revascularization strategy should be based on the acuity of the patient's condition, the angiographic characteristics of the culprit lesion, and the complexity of the patient's anatomy and, when appropriate, should include a Heart Team discussion (Guideline: Circulation 2022;145:4). CABG often preferred for 3VD (NEJM 2009;360:961), L main disease (NEJM 2016;375:2223), 2VD with prox LAD stenosis or EF <50%, DM + 2VD w/ involvement of LAD (NEJM 2012;367:2375).

**Multivessel Disease PCI Strategies**

- STEMI w/o cardiogenic shock: complete revascularization strategy (culprit + non-culprit) has ↓risk of CV death and MI at 3y (COMPLETE, NEJM 2019;381:1411)
- STEMI OR NSTE-ACS + cardiogenic shock: culprit-lesion only PCI has a ↓risk of death/RRT (CULPRIT-SHOCK, NEJM 2018;379:1699). Consider staged complete revascularization
- NSTE-ACS w/o cardiogenic shock: complete revascularization strategy (BIOVASC, Lancet 2023;401:1172)

## Adjuncts to Revascularization

**Adjuncts at Presentation:**

1. **ASA**: established mortality benefit, give to all pts in an immediate load/maintenance strategy (325mg/81mg) (Lancet 1988;2:8607)
2. **Peri-Intervention Anticoagulation**: start on Dx of ACS. Usually stopped after PCI if no additional indication for AC (eg Afib, PE). If no PCI and medically managed, usually d/c at 48h if ECG changes improving and c/f ongoing ischemia resolved (BMJ 1996;313:652). If chronically on warfarin/DOAC, discuss transition to short acting AC with pharmacy pre-cath.
   - **UFH**: Standard. Start gtt w/ bolus and use **low intensity PTT goal** (50-70). Anti-Xa protocol also available. 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 ↑catheter thrombosis/complications (JAMA 2006;295:1519)
   - **GPIIb/IIa Inhibitors**: eptifibatide (Integrilin) used at MGH. Initiated in cath lab if PCI high-risk (extensive thrombus)
   - **Bivalirudin/Argatroban**: direct thrombin inhibitor, preferred for patients w/ HIT. Emerging evidence suggests benefit over UFH in STEMI (BRIGHT-4 Lancet 2022;400:1847)
3. **Statin**: 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 anti-inflammatory effect may stabilize plaque (JAMA 2001;285:1711; JAMA 2004;291:1071)
   - If very high risk clinical ASCVD w/ LDL-c >70 mg/dL, add **ezetimibe** and consider PCSK9i (JACC 2019;73:3168)
4. **Nitrates**: TNG SL (0.3-0.6mg) x3, if refractory → gtt (start 5-10mcg/min titrate to chest pain free). Nitropaste 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 refractory CP indication for earlier cath.
5. **Morphine**: not recommended. Consider only if unacceptable level of pain refractory to TNG, careful if suspicious for inferior MI/RVMI
6. Discontinue NSAIDs: ↑risk of mortality, re-infarction, HF, and myocardial rupture after ACS

**Adjuncts to start within 24h or Post-Revasc**

7. **P2Y12 Inhibitors*: Pre-cath load not done at MGH. Do not start w/o asking cards***. Controversial benefit & may delay CABG by 5-7d (Circulation 2022;145:4). If relevant, see MGH $P2Y_{12}$ switching guidelines **here** (does not apply to patients on triple therapy)
   - Ticagrelor: ↓mortality compared to clopidogrel w/o increasing major bleeding. Reversible with platelet transfusion. Side effect: **dyspnea** (14-21%, often mild & transient, but can be severe enough to warrant discontinuation), risk of pneumonitis w/ alveolar hemorrhage. 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;358:527l). Prodrug, metabolized by CYP219, less effective in those with LOF allele (NEJM 2009;360:354). May benefit from PPI ppx for ↓UGIB (NEJM 2010;363:1909). ↓Bleeding compared to ticagrelor and prasugrel but ↑ischemic events (Circulation 2020;142:150).
   - Cangrelor: IV reversible inhibitor with immediate onset and return of platelet function in 1h.

   **DAPT duration**: Default 12 months after ACS. Use DAPT score to help risk stratify. Evolving movement to shorten DAPT duration (Select DAPT trials: TWILIGHT, TICO, STOPDAPT-2, SMART CHOICE, GLOBAL LEADERS, MASTER DAPT, HOST-EXAM)
   - Bottom line: In select patients, single agent P2Y12 inhibitor after 1-3 months (vs. longer duration DAPT) is non-inferior in reduction of cardiovascular events, with reduced bleeding. Decisions on DAPT should involve interventional cardiology
   - **If on longterm AC (eg AFib, PE)**: P2Y12 inhibitor + DOAC > triple therapy. ↓bleeding and non-inferior for ischemic events (AUGUSTUS NEJM 2019;380;1509; RE-DUAL PCI NEJM 2017;377:1513; NEJM 2016; 375:2423). (Guideline JACC 2021;77:629).
     - Common example: initiate triple therapy (ASA/clopidogrel/AC) for 1-4wks and then d/c ASA → AC + clopidogrel
8. **Beta Blockers**: start within 24h (1B for STEMI, 1A for NSTE-ACS), mortality benefit. Consider early initiation if ischemic arrhythmias present. Not indicated for stable ischemic heart disease s/p cath, but rec'd after CABG (Circulation 2022;145:4). Long term BB s/p MI w/ LVEF >50%, does not reduce mortality or recurrent MI (NEJM 2024;390:1372)
   - Caution in decompensated HF, ↑risk for cardiogenic shock (>70y, SBP <120, HR >110 or <60)
   - Contraindications: shock, cocaine-induced MI, PR>240ms, 2nd or 3rd degree AVB, severe bronchospasm (Lancet 2005;366:1622)
9. **ACEi or ARB**: start ACE within 24h in all patients if BP/renal function normal; mortality benefit in anterior STEMI; use ARB if intolerant of ACE. ARB > ACE in patients with HF or LVEF <40% (Circulation 2008; 117:269).
10. **Aldosterone antagonist:** s/p MI on ACE and BB, and have LVEF<=40 + DM or sx of HF (Circulation 2008; 117:269)
11. **Lifestyle**: smoking cessation, BP <130/80 (esp. if comorbid DM or CKD), cardiac rehab, depression screening; Flu vaccination

# Cardiology — MI Complications

## ▪ MECHANICAL COMPLICATIONS (JACC Cardiovasc Interv 2019;12:1825; JSCAI 2023;2:100791; Circ 2021;144:e16)

| | Complication | Prevalence / Risk Factors | Timing / Clinical Signs | Evaluation | Treatment |
|---|---|---|---|---|---|
| EARLY (Hours – Days) | **Cardiogenic Shock** (see *Inpatient HF*) | ▪ STEMI~6%, NSTEMI~3%<br>▪ Anterior MI, LBBB, prior MI, 3VD, age, HTN, DM, mechanical complications<br>▪ 50% of post-MI death | ▪ STEMI: 50% develop shock w/in 6h of MI, 75% w/in 24h<br>▪ NSTEMI: 72-96h after MI<br>▪ New CP, cold/wet physiology, HoTN, tachycardia, dyspnea, JVD, rales, new murmur | ▪ **TTE**<br>▪ PAC (CI<2.2, PCWP>18)<br>▪ Markers of end organ hypo-perfusion ( ↑ lactate , AKI, ↑ LFTs) | ▪ Inotropes/pressors<br>▪ Emergent PCI/CABG (NEJM 1999;341:625)<br>▪ Temporary MCS (NEJM 2024;390:1382) |
| | **Myocardial Free Wall Rupture** (Pseudoaneurysm: LV defect contained by only pericardium, scar, more prone to rupture than true aneurysm) | ▪ 0.01% STEMIs & NSTEMIs<br>▪ Transmural MI, 1-vessel MI, 1st MI (poor collaterals), anterior & lateral MI, HTN, late thrombolysis (>14h), fibrinolysis>>PCI, NSAIDs, female, age >70<br>▪ 10% post-MI death | ▪ 40% w/in 24h, 90% w/in 2w<br>▪ Tamponade physiology (↑JVP, pulsus paradoxus, muffled heart sounds) in 85%<br>▪ PEA arrest , aberrant T wave evolution, abrupt episodes of ↓HR/BP | ▪ **TTE** (pericardial effusion w/ high acoustic echoes indicating clot)<br>▪ STAT cardiac surgery consult | ▪ If tamponade, consider pericardiocentesis as a bridge to cardiac surgery<br>▪ Emergent surgery for resection of ruptured myocardium w/ primary reconstruction<br>▪ Fluids, inotropes and pressors, +/- ECMO |
| | **Interventricular Septal Rupture (VSD)** | ▪ 0.21% STEMIs, 0.04% NSTEMIs<br>▪ 1st MI, 1-vessel MI (esp. LAD), CKD, anterior infarct w/ inferior STE due to wrap-around LAD, older age, female, delayed reperfusion<br>▪ 5% of post-MI death | ▪ Bimodal: 24h & 3-5d to up to 2w from event<br>▪ New, harsh holosystolic murmur (50% w/ thrill), S3, loud P2, hypotension, BiV failure symptoms (R>L), circulatory collapse | ▪ **TTE** w/ doppler (L to R shunt, RV overload, high continuous wave doppler velocity)<br>▪ RHC: step up in O2 sat from RA to PA >5, large V waves | ▪ Vasodilators (use cautiously) to decrease L to R shunt (nitroprusside or nitroglycerin)<br>▪ IABP/MCS<br>▪ Emergency surgery or transcatheter closure device if unstable |
| | **Papillary Muscle Rupture (leading to acute MR)** | ▪ 0.05% STEMIs, 0.01% NSTEMIs<br>▪ Posteromedial (supplied by PDA, with inf. or post. MI) >> anterolateral (dual blood supply by LAD/Lx)<br>▪ Poor collaterals, 1st MI, single vessel disease<br>▪ 5% of post-MI death | ▪ No reperfusion: 2-7d<br>▪ With reperfusion: median 13h<br>▪ Abrupt dyspnea, pulmonary edema, hypotension<br>▪ Hyperdynamic LV, holosystolic murmur at apex, murmur may be absent in torrential MR or severe HF | ▪ **TTE** (eccentric/broad jet severe MR)<br>▪ CXR: edema (can be asymmetric)<br>▪ Tall *c-v* wave in PCWP tracing | ▪ Aggressive afterload reduction (nitroprusside or nitroglycerin)<br>▪ IABP (afterload reduction)<br>▪ Emergent surgery (mitral valve repair is the treatment of choice) |
| EARLY/LATE | **Coronary Artery Stent Thrombosis** | ▪ Highest risk is absence of P2Y12 inhibitor<br>▪ 1% at 1 year, then ~0.2% per year thereafter | ▪ Most cases occur within 30d of PCI<br>▪ ACS symptomatology | ▪ **ECG**<br>▪ Biomarkers | ▪ PCI<br>▪ DAPT minimum one year |
| | **In-Stent Restenosis** | ▪ Incidence is 10%.<br>▪ 25% of cases p/w AMI<br>▪ DM, female, angiographic factors (multivessel disease, lesion length >20mm), procedural factors (e.g. BMS) | ▪ Classification based on timing (<30 d-early, 30d-1y-late, and >1y-very late)<br>▪ Mechanisms: stent under-expansion, stent fracture, neointimal hyperplasia<br>▪ ACS symptomatology | ▪ **Coronary angiography** with intravascular imaging (OCT, IVUS) | ▪ PCI modalities<br>▪ Assess adherence and consider switch to higher potency DAPT<br>▪ Consider GpIIb/IIIa infusion and prolonged DAPT duration |
| LATE (Weeks – Months) | **LV Aneurysm** (discrete, dyskinetic area of LV with broad neck, rarely ruptures) | ▪ No reperfusion: 10-30%<br>▪ Apical-anterior wall >> inferior posterior<br>▪ Total occlusion of LAD<br>▪ Steroids, NSAIDs | ▪ Days to weeks<br>▪ Acute: diffuse, displaced PMI, S3 and/or S4, MR murmur, CHF<br>▪ Chronic: HF, VT/VF, systemic embolization, may be asymptomatic | ▪ **ECG** w/ persistent STE<br>▪ **TTE**, other imaging (CMR, CT, ventriculography) | ▪ Acute: CHF rx, ACEi, avoid NSAIDs/steroids, start heparin (if EF<35%)<br>▪ Chronic: ACEi, , diuretics, AC (if EF<35%)<br>▪ Surgical repair |
| | **LV Thrombus** | ▪ 5% of AMI patients post-PCI (usually LV apex)<br>▪ Large infarct size, severe apical akinesis or dyskinesis, LV aneurysm, anterior MI | ▪ Can form 24-72h post MI<br>▪ 90% of thrombi at 2w<br>▪ Embolization risk persists for 6mo but most by 3-4mo; risk 10% if not on AC | ▪ **TTE** w contrast<br>▪ CMR or CT | ▪ Warfarin (INR 2-3); DOAC may be alternative (Circ. 2022;146:e205–e223)<br>▪ When to stop AC unclear, check for thrombus on TTE at 3-6mo |
| | **Pericarditis** | ▪ Peri-MI pericarditis has decreased with PCI<br>▪ Friction rub within 2-3 days post MI. Often large infarct | ▪ 10% at 2-4d post-transmural MI<br>▪ May be focal or diffuse<br>Dressler's syndrome (1-6wks): malaise, fever, leukocytosis, late autoimmune carditis, rare | ▪ **ECG** (diffuse STE, PR depressions)<br>▪ **TTE** (effusion)<br>▪ CMR or cardiac CT | ▪ ASA + colchicine<br>▪ Avoid NSAIDs and steroids post MI<br>▪ *See Pericarditis* |

# Cardiology MI Complications

## Urgent Assessment of Post-MI Complication

- PAGE Cardiology (STAT)
- Assess for instability, focused physical exam (new murmur, pericardial friction rub, elevated JVP, crackles, access site(s))
- STAT labs (troponin, PT/INR, VBG, PTT, T&S, BMP, CBC, LFT, lactate), ensure adequate vascular access (≥2 PIVs)
- Run telemetry, repeat **ECG**, **STAT TTE**, consider STAT CTA if concern for RP bleed/aortic dissection, notify interventional team

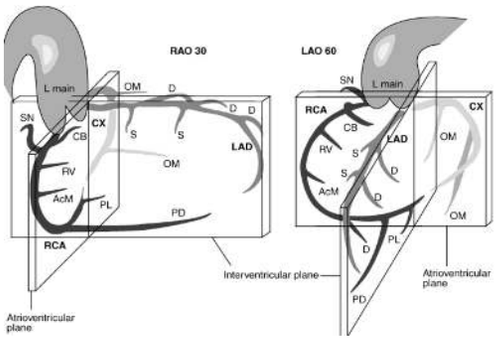
## Electrical Complications

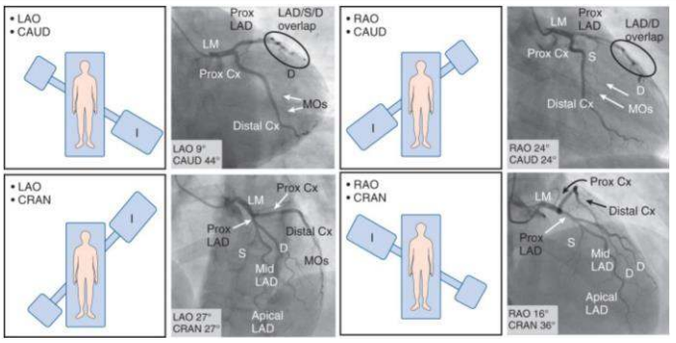
**Overview**

- 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 |
|---|---|---|---|---|
| Bradyarrhythmia | Sinus bradycardia | ▪ Inferior and posterior MI<br>▪ Beneficial: ↓myocardial O2 demand | ▪ Up to 40% of acute MI<br>▪ Occurs early in STEMI | ▪ Atropine, temp pacing or dopa/epi if unstable |
| | First degree AV block | ▪ Inferior: ↑vagal tone *or* AV node ischemia (RCA), narrow QRS<br>▪ Anterior: septal necrosis below AV node, RBBB, wide QRS | ▪ More common in inferior MI | ▪ If due to inferior MI, transient (vagal)<br>▪ 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 | ▪ Usually transient; observe<br>▪ Atropine if symptoms or HR <45 |
| | Second degree AV block: Mobitz Type II | ▪ Usually anterior MI with infranodal conduction injury, wide QRS, HR often <30bpm, 33% progress to CHB | ▪ Usually within first 24h of MI | ▪ Consider temporary pacing<br>▪ In infranodal block, *atropine may paradoxically worsen AV block* |
| | Third degree AV block (CHB) | ▪ If inferior MI: intra-nodal lesion; narrower QRS escape<br>▪ If anterior MI: infra-nodal lesion; wide, unstable escape rhythm | ▪ 3-7% acute MI<br>▪ Inferior: gradual, stable<br>▪ Anterior: sudden, 12-24h after MI | ▪ Recovery 5-7d; temp pacing required +/- PPM<br>▪ Inferior: transient, resolves on its own<br>▪ Anterior: high mortality (80%) and indicates extensive conduction system necrosis |
| **Intraventricular Conduction Blocks** | | ▪ 50% already present on first ECG, may represent antecedent disease of conduction syndrome<br>▪ Suggests more extensive infarct | ▪ 2-5% of MI | ▪ Patients w/ BBB are more likely to have comorbid conditions, larger area infarcts, and higher mortality |
| Supraventricular Arrhythmias | Sinus tachycardia | ▪ May be compensatory for LV dysfunction, common in anterior MI<br>▪ Pain, anxiety, pericarditis, fever | ▪ 25% of acute MI | ▪ Undesirable as ↑myocardial oxygen demand, ↓diastole time causes ↓coronary perfusion<br>▪ Treat underlying cause |
| | Atrial fibrillation, Atrial flutter | ▪ Early: may be transient due to ↑sympathetic; atrial ischemia<br>▪ Late: due to atrial stretch/HF | ▪ 6-8%, may be >30% of acute MI | ▪ A/w mortality, particularly if late (>30d) AF (Circ 2011;123:2094)<br>▪ If unstable, cardioversion; consider BB, amiodarone, digoxin, anticoagulation |
| Ventricular Tachyarrhythmias | Premature Ventricular Contraction | ▪ Due to electrical instability and increased sympathetic tone | ▪ Variable | ▪ 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 | ▪ Up to 20% of STEMI<br>▪ Usually within 12-48h, can occur after reperfusion | ▪ Do not treat unless symptomatic or hemodynamically unstable, usually short duration & does not affect prognosis |
| | Ventricular Tachycardia | ▪ Monomorphic VT <170bpm is unusual early after STEMI, suggests pre-existing arrhythmogenic scar; recurrent ischemia usually polymorphic VT | ▪ NSVT 1-7%, sustained VT (2-3% of STEMI, <1% NSTEMI)<br>▪ Usually 48h post STEMI, late VT (>48h) has very poor prognosis | ▪ Antiarrhythmic agents (amiodarone, lidocaine)<br>▪ Urgent revascularization if due to ischemia<br>▪ Cardioversion/defibrillation to prevent VF and restore hemodynamic stability<br>▪ Correct underlying abnormalities (pH, K, Mg, hypoxemia) |
| | Ventricular Fibrillation | ▪ Risk factors: ↑age, prior MI (scar), anterior MI, cardiogenic shock, ↓LVEF, CKD<br>▪ VF >48h post-MI may indicate LV dysfunction | ▪ 5% of STEMI<br>▪ 1% of NSTEMI | ▪ ACLS/defibrillation<br>▪ Anti-arrhythmic infusion (24-48h amiodarone post-defibrillation)<br>▪ Maintain K>4, Mg>2.2 |

# Cardiology — Cardiac Catheterization




- Note: RAO caudal: best overall view & best for LCx; LAO caudal: LM, prox LAD, prox LCx; LAO + RAO cran: mid+distal LAD

## Left vs Right Heart Catheterization

- LHC: Arterial access (radial, fem). Assess coronary anatomy/lesions (described as coronary angiogram), LV & Ao pressures; PCI
- RHC: Venous access (IJ, fem). Assess hemodynamics (see *Pulmonary Artery Catherization*); cardiac biopsies (usually RV)

## Coronary 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

- NPO MN vs clear liquid diet at midnight, then NPO 2hr prior (EHJ 2024:45:47) ; INR<2 for radial, <1.8 for fem/IJ; monitor Cr, no ppx abx. Cont ASA, statin, BB. Hold AC (ellucid): UFH gtt (hold when on call), LMWH (hold tx dose 24h prior, DVT ppx 12h prior), DOACs >48hr or >72hr if CrCl<30. Hold metformin (1d pre, 2d post), may hold ACEi or SGLT2i (procedure dependent)
- Document b/l radial, femoral, popliteal, DP pulses, & Allen's test. Check for bruits. Note history of HIT, PAD, Ao aneurysm/dissection
- **Contrast allergy**: pre-tx w/ steroids & benadryl if patient has documented allergy. See *Contrast Allergy* for MGH-specific protocols
- 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

## Percutaneous Coronary Intervention Considerations

- Access: fewer bleeding/vascular complications if radial (vs femoral) esp for PCI iso ACS, possible ↓death in ACS (JACC 2018;71:1167); due to radial vasospasm, CCB and/or nitroglycerin is administered along with UFH to prevent arterial occlusion
- Identifying HD significant lesions: fractional flow reserve (FFR), diastolic hyperemia-free ratio (DFR), and instant wave free ratio (iFR) assess functional impact of lesion; intravascular ultrasound (IVUS) evaluates lumen diameter, lesion length, and lesion calcification
- 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 post cath. DAPT duration decided with interventional team
  - Not high bleeding risk: ACS → 12mo DAPT; stable IHD → ≥6mo DAPT if DES or ≥1mo if BMS
  - High bleeding risk: ACS → 6mo DAPT, consider DAPT 1-3mo followed by P2Y12i; stable IHD → ≥3mo DAPT if DES or ≥1mo if BMS, consider 1-3mo DAPT followed by P2Y12i (JACC Cardiovasc Interv 2024;17:2197)
  - Triple therapy for patients requiring AC: see *ACS*. Usually, 1 wk triple therapy then P2Y12 inhibitor + DOAC

## Post-Procedure Care

- Femoral access: 4-6h bedrest (HOB<30°) 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: usually removed when PTT<60, confirm with interventional fellow; **only fellows remove sheaths**
- Radial access: TR band for 4-6h driven by RN protocol. If paresthesias/numbness, examine, check finger sat probe for perfusion, can remove several mLs of air from band if necessary and if no complications. NOTE: if hematoma do not remove until fellow assesses

## Post-Catherization Complications

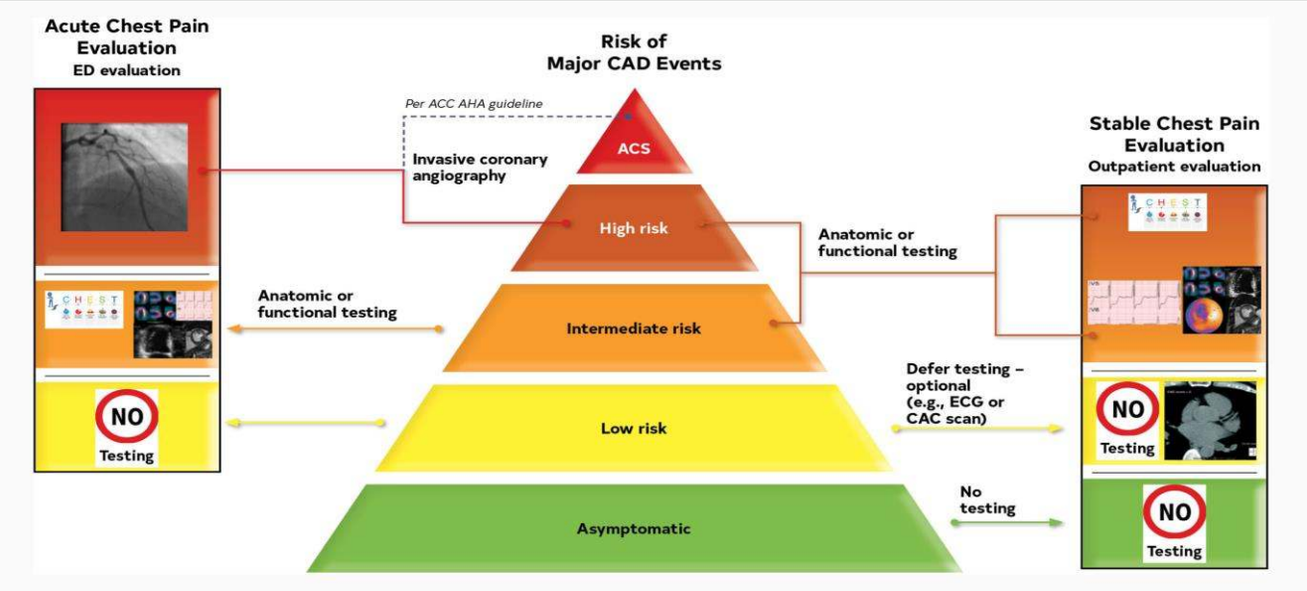
- Access site complications: always inform the interventional fellow who performed the procedure, **diagnose by exam and US**
  - **Hematoma**: mass w/o bruit. Apply **compression**. Fellow may recommend FemoStop device if unable to control
  - **Pseudoaneurysm**: pulsatile mass with bruit at access site. Tx w/ **compression**; if <2cm, may require thrombin injection or surgery if >2 cm. Urgent arterial US & Vascular Surgery consult
  - **AV fistula**: continuous bruit with no mass. Evaluate w/ arterial 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. Obtain large bore IV access, IVF, transfuse, discuss with attending about stopping/reversing anticoagulation
- Other complications:
  - **Infection:** higher risk with 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**: narrow PP, **hypotension** 2/2 coronary/cardiac perf. Check pulsus (>10 mmHg), STAT TTE, alert cath fellow.
  - **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
  - **Delayed Hemostasis**: apply indirect pressure several cm cranial to site of skin access. Page gen cards fellow to discuss escalation to cath fellow/vasc surg (see ellucid escalation pathway)

# Cardiology — Non-Invasive Cardiac Testing

## Basics

- Non-invasive cardiac testing includes functional and anatomic testing
- Approach to testing: 1) clinical question being asked, 2) symptom acuity, 3) baseline CVD risk/known CAD hx, 4) patient-specific C.I.
- For guideline-based assistance in decision making, use **Stressing Wisely.** For examples of (+) and (-) tests, use **Radiopaedia.**

## Role of Non-invasive Cardiac Testing in Chest Pain Evaluation




*Source: 2021 ACC/AHA Guidelines for Evaluation and Diagnosis of Chest Pain (Circ 2021;144:e368-e454)*

**Deciding between CCTA (anatomic) and stress imaging in an intermediate-high risk patient:**

- CCTA favored: Age<65y and no prior CAD, rule out obstructive CAD, detect non-obstructive CAD, prior functional study w/o conclusive results, bypass graft assessment, known anomalous coronaries, parallel evaluation of aorta, pulmonary arteries, or LAA
- Stress imaging favored: Age>65y, if known >50% (obstructive) CAD to assess for specific areas of ischemia, prior CCTA w/o conclusive results, parallel evaluation for scar or microvascular dysfunction (PET or CMR)
- CCTA has higher sensitivity and similar angiography rates as conventional stress imaging; however, CCTA may lead to better outcomes overall as it can detect non-obstructive CAD and therefore drive preventive care (NEJM 2018;379:924)

## Stress/Functional Testing

- **Indications**:
  - Diagnose CAD: Workup *stable* angina in pts with *intermediate-high risk* of CAD. Consider spectrum of non-invasive tests vs. cath in intermediate-risk pts presenting with more acute sx. Not indicated in pts with no symptoms or at low risk
  - Evaluate new or changing sx concerning for ischemia in pts with known CAD
  - Post-revascularization: Evaluate pts with angina or asymptomatic pts if incomplete revasc or >2y post-PCI/5y post-CABG.
  - Pre-op risk assessment: If indicated (see *Perioperative Medicine*)
  - Other: Newly diagnosed HF or cardiomyopathy likely secondary to ischemia, functional capacity (for exercise prescription), viability testing, valvular disorders, dobutamine stress echo in LFLG AS, quantify microvascular disease (PET)
- **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 BB >24h for dobutamine stress test; hold caffeine >12h for adenosine
    - *Positive test results*: Optimize medical rx. Decision re: angiography/revascularization varies by pt (degree of sx, tolerance of medical therapy). In ISCHEMIA trial, initial revasc vs. medical therapy did not reduce risk of ischemic CV events for pts with moderate to severe *stable* ischemic heart disease (NEJM 2020;382:1395). In pts w/ stable angina, PCI does not increase exercise tolerance (Lancet 2018;391:31), but for pts who cannot tolerate medical therapy, PCI improved symptoms (NEJM 2023;389:2319)
- *Caveats*:
  - Majority of vulnerable plaques are angiographically insignificant (<70% stenosis) → CCTA more sensitive for their detection
  - **Angiographically significant 3VD may produce false-negative vasodilator stress test → "balanced ischemia"**
    - Balanced ischemia can be detected as *transient ischemic dilatation* (enlargement of LV cavity during stress)
    - PET has higher accuracy in 3VD than SPECT/MIBI, because PET quantifies blood flow
- **MGH inpatient: Exercise/ECG or TTE if patient can exercise and has no ST/T wave abnormalities or LBBB at baseline. CCTA, Regadenoson/MIBI, and dobutamine/TTE most common overall. See below for full considerations.**
- **MGH outpatient: See below options**

**Approach to choosing a stressor and evaluation modality**:

- See Table 5 for full list of **contraindications** by test type (*Circ 2021;144:e368-e454*).

Choosing a stressor:

- Exercise: Preferred if patient can reach goal exertion. More relevant to real-world stress
- Adenosine/Regadenoson:
  - *Mechanism*: Vasodilation via cAMP, detect ischemia by coronary steal (stenosed coronary arteries are unable to further dilate, creating a relative perfusion deficit in diseased vessels).
  - *Side effects:* Wheezing, bradycardia, HoTN. *Caution if* ACTIVE bronchospasm, high grade AVB, SSS, severe AS
    - Regadenoson (vs adenosine) has decreased respiratory/conduction side effects, is more cost-effective in obese pts, but *caution if* seizure hx (reversal agent aminophylline ↑seizure risk)
- Dobutamine:
  - *Mechanism:* Positive inotropy and chronotropy via β-1 receptor agonism. Extremely high dose (up to 40 mcg/kg/min)
  - *Side effects:* tachyarrhyth. *Caution if* MI <48h, hx malignant arrhyth, sev AS, HOCM, sev HTN, sev PAH, aortic dissection

Choosing an evaluation modality:

- ECG: Only used as stand-alone with exercise. Do not use with any longstanding ST/T wave abnormalities.
- TTE: Can define ischemia severity and risk-stratify. Additional info on hemodynamics/valves. ECG also obtained simultaneously.
  - *Do not use* in pts with LBBB, V-pacing, or extensive wall motion abnormalities at rest
- Nuclear imaging (PET or SPECT/MIBI myocardial perfusion imaging):
  - Uses a radiotracer (MIBI in SPECT, multiple options in PET) to detect areas of ↓perfusion between rest and stress states. Can measure LV function, transient LV dilatation, myocardial blood flow reserve. PET can detect microvascular ischemia.
  - More expensive than TTE & high amount of radiation (SPECT > PET)
  - PET more Sn & Sp than SPECT with faster image acquisition. Less widely available & more expensive. Additional uses for imaging in rheumatologic (i.e. cardiac sarcoid) and oncologic contexts (i.e. cardiac myxoma, metastases).
- Cardiac MRI (CMR):
  - Localize ischemia and infarction, assess LV and RV function, determine myocardial viability. Can also detect microvascular dysfunction and tissue properties of the heart (inflammation, scarring, infiltration, cardiac tumors, pericardial disease)

**Exercise Tolerance Test (ETT)**:

- *Approach*: ETT refers to exercise + ECG (cheap, available), or exercise + imaging eval (TTE, SPECT) (↑sensitivity)
- *Protocols*: Bruce (large changes in workload between stages), modified Bruce (for less fit pts → adds stages of lower workload)
- *Assess*: 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)).
- *Diagnostic if*: >85% max-predict HR (220-age), peak double product (HRxBP) >20k, HR recovery ($HR_{peak}$ – $HR_{1min\ post\text{-}exercise}$) >12, STEs - also localize to vascular territory
- Increased probability of ischemia with: ↑ # of leads with STD especially horizontal or downsloping, ↑ degree of max STD, ↓ METs when ECG changes occur, ventricular ectopy during recovery, increased time to recovery of ECG, failure of SBP to rise with exercise.

**Viability testing:**

- *Indication*: Determine viability of ischemic myocardium (assess for hibernating tissue) that may be salvaged w/ revascularization.
- *Modalities*: SPECT, PET, TTE, MRI with exercise or pharmacologic stress. Looking for metabolic or contractile reserve.

## ANATOMIC TESTING

**Coronary CTA (CCTA)**:

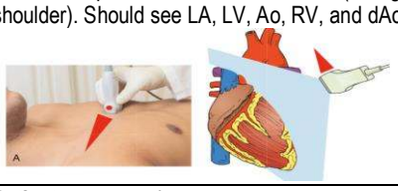
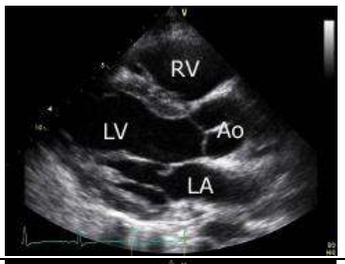
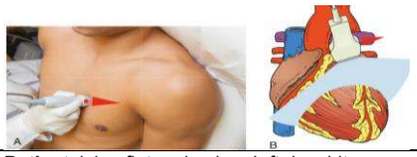
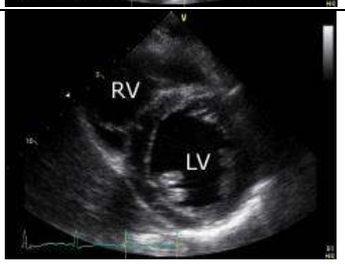
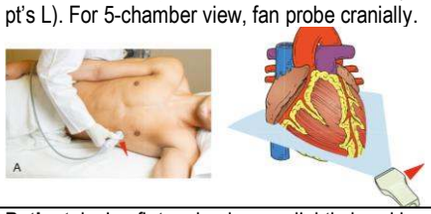
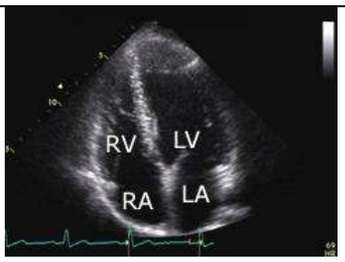
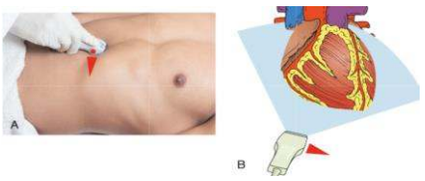
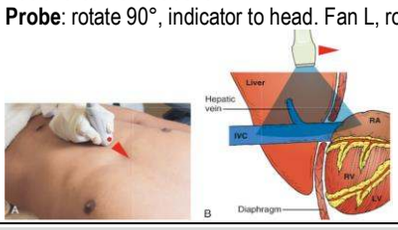
- *Indications*:
  - Evaluate for the presence and extent of CAD. Primarily anatomic info, though offers plaque characterization and CT FFR.
  - Asymptomatic pts: NOT for screening use. Low-risk pts with sx: high NPV (99%) for CAD rule-out (JACC 2008;52:1724). Moderate-risk pts with sx: reasonable for risk stratification (especially after equivocal stress test).
- *Preparation*: Requires cardiac gating (goal HR 60-70, may need to give BB) and respiratory gating (breath hold for 5+ sec).
- *Results*:
  - 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)
- Caveats: Less useful in pts with extensive calcifications (older) or stented vessels due to "blooming" artifact (cannot eval patency).

**Coronary Artery Calcium (CAC) Scan**:

- *Indications*:
  - Risk-assessment for ASCVD risk stratification. Used to guide decision-making for primary prevention/statin therapy in asymptomatic pts, ≥40y at intermediate-risk (7.5-19.9% 10y ASCVD risk). DO NOT use in symptomatic pts or high risk pts.
- *Preparation*: Non-gated, non-contrast (if done independent of CCTA) CT scan.
- *Results*: MESA score accounts for CAC score and is able to refine 10 year risk estimates
  - If CAC score 0 and pt without significant risk factors, reasonable to defer statin therapy for up to 5 years (Circ 2019;140:496).
  - If CAC score ≥100 or >75%ile for age & gender, recommend aggressive lifestyle changes, ASCVD RF modification (BP, smoking cessation, diabetes treatment), & statin therapy (JACC 2019;73:285)

**Cardiac MRI**: provides both stress/functional and anatomic testing options

# Cardiology — Echocardiography

| View | Position | View* |
|---|---|---|
| **PARASTERNAL LONG AXIS**<br>• LV size, function, wall thickness (septum/posterior wall)<br>• MV/AoV function/flow (w/ Doppler)<br>• LVOT diameter, aortic root size<br>• Pericardial effusion | **Patient**: lying on left side, with left arm under head<br>**Probe**: 2-3 inches left of sternum at 3rd-4th intercostal space, indicator at 10 o'clock (facing R shoulder). Should see LA, LV, Ao, RV, and dAorta<br>  |  |
| **PARASTERNAL SHORT AXIS**<br>• Cross-sectional views of the heart from base to apex, at level of AoV, MV and mid-ventricle/papillary muscles<br>• MV/AoV/RVOT flow (w/ Doppler) | **Patient**: same as above<br>**Probe**: from long axis view, rotate probe clockwise until indicator at 2 o'clock (facing L shoulder). Fan probe to L hip until at level of papillary muscles.<br>  |  |
| **APICAL 4 CHAMBER**<br>• RV/LV size, function, thrombus<br>• TV/MV function/flow (w/ Doppler)<br>• Septal size/motion<br>• Pericardial effusion<br>• In 5-chamber view, can see AoV and proximal ascending aorta | **Patient**: lying flat on back or left decubitus<br>**Probe**: at PMI w/ probe indicator at 3 o'clock (to the pt's L). For 5-chamber view, fan probe cranially.<br>  |  |
| **SUBXIPHOID (aka subcostal)**<br>• RV/LV size, function<br>• Pericardial effusion | **Patient**: laying flat on back, can slightly bend legs<br>**Probe**: below xyphoid process, indicator to pt's R<br>  | |
| **INFERIOR VENA CAVA**<br>• IVC diameter and respiratory variation gives estimate of volume status and RA pressure<br>• Most helpful for extremes of volume (i.e. very dry or very wet)<br>• Hepatic vein flow reversal<br>*Images from: Soni, N. J., Arntfield, R., & Kory, P. (2020). *Point of care ultrasound*. Elsevier. | **Patient**: same as above<br>**Probe**: rotate 90°, indicator to head. Fan L, rock up<br>  | |

**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), leaflets, vegetations
- Structure/chamber dimensions: aorta, LVIDd & LVIDs (LV internal diameter in diastole, range: 42 – 58mm & systole, range: 25 – 40mm), IVS (septum, 6-10mm), PWT (posterior wall thickness, 6-10mm, ↑ in LVH, diastolic dysfunction), LV volume (ULN: 74ml/m$^2$ in men 61 in women, <40 suggest restrictive), LA volume (ULN: 34ml/m$^2$, ↑in MR/MS, diastolic dysfunction, AF)
- EF: "preserved" EF ≥50%, "mildly reduced" 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=4v$^2$ + RAP. **RAP assumed to be 10 mmHg** and v = TR jet velocity. RVSP >35mmHg (<60yrs) and >40mmHg (> 60yrs) is elevated.
- Shunt detection: agitated saline contrast study (i.e. TTE w/ bubble) to detect PFOs, ASDs, and pulmonary arteriovenous shunts

**Indications for STAT TTE:**
- Eval hemodynamic instability of suspected cardiac etiology (e.g. post cath / TAVR / PPM placement)
- Eval for early MI complication
- Suspected MI w/ non-diagnostic biomarkers and EKG

**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: effusion, RA collapse in systole (earliest sonographic sign; high sensitivity), RV collapse in diastole (high specificity), respirophasic variation in mitral inflow velocity by > 25%), interventricular septal bowing, plethoric IVC (no ↓ w/ inspiration)
- ACS and associated mechanical complications: 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
- Diastolic dysfunction: LA enlargement, E/e' >14, LVH (note: diastolic dysfunction not typically reported on MGH TTE reports)
- Constrictive pericarditis: thickened or hyperechoic pericardium, abnormal septal motion, respiratory variation in ventricular size, dilated IVC
- Cardiac amyloid: biatrial enlargement, increased LV and RV wall thickening, valvular thickening, diastolic dysfunction, paradoxical LFLG AS, strain imaging with reduced global longitudinal strain and apical sparing

# Cardiology — Heart Failure

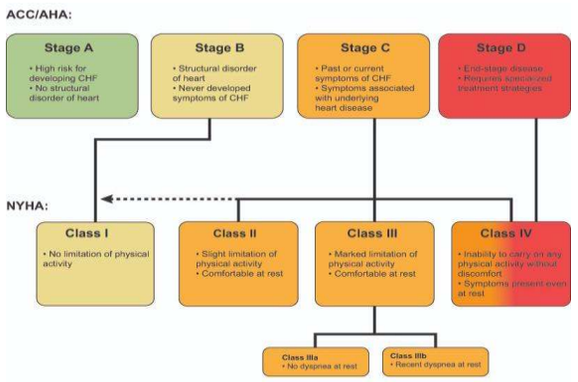
## Basic Framework

**Diagnosis of heart failure vs cardiomyopathy (CM)**

- Heart failure is a clinical diagnosis – requires signs/symptoms of volume overload (e.g. orthopnea, leg swelling, crackles, ↑JVP) attributable to a structural or functional impairment in ventricular ejection or filling
- Heart failure ≠ cardiomyopathy – a CM is an abnormality in myocardial structure or function, usually visualized by TTE (does not require signs/symptoms of volume overload)

**Classifications of heart failure**

- LVEF classes: HFpEF (LVEF >50%), HFmrEF ('mildly reduced' EF; LVEF 41-49%), HFrEF (LVEF ≤40%), HFimpEF ('improved' EF; previous LVEF ≤40% and a follow-up measurement of LFEF > 40%)
- ACC/AHA Stage and NYHA Functional Class (see Figure)




**Identifying underlying etiology**

| Category | Cardiomyopathy etiologies |
|---|---|
| Most common | *ischemic, hypertensive, valvular* |
| Metabolic | *diabetic, nutritional deficiency (e.g. beriberi)* |
| High-output | *septic, peripartum, hyperthyroid, anemia, liver failure, Paget's, AV shunts* |
| Toxins/drugs | *alcohol, cocaine/amphetamines, chemotherapy, immune checkpoint inhibitors* |
| Infectious | *HIV, coxsackie, echovirus, EBV, CMV, Lyme, Chagas disease, tuberculosis* |
| Infiltrative | *amyloidosis (ATTR or AL), hemochromatosis, sarcoidosis, Löffler's* |
| Genetic | *hypertrophic cardiomyopathy/HOCM, ARVC, familial neuromuscular disorders, glycogen storage disorders, LVNC* |
| Inflammatory | *connective tissue diseases, giant cell myocarditis* |
| Other | *pulmonary (cor pulmonale), stress-induced (Takotsubo), tachyarrhythmia-induced, pericardial disease (e.g. constrictive pericarditis, pericardial effusion)*, radiation, carcinoid, idiopathic |

NOTE: CM can be additional defined as 'dilated,' 'hypertrophic,' and 'restrictive' based on morphology/structure seen on imaging

**Workup**

- Initial workup: signs/sxs of volume overload, troponin, NTproBNP, ECG, tele, CXR, TTE
- Ischemic CM workup: family hx, smoking hx, lipid panel, A1c, see *Non-Invasive Testing* and *Cardiac Catherization*
- Non-ischemic CM workup: family hx, med hx, substance use hx, tox screen, β-hCG, iron studies, SPEP/UPEP/FLC, TSH, HIV, ANA
- Extended workup (when applicable): chest CT, cardiac MRI, RHC, endomyocardial biopsy, PYP scan, viral serology panel, Lyme serologies, *T. cruzi* serologies, ACE level, thiamine/carnitine/selenium, genetic testing, antimyosin Ab

**Management of heart failure**

- Treat the underlying causes of (1) cardiomyopathy and (2) decompensation triggers
- Basic elements of treatment: diuresis, afterload reduction, consideration of device/advanced therapies
- Guideline-directed medical therapy (GDMT):
  - HFrEF/HFmrEF/HFimpEF = BB, ACEi/ARB/ARNi, MRA, SGLT2i
  - HFpEF = MRA, SGLT2i
- Cardiomyopathy-specific interventions: ischemic = PCI, CABG; valvular = TAVR, MitraClip, other valve interventions; tachyarrhytmia-induced = ablation, PPM, CRT; ATTR amyloid = tafamadis ↓TTR deposition (NEJM 2018;379:1007), acoramadis, vutrisiran; sarcoid = prednisone, steroid-sparing IST

**2022 ACC/AHA HF Guidelines: Circ 2022;145:895**

## Considerations for Select Cardiomyopathies

**Hypertrophic Cardiomyopathy (HCM)** (Circulation 2024;149 :e1239)

Characteristics: LV and/or RV hypertrophy ± LVOT dynamic obstruction (**HOCM**), diastolic dysfxn, ischemia, MR; **risk of SCD**
Exam: SEM at LLSB/apex that augments with Valsalva or on standing (due to ↓preload); S2 paradox split, S4
Dx: **ECG** (prominent voltages w/ depol abnormalities, large Q waves in inferior/lateral leads, LAD, negative T waves in V2-V4 (apical HCM), **TTE** (LVH >15mm, SAM of MV, outflow tract gradient +/- provocative test), **cMRI** (late gadolinium enhancement [LGE] = fibrosis)
Clinical **genetic testing** (mutation in ~70%) helpful for family screening; not useful for dx or risk stratification
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 (disopyramide, BB > verapamil). Cardiac myosin inhibitors (e.g. aficamten, mavacamten) if LVEF ≥ 55% (VALOR-HCM); septal ablation or surgical myectomy if medically refractory, ICD ifhigh risk
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; h/o suspected cardiac syncope; EF<50%

- **Amyloidosis (AL, TTR):** HF + amyloid findings (e.g. renal), low voltage ECG, thick LV/RV on TTE, LGE in subendocardium on cMRI
- **Hemochromatosis:** hereditary or secondary, ECG with SVT, dilated LV on TTE, iron overload on T2 protocol of cMRI
- **Sarcoidosis:** ECG with atypical infarct pattern or block, patchy enhancement of basal and LV walls on cMRI

## Acute Decompensated Heart Failure Management – Floor/SDU

*Frederick Lang, Emily Manning*



Suggest an Edit

# Cardiology — Heart Failure

**Identify hemodynamic profile and triage accordingly** (JACC 2019;74:1966)

- Warm vs Cold: consider AMS, lactate, cool extremities, narrow pulse pressure
- Dry vs Wet: presence vs absence of congestion
- Evaluate for pulmonary congestion on exam. Pulm edema may be absent on CXR due to lymphatic compensation (Chest 2004;125:669)
- Majority of HFrEF and HFpEF pts will be warm and wet
- See 'Right Ventricular Failure' for special considerations for patients with primarily right-sided heart disease

| | | Congestion at Rest (PCWP) | |
|---|---|---|---|
| | | **Yes** | **No** |
| **Low Perfusion at Rest? (CO)** | **Yes** | Warm & Dry (Compensated) *Outpatient mgmt.* | Warm & Wet (Congested) *Diuresis ± Vasodilators* |
| | **No** | Cold & Dry (Low Flow State) *Inotropes, vasodilators* | Cold & Wet (Decompensated) *Tailored Therapy (ICU)* |

**History**

- Identify decompensation triggers: Mnemonic **FAILURE** – **F** = forgot meds, **A** = arrhythmia/anemia/afterload, **I** = infection/ischemia, **L** = lifestyle (salty diet), **U** = upregulation of cardiac output (e.g. pregnancy, hyperthyroid), **R** = renal failure, **E** = embolism. Other triggers: progression of CM, inadequate diuretic dose, meds (NSAIDs, steroids, CCB, anthracyclines), toxins (EtOH), new/worsened valve
- HF history (prior CM dx, dry weight, last NTproBNP, last TTE/EF, prior ischemic w/u, outpt cardiologist), accurate PAML, social/fam hx

**Admission considerations**

- Admission orders: tele, 2g Na-restricted diet, daily standing weights, strict I/Os, DVT ppx, (SDU only) electrolyte replenishment scales
- SDU admission indications: EF <25%, NTproBNP ≥ 2,500, arrhythmia-induced HF. Black & Latinx pts w/ HF are less likely to be admitted to cardiology services, contributing to racial inequities in HF outcomes (Circ Heart Fail 2019;12:e006214)
- Avoid: CCB (esp. non-dihydropyridines), NSAIDs, flecainide
- Check NT-proBNP (& weight) on admission. 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, HFpEF
- Screen for and 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)
  - Tx: replete with IV iron (JACC 2018;71:782) to ↓sx, ↑functional capacity, and possibly improve outcomes (NEJM 2023;389:975)

**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 (furosemide, torsemide, bumetanide), start w/ 20-40mg IV furosemide if diuretic-naïve otherwise start w/ 2-2.5x home dose (IV/PO). No difference b/w continuous gtt vs bolus (NEJM 2011;364:797). See *Advanced Diuresis*
  - Refractory diuresis: add metolazone 2.5-5mg (or chlorothiazide 500mg IV) administered 30min before loop diuretic. May need RHC to clarify hemodynamics or inotropes to augment diuresis. Acetazolamide (500mg daily), as well as dapagliflozin (10mg daily), may also augment successful decongestion (NEJM 2022;387:1185; EHJ 2023;44:2966). Step-up pharmacologic therapy superior to RRT in the setting of cardiorenal syndrome (NEJM 2012;367:2296)
  - Worsening renal function: Common occurrence. Mild-mod "Cr bumps" likely benign, 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, lung and JVP POCUS are useful adjuncts to ensure diuresis to euvolemia. B-lines on lung US portend ↑risk of HF admissions/death (EHJ 2016;37:1244)
- If acute pulmonary edema, NIPPV may improve mortality and reduce need for intubation (Annals 2010;152:590)
- Vasodilators: arterial/venous dilation can relieve symptoms by ↓afterload, ↓PCWP. Consider esp. in severe HTN, acute MR or AR
  - Floor: isosorbide dinitrate, hydralazine, nitropaste, captopril; SDU/CCU: nitro gtt, nitroprusside gtt (caution if uncorrected CAD)
- Home GDMT continuation: if not in cardiogenic shock or new AKI, continue ACEi/ARB/ARNi and βB (at fractionated dose) during ADHF (but do not newly initiate βB) (EHJ 2009;30:2186). Hold SGLT2i as it may preclude procedure

**Guideline-directed medical therapy (GDMT)**

- HFrEF, HFmrEF (+/- HFimpEF): prioritize initiation of low-dose quadruple GDMT prior to d/c
  - Beta-blockers (BB): initiate BB (carvedilol, metoprolol succ., bisoprolol) (COPERNICUS; MERIT-HF). Caution if recent inotropes
  - RAAS inhibitors: if renal fxn stable, initiate/titrate ARNI (sacubitril/valsartan) (PARADIGM-HF; PIONEER-HF), second line ACEi/ARB (CONSENSUS; CHARM). Switch to ARNI from ACEi/ARB if no C.I./cost concerns, 36h washout period for ACEi prior to ARNI
  - MRA: 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)
  - SGLT2i: dapaglifozin and empagliflozin reduce mortality and HF admissions regardless of DM (DAPA-HF; EMPEROR-Reduced)
  - Guidance for GDMT in advanced CKD: JACC HF 2019;7:371
  - GDMT dosing - AHA/ACC/HFSA 2022 Guidelines (Circ 2022;145:895)

| | βB | | ARNi/ACEi/ARB | | | MRA | | SGLT2i | |
|---|---|---|---|---|---|---|---|---|---|
| | metop succ | carvedilol | sacub/val | lisinopril | losartan | spirono | epler | dapag | empag |
| **Initial Dose (mg)** | 12.5-25 qD | 3.125 BID | 49/51 BID | 2.5-5 qD | 25-50 qD | 12.5-25 qD | 25 qD | 10 qD | 10 qD |
| **Target Dose (mg)** | 200 qD | 25-50 BID | 97/103 BID | 20-40 qD | 50-150 qD | 25-50 qD | 50 qD | 10 qD | 10 qD |

- HFpEF: improve volume overload with diuretics, treat comorbidities (DM, HTN, AF), add GDMT
  - SGLT2i found to ↓CV death/hospitalizations in pts with EF >40% (EMPEROR-Preserved, DELIVER)
  - 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)
  - New options: finerenone (nonsteroidal MRA) (NEJM 2024;391:1475), semaglutide (GLP1ra) (NEJM 2023;389:2221)

- 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)

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Suggest an Edit

**Pre-discharge optimization**

- Document d/c weight and NTproBNP**,** appt in HF Transitions Clinic, referral to cardiac rehab
- Optimization of GDMT as above
- Diuretic plan: determine maintenance oral diuretic dose and provide specific instructions for taking additional rescue doses. Consider inpatient observation on maintenance dose and decide if needs K replacement.

## CARDIOGENIC SHOCK – CCU

- Stages: **A. "At risk" B. "Beginning"**=HDUS pt w/o hypoperfusion (e.g. oliguria, ↑lactate, ↑ Cr.), **C. "Classic"**=signs of hypoperfusion (HoTN maybe absent), **D. "Deteriorating"**=no improvement to initial therapy, **E. "Extremis"** (JSCAI 2021:1:1)
- Evaluation: ECG, 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 $MVO_2$ monitoring

Immediate Management:

- If c/f **acute MI**, activate cath lab for PCI (only intervention proven to improve outcomes in cardiogenic shock) (NEJM 1999;341:625)
- Consider early **SHOCK consult** (p11511). Escalating inotropes/pressors a/w poor outcomes. Evidence for early initiation of MCS
- 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. See *Pulmonary Artery Catheterization.*

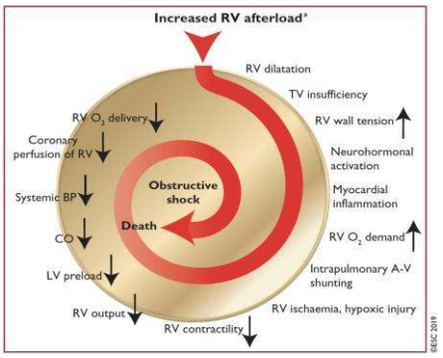
- **Goals**: tissue perfusion (↑CO, MAP), decongestion (↓CVP, PCWP), ventricular unloading (minimize myocardial $O_2$ demand)
  - **Preload**: LVEDV ∝ LVEDP ≈ PCWP; goal **PCWP 14-18, PAD 16-20, CVP 8-12** → diuresis, UF with RRT
  - **Afterload**: wall stress ∝ MAP (Laplace's law); SVR = (MAP - CVP)/CO; goal **MAP >60, SVR <800-1200**
    - Vasodilators: captopril, hydralazine, nitroprusside, TNG, isosorbide dinitrate
    - Vasopressors: ↑afterload, sometimes needed to ↑MAP in mixed shock or to counteract vasodilatory effect of inodilators
  - **Contractility**: ∝ CO for given preload/afterload; goal **CO>4, CI >2.0-2.2, $MVO_2$ >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
      - Preferred in patients w/ RV failure. Renally cleared. Often choice for home inotrope for palliative therapy
    - **Epi** (inopressor): use if severe HoTN often in combo with inodilators. Watch for arrhythmias, end-organ hypoperfusion
  - **Advanced**: consideration of need for MCS or transplant to improve systemic perfusion; see *Mechanical Circulatory Support*

# Cardiology — Right Ventricular Failure

## Pathophysiology and Etiologies (NEJM 2023;388:1111)

- Normal RV function: governed by systemic venous return, PA pressure, pericardial compliance, and native contractility of the RV free wall and interventricular septum (where RV and LV are "tethered")
  - The RV is coupled to the high-compliance, low-resistance pulm circulation → RV ejects blood at lower pressure compared to LV → RV is more afterload sensitive than LV. RV can adapt to changes in volume > pressure.
- Acute RV Failure: RV & LV interdependent → failure of RV → failure of LV via: (1) decreased LV preload, as RV output = LV preload & (2) septal bowing into LV, causing diastolic impairment ("Diastolic Ventricular Interaction")
  - ↑RV afterload (e.g. PE, hypoxemia, 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 -> "death spiral"
- Chronic RV Failure: gradual ↑RV afterload (e.g. from pulmonary hypertension / pulmonic stenosis / tricuspid regurgitation)

**RV "death spiral"**




Eur Heart J 2020;41:543

## Clinical Features and Workup (Circ 2018;137:e578-e622)

- Exam: ↑JVP, Kussmaul's sign (↑JVP with inspiration), peripheral edema, RV heave, pulsatile liver, split S2, new TR murmur
- EKG: RAD, R:S amplitude >1 in V1, p-wave > 2.5mm in inferior leads (P pulmonale), S1Q3T3 (RV strain in PE), atrial arrhythmias
- Labs: NT-proBNP, troponin, also ↑Cr and LFTs secondary to venous congestion (LFTs may be normal in chronic RV failure)
- Imaging: PA/lateral CXR; chest CT → RV/LV ratio >0.9 suggests RV strain
- Echo: measure RV size/fxn/pressure to elucidate etiology. Aortic root, LA, RV should be ~1:1:1 in size (PSL view). RV should be < LV in size (Apical 4Ch view). RVEF based on displacement of base towards apex, correlates with TAPSE = tricuspid annular plane systolic excursion (normal ≥ 17 mm; reflects apex-to-base shortening). RVSP calculated from TR jet, correlates w/ RHC but can vary within 10mmHg (esp w/ lung disease, PPV)
- RHC w/ placement of PA line: gold standard for measurement of ventricular filling pressures, CO, PA pressures
  - Assessments of RV function – CVP/PCWP ratio: normal = 0.5, ↑ is sign of RV dysfunction; PAPi: (PAs – PAd)/CVP <0.9 = RV failure, for pts w/ VAD < 1.85 = RV failure; RV stroke work index: (mPAP – CVP) x (CI/HR) x 0.0136 (normal 8-12 g/m/beat/$m^2$)

## Management (Circ 2018;137:e578)

- Treat reversible causes (e.g. pericardial disease, RVMI, PE, hypoxemia, infections)
- Preload (CVP goal 8-12mmHg): both hypo- and hypervolemia can ↓CO
  - Volume responsive (PE, RVMI): judicious IVF (0.5-1L) in absence of CVP elevation (goal CVP 10-14 in RVMI)
  - Volume overload: IV diuresis to ↓RV pressures, ↓functional TR, and improve LV CO; consider CRRT if refractory to diuresis
- Afterload:
  - Systemic: if pt hypotensive, start pressors – do not tolerate HoTN as propagates RV death spiral (↓CPP); Goal MAP>65 & MAP>mPAP (EHJ Acute CV Care 2022;11:77) no clinical data regarding pressor of choice, but often choose vasopressin or norepinephrine (vaso affects PVR less than norepi) (Crit Care Med 2007;35:2037)
  - 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 (Veletri), inhaled or IV), endothelin antagonists (e.g. bosentan, ambrisentan), nitric oxide enhancers (e.g. PDE-5 inhibitors: sildenafil, tadalafil)
- Contractility: milrinone (↓RV afterload by pulm vasodilation but ↑HoTN risk); epinephrine (↑RV contractility, ↑MAP). In RVMI, important to revascularize urgently as inotropes can exacerbate ischemia.
- Devices: if refractory RVF, consider RV MCS and/or biventricular support (ProtekDuo, Impella RP, VA-ECMO)

## Intubation and Mechanical Ventilation (Curr Heart Fail Rep 2012;9:228)

- RV preload is "extrathoracic" and afterload is "intrathoracic" → intubation/PPV ↑ PVR & RV afterload→↑ RV dilation→"death spiral"
- Mech vent/NIPPV in RV failure precipitate risk for hemodynamic collapse & cardiac arrest; trial of HFNC for hypoxemic respiratory failure preferred prior to MV/NIPPV given minimal effect on RV afterload.
  - Drugs commonly used in intubation (BZDs, propofol, muscle relaxants) → tendency towards vasodilation and negative inotropy → decreased venous return → decreased RV/LV preload → systemic hypoTN → propagates "death spiral"
  - Consider rapid sequence intubation w/ hemodynamically stable induction agents (ketamine/etomidate >> propofol for induction) & push dose epinephrine (5-20mcg) or phenylephrine if emergent intubation; have norepi in line anticipating hypotension.
- Vent management: prevent hypoxemia & hypercarbia (↑PVR), consider moderate TV (~8cc/kg), low PEEP (<8 cm $H_2O$), and moderate plateau pressure goal (<30 mmHg) to help minimize RV afterload

## Right Ventricular Myocardial Infarction (ACC/AHA: Circ 2013;127:e362)

- EKG: check R-sided ECG 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

# Cardiology — Mechanical Circulatory Support

## MECHANICAL CIRCULATORY SUPPORT (MCS) (JACC HF 2020; 8(11):879 ; Heart Int 2022; 16(1):37)

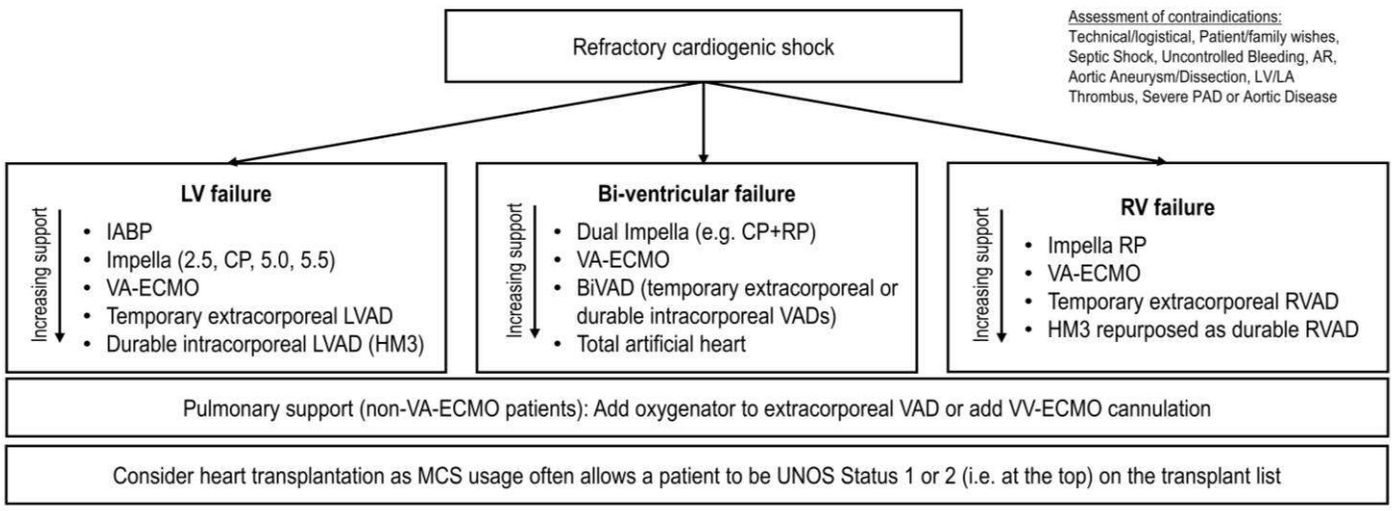
***Note:*** If inotrope-refractory cardiogenic shock, call SHOCK team (p11511) and/or HCICU attending (p29151). VAD Coordinator (p11045).

| Device | Indications | Support Provided | Considerations* | Management | Complications |
|---|---|---|---|---|---|
| **IABP (intra-aortic balloon bump)** | - Refractory heart failure (**bridge** to durable MCS or transplant, bridge-to-bridge)<br>- Refractory ischemia | - Mechanism: balloon inflation/deflation timed with cardiac cycle; **↓LV afterload** (deflation), **↑coronary perfusion** (inflation)<br>- Minimal **LV-only** support **(0.3-0.5 L/min)**<br>- Amount of support determined by balloon cycle per # of cardiac cycles (1:1>1:2>1:3) | - Requires **native contractility** and **stable rhythm**<br>- Bedside insertion but often placed in cath lab under fluoroscopy<br>- Does not always require AC (no AC need when at 1:1)<br>- No ↓mortality in cardiogenic shock (IABP-SHOCK II)<br>- Prevents mobility | - Check **CXR** daily (tip 1-4cm below aortic knob)<br>- Check **waveform** twice daily<br>- Daily pulse checks<br>- Wean by ↓ ratio (then return to 1:1, stop AC, pull) | - **Limb ischemia**<br>- Vascular injury<br>- Thromboembolism<br>- Thrombocytopenia<br>- Bleeding<br>- Infection<br>- Balloon leak/rupture (STAT c/s to attending and vascular surg) |
| **Impella** | - **Cardiogenic shock** or massive PE<br>- Refractory malignant **arrhythmias**<br>- Support during **high-risk procedures**:<br>○ Complex PCI<br>○ Ablation of ventricular arrhythmias<br>○ Percutaneous valve repair<br>- Acute allograft failure | - Mechanism: axial-flow continuous pump; unloads ventricle<br>- **Partial LV-only support (LV→aorta):**<br>Cath lab (percutaneous) placement: Impella 2.5 (**2.5 L/min**), Impella CP (**3.5 L/min**)<br>OR placement: Impella 5.0 (**5 L/min**) or 5.5 (**6.5 L/min**)<br>- **Partial RV-only support (IVC→PA)** Impella RP **(>4 L/min)**<br>- Amount of support determined by pump power [P1 (low) to P9 (high] | - **Requires AC** (purge ± systemic); purge solution can be heparin or bicarbonate<br>- Upgrade to Impella 5.5 when able (fewer complications, allows pt **mobilization**)<br>- Days to weeks of support<br>- ↓ mortality in cardiogenic shock due to MI (DanGer Shock)<br>- Controversial benefit over IABP | - Check daily hemolysis markers<br>- Daily limited TTE (to check position)<br>- Check **suction events** (can indicate ↓preload, RV failure, thrombosis, mispositioning)<br>- Check telemetry (ventricular arrhythmias may indicate device migration)<br>- **Position alarm** (reposition under fluoro/echo) | - **Hemolysis**<br>- **Ventricular arrhythmias**<br>- Bleeding<br>- Limb ischemia<br>- Infection<br>- Thromboembolism<br>- Thrombocytopenia<br>- Vascular injury |
| **VA-ECMO** | | - Mechanism: heart-lung bypass device<br>- **Full bi-ventricular support** (**4-10 L/min**) + oxygenation & CO2 clearance | - Bedside and urgent insertion possible<br>- Days to weeks of support<br>- Often requires Impella for LV venting (prevents complications such as pulmonary edema) | See *ECMO* | |
| **Durable VAD** | - Bridge to transplant<br>- Bridge to candidacy<br>- Destination therapy<br>- Bridge to recovery (LV unloading can be therapeutic) | - Mechanism: continuous centrifugal-flow intracorporeal pump designed for long-term out-of-hospital use<br>- **Full LV-only support (LV→aorta) at 10 L/min**<br>- Off-label for RV support (RVAD) or both (BiVAD)<br>- **HeartMate 3 (HM3)** device is most utilized (HeartMate II and HeartWare HVAD now discontinued, but remain in patients with implantation prior to removal off the market) | - Requires surgical implantation<br>- Full **mobility**<br>- Long-term support (years)<br>- **Requires lifelong AC with warfarin**<br>- Lack of social support is a limitation to VAD candidacy<br>- 48% reduction in all-cause mortality with durable LVAD as compared to optimal GDMT in Class IV HF (REMATCH) | - **BP via manual cuff w/ doppler** (goal MAP 70-80); continuous flow device does not generate pulse<br>- If hypotensive: A-line<br>- If unconscious, w/o hum and unable to troubleshoot OR MAP<50: chest compressions<br>- TTE if any concern | - **Driveline infections**<br>- **RV failure**<br>- **Bleeding, vWF def., hemolysis**<br>- Arrhythmias<br>- Thromboembolism<br>- Pump thrombosis<br>- Stroke<br>- AR/AI<br>- Outflow graft obstruction |

*Major inequities affect MCS access and post-MCS outcomes in historically marginalized populations (JAHA 2024;13, J Clin Med 2021;10)

## INDICATIONS FOR HEART TRANSPLANT (CURR OPIN NEPHROL HYPERTENS 2025;34:16)

Advanced HF refractory to therapy, defined as: **(1)** cardiogenic shock requiring inotrope or MCS, or **(2)** NYHA class IV sx refractory to maximal therapy alongside low HF prognosis score or poor CPET results, or **(3)** refractory life-threatening arrhythmias

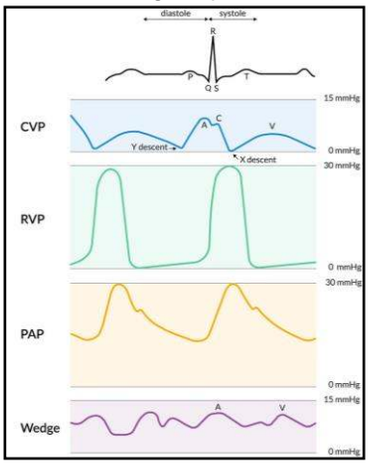



*Frederick Lang, Oreoluwa Olakunle*

# Cardiology — Pulmonary Artery Catheterization

## Overview

- Indications: PA catheter (PAC) for tailored therapy; diagnose (1) undifferentiated shock (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 empiric use of PAC in pts w/ ADHF off inotropes. Recent observational study (JACC Heart Fail 2020:8:11) mortality benefit for cardiogenic shock. PACs are still guideline-recommended in carefully selected patients (e.g. pts w/ MCS) (Circulation 2022;145:e895)
- Line course: central vein (IJ/fem)→SVC/IVC→RA→RV→PA→distal pulmonary arteriole

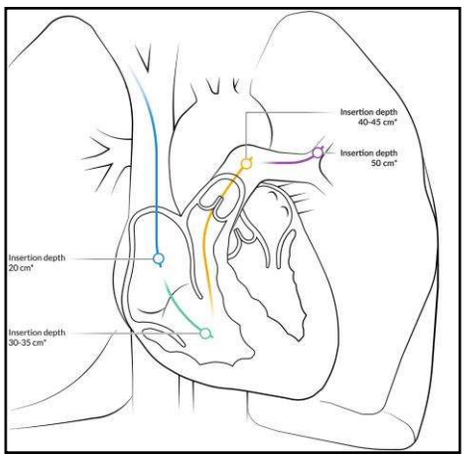



## Venous Waveforms (CVP/PCWP)

- **a wave**: atrial contraction; coincides with the QRS complex (on CVP tracing)
- **c wave**: bowing of TV into atrium during ventricular contraction; more visible in 1st degree AVB
- **x descent**: atrial relaxation (early x descent), downward movement of TV (late x descent)
- **v wave**: passive atrial filling (venous return) when TV/MV closed; coincides with T wave
- **y descent**: rapid atrial emptying following opening of the TV (ventricular diastole)
- Sample waveforms available in J Clin Monit Comput 2022;36:5

## Obtaining PA Line Numbers on AM Rounds

1) Position patient supine with head-of-bed between 0-60°
2) Align transducer with mid-axillary line (4th intercostal space)
3) Zero transducer to air & assess waveform for dampness
4) Record PA systolic, PA diastolic, PA mean, CVP, & line position
5) Open the PA catheter balloon port & remove 1.5cc air
6) Inject 1.5cc air slowly until PCWP waveform observed (use minimum air required to ↓ risk of PA infarction/rupture) & record PCWP (limit balloon inflation <10 seconds)
7) Release safety syringe & allow balloon to deflate passively; verify balloon deflated by visualizing the PA waveform
8) **Troubleshooting**: CXR to evaluate position (obtained daily)
   a. **Arrhythmia**: catheter may be in RVOT; consider repositioning
   b. **Dampened waveform**: kinked tubing, air/thrombus, or catheter tip against vessel wall; flush and/or withdraw catheter
   c. **No PCWP tracing**: catheter tip is not far enough, balloon has ruptured, or catheter is coiled in RV
   d. **Continuous PCWP**: catheter tip is advanced too far ("overwedged")
   e. **mvO2 resembles arterial O2**: 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** = $VO_2$ / (13.4 * Hgb * [$SpO_2$ – $MvO_2$]) [*nml*: 4-8 L/min]
    - $VO_2 \approx$ 250 ml/min *OR* 3*wt(kg) *OR* 125*BSA
  - **Thermodilution** (**TD**): temp change (measured by thermistor) is proportional to LV CO (inaccurate if: severe TR, intracardiac shunt, very low CO)
- Cardiac index = CO/BSA [*nl*: 2.2-4.2 L/min/$m^2$] (nl ↓ w/ age)
- SVR = (MAP-CVP) / CO x 80 [*nl*: 700-1200 dynes*s*$cm^5$]
- PVR = (mPAP-PCWP) / CO [*nl*: <2 Woods units]
- PAPi = (PASP – PADP) / RAP [PAPi < 0.9 → severe RV dysfxn]

**Hemodynamic Profiles of Shock**

| Subtype | CVP [JVP] | PCWP [CXR] | CO/CI [MvO2, 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 (allowing for less frequent wedging)

## 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)
- Position: on CXR, should be in middle 1/3 of the chest bilaterally; ability to wedge more important than CXR position
- Complications: infection, bleeding, thrombosis, PTX, arrythmia (PVC, NSVT, VT), RBBB, CHB, valve trauma, PA rupture (place patient on side with the catheter "bleeding side down", order STAT CXR, CBC, coags, CT surgery consult), RV perforation, pulm infarct, PE, catheter knotting (difficult removal), balloon rupture & embolization

*Lianet Vazquez*



Suggest an Edit

# Cardiology Cardiac Devices: PPM, ICD, CPP & CCM

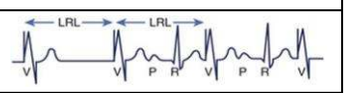
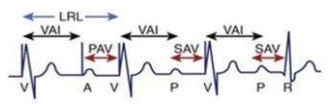
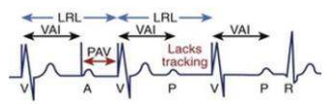
## Permanent Pacemakers (PPM), Implantable Cardioverter-Defibrillators (ICD), Cardiac Physiological Pacing (CPP), & Cardiac Contractility Modulation (CCM)

- 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 ventricular arrhythmias via anti-tachycardia pacing, cardioversion, or defibrillation
  - CPP: any form of cardiac pacing intended to restore/preserve synchrony of ventricular contraction, including: Cardiac Resynchronization Therapy (CRT): provides simultaneous RV + LV pacing in HFrEF pts w/ wide QRS to ↓desynchrony → LV reverse remodeling & ↑LVEF
  - Conduction System Pacing (CSP): recruitment of intrinsic conduction system by either His bundle pacing or LBB area pacing
- CCM: delivers biphasic electric stimulation to the ventricular myocardium during absolute refractory period to augment LV contraction
  - 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** (Micra, 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: EP Technician (p16939) business hours; EP fellow on call after-hours/weekend
- MRI compatibility: not all devices are MRI compatible (find out device model); however, even non-MRI compatible devices may be safe to scan after re-programming (NEJM 2017;376:755). Case-by-case.
- Magnet response: PPM: asynchronous pacing (DOO/VOO); ICD: suspends detection/treatment of tachyarrhythmias (no effect on pacing)

| 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 (T+I) | |

| Code | Action | Use | Waveform |
|---|---|---|---|
| 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 | AOO: Obsolete, VOO: Temp wire pacing |  |
| Dual Chamber Modes | | | |
| Tracking Modes | | | |
| DDD | Synchronous; paces senses in A & V; atrial activity is tracked/triggers ventricular activity | 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 A & V; atrial activity not tracked; atrial tachyarrhythmia does not trigger RVR | SSS or sinus brady with intermittent atrial tachycardias |  |
| DOO | Asynchronous Fixed Rate; paces A & V, no sensing | Avoid sensing electrocautery or electromagnetic interference | |

*Different pacing modes.* LRL, *Lower rate limit;* P, *intrinsic P wave;* A, *atrial paced event;* R, *intrinsic R wave;* V, *ventricular paced event;* VAI, *ventriculoatrial interval;* PAV, *paced atrioventricular interval;* SAV, *sensed atrioventricular interval.*

## PPM Indications (Class I) (JACC 2019;74:e51)

Sinus Node Dysfunction:

- Symptomatic sinus brady (± sinus pauses) or chronotropic incompetence
  - DDD for symptomatic SND with extension of AV interval to minimize V-pacing; prefer physiologic pacing
- Symptomatic medication-induced bradycardia if no accepted alternative medication
- Permanent AF and symptomatic bradycardia

AV Block (AVB)/Conduction Disease:

- 3°AVB
- Symptomatic 2° AVB Mobitz I or II
- Permanent 2° AVB Mobitz II or intermittent 3° AVB
- Alternating bundle branch block

Neurocardiogenic: only if syncope associated with marked cardioinhibitory or bradycardic event

## ICD Indications (Class I) (JACC 2018;72:e91, 2022 AHA HF Guideline)

| Primary Prevention (on optimal GDMT and estimated >1-yr survival) | Secondary Prevention |
|---|---|
| Ischemic CM: NYHA Class I: EF ≤30%, >40d s/p MI & ≥90d s/p revascularization<br>NYHA Class II/III: EF ≤35%, >40d s/p MI & ≥90d s/p revascularization<br>Other: EF ≤40%, >40d s/p MI + NSVT + inducible VT/VF | - Prior cardiac arrest (VF/pVT) OR sustained VT if no reversible cause found (excludes <48h of MI)<br>- Cardiac syncope w/ LVEF<35% OR cardiac syncope w/ inducible VT/VF on EP study OR cardiac syncope where VT/VF is most likely etiology |
| Non-ischemic CM: EF ≤35% + NYHA Class II/III | |
| - HoCM with known arrhythmias or after risk stratification (Circ 2024;149)<br>- Channelopathies after risk stratification (EHJ 2022:43) | |

## CPP Indications (2022 AHA HF Guideline), 2023 HRS Guideline on CPP)

- CRT Class I: NYHA II-III or ambulatory IV + LVEF ≤35% + Normal Sinus Rhythm + QRS >150ms w/ LBBB

## CCM Indications

- LVEF 25-45% + NYHA III on GDMT + no indication for CRT

# Cardiology — Valvular Heart Disease

## AORTIC STENOSIS

- **Etiology**: degenerative calcific AS (age-related; precursor is aortic sclerosis; most common cause >70yo), bicuspid valve (most common cause <70yo), rheumatic heart disease (RHD; often w/ leaflet fusion, concurrent MV dz), radiation
- **Clinical Manifestations**: most important determinant of prognosis = sxs: 50% mortality at 5y if angina, 3y if syncope, 2y if HF
  - Angina: ↑afterload → ↑LV pressures → LVH → ↑O2 demand → supply-demand mismatch w/ exertion or tachycardia
  - Syncope: caused by exercise-induced vasodilation w/ fixed ability to augment CO due to stenosis
  - Heart failure (dyspnea): LVH → diastolic dysfunction (*systolic dysfunction is a late finding*)
  - Acquired vWF def: 20% of severe AS, can worsen bleeding from GI AVMs "Heyde syndrome" (NEJM 2012;367:1954)
- **Diagnosis**:
  - Physical exam: harsh crescendo-decrescendo murmur at RUSB radiating to carotids. **Signs of severe AS**: late-peaking murmur (long ejection time), delayed carotid upstroke (pulsus parvus et tardus), soft or paradoxical split S2, diminished murmur (low flow)
  - TTE: measure mean (not peak) gradient, valve area, & peak jet velocity; assess EF as ↓ flow →↓ gradient confounds severity
- **Severe AS**: peak AV velocity ≥4m/s, **mean** AV pressure grad **≥40mmHg**, or AV **area (AVA) ≤1cm²** (ACC/AHA: Circ 2021;143:e35)
  - ECG: LVH, LAE, LAFB, LBBB
  - Exercise stress testing: recommended in asymptomatic severe AS to assess for symptoms; do **not** perform in pts w/ sx
  - Low-flow/low-gradient AS**:** severity underestimated in reduced EF as ↓ flow →↓ gradient. Subsets distinguished by flow (low-flow: SVi <35 mL/m²), gradient (low-gradient: <40mmHg), LVEF, and **dobutamine stress TTE (DSE)** (Circ 2011;124:739)
    - True LF/LG AS: low EF, flow, & gradient; confirm w/ DSE $V_{max}$>4m/s or gradient>40mmHg w/ AVA<1cm²; poor outcomes
    - Pseudosevere AS: a normal valve w/ low measured AVA in the setting of low EF; due to flow-dependent AVA estimation and decreased ability of weakened ventricle to fully open aortic valve; confirm w/ DSE with improved AVA >1cm²
    - Paradoxical LF/LG AS: **preserved EF**, yet low-flow and low-gradient; poor outcomes (Circulation 2013;128:1781)
- **Natural History**: highly variable, but on average, AVA ↓ ~0.1 cm²/yr & mean gradient ↑8mmHg/yr (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): indications based on: **symptoms, severity** (TTE criteria), **LVEF**
  - Symptomatic, severe AS (Stage D): prompt AVR indicated due to risk of sudden death
  - Asymptomatic, severe AS (Stage C): AVR appropriate if: LVEF<50%; symptoms provoked with exercise testing; 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). For asymptomatic severe AS, early TAVR may reduce unplanned CV hospitalization (EARLY TAVR).
  - Low-flow, low-gradient AS**:** true LF/LG = AVR indicated, paradoxical = AVR if symptomatic, pseudosevere = AVR not indicated
  - **Bioprosthetic vs Mechanical:** if contraindications to AC with VKA, must offer bioprosthetic; if pt <50 years of age without contraindications to AC, SAVR w/ mechanical valve recommended (COR 1; Circulation 2021;143:35); if >65 yrs of age, bioprosthetic recommended (COR 2a); 50-65 years of age require shared decision making
  - **SAVR vs TAVR for bioprosthetic**: pts <65yr, SAVR recommended d/t increased durability; >80yr TAVR recommended
    - 65-80 yrs of age: depends on surgical risk (STS-PROM score), concomitant heart/vascular disease, valvular/vascular anatomy that is amenable to TAVR (Circulation 2021;143:35)
    - TAVR is recommended for those at extreme surgical risk (compared to medical therapy, PARTNER); noninferior to SAVR in those at high (NEJM 2011;364:2187), intermediate (PARTNER 2), & low surgical risk (PARTNER 3). Valve-in-valve TAVR may additionally be beneficial in pts with surgical bioprosthetic AV failure (JACC 2017;69:2253)
  - **TAVR Evaluation**: c/s **structural cardiology**, **cardiac surgery**. Obtain **TTE**, TAVR-protocol **CT**, **dental clearance** (Panorex)
  - **TAVR Complications**: Valve: embolization, paravalvular leak; Stroke: embolic (first 48h), ischemic/hemorrhagic; Conduction: HAVB requiring PPM (Major RF: baseline RBBB, need for pacing or HAVB s/p TAVR; Minor: h/o AF, valve oversized >15%; Card Fail Rev 2021; 7:e12); Bleeding; Access site complication; Hemodynamics: dynamic LVOT obstruction due to LVH ("suicide LV"), HTN (sudden ↓ in obstruction after TAVR), hypotension (d/t ↓preload), tamponade (perforation, usually immediate); AKI
- **Medical Management**: *AS is a surgical disease & medical management is only utilized for treatment of sx*
  - Treat HTN: reduce the "double load" on the ventricle. In theory, ACE-I beneficial for LV fibrosis; however, no optimal regimen exists because anti-hypertensives can lead to hemodynamic issues. 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**:
  - 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, older generaction mechanical AVR (Circ 2021;143:e35)
  - Bleeding risk: mechanical > bioprosthetic (likely AC related). Reoperation risk: bioprosthetic > mechanical
  - TAVR: ASA monotherapy non-inferior to DAPT for thrombotic events & associated with less bleeding (NEJM 2020;383:1447)
  - If need AC for AF, DOACs similar outcome after TAVR, not approved for valvular MS (moderate+) (JAHA 2021;11:e023561)

| Prosthesis | Location | Timing and Risk Factors for AC | 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)** | IIa |
| | | >3 months after placement | **ASA 81** | IIa |
| **TAVR** | **Aortic** | No AC; indefinite antiplatelet monotherapy | **ASA 81 or Clopidogrel 75** | IIa |

# Cardiology — Valvular Heart Disease

## Aortic Regurgitation (aka Insufficiency)

- **Etiology**: Acute: IE, aortic dissection, traumatic, prosthetic valve failure; Chronic: primary valve disease (bicuspid valve, endocarditis, RHD, CTD, myxomatous degeneration) or secondary root dilation (in aortic aneurysm due to HTN, CTD, syphilis)
- **Pathophysiology**: Acute: diastolic regurgitant flow → *sudden* ↑LVEDP (w/o remodeling time) → ↓CO → pulmonary edema; Chronic: diastolic regurgitant flow → ↑LVEDP → initial maintenance of SV/CO → progressive ventricular dilatation → LV failure
- **Clinical/Exam**: angina, L-sided HF. Acute: cardiogenic shock. Chronic: ↑pulse pressure (bounding pulses, bouncing head/uvula, nail bed capillary pulse; Int J Card 2006;107:421)
  - Auscultation: high-pitched, blowing diastolic decrescendo murmur along LSB. Longer murmur = more severe/chronic. May hear low-pitched diastolic murmur at apex secondary to regurgitant jet displacing anterior mitral leaflet ("Austin Flint murmur")
- **Treatment:**
  - Acute: usually needs surgery. Nitroprusside to ↓afterload; ino- and chronotrocpes to ↓diastolic time. **Do not use vasoconstrictors or IABP** (which worsen regurg) **or beta-blockers** (which block compensation and ↑diastolic regurgitant time)
  - Chronic: ACEi/ARB/ARNI first line, CCB or hydralazine/nitrates 2nd line to reduce LV afterload. AV replacement if: severe AR AND symptomatic, LVEF<55%, LV end-systolic dimension >50mm, or undergoing other cardiac surgery (JACC 2021;77:e25)

## Mitral Stenosis

- **Etiology**: RHD (~80% of MS; only 50-70% report h/o rheumatic fever), IE, annular calcification, congenital, autoimmune valvulitis (SLE, RA), carcinoid syndrome, endomyocardial fibroelastosis, radiation (e.g., 10-20y after Hodgkin's tx)
- **Pathophysiology**: elevated LAP → pHTN, **AFib (47%)**. Demand for ↑CO precipitates symptoms. Valve narrows ~0.1cm$^2$/y
- **Clinical/Exam**: dyspnea (most common), pulmonary edema, hemoptysis, VTE even w/o AFib (Am Heart J 2000; 140:658), RV failure
  - Auscultation: loud S1, high-pitched opening snap (more severe if earlier, indicating higher LAP); low-pitched diastolic rumble
- **Treatment:** Medical: warfarin if LA thrombus, AFib, prior embolism (Class I) or LA > 55mm (Class IIb). Beta-blockers if tachycardic or dyspneic, diuresis if pulm edema. If rheumatic, secondary ppx against strep as below (Circulation 2021;143:e35)
  - Intervention: generally, need to have severe MS (MV area ≤1cm$^2$) + symptoms to be considered for intervention
    - **Rheumatic MS:** symptomatic pts with severe rheumatic MS and favorable valve morphology (based on TTE, Wilkins Score) → **Percutaneous mitral balloon commissurotomy (PMBC).** Consider PMBC if asymptomatic AND elevated pulmonary pressures (>50mmHg; COR 2a) or new AF (COR 2b). Proceed to surgical MVR if: severe symptomatic MS AND either not PBMC candidate, PBMC fails, or undergoing another cardiac surgery (JACC 2021;77:e25)
    - **Nonrheumatic Calcific MS:** because calcification involves the annulus and base of the leaflets without commissural fusion, there is no role for PMBC or surgical commissurotomy; consider MVR only after discussion of high risk (COR 2b)

## Mitral Regurgitation

- **Etiology**: Acute: ischemic (often inferior MI), IE, traumatic, spontaneous chordal rupture; Chronic: primary (MVP, ischemic, degenerative, RHD, IE, CTD) or secondary ("functional MR": dilated LV/annulus in dilated CM, systolic anterior motion in HCM)
- **Pathophysiology**: LA/LV volume overload → LV dysfxn, progressive enlargement of LV → dilated mitral annulus → regurgitation
- **Clinical**: Acute: flash pulmonary edema, hypotension, shock; Chronic: DOE, orthopnea, PND, AFib, pulmonary → periph edema
- **Exam**: holosystolic murmur at apex radiating to axilla, S3, displaced PMI. If acute: early diastolic rumble and S3 may be only signs
- **Treatment:**
  - Acute: ↓afterload, inotropes (dobutamine), diuresis. If hemodynamically unstable (esp. post-MI or endocarditis), consider IABP and/or urgent surgical repair (NEJM 2012;366:2466). If ischemic, consider revascularization
  - Chronic: GDMT for HF if applicable
    - **Severe primary MR**: symptomatic w/ any EF OR asymptomatic w/ EF ≤ 60% or LVESD ≥ 40mm → MVR (Circulation 2021;143:e35); primary MR w/ high surgical risk, transcatheter edge to edge repair (M-TEER) (COR 2a; EVEREST II).
    - **Severe "functional MR":** if LVEF ≥50% OR unfavorable anatomy AND symptomatic on maximal GDMT OR undergoing CABG → MVR; if LVEF <50% AND persistent symptoms on maximal GDMT AND anatomy favorable → M-TEER (COAPT).

## Tricuspid Regurgitation

- **Etiology**: Primary: IE, RHD, iatrogenic (device leads, etc), congenital, trauma, carcinoid, drugs, ischemic papillary muscle dysfunction; Secondary: dilated RV in pulm HTN, dilated CM, RV volume overload; dilated annulus (associated w/ AF)
- **Pathophysiology**: similar to mitral regurgitation, but involving RA/RV and tricuspid annulus
- **Clinical**: Right-sided heart failure: hepatosplenomegaly, ascites, peripheral edema, large V in JVP, pulsatile liver, substernal pulsation
  - Ausculation**:** holosystolic murmur at left mid- or lower- sternal border that increases with inspiration, S3
- **Treatment: Medical:** Diuresis (COR 2a), management of underlying cause
  - Tricuspid valve replacement if: (1) severe TR undergoing left-sided valve surgery; (2) symptomatic (i.e., with R heart failure) primary severe TR; (3) symptomatic secondary severe TR poorly responsive to GDMT without ↑PAP or left HF (4) progressive TR if undergoing L valve surgery AND either tricuspid annular dilation >4 cm or R heart failure (5) consider in asymptomatic primary severe TR with progressive RV dilation / systolic dysfunction (JACC 2021;77:e25)
  - Transcatheter therapies (T-TEER) are emerging which may ↓ TR severity and ↑ QoL in severe TR (NEJM 2023;388:1833)

## General Principles

- **Rheumatic Disease:** secondary ppx against streptococcus recommended for 10yr or until 40 yrs old (whichever longer, COR I)
- **AF and Valvular disease:** w/o mechanical valve, DOAC reasonable VKA except in rheumatic MS, practice variable for nonrheum MS
- **IE Prophylaxis:** Reasonable in pts undergoing high-risk dental manipulation with 1) prosthetic valves, 2) prosthetic material used in valve repair, 3) prior IE, 4) CHD unrepaired or incompletely repaired, 5) s/p cardiac transplant with valvulopathy, 6) CHD completely repaired with prosthetic material for 1st 6 months post-op (COR 2a; Circulation 2021; 143:35)

# 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, infectious, HF, autoimmune (Am J Med 2000;109:95). Tamponade more likely in malignant, post-viral (including SARS-CoV-2), 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; *elevated BP does not rule out*
- Pulsus paradoxus (PP): exaggeration of normal decrease in SBP during inspiration (If >10mmHg, ⊕LR=3.3. If ≤10 mmHg, ⊕LR=0.03)
  1. Slowly deflate BP cuff→note pressure when systolic Korotkoff sounds only heard during expiration (will sound irregular) (**a**) → continue slowly deflating BP cuff until Korotkoff sounds heard throughout; (**b**) **PP = a – b**
  2. Via A-line tracing (**PP = height exp. – height insp. systolic waveform**)
- ECG: sinus tach, low QRS voltage (50%; limb ≤5mm, precordial ≤10mm), 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

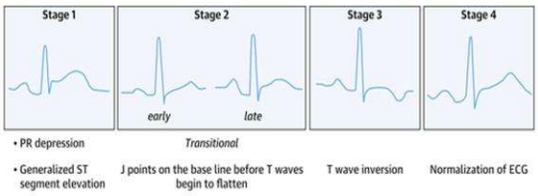
**Treatment**:

- **Fluid resuscitation**: administer volume urgently to increase intracardiac pressures (monitor closely as overfilling can worsen tamponade), starting w/ 250-500cc bolus; greatest benefit for SBP < 100 mmHg (Circ 2008;117:1545). Inotrope if needed. **Avoid BB**
- PPV: avoid if possible as ↑positive intrathoracic pressure will further impede ventricular filling
- Drainage: catheter **pericardiocentesis**, surgical pericardiectomy (if aortic/myocardial rupture), or HD (if uremic)
  - Analysis of pericardial fluid: cell count, total protein, LDH, gram stain/cx, fungal or AFB smear/cx (if relevant), ADA/IFN-gamma/lysozyme (if concerned for TB), cytology/tumor markers
  - Removal of drain: when output **<50cc/d**, otherwise consider **pericardial window** (pleural>abdominal). See *Pericardial Drain*

## PERICARDITIS

- Classification: acute (<6w), incessant (>6w w/o remission), recurrent (return after symptom-free interval of 4-6 wks), chronic (>3months)
- Epidemiology: 5% ED pts w/ non-ischemic chest pain, M > F, young > elderly
- Etiology: 80-90% idiopathic (usually viral/post-viral), bacterial, fungal, post-MI, post-cardiac injury syndromes (e.g. post-CABG, ablations etc.), uremic, mycobacterial (TB), autoimmune (CTD, vasculitis), malignancy, XRT, drugs (procainamide, hydral, INH) (NEJM 2014;371:2410)

**ECG Evolution in Pericarditis (JACC 2020;75:76)**




**Clinical Manifestations and Diagnosis**:

- Symptoms: sudden onset, pleuritic, retrosternal **CP relieved w/ sitting up & leaning forward** ± viral prodrome if infectious etiology. In uremic or CTD pericarditis, CP may be absent
- Exam: pericardial **friction rub** (~30% cases), often described as "leather rubbing on leather", best heard at LLSB w/ diaphragm of stethoscope at end-expiration w/ pt leaning forward. (Friction Rub Examples)
- ECG: 4 stages: (1) **diffuse concave ↑ST & ↓PR** (↑PR & ↓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.
- 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, HCV, IGRA, ESR/CRP, troponin (elevated in ~30%, c/f myopericarditis)
  - TTE: assess for presence/size/location of co-existent pericardial effusion
  - Pericardiocentesis/Surgical Drainage: if (1) suspect **malignancy** or **bacterial** etiology (2) large effusion (>2cm) (3) tamponade
  - Cardiac MRI: adjuvant test if dx uncertain or c/f myocardial involvement (JACC 2020;75:76)

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

- Hospitalize if: fever, ↑WBC, large effusion (>2cm), immunosuppressed, 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 650-975 TID; indomethacin 25-50mg TID) ± **colchicine** 0.6mg BID (qd if pt <70kg) + PPI in select pts for GI ppx (hx PUD, age>65, concomitant anticoagulation/steroid)
  - **ASA**: preferred over NSAIDs if: post-MI, CKD (GFR <45), concomitant anti-platelet/anticoagulant therapy
  - Activity restriction: avoid strenuous activity until symptom resolution
- **Glucocorticoids** (prednisone 0.25-0.5mg/kg/d): preferred over NSAIDs if: sx refractory to 7d of NSAID treatment, recurrent (>2 episodes), uremic pericarditis, CTD pericarditis, or contraindication to NSAIDs. Associated w/ **↑recurrence** if first idiopathic episode due to flares during weaning. Duration: *NSAIDs*: until sx resolve (1-2w), then taper (total 3-4w). *Colchicine*: 3mo (no taper). *Glucocorticoids*: 2w, then taper (2-4 mo total)

**Recurrent pericarditis**

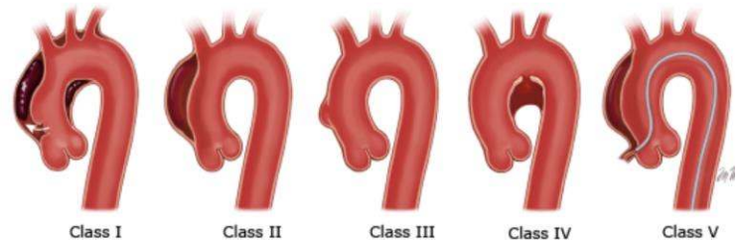
- Treatment: generally same as initial episode but longer wean (colchicine for 6+ months and wean NSAID by CRP trend)
- Consider IL-1 inhibitors (NEJM 2021;384:31)
- MGH Cardiology has a Pericardial Disease Program for complex pericardial pathologies.

**Constrictive pericarditis** (Adherence of the visceral and parietal pericardium due to chronic inflammation)

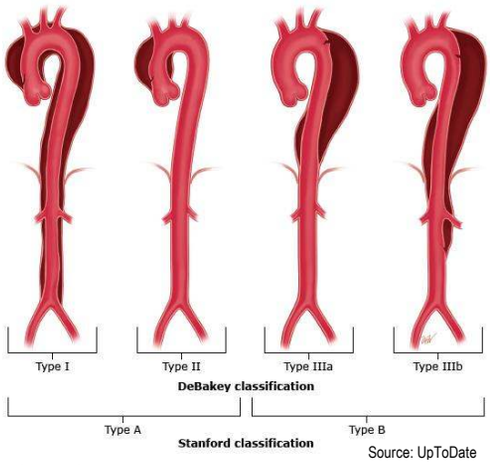
- Clinical presentation of constrictive pericarditis can mimic decompensated heart failure or volume overload
- Definitive treatment is pericardiectomy + treatment of underlying cause

# Cardiology — Aortic Disease

## ACUTE AORTIC SYNDROMES (AAS) (Nat Rev Cardiol 2015;12:103)(Lancet 2023;401;p773)




Source: UpToDate




Source: UpToDate

**Etiology**: five distinct processes with risk of rupture
- Class I: Classic dissection (intimal tear resulting in a false lumen)
- Class II: Intramural hematoma (IMH, rupture of vasa vasorum causing hematoma within aortic wall without tear)
- Class III: Limited dissection (limited intimal tear without dissection)
- Class IV: Atherosclerotic ulcer (PAU, penetrating adventitia with surrounding hematoma)
- Class V: Iatrogenic/traumatic

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

**Epidemiology**:
- Prevalence: aortic dissection most common (62-88%), followed by IMH (10-30%) & penetrating atherosclerotic ulcer (PAU) (2-8%)
- Risk factors: male, HTN, age 60-70 (if <40yo, think Marfan syndrome, Ehlers-Danlos type IV, CTD, 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*: 8% in-hospital mortality, 15% 1y, 24% 3y, 57% 10y (J Vasc Surg 2021;73:48)
- IMH will progress to complete dissection in 28-47% of cases. 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), decompensated heart failure
  - Sx: chest or back pain (radiates to neck/jaw if ascending; back/abdomen if descending; may migrate as dissection propagates)
- Complications: syncope, shock, **malperfusion syndrome** secondary to branch artery occlusion (MI, stroke, paraplegia, limb ischemia, renal failure); aortic valve regurgitation, pericardial effusion, cardiac tamponade
- Risk Score: Aortic Dissection Detection Risk Score (ADD-RS): d-dimer versus directly to CTA (Circ 2018;3;250) and AORTA simplified score (AORTAs): increased sensitivity, decreased sensitivity (JAHA 2021;10:3)
- Labs: *rule out* if **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-A** | - Sn 95%, Sp 87-100%; **first-line modality** in pts w/ high clinical probability of AAS<br>- Combined I+/I- (assess for IMH, mediastinum hemorrhage, or hemopericardium) |
| **TTE** | - Sn 73-100%, Sp 71-91%, least accurate of diagnostic imaging modalities<br>- 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<br>- Invasive nature limits use; cannot detect pathology below the diaphragm |

**Management**:
- Goal: "**impulse control**" → minimize aortic wall stress by ↓LV ejection force (**dP/dT**): goal HR 60-80 SBP <120mmHg
- Agents:
  - **IV beta blockade** (esmolol, labetalol); **except** if acute severe AI or other contraindication.
  - If additional BP control required: IV nitroprusside, TNG, nicardipine. If refractory HTN, consider renal artery involvement.
    - **NEVER** use vasodilators for AA without AI without concomitant beta blockade → will increase wall stress via reflex tachycardia, thereby increasing dP/dT. **Opiate analgesia** attenuates release of catecholamines (Lancet 2015;385:800)
- Urgent surgical consultation (CT surgery)
- 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. However, INSTEAD-XL showed improved outcomes with low-risk preemptive TEVAR in all Type B dissections
- IMH & PAU: **Type A**: urgent (i.e., within days) open surgical repair **vs. Type B**: medical management or TEVAR

## AORTIC ANEURYSMS (Circulation 2022 ;146 ; e334)

| | Abdominal Aortic Aneurysm (AAA) | Thoracic Aortic Aneurysm (TAA) |
|---|---|---|
| **Epidemiology** | • M>F; >65yo, mostly infrarenal | • M>F, mostly 50-70yo, 50% ascending Ao, 40% descending Ao, 10% arch |
| **Etiology** | • Usually due to **atherosclerotic disease**<br>• RFs: **smoking, male sex, age, pre-existing atherosclerosis**, obesity, HLD, HTN, FHx | • **Atherosclerotic/degen,** RFs: **smoking, HLD, HTN**<br>• Traumatic<br>• **Genetic (5%)**: mostly root & ascending aorta. CTD [Marfan (*FBN-1*), Ehlers-Danlos (T3 procollagen), Loeys-Dietz (TGF-β)], Turner, bicuspid AoV, familial<br>• **Infectious**: 3° syphilis, mycotic aneurysm (most common org: *Staph* spp., *Salmonella* spp.)<br>• **Inflammatory**: GCA (~10% have TAA), Takayasu, RA, psoriasis, Behcet's, Wegener's, IgG4 |
| **Screening / Surveillance** | • **ACC/AHA**: one-time abdominal US in all men >60 w/ FHx of AAA & all men 65-75 who have ever smoked<br>• **Surveillance** (J Vasc Surg 2018;67:2): interval depends on size<br>  • 3.0-3.9cm: q2-3y; 4.0-4.9cm: q12 months; 5.0-5.4cm: q6 months<br>  • Diameter can be normalized to BSA or height | • **General population**: not recommended<br>• **Indications**: at time of dx of Marfan, Turner, Loeys-Dietz, Takayasu or GCA. 1° relatives of pt w/ TAA, dissection, bicuspid valve (even if no disease-causing variant identified on genetic testing)<br>• **Surveillance**: interval depends on presence of aneurysm etiology/location; primarily CT/MRI, TTE (if valvular disease) ranging from q6-12months<br>• **Associated aneurysm:** screen for abdominal, intracranial and lower extremity aneurysms<br>**Genetic Testing**<br>• Indicated in proband (first person in family in whom clinical concern is raised)<br>• Genetic counseling and cascade testing if pathogenic or likely pathogenic variant detected |
| **Imaging Modalities** | • **Abdominal US**: screening and surveillance of infrarenal AAAs. High Sn/Sp (>90%), operator-dependent<br>• **CTA**: high Sn/Sp, >>US for suprarenal AAA; ECG-gated CT (synced w/ diastole via ECG) increases resolution<br>• **MRI/MRA**: good Sn/Sp, preferred for aortic root imaging & for imaging tortuous aortas<br>• **CXR**: "enlarged aorta" nonspecific (tortuous aorta vs aneurysm)<br>• **TTE**: useful for root & proximal thoracic aorta; **TEE**: will visualize entire thoracic aorta but rarely used | |
| **Treatment** | **Medical**<br>• **Smoking cessation** (slows growth) (J Vasc Surg 2010:52:539)<br>• **Reduce BP** per ACC/AHA guidelines<br>• Meds: statins (reduce all-cause mortality in pts s/p surgery)(JAHA 2018:7:19) ; BBs (have not been clearly shown to slow expansion)(J Vasc Surg 2002:35:72); ACEi (controversial); low dose ASA (may slow growth); avoid fluoroquinolones<br><br>**Surgical**<br>• Men: **>5.5cm** *OR* **growing >0.5cm/6mo or >1.0cm/y** *OR* symptomatic<br>Women: >4.5-5cm (controversial)<br>• Open repair vs EVAR | **Medical**<br>• **Reduce BP** (SBP goal of 105-120)<br>• Meds: BBs (decrease TAA growth in Marfan pts), ARBs (slows expansion in Marfan pts)(JACC 2014:64:1725), ACEi, statins (goal LDL<70)<br>• Behavioral: Smoking cessation, avoid straining<br>• Avoid fluoroquinolones<br>**Surgical**<br>• Root/ascending TAAs: ± concomitant AVR: Intervention indicated at 5 cm (threshold lower in patients w/ heritable conditions)*<br>• Arch/descending TAAs: Intervention indicated if diameter is ≥5.5 cm*<br>*Repair indicated earlier if rapid expansion (>0.3-0.5cm/yr)<br>*Threshold for intervention varies for patients with underlying genetic aortopathies |
| **Acute Presentations** | • **Rupture**: devastating mortality. Risk factors: size, rate of expansion, female gender. Sx: triad of **abd/back pain** + **pulsatile abd mass** + **HoTN** → immediate OR<br>• **Dissection**: **pain** (chest/abdomen/back), **occlusion of aortic vessels**, **thromboembolism, discrepant blood pressure in upper extremities** | |
| **Surgical Complications** | • **Endovascular Repair:** Endoleak, graft failure, thrombosis<br>• **Open Repair:** MI, embolization, AKI, ischemic colitis | |

# Cardiology — Syncope

## 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), facial trauma (lack of warning time)
  - Risk calculators have high NPV (>95%) but do NOT replace clinical judgment
    - San Francisco Syncope Rule (SFSR): admit pt if ≥1: ECG changes or non-sinus rhythm, dyspnea, Hct<30, SBP<90, HF
- Ddx: seizure, metabolic causes (hypoglycemia, hypoxia), intoxication/meds, vertebrobasilar TIA, fall, psychiatric, autonomic failure

## ETIOLOGY AND DIAGNOSIS: (AHA/ACC/HRS: JACC 2017;70:e39)

| Etiology | Historical Features | Diagnosis | Treatment |
|---|---|---|---|
| **Reflex** (60%)<br>• Vasovagal<br>• Situational<br>• Carotid sinus syncope | Vasovagal: prodrome of dizziness, nausea, warmth, diaphoresis, pallor; a/w intense emotion, pain, stress, or prolonged standing.<br>Situational: cough, sneeze, laugh, micturition, defecation, post exercise<br>CSS: neck turning/ surgery/irradiation | • Vasovagal: can dx w/ tilt table test, not necessary if clear dx by history (JACC 1996;28:263)<br>• Carotid sinus syncope: diagnose via carotid sinus massage (if no underlying bruits or CVA history) | • Avoid provocative stimuli<br>• Isometric counterpressure maneuvers of the limbs (e.g. leg crossing, hand grip, arm tensing, Valsalva, squatting)<br>• Meds for select cases (i.e. midodrine, fludrocortisone, βB) (NEJM 2005;352:1004) |
| **Orthostasis** (15%)<br>• Autonomic failure (1° or 2°)<br>• Drug-induced<br>• Volume depletion | Prodrome of dizziness, nausea, warmth, diaphoresis, pallor<br>Risk factors for autonomic failure:<br>- 1°: PD, Lewy body, MSA<br>- 2°: DM, amyloid, spinal cord injury, chronic EtOH, B12 deficiency, meds (vasodilators, diuretics, BB, TCAs, PD meds, opiates, α-blockers) | • Orthostatic vital signs (systolic ↓≥20mmHg or diastolic ↓≥10mmHg w/in 3min of standing or on a head-up tilt test ≥60°)(Circ EP 2022;15:3)<br>- ↑HR is **NOT** part of definition<br>- Variant: smaller, but symptomatic, reduction in SBP when supine SBP is low (90-100mmHg) but drops well below this.<br>• Consider: Hct, A1C, SPEP if c/f amyloid, B12 | • Primary: **fludrocortisone** (0.05-0.3mg qd), **midodrine** (2.5-10mg bid or tid), pyridostigmine, droxidopa (for PD-associated orthostasis)<br>• Secondary: treat underlying etiology, replenish volume, adjust culprit meds |
| **Cardiac** (15%)<br>• Arrhythmia<br>• Structural (AS, LVOT obs.)<br>• Obstruction (e.g., PE, tamponade)<br>• Dissection | **No prodrome**, syncope while in sitting or supine position, palpitations, FHx or personal history of heart disease | • Causes of cardiac syncope in young people (+ ECG signs):<br>1. WPW (delta wave)<br>2. HOCM (LVH, apical TWI)<br>3. Brugada (pseudo-RBBB with coved/saddleback pattern in V1-V2)<br>4. Long QTc syndrome (QTc >500ms)<br>5. ARVC (Epsilon wave)<br>6. CPVT ( nl ECG, dx w/ exercise test)<br>• **Consider cardiac monitoring** on basis of frequency and nature of syncope events (inpatient telemetry, Holter, Zio patch, implantable cardiac monitor)<br>• **TTE only if H&P suggestive** of cardiac cause (<1% yield if no underlying heart disease and normal ECG)<br>○ ROMEO criteria: Sn 99.5%, Sp 15.4% (JHM 2018;13:823)<br>• **Consider PE** if no other apparent cause → identified in 17.3% hospitalized w/ 1st syncope (& 25.4% w/ no other apparent cause for syncope) (NEJM 2016;375:1524) | • VT- AAD or catheter ablation, consider ICD (JACC 2017:70:e39)<br>• SVT (Less common)- If evidence of accessory pathway is found, should be treated with catheter ablation.<br>• Bradyarrythmmias- Depending on etiology of bradycardia, pacemaker therapy could be indicated<br>• AS- If all other sources of syncope are ruled out, AVR may be indicated |
| **Neurologic** (<10%)<br>• Seizure<br>• Stroke/TIA<br>• Subclavian steal | Seizure: lateral tongue biting (Sn 20-33%, Sp 96-100%), urinary/fecal incontinence (Sn 38%, Sp 57%), aura, postictal confusion; note that myoclonus after any syncopal event can be confused with seizure activity<br>Focal deficits: stroke, TIA<br>Steal: syncope after arm exercise | • Seizure: EEG<br>• Stroke: CT, MRI/MRA<br>• Steal: UENI w/ Dopplers (specify for subclavian steal)<br>• Carotid dopplers are of low clinical utility (changes management in <2% of patients) (JAHA 2014;3:e001063) | • Based on etiology, consider neurology consult and follow guideline-directed management & therapy |

# Cardiology Asx Markedly Elevated BP & HTN Emergency

**DEFINITIONS, TRIAGE, AND MANAGEMENT**: see *Outpatient CV Health* for workup (NEJM 2019;381:1843; HTN 2024;81:e94)

**Asymptomatic markedly elevated BP** (formerly HTN urgency): SBP≥180 or DBP≥110-120 mmHg w/o evidence of end-organ damage
**Hypertensive emergency**: SBP≥180 or DBP≥110-120 mmHg with evidence of end-organ damage
**Asymptomatic elevated BP:** SBP≤180 and DBP≤110 mmHg (not markedly elevated per AHA)
End-organ damage: Neuro: HTN encephalopathy (severe HA, seizure, AMS), PRES, TIA, CVA (SAH, ICH); Retinopathy: papilledema, hemorrhage; Resp/CV: flash pulmonary edema, MI, angina, Ao dissection; Heme: MAHA; Renal: AKI, hematuria

***Assess: measurement variables** (positioning, cuff size, device type, time of day); **underlying causes** (pain, anxiety, urine retention, meds (e.g. steroids), OSA, nausea, withdrawal; **adherence to prior treatment** (before aggressive overcorrection)

| | Asymptomatic Markedly Elevated BP (JHM 2018;13:860) | Hypertensive Emergency |
|---|---|---|
| Triage location | Floor vs outpatient mgmt (with close follow up) (HTN 2024) | Floor vs ICU (ICU if needs arterial line, antihypertensive gtt, or if severe end-organ damage) |
| Correction time course | **If established chronic HTN:** ↓BP no more than 25-30% over hrs-days; then to goal as outpt. If hospitalized for non-cardiac reason, worse outcomes w/ intensifying anti-HTN during admission (JAMA IM 2021;181:345-352)<br>**If no established chronic HTN:** Risks may outweigh benefits for initiating anti-HTN regimen; consider permissive HTN | MAP ↓ by 10-20% in 1st hr, further 5-15% over next 23 hrs. Reduce BP by max 25% within first hour, and to no lower than 160/100 within 2-6h; reduce to normal over 24-48h |
| Route of med administration | PO meds; avoid IV or high-dose meds (risk for AKI, stroke, MI d/t hypoperfusion) | Start with short-acting, titratable IV agents; transition to PO agents for floor/discharge |
| Suggested meds (see below) | PO: start captopril, labetalol >> hydralazine (unpredictable reflex tachy) & convert to long-acting before discharge **OR** start long-acting agents | IV: labetalol >> hydralazine (high risk of overcorrection)<br>Topical: nitro paste or patch (may be used on the floor)<br>Drips: see below |

**Disease Process-Specific Recommendations for Hypertensive Emergency**

| | BP Goal | Suggested Medications |
|---|---|---|
| ACS | SBP <140 w/in 1h; keep DBP >60 | Nitro (topical, gtt), esmolol > labetalol, nicardipine/clevidipine. No BB if LV failure w/ pulm edema, HR <60, SBP <100, shock, high-grade HB. Judicious nitro if RVMI. No nitroprusside (coronary steal) or hydral (ischemia). |
| Acute pulm edema | SBP <140 w/in 1h | Nitro (topical, gtt), nitroprusside, nicard/clevid; BBs not preferred |
| Aortic dissection | Fast!-SBP <120 & HR <60 w/in 20min | IV BB (labetalol, esmolol), followed by vasodilator (nicardipine/clevidipine) |
| Ischemic stroke | <185/110 if lysis; <220/120 if no lysis or organ damage (permissive HTN) | Labetalol, Nicardipine, Clevidipine |
| Hemorrhagic stroke | SBP >220, reduce by 25%. If SBP 180-220, target reduction to 140-160 | |
| PRES | Immediate MAP decline 20%–25% | |

**Antihypertensive Dosing – ICU**

| Agent | Dosing | Onset | Duration | Indications |
|---|---|---|---|---|
| Esmolol (IV) | 500µg/kg load (given over 1 min) + infusion 25-50µg/kg/min; then adjust by 25µg/kg/min q10-20min up to 300µg/kg/min | <1min | 10-20min | Ao dissection, CAD, peri-op HTN, avoid in ADHF |
| Labetalol (IV) | 10-20 mg load + 20-80mg bolus q10min or 20 mg load + 0.5-2mg/min infusion, adjust to goal, max dose 300 mg | <5min | 3-6h | Ao dissection, CVA, avoid in ADHF/pulm edema |
| Nitroprusside (IV) | 0.25-2µg/kg/min (dose limit to avoid cyanide toxicity), temporarily (<10min) can use up to max 10µg/kg/min | <1min | <2min | AS/LVSD and HF; avoid in ACS/CAD or CVA |
| Nitroglycerin (IV) | Start 10-30µg/min, titrate by 10-20µg/min q5-10min; max 400 µg/min (if no response by 200 µg/min = non-responder) | 2-5min | 5-10min | ACS, flash pulm edema (FPE) |
| Nicardipine (IV) | Start at 5mg/h; # by 2.5mg/h q5-15min; max 15mg/h | 5-10min | 15min-4h | SAH, CVA, Ao diss, FPE |
| Clevidipine (IV) | Start at 1-2mg/h; most respond to 4-6mg/h, max 21mg/h | 2-4min | 5-15min | SAH, CVA, Ao diss, FPE |

**Antihypertensive Dosing – Floor**

| Agent | | Dosing | Onset | Duration | Indications |
|---|---|---|---|---|---|
| Labetalol | IV | 5-20mg, followed by 10-80mg q10min prn, then use PO | 5-10min | 3-6h | Ao dissection, CVA; avoid in ADHF / FPE |
| | PO | Start 100mg q8-q12h (max: 2400mg/d) | 20min | 8-12h | |
| Hydralazine | IV | 5-20mg q15-30min until effect seen, then PO, careful of unpredictable response (10-40mg IM if no access) | 10-20min | 1-4h | Eclampsia. Otherwise, no specific indications |
| | PO | Start 10mg q6h, inc by 10-25mg/dose q2-5d | 20-30min | ~8h | |
| Captopril (PO) | | 12.5-25mg q8h (ensure q8h not TID) | 30-90min | 6-8h | Scleroderma renal crisis |
| Lisinopril (PO) | | Start 2.5-5mg qd. Inc 10mg q2w to max 40mg qd. (Can use ARB if ACEi intolerance) | 1h | 24h | T2DM, proteinuria, HF |
| Amlodipine (PO) | | Start 2.5-5mg qd. Inc 2.5mg q7d to max 10mg qd. Requires few days to take effect | 24-48h | 24h | No specific indications |
| Nifedipine (PO) | | 10-30mg TID. May cause pronounced vasodilation/orthostasis | 20min | 6-8h | Post-partum HTN |
| HCTZ (PO) | | Start 12.5mg qd (max: 50mg qd, doses >25 mg a/w electrolyte derangements) | 2h | 6-12h | CKD1-3a/b |
| Isosorbide dinitrate (PO) | | Start 5-20mg 2-3 times/d (dose TID not q8h for nitrate holiday). Mononitrate = long-acting | 1h | ~8h | Angina, ESRD, HF |

# Cardiology — Peripheral Artery Disease

## Overview (2024 Guideline)

- Definition: arterial stenosis or occlusion causing an imbalance of blood flow relative to muscular metabolism (legs > arms)
- Epidemiology: **smoking, DM**, HTN, HLD, ↑age (20% prevalence >70y), CKD, microvascular disease (Lancet 2013;382:1329)

## Clinical Presentation and Diagnosis

- Symptoms: (Circ 2006;113:e463)
  - **Classic claudication** (10-35%) - reproducible exertional pain (buttock, thigh, calf, ankle), relieved by rest (differentiate from pseudo-claudication from spinal stenosis); **atypical leg pain** (most common, 40-50%); **asymptomatic (20-50%).**
  - **Threatened limb** (1-2%): pain at rest (improved w/ hanging feet off bed or walking), ulcers at pressure points, dry gangrene
  - Rutherford classification: clinical criteria +/- objective data from treadmill test and ankle BP (JVascSurg;1997;26:517)
- Exam: arterial bruit, ↓**peripheral pulses** (palpation, Doppler), ↓cap refill, pallor on elevation, ulcers, atrophic changes, ↓hair
- Diagnostics:
  - ABI: Doppler US. Ratio of DP/PT (higher value) SBP to brachial SBP.
    - Abnormal: **≤0.9** (95% Sn and 100% Sp for detecting arteriogram-positive lesions with ≥50% stenosis). ABI ≥1.40 suggests ↓compressibility usually due to ↑calcifications (e.g., elderly, DM, ESRD)
    - If ABI ≥1.40, a toe brachial index can be used for diagnosis
  - If ABI abnormal: obtain segmental ABI with pulse volume recordings (**PVR**) to localize disease
  - Exercise testing: if high suspicion for PAD & normal resting ABIs
  - If considering endovascular or surgical revascularization: Duplex US, CTA (with distal run off), MRA, or angiography
  - Concern for chronic limb-threatening ischemia: skin perfusion pressure and transcutaneous oxygen pressure

| ABI | Interpretation |
|---|---|
| >1.40 | Noncompressible vessel (not interpretable). Due to extra-luminal vessel calcification |
| 1.00 - 1.40 | Normal |
| 0.91 - 0.99 | Borderline |
| 0.41 - 0.90 | Mild to moderate PAD |
| 0.00 - 0.40 | Severe PAD |

| Rutherford Grade | Rutherford Stage | Clinical Description |
|---|---|---|
| 0 | 0 | Asymptomatic |
| I | 1 | Mild claudication |
| | 2 | Moderate claudication |
| | 3 | Severe claudication |
| II | 4 | Rest Pain |
| III | 5 | Minor tissue loss |
| | 6 | Major tissue loss |

## Treatment

- Optimize CV risk factors (e.g., HTN, DM, HLD, weight loss), high-intensity statin, smoking cessation
- Formal exercise program
  - CLEVER-RCT: supervised exercise therapy is at least as effective as stenting (JACC 2015;12:2055)
  - ERASE-RCT: supervised exercise therapy + revascularization > exercise alone (JAMA 2015;314:1936)
- Anti-platelets: For secondary prevention. If symptomatic, **ASA** 75-162mg qd *or* **clopidogrel** 75mg qd: ↓MI, CVA, vascular death (NEJM 2017;376:32).If asymptomatic, consider ASA 81mg. **Avoid DAPT** (NEJM 2006;354:1706) unless clinically indicated, usually post-revascularization for 1-6 months. Review w/ clinical decision making algorithm (JACC 2018;71:2450).
- Anti-coagulation: rivaroxaban 2.5mg BID + ASA if symptomatic or after revascularization: ↓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: Start 100mg BID. PDE3 inhibitor w/ vasodilatory and anti-platelet effects. Adjunct for symptom relief refractory to exercise therapy/smoking cessation. Use in combination with ASA or anti platelet (Chest 2012; 142:1608). Only AHA/ACC recommended med to ↑exercise capacity (Circ 2017;135:e686). Contraindicated in HF.
- Revascularization (endovascular, surgical, or hybrid): If threatened limb and/or severe symptoms refractory to medical management. Choice of endovascular versus surgical repair depends on patient factors and anatomy (NEJM 2022;387:2305)
- Ulcers/footcare: surveillance by clinicians and patients; wound care and pressure offloading to promote healing, may need revascularization for appropriate healing; amputation if no revascularization strategy. Use WIfI (J Vasc Surg 2013; 59:220) and GLASS classification tools to guide revascularization vs amputation.

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

- Sudden decrease (<2 wk) in limb perfusion threatening viability. **Emergency** – STAT consult Vascular Surgery and Vascular Medicine
  - *Viable*: no immediate threat of tissue loss; audible arterial and venous Doppler signal, intact motor/sensory (category I)
  - *Threatened*: salvage requires prompt intervention; inaudible arterial Doppler signal, audible venous Doppler signal, motor or sensory deficits (category II)
  - *Irreversible*: inaudible arterial and venous Doppler signal, complete loss of motor function and sensation (category III)
- Etiologies: embolic (e.g., AF, endocarditis) > thrombosis (e.g., atherosclerosis, APLAS, HIT), trauma, connective tissue disease
- Precipitating factors: dehydration, HoTN, abnormal posture (i.e. kneeling), malignancy, hyperviscosity, hypercoagulability
- Presentation: (6Ps) **P**ain, **P**oikilothermia, **P**allor, **P**ulselessness, **P**aresthesia (unable to sense light touch), **P**aralysis
- Diagnosis: pulse (w/ Doppler) + neuro checks; angiography (CTA w/ run-off or arteriography)
- Treatment: anti-coagulation (UFH) ± IA lytic; endovascular or surgical repair vs thrombectomy if viable or threatened (category I and II); may require prophylactic fasciotomy if threatened (category II); amputation if irreversible (category III)
- After treatment, monitor for reperfusion acidosis, hyper-K, rhabdomyolysis, & compartment syndrome

# Cardiology — Anti-Arrhythmic Medications

| Class | Name | Mechanism | Usage | Dosing (ALWAYS check with pharmacy) | Side effects, Contraindications (CI) |
|---|---|---|---|---|---|
| IA | Procainamide (IV) | $Na^+$ channel blockade; conduction slowing; ↑action potential; also has Class III action | 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%<br>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.<br>CI: CHB, AVB, SLE, TdP |
| | **Disopyramide** (PO) | $Na^+$ channel blockade; anticholinergic effects | **HOCM** (efficacy relates to negative inotropic effect), VT, AF, Aflutter | VT: if <50kg→load 200mg x1, then 100mg q6h; if >50kg→load 200mg x1, then 150mg q6h<br>AF conversion: 200mg q4-6h<br>AF prevention: 400-750mg, divide q6h (w/ BB/CCB)<br>HOCM: 200mg q12h, CR form is oral | **Anticholinergic** side effects, **neg. inotropy,** HoTN,<br>CI: ↑QTc, HFrEF |
| IB | Lidocaine (IV)*† | $Na^+$ channel blockade; no effect on conduction; may ↓action potential | **VT, VT/VF arrest, polymorphic VT** | 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<br>Maintenance: **1-4mg/min (30-50mcg/kg/min)** | Bradycardia, junctional arrhythmia, HoTN, angina, AMS, tremor, seizure, dysarthria, paresthesias, tinnitus, dizziness |
| | **Mexiletine** (PO) | PO analogue of lidocaine | **VT** | Load: 400mg x1<br>Maintenance: 200mg q8h | Tremor, n/v, dizziness, GI upset<br>CI: cardio shock, 2°/3° AVB |
| IC | **Flecainide** (PO)* | $Na^+$ channel blockade | **pAFib** ("pill in the pocket"), rarely ventricular arrhythmia | Pill in the pocket: 200mg (<70kg) or 300mg (>70kg)<br>Sinus rhythm maintenance: 50-150mg bid<br>Requires inpatient initiation & concomitant BB | **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)<br>Sinus rhythm maintenance: 225-425 bid ER q12h<br>Requires inpatient initiation & concomitant BB | **Ventricular arrhythmia** (↑risk if structural heart dz), GI sx, dizzy.<br>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<br>Maintenance: 2-21mg/min IV (25-300mcg/kg/min) | Same as other β-blockers |
| | 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, pheo, anxiety | IV: 0.5-1mg load→1-3mg every several hours<br>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) | AMS, HoTN |
| III | Amiodarone (IV/PO)† | $K^+$ channel blockade, slows repol. Multiple effects incl class Ia, II, & IV. **Class II (i.e. βB) = fastest effect** | **SVT, VT, pulseless VT/VF, (off-label) AFib** | Pulseless VT/VF: **300mg IV** push, may repeat 150 mg IV push every 3-5min as needed<br>WCT:<br>- IV: **150mg x1** (repeat q10 min prn)→**1mg/min x6h (360mg)→0.5mg/min x18h (540mg)**<br>- PO: total **8-10g** over days (200-400mg, BID-TID)<br>- Maintenance: 100-200mg PO QD-BID<br>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 or pre-excitation**.<br>CI: ↑QTc, SSS, 2°/3° AVB, sx bradycardia, cardiogenic shock |
| | Sotalol (IV, PO)* | Nonselective β1/β2 antagonist, K+ channel blockade | **AFib, VT** | IV: 75mg q12h, may ↑dose by 37.5mg q3d (max: 300mg/d)<br>PO: 80mg q12h, may ↑dose by 40mg q3d (max: 320mg/d). Adjust dosing interval in renal impairment<br>Requires inpatient initiation | ↑QT, typical effects of β-blockade; CI: CrCl <40, LVH, HFrEF, ↑QTc, hypoK |
| | **Ibutilide** (IV) | K+ channel blockade, prolongs action potential | **AFib, AFlutter** | >60kg: 1mg over 10min; can repeat x1 in 10min;<br><60kg: same except dose is 0.01mg/kg | ↑QT, TdP, HA |
| | **Dofetilide** (PO)* | | **AFib, AFlutter**, SVT | Initial dose 500mcg bid max<br>Decrease dose by 50% if CrCl<60 or QT prolonged<br>Requires inpatient initiation | ↑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 | **AFib, AFlutter**, SVT, MAT, angina, HTN | IV: 0.25mg/kg (≤25mg) q15min prn; gtt **5-15mg/h**<br>PO: 120-320mg ER qd or ≤480mg/d IR q6h | ↓ inotropy<br>CI: SSS, bradycardia, 2°/3°AVB, VT, AF + WPW, HoTN, pulm edema, HFrEF (<40%), ADHF |
| | Verapamil (IV, PO) | | | IV infusion: 5-10mg, repeat q15-30min PRN (≤20-30mg); gtt 5-20mg/h if needed<br>PO : 120-360mg ER qd or ≤480mg/d IR q8h | |
| Misc. | Digoxin (IV, PO)*† | Na/K ATPase inhibition→Ca influx. AV node conduction suppression, ↑vagal tone, +inotrope | **AFib, Aflutter**, HFrEF, SVT | IV (initial): IV 8-12**mcg**/kg IBW divided in 3 doses (50% load then two 25% doses q4-8h or use "Digoxin IV load panel" in Epic) Max 1.5mg in 24hr. Check level 6-24h after load (goal <1.2 in AF)<br>Oral (maintenance): 0.125-0.25mg qd | Dig tox (>2ng/mL usually), N/V, hyperK, visual disturbance, atrial tachycardia with AVB, PVCs, VT, VF. CI: VF. Dig tox tx: digibind |
| | Adenosine (IV) | AV node conduction slowing, coronary vasodilation | **Treating SVT** Differentiating re-entry SVT from a-fib/flutter/tach | IV (admin over 1-2sec, PIV): 6mg→12mg after 1-2min if ineffective, repeat x1 if needed, flush immediately. **Half dose** if patient using central line, or receiving carbamazepine or dipyridamole. | Arrhythmia, angina, HA, flushing, GI distress, dyspnea.<br>CI: 2°/3° AVB, SSS, sx brady, lung dz, asthma, s/p OHT |

*Renal dosing required

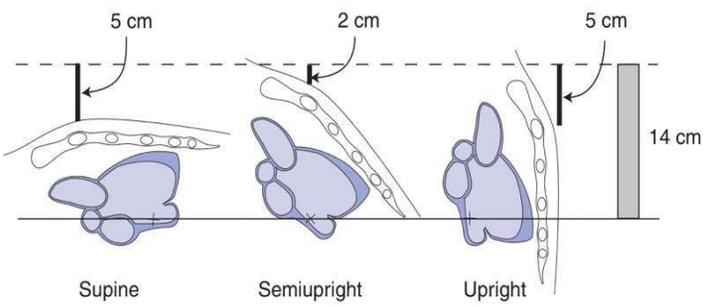
†Green = commonly used drugs at MGH

# Cardiology — Telemetry and Physical Exam

## Brief Physical Exam Tips (McGee 2021)

| | Pathophysiology | Tips for measurement | Sens/Spec & Likelihood Ratios | Diagnosis |
|---|---|---|---|---|
| **JVP** | Jugular vein is a central vein that is contiguous with the right atrium and acts as a proxy for right atrial pressure | The angle changes measurement (see below); veins have respiratory variation & rise w/ hepatojugular reflex; nonpalpable. Add 5cm to approximate RA pressure; Reported in cm H2O | For measured CVP >8cm: Sn 47-92%, Sp 83-96%, +LR 8.9, -LR 0.3. Preop JVD +LR 11.3 for postop edema/+LR 9.4 for postop MI (if no rx) | Elevated in HF, tension PTX, tamponade, SVC syndrome, tricuspid stenosis and large CV waves in TR |
| **S3** | "Sloshing" of blood as it hits compliant ventricular wall. Occurs after S2; Early to middle diastolic sound | Heard best with bell at apex in left lateral decubitus | For EF <30%: Sn 68-78%, Sp 80-88%; +LR 4.1, -LR 0.3 | Associated with HF; can be physiological in younger patients |
| **S4** | Flow of blood from atrial kick into stiff ventricular wall; late diastolic heart sound, right before S1 | Heard best with bell at apex in L lateral decubitus. Longer interval b/w S4/S1 → poorer prognosis | For elevated L heart filling pressure: Sn 35-71%, Sp 50-70% | A/w LVH, acute MI, cardiomyopathy; can be normal in older adults; Cannot have in AF (no atrial kick) |
| **Peripheral edema** | Occurs when capillary hydrostatic pressure overwhelms ability of lymphatics to drain fluid from the instertitum; the lymphatic valves fail and the lymphatic vessels dilate. | +1 = 2mm depression, quick rebound<br>+2 = 3-4 mm depression, quick rebound<br>+3 = 5-6 mm depression, rebound <1min<br>+4 = 8mm+ of depression, rebound 2-3min<br>Measure in dependent area (i.e. sacrum for bedbound pts) and assess how far up extends | For elevated L heart filling pressure: Sn 10% Sp 93-96%, nonsignificant LR | Volume overload (if in context of heart failure) |
| **RV heave** | An indication of RV (or, rarely, LA) enlargement | Felt best over left parasternal region; if heel of hand rises with systole, there is heave | Limited; for pHTN, Sn 42%/Sp84%, nonsig LR | RV enlargement (incl pHTN, RV volume overload), or MR, rarely LA enlargement |
| **AS murmur** | Turbulent flow across stenotic AV; as severity increases & ejection takes longer, murmur becomes later & diminishes S2 | Loudest R 2nd intercostal space, radiates to R carotid 1st as severity increases | For mild or worse AS: Sn 79-90%, Sp 85-87%, +LR 10.5, -LR 0.1. For severe AS Sn 83-98%, Sp 71-76%, +LR 3.5, -LR 0.1 | AS; DDx increased Ao flow without obstruction (anemia, fever, pregnancy, nonobstructing calcification) |

## JVP Measurement Pearls (NEJM 2020;383:e132)




**EJV** is a good proxy for IJV in most patients; good reliability for discriminating high from low CVP (Chest 2011;139:95)

**Distance from sternal angle to right atrium** is variable between patients and across positions (JGIM 2002;17:852 median 5 cm at 0°, 8 cm at 30°, 10 cm at 60°); interpret JVP in clinical context and trend while intervening on volume status (**McGee 2021**)

**Sonographic JVP** when bedside JVP difficult to visualize; correlates well with right atrial pressure (Ann Intern Med 2022;175:344, JASE 2023;36:278). Lay patient 30° - 45°, scan with vascular probe in short-axis just above the clavicle to find IJV and CA and slide cranially to find the IJV meniscus, then usual JVP calculation. Alternatively, if the IJV is distended (> carotid) with minimal pulsation just above the clavicle at 45°, can call JVD (JASE 2023;36:278). Easy rules: if IJ > carotid in short axis at 90°, rules in elevated RAP. If IJ < carotid in short axis at 30°, rules out elevated RAP

## Cardiac Telemetry: "Running the tele"

**Step 1:** Locate the name of the desired patient on the telemetry monitor and select their telemetry strip.
**Step 2:** Once on patient's telemetry strip, select "**Patient Data**."
**Step 3:** Click "**Event Review**" which will show you any abnormal events the patient had since being placed on telemetry. From this list, click the desired episode of choice.
**Step 4:** After clicking on the desired event, you will have multiple options to choose from:

- 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 (e.g. abrupt HR jump from sinus into AVNRT)
- Calipers: interactive calipers used to **calculate intervals** on telemetry strip

While a patient is on telemetry, review indication daily and discontinue if not using monitoring for clinical decision-making (see Monitoring and Prophylaxis page)

# 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 seen when $SpO_2$ <80%)
- ↑WOB (nose flaring, retractions, grunting, tripod stance, diaphoresis)
- Obstruction (wheezing, stridor)

### Dyspnea DDx

- CV: MI, HF, VHD, arrhythmia, tamponade, PE, PHT
- AIRWAYS: asthma, COPD, mucus plugging, angioedema, anaphylaxis, vocal cord dysfxn
- 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

### Approach

1) **Confirm code status**
2) **Low threshold to call Rapid Response for assistance**
3) **Assess airway, breathing, circulation, sit up pt, confirm access**
   - **Place on supplemental $O_2$**: NRB to start, can always wean later
   - **Red flags (RICU STAT)**: Inability to protect airway due to AMS, pooling secretions, hemoptysis, life-threatening hypoxemia despite supplemental $O_2$ ($SpO_2$ <80%, $PaO_2$ <55mmHg), severe hypercapnia despite BiPAP, tiring out (↑WOB, progressive hypercapnia), RR >35.
   - **Temporize**: suction, head-tilt chin lift (preferred if no concern for C-spine injury) vs jaw-thrust to open airway, bag-mask ventilation (enough volume to see chest rise, about 500-600mL/breath; 10 breaths/min). If the use of bag-mask will be prolonged & pt unresponsive, consider OP airway prior to intubation
4) **Initial workup**:
   - **CXR** (order STAT, must call x**6-3050**): look for new infiltrate (aspiration, PNA), pulmonary edema, lobar collapse (mucus plug), PTX. For read, call **x4-1533.** If nl, consider: ischemia, PE, acidosis
   - **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
   - **ABG**: Worrisome if $PaCO_2$ >45mmHg (*poor ventilation*), $PaO_2$ <60mmHg (*poor oxygenation*), pH <7.25. MD or RT can obtain.
   - **Additional studies based on clinical suspicion**: CT-PE (if stable to travel), TTE (acute valvular dz, RV strain), US (PTX/effusion)
   - You can always call RICU to **consult** if you are concerned about a patient with no "Red Flags."

**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 following information ready prior to intubation

**- Code status & urgency/acuity of decline**

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

**- Aspiration risk**: NPO, last meal, risk factors

**- 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

### Treatment

- **Supplemental oxygen therapy** (see *Oxygen Delivery Therapies* for more detail):
  - NC: for every liter increase in O2, approx. ↑$FiO_2$ 0.03/L (max: 6L = 0.40 FiO2, dependent on $V_e$/entrainment)
  - NRB: can give $FiO_2$ ~0.90, but in tachypneic patients, $FiO_2$ ~0.60 *(due to entrainment of room air)*
  - HFNC: $FiO_2$ 0.6 to 1.0 at 10-60 L/min (humidified air); ↓90d mortality vs NIPPV for pts with hypoxemic 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, $P_aCO_2$ >45mmHg
- **Intubation**: see **red flags** above

### Disease Specific Treatment

- **CHF**: CPAP, IV diuresis, nitrates (*paste or drip*, if BP room)
- **Asthma**: nebulizers (albuterol 2.5-5mg q20min or stacked DuoNeb), steroids (IV methylpred 125mg q6h), Mg (2g/20 min). Trial BiPAP; however, if RR remains >25, VBG w/ nl or rising CO2, AMS, or bradycardia, discuss intubation. Decreasing wheeze can portend respiratory collapse (sign of worsening air movement/increased bronchoconstriction).
- **COPD**: BiPAP, stacked DuoNebs, steroids (IV methylpred 60-125mg); abx if 2/3: #sputum volume, purulence, dyspnea
- **Hemoptysis (massive)**: place pt in lateral decub, bleeding lung side **DOWN**; volume resuscitate, reverse coagulopathies, call IP and RICU STAT.
- **Mucus plugging**: airway suctioning, percussion/chest PT, guaifenesin, place pt in lateral decubitus, good lung side down
- **PE** (see *VTE Treatment);* if high suspicion and no contraindication, start **empiric AC** (LMWH therapeutic faster vs UFH gtt). **Consult PERT x4-7378**
- **PTX**: if unstable, bedside needle thoracostomy (**STAT page Thoracic Surgery**, *14G angiocath, 5th intercostal space at mid-axillary line or 2nd intercostal space at mid-clavicular line*); then chest tube (Thoracic Surgery or IP)
- **Pleural effusion**: Consult IP for thoracentesis (see *Thoracentesis* )
- **Opioid overdose**: Narcan 0.4-2mg IV/IM q2min, observe response, up titrate 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**: MGH Pathway 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, if persistent may require epi gtt.
- **ACS** (*see ACS)*: ASA 325mg, atorvastatin 80mg, nitrates (SL/nitro paste/nitro gtt), heparin, consult Cardiology

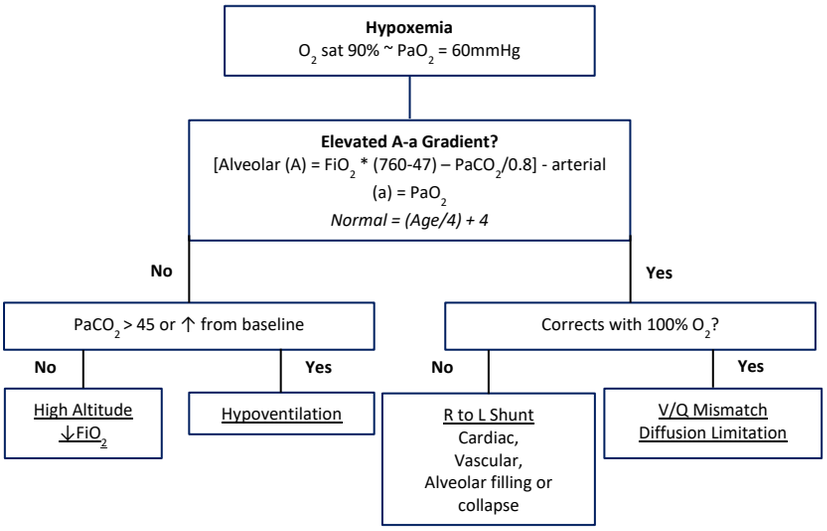
*Lauren Nguyen*

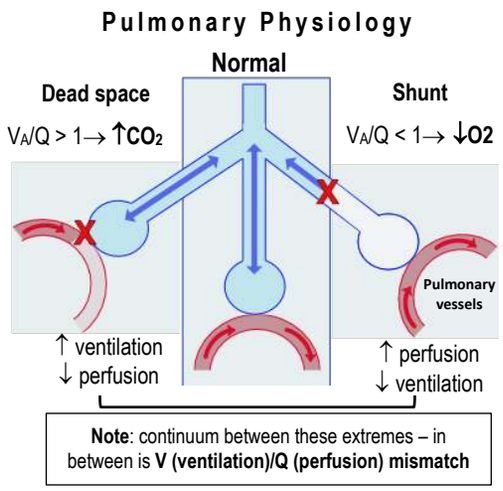


Suggest an Edit

# Pulmonary & Critical Care — Hypoxemia & Hypercapnia

**Respiratory Failure**: inability to oxygenate (deliver $O_2$) or ventilate (blow off $CO_2$). Can be **hypoxemic** ($PaO_2$ <60mmHg), **hypercapnic** ($PaCO_2$ >45mmHg), or both. **P:F Ratio** (P=$PaO_2$/F=$FiO_2$) 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.

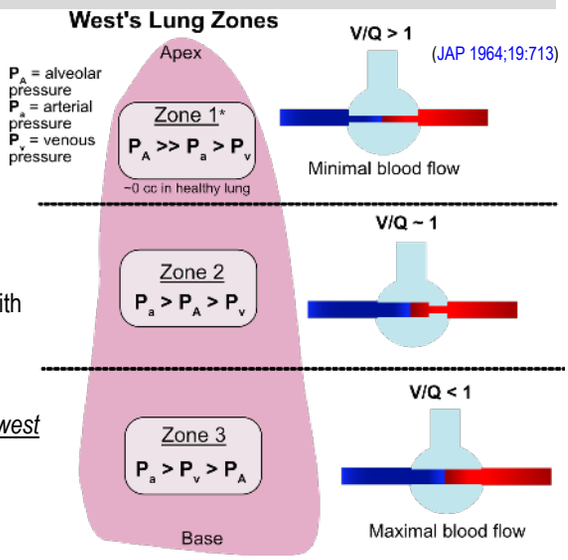



*Pulse oximetry may *over*estimate SpO2 in pts with darker skin, delaying detection of hypoxemia. Consider ABG (JAMA 2022;182(7))

## Hypoxemic Respiratory Failure

- **Hypoventilation & low $FiO_2$**: decreased $O_2$ delivery to lungs
- **V/Q mismatch**: imbalance in delivery of oxygenated air & blood flow
  - ↑ pulmonary vasoconstriction can ↓hypoxemia by ↓Q to poorly ventilated regions to ↑V/Q matching (ratio closer to 1)
  1. ***FOCAL* alveolar infiltrates**: pus (PNA), edema, hemorrhage (DAH), cells (cancer), aspiration, lipids/protein (PAP)
  2. **Airway**: asthma, COPD, bronchiectasis
  3. **Vascular**: pHTN, PE
- **Shunt**: flow of blood through lung without encountering oxygenated air, *"perfusion without ventilation"* (severe V/Q mismatch). Will not improve with supplemental oxygen *(refractory hypoxemia)*
  1. ***DIFFUSE* alveolar infiltrates**: above + ARDS
  2. **Alveolar collapse**: PTX, atelectasis, mucus plug
  3. **Intra-cardiac/pulm shunts**: PFO/ASD/VSD *(↑PEEP worsens this by ↑west zones 1&2 = ↑RV afterload)*, AVM (e.g., hepatopulmonary syndrome)
- **Impaired diffusion (↓DLCO)**: hypoxemia worse w/ exertion, 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), myxedema coma
- **"Can't breathe" (↓$V_A$)**:
  1. ↑ **Dead space**: airspace not participating in gas exchange; *"V without Q"*
     - Anatomic: (~150cc upper airway air without perfusion) + alveolar (*AKA West Zone 1)* ~0 normally; in disease, capillaries get destroyed or compressed → ↑$V_D$
     - Parenchyma: emphysema, ILD/fibrosis, HF, PNA, ARDS
     - Airway: asthma/COPD, CF, bronchiectasis, OSA, tumor, high PEEP
     - Vascular: severe PE → wasted V due to blocked Q
  2. **Chest wall/pleural constraints → ↓ lung volume**: effusion/fibrosis, obesity, kyphosis/scoliosis, abd distension, PTX
  3. **Neuromuscular** (Neurol Clin 2012;30:161): most apparent if unable to augment ventilation (eg in ALS: more often see ↓pCO2 secondary to hyperventilation); trend at bedside with single breath test (non-intubated pts) or 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
- **↑$CO_2$ production ($V_{CO_2}$)**: ↑WOB, fever, seizure, sepsis, steroids, overfeeding, thyrotoxicosis

### Acid-Base Interpretation

**Hypercapnia**→ Resp acidosis (↑pCO2)
- Acute: HCO3 ↑ by 1 (per pCO2 ↑ 10)
- Chronic: HCO3 ↑ by 3-4 (per pCO2 ↑ 10)

**Hypocapnia**→ Resp alkalosis (↓pCO2)
- Acute: HCO3 ↓ by 2 (per pCO2 ↓ 10)
- Chronic: HCO3 ↓ by 5 (per pCO2 ↓ 10)

# Pulmonary & Critical Care — Non-Invasive Oxygenation/Ventilation

## CONVENTIONAL OXYGEN DELIVERY DEVICES

**Recommendations for Supplemental Oxygen Therapy**

- Target $SpO_2$ 91-96%: Recent trials of $O_2$ targets found no benefit to higher/lower targets in critical illness (ARJCCM 2021, PILOT)
- Lower target ($SpO_2$ 88-92%): Baseline hypercapnia or at risk for hypercapnic respiratory failure (COPD, OHS, OSA, decreased central respiratory drive, neuromuscular respiratory disease)
- Higher Target (~$SpO_2$ ~100%): CO poisoning, cluster headaches, sickle cell crisis, pneumothorax

| Mask Type | Flow (LPM) | $FiO_2$ (%) | Notes | Aerosol? |
|---|---|---|---|---|
| Nasal Cannula | 1 - 6 | 24 - 44 | $FiO_2$ ↑ by 0.04 per L<br>Allows patient to eat/speak. Consider humidification if >3LPM | N |
| Oxymizer | 1 - 15 | 24 - 60 | 20mL reservoir allows for higher $FiO_2$ compared to NC | N |
| Simple Facemask | 6 - 10 | 40 - 60 | Flow rates < 6LPM lead to re-breathing of $CO_2$ | N |
| Face Tent (Shovel mask) | 10 - 15 | 28 - 100 | Less claustrophobic, $FiO_2$ variable (lots of leakage) due to lack of nose seal.<br>Use if stable $O_2$ needs, not good for high FiO2 delivery<br>Offers humidification without a mask | Y, if humidified |
| Non-Rebreather | 10 - 15 | 60 - 90 | **Consider first for acute hypoxemia (easily accessible)**<br>↑$FiO_2$ with tachypnea and ↑Vt due to entrainment<br>Titrate flow rate to avoid reservoir bag collapse (<1/3) on inspiration | N |
| Venturi | Variable | 24 - 60 | Color-coded adapters determine flow and $FiO_2$ independent of ventilatory demand.<br>Useful for set $SpO_2$ goals (e.g., COPD)<br>**NOT** for acute respiratory distress | Y, if >15 LPM or humidified |

**Racial disparities in pulse oximeter measurement:** ↓accuracy in Black patients → ↑ in occult hypoxemia (NEJM 2020, Annals of ATS 2022)

## HIGH FLOW NASAL CANNULA (HFNC) & NONINVASIVE POSITIVE PRESSURE VENTILATION (NIPPV) NEJM 2022;387:1688-98

| | HFNC | NIPPV (CPAP + BiPAP) |
|---|---|---|
| Parameters | **Flow**: 10-60 LPM (up to 80 LPM at some institutions)<br>**$FiO_2$ (%)**: 21-100<br>PEEP generated with a closed mouth is about 1 cm of water pressure for 10L flow | **CPAP:** constant level of pos. pressure; targets oxygenation<br>**BLPAP (or BiPAP™):** provides positive inspiratory pressure (IPAP) above PEEP with each pt-triggered breath; targets ventilation *and* oxygenation |
| Physiologic Effects | **Oxygenation:** ↑ delivery of $O_2$, some PEEP<br>**Ventilation:** ↑ventilation (↓dead space during expiration)<br>**Other:** Humidification ↑mucociliary clearance of secretions | **Oxygenation:** ↓atelectasis, ↓upper airway obstruction, ↓WOB (& $O_2$ consumption)<br>**Ventilation:** ↑tidal volume and minute ventilation (via IPAP)<br>**Other:** ↓venous return (↓LV & RV preload), ↓LV afterload |
| **Clinical Scenarios** | | |
| Acute hypoxemic respiratory failure (AHRF) | - Mixed evidence for **HFNC** in NON-hypercapnic resp. failure. May ↓intubation, but no Δ in mortality or LOS vs standard O2 tx (Cochrane 2020).<br>- Consider HF 1st if ILD, ARDS physio, and may be non-inf to BIPAP in PNA. Can be used as rescue in asthma or in pts that can't tolerate BiPAP to help w/ dead space wash and intubation eval | **NIPPV** may ↓mortality & ↓intubation (JAMA 2020;324:57).<br>- Consider if also significant hypercapnia, e.g. OHS, neuromuscular failure (e.g. ALS, MG).<br>Caveats: (AJRCCM 2017;195:67-77)<br>**- P:F < 150**: ↑ death vs. up-front intubation<br>**- TV > 9-9.5 cc/kg IDW:** ↑death, ↑intubation |
| Acute COPD exacerbation w resp. acidosis | **Strong indication for BiPAP** (ERS/ATS: ERJ 2017;50) to off-load respiratory muscles, counteract dynamic hyperinflation, ↑ventilation a ↓mortality, ↓intubation, & ↓ LOS (Cochrane Rev 2017). Asthma can be treated similarly but there is less evidence to support. | |
| Acute cardiogenic pulmonary edema | **NIPPV (BiPAP / CPAP)** ↓intubation, ↓in-hospital mortality by ↓ WOB, ↑FRC, ↓LV / RV preload, ↓LV afterload (NEJM 2008;359:142; Cochrane Rev 2013) | |
| Post-extubation | Extub. to NIPPV or HFNC to ↓ reintubation and post-extub. resp. failure in ↑risk pts: COPD, obesity (JAMA 2016;316:1565) | |

**Contraindications to NIPPV:**

- **Risk of delay**: emergent indication for intubation, acute life-threatening non-respiratory organ failure
- **Risk of aspiration (d/t gastric insufflation)**: cannot clear secretions, AMS if pt cannot remove mask (*exception*: AMS due to hypercapnia)
- **Risk of injury**: PTX (can induce tension physiology), recent esophageal anastomosis or tear, cannot tolerate ↓preload from ↓venous return, recent facial trauma/surgery

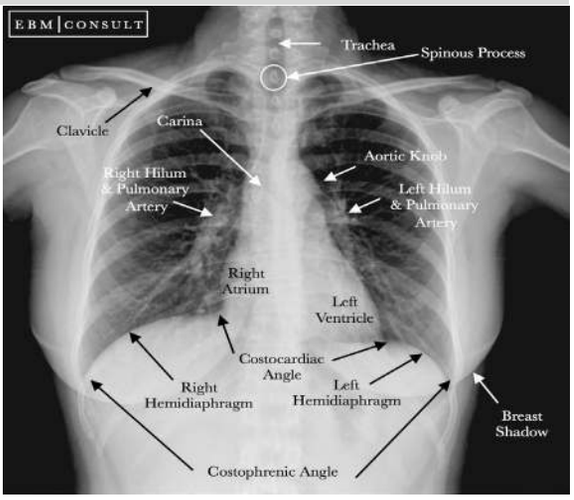
**Monitoring for and Preventing Failure**

- Risk of failure varies based on cause (15-20% COPD exacerbations, 40-60% AHRF) and ↑ with severity of respiratory failure
- **ROX index:** tool for prediction of HFNC failure & monitoring for need for intubation in pts with pneumonia (AJRCCM 2019;199:1468-76)
- **HACOR score**: tool for prediction of NIPPV failure & need for intubation (ICU Med 2017;43:192-9)
- **Sedation**: IV Precedex, Haldol, and Zyprexa can be considered to help pts tolerate NIPPV w/o suppressing resp drive (see *sedation)*

**BiPAP/HFNC on the floor**: huddle with nursing and RT (also notify SrOn). Trial BiPAP or HFNC for 2-3 hours and assess response; consider ABG/VBG to assess oxygenation/ventilation. If no improvement, discuss escalation of care to ICU
**REMEMBER: BiPAP/HFNC MUST NOT DELAY AN INDICATED INTUBATION!**

# Pulmonary & Critical Care — Interpretation of Chest Imaging

## CHEST X-RAY




**Systematic approach to CXR (ABCDEF approach):**

**1. (A)**ssess technical quality and **(A)**irways:

- Rotation: ensure spinous processes bisect btwn medial end of clavicles
- Lung volumes: adequate inspiratory effort is 9-10 posterior ribs
- Penetration: good when vertebral bodies visible behind cardiac silhouette
- Airways: look for narrowing, deviation, foreign bodies. ↑ITP pushes trachea away (PTX). ↓ITP pulls trachea towards (atelectasis/plugging).
- **(A)**lways compare previous studies.

**2. (B)**ones/soft tissue: subcutaneous air, rib fractures, cervical ribs

**3. (C)**ardiac Silhouette (mediastinum/hilum): AP films ↑ cardiac silhouette. CT ratio=max cardiac width/max thoracic width, >50% suggests cardiomegaly (only PA films). Widened mediastinum generally >8cm (watch out for rotation).

**4. (D)**iaphragm (gastric bubble): left hemidiaphragm is usually lower than right. Flattening of diaphragm sensitive for emphysema.

**5. (E)**ffusions: blunting of CP angle. Small effusions seen 1st on PA lateral. Fluid not seen on upright chest until >250ml. ↓ sensitivity when semi recumbent or supine. Can assess free flowing vs. loculated effusions on lateral decubitus view (free flowing will track equality on horizontal plane vs. loculated will not).

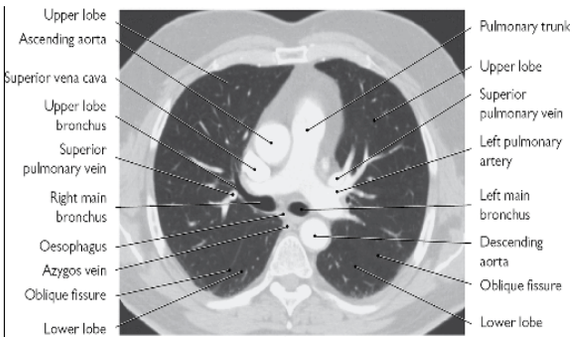
**6. (F)**ields (lung fields) & **(F)**oreign bodies (lines/drains): Look for focal vs. diffuse processes PTX, PNA, pulm edema. Look for s*ilhouette sign* (loss of the normal visible border of an intrathoracic structure) that indicates pulmonary density. Look for lines/tubes (*see Interpretation of Common Studies*). ETT ideally 3-5cm from carina, adjust if not.

## CT CHEST

- To characterize abnormal CXR w/ cross-section or w/ suspicion for pathology despite unrevealing CXR
- HRCT (thin-section CT, <2mm): for diagnosing diffuse lung path. Must be non-con. Includes expiratory, inspiratory, prone and supine images.

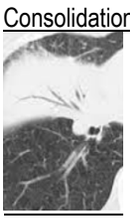
**Approach to interpretation:**

- Review scout imaging: gives anatomic overview.
- Review lines/tubes, extra-thoracic abnormalities.
- Mediastinum/Heart/Vessels: soft tissue window: LV>RV normally. Diameter of main PA should be < ascending aorta (PA >= 29 mm: PPV 97% for pHTN, Pulm HTN radiology). Cor calcium visible on non-con.
- Airways: review in soft tissue and lung windows. *Inspiratory HRCT*= round trachea; *Expiratory HRCT*= "D-shaped" trachea.

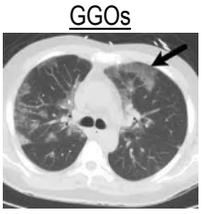



| Common Findings | Definition | Associated Etiologies |
|---|---|---|
| Consolidations | Complete filling of alveoli, dense ↑ attenuation obscuring underlying lung architecture +/- air bronchograms | PNA > Malignancy |
| GGOs | Partial filling of alveoli +/- interstitium, appears as hazy ↑ lung attenuation (light gray) that does NOT obscure underlying architecture | Infxn, edema, blood, fibrosis, malignancy |
| Tree-in-Bud (AJR 2009; 193:472) | Branching linear opacities & nodules that represent dz'd lobular bronchioles or bronchiolitis & filling with fluid, pus, mucus, or tumor emboli | Infxn (incl. TB), CTD, ABPA, malignancy, endarteritis, CF |
| Emphysema | Airspace enlargement > 1-2 cm in diameter. "Bleb" = similar, but < 1-2 cm | COPD, congenital, spontaneous |
| Mosaic Attenuation | Patchy ↓ and ↑attenuation areas due to air trapping, decreased perfusion, GGOs. Air trapping identified as worsening with expiratory films. | HP, obstruction, CTEPH, Infxn, Edema/hemorrhage |
| Honeycombing | Clustering of cystic airspace disease. Microcystic <4mm, macrocystic >4mm | ILD: NSIP <4mm; IPF>4mm |
| Subpleural Retic. | Linear opacification of the inter/intralobar septae around 1 cm from pleura. | UIP>NSIP, normal w/ aging |
| Atelectasis, Effusion | Atelectasis enhances w/ con, resolves proned. Effusion more homogeneous | |

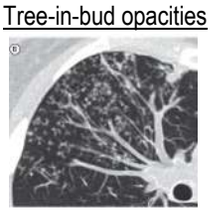
Consolidations



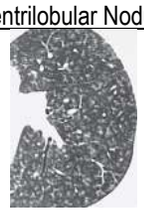
GGOs



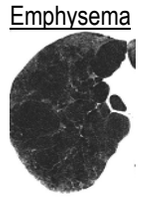
Tree-in-bud opacities



Centrilobular Nodules

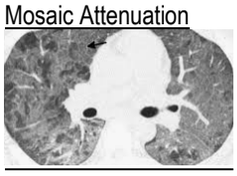


Emphysema

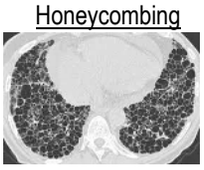


Atelectasis & Eff.

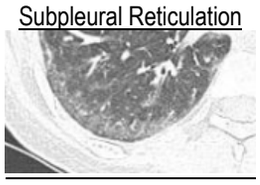
Mosaic Attenuation



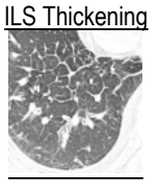
Honeycombing



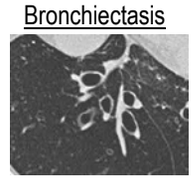
Subpleural Reticulation



ILS Thickening



Bronchiectasis



## Pulmonary Function Testing (PFTs)

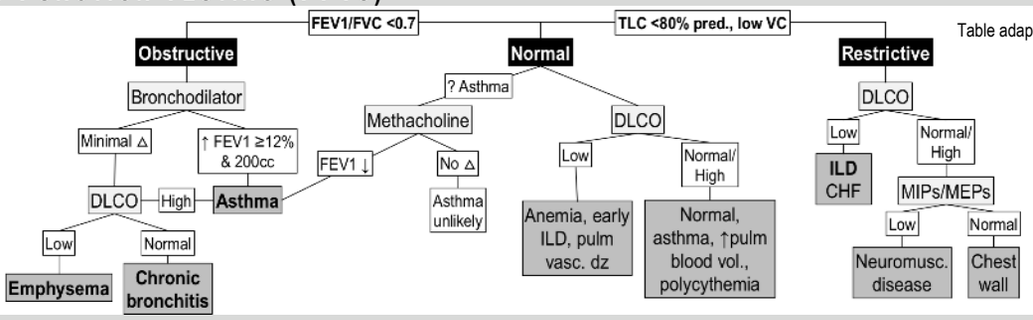



Table adapted from Up To Date

## Asthma (GINA 2024, NAEPP 2020)

*note: dx criteria currently vary between societies (e.g., ATS vs GINA)

Definition: heterogeneous condition with resp sx (wheeze, SOB, chest tightness, cough) and variable expiratory airflow limitation

| | |
|---|---|
| Symptoms | Resp sx (wheeze, SOB, cough, chest tightness) that vary over time & intensity, worse @ night/early AM |
| Triggers | Exercise, cold air, allergens, irritants (e.g., smoke), viral respiratory infections, drugs (ASA, NSAIDS, β-blockers) |
| Diagnosis: Spirometry/peak expiratory flow (PEF) | (+) Bronchodilator response (↑FEV1 or FVC ≥12% & >200mL or PEF (*if no spirometry avail) ≥20%), improvement w/ ICS x4wks (↑FEV1 ≥12% & >200mL or PEF ≥20%), variability in BID PEF x 2wks (avg variability >10%), worsens w/ methacholine (FEV1 ↓≥20%), high variability between visits (FEV1 ≥12% & >200mL or PEF ≥20%) |
| Inflammatory phenotype | Type 2 inflammation high (↑eos, ↑FeNO, ↑IgE, atopy; consider biologics in severe asthma) T2-low (increased neutrophils, often steroid-refractory) |
| New-onset adult cases ddx: systemic disease (ABPA, EGPA, systemic mastocytosis), occupational asthma (10-25%; NEJM 2014;370:640), ASA-exacerbated resp. disease (7%, esp. if nasal polyps; J Allergy Clin Immunol 2015;135:676) | |

### Outpatient Care

- **Controller + reliever**: stepwise based on severity (*below*); step up if not controlled; step down if well controlled >3mo
  - Note: *GINA guidelines rec ICS-containing controller*; no longer rec. tx w/ SABA a/w ↑allergic responses & airway inflammation, ↓response, & overuse a/w ↑severe exacerbations, though NAEPP still recs SABA PRN
  - May be some phenotypes w/ low eos. inflamm. (<2% in sputum) in whom ICS ↓effective (NEJM 2019;380:2009)
- **Non-pharm interventions**: smoking cessation, regular physical activity, vaccines, breathing exercises, weight loss if obese

NEJM 2019;238:2020; NEJM 2018;378:1865; NEJM 2018;378:1877; AJRCCM 2005;171:129; Chest 2006;129:246; Lancet 2011;377:650

| *Adapted from GINA 2024* | **Mild intermittent STEP 1** | **Mild persistent STEP 2** | **Moderate persistent STEP 3** | **Severe persistent STEP 4** | **Severe STEP 5** |
|---|---|---|---|---|---|
| **Symptom frequency** | Infrequent | 2-7d/week | Most days | All day | All day |
| **Nighttime awakenings** | <2/month | 3-4n/month | >1/week | Nightly | Nightly |
| **Exacerbations** | 0-1/year | >2/year | >2/year | >2/year | >2/year |
| **Baseline FEV1** | Normal | Normal | 60-80% predicted | <60% | <60% |
| **Controller (Preferred)** | **PRN low-dose ICS-formoterol** | | **Low-dose ICS-formoterol** | **Medium-dose ICS-formoterol** | **Medium-dose ICS-formoterol + LAMA** *Consider: phenotypic assessment, high dose ICS-formoterol, +/- biologics** |
| *Controller alternative* | *Low-dose ICS whenever using PRN SABA* | *Low dose ICS* | *Low dose ICS-LABA*** | *Med/high dose ICS-LABA* | *Same as above, can consider LTRA, azithromycin, and oral steroids* |
| **Reliever (Preferred)** | PRN low dose ICS-formoterol | | | | |
| *Reliever alternative* | *PRN SABA or ICS-SABA* | | | | |

***Biologics**: anti-IL4R-alpha, anti-IgE, anti-IL5, anti-TSLP. **LABA w/o ICS ↑ rates of death (CHEST 2006;129:15; NEJM 2010;362:1169).

### Asthma Exacerbations

**OUTPATIENT:** short course pred. 40-50mg x5-7d + controller/reliever regimen, consider 4x controller ICS if mild (NEJM 2018;278:902)

**INPATIENT:** assess severity of exacerbation (VS, mental status, $SpO_2$, WOB, PEF <50%), consider VBG/ABG if severe

Severe: ↑resp drive→↑RR→↓$pCO_2$, nl/↓pH suggest resp. failure. If sig hypoxemia, consider resp. failure vs PTX, PNA, PE, plug, etc.

| Floor Patient | ICU Patient (Thorax 2003;58:81; J Clin Med 2019) |
|---|---|
| - **Bronchodilators**: albuterol (2.5-5g) ± ipratropium (0.5-1.5mg) q20m x3<br>  - DuoNebs in ED a/w ↓admit (Cochrane Rev 2017)<br>- **Steroids**: **pred 40-60mg** total **x5-7d** (Cochrane Rev 2016)<br>- **$O_2$** 93-95%; >95% increases $pCO_2$; Thorax 2011;66:937) | - **Bronchodilators**: albuterol + ipratropium**, Methylpred 125mg IV q6h**<br>- **NIV**: short trial, typically BiPAP<br>- **Rescue therapies**: Mg IV 2g, continuous albuterol (CAB). Less data: IV β-agonist, ketamine, inhaled anesthetic, Heliox. *ECMO=last resort*<br>- **Mechanical ventilation:** large ETT (8+), ↑insp flow rate (80-100L/min), ↓$V_T$ (6-8cc/kg), ↓RR (10-14), ↓PEEP, paralysis; **Goal:** max exp. phase, minimize hyperinflation, permissive hypercapnia |
| - **If impending respiratory failure**: stacked DuoNebs (x3/h), methylpred IV 60-125mg q6h, Mg IV 2g/20min, transfer to ICU | |

### Asthma/COPD Overlap (ACO) (GINA 2024;131; AJRCCM 2017;196:375; NEJM 2015;373:1241)

- Some patients have persistent airflow limitation together with clinical features c/w both asthma & COPD
- **ICS-containing treatment is essential**; Also need LABA and/or LAMA. Can escalate to triple therapy, biologics

# Pulmonary & Critical Care — COPD

**DEFINITION**: persistent respiratory symptoms (dyspnea, cough, sputum production, recurrent wheezing, exacerbations) d/t abnormalities of airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that lead to persistent airflow obstruction (GOLD 2025)

## Diagnosis and Staging (GOLD 2025; AJRCCM 2017;195:557)

1. **Diagnosis**: respiratory sx + fixed obstruction w/ FEV1/FVC <0.7 or <LLN on spirometry post-bronchodilator
2. **GOLD *Grade*** (1-4) is defined by severity of airflow limitation (FEV1% of predicted); helps establish prognosis & guide non-medical therapy
3. **GOLD *Group*** ("ABE") is defined by exacerbations & sx guide therapy (mMRC, CAT score)
4. **Other testing**: lung volumes, DLCO (<60% a/w sx, exercise, ↓health), exercise test (6MWT), α1-antitrypsin

| | mMRC 0-1 CAT<10 | mMRC ≥ 2 CAT ≥ 10 |
|---|---|---|
| ≥ 2 exacerbations OR ≥1 admission | E | |
| 0-1 exacerbations wo admission | A | B |

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

## Differential

**Pre-COPD:** respiratory symptoms with structural lung lesions (emphysema) and/or physiological abnormalities w/o airflow obstruction. **Preserved Ratio Impaired Spirometry (PRISm):** respiratory sx w/ normal ratio (FEV1/FVC > 0.7) but impaired FEV1 (< 80) after bronchodilation. **Chronic bronchitis**: overlapping condition; chronic cough + sputum > 3 months / yr for 2+ years. **Asthma**: see "*PFTs and Asthma.*" **Bronchiectasis**: large vol of purulent sputum, a/w bacterial infxn & bronchial dilation on CXR/HRCT. **Obliterative bronchiolitis**: consider after lung/BM transplant, HRCT: hypodense areas on exp.
**Diffuse pan-bronchiolitis**: Asian pts, chronic sinusitis, CXR/HRCT: diffuse small centrilobular nodular opacities & hyperinflation

## Management of Stable COPD (GOLD 2025; NEJM 2019;381:1257); Chart w/list of common inhalers: American Lung Association

**Pharmacologic interventions**:↓symptoms, ↓risk/severity of exacerbations, ↑health status, survival

| | GOLD A | GOLD B | GOLD E |
|---|---|---|---|
| **Starting tx:** | Bronchodilator (LABA or LAMA) | LABA+LAMA | LABA+LAMA. If eos>300 or asthma: LABA+LAMA+ICS |
| **Rescue therapy:** | Short-acting bronchodilator | | |
| **Escalate to:** | Dyspnea: LAMA + LABA<br>Exacerbation: LAMA + LABA | Dyspnea: Switch inhaler device or molecules. Nebulizers may be helpful in severe COPD.<br>Exacerb: Eos >100: LAMA+LABA+ICS (Lancet RM 2018;6:117), consider adding biologics (i.e. dupilumab (BOREAS Trial); FEV1 <50% + bronchitis, eos <100: Roflumilast (Lancet 2015;385:857); former smokers: Azithro (Lancet RM 2014;2:361; Cochrane Rev 2018) | |
| **Notes** | - Long-acting>short-acting unless occ. dyspnea<br>- Tiotropium may slow decline in FEV1 in early COPD (NEJM 2017;377:923) | - LABA+LAMA > mono-therapy (Chest 2014;145:981; Cochrane Rev 2015) | - Include ICS if features of asthma<br>- LAMA+LABA+ICS > LAMA+LABA to ↓exacerbations, but may ↑PNA (TRIBUTE; IMPACT; ETHOS). *Consider d/c ICS if persist. exacerbations or PNA**<br>**if eos >300, high risk ↑exacerbations w/ d/c of ICS* |

**Non-Rx interventions**: **Smoking cessation:**↓mortality; Annals 2005;142:233, **Vax:** Flu, COVID, PCV20, Tdap, Zoster, RSV
**Lung CA screening**: annual low-dose CT (age 50-80 & ≥ 20 pack-years & has smoked in last 15y) (USPSTF 2021)
**Pulmonary rehab (GOLD B/E)**: ↑QoL, ↑exercise capacity (Cochrane Rev 2015), possibly ↓mortality (JAMA 2020;323:1813)
**Home $O_2$**: if $PaO_2$ ≤55 or $SpO_2$ ≤88% (if $PaO_2$ ≤59 or $SpO_2$ ≤89 in pulmonary HTN, Hct >55%, or CHF) for goal SpO2 >90%; reassess in 60-90d
**Nocturnal NIPPV**: if daytime pCO2 >53 & nocturnal $SpO_2$ ≤88% (despite 2L $O_2$) or recent exacerb. & persistent $PaCO_2$ >53 (↓risk of readmit & mortality: JAMA 2017;317:2177); **Interventional therapies:** bronchoscopic lung reduction (emphysema + hyperinflation), bullectomy, **Lung transplant:** progressive dx despite max rx; non-surgical candidate if BODE index 5+, frequent exacerb, low FEV1 (20-25%), or rapidly ↑ BODE)

## COPD Exacerbation (ERS/ATS: GOLD 2025, ERJ 2017;49)

- **Hx**: ↑**dyspnea**, ↑/Δ sputum, and/or ↑cough < 14d; ask re: prior exacerbations/steroids/intubations/abx; DDx: URI/PNA, CHF, VTE
- **W-up**: CXR, ABG/VBG, ECG, trop, NT-proBNP, sputum cx, RVP, CRP, PE (in 25% severe exacerb w/o clear trigger: Annals 2006;144:390)

**Management**:

- **$SpO_2$ 88-92%**: hyperoxia → ↓vent. via Haldane effect & hypoxic vasoconstriction→ ↑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, but ↑PNA risk
  - If severe: IV methylpred 60-125mg q6-q12x72h, budesonide neb.
- **NIPPV**: if resp acidosis (pH < 7.35 & PaCO2 > 45), severe dyspnea, ↑WOB, pers hypoxemia. ↓mortality, intub., LOS (Cochrane Rev 2004).
- **Intubation:** NIV failure, s/p arrest, aspiration/vomiting, HDUS
- **Antibiotics**: controversial; ↓mortality but challenging to identify who will benefit (Chest 2008;133:756; Coch Rev 2012)
  - Indicated if: ↑all 3 cardinal sx, 2/3 w/↑sputum **purulence**, or require NIPPV/mechanical ventilation
    - CRP may be useful (NEJM 2019;381:111). Procalcitonin may be useful but ↑mortality when used in ICU (Eur Resp Rev 2017;26; ICM 2018;44:428)
  - Choice: based on PsA risk, prior sputum cx, resist. ⊖ PsA RFs: CTX, FQ, amox/clav, azithro, doxy. Å PsA RFs: FQ, cefe, pip/tazo.
    Duration: 5-7d inpt; 3-5 outpt (vary by drug)
    - Concurrent CAP: treat by CAP guidelines
- **Antivirals**: oseltamivir if flu A, even if ≥48-72h
- **VTE ppx**

## Inhaled Therapies for Asthma & COPD

| Class | Example Meds |
|---|---|
| Short-acting β-agonist (**SABA**) | Albuterol, levalbuterol (SE: ↑HR; levalbuterol more selective so less HR effect but $$) |
| Short-acting muscarinic antagonist (**SAMA**) | Ipratropium (Atrovent) (SE: 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 (NEJM 2022;387:533; RM 2020;166)

| | |
|---|---|
| **Definition** | Permanent airway dilatation from recurrent infxn/inflammation |
| **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<br>**Impaired immunity**: ↓mucus clearance (CF, 1° ciliary dyskinesia [PCD]), immunodeficiency (e.g., HIV, CVID, ↓IgG)<br>**Obstruction**: foreign body, tumor, COPD, tracheomalacia/tracheobronchomegaly, Marfan's, radiation<br>**Systemic disease**: RA, Sjogren's, SLE, IBD, A1AT**; Idiopathic** = ~50% |
| **Workup** | **Dx:** 1) productive cough most days/week, 2) exacerbations, **and** 3) CT w/ ≥1 of: bronchial diameter > adj artery (signet-ring sign)**,** thickened bronchi w/ lack of tapering (tram track sign), radiographically visible airways in perimeter<br>**Initial**: High-resolution CT, PFTs, CBC/diff, Ig levels, sputum cx (bacterial, mycobacterial, fungal)<br>**As indicated**: CF eval (gene/sweat $Cl^-$ testing), Aspergillus IgE, ANA, RF/CCP, SSA/SSB, A1AT, HIV, Ig levels; consider nasal NO (PCD), pneumococcal vaccine titers (often low), bronch w/BAL, colonoscopy (IBD), pH/motility testing |
| **Natural Hx** | Exacerbations, ↓ in $FEV_1$, PsA colonization → worsening disease; prog. w/ Bronchiectasis Severity Index or FACED |

| Chronic Management | Acute Exacerbation |
|---|---|
| non-CF: Eur Resp J 2017;50; AJRCCM 2013;188:647; Thorax 2019:74 \| CF: AJRCCM 2013;187:680 | |
| • **Airway clearance**: nebs (albuterol, 3% NaCl), chest PT (acapella, vest)<br>  ○ CF: add DNase to neb bundle; not effective in non-CF<br>• **Antimicrobials/anti-inflammatories**:<br>  ○ Non-CF: Long-term azithro ↓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<br>  ▪ Intermittent abx (FLQ, β-lactam, tobra) in pts w/ ≥3 exacerb/y ↓exacerb but ↑abx resistance (Coch Rev 2022)<br>  ▪ Trial inhaled abx if PsA colonization & ≥3 exacerb/y<br>  ○ CF: azithro + inhaled tobramycin (for PsA; alt: aztreonam, colistin)<br>• **Disease specific treatment**:<br>  ○ Non-CF: treat underlying cause if found; consider PPI/$H_2$ blocker<br>  ○ CF: CFTR mut→ defective $Cl^-/HCO_3^-$ transport on airway surface<br>  ▪ Potentiators open CFTR channel (**ivacaftor**); correctors bring CFTR to surface (**lumacaftor, tezacaftor, elexacaftor**)<br>  ▪ Dual/triple tx→ long-term FEV1 benefits (NEJM 2015;373;220; NEJM 2017;377:2013; NEJM 2018;379:1599; NEJM 2019;381:1809)<br>  ▪ **Pancreatic enzyme supplementation**, vitamins ADEK | • **Sx**: Δ in ≥3: cough/sputum, purulent sputum, dyspnea, fatigue, hemoptysis, or high clinical suspicion (Eur Resp J 2017;49)<br>• **Obtain resp cx prior to abx and CXR**<br>• Micro: *PsA, S. aureus* > *H. flu, Moraxella, Burkholderia*; treat *Stenotrophomonas*, *Achromobacter* as pathogenic; *Aspergillus* in CF not always pathogenic<br>• **Abx**: use previous Cx data as guide; **tx 10-14d**<br>  ○ No prior cx data: empiric FLQ (for PsA)<br>  ○ If prior R-PsA: IV abx; 2 agents – β-lactam & either FLQ or IV tobra (dosed qd)<br>  ▪ *No great evidence for double coverage of PsA though is standard of care* in CF<br>  ○ If β-lactamase⊕ *H flu* or *Moraxella*: amox/clav, CTX, doxy, macrolide, or FQ<br>  ○ Cont. home azithro ± tobra (practice varies)<br>• Steroids only w/ concomitant asthma, COPD, ABPA<br>• Continue chronic treatment (airway clearance) |

## HEMOPTYSIS (Chest 2020;157:77; Am Fam Physician 2022;105:144)

| | |
|---|---|
| **Definition** | Expectoration of blood from lower respiratory tract. **Non-massive**: if minimal (<30mL) & benign (eg. infxn/bronchiectasis): observe. If active, recurrent, >1w: CT → bronch. **MASSIVE HEMOPTYSIS** (>500mL/d or >100mL/h) = **life-threatening emergency** with mortality 50-80%. Asphyxiation, NOT exsanguination, is mechanism of death (maximum pulmonary blood volume ~500mL) |
| **Etiology** (common & life-threatening) | • **Airway**: bronchitis, bronchiectasis (incl. CF), masses (usually 1* lung CA), trauma (incl. foreign body)<br>• **Pulmonary parenchyma**: infection (PNA, abscess, TB, aspergilloma), vasculitis (ANCA, anti-GBM, immune-complex, drug-induced; see *Vasculitis* and *Autoantibodies*), coagulopathy, endometriosis, inhalation injury, collagen defect, sarcoid, pulmonary hemosiderosis, trauma<br>• **Pulmonary vascular**: PE, CHF (esp. if on AC), mitral valve dz, bronchovascular fistula, aneurysm, AVM |
| **Work-up** | 1) Consider pseudohemoptysis from other sources (GI or nasopharyngeal)<br>2) **CXR (most important),** CBC, coags, U/A (vasculitis, anti-GBM), sputum Cx, CTA chest (if stable), bronch<br>3) Consider NT-proBNP, D-dimer, ESR/CRP, C3/C4, ANA, ANCA, anti-GBM, APLAS, IGRA/AFB, RVP |

**LIE PATIENT WITH SIDE OF SUSPECTED BLEED DOWN** (preserve gas exchange in unaffected lung)
- Ensure hemodynamic stability, active T&S, correct coagulopathy. Trial inhaled TXA nebs (Chest 2023;163:1176)
- **STAT RICU** (x6-3333) → control airway if dyspneic, rapid bleed, largest possible ETT (8mm+), suction as blood can fill ETT
- **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. *If refractory*, call thoracic surgery
- Consider pulse dose methylprednisolone if vasculitis suspected

## DIFFUSE ALVEOLAR HEMORRHAGE (Chest 2010;137:1164)

**Presentation**: hemoptysis (can be absent in 1/3), cough, fever, dyspnea, diffuse radiographic opacities, abnormal gas exchange
**Etiology**: disruption of alveolar-capillary basement membrane from: capillaritis (rheum, drugs, idiopathic), bland hemorrhage (AC, ↓plt, HF), or diffuse alveolar damage (ARDS, infxn, PE, drugs)
**Workup**: CXR, CT (diffuse GGO central > peripheral), BAL (serial washings show ↑blood), labs guided by clinical picture
**Management:** Primarily supportive. Manage hypoxemia and treat underlying etiology, eg.: Capillaritis/AI syndromes: Systemic glucocorticoids (pulse dose IV methylpred 500-1000mg/d up to 5 doses w/ taper), cyclophosphamide, rituximab ± plasmapheresis. Excess AC/bleeding disorder: reverse AC. (Int J Mol Sci. 2021;22:793)

*Alexandra Miller*



Suggest an Edit

# Pulmonary & Critical Care — Interstitial Lung Disease

## OVERVIEW (JAMA 2024;331:1655)

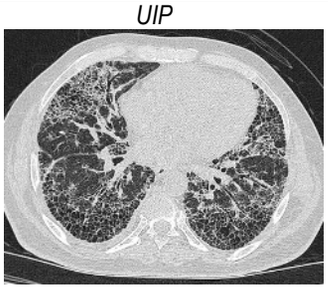
Heterogeneous group of lung diseases defined by the replacement of normal lung with varying degrees of inflammation and fibrosis.
**Presentation**: progressive dyspnea, non-productive cough, hypoxemia (esp. w/exertion); some w/ constitutional sx (AIP, HSP, COP)
**History**: tempo, hx CTD/IBD/malig/thoracic XRT, rheum dz, meds, exposures (chemicals, dust, humidity, pets, barns), smoking, FHx
**Exam**: "velcro-like" crackles, inspiratory squeaks, clubbing, e/o CTD (heliotrope rash, Gottron's papules, mechanic's hands, synovitis, foot/wrist drop, sclerodactyly, sicca), vasculitic rash, extrapulmonary manifestations of systemic dz (sarcoid, amyloid, IBD, cancer)

## ETIOLOGIES: idiopathic (most common ILD) & known (e.g., connective tissue disease or CTD-ILD) (ATS/ERS: AJRCCM 2013;188:733)

| Idiopathic Interstitial PNAs (IIPs) | Connective Tissue Disease[8] | Exposure-Related | Granulomatous |
|---|---|---|---|
| Idiopathic Pulmonary Fibrosis (IPF)[1]<br>Idiopathic Non-Specific Interstitial PNA (NSIP)[2]<br>Acute Interstitial PNA (AIP)[3]<br>Cryptogenic Organizing PNA (COP)[4]<br>Respiratory Bronchiolitis-ILD (RB-ILD)[5]<br>Desquamative Interstitial PNA (DIP)[6]<br>Lymphoid Interstitial PNA (LIP)[7] | Scleroderma<br>Sjogren's syndrome[7]<br>MCTD<br>Polymyositis/Dermatomyositis<br>Anti-synthetase syndrome<br>Rheumatoid arthritis<br>Lupus | **Organic**: grain, mold, birds, hay *(cause HSP)*[9]<br>**Inorganic**: silica, asbestos, coal, metals (*causes pneumoconiosis*)<br>**Drugs**: nitrofurantoin, MTX, amiodarone, pembro/nivo (see: PneumoTox)<br>**Radiation** | Sarcoidosis[10]<br>Hypersensitivity pneumonitis[9]<br>Mycobacterial disease<br>Fungal disease<br>Langerhans cell histiocytosis[11] |

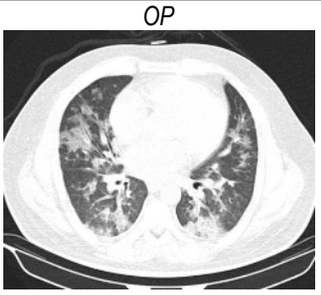
**Radiographic Associations:** (91% sensitive, 71% specific JAMA 2024;331:1655), *(ARCCM 2002;165:277)*[7]
[1] *Usual interstitial pneumonia* (**UIP**) pattern: heterogenous subpleural/basal predominant, honeycombing, traction bronchiectasis
[2] *Non-specific interstitial pneumonia* (**NISP**) pattern: lower lobe predominant, reticulation/GGOs predominantly in periphery, micronodules
[3] *Diffuse alveolar damage* (DAD) pattern: diffuse, bilateral, central>peripheral ground glass or consolidative opacities
[4] *Organizing PNA* (OP) *pattern:* bilateral peripheral, perilobular consolidations with subpleural sparing
[5] *Respiratory-bronchiolitis* (RB) pattern: centrilobular nodules (usually in upper zones), GGOs, interlobular septal thickening
[6] *Desquamative interstitial pneumonia* pattern: homogeneous or patchy GGOs in mid/lower lung zones
[7] *Lymphoid interstitial pneumonia (LIP) pattern:* diffuse, centrilobular GGOs, septal & bronchovascular thickening, thin-walled cysts
[8] May be associated with **any** pattern (UIP & NISP most common, LIP rare but seen in Sjogren's Syndrome)
[9] May be associated with RB pattern (see [5]), with progression to traction bronchiectiectasis, honeycombing, centrilobular nodules
[10] Peribronchovascular, hilar, subpleural nodules (granulomas)
[11] Stellate nodules, thick-walled cysts, bullae

*UIP*

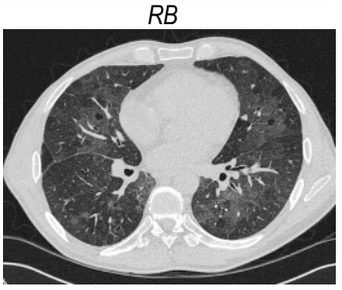


*NSIP*

*OP*



*RB*



## DIAGNOSTIC EVALUATION

- Requires multidisciplinary evaluation and discussion
- **Exclude** fungal/atypical bact. infxn, esp. in immunocompromised pts; consider sputum bacterial/fungal culture, HIV/hepatitis testing
- **General Approach**: **remove potential environmental causes**. If improvement, no further w/u. If not, **assess for systemic dz**. If unlikely systemic dz, HRCT (see Radiographic Associations above), consider bronch and/or biopsy based on findings
- **Labs**: CBC, CMP, C3/C4, CK/aldolase, myositis and hypersensitivity panels, auto-Abs: ANA, RF/CCP, RNP, Ro/La, Scl-70, ANCA, GBM
  **Lung biopsy:** If dx unclear (atypical presentation or c/f malignancy) + Δ tx. Bronchoscopic transbronchial cryobiopsy is less invasive than VATS. Not helpful if known CTD. If definite UIP, rec against (high morbidity, ↑exacerbations) (AJRCCM 2018;198:e44).
- **Assess Severity:** 6 minute walk test and PFTs: Restrictive (↓TLC, ↓FRC, ↓RV; FEV1/FVC normal to ↑); ↓DLCO can be early sign

## TREATMENT

- **IPF** (AJRCCM 2015;192:e3): Acute exacerbations: ddx includes infxn, PE, HF; send BNP, trop, procal, d-dimer, blood cultures, *S. pneumo* & *Legionella* urinary antigens, extended RVP. Treat with **pred** ~1mg/kg/d & broad-spectrum **abx** (vanc/cefe/azithro) X 7d.
  Chronic therapy: Antifibrotics: **pirfenidone** (TGF-βi; NEJM 2014;370:2083), **nintedanib** (TKi; NEJM 2014;370:2071), common SE: nausea, fatigue, diarrhea. Promising data for new PDE4 inhibitors (NEJM 2022; 386:2178). All ↓FVC decline, may not Δ overall survival. GERD tx to benefit lung disease is *not* recommended (ATS 2022;205:18)
- **NSIP**: remove inciting exposures, tx underlying condition; can be **steroid-responsive** (pred 0.5-1mg/kg/d or pulse methylpred if hospitalized); **2nd agent** (AZA, MMF, Rituximab, Cytoxan) 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 (see ARDS)
- **Systemic Sclerosis:** Nintedanib, MMF, Cytoxan, Rituximab, and/or Tocilizumab depending on symptoms (JAMA 2024;331:1655)

**Oxygen Therapy** (AJRCCM 2020;202:121): long-term O2 therapy (>15hrs/day) for severe hypoxemia at rest (SpO2 < 88%), consider ambulatory O2 for severe exertional hypoxemia (SpO2 ≤ 88% on 6 min walk test)
**Transplant Referral** (JHLT 2022;40:1349): Any ILD: FVC<80% or DLCO<40% predicted; decline in FVC by ≥ 10% over 2 years, decline in DLCO by ≥ 15% over 2 years, or decline in FVC ≥ 5% over 2 years w/ worsening dyspnea or radiographic progression; supplemental O2 at rest or exertion. OR: IPF: Time of dx. Inflam ILD: progression of dz despite tx. CTD or familial: early referral.

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Suggest an Edit

# Pulmonary & Critical Care — VTE Diagnostics

## Clinical Manifestations

### Signs/Symptoms

#### Deep Vein Thrombosis (DVT)

- S/Sx: pain, warmth, erythema or cyanosis, edema (esp. asymm.), palpable cord, superficial venous distention, Homan's sign (sudden dorsiflexion of ankle w/ knee flexed → pain in upper calf); can be asymptomatic (Arch IM 1998;158:2315)
- 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 → requires immediate thrombolysis)
  - May-Thurner syndrome: anatomic variant → compression of L common iliac vein by R iliac artery → can present w or w/o DVT → acute LLE swelling, venous claudication, severe venous insufficiency
- Central venous catheters are most common cause of upper extremity DVT (PICC > CIC > Ports) (Hematology ASH 2014;1;306).
- Ddx: superficial thrombophlebitis, cellulitis, arterial occlusion, varicose veins, lymphedema, ruptured Baker cyst, chronic venous insufficiency (Arch IM 1998;158:2315)

#### Pulmonary Embolism (PE)

- Sx: **dyspnea**, **pleuritic CP**, **cough**, orthopnea, leg swelling/pain, syncope, hemoptysis, diaphoresis, palpitations, **can be asymptomatic** (Chest. 1991;100(3):598)
- Signs: **↑RR, ↑HR,** hypoxemia, hypotension, rales, S4, ↑P2, ↓breath sounds, JVD, fever, wheezing, RV heave, pleural friction rub, S3
- **EKG Δs**: sinus tach, atrial arrhythmias (AF, AFL), RAD, RBBB, inf. Q, anterior STΔs/TWIs, S1Q3T3 (ERJ 2005;25:843)

### Risk Factors: Virchow's triad of venous stasis, vascular injury, hypercoagulability (Circulation 2003;107:I9; ERJ; 2020;41:543)

| Strong | Moderate | | Weak | |
|---|---|---|---|---|
| - Hospitalization for HF or AF (w/in 3 mo)<br>- MI (w/in 3mo)<br>- Hip/knee replacement<br>- Lower limb fracture<br>- Major gen. surgery/trauma<br>- Spinal cord injury | - Thrombophilia<br>- Prior VTE<br>- Arthroscopic knee surgery<br>- CVC (Lancet 2013;382:311)<br>- Estrogen-containing meds<br>- Pregnancy (postpartum)<br>- IVF<br>- Malignancy<br>- Some forms of chemotherapy<br>- HIV | - CHF (JACC 2020;75:148)<br>- Resp. failure, asthma (ERJ 2014;43:801)<br>- Paralytic stroke<br>- IBD, nephrotic syndrome<br>- Infection/sepsis (Chest 2015;148:1224)<br>- Autoimmune disease, IBD<br>- EPO<br>- Blood transfusions | - Bed rest >3d<br>- Immobility due to sitting (e.g. airplane, car)<br>- Increased age<br>- Lap surgery (e.g. CCY)<br>- Obesity (Circ 2008;117:93)<br>- Pregnancy (antepartum) | -CKD (J Thromb. Haemost 2014;12:1449)<br>-Diabetes<br>- Cirrhosis (Thromb Haemost 2017;117:139)<br>- Varicose Veins |

## Diagnosis/Risk Stratification (ASH: Blood Adv 2018;2:3226; ESC: EHJ 2019;41:543; JAMA 2018;320:1583)

- **Pre-test prob**: Wells for LE DVT and PE, Constans' for UE (Thromb Haemost 2008;99:202), Geneva for PE
  - If **low** (or mod. DVT), can r/o w/ D-dimer (see below) or PERC score for PE; if D-dimer ⊕ need further eval. If **high** (or mod. PE) → imaging
  - Wells score discriminates risk of VTE for outpatients; not sufficient to r/o DVT in hospitalized patients (JAMA 2015; 175; 1112)
- **DVT diagnosis**: venous Doppler US of lower or upper extremity (LENI, UENI).
- **PE diagnosis**:
  - CTPA: study of choice; may also detect alternate dx (NEJM 2006;354:2317)
  - V/Q scan: validated (JAMA 1990;263:2753). Performed if c/i to CTPE, **Need nl CXR** (minimize other causes of V/Q mismatch), cannot be done urgently; often hard to interpret bc of indeterminate scans
  - LENIs: if suspect PE, unable to CT or V/Q, & ⊕, can treat; if ⊖, 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-in-transit or new RV strain can provide presumptive diagnosis if needed rapidly
  - ABG: can see hypoxemia (↑A-a gradient, normal in ~20%), resp. alkalosis
- **PE risk scores: PESI** (PE Severity Index): **prediction of morbidity/mortality in patients w/ newly diagnosed PE,** sPESI (simplified PE Severity Index), and BOVA for PE complications in HDS patients.

### Interpreting D-Dimer (nl <500)

- If nl and 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 x10 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/infxn, ESLD, CHF, CKD, aortic dissection, trauma, surgery

| Risk | Risk Stratification | | | |
|---|---|---|---|---|
| | HDUS: shock, SBP <90, cardiac arrest | Elevated Cardiac Biomarkers[a] | Imaging Evidence of RV Dysfunction[b] | PESI Class III-V and/or sPESI≥1 |
| **High*** | + | + | + | +[c] |
| **Intermediate-High** | - | + | + | + |
| **Intermediate-Low** | - | One of two + | | + |
| **Low** | - | - | - | - |

*Syncope and clot in transit are also considered high risk

[a] Biomarker Evidence: ↑hs-TnT: ≥14 in age <75 & ≥45 in age >75 may ↑NPV (ERJ 2015;45:1323); ↑NT-proBNP (ERJ 2014;43:1669)

[b] Imaging Evidence: CT: RV/LV diameter ratio >0.9 (*JCM 2024;13:257*); TTE: RV Overload/Dysfunction - enlarged RV, flattened IVS, mod/severe TR, McConnell's Sign (RV free wall akinesis sparing apex; Circ 2008;118:517), ↓TAPSE (JEM 2020;58:449).

[c] Hemodynamic instability and confirmed PE on CTPA and/or RV dysfunction on TTE = high-risk. PESI classes/cardiac biomarkers unnecessary.

# Pulmonary & Critical Care — VTE Management

## MANAGEMENT OF VTE (CHEST: Chest 2021;160:545); ESC: EHJ 2020;41:543); ASH: Blood Adv 2020;19;4693)

### Proximal DVT (popliteal, femoral, iliac vv.)

**Anti-coagulate** (unless contraindications), regardless of sx
Agent: **DOAC** > VKA > LMWH; if malig.: **DOAC > LMWH** > VKA
(for dosing & info on choosing agent, see AC and AC Mgmt sections)
Duration: at least 3mo for all. **Individualized decision** to extend >3 mo balancing risk factors of recurrence and bleeding risk:
- 6-12 mo: persistent but reversible risk factors
- indefinite: low bleeding risk AND non provoked, active cancer, other non-modifiable risk factors (IBD, nephrotic syndrome, etc.)

If AC stopped/declined, consider ASA for 2° prevention (extended phase AC), but ASA is **inferior** to reduced dose DOAC which should be offered first (NEJM2017; 30:367; CHEST2021;160:2247).

**IVC filter:** Only if contraindications to AC (e.g. active bleeding, recent/planned high bleeding-risk procedure, major trauma, acute ICH)
- **Remove** once no longer needed (typical implantation time ~1-2mo; JVIR 2011;22:1522). Complications incl. IVC thrombosis, acute/recurrent DVT or PE, filter migration/erosion/fracture

### Distal DVT (calf: ant./post. tibial, peroneal vv.)

**Serial imaging vs. anticoagulation**
Serial imaging: if asymptomatic, low risk for extension, or high risk for bleeding
- **Repeat US** at 1-2w (1/3 will extend; ↓risk in muscular veins: soleal, gastrocnemius)

Anti-coagulate (same AC regimen as proximal DVT) if:
- 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, thrombus extends into or towards proximal veins within 1-2 cm.
- Patient prefers treatment over serial imaging

**Post-thrombotic syndrome:** Long-term sequelae of DVT due to poor venous flow. Treatment with compression +/- endovascular/surgical intervention (Cardiovasc Diagn Ther 2016;6;623).

**UE DVT** (NEJM 2011;364:861): brachial, axillary, subclavian; ↓complications vs. LE DVT. Tx same as LE DVT. If PICC/CVC (catheter-associated), no need for catheter removal if needed/functional/⊘infected. **AC**: use for catheter associated and/or proximal vein (e.g., axillary, subclavian) clots; **Thrombolysis**: generally not recommended, but consider in select pts (e.g., severe sxs) (JCM 2020;9:2069)

**Bleeding risk**: low = 0 risk factors (1.6%/3mo; 0.8%/y after 3mo); mod = 1 (3.2%/3mo; 1.6%/y); high = ≥2 (12.8%/3mo; ≥6.5%/y)
Risk factors: 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

**Further diagnostic testing in unprovoked VTE**: age-appropriate cancer screening (found in 5% within 1y; Annals 2017;167:410), hypercoagulability w/u limited during acute episode

***Superficial vein thrombosis**: Tx w/reduced-dose DOAC for 45 days in some patients (Chest 2021;160;545), otherwise, heat/elevation*

### High Risk PE / Intermediate Risk PE / Low Risk PE

**PERT c/s (x47378)**: for **intermediate-high or high risk, consider SHOCK c/s (p11511) for high risk**

**Resuscitation**:
- Cautious IVF: can trial if CVP low, but ↑RV distention →RV ischemia + septal bowing→↓LV SV →↓CO (RV death spiral)
- Inotropes: if low CO, consider dobutamine
  Vasopressors: norepi, epi, or vaso
- $O_2$: HFNC preferred. *Mech vent high risk*: HoTN from induction & PPV → ↓venous return → ↓RV CO, ↑RV failure
- Circulatory collapse/arrest: Pulse = tPA
  Pulseless = TNK and CPR for 15 minutes to ensure circulation; eval for VA ECMO

**Anticoagulation**: LMWH vs UFH (w/ bolus)
**Thrombolysis**: systemic, though some cases warrant catheter-directed tPA thrombolysis
**Embolectomy**: if thrombolysis contraindicated or fails; can be catheter-directed; surgery if all options contraindicated/fail or if clot in transit in RA/RV, PFO

**Anticoagulation**: LMWH preferred > UFH (faster time to therapeutic range) unless impending hemodynamic collapse, thrombolysis (or CrCl <30 or severe obesity).
- Intermediate-high risk: transition to long-term AC agent after 48-72h of stability
- Intermediate-low risk: transition after 24h

**Thrombolytic therapy (catheter-directed preferred over systemic) in select pts**: (Circ 2011;123:1788) No strict guidelines, indications include: developing shock, resp failure, mod/severe RV dysfunction on TTE (RV hypokinesis, RVSP >40) w/ ↑↑ hs-TnT/NT-proBNP
- 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; Am J Med 2019;132:240)

**Anticoagulation**:
See above (DVT) and AC, AC Mgmt sections

**Discharge**: if no other reasons for hospitalization, can d/c; use Hestia score to stratify for outpatient treatment

**Isolated Subsegmental PE (w/no DVT)**: Rule out proximal DVT. If low risk of recurrent VTE, can consider surveillance with repeat imaging. If higher risk, anticoagulate (Chest 2021; 160:e545)

**Thrombolysis** (Circ 2014;129:479; JAMA 2014;311:2414; Am J Card 2019;123:684; CDSR 2021;4:CD00437): may ↓mortality and improve hemodynamics (↓RVSP, ↓RV/LV ratio), is better than heparin alone, but ↑adverse events (e.g., bleeding, ICH)
Systemic: Patient with pulse = tPA 50-100mg/2h. Cardiac arrest = weight based TNK over 5 sec (see Ellucid thrombolysis guidelines). Hold AC during infusion (but don't delay TNK if already got LMWH), restart heparin when PTT <2x ULN. Trend fibrinogen q6h.
- *Absolute contraindications:* CNS neoplasm, CNS surgery/trauma <2-3mo, h/o ICH, active bleeding, non-ICH stroke <3mo

Catheter-directed: infused into pulmonary artery via PA catheter, significantly less lytic agent than systemic lysis. Consider if high bleeding risk, failed systemic lysis, or intermediate risk PE; US-assisted thrombolysis (EKOS) (JACC Card Interv 2015;8:1382; Am J Card 2019;124:1470) may enhance mechanical clot breakdown

**Orders**: CBC/diff, BMP, LFTs, lactate, D-dimer, ABG, PT/INR, PTT, T&S, NT-proBNP, hs-TnT, EKG, CT-PA, LENIs, TTE
**Consults: PERT (x47378)**: call for intermediate-high/high risk PE (hemodynamic instability, e/o RH strain), large or saddle PE; consider **ECMO** & page **SHOCK (p11511)** if worsening/refractory hypoxemia or hemodynamic instability
**Monitoring:** Routine evaluation at 3-6mo; if ongoing symptoms, consider PH/CTEPH (evaluate w/ V/Q scan, TTE, BNP and/or CPT).

# Pulmonary & Critical Care — Pulmonary Hypertension

## OVERVIEW (ERJ 2019;53:1801904)

**DEFINITION:** mean PA pressure (mPAP) ≥20 mmHg
PVR = (mPAP - PCWP) / CO; rearranged: mPAP = (PVR x CO) + PCWP ∴ ↑ in PVR or PCWP can → pulmonary hypertension (PH)

- *Pre*-capillary PH: PVR >2, PCWP ≤15, ↑DPG** & TPG*
- *Post*-capillary PH: PVR ≤2, PCWP >15, nl DPG & TPG
- *Mixed PH*: PVR >2, PCWP >15, ↑DPG & TPG

*Transpulmonary gradient (TPG) = mPAP – PCWP; nl <12
**Diastolic pulmonary gradient (DPG) = PA diastolic (PAd) – PCWP; nl <7

**DIAGNOSIS:** Gold standard: RHC (may not be needed in all circumstances) ± **iNO vasoreactivity testing** (+ response = ↓mPAP ≥10 mmHg to reach mPAP <40 mmHg w/o ↓CO; guides treatment in idiopathic PH)

**Workup to identify etiology of pHTN**:
- TTE (w/ agitated bubble): eval for left HF and shunt (& whether severity explains PH); ↑ RVSP may suggest PH but is not sufficient to diagnose/categorize
- RUQUS: Assess for portopulmonary HTN, portocaval shunt
- PFTs, high-res chest CT, polysomnography: chronic lung disease, OSA
- CPET: determine etiology of exercise intolerance (cardiac vs pulmonary/PAH 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, CTD (ANA, RF/CCP, ANCA, Scl-70, Ro/La), schistosomiasis (if clinically appropriate), urine & serum toxicology

**CLINICAL MANIFESTATIONS:** nonspecific; 2y delay to dx in 20% (Chest 2011;140:19)
- Early: **DOE**, lethargy, **fatigue** (2/2 inadequate CO w/ activity
- Late: exertional CP, **syncope**, edema, anorexia, abdominal pain and distention (secondary to progressive RV failure)
- Rare: cough, hemoptysis, hoarseness (Ortner's syndrome)

**Exam**: loud P2; ↑JVP, edema, ascites, TR murmur, R-sided gallop, parasternal heave (LSB), PV tap (L 2nd 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
**ECG**: normal vs signs of RV hypertrophy/strain: RAD, R/S >1 in V1, RBBB, P pulmonale in II (RAE)
**TTE**: TR peak velocity ≥2.8 (= PASP >35mmHg), PA diameter ≥25mm; RVOT AT <105ms, TAPSE/PASP <0.55mm/mmHg, RV dilation/hypokinesis, RV/LV >1,

## WHO CLASSIFICATION (7th World Symposium on PH: ERJ 2019;53:1801914; ERJ 2023;62:2300449; ERJ 2024;64:2401324; JACC 2013;62:D34)

| Pre-Capillary | | | Post-Capillary |
|---|---|---|---|
| **Group 1: Pulmonary Arterial Hypertension (PAH)** | **Group 3: Lung disease and/or hypoxemia** | **Group 4: Pulmonary artery obstructions** | **Group 2: Left heart disease** |
| - **Idiopathic** (♀>♂)<br>- **Heritable** (e.g. *BMPR2*)<br>- **Drug/toxin-induced**: cocaine, anorexigens, etc<br>- Associated with: **CTD** (MCTD, SSc, SLE), **HIV**, **portal HTN**, congenital heart disease, schisto<br>- PAH long-term responders to CCBs<br>- PVOD and/or pulm. capillary hemangiomatosis<br>- Persistent PH of newborn | Obstructive: **COPD**<br>Restrictive: **ILD**<br>Mixed obstructive/restrictive<br>Chronic hypoxia w/o lung disease: **OSA, OHS**<br>Developmental lung dz () | **Chronic thromboembolic disease**<br>*NB*: only ~33-75% had known prior VTE. Occurs after ~3% of Pes. Other PA obstructions: malig., arteritis w/out CTD, parasites, congenital PA stenosis | **HFpEF, HFrEF, and valvular disease**<br>CM (HCM, amyloid, Fabry, Chagas)<br>Congenital/acquired conditions |
| **Group 5**: **Misc.** chronic hemolytic anemia (e.g., sickle cell), MPN, sarcoid, pulm LCH, NF1, metabolic d/o, complex congenital heart disease | | | |

**WHO Functional Classes**: Class I = asx w/ ordinary activity, II = sx w/ ordinary activity, III = sx w/ minimal activity, IV = sx at rest

## MANAGEMENT

Treat underlying etiology: CTD, CHF, hypoxemia, VTE, etc. Advanced therapies (below): *guided by WHO functional class II-IV.* **DO NOT** abruptly stop advanced therapies if admitted inpatient. Call PH team w questions about medications. **Most evidence in Group 1**. Initiating Therapy based on ERS/ESC risk stratification guidelines (ERJ 2023;61:2200879): *refer to Pulm HTN clinic.* Surgery: pulmonary thromboendarterectomy (CTEPH), atrial septostomy (R→ L shunt), lung transplant in select pts. General: exercise/pulm rehab, $O_2$, diuresis, contraception required in ♀(2 forms vs permanent form), vaccines

| Mechanism | | Medication | Indication | Side effects |
|---|---|---|---|---|
| **Endothelin receptor antagonists** | Blocks pulmonary vasoconstriction & proliferation | Bosentan, ambrisentan, macitentan | Group 1: ↓sx, ↑6MWT, ↓clinical failure[1,2,3]<br>Macitentan: ↓morbidity/mortality[4] | Anemia, PNA, edema, hepatotox.<br>Macitentan: flu-like sx, HA, UTI, bronchitis |
| **(NO)-cGMP enhancers** | ↑ cGMP → vasodilation, blocks proliferation | PDE5 inhibitors*: sildenafil, tadalafil, vardenafil (not FDA approved for PAH) | Group 1 (sildenafil studied in some etiologies of Group 2 and 5): ↓sx, ↑6MWT[5,6] | Erythema, flushing, indigestion, HA, insomnia, epistaxis, rhinitis, retinal hemorrhage, **contraindicated if using nitrates* |
| | | sGC stimulator: riociguat | Group 1 & Group 4: ↓sx, ↑6MWT[7] | ↓BP, n/v/d/const., GERD, anemia, dizziness, HA, hemorrhage |
| **Prostacyclin pathway agonists (PPA)** | ↑ cAMP → vasodilation, blocks proliferation | Analogues: iloprost, epoprostenol, treprostinil, | Group 1: ↑6MWT, ↑QOL, ↓mortality w/ epopros.; reserved for sickest patients[8].<br>Group 3: ↑6MWT, ↓NTpro w/ treprost.[9]<br>Group 5: some etiologies | CP, ↓BP, ↑HR, flushing, abd pain, anorexia, n/v/d, MSK & jaw pain, dizziness, HA, hemorrhage |
| | | Receptor agonist: selexipag | Group 1: ↓hospitalization; no Δ mortality[10] | Diarrhea, nausea, jaw pain, HA, anemia |
| **CCB (trial)** | Vasodilation | Nifedipine, diltiazem | ⊕ iNO vasoreactivity test, ⊘ RV failure | ↓BP, LE edema |
| **Activin A receptor IIA inhibitor** | Regulates pulm. vascular proliferation | Sotatercept | Group 1: ↓sx & clinical worsening, ↓PVR. PAP, RAP, NT-proBNP, ↑ 6MWT[11, 12] | Epistaxis, telangiectasia, polycythemia, dizziness; unknown long-term effects, cost prohibitive |

References: 1:NEJM 2002;346:896; 2: Circ 2008;117:3010; 3: NEJM 2015;373:834; 4:NEJM 2013;369:809; 5: NEJM 2005;353:2148; 6: NEJM 2009;361:1864; 7: NEJM 2013;369:330 ; 8: NEJM 1996;334:296 ; 9: (NEJM 2021;384:325) ; 10: NEJM 2015;373:2522; 11: Am J Cardiovasc Drugs 25, 17–24 (2025) ; 12: NEJM 2021;384:1204-1215;

**Risk stratification criteria:** WHO functional class, 6MWT, NT-proBNP, TTE/cMRI, RHC at dx, consider CPET. Low/intermediate risk: dual oral therapy (target ERA/NO pathways; ambrisentan and tadalafil preferred). Can add CCB if vasoreactive. High risk: IV prostacyclin agonist (epoprostenol preferred) + ERA + PDE5i

**Goal of therapy is to attain low risk criteria:** NT-proBNP < 300, WHO/NYHA class I or II, 6MWT>440m. May add IV/SQ prostacyclin if low risk criteria are not met 3-6mo after initiation of oral agents (ERJ 2017;50:1700889)

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Suggest an Edit

# Pulmonary & Critical Care — Mechanical Ventilation

## Indications for Intubation

- **Failure of NIPPV**: unable to tolerate, progressive hypoxemia/hypercapnia, high pressures, ↓mental status, ↑fatigue/WOB
- **Poor ventilation**: $PaCO_2$ >60 w/ severe acidemia (pH <7.20) (COPD/asthma, sedation, neuromuscular disease, resp. muscle fatigue, trauma)
- **Poor oxygenation**: worsening P:F ratio (PNA, pulmonary edema, ARDS, PE)
- **Airway protection**: AMS/↓secretion management, shock, facial/head trauma, n/v/UGIB, severe bronchospasm/anaphylaxis, procedural necessity
- **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 ↑ intrathoracic pressure → ↓ LV & RV preload, ↑ PVR/RV afterload (variable) & ↓ LV afterload. Can precipitate RV failure in pHTN and RV dysfxn.
- In acidosis such as DKA, can be difficult to match RR to physiologic needs
- Vasoplegia and loss of compensatory tachycardia from sedatives ↓ sympathetic tone = ↓ BP; have appropriate pressors ready

## 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 $P_aCO_2$: ↓$P_aCO_2$ by increasing RR and/or $V_T$** (↑minute ventilation where MV = RR x $V_T$)
  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 $P_{plat}$ ≤30 & driving pressure ($\Delta P = P_{plat} - PEEP$) ≤15 to minimize lung injury
- **Oxygenation: ↑$PaO_2$ by ↑$FiO_2$ and/or PEEP**
  3) $FiO_2$: avoid $FiO_2$ >0.6 for prolonged periods due to oxygen toxicity
  4) PEEP: if recruitable lung present, ↑PEEP will ↑alveolar recruitment, improve V/Q match and compliance → ↑P:F & $P_{drive}$ stable/↓; if ↑PEEP → no Δ/↓ P:F, ↑$P_aCO_2$, or ↑$P_{drive}$, lung is not recruitable & ↑PEEP = ↑dead space/↓compliance due to overdistention

## Ventilator Modes: (Respir Care 2007;52:301)

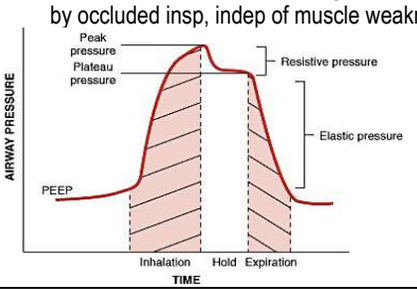
| MODE | SET *Indep. Var.* | MEASURED *Dep. Var.* | PROS/CONS | HOW TO READ | WHEN TO USE |
|---|---|---|---|---|---|
| **AC/VC** *Assist Control/Volume Control: delivers a breath until set tidal volume is reached* | **$V_T$**<br>PEEP<br>RR<br>$FiO_2$<br>I:E or flow | PIP & $P_{plat}$<br>I:E or flow | ☺: ↑control (fixed $V_T$ prevents barotrauma or atelectrauma)<br>☹: 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 $V_T$ ~400 for MV of 6.4L" | - Acute resp failure<br>- ARDS<br>- Airflow limitation (e.g. COPD, asthma) |
| **AC/PC** *Assist Control/Pressure Control: delivers a breath until set pressure is reached* | **$P_{insp}$**<br>PEEP<br>RR<br>$FiO_2$<br>I:E | Flow<br>$V_T$ | ☺: variable flow (& $V_T$) during inspiration to satisfy pt demand, ↓dyssynchrony<br>☹: 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 $V_T$ ~400, at set rate of 16 (or over) for a MV of 6.4L." | - Air leak (e.g. PTX)<br>- May trial in situations of vent dyssynchrony |
| **PSV** *Pressure Support Ventilation: delivers set pressure triggered by pt's spontaneous breaths* | $P_{insp}$<br>PEEP<br>$FiO_2$<br>RR (backup) | I:E<br>Flow<br>$V_T$<br>RR | ☺: better tolerated, less sedation, trial pre-extubation (e.g. SBT on 0/0 or 5/5)<br>☹: ↓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)<br>**- Weaning vent**<br>- Severe met acidosis |

## Monitoring Mechanics

| Parameter | Target | Evidence |
|---|---|---|
| Tidal Volume ($V_T$) | ARDS: 4-8 cc/kg PBW<br>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)<br>Non-ARDS: $V_T$ 10cc/kg vs 4cc/kg → no Δ mortality or vent-free days (JAMA 2018;320:1872) |
| Plateau pressure ($P_{plat}$)<br>Driving pressure ($\Delta P = P_{plat}$-PEEP) | <30<br><15 | ARDS: ↓driving pressure a/w ↑survival (NEJM 2015;372:747)<br>Non-ARDS: driving pressure not a/w 30d mortality (Crit Care 2019;23:424) |
| Compliance ($V_T/\Delta P$)<br>Airway Resistance (PIP-$P_{plat}$) | >50<br><10 | Maximizing $O_2$ transport and minimizing dead-space occurred at the **greatest total static compliance** (ICM 2005;31:1370) |

## Ventilator Maneuvers for Monitoring Mechanics

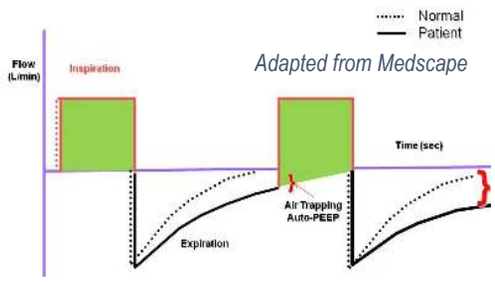
- *Inspiratory hold*: end inspiratory pause; measure $P_{plat}$ → calculate ΔP, airway resistance, compliance
- *Exp hold*: end expiratory pause; quantifies autoPEEP
- *$P_{0.1}$*: measures resp drive w/ neg pressure generated by occluded insp, indep of muscle weakness, C, R



# Pulmonary & Critical Care — Mechanical Ventilation

## VENTILATOR COMPLICATIONS

- **Dynamic hyperinflation (auto-PEEP)**: measured by end expiratory hold. Auto PEEP = end exp pressure – set PEEP
  - Diagnosis: end-expiratory flow >0 due to incomplete alveolar emptying
  - RFs: vent strategy causing hyperinflation (high RR, ↑I:E ratio) or obstructive disease (asthma, COPD, CF), ↑RR w/ bag-valve mask
  - Consequences: adverse hemodynamic effects (HoTN secondary to ↓venous return), alveolar over-distention (→ volu-/barotrauma); ↑effort to trigger breath
  - Tx: longer exhalation (↓I:E ratio, ↓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 →↑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 adjacent alveoli/airways
  - **Biotrauma**: cytokine release from lung epithelium → multi-organ dysfunction (Crit Care 2005;9:280)
  - **Oxytrauma**: ↑$FiO_2$ →free radical production, lung injury
  - **Barotrauma**: injury from high $P_{plat}$ (highest risk >35) → PTX, subcutaneous emphysema, pneumomediastinum
- ↑ **Peak inspiratory pressure (PIP)** = airway resistance + elastic resistance ($P_{plat}$). To troubleshoot, determine $P_{plat}$ with insp. hold
  - If normal $P_{plat}$ (<30): ↑airway resistance: bronchospasm, secretions/mucus plug, ET malposition/kink/biting, airway edema
  - If elevated $P_{plat}$ (>30): ↑elastic pressure = ↓compliance
    - Decreased functional lung size/overdistention: auto-peep, atelectasis, R main stem, ARDS, PNA, DAH, pulmonary edema
    - Increased thoracic pressure: obesity, kyphosis, burns, abdominal compartment/ascites, effusions, PTX, Tberg position
    - Parenchymal disease: ILD, post radiation
  - Low PIP? leak in the system: bronchopleural fistula, ET cuff rupture/dislodge, tubing damage
- **Other complications**: VAP, laryngeal edema, tracheal stenosis, PTX

## 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; plan to improve $PaO_2$ (i.e. diuresis, pulmonary vasodilators) and/or $PCO_2$ (i.e. 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 and hemodynamic stability
  (2) adequate oxygenation and ventilation: $PaO_2/FiO_2$ ≥150-200, PEEP ≤5-8, $FiO_2$ ≤0.4-0.5, pH >7.25
    - **Rapid Shallow Breathing Index (RSBI) = RR/$V_T$**; RSBI >105 predicts extubation failure (Sn>Sp) (NEJM 1991;324:1445)

  (3) ability to cough/manage secretions (ideally alert/following commands, but if protecting airway, AMS does not preclude extubation)
  (4) +cuff leak. Absence of cuff leak is concerning for laryngeal edema → consider methylpred 20mg IV q4h 12hrs prior to extubation or IV methylpred 40mg x1 4hrs prior or IV dexamethasone 5mg q6h (Eur J Anaesthesiol 2010;27:534).
- **Liberation protocol**: daily **Spontaneous Awakening Trial (SAT)** + **Spontaneous Breathing Trial (SBT)**
  - **SAT**: ↓ 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)=↓ vent time (NEJM 1996;335:1864; NEJM 1995;332:345)
    Ways to fail: hypoxemia ($SaO_2$ <90%, $PaO_2$<60), hypercapnia ($PaCO_2$ ↑ by >10), low $V_T$, respiratory distress (↑HR/RR, HTN, accessory muscle use), arrhythmia, hemodynamic instability, anxiety/agitation, somnolence, inability to follow commands
    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 / risk factors for reintubation → ↓ post-extubation respiratory failure (Lancet 2009;374:1082; JAMA 2016;316:1565). HFNC w/ intermittent NIPPV post-extubation → ↓ reintubation compared to HFNC alone (JAMA 2019;322:1465).
  - If **agitation** is limiting ability to extubate, consider dexmedetomidine → 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 14-21 days. Early tracheostomy (7 days) if expect intubation >14 days → ↑comfort, allows ↓ sedation, ↓ risk of tracheal stenosis, ↓ vent-free and ↓ ICU days, though no change in VAP rate (JAMA 2010;303:1483; Crit Care 2015;19:424; Br J Anaesth 2015;114:396)

# Pulmonary & Critical Care — ARDS

## PATHOPHYSIOLOGY OF ARDS

**Caused by: Direct lung injury**: pneumonia, aspiration, inhalational injury, near drowning, pulmonary contusion **or Indirect lung injury**: sepsis, trauma, pancreatitis, drugs, burns, cardiopulmonary bypass/pump, transfusion-related acute lung injury (TRALI)
**Ddx (ARDS Mimics):** Eosinophilic PNA (AEP), acute interstitial PNA (AIP), organizing PNA
**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)

**Global Definition for ARDS & Management Summary** (AJRCCM 2024;209:37, AJRCCM 2024;209:24)

1) Onset or worsening within **1 week** of insult
2) **Not** primarily due to hydrostatic/**cardiogenic pulmonary edema**
3) Imaging showing **bilateral opacities** on CXR/CT or bilateral B lines/consolidations on ultrasound
4) **$PaO_2$:$FiO_2$ (P:F) ratio ≤ 300** or **$SpO_2$:$FiO_2$ (S:F) ratio ≤ 315**
   A. **Nonintubated**: on HFNC ≥ 30L/min or NIV/CPAP ≥5cm $H_2O$
   B. **Intubated**: with PEEP ≥5cm $H_2O$
   C. **Resource Limited**: No minimum flow rate or PEEP required for Dx

**Mild ARDS**
- P:F 200-300 or S:F 235-315
- Mortality: 27%

**Moderate ARDS**
- P:F 100-200 or S:F 148-235
- Mortality: 32%

**Severe ARDS**
- P:F ≤100 or S:F ≤148
- Mortality: 45%

Is the patient stable, tolerating NIV, P:F >200?

**NO** → **Mechanical Ventilation**
- $V_T$ 4-8cc/kg predicted body weight (PBW) (Goal 6), Pplat ≤30, ΔP ≤15
- Optimal PEEP titration (see below)
- Maintain $PaO_2$ 55-80 mmHg or $SpO_2$ 88-94% with pH ≥7.25

**YES** → Nonintubated ARDS
Continue noninvasive ventilation
NIPPV = HFNC
(Chest 2017;151:764)

**Is P:F ≤150?**

**YES** →
1) Prone
2) Paralysis (P:F ≤100)
3) Consider pulm vasodilator

→ **Is P:F ≤80?** → Consider VV ECMO

## MANAGEMENT PRINCIPLES IN ARDS: (ATS/ESICM/SCCM: AJRCCM 2024;209:24)

| | Strategy (in order of decreasing level of evidence) | Effects |
|---|---|---|
| **Low Tidal Volume Ventilation (LTVV)** (NEJM 2007;357:1113) (NEJM 2000;342:1301) (AJRCCM 2024;209:24) | • **Maintain oxygenation** while **preventing ventilator-induced lung injury** (VILI)<br>• $V_T$ 4-8 cc/kg PBW w/ goal Pplat ≤30, driving pressure (Pplat-PEEP) ≤15<br>○ May allow ↑Pplat if ascites, obesity, etc. as may not accurately reflect transpulmonary pressure (see "esophageal balloon catheter" on next page)<br>• Permissive hypercapnia: pH goal ≥7.20-7.25 permits lower $V_T$ to minimize VILI<br>○ *Contraind*: ↑ICP, RV failure/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) (Chest 2023;163:533) | • Initiate within 36h in pts with P:F<150 on FiO2≥0.6, PEEP≥5cm$H_2O$<br>• ↓V/Q mismatch by ↓compressive atelectasis from heart & diaphragm → more homogenous ventilation → ↑alveolar recruit. → ↓regional volutrauma & ↑compliance<br>• *Contraind.*: hemodynamic instability, ↑ICP, inability to turn neck (fixed/unstable C-spine), 2/3rd trimester pregnancy, recent sternotomy | ↓**mortality** (28d & 90d) in mod/severe ARDS |
| **Conservative Fluid Management** (NEJM 2006;354:2564) | • Minimize pulmonary edema, avoid ⊕ fluid balance after reversal of shock<br>• Dynamic assessment of volume responsiveness (i.e. pulse pressure variation, passive leg raise) (CCM 2017;45:1538)<br>• FACTT Trial: Compared Conservative (CVP<4) vs. Liberal (CVP ≤10-14) fluid strategy in patients with ARDS on mechanical ventilation (NEJM 2006;2564-2575) | Conservative strategy: ↓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) | • Maximize recruitment, minimize trauma from cyclic atelectasis<br>• Higher PEEP distributes $V_T$ over more alveoli → less over-distention → improves oxygenation (via ↓V/Q mismatch and ↓shunt fraction) & compliance<br>• CV effects of PEEP: ↓preload/SV, RV afterload varies, ↓LV "afterload", ↓BP<br>• 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) (AJRCCM 2024;209:24) | • ↑oxygenation and ↓VILI by ↓vent dyssynchrony and chest wall compliance<br>• No survival benefit to routine early paralysis for mod-severe ARDS (P:F <150) as compared to light sedation, possible mortality benefit when used for vent synchrony or in early severe ARDS when deep sedation is otherwise required<br>• Can use as bolus/infusion to maintain vent synchrony in mod-severe ARDS | Possible ↓mortality & ↑vent free days when used for synchrony; probable ↓barotrauma<br>**Risk:** ↑ICU-acquired weakness |

*Emma Kurz and Adam Gross*



Suggest an Edit

# Pulmonary & Critical Care — ARDS

## Summary of Rescue Therapies for Hypoxemia (6 Ps of hypoxemia)

- Pee: consider diuresis to reduce pulmonary edema (see "conservative fluid management" above)
- PEEP: optimize PEEP for maximal alveolar recruitment (see "PEEP" below)
- Prone positioning: should be implemented *early* (12-24h) if P:F <150 (or 200) despite optimal PEEP titration
  - Maintain prone >12hrs/day. 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% ↑$PaO_2$, 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; inhaled pulmonary vasodilators exhibit tachyphylaxis
- Paralysis: can be used to maintain vent synchrony (see "neuromuscular blockade" above), esp. when double triggering – permits maintenance of Low Tidal Volume Ventilation. Conditionally recommended in early ARDS (<48h) w/ P:F <100 if already under deep sedation. 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). Do NOT wean sedation while under blockade (RASS goal -5 prior to initiation). Monitor depth of sedation with BIS (target 40-60)
- Perfusion (VV-ECMO): for severe, refractory hypoxemia with P:F ≤ 80 +/- hypercarbia w/ pH <7.25 and pCO2 >60. Used generally as bridge to recovery or transplant. Pooled analysis demonstrated probable ↓mortality, ↑ventilator, vasopressor, and RRT-free days. (AJRCCM 2024;209:24) (Lancet 2009; 374:1351) (NEJM 2018;378:1965) see *ECMO*

## Lung Protective (ARDSNet) Ventilation

- **Initial ventilator set-up**: $V_T$ = 6 cc/kg PBW, RR to approximate baseline MV (RR <35), moderate PEEP (8-10)
- **Adjustments**: (also see *Mechanical Ventilation*)
  - Oxygenation: goal **$PaO_2$ 55-80 mmHg** or **$SaO_2$ 88-95%**
    - $SpO_2$ <94% a/w ↓mortality; hyperoxia leads to ↑mortality (JAMA 2016;316:1583; Crit Care 2014;18:711)
    - If persistent hypoxemia requiring $FiO_2$ >~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 → ↑$pCO_2$ & ↓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 $PaCO_2$ <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<br>$SaO_2$ 88-95% |
| Mechanics | Plateau pressure (Pplat) ≤30<br>Driving pressure (ΔP) ≤15 |
| pH | 7.20-7.25 to 7.45 |

## Optimal PEEP for ARDS

- **ARDSNet $FiO_2$/PEEP scale**:
  - If P:F <150 w/ PEEP 5cm $H_2O$, assess ability to recruit lung by increasing PEEP from 5 → 15cm $H_2O$
  - If improvement, use ARDSNet high PEEP/low $FiO_2$ scale; if no improvement, use low PEEP/high $FiO_2$ scale (see right)
- **Best PEEP trial**: select the PEEP corresponding to best global recruitment with lowest risk for overdistention based on **resp system compliance ($C_{RS}$ = $V_T$ / [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

NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary

Lower PEEP/higher FiO2

| $FiO_2$ | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 |
|---|---|---|---|---|---|---|---|---|
| PEEP | 5 | 5 | 8 | 8 | 10 | 10 | 10 | 12 |

| $FiO_2$ | 0.7 | 0.8 | 0.9 | 0.9 | 0.9 | 1.0 |
|---|---|---|---|---|---|---|
| PEEP | 14 | 14 | 14 | 16 | 18 | 18-24 |

Higher PEEP/lower FiO2

| $FiO_2$ | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.5 |
|---|---|---|---|---|---|---|---|---|
| PEEP | 5 | 8 | 10 | 12 | 14 | 14 | 16 | 16 |

| $FiO_2$ | 0.5 | 0.5-0.8 | 0.8 | 0.9 | 1.0 | 1.0 |
|---|---|---|---|---|---|---|
| PEEP | 18 | 20 | 22 | 22 | 22 | 24 |

- **Driving pressure**: ΔP = Pplat - PEEP (goal: ≤15)
  - Distending pressure. Represents the relationship between tidal volume and lung compliance (ΔP = $V_T/C_{RS}$)
  - 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 alveoli, then 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** ↑↑↑PIPs (>50)
  - Seem to be falling out of favor and **strong recommendation against** prolonged lung recruitment maneuvers in moderate-severe ARDS (AJRCCM 2024;209:24)
- **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)

## 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:** suggested in ARDS (P:F ratio ≤ 300) but optimal regimen unknown (conditional rec, moderate certainty); a/w ↓mortality, ↓duration of ventilation (low certainty), and ↓LOS (low certainty) (AJRCCM 2024;209:24).There are 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).

*Emma Kurz and Adam Gross*



Suggest an Edit

# Pulmonary & Critical Care — ECMO

**To call ECMO consult**:
- MGH STAT App
- Directory: type "ECMO Consult" or **p24252**
# 857-310-0335

## TYPES OF ECMO (JACC 2018; 11:1941)

1. **Venoarterial** (*VA*, **replaces heart and lungs**): primarily cardiogenic shock
   - Venous blood is removed, oxygenated, $CO_2$ extracted, and reinfused in arterial system
   - Venous cannula in com. femoral vein (drainage from IVC or RA); arterial cannula in R fem. artery
2. **Venovenous** (*VV*, **replaces lungs**): manages hypoxemic resp. failure; relies on native cardiac output
   - Venous blood is removed, oxygenated, $CO_2$ extracted, and reinfused in venous system
   - Either two venous cannulae (common fem. vein and SVC) or a bicaval dual lumen single cannula via R IJ that allows for mobility

**Indications**:
- Reversible acute resp failure (VV): *e.g. ARDS, bridge to transplant or recovery.* $PaO_2/FiO_2$ <80 despite optimization, unable to achieve safe inflation pressures (Pplat <30), CO2 retention (pH<7.25 w/ PCO2 > 60) with inability to mechanically ventilate. See ELSO.
- Reversible cardiogenic shock (VA): *e.g. PE, cardiac arrest.* Refractory low cardiac index (<2L/min/m$^2$) & HoTN despite adequate volume, inotropes, & MCS (e.g., Impella, IABP)
- Bridge to definitive therapy (transplantation, VAD, recovery)

**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; aortic dissection; severe AI; ESLD/ESRD
- Absolute VV: severe right or left HF
- Relative: age>70; multi-organ failure; severe pHTN; unknown neuro status; GVHD; active cancer; immunosuppression; ventilated >7d; DIC; survival <30% (via RESP and SAVE scores)

## ECMO VARIABLES

**Drainage Cannula in large central veins (IVC, SVC, or RA) || Return Cannula in RA or Ao (depending on configuration)**

- **Sweep** (aka gas flow, replaces ventilation (L/min)): ↑sweep → ↓$P_aCO_2$ in blood returning to pt therefore ↑sweep requirements = worsening ventilation vs ↑ **$CO_2$ production** (fever, infection, renal failure). Controls O2 delivery if any. When sweep is weaned off or "capped" in VV-ECMO, ECMO support for ventilation & oxygenation is also off.
- **$FdO_2$** (fraction *delivered* **O2 in sweep gas flow**): Generally set at 1.0
- **RPM**: Predominant determinant of **blood flow** (2-5L/min; >7LPM limited by membrane lung efficiency also affected by cannula size & native CO). VV ECMO: RPM based on BSA to estimate $O_2$ consumption (BMI may limit candidacy), partially weaned. VA ECMO: RPM indicates % of CO support from ECMO, main weaning variable.
- **Transmembrane Pressure** (dP or ΔP = $P_{pre}$ - $P_{post}$): reflects oxygenator (membrane) function, trended daily
  - ↑ ΔP: check membrane for clots and ABG to assess impact on gas exchange. Check RPM (ΔP = BF x R so may reflect ↑ flow).
  - ↓ ΔP: check ECMO circuit for kinks either at the inflow or outflow sites
- **AC**: UFH, follow PTT, Xa, AT-III per discussion with attending/pharmacist *(type of AC used may vary between centers)*
- **Mechanical Ventilation**: Pt may be placed on PC with low $P_{insp}$ to enable "lung rest." Increasing spontaneous $V_T$ reflects improvement in lung function/ability to wean circuit. Once lung function improved, wean sweep to assess ability to ventilate endogenously, and from there can attempt to wean off VV-ECMO Surg Clin North Am 2022;102:23

## COMPLICATIONS (Heart Lung Circ 2014;23:10)

- **ECMO: clots** (oxygenator, pump, tubing, hemofilter; 0.13-22%); **cannula displacement** (0.8-8%); **air embolism, oxygenator failure, pump failure. For emergencies, STAT page ECMO team.**
- **Patient: bleeds** (access sites, ENT/Pulm/GI/GU, intracranial, hemolysis, DIC; 5.3-79%); **neuro** (ICH, stroke, seizure, encephalopathy; 10-33%); **limb ischemia** (13-25%); **infection** (17-49%; to help minimize this risk NO additional access placed after ECMO placed- all labs drawn off circuit); **AKI** (30-58%); **multi-organ failure** (10%); **cannular** (4.8%)

## TROUBLESHOOTING THE CIRCUIT

Consider early involvement of the ECMO team/attending if issues arise.

- **Baseline lab goals**: Hgb >7.5g/dL; plt >75K; fibrinogen >150; active T&S. Maintain $SpO_2$ > 85% and PaO2 > 55.
- **Chatter**: shaking/sound caused by ↑⊖pressure in tubing; can be due to **venous collapse**, **hypovolemia, thrombosis, tamponade, other cause of ↓CO, straining, kinking**. Tx: volume resuscitation (usually albumin), ↓ RPMs, cannula, and/or repositioning
- **Hypoxemia** (as measured on **patient ABG or sats**):
  a) Recirculation: blood travels from the outflow (return) catheter back into the inflow (drainage) catheter, bypassing body. Can be NL if <25 % recirculation. If >25% or ↑ consider catheter malposition. Dx: unexplained ↑inflow $O_2$ sat, BRB in drainage catheter Tx: reposition cannula (10 cm apart) or switch to dual lumen cannula, ↓RPM
  b) Membrane failure: often due to excessive and/or abnormal clots/fibrin Dx: visual inspection of circuit with worsening hypoxemia on outflow sat/ABG ($PaO_2$<200 on 100% $F_dO_2$) or ↑ΔP by 20 in 4hrs Tx: replace membrane
  c) Shunt: occurs if native CO >> ECMO flow or w/ improving native CO (larger % of blood never travels through ECMO circuit and is poorly oxygenated) Dx: hypoxemia on pt ABG/sats. Tx: ↑RPM to ↑flow. To ↑ CO: ↓fever, ↓inotropes, ßB, CCB, phenylephrine
- **Harlequin (North-South) syndrome** (VA only): **hypoxia of upper extremities R worse than L, 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. Dx: low sats on R arm but normal sats on L (need R radial art line in VA ECMO) Tx: add a venous return cannula/transition to V-AV ECMO (Heart Lung Ves 2015;7:320)

## OUTCOMES

- **Acute respiratory failure**: 2 major studies show ↓mortality, but unclear if from referral to ECMO center or ECMO itself: CESAR: (Lancet 2009;374:135) & EOLIA: (NEJM 2018;378:1965) with similar mortality in COVID-19 ARDS Lancet 2020;396:1071)
- **Refractory cardiogenic shock**: ~40% discharge survival; time CPR→ECMO = best death predictor (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; no difference between 30d outcomes with ECLS vs traditional therapy for out-of-hospital cardiac arrest (NEJM 2023;388:299) and MI related cardiogenic shock (NEJM 2023;389:1286). Consider calling ECMO team if ~10 min. of CPR w/o ROSC to discuss VA ECMO.

*Anna Crosetti*



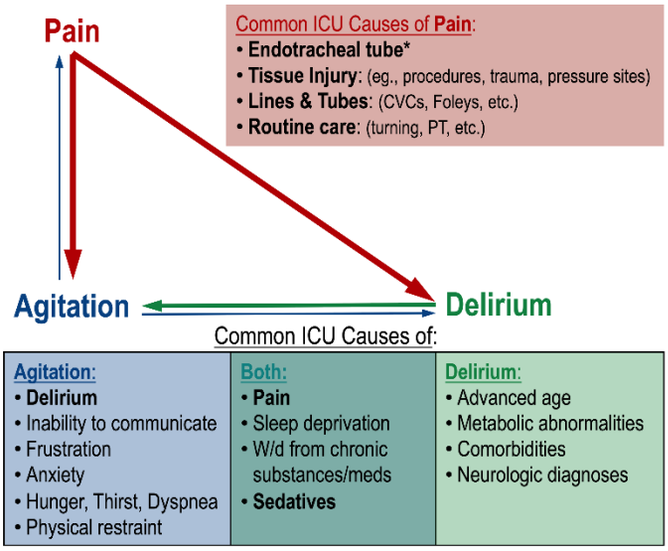
Suggest an Edit

# Pulmonary & Critical Care — Sedation

## GOAL OF ICU SEDATION: addressing ICU triad of pain, agitation, & delirium (NEJM 2014;370:444)

1. **Pain**: common, ↑energy expenditure; analgesia alone adequate in some (Lancet 2010;375:475)
2. **Agitation**: target light sedation in intubated pts; no benefit to non-sedation (NEJM 2020;382:1103)
3. **Delirium**: 16-89% ICU pts; a/w worse mortality, QOL, cognitive outcomes (NEJM 2014;370:444); ↑risk w/ deep sedation, BZD use (Intensive Care Med 2007;33:66; JAMA 2007;298:2644)

***ICU Triad of Pain, Delirium, and Agitation***




*Adaptated from Reade and Finfer, NEJM. 2015; 370;444.*

| 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 & 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 | Mvmt/opens eyes to physical stimulation but not voice |
| -5 | Unarousable | No response to voice or physical stimulation |
| †Goal for most pts w/o indication for deep sedation | | |

| A2F Bundle ↓mortality ↓delirium (Crit Care Med 2019;47:3) | |
|---|---|
| A | **A**ssess, Prevent, and Manage Pain |
| B | **B**oth Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT) |
| C | **C**hoice of analgesia and sedation |
| D | **D**elirium: Assess, Prevent, and Manage |
| E | **E**arly Mobility |
| F | **F**amily engagement and empowerment |

**Strategies for weaning sedation**:
Assess daily for improving resp failure (↓FiO2, PEEP, no NMB).
MGH criteria for extended taper:
Sedation > 7 days + P:F > 200 + transition to PS in 24-48h

- ↓BZDs ~20-25%/day → **phenobarbital** or **lorazepam**
- ↓dexmedetomidine ~20-25% q6h → **clonidine** q8-12h or patch
- ↓opioids ~20-25%/day (taper last) → PO opioid (**methadone**)

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

### Sedative-Hypnotics (Non-Benzodiazepine)

**Propofol:** GABA agonist. Dose: 5-50 µg/kg/min (Max 83)

**1st line Sedative**. Earlier extubation, ↓ICU LOS, & ↓mortality vs BZDs (AJRCCM 2014;189:1383)
Onset/Duration: **Fast on** (30-60sec) **Easily titratable**. **Often rapid awakening but has "context-sensitive" $T_{1/2}$** d/t ↑ lipid solubility. **Duration prolonged by 1) long infusion time, 2) ↑BMI, 3) adv. liver failure** (hepatic metab.; still 1st line in ESLD)
Analgesia: **None**
Respiratory: Powerful resp. depressant → cannot use w/out ETT outside an OR.
CV: Powerful vasodilator & direct cardiac depressant →↓↓**BP and ↓HR**
- ↓ICP & anti-seizure effects → **use in EtOH w/d & status epilepticus**.
- Monitor TGs with prolonged use. TG > 500 → risk of pancreatitis
- Propofol Infusion Syndrome: Rare. ↑ Risk if >48h of gtt ↑infusion rate. Rhabdo, AGMA, ↓HR, LV dysfxn, HSM, Liver/Renal failure

**Dexmedetomidine** (Precedex): $\alpha_2$-agonist Dose: 0.2-0.7 µg/kg/min (Max 1.5)

**Use as Early Adjunct: ↓delirium & earlier extubation** (JAMA 2016;315:1460) (Has EEG pattern most similar to natural sleep). (Anesthesiology 2015;123:937).
Onset/Duration: **Slow on** (5-10min, peak 15-30min). **Slow off** (>1-4hr). Therefore, less versatile & less titratable vs. propofol.
Analgesia: **Mild,** unclear mechanism (**use as adjunct, not primary analgesic**).
Respiratory: Less resp. depression vs. other hypnotics → **OK for non-intubated patients in monitored setting** (e.g., the ICU).
CV: Strong **negative chronotropy,** dose-limiting SEs = ↓HR & high-grade AVNB. Less vasodilation/↓BP vs. propofol.
- Falsely **low** BIS (interpret with caution in paralyzed patients)
- **Precedex Fever**: idiosyncratic high-grade fever, resolves w/ drug d/c.
- Can have withdrawal after prolonged use (tachycardia, hypertension) →use clonidine taper to wean

**Ketamine:** NMDA-antagonist. Dose: 5-20 (Max 30) µg/kg/min

Onset/Duration: **Fast on** (30-60sec). **Slow off** 2.5hrs; accumulates in renal/liver failure
Analgesia: **Clinically relevant analgesia** via anti-NMDA; synergistic w/ opioids.
Respiratory: **Minimal respiratory depression**. Bronchodilatory. ↑**Secretions**: caution peri-/post-extubation
CV: ***Indirect* sympathomimetic:** ↑HR + ↑BP in early illness/stable pts.
***Direct negative* inotrope:** ↓BP in extremis/↓cardiac reserve (no longer offset by endogenous catecholamine release). (Br J Anaesth 2021;127:23)
- Dissociation/**nightmares** if used w/out GABA agent. Higher risk in elderly.
- Falsely **high** BIS
- **Epileptogenic**. May p/w non-convulsive status. **Avoid if seizure risk**.
- **DILI**: ALT>AST rise first, then ALP. ↑ risk w/ chronic EtOH. **Monitor daily LFTs**.



Suggest an Edit

## SEDATION AGENTS (continued)

**Opioid Analgesics** (as a class)**:** μ-opioid agonists

Analgesia: All are strong analgesics. No amnestic effects. Tolerance & w/d w/ prolonged use (~10-14d) and/or abrupt d/c.
Respiratory: All are **respiratory depressants** and **synergistic with most other sedatives.**
CV: All are **sympatholytic**, but most have limited direct cardiovascular effects → **less ↓BP & less ↓HR vs. propofol.**
- As a class, opioids frequently can cause **constipation/Ileus.**

**Hydromorphone:** Dosing – gtt: 0.5-4mg/hr, bolus: 0.25-1mg q1-q3hr,

Onset/Duration: Intermediate onset (5 min), Intermediate duration ($T_{1/2}$ = 3-4h). **Fewer renal metabolites** vs. morphine/oxy.
- Less adipose accumulation vs. Fentanyl & Morphine → **preferred agent for treatment duration > 24h**.
- Quick onset + short $T_{1/2}$ (vs. morphine) = can be useful for procedural sedation, though less titratable than fentanyl.

**Fentanyl:** Dosing – gtt: 50-200mcg/hr, bolus: 25-100mcg q30-60m

Onset/Duration: **Fast on** (1 min), Context-sensitive $T_{1/2}$ (↑ lipid solubility)→Bolus $T_{1/2}$: 1-3h vs. gtt $T_{1/2}$: 9-16h. No renal metabolite.
- **Adipose accumulation** → delayed awakening. **Avoid gtt if need frequent neuro checks** (bolus may be useful)
- Rapid onset + short $T_{1/2}$ (if context is short treatment duration) = **useful for procedural sedation.**

**Morphine:** Dosing – gtt: 2-10mg/hr, bolus: 2-4mg q1-q4hr

Cheaper, but **generally less preferred agent**. Fewer ventilator-free & ICU-free days vs. fentanyl (AJRCCM 2021;204:1286)
Onset/Duration: **Slower on** (5-10 min) & **long-acting** ($T_{1/2}$ = 3-5h). Accumulates in renal failure → **avoid if CrCl < 30mL/min**.
Respiratory: Histamine release can cause/exacerbate bronchospasm → **Avoid in reactive airway disease.**
CV: Both longer duration of effect and vasodilatory SEs d/t histamine → **prefer Hydromorphone or Fentanyl if HDUS**.
- Histamine release → **pruritis, urticaria, flushing.**

Neurologic: the metabolite morphine-3-glucuronide is neurotoxic and causes seizures and accumulates w/ renal failure

**Benzodiazepines** (as a class)**:** GABA agonists

**Avoid whenever possible:** *BZDs ↑Mortality, ↑time to light sedation & extubation, & ↑delirium*
Analgesia: **None**. || Respiratory: Resp. depression at higher doses. **Synergistic w/ opioids**: be cautious w/ co-administration.
CV: Sympatholytic and synergistic w/ opioids. Be cautious in acutely unstable patients unless prepared to intubate.

**Midazolam** (Versed): Dosing – gtt: 2-5mg/hr, bolus: 0.5-4.0mg (> 2mg more likely to → apnea), IM=100% bioavailable

Onset/Duration: Bolus = **Fast on** (<1 min) & **Fast off** (bolus lasts 1-2h). Gtt **accumulates in liver/renal failure** and in adipose.
- CYP3A4 substrate: many PO drug-drug interactions (e.g., fluconazole, macrolides, Flagyl, amiodarone) w/ 1st pass metabolism
- Rapid onset + short $T_{1/2}$ (if context is short treatment duration) = useful for procedural sedation
- Associated with increase time to extubation (Journal of Critical Care 2021;91-99)

**Lorazepam** (Ativan)**:** Dosing: (only) bolus: 0.5-2.0mg, status epilepticus= 4mg, IV=PO, Ativan 1mg ≈ 2mg Midaz ≈ 6mg Diazepam

Onset/Duration: Bolus = **Fast on** (1-2 min) but **longer-acting** (6-8h). Not renally cleared.
- Propylene glycol (solvent) toxicity w/ ↑dose (p/w ↑lactate, ↓BP, arrhythmia, AGMA)
- Longer $T_{1/2}$ = ↑accumulation risk, particularly with shorter bolus intervals

**Adjunct Agents:** Dopamine Antagonists**: Quetiapine** (50mg q6-12h, max 400mg/d), **Haloperidol** (2.5-5mg IV q4-8h), **Olanzapine** (2.5-5mg IV or IM). SEs: ↑**QTc** → risk of TdP; ↓gastric motility; extrapyramidal effects, **NMS** (rare, but an emergency) – high fever, "lead pipe" paralysis, hyporeflexia, Rx = dantrolene (takes a long time to prepare).
Antiseizure medications: **Valproate (**10-15 mg/kg, titrated to level). Many serious SEs: **DILI (boxed warning)**; severe **pancreatitis (boxed warning)**; multiple **cytopenias**: ↓PLTs, aplastic anemia, neutropenia, acquired vWD; SJS/TEN and DRESS.
Barbiturates: **Phenobarbital** (consult pharmacy for dose). Highly effective anti-seizure & ↓ICP; CYP450 inducer (many drug-drug interactions); many serious SEs: CNS depression, respiratory depression, hypotension, bradycardia, SJS/TEN

# Pulmonary & Critical Care — Shock

## Overview (NEJM 2013;369:1726)

**Definition**: state of tissue hypoxia due to decreased/dysregulated oxygen delivery or extraction, resulting in end-organ damage
**Clinical manifestations**: **hypotension** (SBP <90mmHg or ↓SBP >40mmHg from baseline); **end-organ dysfunction**: *oliguria* (UOP <0.5cc/kg/h), **AMS**, metabolic acidosis (± anion gap, **↑lactate**, ↓bicarb 2/2 renal failure); cool & clammy vs. warm & flushed extremities. (Any of these can be **normal—including BP**—in a patient in shock, so a **high index of suspicion** is needed)
**Initial workup**: focused H&P, ensure **access**, review meds, ECG/CXR, ABG/VBG, CBC/diff, CMP, TnT, lactate, CVO2, monitor UOP
**MAP**: determined by **CO** (cardiac output) & **SVR** (systemic vascular resistance)

**MAP = CO x 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 | Type B |
|---|---|
| *tissue hypoperfusion*, typical in shock; can be profound iso bowel ischemia, necrosis | *NOT marked tissue hypoperfusion*. Metformin, cancer (e.g., Warburg), EtOH, ↓thiamine, albuterol, D-lactate, mitochondrial dysfxn., liver dz |

## Etiologies of Shock

**Signs of ↑CO:**
- Widened pulse pressure
- Low diastolic BP
- Warm extremities
- Normal cap refill

**SHOCK** → ↑CO / ↓CO

**Signs of ↓CO:**
- Narrow pulse pressure
- Cold extremities
- Slow cap refill

| | Distributive (66%) | Hypovolemic (16%) | Cardiogenic (16%) | Obstructive (2%) |
|---|---|---|---|---|
| **Pathophysiology** | ↓SVR & altered oxygen *extraction* | ↓cardiac output → inadequate oxygen *delivery* | | |
| **Examples** | Sepsis, anaphylaxis, adrenal insuff., liver fail., tox/med, neurogenic (NEJM 2013;369:840; NEJM 2001;345:588) | **Hemorrhagic**, 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 (Preload)** | ↓/normal | ↓↓ (< 5 mmHg) | ↑↑(> 7 mmHg) | ↑/normal |
| **CO or $CVO_2$** | ↑/normal (Can be low pre-resuscitation) | ↓ (<70%) | ↓ (<70%) | ↓ (<70%) |
| **SVR (Afterload)** | ↓↓ | ↑ | ↑ | ↑ |
| **TTE Findings** | Normal chamber size, normal/↑ contractility | Small chambers, normal/↑contractility | Large chambers, poor contractility | Tamponade: pericardial effusion<br>PE/PTX: dilated RV |

## General Considerations (Any Etiology)

- Vasoactive agents (*Vasopressors*): titrate **MAP >65 mmHg** (cardiogenic MAP >60 mmHg); acidosis = ↓vascular response to pressors
- Ventilatory support: intubate if necessary (concomitant respiratory failure, unable to compensate for metabolic acidosis, marked hemodynamic instability), with pressors available; SpO2 may be unreliable due to peripheral vasoconstriction, use ABG
- PA catheter**:** no mortality/LOS/cost benefit in undifferentiated shock or ICU all-comers but may be associated with improved mortality in cardiogenic shock Cochrane Rev 2013; JAMA 2005;294:1625; Lancet 2005;366:472, JACC 2020;903-913
- Steroids: known adrenal insufficiency / chronic steroids, stress-dose steroids (hydrocortisone 50mg q6h / 100mg q8h x5-7d)
- Bicarbonate: if pH <7.1 or <7.2 w/ severe AKI, can use bicarb amps or bicarb gtt. No mortality benefit except in AKI (Lancet 2018;392:31)
- Refractory Shock: *Consider:* dynamic LVOT obstruction (due ↑inotropy), anaphylaxis, abdominal compartment syndrome, abdominal catastrophe (can be masked by steroids), new obstructive shock (HOCM/PE), hypocalcemia, and refractory vasodilation
- Rescue therapies: hydroxocobalamin (NO scavenger), angiotensin II, methylene blue (reverse NO mediated vasodilation), thiamine, ECMO

## Distributive Shock

**Septic Shock** (see *Sepsis)*; **Anaphylactic Shock** (see *Anaphylaxis*)**; Neurogenic Shock**: Suspect if hypotension is in the context of TBI or SCI. Fluid resuscitate with NS, ***not*** LR (slightly hypotonic and will worsen edema in TBI), watch for signs of increased ICP

## Hypovolemic Shock

- Access: obtain 3 IVs (16G or less) if possible. Consider Cordis for rapid infusion; TLC, PICC cannot resus. as quickly
- Etiology: poor PO, GI (vomit/stool/fistula), GU (osmotic diuresis/diuretics, hypoaldo, salt wasting), burns, heat stroke, third spacing (pancreatitis, low albumin, trauma), hemorrhage (trauma, surgery, GIB)
- Fluid resuscitation: Crystalloid boluses (LR>NS) unless hemorrhagic shock, then use minimal necessary to bridge to blood availability

If Major Bleeding: obtain STAT coags, CBC, fibrinogen, $iCa^{2+}$. Ensure access. Hold pressure. Correct coagulopathies and consider AC reversal. If INR >2.5, use 4F-PCC (unless ESLD, no INR goal); Plt <50, transfuse plts; fibrinogen <100, use cryo. If iCal <1.10, give IV Ca.
  - If suspect bleed secondary to variceal bleeding, administer octreotide for splanchnic vasoconstriction (*see UGIB*)
  - If surgical/trauma/gyn, consider TXA (1g IV over 10 min → 1g over 8h) or aminocaproic acid (5g IV over 1hr → 1g per hr x 8hr)
- Resuscitation: Transfuse to hemodynamics if bleeding is driving shock. Call for Emergency Blood or Massive Transfusion (*see MTP*)
- Obtain source control: Call surgery/vascular/GI/IR/ pending location of bleeding. Obtain STAT CTA if stable.

## Cardiogenic Shock

- Cardiomyopathic: Ionotropic support with dobutamine (note: unclear use in mixed septic shock), 2-5 mcg/kg/min, diuresis. In MI, revascularization w/ PCI or CABG.
- Arrhythmogenic: *Tachyarrhythmia:* synchronized DCCV, vagal maneuver, adenosine, βB. *Bradyarrhythmia:* atropine, pacing.
- Mechanical: (e.g. due to acute valvular insufficiency). Hemodynamic support, endovascular or surgical intervention.

## Obstructive Shock

Relief of obstruction is primary management strategy (see *Tamponade*) (see *PE*)
- PTX: O2, needle decompression or chest tube placement); Avoid mechanical ventilation or BIPPV

# 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 (↑SOFA score ≥2) from dysregulated host response to infection
- **Septic shock**: sepsis + (1) pressors to sustain MAP >65 **AND** (2) lactate >2 w/o hypovolemia
- **SIRS may reflect appropriate host response**. SIRS + infectious source not sensitive for sepsis (NEJM 2015;372:1629)

**qSOFA**
1. RR>22
2. AMS
3. SBP≤100

**Sequential Organ Failure Assessment** (SOFA) **score**: includes PaO2/FiO2, plts, bili, BP, GCS, Cr/UOP
- **qSOFA ≥2** can be used to identify pts outside ICU w/ suspected infection likely to have poor outcomes (↑ICU LOS, ↑mortality)
- Surviving Sepsis Campaign guidelines recommend against qSOFA vs other screening tools as single-screening tool for sepsis and septic shock (Crit Care Med 2021;49:e1063)

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

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

| | |
|---|---|
| **Cardiovascular** | **Vasodilation** → hypotension; ventricular function may be either hyperdynamic or depressed |
| **Pulmonary** | Pulmonary edema, **ARDS** |
| **GI** | ↑intestinal permeability → ↑bacterial translocation → 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**, **↓plt** |
| **Endocrine** | Altered glycemic control, adrenal dysfunction, sick euthyroid syndrome |
| **Neurologic** | Encephalopathy |

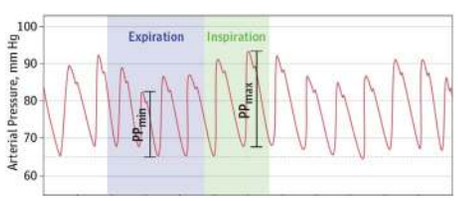
## INITIAL MANAGEMENT (2021 Surviving Sepsis: Crit Care Med 2021;49:e1063)

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

**1) Antibiotics**: **administer empiric broad spectrum IV antibiotics ideally within one hour of recognition**. **Order STAT**.
- Delay → ↑mortality by 7.6%/h (CCM 2006;34:1589; CCM 2010;38:1045). More rapid abx →↑ mortality (NEJM 2017;376:2235)
- **Abx selection**: guided by infection site, prior micro, community resistance patterns, exposures (SNF, lines, hx abx), host immunity
  - Consider double coverage for gram-negative organisms if severe sepsis/septic shock and high suspicion/risk for resistant organisms (neutropenic or burn patients). Usually β-lactam + (FLQ or aminoglycoside) (J Infect Dis. 2020;222:S119)
  - For ESBL organisms in non-GU infections, carbapenems are preferred to pip-tazo despite micro sensitivity (JAMA 2018;320:984)
  - If there is suspicion of toxic shock syndrome, add **clindamycin or linezolid** for anti-toxin effect (& more 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**)
- **β-lactam Admin.:** After load, extended or continuous infusion of beta-lactams is recommended (Lancet Infect Dis 2018;18:108)
- **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 of abx (Lancet 2010;375:463; Lancet ID 2016;16:819; CCM 2018;46:684)

**2) Resuscitation**: **initial resuscitation with crystalloid completed w/in 3 hrs (~30 mL/kg in most pts, ↑ caution w/heart/renal failure)**
- **Balanced crystalloids** (e.g. LR) with ↓ mortality and ↓ 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)
- New data are emerging to suggest **isotonic bicarbonate resuscitation** may ↓ rates of complications like ARDS and multiorgan dysfunction in hemorrhagic shock; though no clear mortality benefit (AmJEM. 2024:76:41-47. Medicine.202218;101(46):e31671
- **Targets of resuscitation**: lactate clearance (normalization or >20% / 2h) (JAMA 2010;303:739); cap. refill (<3s) (JAMA 2019;321:654)
- Fluid resuscitation goals in sepsis remain controversial. Recent data suggests that mortality and secondary outcomes are similar between restrictive vs liberal fluid strategies (NEJM 2023;388:499). Utilize clinical judgement to prevent volume overload.

### ASSESSING FLUID RESPONSIVENESS (JAMA 2016;316:1298)

| Method | Fluid responsive if: |
|---|---|
| **Pulse pressure variation**: validated in mechanically ventilated w/ $V_T$ ≥8cc/kg, not spontaneously triggering ventilator, & in NSR (Crit Care 2014;18:650)<br>Mech ventilation = pos. pressure during inspiration → ↓venous return & RV preload → ↑LV filling/output → $PP_{max}$ in inspiration, $PP_{min}$ in expiration<br>**PPV** = $(PP_{max} - PP_{min})/PP_{mean}$<br>  | PPV ≥13%<br>If on ascending portion of Starling curve, sensitive to Δs 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 → "autotransfusion" of ~250-350cc; assess Δ in hemodynamics<br> | ↑PP ≥10% (surrogate for ↑SV if no invasive measure of CO) |
| **Fluid challenge**: bolus 250-500cc fluids; check CVP before & immediately after, if ↑ ≥2, adequate volume challenge | Improved hemodynamics, UOP, lactate; ↑PP ≥10% |

# Pulmonary & Critical Care — Sepsis

## Initial Management Continued

**3) Vasopressors: target a mean arterial pressure (MAP) of >65mmHg** (NEJM 2014;370:1583) (see *Vasopressors* for full details)
*NOTE: permissive hypotension (MAP goal >60) reduces vasopressor use and may be appropriate in select patients (JAMA 2020;323:938).*

- Norepinephrine ("levo"): **first choice vasopressor**
- Vasopressin ("vaso"): add when NE at 5-15mcg/min to ↑kidney function. Not titrated, on or off at 0.04U/min (NEJM 2008;358:877)
- Epinephrine ("epi"): 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: used in refractory distributive shock, AE: risk of hemolytic anemia in pt with G6PD deficiency, serotonin syndrome in pts on serotonergic meds)
- Hydroxocobalamin (Cyanokit): used in refractory distributive shock, similar mechanism of action as methylene blue
- Angiotensin II: newly available at MGH since 12/2024; used in refractory distributive shock; ATHOS-3 trial (NEJM 2017;377:419)

**4) Source Identification and Control**

- Cultures: **obtain cultures prior to antimicrobials** (unless will significantly delay administration) as ↑Sn (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 fungal infection
- 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
- **Once stabilized, low threshold to obtain cross-sectional imaging to identify infectious source**

> ***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

**Corticosteroids**

- Rationale: critical illness affects HPA axis, may cause relative "critical illness-related corticosteroid insufficiency" (CIRCI)
- Conflicting evidence regarding mortality benefit of corticosteroids in septic shock:
  - "Annane/French trial" (JAMA 2002;288:862) ↓mortality w/ IV hydrocort 50mg q6h + fludrocort 50mcg/d x7d in pts w/ septic shock, replicated (NEJM 2018;378:809), others showed no Δ mortality (NEJM 2008;358:111; JAMA 2016;316:1775; NEJM 2018;378:797).
  - Combination fludrocortisone + hydrocortisone may improve some outcomes (JAMA Intern Med 2023;183:451), but recent study showed no difference in time to resolution of shock or mortality (ICM 2024;50:2050)
- CAPE COD trial showed mortality benefit for patients hospitalized with severe bacterial CAP (NEJM 2023;388:1931)
- Consider **hydrocort 50mg q6h or 100mg q8h** (≤400mg/d) **+ 0.1 mg fludrocort** in septic shock with ongoing vasopressor requirement (e.g., NE >15-25 mcg/min) (Crit Care Med 2021;49:e1063; Crit Care Med 2024)

**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 → $NaHCO_3$ 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 unless cardiac ischemia or active hemorrhage (NEJM 2014;371:1381)

## Interventions Without Clear Benefit

**Vitamin C**

- Rationale: Vitamin C is an antioxidant; may also act synergistically with hydrocortisone and thiamine to ↓inflammation. IV Vitamin C associated w/↑mortality and organ dysfunction compared to placebo in adults w/sepsis (NEJM 2022;386:2387).

**Thiamine**

- Rationale: thiamine deficiency may raise lactate, increase oxidative stress, affect inflammation, and has been associated with impaired organ function. IV thiamine associated w/ ↑ number of ICU-free days (AJRCCM 2023;208:570), no mortality benefit

**Short-Acting Beta Blockers**

- 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%). Subsequent RCT of landiolol in septic shock did not demonstrate mortality benefit, and point estimate favored standard care group (37.1% vs 28.6%) (JAMA 2023;330:1641)
  - Conclusion: need further validation of findings; short-acting beta blockers **not routinely used** in septic shock

# Pulmonary & Critical Care

## Vasopressors

| Category | Name | α | $\beta_1$ | $\beta_2$ | D | PVR | SVR | CO |
|---|---|---|---|---|---|---|---|---|
| Vasoconstrictors | Phenylephrine | 5+ | 0 | 0 | 0 | 2+ | ⇧ | ⇩ |
| | Vasopressin | $V_1$ | | | | ± | ⇧ | -/⇩ |
| | Angiotensin II | AT1 receptor | | | | 1+ | ⇧ | -/⇩ |
| 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 | ⇩ | ⇧ |

**$\alpha_1$:** vasoconstriction, ↑duration of heart contraction
**$\alpha_2$:** sedation/analgesia, vasoconstriction (if peripheral) vs vasodilation (if central, e.g. clonidine)
**$\beta_1$:** ↑inotropy, ↑chronotropy
**$\beta_2$:** ↑vasodilation
**D**: renal/splanchnic/coronary/cerebral vasodilation
**$V_1$**: vasoconstriction (especially splanchnic)

**Access: Ideal access is central (CVC, IO)**
Temporize w/ peripheral levo (<15 mcg/min) or neo (<150 mcg/min) for <72 hrs. Requires PIVx2, <20G w/ blood return in upper extremity AC or more prox. Check q2h given risk of extravasation (policy). If extravasation, draw back any infusing medication, give **phentolamine** 5-10mg in 10cc NS directly into area of extravasation, apply dry warm compress.

**Pressor Initiation/titration:** Start when SBP drops by >30 or MAP <65 WITH end-organ dysfunction despite optimization of volume status. Monitor MAP, UOP, mentation to titrate pressor dose. Responsiveness may decrease over time.
*Subcutaneous medications may ↓effectiveness due to ↑vasoconstriction.

**VASOPRESSORS & INOTROPES** (Intensive Care Medicine 2019;45:1503)

| | Name | Mechanism | Uses | Side effects | Dosing |
|---|---|---|---|---|---|
| VASOPRESSORS | Norepinephrine<br>*Levophed*<br>**"Levo"** | $\alpha_1$ > $\beta_1$ agonist:<br>**↑↑SVR, ↑CO** | **Septic shock (1st)**<br>**Cardiogenic shock (1st)**<br>**Hypovolemic shock (1st)** | Arrhythmia, ↑LVOT obstruction, Digital ischemia, ↑FSBG (by ↓insulin sensitivity), Immunosuppression (AJRCCM 2020;202:830) | Initial: 2-12mcg/min (0.1-0.15mcg/kg/min)<br>*PIV: <10mcg/min*<br>Max: 35-100mcg/min (0.75mcg/kg/min) |
| | Phenylephrine<br>*Neosynephrine*<br>**"Neo"** | Pure vasopressor<br>$\alpha_1$ agonist: **↑↑ SVR** | Septic shock if ↑↑HR from NE or ↑CO w/ ↓↓BP or 3rd agent needed<br>**AFRVR, HOCM, AS,** | **Reflex bradycardia**<br>↓CO, ↑PAP, ↑SVR<br>Digital ischemia | Initial: 50-180mcg/min (0.5-2mcg/kg/min)<br>*PIV: <150mcg/min*<br>Max: 360-1000mcg/min (6mcg/kg/min) |
| | Vasopressin<br>*Pitressin*<br>**"Vaso"** | $V_1$ agonist: **↑SVR**<br>$V_2$ agonist: ↑renal $H_2O$ reabsorption | Septic shock (2nd), add when NE 5-15 mcg/min<br>Anaphylaxis (2nd)<br>Pulmonary HTN/RV failure<br>Hepatorenal syndrome | Digital ischemia<br>Coronary ischemia<br>Mesenteric ischemia (especially high dose)<br>↓Na | Usual: 0.04U/min<br>Consider when NE 5-15<br>Max: 0.08U/min (only as salvage therapy) |
| | Epinephrine<br>*Adrenalin*<br>**"Epi"** | Low: $\beta_1$ > $\beta_2$ > $\alpha_1$:<br>**↑CO,** neutral **SVR**<br>High: $\alpha_1$ > $\beta_1$ > $\beta_2$:<br>**↑CO, ↑SVR** | **ACLS (1st)**<br>**Anaphylaxis (1st)**<br>**Symptomatic bradycardia (2nd)**<br>Septic shock<br>Bronchospasm | ↑HR, arrhythmias, ↑LVOT obst, Myocardial ischemia, ↑lactate, ↑splanchnic SVR<br>↑FSBG | Low: 1-4mcg/min<br>High: 5-35mcg/min |
| | Angiotensin II<br>(MGH Ellucid Policy) | AT1R agonist: **↑SVR** | Refractory distributive shock (MGH practice = already on 2 vasopressors + stress dose steroids)<br>MCS/CBP vasoplegia | Ischemia (digital, myocardial, gut), Potential increased risk of VTE (NEJM 2017;377:419) | Initial: 5-10 ng/kg/min<br>Max: 80 ng/kg/min |
| | Dopamine<br>*Intropin*<br>**"Dopa"** | Low: $D_1$ > $\beta_1$:<br>**↑CO, ↑UOP**<br>Med: $\beta_1$ > $D_1$:<br>**↑CO, ↑SVR**<br>High: $\alpha_1$ > $\beta_1$ > $D_1$:<br>**↑SVR** | Symptomatic bradycardia<br>Septic shock w/ bradycardia<br>**↑mortality vs. NE** in septic (CCM 2017;45:486) & cardiogenic shock (NEJM 2010;362:779) | Tachyarrhythmia<br>Myocardial ischemia<br>↓BP (low dose)<br>↑PCWP, pulm shunt<br>↑FSBG | Low: 1-2mcg/kg/min<br>Med: 5-10mcg/kg/min<br>High: 10-50 mcg/kg/min |
| | Methylene blue | ↓NO and cGMP, ↑smooth muscle tone:<br>**↑SVR** | Refractory vasoplegia in distributive shock, Post-cardiopulm bypass, Amlodipine overdose, Metformin overdose, Methemoglobinemia | Falsely ↓$SpO_2$, Arrhythmias<br>↑PVR, Rash, hemolysis, serotonin syndrome,<br>⊘⊘⊘ in G6PD, Avoid in severe PH (↑PA pressure) | Initial: 1-2mg/kg<br>Max: 5mg/kg |
| | Hydroxocobalamin<br>*Cyanokit* | IV vit B12, NO synthase inhibition; Modifies H2S (NO and smooth muscle activity) | Tx of vasoplegia refractory to methylene blue treatment (or if methylene blue contraindicated) | Urine discoloration<br>Interference w/ many labs (Clin Biochem 2021;91:31) | Initial: 5g over 15 minutes<br>Max: 30g in 24 hrs |
| INODILATORS | Dobutamine<br>*Dobutrex*<br>**"Dobuta"** | $\beta_1$, $\beta_2$ > $\alpha_1$ agonist:<br>**↑CO, ↓SVR** | Cardiogenic shock<br>Sepsis + ↓LV EF (add to NE/vaso) | **↓BP, ↑HR,** Arrhythmias, Myocardial ischemia, Tachyphylaxis | Initial: 0.5-1 mcg/kg/min<br>Max: 20-40mcg/kg/min |
| | Milrinone<br>*Primacor* | PDE inhibitor (↑cAMP), ↑inotropy, vasodilation:<br>**↑CO, ↓PVR/SVR** | Cardiogenic shock<br>RV failure (↓PVR, ↓LVEDV) | **Hypotension**<br>Arrhythmias<br>Myocardial ischemia | Initial: 0.125mcg/kg/min<br>Max: 0.75mcg/kg/min |
| | Isoproterenol<br>*Isuprel* | $\beta_1$ = $\beta_2$ agonist:<br>**↑HR, ↓SVR** | Symptomatic bradycardia<br>Mg-refractory torsades de pointes | ↓BP, ↑HR<br>Arrhythmias<br>Myocardial ischemia<br>Flushing, anxiety | Initial: 2-10mcg/min (can bolus 2-6mcg first)<br>Max: 30mcg/min |

# Pulmonary & Critical Care — Toxicology

**BWH Tox fellow pager 30435 • Poison Control 1-800-222-1222 • MGH Lab Tox Screen Guru: Dr. Jim Flood**

| | 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, max 50g) if <1h, benzodiazepines (BZD) for agitation & seizure, 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, EKG, BMP, CPK, lactate. Can monitor RBC AChE inhibitor if available | 100% $O_2$, avoid succinylcholine for intubation, 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), BZD for seizure |
| | **Sympathomimetics** Amphetamines, MDMA, cathinones "bath salts" | Agitation, mydriasis, hallucinations, paranoia, tachycardia, HTN, diaphoresis, hyperthermia, piloerection, seizure, vasospasm, ACS | EKG, BMP, lactate, CPK, LFTs, coags | IV BZDs, atypical antipsychotics, cooling. For refractory agitation, avoid succinylcholine and ketamine |
| | **Neuroleptic Malignant Syndrome (NMS)** Dopamine blockade, dopaminergic w/d | AMS, "lead pipe" rigidity, sialorrhea, hyperthermia, dysautonomia, diaphoresis Typically no N/V/D or hyperreflexia | Search for causative agent. CPK (↑↑), CBC (↑WBC), LDH, LFTs, BMP, serum Fe (often ↓); consider brain imaging, LP, EEG | D/c causative agent or restart dopamine if stopped, 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 + seizure |
| | **Antipsychotics** | Physiologic depression, miosis, anticholinergic effects, extrapyramidal reactions/NMS, tachycardia | CMP, CBC, CPK, LDH, LFTs, serum iron, EKG, EEG | $NaHCO_3$ for QRS prolong.; Mg, isoproterenol, overdrive pacing if torsades. Avoid class IA, IC, and III antiarrhythmics |
| | **TCAs** | Prolonged QRS, arrhythmia, hypotension, anticholinergic toxicity, myoclonus, hyperthermia, AMS, coma, seizure | CPK, tox screen, EKG: ↑QRS duration (>100ms, 26% seizure risk; >160, 50% risk), terminal R wave >3mm in aVR. Watch for ventricular arrhythmia | $NaHCO_3$ if QRS >100ms or HoTN. BZDs for seizure. Salvage: 3% NaCl, lipid emulsion, avoid physostigmine. VA-ECMO for refractory cardiac toxicity and shock. |
| | **Lithium** | N/V/D, tremor, hyperreflexia, clonus, ataxia, AMS, seizure, 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 flowcharts in *Consensus Statement*: JAMA 2023;6(8)e2327739 and See *Acute Liver Injury & Failure* | |
| | **Opioids** | ↓RR & $V_T$, CNS depression, ↓bowel sounds, miosis | EKG, core temp, finger-stick blood glucose, 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 blood glucose) | 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), $NaHCO_3$ to alkalinize urine to pH 7.5-8, avoid acetazolamide. Consider HD |
| Cardiac medication | **CCBs** | N/V, HoTN, CHF, ↓HR, AV block, stupor, cardiac arrest, ↑blood glucose | 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) + D10, IVF; consider pacing, atropine, ECMO |
| | **B-Blockers** | HoTN, ↓HR, AV block, long QTc (sotalol), CHF, bronchospasm, ↓FSBG, stupor, ↑K, seizure (propranolol), miosis | Hx, EKG, blood levels (slow, correlate poorly); propranolol highest mortality | Pressors, calcium, glucagon (5 mg bolus, if no improvement of HR or BP repeat in 10-15 min), high-dose insulin (see CCB), IVF; atropine, pacing, ECMO. HD for atenolol, sotalol |
| | **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 (if K>5.5, severe end-organ dysfxn, or life-threatening arrhythmia), Mg, **AVOID** hypokalemia |
| Other | **Cocaine** | Agitation, psychosis, seizure, HTN, ↑HR, vasospasm/MI, arrhythmia, stroke, vasculitis, lung injury, rhabdo | Serum/urine tox (metabolites detectable for 2-5d), EKG, cardiac biomarkers if chest pain, CPK, UA | Hyperthermia treatment (cooling, BZDs), treat chest pain with ASA, CCB, nitrates, (no pure βB). Lido/sodium bicarb for WCT. |

# Pulmonary & Critical Care — Toxicology

| | Drug/Toxin | Presenting Symptoms | Diagnostic Workup | Management |
|---|---|---|---|---|
| Other Exposure | **Carbon Monoxide** | Minor sx: headache, N/V<br>Major sx: confusion, LOC, seizure, coma, cardiac ischemia, arrhythmias | Hx (house fire, winter w/ space heaters), cyanide & carboxyhemoglobin levels, co-oximetry (SpO2 invalid), AG acidosis, EKG, TnT | 100% $O_2$ (t½ 250-320 mins→75-90 min); hyperbaric $O_2$ (t½ 250-320 mins→30 min); watch for delayed neuropsychiatric sequelae |
| | **Cyanide** | HA, nausea, AMS, seizure, 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-hydroxy-butyrate (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, β-hCG | Supportive; BZDs for withdrawal. *Note*: OD at low dose if on protease inhibitors |
| | **Synthetic Cannabinoids** "Spice" or "K2" | Anxiety, paranoia, sedation, memory impairment, hallucinations, psychosis, seizure, tachycardia, HTN, N/V, AKI | Not detected on routine tox screen, can send blood & urine for send-out | Supportive care. BZDs for agitation and seizure. Antipsychotics for agitation |

(Pharmacotherapy 2015;35:189; Chest 2011;140:795; Crit Care Clin 2012;28:479; Circulation 2023;148:149); see nephrology for alcohols

## Decontamination Therapies

- **Activated Charcoal:** Most effective if given when substance is **still in stomach** (usually considered to be **within 1h of ingestion**, but data are 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 to induce vomiting
- **Dialysis and Acid/Alkaline Diuresis** (consult Nephrology):
  - Dialyzable toxins: methanol, isopropyl alcohol, glycol, acetone, lithium, salicylates, barbiturates, INH, atenolol/sotalol, rarely EtOH
    - Acid diuresis (give vitamin C): quinine, PCP; Alkaline diuresis (give $NaHCO_3$): phenobarbital, salicylates, MTX, TCAs

## Lung Transplant Overview

- **Lung composite allocation score:** waiting list urgency score (age, labs, dx, resp status), + post-lung transplant (LT) outcomes score (labs, cardiac index) + biological disadvantages score (blood type/antibodies & height) + patient access score (+points for some groups) + efficiency score (travel + proximity efficiency) (AJT 2022; 22:2971), (OPTN LT policy 2022), (OPTN LT policy change 2023)
- **Procedure choice:** bilateral LT (BLT) is most common (~80%) d/t better long-term outcomes, but ongoing controversy regarding benefit of BLT vs. single LT (SLT) in COPD and IPF; SLT often not recommended in CF and pHTN (JTD 2018;10:4588)
- **Outcomes**: median survival in adults post-LT is 6.7 yrs, some dx have more favorable outcomes (e.g., CF) (JHLT 2019;38:1042)

## Lung Transplant Evaluation

**As a medicine provider:** healthcare maintenance, tx comorbidities, ⊘ substance use, optimize weight, limit blood product, early referral
**Pre-op assessments:** Medical: cardiac, pulm, ID, GI, renal, healthcare maintenance; Surgical/anesthesia; Functional: 6MWT, pulm rehab, nutrition; Psychosocial: SW, psych, financial services, caregiver eval
**Contraindications to transplant** (JHLT 2021;40(1350))

- Absolute: acute medical instability, significant multiorgan dysfunction (+ untreatable coagulopathy), high risk malignancy, uncontrolled HIV, active TB, hx of non-adherence to medical therapies, active substance use, uncontrollable bleeding disorder
- Relative: age >70, BMI > 35, EF<40%, active hepatitis, MDRO colonization/infxn, hx chest surg, severe esophageal dysmotility

## Post-Transplant Complications

**Early**: surgical (post-op hemorrhage), airway (stenosis, necrosis, bronchomalacia), infection, 1° graft failure (ischemic-reperfusion injury)
**Late Complications** (JCS 2022;55:338)

- Infectious: typically, donor-derived pathogens in immediate post-op period; bacterial (esp. P. aeruginosa, S. aureus, B. cepacian, E. faecalis), viral (esp. CMV, HHV), fungal (esp. Aspergillus)
- Malignancy: esp. dermatologic, SCC #1, post-transplant lymphoproliferative disorder (ATM 2020:02:126)

| | *Complication* | *Diagnostics* | *Treatment* |
|---|---|---|---|
| Immunologic | **Acute-Cellular Rejection (ACR)** (ATM 2020;8:410) | Graded on scale of 0-4 histology, degree of perivascular, interstitial, & air-space mononuclear inflammation | **Initial therapy**: Pulse dose steroids<br>**Refractory**: Repeat steroids, change cyclosporine > tacro, ATG*, sirolimus, ECP*, Cytoxan |
| | **Antibody-Mediated Rejection (AMR)** (ATM 2020:8:411) | Clinical diagnosis, detection of donor-specific abs, histology, lung bx C4d staining | Plasmapheresis, IVIG, rituximab, proteasome and complement inhibitors (usually steroid-resistant) |
| | **Chronic Lung Allograft Dysfunction (CLAD):** Bronchiolitis Obliterans Syndrome (BOS) & Restrictive Allograft Syndrome (RAS) (JHLT 2019;35:493) | Diagnose based on PFTs – CLAD staged 0-4 depending on FEV1 compared to baseline. BOS is obstructive; RAS is restrictive. RAS mortality > BOS | **BOS**: change tacro → cyclosporine, azithro, TLI*, fundoplication if +GERD, NO steroids<br>**RAS**: experimental antifibrotics |

*Extracorporeal photopheresis (ECP), total, lymphoid irradiation (TLI), antithymocyte globulin (ATG)

## Immunosuppression (ATM 2020;8:409)

**Induction**: basiliximab (anti IL-2R), alemtuzumab (anti CD52), ATG
**Maintenance**: tacrolimus/cyclosporine (CNIs), mycophenolate/AZA (anti-proliferative), sirolimus/everolimus (mTORi), steroids

## ACUTE UPPER GI BLEED (AJG 2021;116:5; Annals 2019;171:805; NEJM 2016;374:2367)

| Etiologies (Dig Dis Sci 2018;63:1286) |
|---|
| **PUD** (~50%; duodenal>gastric): H. pylori, NSAID, EtOH, tobacco, Cameron Lesion (in hiatal hernia), Zollinger-Ellison |
| **Esophagitis or gastritis** (~30%): GERD, pill (e.g. doxycycline, iron tablets), ASA, NSAID, clopidogrel, EtOH, infectious |
| **Varices** (~5%): EVB (esophageal) > gastric |
| **Vascular malformation** (~5-10%): Dieulafoy's lesion, AVM, GAVE, HHT, vascular ectasia 2/2 XRT, aorto-enteric fistula |
| **Traumatic** (~5%): Mallory-Weiss, foreign body, Boerhaave's |
| **Neoplastic** (~5%): primary > metastatic |
| **Post-procedural** (varies): polypectomy, sphincterotomy |
| **Biliary**: hemobilia, hemosuccus pancreaticus |

- **Definition**: bleeding proximal to the ligament of Treitz
- **S/Sx**: hematemesis, melena, hematochezia if brisk UGIB. Clots in stool make UGIB less likely
- **Risk Stratification and Triage:**
  - High-Risk Features in UGIB: HoTN, tachy, coagulopathy (INR > 1.5), Hgb <10, AMS, syncope, age > 65, liver dx, CHF
  - Risk scores: Glasgow-Blatchford Score and ABC score. Blatchford 0-1 = low risk of rebleeding, consider outpt management) (Annals 2019;171:805; BMJ 2017;356:6432; Gut 2021;70:707;)
  - Triage: May need ICU if BP <90 and HR >100 x2 30min apart; Hct <20/Hgb <7 regardless of vital signs with evidence of active significant bleed in past 12hrs; require >2L IVF or 2u pRBCs to prevent instability/keep Hct >25.
- **Assessment/Management**: Stabilize → Intervene
  - Initial Workup**:** CBC (q2-8hr), CMP, coags, type & screen, orthostatics, abdominal exam, rectal exam to assess stool color (dark color stool easier to assess if stool smear onto white disposable napkin)
  - Stabilization: NPO, intubation if high-risk for aspiration (large volume hematemesis, AMS); ensure ≥2 PIV (18G or larger).
    - Resuscitation/Transfusion: IVF (isotonic crystalloid) for hypotension. Do not delay transfusion if active hemorrhage, otherwise transfuse pRBCs for Hgb >7 (NEJM 2013;368:11; Lancet 2017;2:354) or Hgb >8 if CAD (Annals 2019;171:805). Note: Hct drop lags 24-72h from onset of bleeding. For severe/ongoing bleeding (generally after 4u pRBCs), activate massive transfusion protocol see Transfusion Medicine - MGH Transfusion Guide. Avoid over-transfusion, extra volume can ↑ portal pressures and worsen bleeding from EV
    - Correct coagulopathy: Transfuse for plt >50k. For INR >1.5 consider PCC (preferred over FFP for lower volume, faster onset). If ESLD, INR inaccurate - avoid FFP (↑volume→↑portal HTN). If uremic, consider ddAVP. No utility to TXA.
    - Consults: GI for EGD and/or colonoscopy, surgery/IR if hemodynamic instability or if endoscopy not preferred
      - **EGD generally within 24hrs**, but no Δ in outcomes if between 0-6hrs vs. 6-24hrs for non-variceal or non-HDUS bleeds (NEJM 2020;382:1299).Barium studies are contraindicated d/t interference with EGD/angiography. NGT placement/lavage is not associated with improved outcomes (ERGH 2017;12:63) and not generally recommended
  - Pre-EGD Pharmacotherapy:
    - **IV PPI**: pantoprazole 40mg BID (neutralizing acid stabilizes clots); ↓ high-risk lesions requiring endoscopic therapy but unclear clinical impact pre-EGD (Cochrane Rev. 2010)
    - **IV prokinetics:** erythromycin 250mg 30m prior to EGD ↑gut motility & visualization (Ann Gastroenterol 2016;29:312 - takes time to come from pharmacy so STAT prepare). If unable to obtain, substitute 10mg IV metoclopramide
    - For cirrhosis**: IV octreotide** 50 mcg bolus (may repeat bolus in first hour if bleeding uncontrolled) followed by gtt at 50 mcg/hr for 2-5 days. **IV CTX** 1g q24hr x7 days for ppx against bacterial infections and mortality benefit (Gastro 2006;131:1049; APT 2011;34:509). Hold *β*-blockers through day 5.
  - Anticoagulation/Antiplatelet Management: (Gastrointest Endosc 2016;83:3; Am J Gastroenterol 2022;117:542)
    - **Warfarin**: Hold during bleed. For reversal, consider PCC, but FFP or vit K NOT recommended. Resume after hemostasis (w/ UFH bridge for ~48hrs if indicated). ↓ risk of thrombosis/death in AF if resumed within 7d (Am J Cardiol 2014;113:662).
    - **DOAC**: Hold during bleed. Reversal with idarucizumab, andexanet alfa, or PCC NOT recommended. Resume within 72hrs in high thrombotic risk pts, within 7d for low thrombotic risk pts.
    - **ASA**: Continue during bleed if low-moderate risk, hold if high risk (unless recent PCI/ACS – see below). Resume ASA for 2° prevention after hemostasis endoscopically confirmed (Gastrointest Endosc 2016;83:3) ↑ risk of 30d mortality if not resumed (Annals 2010;152:1); if PUD, add PPI to ↓ risk of re-bleeding.
    - **DAPT for PCI/ACS**: Discuss with cardiologist. Generally if very recent (<30d PCI, <90d ACS), continue both unless life-threatening; if more distant, continue ASA but less risk with holding P2Y12i. Resume within 1-5d pending course
    - Overall, restarting AC/AP sooner → ↓ risk of vascular events, though ↑ risk of bleeding (APT 2019;50:8).
  - Post-EGD Pharmacotherapy/Management: Review GI procedure note for recommendations on specific diet, PPI, etc.
    - For high-risk PUD: **IV pantoprazole** 40mg BID x 72hrs → ↓re-bleeds and need for repeat EGD. Switch to PO PPI after 72hrs, d/c with BID dosing x 2-8wks. **Treat *H. pylori*** if positive (see GERD and Peptic Ulcer Disease).
    - For variceal bleed: consider **octreotide** x 2-5d, continue **IV CTX** 1g q24hr x7 days. Restart βB on day 5.
    - For angiodysplasia: consider long-term **octreotide** (APT 2012;36:587) or **bevacizumab** w/ GI input
      If re-bleed: consider repeat EGD, CTA + surgical/IR consult. If variceal bleeding, consider balloon tamponade or TIPS

# Gastroenterology — Lower GI Bleeding

## Acute Lower GI Bleed

- **Definition**: Bleeding distal to the ligament of Treitz
- **S/Sx**: hematochezia (maroon or bright red blood, blood clots; *Note:* BRBPR can be seen in brisk UGIB); rarely melena (requires blood spending 14hr in GI tract); BUN/Cr typically <20 w/ normal renal fxn
- **Risk stratification**:
  - Risk scores: ABC score predicts 30d mortality; Oakland score <8 may predict safe discharge (JAMA 2020;3:e209630)
- **Assessment/Management**: See Figure 1 in AJG 2023;118:208 for flow chart.
  - Initial Workup: CBC (q2-12hr depending on severity of bleed), CMP, coags, type & screen.
    - Colonoscopy is the diagnostic test of choice for **hemodynamically stable** LGIB. CT angiography is diagnostic test of choice for **hemodynamically significant** LGIB (shock index HR/SBP >1)(AJG 2023;118:208). CTA low yield for minor or improved bleed. Tagged RBC scan more sensitive than CTA, but rarely used due to poor localization.
    - If hemodynamically unstable, consider UGIB. 10-15% of patients with severe hematochezia will have UGIB (AJG 2010;105:2636). Diagnose with EGD.
  - Resuscitation
    - Ensure ≥2 PIV (18G or larger). IVF (isotonic crystalloid) for hypotension. Do not delay transfusion if active hemorrhage, otherwise transfuse pRBCs for Hgb >7 (NEJM 2013;368:11; Lancet 2017;2:354) or Hgb >8 if CAD (Annals 2019;171:805; JAMA 2021;325:552). Note: Hct drop lags 24-72h from onset of bleeding. For severe/ongoing bleeding (generally after 4u pRBCs), activate MTP (see *Transfusion Medicine*). Plt goal >30k or >50k if undergoing procedures.
    - Anticoagulation/Antiplatelet Management
      - Most data extrapolated from UGIB, see AC/AP Management section in *Upper GI Bleeding*
      - Lower GI bleeding data suggests ASA for 1° prevention should be stopped and generally not resumed. ASA for 2° prevention should not be held; if it is, it should be resumed soon after bleed resolves (Gastro 2016;151:271).
  - Approach to intervention:
    - **If hemodynamically UNSTABLE**: Consult GI, IR, and consider surgery.
      - GI: Exonerate UGIB first with EGD (10-15% of patients with severe hematochezia)
      - IR angiography: Employed when patients are too hemodynamically unstable for endoscopy (get CTA first). Therapeutic if embolization performed, but risk of bowel ischemia and vascular injury.
      - Surgical consult for subtotal colectomy if cannot locate or control bleed.
    - **If hemodynamically STABLE:** Consult GI for discussion of colonoscopy vs flexible sigmoidoscopy.
    - Colonoscopy: Recommended for most patients hospitalized with LGIB, unless bleeding subsided and pt had colo with diverticulosis in last year (AJG 2023;118:208)
      - Timing: Colonoscopy at 24-36hrs may be a safe approach in most stable patients (Gastro 2020;158:1)
      - Bowel preparation: No solid food or red liquids for 8 hours prior, use order set "Gastroenterology Bowel Prep"

| 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%); Heyde syndrome |
| 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 | Aorto-enteric fistula |
| Recent SCT/DLI | Graft-vs-host disease |
| HDUS(↑HR,↓BP) | Brisk UGIB (13%) |

## Unidentified Source After EGD/Colonoscopy (ACG: AJG 2015;110:1265)

- **Source**: ~75% small bowel, 25% UGIB/LGIB
- **Small Bowel Causes**: Common: angioectasia, IBD (esp. <40), Dieulafoy's lesion, neoplasm, Meckel's diverticulum (esp. <40), polyposis syndrome (esp. <40), NSAID ulcers; Rare: varices, portal hypertensive enteropathy, amyloid, HHT, Kaposi, inherited CTD, congenital vascular abnormalities. Consider Heyde syndrome (triad of AS, GI bleeding, and acquired VWD).
- **Assessment/Management**: See Figure 1 in ASGE 2017;85:22for flow chart
  - Video capsule (VCE): 1st line but contraindicated if known strictures (risk of retention). Consider post-placement IV erythromycin 250mg IV to promote passage
  - 2nd look EGD ± push enteroscopy: (prox 60cm jejunum) if recurrent UGI sx; 2nd look colo: if recurrent hematochezia
  - CT enterography: if ⊖VCE or if risk of strictures (IBD, XRT, prior SB surgery, suspected stenosis); CTE>MRE
  - Balloon enteroscopy (single vs double): if strong suspicion of SB lesion and therapy required; often after ⊕VCE
  - If brisk bleed: CTA if stable then angio. If unstable, can intervene with embolization, enteroscopy, or surgery
  - If no source found: iron repletion; consider octreotide, anti-angiogenic tx; replace aortic valve if Heyde & ongoing bleeding

# Gastroenterology — Abdominal Pain

| Abdominal Pain History and Physical – Key Elements | Initial Testing to Consider: BMP, Ca, Mg, CBC w/ diff, LFTs, lipase, lactate, ESR/CRP, UA, b-hCG, troponin, coags, T&S Infectious studies as indicated |
|---|---|
| **History**: Location, chronicity, quality, radiation, pain Δ w/ eating or BMs, Δ in BMs (caliber, color, diarrhea, constipation), fever, wt. loss, jaundice, medications (NSAID, abx, steroids), alcohol, travel, sick contacts, surgeries<br>**Exam**: Tenderness, distention, rigidity, rebound, guarding, BS, fluid wave, shifting dullness, auscultation, Castell's sign, McBurney's point, Rovsing's sign, obturator sign, HSM, abdominal veins, caput medusa, jaundice, DRE<br>**Special populations**: immunosuppressed, sexually active, elderly, SCD | |
| **RED FLAGS of Acute Abdominal Pain**<br>HDUS, rigidity, guarding, rebound tenderness, "Pain out of proportion", absent bowel sounds, gross distension + inability to tolerate PO, bilious emeis, hematemesis or hematochezia<br>**Cannot miss dx:** infarct, perforation, extra-instestinal hemorrhage, SBO, ectopic pregnancy, MI | |

## Acute Abdominal Pain – Anatomic Approach (Am Fam Physician 2008;77:971)

### Right Upper Quadrant
- Liver pathologies (hepatitis, abscess, Budd-Chiari, portal vein thrombus, Fitz-Hugh-Curtis)
- Biliary pathologies (cholelithiasis/biliary colic, cholecystitis, cholangitis, Sphincter of Oddi dysfunction)
- Extra-abdominal: PE, PNA, CHF

### Right Lower Quadrant
- Appendicitis • Lymphadenitis • Ileal Crohn's

### Diffuse
Obstruction, ischemia, AAA, perforation, peritonitis, gastroenteritis, IBD, dietary, SBP, toxin, meds (iron, opioids), cancer, DKA, adrenal insufficiency, celiac, Familial Mediterranean Fever, hereditary angioedema, Acute Intermittent Porphyria

### Epigastric
- Pancreatitis
- Gastric pathologies (GERD, PUD, gastritis/gastropathy, functional dyspepsia, gastroparesis)
- Mesenteric ischemia
- Esophagitis
- Extra-abdominal: MI, Aortic dissection

### Periumbilical
- Early appendicitis
- PUD
- Bowel obstruction (SBO >LBO)
- Umbilical hernia

### Suprapubic
- UTI/Cystitis • Prostatitis
- Urinary retention

### Left Upper Quadrant
- Splenic pathologies (splenomegaly, abscess, infarction, rupture, trauma)
- Gastritis, PUD
- Sub-diaphragm or abdominal abscess (either side)

### Left or Right Lower Quadrants
- Intestinal pathologies (diverticulitis, colitis, constipation, IBD, IBS, volvulus, lymphadenitis)
- Renal pathologies (pyelonephritis)
- Pelvic pathologies (ectopic preg, fibroids, ruptured cyst, endometriosis, torsion, PID, abscess, epididymitis)
- Hernia
- Hematoma

## Image Negative Abdominal Pain

Metabolic: DKA, Ca, uremia, heavy metals, AI, AIP Meds/Toxins: EtOH, opioids/opioid withdrawal, cocaine, anticholinergics, lead/heavy metal Functional: IBS, abdominal migraine, functional dyspepsia Episodic: passed kidney stone, sphincter of Oddi dysfunction

### Symptomatology/Diagnosis and Corresponding Imaging

- Diffuse
  - -Acute, nonlocalized pain with fever: CT AP w/ Contrast
  - -SBO: CT AP w/ Contrast over plain film
  - -Mesenteric ischemia: CTA AP
- AAA suspected: HDS stable → CTA AP; HDUS→STAT vascular surgery consult
- Epigastric
  - -PUD: H. pylori stool antigen, EGD
  - -Pancreatitis: CT AP w/ Contrast
  - -Biliary: RUQUS followed by MRCP w/ clinical suspicion
- LUQ:
  - -Abscess: CT AP w/ Contrast
- Lower quadrant,
  - -Appendicitis: CT AP w/ Contrast
  - -Diverticulitis: CT AP w/ Contrast
  - -Nephrolithiasis: CT AP Non-Contrast
  - -Pelvic, b-hCG+: pelvic and transvaginal US

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

*CAPS*: Type of functional GI disorder with freq/near continuous pain not related to impaired gut function, structural, or metabolic causes. Instead caused by CNS sensitization and altered pain signals. Multimodal treatment with therapy/stress reduction/meds. Early psychologic, behavioral, or mindfulness referral (such as Benson-Henry Institute at MGH). Trial SSRI (least analgesic), SNRI, or TCA for 4-6 weeks → dose titration → potentially dual therapy. Psychiatry referral if refractory

*NBS*: Chronic abd. pain treated with acute high-dose or chronic narcotics. Not explained by structural causes/other dx, and pain worsens when ↓ narcotics. Tx: reduce opioid while controlling pain (consider antidepressants and nonpharmacologic therapy). Education key, esp. re: hyperalgesia. Consider inpatient detox. (AJG 2012;107:1426).

### Chronic Abdominal Pain – Etiologies

| 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 (see section), IBS, narcotic bowel syndrome (NBS) |

# Gastroenterology GERD & Peptic Ulcer Disease

## GASTROESOPHAGEAL REFLUX DISEASE (GERD) (ACG: AJG 2022;117:1)

**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 sensation, 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, functional dyspepsia

**Evaluation**: No alarm sxs → trial of 8-wk normal dose or short (1-2 wk) high-dose PPI BID. If alarm symptoms or no/incomplete response to PPI → EGD w/ biopsy: look for tissue damage, complications, or malignancy

- If endoscopy ⊖ but persistent symptoms → ambulatory pH monitoring/impedance testing
- If endoscopy ⊖ but persistent symptoms w/ CP and/or dysphagia → assess for motility disorder w/ esophageal manometry

**Management** (Gastro 2018;154:302):

- Lifestyle Δs: wt loss (goal BMI <25), tobacco cessation, drinking <2 cups of coffee/tea/soda, dietary changes; ≥30 min exercise daily, no eating 2-3 hours before bed, left lateral decubitus sleeping position, head-of-bed elevation 6-8in (JAMA IM 2021;e207238)
  - 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 sx after PPI d/c or if complications (see below). Lowest effective dose. Test for reflux + EGD at 1yr
    Discontinuing PPI: if on PPI >6mo., taper by 50% per wk to prevent rebound hypersecretion.
  - PPI risks**:** *probable association*: ↓Ca, Mg, Fe absorption, AIN, C.diff/other enteric infxns. *Insufficient evidence for* ↑risk of osteoporosis, CKD, or dementia (Gastro 2017;152:706), (Gastro 2020;115:671)
  - Vonoprazan (PCAB): New, expensive. Alternative to PPI. Start 10mg daily (Gastroenterology 2023;164:61)
- H2RAs (famotidine 10-20mg BID): can also use nightly PRN w/ PPI, tachyphylaxis common after wks
- Others: PRN antacids, sodium alginate (APT 2013;38:1059), baclofen (as adjunct)

Severe/Refractory Symptoms: If no relief after 8w on high-dose PPI BID, refer for EGD/impedance testing & re-consider diagnosis e.g. functional dyspepsia, nonerosive reflux disease, reflux hypersensitivity, eosinophilic esophagitis (EoE), rumination, hiatal hernia

  - EoE: dysphagia, GERD sx, food impaction; a/w allergic conditions. Dx with >15 Eos per HPF on biopsy. Tx: PPI, topical steroids (Gastro 2020;158:1776), dupilumab (IL4,13 antibody)
  - Hiatal hernia: Type I (sliding); 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 → intestinal metaplasia (IM). **AdenoCA** risk 0.38% (IM) vs 0.07% (no IM)/yr. Screen w/ EGD in: chronic GERD sx + ≥3 RFs (>50, white, male, central obesity, tobacco hx, FH of BE or adenoCA) (AJD2022;117:559). Mgmt: indefinite PPI. EGD interval depends on degree of dysplasia on biopsy
- **Esophageal stricture**: p/w progressive dysphagia to **solids**. Endoscopy w/ biopsy can differentiate stricture from cancer

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

**S/Sx**: dyspepsia - intermittent gnawing, dull, or "hunger-like" epigastric pain relieved w/ antacids, early satiety, bloating, n/v

**Etiology**: majority caused by H. pylori or NSAIDs (idiopathic becoming more common). *Others*: meds (bisphosphonates, clopidogrel, sirolimus), ZES, mastocytosis, HSV, CMV, EBV, fungal infxn, post-surgical, XRT, ischemia (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 dx active infection. Testing affected by PPI & abx (↑ false ⊖) but not affected by H2RAs. Serology (IgG) not affected by PPI/abx/bismuth but cannot distinguish active vs. past infection; a ⊖ serology excludes infection if low pre-test probability. Bx w/ urease, histology or cx
- **EGD**: biopsy malignant-appearing & select benign-appearing ulcers; obtain samples for H. pylori testing. Rebleed risk per Forrest classification.

| Forrest Class - Description | Re-bleed |
|---|---|
| Ia - Active arterial bleeding | 85% |
| Ib - Oozing w/o visible vessel | 30 % |
| IIa - Non-bleeding visible vessel | 40% |
| IIb - Adherent clot | 25% |
| IIc - Flat spot | 10% |
| III - Clean ulcer base | 3% |

**Management**: PPI (duration depends on etiology); if need to continue ASA, continue w/ PPI (NEJM 2005;352:238). F/u EGD after 8-12w if refractory sx (see below) or most gastric ulcers to exclude malignancy

**Treatment for H. pylori** (AJG 2017;112:2)

- First line = quadruple therapy: PPI BID, bismuth 300mg QID, tetracycline 500mg QID (alternative: doxy 100mg BID), metronidazole 500 QID x 14d. Combo pill (Pylera) available.
- Salvage therapy: Avoid antibiotics used previously. Trial clarithromycin, levofloxacin, or amoxicillin-based regimens. Recently approved combined treatment with rifabutin, amoxicillin, and PPI BID for 14d (as salvage therapy) was shown to have no difference in eradication rates but ↑ compliance and ↓ AEs compared to bismuth quad. therapy (J Inf Dis 2023;228:511).
- Confirmation of eradication: confirm for all pts w/ stool Ag, urea breath test, or EGD >4 wks after completion of abx and off PPI for 2w.

**Refractory 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 after cessation); secretin stimulation test if non-diagnostic. Search for rare causes.
- Continue PPI x additional 12w and then repeat EGD. Surgical tx: rarely required; resection, vagotomy, partial gastrectomy

**Complications and Management**: Ulcer considered *complicated* if any of the following are present: bleeding, perforation, or gastric outlet obstruction: pyloric channel/duodenal ulceration → inflammation → fibrosis/scarring; May need endoscopic dilatation or surgical tx if persists despite medical mgmt. If gastric outlet obstruction sxs - exclude malignancy.

# Gastroenterology — Nausea, Vomiting, & Gastroparesis

## APPROACH TO PATIENT WITH ACUTE (<1MO.) NAUSEA/VOMITING (AFP 2007;76:1)

1) **Initial assessment**
   a. **Rule out life-threatening causes:** bowel obstruction, perforation, mesenteric ischemia, pancreatitis, MI, DKA, ↑ ICP
   b. **History:** onset, frequency, & severity, hematemesis, feculent vomit. Last BM, LMP
      Triggers: relation to POs, relation to time of day, recent foods/meds, sick contacts, substance use (opioids, marijuana)
      Other symptoms: abd pain, fever, wt loss, diarrhea, melena, heartburn, vertigo, headache, CP, SOB
      PMH: head trauma, prior abd surgery, uncontrolled DM, migraines, recent cessation of chronic steroids (i.e. secondary AI)
   c. **Exam:** volume exam, jaundice, abdominal tenderness, masses, lymphadenopathy, CN exam/nystagmus, gait
2) **Labs to consider:** BMP, LFTs, lipase, B-hCG, UTox, UA, ABG, lactate, cort stim, TSH, Troponin
3) **Studies to consider:** KUB, EKG, CT abdomen (I+/O+), Barium swallow or EGD, Gastric emptying study, CT head
4) **Manage complications:** IVF to correct hypovolemia. Address electrolyte abnormalities (hyperchloremic metabolic alkalosis, HypoK)
5) **Address underlying cause while treating sxs** (see table)
   - Chemo PPX: dex ± lorazepam ± ondansetron ± aprepitant ± olanzapine (NEJM 2016;375:134)
   - Adhesive SBO (prior GI surg, hernias, neoplasms, Crohn's disease): conserv. mgmt x 48h (NGT with suction, NPO) → gastrografin per NGT ↓ surgery by 74% (BJS 2010;97:470)
6) **Practical approach to empiric inpatient nausea treatment** (see table with meds and doses below)**:**
   Normal QTc → Start with ondansetron; add prochlorperazine if persistent. Prolonged QTc → Consider lorazepam. If cannot use benzos, can try dexamethasone, scopolamine, or diphenhydramine. If persistent, further work up
   Non-pharm options: acupuncture, meditation, ginger root, inhaled alcohol (AEM 2018;72:2)

| Etiologies (VVOOMMIIITING) | | Receptor | Targeted treatment |
|---|---|---|---|
| **V**estibular & **V**ertigo | Acute/gait instability; labyrinthitis, BPPV, vestibular neuritis, Meniere's disease | Ach, $H_1$ | Scopolamine, dimenhydrinate, diphenhydramine, meclizine, Dix-Hallpike → Epley maneuver |
| **O**bstruction | Adhesions, hernia, volvulus, constipation, gastric outlet obstruction | Multiple | NGT, bowel rest, IVF, surgery consult, serial exams<br>Meds: Prochlorperazine, ondansetron (can worsen constipation), NO metoclopramide (risk of perf) |
| **O**perative | Post-op n/v (risk factors: F > M, post-op opioids, type of surgery), 1/3 cases | Multiple | Ondansetron, aprepitant, dexamethasone (use 2 in combo as ppx if 3+ RFs), gabapentin |
| **M**otility | Gastroparesis (common in uncontrolled DM), autonomic dysfunction, cyclic vomiting syndrome, chronic idiopathic nausea | $D_2$ (periph) | Low fat & insoluble fiber diet, metoclopramide, erythromycin (tachyphylaxis after 4 wks; motilin agonist), diphenhydramine, cannabis abstinence, TCAs, olanzapine, benzos, SSRI/SNRI |
| **M**eds | Antibiotics, AEDs, chemo, opioids, cannabis hyperemesis, anti-arrhythmic | $D_2$ (central) | Stop offending med if possible, prochlorperazine, haloperidol |
| **I**nflammation/ **I**nfection/ **I**schemia | 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.) |
| **T**oxins | Uremia, ketoacidosis, hypercalcemia, food poisoning, hypo/hyperglycemia | $D_2$ (central) | Prochlorperazine, haloperidol, treat underlying disorder |
| **I**ntracranial | Elevated ICP, migraine, meningeal irritation, acute glaucoma | Ach, $H_1$, 5-$HT_3$ | Dexamethasone (if ↑ICP), treat underlying disorder |
| **N**erves | Anxiety, depression, anticipatory nausea, pain | Multiple | Lorazepam (anticipatory N/V), dex, pain control |
| **G**ums/mouth | Mucositis thrush, oral HSV | Multiple | Treat cause; magic mouthwash |

| Recep. | Med | Dose | QTc | Other side effects |
|---|---|---|---|---|
| 5$HT_3$ | Ondansetron (Zofran) | 2-8 mg PO/IV q8h | ↑ | **constipation**, HA |
| | Palonosetron (Aloxi) | 0.075-0.25 mg 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) | 4-8 mg PO q4-6h | - | **psychosis**, CHF, ↑appetite |
| | Lorazepam (Ativan) | 0.5-2 mg PO/IV q6h | - | **delirium**, sedation |
| $NK_1$ | Aprepitant (Emend) | 125 mg day 1, 80mg days 2-3 | - | CYP3A4 inhib, GI upset |
| $CB_1$ | Dronabinol (Marinol) | 2.5-10 mg q4-6h | - | dysphoria, asthenia, ↑appetite |
| 5$HT_{2A}$, $D_2$ | Olanzapine (Zyprexa) | 5-10 mg PO QD | ↑ | metabolic (wt gain, ↑lipids); ↑ mortality in dementia (black box) |
| $H_1$, ACh, D2 | 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, blurred vision |
| | Hyoscyamine | 0.125-0.25 mg SL/PO/IV q4h | - | |
| | Diphenhydramine (Benadryl) | 25-50 mg PO/IV q6h | - | |

# Gastroenterology Nausea, Vomiting, & Gastroparesis

## APPROACH TO CHRONIC (>1MO.) NAUSEA/VOMITING* (AJG 2018;113:647)

| Pathology | Symptoms/Diagnosis | Targeted treatment |
|---|---|---|
| GERD | - Heartburn, epigastric pain, vomiting, regurgitation<br>- Dx clinically or with pH monitor, EGD | Acid suppression, weight loss, diet/habit modification |
| Gastric Outlet Obstruction | - Epigastric pain, bloating, early satiety, abd distention, abd pain, weight loss<br>- Can be malignant, inflammatory (related to PUD, pancreatitis, caustic ingestion), infiltrative (Crohn's, TB), or iatrogenic.<br>- Dx with CT, barium swallow, EGD | Supportive care, endoscopic intervention (eg dilation), treat underlying cause. May need NGT decompression |
| Eosinophilic Gastroenteritis | - Abdominal pain, early satiety, N/V diarrhea, weight loss. Can involve anywhere in GI tract. Likely allergic etiology<br>- Dx with eosinophilic infiltration of stomach on histology | Elimination diet, PO steroids |
| Cyclic Vomiting Syndrome | Rome IV criteria (must include all):<br>- Stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week)<br>≥- 3 episodes/year AND 2 episodes in past 6 months, occurring at least 1 week apart<br>- Absence of vomiting between episodes, but other milder symptoms can be present between cycles<br>- Family history of migraine headaches supports diagnosis<br>- Four-phase cycle: prodrome (intense nausea, panic symptoms), vomiting/retching phase (±migraine), recovery phase (hours-days), inter-episodic phase | Supportive care (IV fluids + mIVF w/ dextrose, antiemetics), abortive (sumatriptan, aprepitant, Zofran, antihistamine, BZD), prophylactic (TCA, anticonvulsant, CoQ10) |
| Cannabinoid Hyperemesis Syndrome | Rome IV criteria (must include all):<br>- Cannabis use >1 year before symptom onset and >4 times/week average use<br>- Relief with cessation for ≥6 months or duration spanning 3 typical cycles<br>- May have pathologic bathing behavior (prolonged hot baths/showers) | Acute: Supportive (IV fluids, antiemetics, dopamine antagonist, capsaicin cream)<br>Long term: Cannabis cessation |
| Rumination Syndrome | Rome IV criteria (must include all)<br>- Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or mastication and swallowing. (Note: regurgitation is commonly misdiagnosed as vomiting)<br>- Regurgitation is not preceded by retching<br><br>Dx: Consider pH study/manometry to confirm dx and imaging/EGD to rule out obstruction. History helps distinguish from GERD. Regurgitation typically lacks acidic taste, and sx are refractory to PPI/ less likely nocturnal. | Reassurance, Diaphragmatic breathing (mainstay of treatment, reduces intragastric pressure), baclofen for refractory sx |
| Pregnancy Associated and Hyperemesis Gravidarum | -Starts at 5-6wks, often peaking at 9wks and subsiding by 20 wks. If n/v starts in latter half of pregnancy, alternative dx should be ruled out<br>-HG: ketonuria, weight loss of >5% or vomiting >3/day and 3kg weight loss | Supportive: Frequent, small, cold meals with high protein content separated from fluid intake. Ginger and Vitamin B6 +/- doxylamine are first line. If not resolved and no hypovolemia, switch to diphenhydramine. If hypovolemic, call MFM, IVF + thiamine and trial ondansetron if >10wks. |

*Also consider non-GI causes such as medications, pregnancy, vestibular, and neurologic disorders

## GASTROPARESIS (AJG 2022;117:1197)

Definition: delayed gastric emptying of solid food w/o mechanical obstruction
Sx: **nausea, vomiting of undigested food, early satiety**, postprandial fullness, bloating ± abd pain
Etiologies: idiopathic, **diabetes** (vagus nerve damage 2/2 hyperglycemia), **post-viral**, post-surgical (e.g. vagus nerve injury post-bariatric surgery), systemic disease (thyroid, critical illness, Parkinson's, CTD), **meds** (opiates, CCB, anti-cholinergics), chronically decreased PO Dx: Gastric emptying tests (hold motility meds, opiates, cannabinoids 48h prior). Diagnose with scintigraphy (most common) or wireless motility capsule/C13 breath test. EGD to exclude obstruction.

- Gastric scintigraphy: (radiolabeled egg > liquid) positive if >10% retention at 4hr
  - **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, motility agents or opiates within 48-72 hours

Labs: TSH, ANA, A1c, total protein, albumin, CBC/diff, CMP

**Treatment:** Optimize glucose control, small meals w/ low fat & low non-digestible fiber. Prokinetic before meals: (metoclopramide, risk of TD, restrict use <12 wk), erythromycin (tachyphylaxis, give drug holidays after 1-4wks), D2 agonists (domperidone). Antiemetics (zofran, benadryl). Venting G-tube or pyloromyotomy if refractory. J-tube for nutrition if wt loss

# Gastroenterology — Diarrhea

**ACUTE DIARRHEA**: ≥3 loose stools/d for <14day (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. Most acute diarrhea is infectious/viral
  Exposure hx: travel, abx, hospitalization, food, sick contact, daycare
  "***High Risk***": immunocomp/HIV, IBD, age >70, CAD, pregnant
  "***Severe***": fever > 101.3F, >6 BMs/24hr, hypovolemia, severe pain
- **Workup**: BMP, C.diff, stool PCR (if high risk, severe sx, bloody diarrhea, sx >1wk), stool O&P (3 samples q24h if high risk travel, MSM, immunocomp). If blood, check shigatoxin and fecal leukocytes.
- **Common pathogens**: *See table*.
  Immunocomp: CMV, C. diff, Cryptospor., Microsporidia, MAC, TB, Histoplasma
- **Treatment**: volume & electrolyte repletion. Empiric abx: controversial; consider FQ or azithro if severe sx, high risk, septic, bloody diarrhea, age ≥70, or serious comorbidities. **Avoid abx if c/f Shiga toxin-producing E. coli (STEC)** as ↑HUS risk. Probiotics not recommended
- **Anti-diarrheals**: If NO fever/blood/C. diff consider loperamide 4mg x1 then 2mg after BM (max 16 mg/d), diphenoxylate, soluble fiber. If fever/bloody stool consider PeptoBismol 30mL q30min (for 8 doses). **Diet:** potatoes, noodles, rice, oats, bananas, soup

| Pathogen | Details |
|---|---|
| Norovirus | Outbreaks during winter; n/v prominent |
| Rotavirus | Daycare-associated |
| Adenovirus | A/w conjunctivitis + pharyngitis |
| E. coli | Toxigenic = traveler's diarrhea; hemorrhagic, O157:H7 = undercooked meats, a/w Shiga toxin, HUS |
| Campylobacter | Undercooked/unpasteurized foods, a/w reactive arthritis, GBS |
| Salmonella | Eggs, poultry, milk, concurrent bacteremia common |
| Shigella | Low inoculum, often hematochezia |
| Vibrio spp. | Shellfish/salt water; severe disease if cirrhosis |
| Yersinia | Undercooked pork, "pseudo-appendicitis" due to RLQ pain |
| C. diff | See *C. diff* |
| Giardia | In MA, outdoor streams; watery stool progressing to malabsorptive/greasy |
| Cryptosporidium | Water-related outbreaks |
| Cystoisospora | Contaminated produce |
| E. histolytica | Contaminated food/water outside US; liver abscesses |

**CHRONIC OR PERSISTENT DIARRHEA**: Chronic = ≥3 loose stools/day for >4wk; Persistent = between 14-30 days

**Evaluation** (Gastro 2017;152:515; CGH 2017;15:182)

- Hx: freq., stool vol., tenesmus, abd pain, bloating, postprandial sx, steatorrhea, surgical hx, travel, immunocomp., meds, diet.
- Alarm features: onset >50y, bleeding, nocturnal pain/diarrhea, progressive pain, unexplained fever/weight loss
- Labs: CBC, BMP, LFTs TSH; stool lytes (Na, K, pH), fecal calprotectin (marker of neutrophil activity)/lactoferrin (marker for fecal leukocytes), fecal elastase, fecal fat (24-48h collection), FOBT, *Giardia*, celiac panel (Gastroenterology 2019;157(3):851)
  - Negative fecal calprotectin/lactoferrin rules out IBD; ⊕ FOBT w/ diarrhea suggests chronic infection or IBD. Other tests to consider: colo (if alarm features or c/f IBD/microscopic colitis), stool bile acid, *C. diff*, parasites, KUB (overflow incontinence)
- **Stool osmotic gap for watery diarrhea**: 290 – 2*(stool [Na] + [K]); normal 50-100mOsm/kg

| | Watery | | | Fatty | Inflammatory |
|---|---|---|---|---|---|
| | *Secretory* | *Osmotic* | *Functional* | *Malabsorptive/Maldigestive:* | |
| **Etiologies** | Addison's, neuroendocrine tumors, hyperthyroid, medullary thyroid CA, mastocytosis, **microscopic colitis (lymphocytic, collagenous),** DM autonomic neuropathy, amyloidosis, **bile salt (4-5%)**, lymphoma, villous adenoma | Lactose intolerance, mannitol, sorbitol, magnesium, laxative use, FODMAPs* | IBS, functional diarrhea (see *IBS*) | Malabsorption: mesenteric ischemia, mucosal disease (CD, Whipple's), short gut syndrome, SIBO<br>Maldigestion: bile acid malabsorption (ileal disease) or ↓ synthesis, pancreatic exocrine insufficiency | IBD, invasive bacteria/parasite (C. diff, E. histolytica, Yersinia, TB), ulcerating virus (CMV, HSV), colon CA, lymphoma, radiation, ICI colitis |
| **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 | Usually >50 | Usually <50 |
| **Response to fasting** | No change | Improves | Variable | Improves | No change |
| **Further Testing** | Exclude infxn. +/- colo with bx (esp. if immunocomp). 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 | Exclude infxn. Calprotectin, fecal leukocytes, colo w/ bx |
| **Treatment** | Bile salt: cholestyr. 4g QD-QID<br>Microscopic colitis: budesonide, cont. loperamide, no NSAIDs<br>VIP: somatostatin (octreotide 50-250ug SQ TID)<br>Other: loperamide 2-4mg QID, diphenoxylate 2.5-5mg QID, tincture of opium | D/c offending agent; dietary review | Fiber (psyllium), Viberzi (+pain), hyoscyamine (antispasmodic), Rifaximin (+bloating), probiotics, TCA/SSRIs | Pancreatic dysfxn: enzyme replacement therapy (pancrealipase 500-2500u/kg/meal);<br>S/p CCY: cholestyramine 4g QD-QID | Antimicrobial vs. immunosuppression (induction vs maintenance tx) |

*Fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs)

# Gastroenterology Constipation, IBS, & Colonic Disorders

## CONSTIPATION

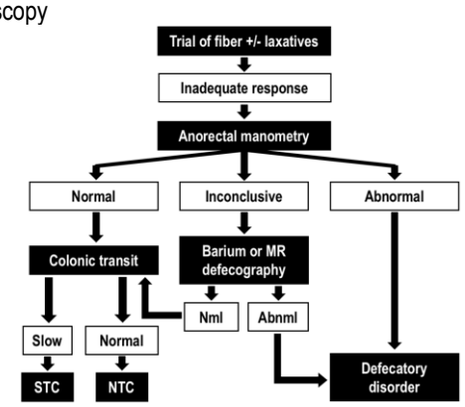
**Symptoms**: Dissatisfaction with defecation with at least 2 of the following: <3 spontaneous BM per week, hard stools, straining, sensation of incomplete evacuation, sensation of anorectal blockage/obstruction, or manual facilitation of BM. See Rome IV for exact criteria.

**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 w/o identifiable cause
  - Dyssynergic defecation (e.g. pelvic floor dysfunction): 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, dehydration, sedentary
  - Medications: analgesics, opioids, anticholinergics (antihistamines, antidepressants, antipsychotics), iron, aluminum (antacids, sucralfate), diuretics, clonidine, amiodarone, CCB, ondansetron, barium
  - CTD: amyloidosis, sarcoidosis
  - Metabolic: ↑Ca, hypothyroid, ↓Mg, ↓K, uremia, heavy metal poisoning, pregnancy, anorexia nervosa
  - Neuro: autonomic neuropathy, DM, Hirschsprung's, multiple sclerosis, anorexia nervosa, spinal cord injury, PD, stroke
  - Obstruction: anal stenosis, colon ca, stricture, rectocele, compression

**Diagnosis/Treatment** (JAMA 2016;315:185; AJG 2023;118:936-954)

- 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, iron deficiency anemia, weight loss, strong FH of CRC or IBD), **medications**
- Initial workup: DRE (fissures, hemorrhoids, tone), CBC (for anemia); consider colonoscopy
- Further workup (primarily outpatient): see algorithm from AGA guidelines
  - **Anorectal manometry (ARM), balloon expulsion test:** identifies dyssynergia
  - **Barium, MR defecography**: useful when ARM inconsistent with clinical impression, can identify anatomic abnormalities
  - **Colonic transit study**: via radio-opaque makers (Sitz markers), scintigraphy,or wireless motility capsule study (less common)
- Management: see medications below
  - **Secondary constipation**: treat underlying cause
  - **STC/NTC**: fiber, laxatives (osmotic such as PEG, lactulose, mag ox or stimulant laxatives such as bisacodyl, senna), hydration; add secretory agents if persists; consider transit study on meds or UGI eval if no improvement
  - **Dyssynergic defecation**: 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)
- General ppx for at-risk patients: **senna 2 tabs QHS standing + Miralax 17g daily PRN**
- High-risk ppx for patients on opioids: **senna 2 tabs BID standing + Miralax 17g PRN**
- Stepwise approach: **senna + Miralax → ↑Miralax to 34 g → mag citrate/lactulose → bisacodyl PR → enemas → disimpaction → 1-2 L GoLYTELY** (*Note*: disimpaction can cause vasovagal; all rectal procedures are contraindicated in neutropenia); in patients with opioid induced constipation w/o bowel obstruction, consider subcutaneous methylnaltrexone
  - Types of enemas (stepwise): **tap water/saline → soap suds/mineral oil → milk and molasses (MGH specific) → Fleets**
- Avoid Mg and Phos containing products in renal insufficiency (MOM, Mg citrate, Fleets enema) → can cause nephrocalcinosis

## IRRITABLE BOWEL SYNDROME (IBS) (AGA: Gastro 2022;163:118,137)

- Definition: recurrent abd discomfort ≥ 1x/wk for 3 months a/w 2+ of: (1) related to defecation, (2) Δ in stool frequency, (3) Δ in stool form. No alarm symptoms (e.g. sudden change in BMs in >50 y/o, nocturnal diarrhea, etc.)
- Epidemiology: 10-15% of US adults; younger age pop, ♀ > ♂. Assoc. with fibromyalgia, chronic fatigue syndrome, psych disorders (major depression, anxiety, somatization), GERD, non-cardiac chest pain
- Types: IBS-C (constipation-predominant), IBS-D (diarrhea-predominant), IBS-M (mixed), IBS-U (unclassified), by Bristol Stool Scale
- Initial workup: phys exam as per above; if IBS-D, send calprotec/lactoferrin, Giardia, celiac serologies
- Treatment: all - exercise, diet Δ (low FODMAP), soluble fiber (psyllium preferred, particularly for IBS-M as helps normalize stool)
  - Mild: IBS-C - osmotic lax (e.g. PEG) +/- antispasmodics (dicyclomine, hyoscyamine, peppermint oil); IBS-D – loperamide (45 min before meal, sched), bile acid sequestrant (cholestyramine), rifaximin in refractory patients
  - Moderate/Severe: IBS-C – secretagogues; IBS-D – rifaximin (2 week trial,), TCAs (start at 10mg), alosetron (♀), eluxadoline (↑risk of pancreatitis, contraindicated for patients w/o gallbladder, biliary hx, or significant alcohol use)

## COLONOSCOPY PREP

- Adequate preparation = essential. Place pt on clears at noon the day prior to colonoscopy; the prep should start no later than 6PM.
- To prep: 6oz SUPREP (↑ tolerability (AJG 2019;144:305)) + 10oz water → 32oz water over the following hour → repeat both steps in the morning. If stool is not clear, give additional 6oz SUPREP. Contact GI team if not completely see-through to reschedule

# Gastroenterology Constipation, IBS, & Colonic Disorders

## MEDICATIONS FOR CONSTIPATION (ACG: AJG 2023;118:936-954)

| Type | Agent | Dose | Notes |
|---|---|---|---|
| **Bulk agents** | **Fiber:** Psyllium (Metamucil), Methylcellulose (Citrucel) | 1 tsp up to TID (for psyllium: up to 30g/d) | Fiber is first-line agent. In some (esp. STC), can ↑ bloating in large amounts. Start low dose |
| **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 QHS or BID | ↑ colon secretions, motility. Can cause cramping |
| | **Bisacodyl** (Dulcolax) | 5-15 mg up to 3x/w up to 4wk | ↑ 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/better tolerated (less bloating) than lactulose (Cochrane Rev 2010). |
| | **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 gastric acid neutralization and water retention in stool. Avoid in renal insufficiency |
| | **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 in renal insufficiency |
| **Enemas** | **Tap water, soap suds, mineral oil, Fleets** (sodium phos.)**, milk & molasses, barium** | Varies | All work via lubrication. Soapsuds also stimulates peristalsis. Fleets is hypertonic and also has osmotic effect. Avoid Fleets in elderly or renal insuff. (phos). |
| **Secretagogue** | **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) **Plecanitide** (Trulance) | 145-290µg QD 3g QD | Guanylate cyclase-C agonists; ↑ Cl/HCO3 secretion & colonic transit; Most common side effect is diarrhea |
| **Pro-kinetic drugs** | **Prucalopride** (Motegrity) | 2mg daily | 5-HT4 selective receptor agonist; ↑ cholinergic and noradrenergic neurotransmission to promote motiltiy |
| **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) |

## COLONIC DISORDERS

**Stercoral Colitis**

- Definition: inflammation of colonic wall 2/2 pressure from impacted feces → ↑ intraluminal pressures → ischemic pressure necrosis
- Epidemiology: nursing home residents; hypothyroid; diabetic enteropathy; opioids; clozapine; other constipating meds
- Treatment: fecal disimpaction if no defects in colonic wall on CT; consider CTX/flagyl if septic. Avoid opiates which ↓ motility.

**Diverticulosis**

- Definition: herniation of colonic mucosa into muscularis propria, where vasa recta penetrate
- Risk factors: low fiber diet ± chronic constipation, ↑BMI, physical inactivity, ↑ age (present in 50% of patients >60yo; common incidental finding), smoking, NSAIDs, ♂ > ♀ . Nuts, seeds, popcorn, alcohol, red meat, and fat consumption are **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) colonoscopy, 2) angio (IR embolization), 3) surgery. See *Lower GI Bleed*
- Diverticulitis develops in roughly 5% of pts with diverticulosis (Clin GI Hep 2013;12:1609).

**Diverticulitis**

- Definition: infection of diverticuli: micro-perforation secondary to 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 & CT A/P (I+,O+) (findings: diverticula, bowel wall >4mm, inflammation w/ pericolic fat ± abscess/fistula)
- Management (AGA: Gastro 2015;149:1944):
  - **Uncomplicated (medical)**: PO abx x7d (cipro/flagyl, bactrim/flagyl, or high-dose augmentin), bowel rest . No abx is noninferior to abx if uncomplicated (Clin GI Hep 2021;19:503; Br J Surg. 2019;106:1542)–use selectively (immunocomp., pregnant, comorbidities, sepsis)
  - **Complicated**: IV abx (CTX/flagyl), bowel rest, and IR/surgical evaluation (peritonitis typically present; evaluation for abscess drainage or colonic resection)
- To prevent recurrence: high fiber diet, avoid NSAID, increase exercise, avoid smoking/alcohol
- Follow-up: consider colonoscopy 6-8w after resolution of acute symptoms to evaluate for malignancy; advised in patients with complicated diverticulitis, first episode of diverticulitis, or alarm symptoms; can be deferred if recent colonoscopy (within 1yr) (Gastroenterology 2021; 160(3):906)

# Gastroenterology Esophageal Disorders and 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.) | Central: tumor, stroke, PD, ALS, MS, polio<br>Peripheral: neuropathy, myasthenia gravis<br>Muscular: polymyositis, muscular dystrophy | 1°: achalasia, esophageal motility disorders (e.g. EGJ outflow obstruction, distal esophageal spasm, hypercontractile "Jackhammer" esoph.), functional dysphagia<br>2°: diabetes, scleroderma, CTD, amyloid, Chagas, MG<br>(Chicago classification: Neurogastro Motil 2021) |
| | **Structural** (solids > liquids) | Intrinsic: tumor, XRT, trauma/surgery/infection, Zenker's<br>Extrinsic: anterior mediastinal mass, goiter, cervical spondylosis | Intrinsic: tumor, stricture, infection, EoE, rings, webs (e.g., Plummer-Vinson), pills (NSAIDs, tetracyc., bisphosph)<br>Extrinsic: vascular rings (e.g. dysphagia lusoria), Ao. enlarged, LA compression, mediastinal, substernal thyroid, LAD |
| **Work-up** | | History: onset & duration, progressive/intermittent, solid/liquid & localization, +/- odynophagia, +/- new dysphonia, underlying conditions (e.g., CNS, malignancy, thyroid, DM, scleroderma), offending meds (pill esophagitis), immunocompromise (Candida, CMV, HSV esophagitis), infectious (Diphtheria, Botulism, Syphilis), XRT, food regurgitation, impaction, h/o recurrent pneumonia. Dysphagia in older adults is **not** normal aging<br>• **Alarm Sx:** acute/subacute onset, age >50, vomiting, GI bleeding, anemia, unexplained wt loss, abd. mass<br>PE: appearance (systemic disease or CNS issue), HEENT exam (evidence of LAD, tumor, asymmetry)<br>Labs (consider): CBC, TFTs, ANA, α-Scl-70, α-centromere, α-RNP, α-Jo, HgbA1C, iron studies, HIV, AChR-Ab | |
| **Diagnostics** | | 1) Bedside swallow, SLP consult, neuro eval<br>2) Modified barium swallow (aka VFSS); ENT if c/f mass, voice change, airway involvement.<br>3) Consider chest/neck CT to dx extrinsic compression | 1) EGD +/- biopsy though barium swallow is often a good first test (mucosal pathology or structural abnormality)<br>2) If normal → esoph. manometry to diagnose motility d/o, EndoFLIP (complementary test to manometry) (Am J GI 2020; 115:1412)<br>3) Consider chest/neck CT to dx extrinsic compression |
| **Selected Conditions** | | **Zenker's diverticulum**: halitosis, regurgitation of food/aspiration, cough. Tx: endoscopic surgery, Z-POEM | |
| | | **Strictures & rings**: if lumen <13mm, dysphagia common. Tx: PPI, dilation, intralesional steroid injection, 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 | |
| | | **Achalasia**: progressive dysphagia solids/liquids + regurgitation; barium swallow: bird's beak distal esophagus; manometry: disruption of peristalsis, incomplete LES relaxation; EGD/CT r/o pseudo-achalasia, often a/w CTD > Chagas. **Tx:** CCB, nitrates, pneumatic dilation, myotomy, POEM, botox, esophagectomy (AGA: AJG 2020) | |
| | | **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 Δs (dairy, wheat > soy, eggs, nuts, fish), topical steroids (MDI/neb/liq.); consider dilation (AGA: Gastro 2020;158:1776) | |

## CELIAC DISEASE (ACG: AJG 2023;118: 59-76)

Pathophysiology: abnormal immune response to gluten → diarrhea, wt loss, abd pain, IDA, vit D def, osteoporosis, dermatitis herpetiformis

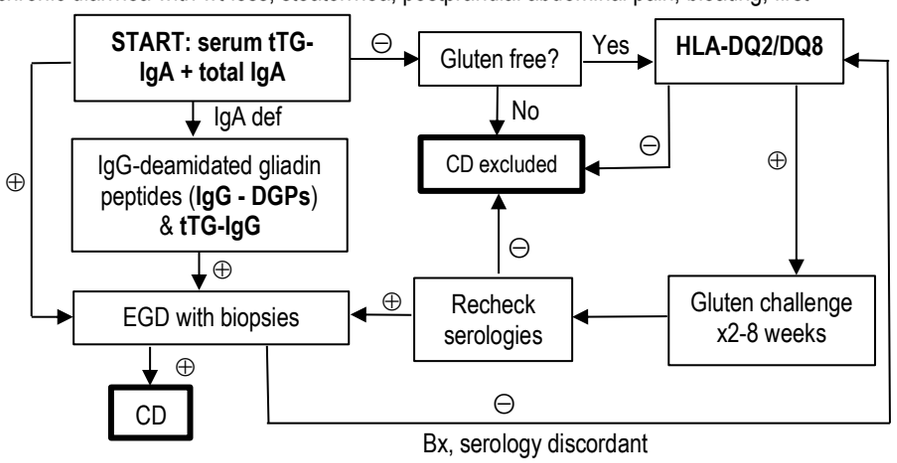
Who: s/sx or laboratory e/o malabsorption i.e., chronic diarrhea with wt loss, steatorrhea, postprandial abdominal pain, bloating; first degree relative; unexplained elevated LFTs; unexplained IDA; diarrhea in T1DM; dermatitis herpetiformis, atrophic glossitis. Adults may have more mild initial presentation than children.

Diagnosis: **see flow diagram**

*Biopsy*: ↑intraepithelial lymphocytes, crypt elongation/hyperplasia, villous atrophy, Marsh Score

*Negative HLA-DQ2/DQ8 = no celiac

Treatment: strict gluten-free diet; IgA anti-TTG titer should normalize over time. At risk of vitamin/mineral deficiencies (A, D, E, B12, copper, zinc, etc), recommend dietician referral (Acad Nut & Diet 2023; 12:1793)



# Gastroenterology — Inflammatory Bowel Disease

## Clinical Presentation

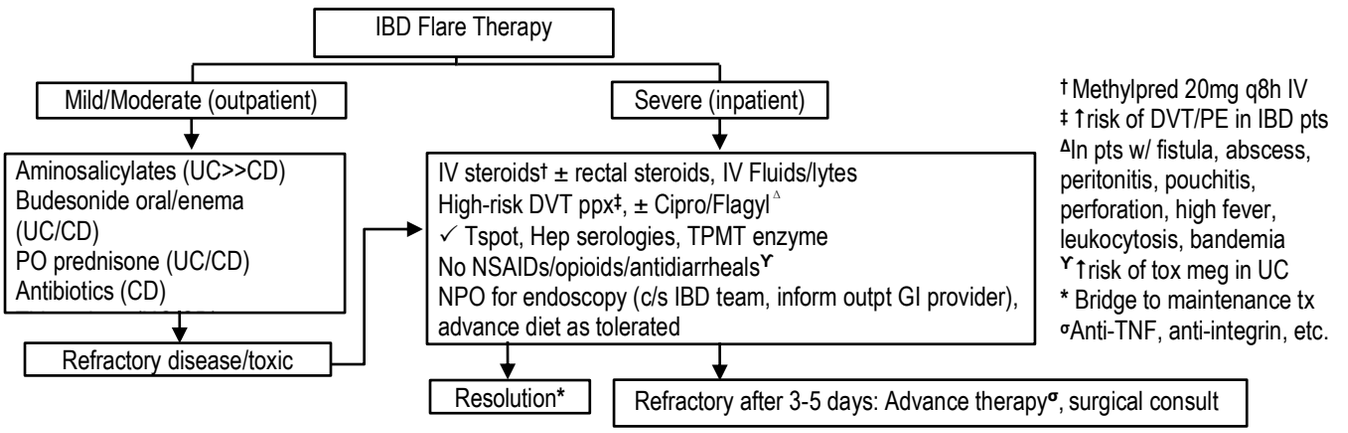
**Epidemiology:** rising US prevalence, onset 15-30y, bimodal w/ 2nd peak 50-80y. Genetic (↑risk: +FamHx, autoimmune dz, female, Ashkenazi Jewish, white; however, increasing rate in non-white) + environment (Western diet, abx, NSAIDs, sleep, smoking ↑CD)
**Pathophysiology:** Inappropriate immune response leading to chronic inflammation of the GI tract. Multifactorial, likely involving genetic susceptibility, immune dysregulation, defective mucosal barriers, and the gut microbiome (NEJM 2020;383:2652)

| | **Ulcerative Colitis** (Lancet 2017;389:1756) | **Crohn's Disease** (Lancet 2017;389:1741) |
|---|---|---|
| **S/S** | Bloody diarrhea (constipation possible in limited rectal dz), lower abd pain, cramps, tenesmus | Abd pain (usually RLQ), diarrhea (+/- bloody) (constipation w/ strictures), n/v, wt loss, perianal fistula/abscess |
| | **Extra-luminal**: rheum (seroneg. arthritis), cutaneous (EN, pyoderma gangrenosum, apthous ulcers), ophthalmic (uveitis, iritis, episcleritis), heme (DVT, AIHA), GU (Ca-Ox / UA stones), pulm (bronchiectasis, ILD), hepatic (PSC) | |
| **Dx** | **Continuous** colonic mucosal inflammation spreading proximally from **rectum,** limited to mucosa/submucosa, crypt abscesses, pseudopolyps | **Skip lesions**, strictures, fistulae, **transmural** inflamm., noncaseating **granulomas**, cobblestoning, may involve **any** part of GI tract (including upper) |
| **Complic.** | Fulminant colitis, anorectal strictures/dysfxn, perforation | Obstruction (2/2 strictures), abscess, fistula, malabsorption |
| | **↑risk CRC**: colo after 8y of active disease, q1-3y w/ random 4-quadrant bx q10cm of colon | |
| **Montreal Classif. Criteria** (Gut 2006;55:749) | Extent (proctitis, left sided, extensive pancolitis)<br>Severity (clinical remission, mild, mod, severe) | Age (<16, 17-40, >40)<br>Location (ileal, colonic, ileocolonic, upper GI)<br>Behavior (non-stricturing and non-penetrating, stricturing, penetrating, perianal involvement) |

## Inpatient Work-up and Management

**Hx:** stool patterns, bloody BM, nocturnal sx, fever, weight loss, rashes, joint pain, ulcers, vision changes
**Ddx:** infectious colitis, ischemic colitis, celiac disease, lactose intolerance, IBS, diverticular colitis, microscopic colitis, lymphocytic colitis, collagenous colitis, appendicitis, functional abdominal pain
**Labs**: CBC, BMP, 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 (metabolizes AZA toxic metabolites) for AZA. Ensure up to date on vaccines (generally, no live vaccine after starting biologics or immunomodulators).
**Imaging**: CT A/P if c/f peritonitis/obstruction/mass (abscess). CT/MR enterography for small intestine. Pelvic MRI to eval perianal dz
**Procedures:** Colonoscopy with biopsy (+/- EGD) necessary to confirm dx

| 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 | Failed advanced tx, toxic, abscess, obstruction, peritonitis, cachexia |




**Step-up therapy:** No longer the standard of care. Treatment now guided by RFs and prognosis. (Gastro 2021;160:2496)
**Poor prognostic factors in CD:** Young age at diagnosis, initial extensive bowel involvement, ileal/ileocolonic involvement, perianal/severe rectal disease, deep ulceration, and patients with penetrating or stenosing disease phenotype (AJG 2018;113:481).
**Poor prognostic factors in UC:** Young age at diagnosis, extensive colitis, hospitalization for colitis, severe endoscopic disease.
**Indications for Surgery**: CD: severe stricture, fistulae, abscess, failing medical tx. UC: refractory dz, perforation, toxic megacolon
**Management Guidelines:**
**CD**: ACG: AJG 2018;113:481, AGA: Gastro 2021;160:2496
**UC**: ACG: AJG 2019;114:384, AGA: Gastro 2024;167:1307

*Olivia Kahn-Boesel*



Suggest an Edit

## Inflammatory Bowel Disease Therapeutics

| 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 (if chronic), diabetes, delirium |
| **Aminosalicylates (UC>>CD)** | Sulfasalazine<br>Mesalamine (PO: Pentasa, Ascol, Lialda, Apriso. PR: Canasa, Rowasa) | Induction + Maintenance for moderate disease | **Sulfasalazine**: pro-drug with more AEs, also systemic effects<br>**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 |
| **Immunomodulators** | Thiopurines<br>Azathioprine (pro-drug)<br>6-MP | Induction + Maintenance | Typically as combination therapy for induction; can be monotherapy for maintenance. Test Thiopurine methyltransferase (TPMT) prior to use. 6-TGN for monitoring. AE: n/v, hepatitis, BM suppression, malignancy (non-melanoma skin cancer, lymphomas) |
| | Antimetabolites<br>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 |
| | Calcineurin Inhibitors<br>Cyclosporine | Induction *only for severe UC* | C.I. for toxic megacolon. Labs: troughs (q2-3d) Cr, Mg, lipids, LFTs<br>AE: renal injury, ↑K, infxn, neurotox/seizures (esp. if ↓Mg or cholesterol) |
| **Biologics** | Anti-TNF<br>Infliximab (Remicade) (IV/SC)<br>Adalimumab (Humira) (SQ)<br>Certolizumab (Cimzia)-CD<br>Golimumab (Simponi)- UC | Induction + Maintenance for mod-severe | **Infliximab** for induction in pts naïve to biologics. Contraindicated if toxic megacolon, pyogenic infxns. Typically in combination with immunomodulator. Preferred agent with concomitant IBD-associated arthritis. **If flare during maintenance**: measure trough (24hrs prior to dose) and antidrug Ab. If non-responsive despite adequate levels -> another class. AE: infxn, TB/HBV reactiv., malignancy |
| | Anti-Integrins<br>Vedolizumab (Entyvio) (IV/SC) (NEJM 2013;369:699; NEJM 2013;369:711)<br>Natalizumab (Tysabri) | 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. Vedolizumab is gut-specific, not felt to lead to significant immunosuppression. AE: infusion reactions, nasopharyngitis<br>ACG recommends against natalizumab due to risk for JC-virus associated PML, can consider if pt adheres to JC virus monitoring |
| | IL-12/23<br>Uztekinumab (Stelara) (NEJM 2019;381:1201)<br>Risankizumab (Skyrizi, IL-23 only) (Lancet 2022;399:2031) | Induction + Maintenance | Ustekinumab shown to have no differences in outcomes compared to adalimumab in Crohn's patients (Lancet 2022;399:2200). Sometimes preferred for less frequent ~q8week dosing.<br>AE: infection, HA, nasopharyngitis, nausea, abdominal pain, arthralgias |
| **Small Molecules (Oral)** | JAK inhibitors<br>Tofacitinib (Xeljanz) (NEJM 2017;376:1723)<br>Upadacitinib (Lancet 2022;399:2113) | Induction + Maintenance | PO, Consider if previously failed anti-TNFs<br>AE: infection, herpes zoster, HA, nasopharyngitis, arthralgias, CPK elevation, acne, thrombosis/ embolic events |
| | Sphingosine-1-phosphate receptor<br>Ozanimod<br>Etradimod (Velsipity) | Induction + remission *moderate to severe UC* | Prior to initiation: CBC, LFTs, EKG. Vaccinate for shingles. Ophthalmic exam (uveitis, macular edema). Need sleep study if at risk for OSA. AE: anemia, nasopharyngitis |

# 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, sepsis, 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 (↓BMs and ↓flatus), abd distention, tympany to percussion, **high pitched or absent BS**, dehydration, **± peritoneal signs** |
| **Studies** | KUB or CT: dilated bowel loops, **air in colon**, **no transition point**, no peritoneal free air | KUB (less useful): decompressed colon, air-fluid levels<br>CT w/ PO+IV contrast: **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, consider methylnaltrexone if hx opioid use, parenteral nutrition if prolonged NPO, treat the underlying etiology | Initial mgmt: Bowel rest, decompression via NGT (note: PEG diameter insufficient for adequate suction and NGT required even if PEG), IVF, replete lytes. Broad spectrum abx if c/f bowel ischemia/necrosis or perf<br>Nonsurgical mgmt: Gastrografin challenge for adhesive SBO only. Draws fluid into the bowel, decreasing wall edema and stimulating peristalsis. C.I. in pregnancy, bowel ischemia/necrosis/perf, abdominal surgery within 6 wk<br>Indications for surgery: **any suspicion for bowel ischemia/necrosis or perf**, closed loop obstruction (volvulus), hernia, intussusception, tumor, foreign body, gallstone, SBO persists after 3-5 days of conservative tx |

**Acute colonic pseudo-obstruction (Ogilvie's):** typically elderly, hospitalized pts. A/w severe illness, systemic dz (thyroid, DM, renal or liver failure), neuro (spinal cord compression/trauma, PD, MS), meds (opiates, CCB, anticholinergics). Dx: CTAP + rectal contrast (C.I. if peritonitis) Tx: conservative (NPO, IVF, NGT/rectal tube), neostigmine if cecal diam. >12cm or fails conservative tx. Colonic decompression if fails. (ASGE: Gastro Endosc 2020;91:228)

**Sigmoid volvulus:** A/w long redundant colon, constipation (may cause sigmoid dilation and prolongation), colonic dysmotility. P/w insidious abdominal pain, constipation, abdominal distention, nausea. Dx: "Bent inner tube" on KUB, confirmed with CTAP. Tx: Alarm signs (perforation or peritonitis): immediate surgical management (detorsion may cause reperfusion injury). No alarm signs: endoscopic de-torsion followed by semi-urgent surgery (allows for complete bowel prep prior to surgery) (World J Emerg Surg 2023;18:34)

## Intestinal Ischemia (ACG: AJG 2015;110:18; NEJM 2016;374:959)

| | Colonic Ischemia | Acute Mesenteric Ischemia | Chronic Mesenteric Ischemia |
|---|---|---|---|
| **Signs/ Symptoms** | - **Cramping pain** (mostly LLQ) → mild/mod **hematochezia**<br>- Uncommon: gangrenous bowel or fulminant colitis | - Arterial: **sudden, pain out of proportion to exam**<br>- Venous: 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<br>- N/V, early satiety, BM Δs<br>- Wt loss, **fear of eating** |
| **Etiology & Risk Factors** | **Non-occlusive** (95%):<br>- Watershed areas (splenic flexure, rectosigmoid) most susceptible; 25% R-sided<br>- Risk factors: cardiopulmonary bypass, MI, HD, aortic surgery, dehydration, extreme exercise<br>- Vessels: SMA, IMA<br>- Prognosis: 85% spontaneously resolve in 2w, 5% recurrence | **SMA occlusion** (~75%): embolic (40-50%): AF/endocarditis/aortic plaque, thrombotic (20-35%): underlying ASCVD, dissection/inflammation (<5%)<br>**Non-occlusive** (5-15%): hypoperfusion or vasospasm after CV event/surgery, cocaine, vasculitis<br>**Mesenteric vein thrombosis** (5-15%): trauma, surgery, thrombophilia, local inflammation (pancreatitis, diverticulitis, biliary infxn), stasis d/t cirrhosis/portal HTN, malignancy<br>Prognosis: mortality 50%, but up to 70-90% if delayed diagnosis leads to intestinal gangrene | - Progressive atherosclerotic narrowing at origins of vessels<br>- Risk Factors: tobacco, HTN, DM, HLD (ASCVD RFs), >60 yo, female, dissection, vasculitis, fibromuscular dysplasia, radiation<br>- Vessels: SMA, IMA, celiac artery<br>- If pain is constant, consider acute thrombosis |
| **Dx** | **Labs**: ↑lactate, WBC, LDH, CK, & amylase if advanced. Stool guaiac ⊕ in ~50%. Stool Cx, O+P, C. diff<br>**Imaging**: CT w PO+IV contrast: wall thickening, edema, thumbprinting, pneumatosis, **no vessel occlusion**<br>**Colonoscopy** (to assess extent): petechial blood, pale mucosa, segmental edema/ulceration | **Labs**: most abnormalities arise after progression to necrosis. ↓pH, ↑lactate, AGMA, WBC >15K<br>**Imaging**: KUB: Ileus, colonic dilatation, pneumatosis. CT A/P (ideally CTA; no PO contrast): wall thickening, pericolonic fat stranding, pneumatosis, arterial occlusion, portomesenteric venous gas.<br>Angiography: if CTA non-diagnostic but high suspicion, or if vasculitis affecting small-medium size vessels; potentially therapeutic with stent/tPA | **Imaging**:<br>- CTA: ⊕ if stenosis of ≥ 2/3 major vessels (celiac, SMA, IMA). 91% with 2 vessels, 55% with all 3 vessels<br>- Doppler U/S: measure mesenteric blood flow and r/o median arcuate ligament syndrome<br>- Gastric tonometry: exercise testing<br>- Angiography: (see left) |
| **Tx** | - Bowel rest, IVF, d/c vasoconstrictive meds<br>- GNR/anaerobic abx if ≥ mod sxs (per ACG guidelines)<br>- If suspicion for bowel necrosis, gangrene, or perf, call surgery<br>- If atherosclerosis on imaging, treat with lipid lowering agent | **Occlusive disease**: NGT/NPO, IVF/blood product<br>- Broad-spectrum **abx**<br>- Anticoagulation (**heparin** +/- tPA) if not bleeding for occlusive dx<br>- If infarction/peritonitis/perf → **surgery**<br>- Thrombectomy/embolectomy vs. intra-arterial vasodilators (papaverine) vs. thrombolysis<br>**Non-occlusive**: treat underlying cause (statins etc.)<br>**Mesenteric vein thrombosis**: AC x3-6 mo | - Surgical revascularization: open vs. endovascular or angioplasty +/- stenting. Peri-op mortality 0-16%; no role for prophylactic intervention if asymptomatic<br>- Restenosis common (7% open revasc; 34% endovascular)<br>- TPN for nutrition support<br>- AC if acute-on-chronic ischemia |

**Celiac artery compression syndrome**: chronic, recurrent abdominal pain related to compression of the celiac artery by the median arcuate ligament. P/w abdominal pain, wt loss +/- nausea, diarrhea. Exam often normal ± epigastric bruit. Dx: arteriography, duplex U/S, gastric tonometry, ganglion nerve block Tx: celiac artery decompression (MIS or open) (Cardiovasc Diagn Ther 2021;11:1172)

# Gastroenterology — Nutrition & Feeding

## General Approach (ACG: AJG 2016;111:315)

1) Assess nutritional status (Clin Nutr ESPEN 2018;26:13)
   - **H&P**: dietary intake/tolerance, n/v/d, muscle/fat wasting, **wt loss**, functionality (grip strength, ADLs). **Screen** for food insecurity
   - **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 1yr
   - **Labs:** INR prolongation may indicate malnutrition. Consider vitamin levels if H&P suggestive. Albumin can be confounded by inflammation. **Avoid** using pre-albumin, transferrin, retinol binding protein as indicators of nutrition.
   - **24-hr calorie count** (if considering enteral or parenteral nutrition). **Nutrition c/s** if c/f malnutrition (**screen** with MUST score)
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)**: NGT if pt unable to tolerate oral diet safely or meet caloric needs through oral diet alone. Measuring gastric residuals not recommended (NEJM 2014;370:1227). In critically ill pts, consider Tylenol absorption test to assess enteral nutrient/med absorption. Place tube post-pyloric (JG/PEG-J) if gastroparesis, gastric outlet obstruction, severe vomiting, or high aspiration risk. Consider PEG if head/neck cancer, dysphagia, neurodegenerative disease, prolonged recovery >4 weeks.
   - **Parenteral**: TPN (central access) > PPN (peripheral). Used when GI tract non-functional, no reliable enteral access anticipated, or not meeting goals with EN.
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) and aspiration.

## 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** (no fiber) **or Jevity 1.0** (with fiber) |
| Long-term TF<br>Prevent constipation (high fiber) | **Jevity 1.5** (fiber) |
| Wound healing (high protein)<br>ICU patients (on propofol) | **Promote** |
| IBD, pancreatitis, malabsorption | **Vital or Peptamen** (semi-elemental) |
| Respiratory failure/ARDS<br>Volume overload (high protein) | **Osmolite 1.5** |
| Renal or liver failure (low Na/K/phos) | **Nepro** |
| Wound healing | **Beneprotein/ProSource Liquid Protein** (modular protein) |
| Max fluid restriction | **TwoCal HN** (normal protein, low fiber) |
| Diabetes | **Glucerna** |

**TPN: "Nutrition Support Team" in PPD (p22445)**
Consider if ≥7d w/o enteral nutrition. Need central access w/ clean dedicated lumen (PICC Preferred). Order by 1PM to start same day. Page about new orders if close to 1 PM.

- 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 TAGs
  - **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 (d/t insulin surge and increased Na/K pump activity), 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, BMI < 20, significant wt loss, age, excessive alcohol and substance use, malnutrition 2/2 chronic dz/malabsorptive conditions, anorexia nervosa, persistent n/v/d, low initial lytes
- Characteristics: **early**: ↓Phos, ↓K, ↓Mg; **late**: heart failure **other s/s**: AMS, n/v, diarrhea, tremors, paresthesia
- Prevention and management: daily BMP, Mg, Ca, Phos (**BID when high risk**) w/ electrolyte replenishment (IV preferred) for first 3 days & administer thiamine **before** refeeding regardless of level, slow initial feeding, consider fluid/Na restriction, cardiac monitoring

## Special Considerations

- **IBD flares, pancreatitis**: early enteral feeding (ideally within 24-72 hrs of admission)
- **Critical care**: EN should start within 48 hrs of ICU stay (superior to TPN if GI tract functional); C.I. include high pressors/unstable (risk of bowel ischemia) or significant GI pathology (e.g. GI bleed, obstruction) for which patient should be NPO (Clin Nutr ESPEN 2019;38:48)
- **Dementia**: avoid dietary restrictions, use supplements PRN; guidelines recommend against TFs in advanced dementia (a/w higher mortality), lack of evidence to support appetite stimulants (Nutr Clin Pract. 2014;29:829)
- **Cirrhosis:** avoid prolonged fasting periods in patients with cirrhosis, encourage high protein diet (even with HE), and provide frequent, small, high protein meals

## Tips for Ordering Inpatient Diets

- **Diabetes: Consistent carbohydrate** (must add carb gram restriction within order)
- **Cardiac: no added salt** (3g) vs **2g Na** (renal/liver/cardiac). Consider fluid restriction (usually 2L) for HF/SIADH
- **GI: low fat (GI)** for gallbladder dz/fat malabsorption/pancreatitis, **red dye restricted** for pre-EGD/colo
- **Renal: low K** (2 g), **low phos** for ESRD, consider fluid restriction
- **Onc: Neutropenic/BMT** (no garnishes), **PET scan** is zero carbohydrate

*Reena Goswami*



Suggest an Edit

# Gastroenterology — Pancreatitis and Pancreatic Mass

## ETIOLOGY (NEJM 2016;375:1972, AJD 2024:119,3:419)

- **Gallstones/sludge** (40-75%): #1 in females
- **Alcohol** (25-35%): #1 in males
- **HyperTG** (10%): #3; suspect if TG>1000
- **Anatomic**: ampullary diverticula/stenosis, duodenal stricture, tumor, divisum, parasites, foreign body
- **Post-ERCP**: 1-30% of ECRP; rectal NSAIDs ↓risk
- **Autoimmune**: type 1:↑IgG4, type 2: IgG4 nml (Am J Gastro 2018;113:1301)
- **Acute hypercalcemia**: $Ca^{2+}$ activates panc enzymes
- **Genetic**: *CFTR, CTRC, PRSS1, SPINK1, A1AT*
- **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, methanol, scorpion, loxosceles
- **Infections**: viral (Coxsackie, EBV, CMV, HIV, Mumps, VZV, HAV, HBV), bacterial (Mycoplasma, Legionella, Leptospira, Salmonella), fungal (Aspergillus), parasitic (Toxoplasma, Crypto, Ascaris)
- **Ischemia**: vasculitis (SLE, PAN), hypoTN/shock, cholesterol emboli
- **Trauma:** blunt, especially s/p MVA **Idiopathic** (10-25%)

## DIAGNOSIS (Revised Atlanta Classification: Gut 2013;62:102)

- **Presentation**: LUQ/epigastric abd pain (90%, band-like pain to back in 50%), N/V (90%), ileus, jaundice, flank/umbilical ecchymoses
- **History**: prior episodes, EtOH/smoking, GI procedures (e.g., CCY, ERCP), new meds/exposures, infectious sx, autoimmune hx, FH
- **Diagnosis – need 2/3**: 1) consistent clinical presentation, 2) lipase >3x ULN, 3) characteristic imaging (US, CT w/contrast, MRI)
- **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 (TAGs). Recheck HCT/BUN <6-8hrs after presentation.
- **Imaging**: All: RUQUS for gallstones; If needed for dx: CT (90% sens), also for complications (~48-72h); MRI/MRCP if c/f necrosis, stricture, or stone w/ neg RUQUS
- **Risk Factors for Severe AP**: VS abnormalities, Age>55, BMI>30, BUN>20, HCT>44, pleural effusion/infiltrate, extra-panc collections
- **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). Organ failure: can use modified Marshall score
- **Prognosis**: Many scoring systems to identify mild type; BISAP is quick/superior. RANSON, APACHE II less practical.

## MANAGEMENT (AJG 2024:119(3)e419; WATERFALL trial NEJM 2022; 389:989)

- **IV fluids**: moderately aggressive in 1st 6-12hrs: infusion 1.5mL/kg + PRN boluses 10mL/kg over 2h if hypovolemic (UOP < 0.5ml/kg/hr or SBP <90). Goal is to prevent Hct or BUN rise, most pt will benefit from ~3L in 1st 24hrs. **LR superior to NS**, avoid LR if ↑Ca. **Avoid aggressive resus after 24-48hrs** (risk of abd compartment syndrome, intubation). Ok to d/c at 20 hr if tolerating PO >8hr.
- **Pain control**: IV opioids **Abx**: No role for prophylactic abx.
- **Nutrition**: start PO (low fat/residue) within 24-48h as tolerated. At 5-7d, if PO not tolerated start continuous TFs (NG > 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 if TG >500 w/ pancreatitis or TG>1000 to prevent pancreatitis. Rate 0.1-0.3U/kg/hr + D5, q1h FSBG (initially), q12h TG. Goal TG <500 (can take days). (See MGH ellucid policy) No good evidence for apheresis. If tolerating PO, fibrates are first line. DC: lifestyle Δs, lipid clinic referral
- **If idiopathic:** Repeat RUQUS and TG as an outpt. If second episode of iAP, recommend CCY +/- genetic testing

## COMMON COMPLICATIONS (NEJM 2016;375:1972)

| Local | | | Vascular | Systemic |
|---|---|---|---|---|
| | <4 weeks | >4 weeks | **Thromboses**: splenic, portal, SMV; AC if portal vein or bowel ischemia<br><br>**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 | **Abd. compartment syndrome**: intra-abd pressure >20 w/ new organ failure. Check bladder pressure in ICU.<br>**ARDS**: via phospholipase degradation of surfactant<br>**Metabolic**: ↓Ca, ↑Glc, ↑TG<br>**GIB**: via pseudoaneurysm<br>**AKI**<br>**DIC** |
| **Interstitial edematous pancreatitis** | **Acute peripancreatic fluid collection**: w/o features of pseudocyst; resolve spontaneously 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) | | |
| **Necrotizing pancreatitis** | **Acute necrotic fluid collection**: intra- or extra-pancreatic | **Walled off necrosis**: encapsulated necrotic collection. Drain at >2-4 wks if sx or infxn (endo vs. perc) | | |
| | **Infected necrosis**: 1/3 become infected, suspect ~7-10d. Early enteral feeding ↓risk Dx: discuss CT-FNA, assume infected if +Bcx/gas. Abx: (cefepime or cipro) + flagyl vs. pip/tazo. Drainage/necrosectomy: urgent if unstable vs delay >4w if stable on abx | | | |

## 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, vitamin deficiencies), endocrine insufficiency (brittle DM). Lipase/amylase may be ↑ early but nrml/low as tissue lost. ⊕ Fecal fat, ↓stool elastase. CT/MRI with calcifications, ductal dilation, parenchymal atrophy. ↑risk of pancreatic CA. Consider genetic testing.
Tx: pancreatic enzyme replacement (Creon), ensure vit ADEK replete, pain control. Refer to MGH Pancreas Center: 617-726-5523

## PANCREATIC MASSES (AJG 2018;113:464 ; Gastro 2015;148:819)

- Solid: adenoCA (85-90%), autoimmune panc, neuroendocrine (1-5%), 1° lymphoma (<1%), mets (melanoma, RCC, etc.)
- Cystic: inflammatory (pseudocyst, paraduodenal wall cyst), neoplastic (malignant potential: main duct IPMN >> side branch IPMN > mucinous cystic = solid pseudopapillary > serous cystadenoma). Refer to MGH cyst clinic.
- Imaging: **CT abd pancreatic mass protocol**; EUS with FNA for lesions >2-3cm (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)

**1) Identify pattern of liver test abnormality.** R-factor = (ALT / ULN) / (Alk-P / ULN)
- Hepatocellular: R factor >5, ↑↑ ALT
- Mixed: R factor 2-5, ↑ ALT, ↑ Alk-P
- Cholestatic: R factor <2, ↑↑ Alk-P, ↑↑ GGT, ↑ ALT

**2) Identify chronicity**
- Acute: < 6 months
- Chronic: > 6 months

**Hepatocellular markers:** *Released from hepatocytes in response to injury*
**ALT:** Expressed primarily in cytosol of liver hepatocytes, **more specific**
**AST:** Expressed in cytosol + mitochondria of liver hepatocytes.
Also cardiac muscle, skeletal muscle, kidney, brain, and RBCs
*Magnitude of ALT and AST elevation:*
- **Extreme elevation (>15x ULN or >1,000 U/L):** Most c/w acute liver injury, including ischemic hepatopathy (shock liver), acetaminophen toxicity.
- **Moderate elevation (5-15x ULN):** Ddx as above AND acute hepatitis A/B/C/E
- **Borderline to mild elevation (<5x ULN):** Broad ddx: meds/toxins (see below), chronic liver disease (EtOH, MASLD, HBV/HCV, autoimmune, hemochromatosis, Wilson's, alpha-1-anti-trypsin deficiency), biliary obstruction (mixed markers)

**AST/ALT ratio:** Usually ALT>AST (AST has shorter serum half-life, 16h vs 35h). Ratio can vary widely, esp. in acute liver injury (2024 Cell Rep Med; 5:101828)
- Mild AST/ALT elevation with ratio ~2:1 suggestive of alcohol related liver disease or injury
- Typical AST/ALT ratio in hepatocytes is 2.5:1, so ratio >2.5:1 consider non-hepatic source of AST (Clin. Bio. Rev.; 2013; 34(3)117)

When approaching the ddx for liver biochemical tests, integrate hx and relevant exposures or clinical factors (travel, meds, supplement use, alcohol, ingestions, co-occurring autoimmunity, recent shock, etc.) rather than completely relying on scoring systems

**Cholestatic markers:** *Released from cells lining bile canaliculi/ducts in response to injury*
**Alk-P:** Expressed in bile duct, liver, kidney, bone, intestinal mucosa, and placenta. Confirm source with GGT/5'-NT as below or fractionated assay (slow to result). If accompanied by other LFT abnormalities (e.g. elevated bili), do not need to confirm source.
**GGT:** Expressed in bile duct, liver, pancreas, and kidney. Supports biliary/hepatic source of Alk-P. Non-specific marker of EtOH use.
**5'-NT**: Expressed in heart, skeletal muscle, and liver. Like GGT, distinguishes biliary vs bone source of Alk-P.
*Magnitude of Alk-P elevation:*
- **1-1.5x ULN:** Common in adults over age 60 (esp women 2/2 increased bone turnover)
- **1-3x ULN:** Any liver disease
- **>4x ULN:** Cholestatic liver dz, infiltrative liver dz (e.g. cancer and amyloidosis), bone conditions characterized by rapid bone turnover. In absence of ↑ bili or ALT/AST, suggests early cholestasis or hepatic infiltration by tumor or granulomatous dz

**Cholestasis**: extrahepatic 2/2 anatomic obstruction to bile flow (e.g. choledocholithiasis, malignancy, PSC, HIV/AIDS cholangiopathy) vs intrahepatic 2/2 functional impairments of bile formation [e.g. PBC, infiltration (sarcoid, atypical fungal infxn, malignancy)]
For more info and work-up, see *Biliary Disease*

**Markers of liver function:**
**Bilirubin:** Heme breakdown product conjugated in the liver and excreted in bile. Decay is related to albumin half-life (3 weeks).
- Conjugated (direct) bilirubinemia: ↑ **total and direct bilirubin** seen in hepatocellular damage, impaired excretion, or biliary obstruction. Only conjugated bilirubin excreted in urine, so bilirubinuria also implies liver disease. Consider bile duct obstruction/stricture, hepatitis (viral, toxic, EtOH, ischemic, autoimmune), PBC, PSC, infiltrative dz, congestive hepatopathy, TPN, HCC, Rotor syndrome, and Dubin-Johnson syndrome.
- Unconjugated (indirect) bilirubin: ↑ **indirect bilirubin** caused by ↑ production, ↓ uptake by the liver, or ↓ conjugation. Consider hemolysis, hematoma resorption, fasting, ineffective erythropoeisis, and Gilbert syndrome (usually < 3mg/dL).

**Albumin:** ↓ in chronic liver disorders such as cirrhosis. Not specific to hepatic dysfunction; can also occur in systemic inflammation, nephrotic syndrome, malnutrition, protein losing enteropathy, ascites (due to marked increase in plasma volume)
**Prothrombin (PT-INR):** ↑ PT-INR due to ↓ vitamin K absorption/use 2/2 parenchymal liver disease. PT measures extrinsic coag pathway and relies on vitamin K dependent coag factors. First, consider consumption of clotting factors (e.g., DIC, GI bleed) and meds.
Vitamin K challenge (10mg IV/PO x3 d): If INR drops after day 1, deficiency (e.g. dietary intake, malabsorption [inadequate bile salts needed for Vit K uptake]) likely a component. Vit K supplementation does NOT improve INR in liver disease.
**Platelet Count:** ↓ platelets associated with ↓ synthesis (liver produces thrombopoietin), splenic sequestration in portal hypertension, and ↑ destruction through multiple pathways.

**Commonly used drugs that cause hepatocellular injury**: acetaminophen, allopurinol, amoxicillin-clavulanate, amiodarone, aspirin, carbamazepine, clindamycin, fluconazole/ketoconazole, fluoxetine, glyburide, heparin, hydralazine, INH, immune checkpoint inhibitors, labetalol, lisinopril, losartan, methotrexate, niacin, nitrofurantoin, NSAIDs, phenytoin, protease inhibitors, statins, sulfa drugs, trazodone, valproic acid. *See* livertox.nih.gov *for full list*
**Supplements:** kava-kava, black cohosh, green tea extract, chaparral, ephedra, ji bu huan, germander, weight loss supplements
**Illicit drugs**: anabolic steroids, cocaine, ecstasy, PCP. **Environmental**: *Amanita* mushrooms
(J Hepatology 2019;70:1222; NEJM 2019;381:264; AJG 2017;112:18)

# Gastroenterology — Biliary Disease

## Gallstone Diseases (J Hep 2016;65:146; J Hep Panc Sci 2018;25:41)

| **Cholelithiasis**: presence of stones in **GB** (6% of M, 9% of F) | **Choledocholithiasis**: stones in **common bile duct** |
|---|---|
| - Sx: aSx (<20% develop clinical events), larger, multiple, older gallstones and Female sex ↑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)<br>- Dx: **RUQUS** (Sn 84%, Sp 99%) > CT (Sn 55-80%); EUS if ⊖; labs wnl<br>- Stone types: *cholesterol* (most common); *pigment*: Crohn's/ileal disease, extravascular hemolysis, TPN<br>- Tx: *asymptomatic*: observe; CCY only if at ↑risk for GB CA (stone >3cm, porcelain GB, GB adenoma); *symptomatic*: elective CCY<br>- Complications: cholecystitis, choledocholithiasis, pancreatitis, GB CA, gallstone ileus, Mirizzi syndrome (compression of CBD/CHD) | - Sx: RUQ pain, n/v, jaundice; may be asx<br>- Labs: ↑ALP, ↑bili ± ↑AST/ALT<br>- Dx: **RUQUS** to look for CBD dilation >7mm (poor Sn for visualizing stones themselves); **repeat RUQUS**, **MRCP,** or EUS if equivocal<br>- Tx: ERCP w/ stone removal; interval CCY<br>- Complications: ascending cholangitis, acute pancreatitis<br>FYI: can occur s/p CCY if de novo formation in CBD |
| **Cholecystitis**: stone in **cystic duct** → inflammation of GB ± infxn | **Cholangitis**: ascending biliary infxn 2/2 **obstruction in CBD** |
| - Sx: RUQ pain (w/ radiation to back/shoulder), Murphy's sign, n/v, fever<br>- Labs: ↑WBC; +/- ↑ALP, Bili; if ↑↑ALP/Bili c/f CBD obstruction<br>- Acalculous cholecystitis: GB stasis/ischemia w/o obstruction. Unexplained fever, ↑WBC. *RF*: trauma, burns, TPN, severe illness, fasting, sepsis, immunosuppression (CGH 2010;8:15)<br>- 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<br>- Tx: **abx** (Zosyn or CTX/Flagyl). **Early (<7d) CCY** during hospitalization → ↓morbidity (Br J Surg 2015;102:1302). If critically ill with biliary sludge and ↑LFTs or high surgical risk & fails to improve after 1-3d abx → **percutaneous cholecystostomy with IR**. Stop abx 24h post-CCY unless septic/perc chole: 4-7d (JAMA Surg 2019;154:873)<br>- Complications: gangrenous cholecystitis, emphysematous cholecystitis (gas-forming organism), perforation, enteric fistula, gallstone ileus | - Etiologies: stone, stricture (malignancy, PSC, AIDS), liver fluke<br>- Sx: *Charcot's triad:* RUQ pain, fever, jaundice; *Reynold's pentad*: + shock and AMS<br>- Labs: ↑WBC, ↑ALP, ↑Bili, ± ↑AST/ALT (can be ↑↑)<br>- Dx: **RUQUS** (ductal dilation), **MRCP**/ERCP. Tokyo Guidelines for dx & severity<br>- Tx: broad spectrum **abx** (Zosyn or CTX/flagyl) x7d; urgent **ERCP** w/ decompression (<24-48h) if severe (associated organ dysfunction/shock) or if fails to improve on abx x 24h. Perc drainage if ERCP not feasible. Interval **CCY** if due to gallstones<br>- Higher risk for cholangitis after palliative CBD stent placement in patients with malignant obstruction<br>- Complications Post-ERCP: pancreatitis, bleeding, infxn, perforation (GIE 2017;85:32) |

## Autoimmune Biliary Diseases

| **Primary Biliary Cholangitis (PBC)** (AASLD: Hepatology 2019;69:394) | **Primary Sclerosing Cholangitis (PSC)** (AASLD: Hepatology 2022;77:659) |
|---|---|
| Autoimmune destruction of *intrahepatic* bile ducts | Affects *intra-* + *extrahepatic* bile ducts |
| - Clinical manifestations: F>M; asx (50-60%), pruritus, fatigue, sicca symptoms, cirrhosis (late)<br>- Dx: ≥*2 of the following*: 1) **ALP** ≥1.5x ULN; 2) **Antimitochondrial Ab**>1:40 titer (95% pts) or other PBC-specific ab if AMA neg (anti-gp210/anti-sp100 highly spec); 3) biopsy findings.<br>- Assoc. with: dyslipidemia, hypothyroidism, osteoporosis, Sjogren's, autoimmune hepatitis (overlap)<br>- Tx: **ursodiol**: 1st line, ↓progression & ↑survival (NEJM 1994;330:1342); **obeticholic acid** (FXR agonist) 2nd line after ursodiol, C.I. in portalHTN/decompensated cirrhosis, **fibrates**: off label altern, C.I. in decomp ESLD; **cholestyramine** for pruritus; **modafinil** for fatigue; **liver transplant**: 22% recurrence in 5yrs | - Clinical manifestations: M>F; asx (50%), pruritus and fatigue (most common), cirrhosis (late); cholangitis due to strictures<br>- Dx: ↑ALP ± bili; may have +auto-Abs but of unclear significance; MRCP (segmental strictures**)**, only biopsy if imaging neg (to dx small-duct PSC); check AMA/IgG4 to exclude alt. dx<br>- Associated with: **IBD** (>70%; UC>Crohn's), **CCA (160-400x ↑ risk)**, gallbladder CA, metabolic bone disease, AIH (overlap)<br>- Tx: *supportive;* ursodiol may improve sx, ERCP for stricture, **liver transplant definitive tx** (MELD exceptions for recurrent cholangitis, intractable pruritus): 20% recurrence 5 years post-LT<br>- Screening: CCA + gallbladder CA surveillance annually (MRI/MRCP + CA 19-9); if cirrhosis present, HCC surveillance. |

## Malignant Disease of the Biliary Tract

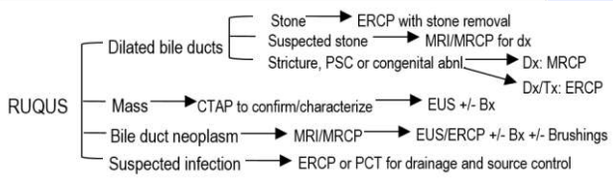
**Gallbladder carcinoma**: risk factors: gallstone disease (34x more likely to develop CA), porcelain GB, GB polyps, PSC, chronic infxn
- Diagnosis: LFTs usually normal, ↑CA19-9/CEA; RUQUS best initial diagnostic test, then CT/MRI/MRCP

**Cholangiocarcinoma (CCA)**: 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 for initial dx, then ERCP/MRCP/EUS

## Sphincter of Oddi Dysfunction

F>M; Often occurs post-CCY, provoked by opioids (due to spasm of sphincter) and associated with idiopathic recurrent pancreatitis, Rome IV criteria (MD Calc). Diagnosis: ERCP/manometry. Treatment: surgical/endoscopic sphincter ablation (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 Injury (ALI): acute liver injury <26w with coagulopathy but NOT encephalopathy**
**Acute Liver Failure (ALF): encephalopathy & coagulopathy (INR >1.5) of <26w in pts without cirrhosis or known liver disease**

**Presentation**: fatigue, lethargy, anorexia, n/v, RUQ pain, pruritis, ± jaundice → ascites, confusion in ALF (and may progress to coma)
**Initial diagnostics**: CBC w/ diff, CMP, PT/INR, fibrinogen, LDH, T&S, lactate, ABG, arterial ammonia, FSBG, hCG, HIV, APAP, blood/urine tox screen, PETH, viral/autoimmune serologies (as below), amylase/lipase, CT head if HE, RUQUS w/ Doppler (JHM 2017;12:184)

| Type | Etiologies | Diagnostics |
|---|---|---|
| **Drugs** (see LiverTox) | Acetaminophen (dose-depend: >6g/day or 150/mg/kg/day for 24-48h, >4g/day or 100 mg/kg/day for >48h): most common cause of ALF in US<br>Toxins: *Amanita phalloides* mushroom, occupational exposures ($CCl_4$)<br>Idiosyncratic DILI (dose-indep): abx (*Augmentin), AEDs, anti-TB, etc.<br>(Alcohol-related hepatitis: considered acute-on-chronic and *not* ALF) | History: all APAP-containing meds, herbal supplements, new meds/OTCs, EtOH use<br>Labs: APAP level, EtOH, tox screen |
| **Viral** | HAV, HBV, HCV (rare w/o HBV co-infection), HDV (↑risk co-infection > superinfection or HBV alone), HEV (pregnant or in endemic areas)<br>Others: HSV (may be anicteric, ↓WBC), adenovirus, EBV (rare), CMV, VZV (if immunocompromised). HIV screen can help guide diagnostics | History: travel, PWID, occupational exposures, sexual exposures, vesicular rash (HSV/VZV), blood transfusion, immunocompromised state<br>Labs: HAV IgM, HBsAg & core IgM (if acute), HCV Ab & PCR, HSV PCR; check HDV if +HBV, HEV if preg., VZV if immunocompromised, EBV PCR |
| **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 | History: HoTN, hypercoag. state, drugs/meds<br>Imaging: RUQUS w/ Doppler; CT or MRI/MRV are alternatives; consider TTE if no known cause |
| **Autoimm.** | AIH: F>M; can present as ALF but uncommon | Labs: 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 | History/exam: FH, slit-lamp exam for KF rings<br>Labs: 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 | Labs: UA if pregnant<br>Liver bx if dx remains elusive after thorough eval |

## Management of Acute Liver Failure (AASLD: Hep 2012;55:965; ACG: Gastro 2023;118:1128; NEJM 2013;369:2525)

- **Consult Hepatology for OLT workup.** Urgency based on HE severity (ASAP if grade 3-4)
- Monitoring: freq. coags, CBC, ABG, CMP, $NH_3$; q2 hr neuro checks to monitor for worsening HE or ↑ICP (esp. gr. 3-4), e.g., Cushing's triad (bradycardia, irregular respirations, and wide pulse pressure with HTN) requiring more intensive monitoring.
- Hemodynamics: IVF (NS) and/or pressors (norepi ± vaso); goal MAP ≥75 for cerebral perfusion
- N-Acetylcysteine (NAC): tx APAP toxicity + non-APAP DILI-related ALF w/ gr 1-2 HE. Initial tx: 150mg/kg/h, 1h, max 15g→ 12.5mg/kg/h, 4h, max 5g→ 6.25mg/kg/h, 16h, max 10g
- **Encephalopathy**: intubation for HE gr. ≥3; **↑cerebral edema** in HE gr. 3 (25-35%) & 4 (75%)
  - Lactulose in ALF controversial: ↑bowel distent. May worsen outcomes.
  - CRRT lowers ammonia levels within 3 days and decreases mortality (Hep 2018;67:711)
  - 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. Check 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 antimicrobials. Avoid nephrotoxic/hepatotoxic abx
- Coagulopathy/bleeding: can trial vit K, routine FFP not recommended. In ICU, ppx w/ PPI. Viscoelastic tests (e.g. TEG) may be more accurate assessment of coagulopathy

| Hepatic Encephalopathy | | |
|---|---|---|
| **Grade** | Mental Status | Asterixis |
| **I** | Attention deficit | ± |
| **II** | Lethargy<br>Moderate confusion | + |
| **III** | Somnolence<br>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 → Ingestion <4h or rising level, give activated charcoal. Ingestion >30g or deranged AST/ALT, give empiric NAC. See Figure 1: treatment pathway, Figure 2: revised nomogram, Figure 3: NAC guidelines in *Consensus Statement*: JAMA 2023;6:e2327739
- HBV/HCV → OLT; possible role for antivirals in HBV
- HAV/HEV → supportive care, possible OLT
- Amanita poisoning → IV silibinin (20-50 mg/kg/d x2-4d), IV NAC
- AFLP/HELLP → delivery; follow up for need for OLT
- HSV/VZV → acyclovir (5-10mg/kg q8h); may need OLT
- AIH → consider glucocorticoids; OLT if needed
- Wilson's → OLT; chelation ineffective
- Budd-Chiari → anticoag, TIPS, surg decompression, lysis, OLT

**King's College Criteria** (specific but not sensitive)– 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 >25 = poor prognosis. HBV, Wilson's, Budd-Chiari, AIH, DILI also associated with poor prognosis.

*Maggie Selesky*



Suggest an Edit

# Gastroenterology — Viral Hepatitis

## HEPATITIS A (CDC 2020)

Fecal-oral route: personal contact, food/water, travel. Incubat. period wks. Sx: abrupt n/v, anorexia, malaise, fever, jaundice, RUQ/abd pain, ↑ALT>AST (often >1000), ↑bili/ALP. Sxs in 70% adults, last 2-8w (often self-limited), jaundice peaks after 2w.
Dx: ⊕ anti-HAV IgM, persists 3-6mo. Anti-HAV IgG forms at 2-3w, confers lifelong immunity. Tx: Care is supportive unless ALF (rare,<1%).
Vaccinate if: MSM, PWID, chronic liver dz, HIV, travel, homeless, certain exposures. Havrix and Vaqta = 2 doses. Twinrix = 3 doses, covers HBV. Pre and post-exposure ppx: Single HAV vaccine +/- immune globulin in non-immune pts w/in 2 wks of exposure.

## HEPATITIS B (AASLD: Hepatology 2018;67:1560; USPSTF: JAMA 2020;324:2452; NEJM2023;388:55)

| | |
|---|---|
| **Screening** | HBsAg. 1x for all adults. Repeat if HIV+, PWID, MSM, close contact of HBV+ person, unexplained elevated LFTs, those requiring certain immunosuppressive therapies (e.g. rituximab, daratumumab) |
| **Risk Factors** | Vertical transmission (SE Asia), sex, tattoo, PWID, needlestick, unvaccinated (US before 1994) |
| **Clinical Pres.** | **Acute**: 70% subclinical, 30% w/ jaundice, <1% ALF. S/S: anorexia, nausea, fatigue, RUQ discomfort. ALT>AST in 1000s, +/- ↑Bili. **Chronic**: ⊕HBsAg >6mo. (often w/ persistent ↑ALT), occurs <5% adults. 40%→cirrhosis |
| **Extrahepatic** | Polyarteritis Nodosa, membranous nephropathy/MPGN, aplastic anemia, arthritis/serum sickness |
| **Diagnosis** | HBsAg, anti-HBs, anti-HBc total (identifies all infected). Test for HDV if severe/protracted course or chronic HBV. HBe Ag/Ab in chronically infected individuals with positive HBV DNA to assist treatment decisions |
| **Treatment** | First line: tenofovir or entecavir. Monitor HBV DNA, LFTs, Cr. **Goal**: suppress HBV DNA, negative HBsAg & HBeAg |
| **HCC Screen** | **Indications**: all HBsAg+ w/ cirrhosis, HBsAg+ & high-risk (Asian/Black M >40; Asian F >50; +HDV; +FH HCC) |

| HBsAg | Anti-HBs | Anti-HBc (total) | Interpretation | Next Steps |
|---|---|---|---|---|
| ⊕ | - | ⊕ | Hepatitis B infected (acute or chronic) | Check anti-HBc IgM (acute vs. chronic), HBV DNA, HBeAg |
| - | ⊕ | ⊕ | Past infection (resolved) | None; ↑ risk of reactivation w/ chemo/immunosuppression |
| - | - | ⊕ | (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 ⊕ anti-HBc *or* false ⊖ HBsAg | Differentiate possibilities w/ anti-HBc IgM (acute infxn vs. others), anti-HBe, HBV DNA, repeat anti-HBc (later). "occult HBV" = DNA⊕ w/ HBsAg⊖ +/- HBcAb⊕. Low risk reactivation but ↑ if chemo/immunosuppression |
| - | ⊕ | - | HBV-immune from prior vaccination | None |
| - | - | - | Uninfected, non-immune | Vaccinate. Engerix-B (3 doses. All ages. Adjust for adults on HD). Heplisav-B (2 doses, >=18 yo, not approved for HD) |

HBV reactivation: indicated by: (1) 1 log ↑ in HBV DNA or LFT vs. baseline or (2) reverse seroconversion from HBsAg-/anti-HBc+ to HBsAg+. Check serologies before high-risk therapies. HBsAg+ is greatest risk, need ppx. HBsAg-/anti-HBc+ is lower risk. PPX w/ entecavir/tenofovir in selected high risk cases.
Tx Indication: (1) acute liver failure, (2) all cirrhosis, (3) If no cirrhosis, depends on HBeAg/ALT/DNA level (Hepatology 2018;67:1560) as well as pregnancy, HCV co-infection, HCC, and immunosuppression.

## HEPATITIS C (AASLD/IDSA: CID 2023)

| | |
|---|---|
| **Screening** | HCV Ab. If positive, order RNA Viral Load (PCR), MGH does not have reflex testing. **18+: *universal one-time screening*** (USPSTF: JAMA 2020;323:970). PWID or MSM w/ HIV: annual. With each pregnancy. |
| **Risk Factors** | PWID, blood products pre-1992, MSM, HIV, chronic HD, incarceration, immigration from ↑prevalence area, HCV infected mother, sex with HCV+ partner |
| **Diagnosis** | ⊕Ab, ⊕RNA = current infection. ⊕Ab, ⊖RNA = cleared or treated (can still get re-infected) |
| **Natural History** | Acute HCV: 75% subclinical. If sx, develop 2-26w after exposure, last 2-12w. Fulminant rare (<1%)<br>Chronic HCV: 80% → chronic; if younger, female sex, genotype 1, jaundice, ↑ALT more likely to clear spontaneously<br>20% → cirrhosis (↑risk if male sex, EtOH, obesity, HIV, immunosupp.). HCC risk 1-13%/yr |
| **Extrahepatic** | Mixed cryo., porphyria cutanea tarda, lichen planus, thyroiditis, Sjogren's, renal dz (e.g., MPGN), NHL |
| **Treatment** | 1) Assess advanced fibrosis with FIB-4 score, U/S Elastography (FibroScan), FibroSure.<br>2) Obtain HIV test (if +, initiate ART 1st), HBsAg/HBcAb/HBsAb, HAV IgG. Get baseline CBC, LFTs, GFR<br>3) If first time HCV diagnosis, no cirrhosis, start simplified tx: pangenotypic therapy [ e.g. Mavyret (Gle/Pib) x8wks or Epclusa (Sof/Vel) x12wks]<br>4) If compensated cirrhosis, see IDSA guidelines. If decompensated cirrhosis, consult hepatology |
| **Follow-up** | HCV RNA and LFTs >12 wk after Tx to assess SVR (eradication of HCV RNA). If cirrhosis, continue HCC surveillance/variceal screening (q6mo U/S, EGD) EVEN after SVR. If no SVR at 12 wk, ID/GI referral and assess for fibrosis q6m (LFTs/CBC/INR) |

## HEPATITIS D (NEJM 2023;389:58)

Coinfection with HBV: HBV but more severe, ↑risk ALF; often biphasic ALT course. Superinfection on HBV: most severe, highest risk ALF & chronic infxn (90%) → cirrhosis in 80% in 5-10y, 3x ↑risk HCC vs. HBV mono-infection. RF: PWID, MSM, multiple transfusions, geography (Mediterranean Basin, Mongolia, Moldova, Western and Middle Africa). Dx: HDV RNA and anti-HBV. Tx: None approved in US.

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

Transmission: contaminated food/water, vertical, blood transfusion. Usually w/o symptoms. Jaundice w/ non-specific sx. Extra-hepatic: arthritis, hematologic, neurologic, pancreatitis, renal, thyroiditis. ↑risk of ALF/mortality in pregnant women (Annals 2007;147:28). Chronic infection if transplant recipient, immunocompromised. Dx: HEV IgG+ IgM, HEV RNA. Tx: supportive care if acute; ribavirin if chronic.

# Gastroenterology — Alcohol-Related Liver Disease

## Alcohol-Related Liver Disease (ALD) (AASLD: Hepatology 2020;71:308; ACG: AJG 2024;119:30)

**Risk factors**: sex (F>M), pattern (↑daily ± ↑binge), obesity, DM2, genetics (e.g. PNPLA3, α-1 antitrypsin), smoking, comorbid HCV/MASLD/etc.; coffee ↓risk. Harmful drinking: Men: ≥3 drinks/d or ≥21/wk. Women: ≥2 drinks/d or ≥14/wk. AUDIT-C screen.
**Pathophysiology**: EtOH → fat accumulation; EtOH → ↑gut permeability → ↑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 ↑AST>ALT, GGT; develops in 90% w/ >60g/d EtOH after 2w; reversible w/ 4-6w abstinence
  - 20-40% develop fibrosis → 8-20% to cirrhosis → 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 → to fibrosis (40-50%) & cirrhosis (>75%)
- Alcohol-related hepatitis (AH): an acute inflammatory syndrome that can occur at any stage of ALD
- Cirrhosis due to ALD: pathologic fibrosis distorting liver architecture -> abnormal blood flow.

**Prognosis**: 5-year mortality 2/2 liver dz ~25% **Treatment**: Cessation of EtOH. Motivational interviewing, CBT, and behavioral intervention (5 "A" model: ask about use, advice to quit/reduce, assess willingness, assist to quit/reduce, and arrange f/u). Pharmacology: Baclofen, acamprosate, naltrexone, gabapentin or topiramate. Suggest against disulfram, C.I. in liver disease
**Alcohol Liver Evaluation Team (ALiVE, p26299)**: eval. inpts w/ ALD or AUD w/o known ALD admitted for non-liver related complaints. Goal earlier identification of subclinical advanced fibrosis and connection to hepatology team for treatment.

## Alcohol-Related Hepatitis

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

- Can lead to acute portal HTN & sequelae (EVs, ascites, HE) w/o cirrhosis due to hepatic swelling & portal venous obstruct.

**Dx**: jaundice within 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 ↑ (50-400) w/ AST/ALT >1.5, Tbili >3. Often ↑WBC (<20k, ↑PMNs), ↑INR

- Must exclude other etiologies of acute hepatitis/jaundice (viral, meds/herbs, ischemia, AIH, Budd-Chiari, biliary obstruct.), decompensated cirrhosis; can be superimposed in 10-20% (Alcohol CER 2004;28:31). Check HAV/HBV/HCV, APAP level, RUQUS w/ Doppler, ± (ANA, ASMA, IgG levels, AMA). Assess for signs of cirrhosis
- Transjugular Bx: consider if atypical presentation and/or labs (e.g., AST/ALT >400), uncertain alcohol intake hx, jaundice >3 months, or suspicion for alternative etiology, such as use of hepatotoxic meds, possible ischemic insult (e.g., HoTN, cocaine use), etc.

**Exclude infection:** May have SIRS/fever due to inflamm., but screen for infxn as at high risk (esp. if severe AH: 12-26% at admission)

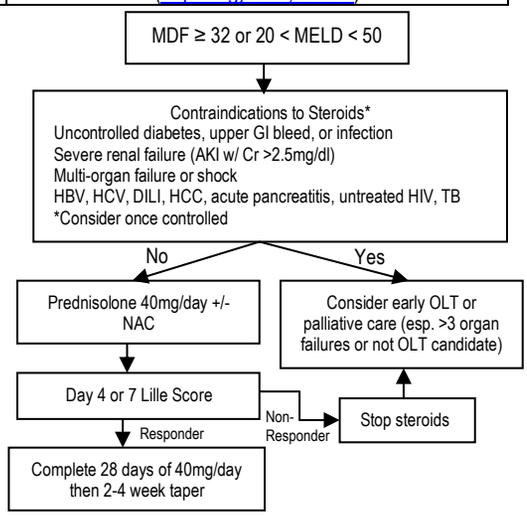
| Prognostic Tool | Use | Components | Stratification |
|---|---|---|---|
| Maddrey Discriminant Function (MDF) | Identify who will benefit from steroid therapy | PT, PT control (14.5 at MGH), Tbili | ≥32 = severe → 1mo. mortality 30-50%; GI consult re: steroids (Gastro 1978:75:193) |
| MELD | | Tbili, INR, Cr, Na | >20 = inpt admission, 3mo. mortality 20%; Consult GI for steroids (Hepatology 2005;41:353) |
| Lille | Perform on day 4 & 7 to assess steroid response | Day 0: Age, Albumin, PT, Cr<br>Day 0, 4, & 7: Tbili | ≥0.45: Nonresponse → stop steroids<br><0.45: Response → continue steroids<br>(Hepatology 2007;45:1348) |

## Treatment of Alcohol-Related Hepatitis

**Corticosteroids**: see algorithm

- Prednisolone used as not metabolized by liver (methylpred 32mg is IV alternative): 40mg x 28d w/ 2-4w taper. Lille score at 4 or 7 days to assess steroid response.
- No mortality difference at 28d or 90d, ↑infxn (NEJM 2015;372:1619).

**NAC**: may benefit, no harm (though is large volume load) x5d
**Supportive therapy**: hold βB if MDF ≥32 as ↑AKI incidence (Liver Int. 2015;35:8)
**Nutrition**: Goal 35 kcal/kg/d with 1.2–1.5 g/kg of protein; supplement w/ MVI, thiamine, folate, B6, B12, and Zn. Low kcal in severe AH a/w ↑infxn (Gastro 2016;150:903). Nutrition consult. If <21 kcal/kg/day, consider TF w/ NGT.
**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 alcohol use treatments were independently associated with complete abstinence (Hepatology 2017;66:1864)




## Liver Transplantation:

Definitive therapy for ALD. Traditionally required 6mo abstinence. ↑6mo 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 6 mo. 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) maddrey discriminant function (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. Can discuss if candidate at MELD >10 to give time for education/evaluation.

**Other therapies with potential efficacy:**

- **NAC**: w/ steroids x5d, may ↓mortality at 1mo, not 3 or 6mo (NEJM 2011;365:1781, Gastro 2015;149:958)
- Pentoxifylline: Not recommended. Consider if steroids contraind, no convincing data on ↓mortality, but does↓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: Small RCT, ↓ 90d mortality but risk of donor related infx (Hepatol Int 2023;17(1):249)

# Gastroenterology — Metabolic Liver Disease

## DEFINITIONS (ANN HEPATOL 2024;29:101133)

**Metabolic dysfunction-associated steatotic liver disease (MASLD)**: presence of hepatic steatosis (imaging or bx) w/o 2° cause (includes MASH)
**Metabolic dysfunction-associated steatohepatitis (MASH):** hepatic steatosis and inflammation with hepatocyte injury ± fibrosis
**Metabolic and alcohol related/associated liver disease (MetALD):** metabolic dysfunction + 140-350 g/wk or 210-420 g/wk of alc for female and male respectively.
**MASH cirrhosis**: cirrhosis with current or previous histological/clinical evidence of steatosis or steatohepatitis

## EPIDEMIOLOGY (Gut 2018;67:963; J. Hepatology 2022;77:1237)

- **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 MASLD)
- **Risk factors for progression:** Obesity, T2DM, HTN, HLD, OSA, PCOS, menopause, alcohol use
- **Progression rates**: MAFLD → cirrhosis: 3% in 15 yrs. Compensated cirrhosis → first decompensation: 33% in 4 yrs.

## 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. However, maintain high index of suspicion in those with RFs (CLD 2021;17:23)
- **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. Uncommon: hypobetalipoproteinemia, LAL deficiency, carnitine/choline deficiency
  - Screen for significant EtOH consumption (>21 standard drinks/wk in men, >14 in women)
  - Evaluate for associated comorbidities (T2DM, obesity, central adiposity, dyslipidemia, 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 MetALD, so if iron sat also elevated, consider HFE testing
- **Imaging**: (1) Vibration-controlled transient elastography or ultrasound elastography; (2) Magnetic resonance elastography
- **Initial fibrosis screening tools**

| 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. If clinical suspicion for metabolic liver disease, FIB-4 recommended in every 1-2 yrs in pre-DM2/DM2 or 2+ metabolic RF vs every 2-3yrs if <2 metabolic RF | < -1.455 (Sn 90%, Sp 60%) | ≥ 0.676 (Sn 67%, Sp 97%) |
| FIB-4* | | < 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 | < 8.0 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%) |

*Typically used first and then followed by either VCTE or ultrasound elastography.

- **Referral to Hepatology**: persistent/significant transaminase elevation (ALT >30) despite loss of ≥5% of body weight, FIB-4 >2.67, VCTE ≥ 8.0, advanced fibrosis (F≥3), clinical features of advanced liver disease, need for liver bx
- **Liver biopsy**: Rarely used; considered to rule out alternative etiologies of liver disease or if non-invasive studies inconclusive

## MANAGEMENT (J. Hepatology 2024;81:492)

- **Lifestyle intervention**: weight loss is 1° therapy. ≥5% reduces hepatic steatosis; 7-10% may improve fibrosis (target ↓500-1000 kcals/d); Mediterranean diet, low carb, higher protein diet associated w/ improvement in weight loss; reducing fructose consumption helpful; exercise can significantly improve insulin resistance & outcomes (see *Obesity and Weight Loss*). Abstain from excessive alcohol use.
- **Pharmacotherapy:** Resmitirom: may slow/reverse steatohepatitis and fibrosis in F2/F3 fibrosis; GLP-1ra or GIP/GLP-1ra: safe in patients with cirrhosis for management of diabetes and obesity; SGLT-2i reduce steatosis on imaging; metformin: improves transplant-free survival and reduces risk of primary liver or extrahepatic cancer.
  - Not recommended: pioglitazone, vitamin E, omega-3 polyunsaturated fatty aids, UDCA, obeticholic acid, elafibranor
- **Surgery**: consider bariatric surg in eligible pts with obesity and MetALD or MASH if liver disease is compensated
- **Other considerations**: Prevent progression of liver disease – vaccinate for HAV/HBV, avoid EtOH consumption. Treat comorbidities (T2DM, HLD, HTN). Statins are recommended in MetALD for CVD risk reduction; no increased risk of hepatotoxicity. Screen for HCC only if severe fibrosis (F≥3). Liver transplant in case of decompensation or HCC

# Gastroenterology — End Stage Liver Disease

## Definitions

- Cirrhosis: irreversible fibrosis and formation of regenerative nodules that distort hepatic architecture and vasculature
  - Compensated: no ascites, encephalopathy, jaundice, or GI bleeding. May have nonbleeding varices. Usually asx
  - Decompensated: ascites, HE, jaundice, SBP, Hepatopulmonary syndrome, variceal bleeding or HRS
- 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 (+LR 7.3), jaundice, spider angiomata (+LR 4.3), gynecomastia, testicular atrophy, palmar erythema, asterixis, white nails, Dupuytren's contracture
- **Labs**: ↑TBili, ↑INR, ↓alb, ↓Na, ↓PLT (<160, +LR 6.3), ± ↓Hgb/Hct, ↓WBC; AST, ALT, alk phos, and GGT may be ↑ or normal
- **Imaging**: RUQUS (with Doppler) to assess echogenicity/morphology of liver, ascites, vascular patency, biliary tree, HCC; US elastography measures liver stiffness by applying mechanical waves and measuring propagation speed through tissue
- **Biopsy**: gold standard but performed less often. Indications are dx uncertainty or indeterminate fibrosis severity (NEJM 2017;377:756). Perc. (can't do through ascites, massive obesity) or transjugular (allows HVPG measurement; pref. if coagulopathy)

## Etiologies

- **Most common**: MASLD, alcohol, viral (HCV, HBV). Global epi: MASLD (54%), HBV (29%), HCV (9%), ALD (2%) (*CLD* 2021; 17:365): in the US, ALD a much higher proportion.
- Genetic disorders: hemochromatosis, Wilson's, α1AT deficiency, CF, hypobetalipoproteinemia, LAL deficiency
- 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 (e.g., schisto), meds (e.g., MTX, isoniazid, amio; see LiverTox), cryptogenic/idiopathic, carnitine/choline deficiency

## Natural History and Risk Stratification (J Hepatol 2006;44:217)

- MELD Na score: predicts 90d mortality, used for transplant allocation using Na, Tbili, INR, Cr,
- New MELD 3.0 added: 1) female sex and albumin to correct transplant disparities for women, 2) interaction between Tbili & Na and albumin &Cr, 3) upper bound of Cr of 3 (Gastro 2021;161:1887)
- Child-Pugh class: assesses cirrhosis severity, predicts 1-2y mortality using Tbili, INR, albumin, ascites, encephalopathy
  - 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 (HPVG) is gold standard measurement for 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 angiomata)
- 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, MELD3.0 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) (J Hepatol 2024;79:5)
- History/source of bleeding, therapies (e.g., banding, sclerotherapy, TIPS), current ppx (βB, prefer carvedilol 6.25–12.5 mg/day)
- 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., 3 BM/day, 500cc stool, mental status improvement)

**Screening/Surgery** (transplant)
- Vaccinations: HAV, HBV, Influenza, pneumococcal, COVID, all other standard vaccines
- Maintenance: alcohol abstinence, avoid NSAIDs, HCC screening with q6mo RUQUS ± AFP
- Transplant status: listed or not listed, MELD score, Milan criteria if HCC

# Gastroenterology — End Stage Liver Disease

## ASCITES (AASLD: Hepatology 2021;74(2):1014))

- Most common cirrhosis complication (50% in 10 years); development of ascites → 15% 1y mortality, 44% 5y mortality
- Pathophys: portal hypertension (>12 mmHg)→ ↑NO, prostaglandins, glucagon → splanchnic arterial vasodilation → ↓intravascular volume and SVR → ↑RAAS, ADH → Na & water retention. Severity of dilutional hypoNa (from ADH secretion) ∝ ↓ survival
- Diagnosis: Ultrasound to visualize. **Dx para** indicated for **ALL** patients with cirrhosis and ascites presenting to the hospital. No role for routine use of ppx FFP or platelets (Hepatology 2021;73:366). EARLY dx paracentesis (within 24h of admission) is associated with reduced inpatient mortality and 30-day readmissions (AJG 2019; 114:1863)
  - Studies: **cell count w/ diff, albumin, total protein, GS/Cx** ± glucose, LDH, amylase, TG, bilirubin, cytology
  - DDx: **portal HTN** vs non-portal HTN. Calculate **SAAG** (serum ascites albumin gradient) to differentiate (Annals 1992;117:215).

| SAAG ≥1.1 g/dL: related to portal HTN | SAAG <1.1 g/dL: NOT related to portal HTN |
|---|---|
| **Etiology related to portal hypertension** | **Etiology not related to portal hypertension** |
| • Cirrhosis (ascites fluid total protein [AFTP] <2.5)<br>• CHF, constrictive pericarditis (AFTP >2.5)<br>• Acute hepatitis (including EtOH)<br>• Acute liver failure<br>• HCC, massive liver metastases<br>Budd-Chiari syndrome (AFTP >2.5)<br>• Portal vein thrombosis | • Infectious (Secondary bacterial peritonitis, Peritoneal TB)<br>• Peritoneal carcinomatosis (+cytology)<br>• Chylous ascites (triglycerides >200)<br>• Hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy, severe malnutrition; Ascitic fluid total protein <2.5)<br>• Serositis (e.g., SLE)<br>• Pancreaticobiliary (i.e., bile leak, disrupted pancreatic duct) |

- Management of ascites:
  - **1st line:** <2g Na, fluid restrict 1L if Na <125, ⊘EtOH/NSAIDs, avoid ACEi/ARB, stop anti-HTN if MAP < 82, diuretics (as below).
    - *Initiating therapy:* **100mg/d spironolactone + 40mg/d furosemide starting dose (5:2 ratio to maintain normal K).** Ideally single, daily AM dosing. Consider spironolactone alone for mild first ascites if outpt (do not give lasix alone).
    - *Ongoing therapy:* ↑dose q3-5 days if inadequate diuresis (5:2 ratio, though can increase lasix PRN if hyperK). Max doses: 400mg spironolactone and 160mg furosemide. Δ to eplerenone ($$) or amiloride if gynecomastia w/ spironolactone
    - Check $U_{Na}/U_K$ ratio if pt gaining weight/requiring LVPs on diuretics; **$U_{Na}/U_K$ <1** suggests ineffective diuretic dose or resistance; **$U_{Na}/U_K$ >1** suggests >2g Na intake**; spot $U_{Na}$ 50-70** indicates adequate diuresis (collect 2h after the diuretic)
  - **Weight loss goals: 0.5 kg/d** (TBB -500) if no peripheral edema (AKI risk if too fast); if edema, 1 kg/d or -1L. **Avoid IV diuretics** (azotemia risk ↑). Ascites mobilizes fluid slower than other compartments at a rate of 0.5L/day (Gastro 1986;90:1827)
  - **Therapeutic LVP**: indicated for tense or refractory ascites or inability to use diuretics; **if >5L removed, give 6-8g albumin for every 1L ascites removed** to reduce risk of post-paracentesis circulatory dysfunction (PPCD); if >8L removed, risk of PPCD ↑
  - Unproven therapies: long-term administration of albumin (40g 1-2x weekly, $$) in pts with cirrhosis and uncomplicated ascites may offer survival benefit (Lancet 2018;391:2417) but no benefit (and potential harm) in hospitalized pts with acute decompensated cirrhosis targeting albumin > 3 (NEJM 2021; 384:808). SGLT2i may ↓ ascites. (Hepatology 2020; 72(5):1880)
- Refractory ascites (10% of patients; associated with decreased survival):
  - Defined as: 1) unresponsive to Na-restriction & high-dose diuretics (or unable to tolerate iso HE, lytes, azotemia) or 2) rapid reaccumulation after LVP; associated with very advanced cirrhosis and low urinary excretion of Na
  - Mgmt: R/o PVT and HCC. D/c diuretics if $U_{Na}$<30mEq/day, discontinue βBs (↑mortality in refractory ascites [Hepatology 2010;52:1017]), midodrine TID (J Hepatol 2012;56:348), serial LVPs (<8L ~q2w), TIPS if intolerant of LVPs (poor TIPS candidate if: MELD>18, Child-Pugh class C cirrhosis, heart failure, severe HE), indwelling peritoneal catheters in certain cases (e.g., EOL)

## SPONTANEOUS BACTERIAL PERITONITIS (SBP) (AASLD: Hepatology 2021;74(2):1014)

- **Must r/o SBP in all inpatients w/ cirrhosis & ascites ASAP w/ dx para and blood Cx**; 10-30% hospitalized pts w/ cirrhosis have SBP. Look for abdominal pain, TTP, ileus, HE, and AKI as presenting sxs, but *1/3 of patients may be asx*
- Diagnosis: **>250 PMN/L** w/ positive GS/Cx (SBP) or negative GS/Cx (CNNA = similar mortality to those w/ +Cx; treat similarly)
  - 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 2nd bacterial peritonitis 2/2 perforation vs. loculated abscesses. C/f bowel perf. if ≥2 of the following: TP >1, LDH >ULN, or Glc <50.
- Treatment:
  - **1) Abx: Community acquired: CTX 2g q24h x 5d;** IV cipro (400mg q12) if allergy to cephalosporin (unless taking cipro for ppx)
    - **Tx should be broader if risk of MDRO infxn** (recent hospitalization, nosocomial infxn): **Pip-Tazo + Daptomycin** (if prior VRE infxn or VRE colonization) **OR Meropenem** if known MDRO or SBP after recent Pip-Tazo exposure
  - **2) 25% albumin:** 1.5g/kg day 1 + 1.0g/kg on day 3, max 100g (given risk of AKI in SBP) (Note: AASLD recommends for all pts *but some groups only recommend for those meeting study pop. criteria: Cr >1, BUN >30, or TBili >4* (NEJM 1999;341:403).
  - **Hold βBs** while inpt (risk of AKI & HRS once SBP is dx), may consider reintroducing once recovered
  - Repeat diagnostic para 48 hours after starting abx to assess response. A negative response is defined by a ↓ in PMN count <25% from baseline → broaden abx and investigate secondary peritonitis w/ CTAP+GI consult. Repeat para may be avoided if an organism is isolated, it is susceptible to the abx used, and pt is improving clinically (not widely in practice yet at MGH)
  - Prophylaxis: **IV CTX 1g q24h x5 days if GIB.** 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 (Cr ≥1.2, BUN ≥25 or Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3) (Hepatology 2021;74(2):1014)

# Gastroenterology — End Stage Liver Disease

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

- Pathophysiology: ↑$NH_3$ → neurotoxic effects, abnl neurotransmission, ↑GABA- & BDZ-like neurotransmitters & altered glutaminergic inputs → ↓excitatory transmission. In ALF, acute ↑$NH_3$ → cerebral edema
- Diagnosis: clinical. Serum $NH_3$ should not be used to screen for HE. **↑$NH_3$ does not add diagnostic or prognostic value** in CLD (JHM 2017;12:659). Only helpful in ALF (predicts mortality). **Trend via exam findings** (see grades). Exclude other causes of AMS.
- Classification: type of underlying disease, severity grade, time course (episodic, recurrent, persistent), precipitations (precipitated vs non-precipitated)
- Asterixis: "flapping tremor" is **negative myoclonus** w/ loss of postural tone; elicit with hyperextension of wrists or squeezing of examiner's fingers (milk maids sign)
- Precipitants: infection, dehydration/overdiuresis, GIB, ↓K or alkalosis (↑renal NH3), renal failure, constipation, hypoxia, sedatives/BZD/opioids, new HCC, new clot, TIPS
- Treatment: ↓GI $NH_3$ absorption, avoid/correct precipitating factors
  - **Lactulose**: Δs gut microbiome → ↓pH → traps $NH_4^+$ in colon; has laxative effect; 30mL q2h until BM → titrate to 3-4 BM/day, often dosed 2-4x a day (PO or enema)
  - **Lactulose + rifaximin 550mg BID > lactulose alone.** Add rifax ($$) if refractory or 2nd admission
  - Nutrition: calories: 35-40kcal/kg/day, protein 1.2-1.5g/kg/day (in general, don't restrict protein intake unless HE worsening)

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

## VARICEAL BLEEDING (AASLD: Hepatology 2024;79:1180)

- Clinically Significant Portal HTN (CSPH): HVPG ≥ 10 OR varices on EGD OR portosystemic collaterals/ascites on imaging OR liver stiffness (LSM)* by transient elastography ≥25 kPa, LSM 20–24.9 kPa w/ plt <150, or LSM 15–19.9 w/ plt <110.
  *Caution: Careful interpretation in obesity, MASLD, ALT > 3xULN, and PSC. PPV of test drops.
- EGD screening: esophageal varices most common. If alt. evidence of CSPH and on NSβB, sEGD may be deferred. Pursue sEGD if unclear LSM w/o surrogate of PH on images and C.I. to empiric NSβB, continue q2yr if ongoing liver injury or q3yr if quiescent. If known varices or decomp cirrhosis and C.I. to NSβB, sEGD q1yr. Avoid sEGD if LSM<20 & plt>150, as high risk varices unlikely

| | |
|---|---|
| 1° PPX | **Compensated cirrhosis without CSPH**: No 1° PPX indicated. Check LSM every 3-5y if LSM5-9.9kPa or annually if 10-14.9kPa.<br>**Compensated cirrhosis with CSPH** or **decompensated cirrhosis w/ only ascites**: NSβB, particularly carvedilol<br>**Decompensated cirrhosis:** NSβB first line. Commonly stopped if 1) hypotension 2) recurrent AKI (esp. iso necessary diuretics).<br>**If C.I. to NSβB:** Serial endoscopic variceal ligation (EVL) q2-8w until eradication in med/large EV with screening q1-2yrs |
| 2° PPX | Prior episode of variceal bleeding without placement of TIPS → **ppx to prevent recurrence** w/ combination of NSβB + serial EVL (q1-4w until obliteration; repeat EGD 3-6mo after & then q6-12mo) |

- **Non-selective beta blocker (NSβB)**: *Carvedilol* (6.25mg qd → 6.25mg BID) most effective at lowering HVPG. Consider *nadolol* (20-40mg qd → 160|80mg qd) or *propranolol* (20-40mg BID → 320|160 BID, without|with ascites) if low SBP. Upon initiation, adjust every 2-3d to goal HR 55-60, SBP>90. C.I. in asthma, AV block, SSS, HR <50. NSβB should be held initially during acute bleed but reinstated *within 7 days* if able.
- **Acute bleeding**: Assess airway and IV access. IV PPI, IV octreotide (50 mcg bolus followed by 50 mcg/hr for 2-5 days), CTX 1g q24h x 5d, EGD. Resuscitate w/ IVF/pRBCs prior to intubation and give erythromycin for EVL. Balloon tamponade as a bridge (GI), urgent TIPS (IR) if cannot band. Conservative transfusion: goal Hgb 7 (NEJM 2013;368:11), avoid attempts to correct INR/plts. Start enteral nutrition w/ control of bleeding and assess for provoking factor (i.e. PVT, HCC, etc). See *Upper GI Bleeding*
- **Indications for TIPS**: early "preemptive" TIPS (<72h) in pts with high risk of treatment failure or rebleeding (Hepatology 2024;79e224); "rescue" TIPS if uncontrolled bleeding or if recurs despite max medical & endoscopic therapy
- Gastric varices: Similar mgmt. of acute bleed but difficult to band. Consider TIPS (favored if EV too), BRTO, or endoscopic glue/coil
- Portal Hypertensive Gastropathy/Enteropathy: mucosal hemorrhage from ↑HVPG. Can similarly consider NSβB, octreotide, and TIPS

## 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, hemolysis). 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), +/- ↓ Vit K→ **↑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 Child-Pugh C or↑ bleeding risk. EGD if EVs prior. VKA, LMWH, or DOAC. VKA dosing c/b ↑baseline PT/INR; LMWH c/b ↓ATIII levels; some DOACs safe (apixaban preferred) – can use w/ caution in Child-Pugh 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 are not generally recommended but in specific instances can reduce need for peri-procedural PLT transfusions (but takes ~10d to ↑PLT) (NEJM 2012;367:716; Gastro 2018;155:705). **No** role for plt transfusion for routine paracentesis (often ok with plt >20k).
  - 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 2023;78:1922)

- 2-4% risk per year. May be asx, lead to decompensation, and/or have sx related to mass effect (pain, early satiety, palpable mass)
- 1° prevention: HBV vax in high-risk pts not vaccinated at birth, HBV/HCV antiviral tx, healthy lifestyle, coffee consumption (1+ cup)
- Screening indicated in:
  - **Cirrhosis due to *any* etiology**, except in Child-Pugh Class C pts not on transplant list (due to low survival time)
  - Chronic HBV w/o cirrhosis if: M >40 / F >50 from endemic ctry, African/African-American >30, FHx HCC, or PAGE-B score ≥10
- Screen with: **RUQUS ± AFP q6mo**; if U/S visualization is limited (e.g., ascites), can use multiphase CT or contrast-enhanced MRI
  - If lesion <1cm, repeat US + AFP in 3-6mo
  - If lesion ≥1cm, AFP ≥20ng/mL, or rising AFP, obtain multiphase CT or MRI & proceed according to LI-RADS class
- Staging:
  - Barcelona (BCLC) system: size, # of nodules, LN & portal vein involvement, mets, Child-Pugh score, performance status
  - Recommended discussion at multidisciplinary tumor board; if HCC > BCLC Stage 0, obtain noncontrast CT chest for eval of mets
- Management:
  - *Curative*: surgical resection (1st line if Child-Pugh A & T1-T2 nodule) ± adjuv ICI, OLT (if non-resectable but within Milan criteria)
  - *Noncurative*: ablation, chemoembolization (TACE), radioembolization (TARE), radiation, chemo, immunotherapy
  - Within Milan criteria → locoregional 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 BCLC stage: *0-A (early)*: >5y, *B (intermediate)*: >2.5y, *C (advanced)*: >2y, *D (terminal)*: 3mo

## HEPATIC HYDROTHORAX (AASLD: Hepatology 2021;74:1014, Hepatology 2020;72:1851)

- ~4-12% pts w/ cirrhosis. Transudative effusion due to **ascites → pleural space** (neg. intrathoracic pressure) via small diaphragmatic defects. Can be seen w/o significant ascites. **Unilateral**: R- (~75%) > L-sided (~15%) > bilateral (~10%) (Medicine 2014;93:135)
- Diagnosis: exclude other causes of pleural effusion; thora + imaging (chest CT, abd U/S, TTE); radioisotope inj. if dx unclear
- Treatment: first line: **diuretics, 2g Na restriction**. Therapeutic thora for dyspnea. Serial thoras, TIPS, pleurodesis, surg. repair or OLT if refractory. **Chest tube not recommended due to risk of serious complications + ↑ mortality 2.5%** (Chest 2019;155:546)
- **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. No e/o PNA. Tx: same as for SBP

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

- V/Q mismatch (shunt) + $O_2$ diffusion limitation **via intrapulmonary vascular dilatations**; mechanism unclear, **possibly ↑ NO**
- Presentation: shunting tends to occur at bases → **platypnea** (dyspnea when upright, relieved when supine) & **orthodeoxia** (upright hypoxemia, $PaO_2$ ↓ by 4 mmHg or ≥3-5%), clubbing, cyanosis, diffuse telangiectasias, hypoxemia (PaO2 <70-80)
- Diagnosis: If $SpO_2$ <96% →↑A-a gradient ≥15mmHg (or ≥20mmHg if age ≥65) or $PaO_2$ <80mmHg → **TTE with late bubbles** (3-6 cardiac cycles after RA vs early bubbles in PFO) → $PaO_2$ to grade severity
  - $^{99m}$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
- Management: no effective medical therapies. Supp O2 for SpO2 goal >88%. Monitoring q6-12mo in mild to moderate HPS. Consider OLT in pts w/ severe/very severe HPS (PaO2 <60); OLT can improve (or reverse) HPS – MELD exception points 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; 3x risk in F > M; ↑ risk in autoimmune liver disease
- 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
- Diagnosis: screening w/ TTE (PASP >30mmHg; 100% NPV); confirmation is euvolemic RHC w/ PAH (mPAP ≥20mmHg, PCWP <15 mmHg, PVR >3) in pt with portal HTN in absence of other etiology (*mild*: mPAP 25-35, *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 ≥50 is a contraindication to transplant

## CIRRHOTIC CARDIOMYOPATHY (AASLD: Hepatology 2024;79:146; EASL: J Hepatol 2018;69:406, JACC 2010;56:539)

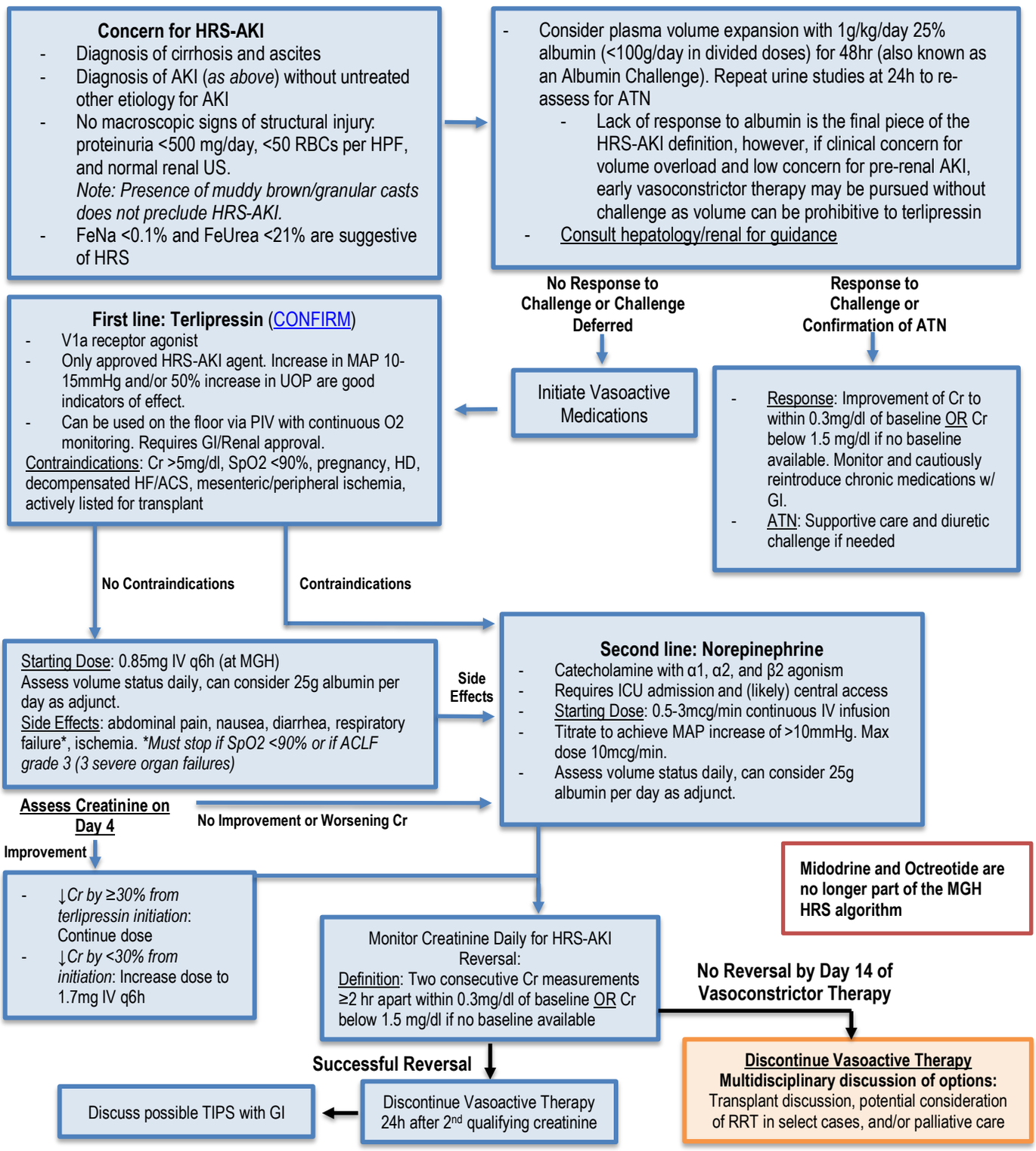
- Chronic cardiac dysfunction in cirrhosis pts w/o known cardiac disease; characterized by 1) impaired cardiac contractility in response to stress, 2) altered diastolic relaxation, 3) electrophysiological abnormalities such as prolonged QTc and chronotropic incompetence
- Pathophysiology: myocardial dysfunction 2/2 systemic inflammation; shear stress from portal hypertension → mechanical force on myocardial fibers; other possible mechanisms involve collagen configuration, sodium retention, activation of RAAS, ↑ bile acids (Biochim. Biophys. 2018;1864:1345)
- Prevalence: up to 50% of pts undergoing liver transplantation have signs of cardiac dysfunction
- Diagnosis & Treatment: echocardiography (CCC Criteria) w/ dynamic stress testing; OLT and HF management as in pts w/o cirrhosis
- Prognosis: largely subclinical; risk with stressors (infection, paracentesis, TIPS, OLT); detailed cardiac assessment before intervention. May be unmasked during terlipressin initiation or volume overload/excess albumin infusion

# Gastroenterology — Hepatorenal Syndrome

## HEPATORENAL SYNDROME (HRS) (Clin Gastro Hep 2018;16:162; BMJ 2020;370:2687, NEJM 2023;388(8)e733, Gastro 2024;166:202)

- Pathophysiology: portal HTN → ↑NO, prostaglandins → splanchnic vasodil. → ↓EABV → ↑RAAS, ADH, SNS → renal vasoconstr.
- Diagnosis: ***dx of exclusion***; need: (1) advanced hepatic failure w/ portal HTN (ascites)
  (2) AKI: ↑sCr > 0.3 mg/dl from baseline within 48 hrs OR ↑sCr >1.5x baseline within past 7d OR UOP <0.5 ml/kg/hr x6hrs
  (3) absence of and/or optimization of alternative AKI etiology. Examples: shock (GIB, sepsis, pancreatitis), infection (SBP), dehydration (diuretics/diarrhea), nephrotoxin (ATN: IV contrast, bile cast nephropathy. AIN: Abx, NSAIDs, PPI), obstruction, glomerular disease (e.g. IgA, MPGN, cryoglobulinemia).
- Type I (HRS-AKI): ↑Cr >2x b/l and >2.5 mg/dL in <2w; Type II (diuretic-resistant ascites): ↑Cr from 1.5-2.5mg/dl, slower progression
- Most Common HRS Precipitants: infection (SBP > other), GI bleed, fluid shifts after LVP, alcohol-related hepatitis
- Prevention: In SBP, albumin day 1 + day 3 has mortality benefit (Clin Gastro Hep 2013;11:123); 1° SBP ppx (Gastro 2007;133:818)
- Management: Obtain history and treat reversible causes. Discontinue diuretics, βB, ACEI/ARB, or other vasodilators or nephrotoxins. Obtain paracentesis for SBP eval. Obtain urine studies for urine sediment, FeNa, FeUrea, and renal ultrasound. Then see algorithm.

### MGH Algorithm for the Diagnosis and Treatment of Hepatorenal Syndrome



# Gastroenterology — Liver Transplant

## 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). (AJT 2005;5:307) Child B cirrhosis w/ portal HTN and low MELD can be considered also. Start/refer for evaluation at MELD >10 (to give time for education/evaluation).
- HCC: *first-line option* w/in Milan criteria but unsuitable for resection (NEJM 1996;334:693; Hepatology 2018;69:182) assigned MELD of 22 after 6 month waiting period; can be "down-staged" to w/in Milan w/ treatment; composite criteria (surrogates of tumor biology: AFP, treatment response, tumor size, number of nodules) may replace conventional criteria. If post-resection recurrence assigned exception points w/o waiting period. See *ESLD: HCC*
- Liver-based metabolic disorders w/ systemic manifestations: A1AT deficiency, familial amyloidosis, Wilson's disease (won't resolve neurologic issues), hemochromatosis, glycogen storage disease, primary oxaluria
- Decompensated biliary disorders: PBC (intractable pruritus), PSC (recurrent cholangitis and sepsis)
- Systemic complications of chronic liver disease: hepatopulmonary syndrome, portopulmonary HTN
- Severe Alcohol-Associated Hepatitis (AH): Failed medical therapy and, typically, no prior history of liver decompensation.
- Conditions qualifying for Exception Points (see below under "Prioritization for Liver Transplant")

**Milan Criteria:**
One lesion ≤5cm or up to 3 lesions all ≤3cm
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/substance use within 6mo (exceptions in AH; see *Alcohol-Related Liver Disease*), uncontrolled sepsis, anatomic abnormality that precludes LT, intrahepatic cholangiocarcinoma, extrahepatic malignancy (other than skin, not meeting criteria for cure), mPAP >35 or PVR >400, fulminant hepatic failure with sustained ICP >50mmHg or CPP <40mmHg, hemangiosarcoma, persistent nonadherence to medical care, lack of adequate social support system
- Relative: BMI ≥40, HIV; age >70 (Mayo Clinic Proceedings 2009; 84)

## Prioritization for Liver Transplant

- Prioritized based on MELD Score (AJT 2015;15:2552)& stratified by blood type
- Certain conditions result in impaired survival but are not directly accounted for in the MELD score → specific disease-related criteria for MELD exceptions that upgrade MELD score w/ subsequent automatic upgrade q6mo
- *Standard MELD exceptions:* HCC (w/in Milan criteria, AFP <1000), hepatopulmonary syndrome (RA PaO2 <60mmHg), portopulmonary HTN (mPAP <35), familial amyloid polyneuropathy (TTR mutation), primary hyperoxaluria, CF (FEV1 <40%), hilar/early-stage cholangiocarcinoma, hepatic artery thrombosis (w/in 14d of LT but not meeting status 1A criteria), cystic fibrosis
- Can also petition review board for non-standard exceptions (e.g., refractory complications) esp if MELD score does not reflect severity of mortality/morbidity related to the liver disease
- Some patients are candidates for double transplantation (e.g. with heart, kidney, lung)

## 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, urine drug screen, PEth, Ca, vitamin D
- Additional tests: ABG (on RA), EKG, CXR, upper endoscopy if cirrhosis/portal HTN, U/S w/ Doppler (assess for anatomic barriers to transplant), multiphase contrast-enhanced abdominal CT or MRI (evaluate for HCC), age-appropriate cancer screening (colonoscopy, mammogram, pap smear), bone density, cardiopulmonary eval as below
- Immunizations: HAV, HBV, pneumococcus, influenza, Tdap, MMR, varicella, COVID19, Zoster, RSV (≥60)
- Consults: Hepatology; will subsequently involve transplant surgery, transplant psychiatry, social work (address psychosocial issues, adequacy of support, financial screening, insurance counseling), nutrition, transplant ID if indicated
- Cardiopulmonary eval: TTE w/ bubble. 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); may consider PCI prior to OLT if significant stenosis. HPS: Pulse Ox, ABG if <96 followed by CXR, PFTs and CT.
- ID eval: eval for LTBI as above and tx pre-OL. Coccidiomycosis, strongyloides testing if from endemic area. Dental extractions pre-OLT. HIV not a contraindication if immune function adequate. HBV tx pre-OLT. HCV can be tx pre- or post-OLT (timing depends on if OLT 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 ≥6wk or GFR ≤25 for ≥6wk; 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. Recipients of LDLT have reduced wait list mortality compared to potential recipients of deceased donor organs.

# Nephrology — Acute Kidney Injury

## DEFINING AKI (KDIGO 2012 Guidelines)

**Diagnostic Tips**

- Serum Cr approximates GFR at steady state only (unable to estimate GFR w/ ΔCr): **must assume GFR <10 if ΔCr > 1 mg/dL/day**
- Drugs can impair Cr excretion without ΔGFR (BUN remains stable): trimethoprim (in Bactrim), H2 blockers (cimetidine), dronaderone
- ↑BUN out of proportion to Cr: pre/post-renal dz, UGIB, steroids. ↑Cr out of proportion to BUN: rhabdo, AIN, TMP-SMX, vancomycin, ↓ nutrition

| Stage | Serum Creatinine | Urine Output |
|---|---|---|
| 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 |
| 2 | ↑**2-2.9x** baseline | <0.5 ml/kg/h for ≥12h |
| 3 | ↑**3x** baseline, Cr ≥4, ↓eGFR to <35 (<18 yo), or RRT | <0.3 ml/kg/h for ≥24h or anuria ≥12h |

## STEPWISE WORKUP

**1) History/exam**: review vitals for 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/found down (rhabdomyolysis), rashes (AIN, vasculitis)

**2) Urinalysis (UA)**: see *Urinalysis*. If AKI and UA demonstrate unexplained blood and protein, consider GN and renal c/s.

**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 or after IVF. Interpret with caution in baseline CKD or chronic prerenal disease (CHF/cirrhosis). GN, rhabdo, & IV contrast can all cause FENa <1%. **Overall limited use in hospital setting**, 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 (high ADH state)
- 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).
- Urine creatinine: use in 12 or 24-hour urine collection to estimate CrCl in dynamic AKI.

**4) Urine sediment**: see *Urinalysis*. Look for casts, RBC morphology.

**5) Eosinophilia/eosinophiluria**: Not recommended - poor test for AIN. Urine eos >1% has Sn 31%, Sp 68% (J Hosp Med 2017;12:343)

**6) Renal U/S**: exclude hydronephrosis; often preceded by bedside bladder ultrasound. 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, UOP, BP, and electrolytes**: assess response to empiric treatment of presumed cause

**8)** If sediment or history suggests glomerular disease, consider serologic workup (see *Glomerular Diseases*). Consider biopsy if expected to change treatment.

## DIFFERENTIAL DIAGNOSIS OF AKI

| PRE-RENAL | INTRINSIC | | | POST-RENAL |
|---|---|---|---|---|
| | GLOMERULAR | TUBULO-INTERSTITIAL | VASCULAR | |
| **↓ Absolute volume**<br>- Bleeding<br>- GI or skin loss<br>- Diuretics<br>- Osmotic diuresis<br>- Cerebral salt wasting<br>**↓ Effective volume**<br>- CHF/cardiorenal<br>-Cirrhosis/hepatorenal<br>- Nephrotic syndrome<br>- Sepsis/third-spacing<br>**Δ renal dynamics**<br>- NSAIDs/COX-2s<br>- ACEi/ARBs<br>- Abdominal compartment syndrome<br>**Relative hypotension** | **Anti-GBM**<br>**ANCA**<br>- Microscopic polyangitis<br>- Granulomatosis with polyangiitis (GPA)<br>- Eosinophilic GPA<br>- Drug-induced ANCA<br>**Immune complex**<br>*Low complement:*<br>- PSGN, SLE, cryo, MPGN, MGRS<br>*Normal complement:*<br>- IgA nephropathy/HSP<br>- Fibrillary, immunotactoid | **ATN**<br>- Ischemia, sepsis, toxic<br>- Contrast, rhabdo, aminoglycosides<br>**AIN**<br>1) Meds (see below)<br>2) Infectious: CMV, leptospirosis, legionella, pyelonephritis<br>3) Autoimmune/infiltrative: TINU, IgG4 disease, sarcoid, Sjogren, CLL<br>**Crystals**<br>- TLS (uric acid), acyclovir, sulfa abx, MTX, cipro, ethylene glycol, oxalate, bile acids<br>**Proteins**<br>- MM, amyloid, Ig deposition, myoglobin, bilirubin | **Microvascular**<br>- TTP/HUS<br>- APLAS<br>- HELLP/eclampsia<br>- Scleroderma<br>- Meds (calcineurin inhibitor/CIN, gemcitabine)<br>**Macrovascular**<br>- RAS (athero, FMD)<br>- Dissection<br>- Renal artery/vein thrombosis<br>- Polyarteritis nodosa | **Urinary retention**<br>- BPH, meds, neurogenic<br>- Foley dysfunction<br>**Urinary obstruction** (bilateral)<br>- Stones (single kidney/transplant)<br>- Malignancy<br>- Retroperitoneal fibrosis (associated with radiation or IgG4 disease)<br>- Congenital anomalies |
| **Common nephrotoxins:** see StatPearls for list of common nephrotoxins<br>**AIN**: commonly NSAIDs, β-lactams, **PPIs.** | | | | |

## MANAGEMENT

1. **Optimize hemodynamics, avoid nephrotoxins**: correct volume status – IVF and hold diuretics if hypovolemic, diuretics if hypervolemic. Stop NSAIDs/ACEi/ARBs. Avoid ↑glucose and contrast. No evidence of benefit for empiric diuretics in oliguria (JAMA 2002;288:2547). If large volume resuscitation or critically ill, generally LR > NS (NEJM 2018;378:819; NEJM 2018;378:829)
2. **Renally dose meds**: use Lexicomp for help dosing by GFR (note: GFR calculation assumes a steady state. Assess trajectory of AKI, if creatinine is rising, assume clearance is lower than GFR. If anuric, assume GFR is 0). Run MAR w/ pharmacy for additional support
3. **Manage complications**:
   - HyperK: check EKG, monitor on telemetry until improved. Can stabilize with calcium gluconate, shift K+ with insulin/dextrose, IVF/Lasix → Remove K from body with sodium zirconium cyclosilicate (lokelma), bowel reg, furosemide. Start low K diet.
   - HyperPhos: start phosphorus binder such as sevelamer (start >5.5 mg/dl) vs. calcium acetate depending on calcium level. **Avoid** IV calcium if Ca/Phos product> 70) as can precipitate. Low phos diet.
   - 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)**: **A**cidosis (esp. pH <7.0, refractory to bicarb), **E**lectrolytes (refractory hyperK$^+$), **I**ntoxication (lithium, ethylene glycol, metformin, salicylates, theophylline), refractory Volume **O**verload, **U**remia (encephalopathy, neuropathy, pericarditis)

## RENAL EMERGENCIES (WHEN TO PAGE THE RENAL FELLOW OVERNIGHT)

- **Acidosis**: severe metabolic acidosis (pH <7.1, <7.2 w/ severe AKI) w/o rapidly reversible cause (i.e. DKA). Temporize with bicarb pushes and isotonic bicarb gtt, intubate and hyperventilate if unable to compensate by breathing off CO2. May need RRT particularly if other indications.
- **Hyperkalemia**: hyperK w/ ECG changes/arrhythmia or K >6.5 (>5.5 if rising rapidly from ongoing cause such as rhabdo/GI bleeding). Temporize with Ca gluconate, diuretics, insulin/D50, albuterol, etc. iHD clears K faster than CVVH so is preferred in stable pts who can tolerate iHD.
- **Hyponatremia**: call if severe (<120), symptomatic (AMS with low GCS, seizures, etc.), or requiring hypertonic saline +/- DDAVP clamp.
- **Anuria w/ ADHF**: place Foley, monitor UOP/MvO2/signs of shock (LFTs, Cr, Lactate, CI). Improving cardiac output (volume optimization with diuretics or HD, ± inotropes) will raise GFR.
- **Ingestions**: lithium, ethylene glycol, methanol (elevated osmolar gap -> elevated anion gap), metformin 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**: abrupt onset of severe HTN followed by oliguric renal failure in a pt w/ diffuse scleroderma. Treat with 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 leads to a low trans-renal perfusion pressure. More of a problem with "under-draining" (congestion) than "under-filling" (perfusion)
  - Treatment**:** relief of renal venous congestion. Trend Cr against TBB and daily weights 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 AKI (CI-AKI, formerly "contrast-induced nephropathy")** (Nat Rev Nephrol 2017;13:169)
  - 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. Recent studies: unclear risk of AKI following contrast, likely lower than previously estimated (Ann Em Med 2017;69:577).
  - Pathophysiology: vasospasm vs acute tubular injury due to osmotic injury.
  - Risk factors: higher contrast load, hyperosmolar contrast, intra-arterial injection (cardiac cath), DM, proteinuria, concomitant AKI
  - Prophylaxis: for high-risk pts (GFR <30 or 30-45 + DM) receiving arterial/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 for anuric patient (Am J Med 2012;125:66).
  - Rule of thumb: balance risk as detailed above with potential harm of delayed diagnosis that guides treatment on individual basis.
- **Crystalline nephropathy**: discontinue drug; fomepizole/HD if ethylene glycol toxicity; rasburicase/HD if TLS (*see Tumor Lysis Syndrome*); IVF and diuresis if Acyclovir toxicity (goal UOP >150 cc/h)
- **HRS**: see *Hepatorenal Syndrome*
- **Myeloma kidney (Cast Nephropathy)**:
  - Dx: Total Protein/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, $\alpha$-antagonists; 5$\alpha$-reductase inhibitor (effect not immediate); urology/IR if perc nephrostomy tube needed
- **Rhabdomyolysis**: AKI unlikely unless CK >20k; aggressive IVF for UOP >250cc/h with NS. Consider isotonic sodium bicarb if marked acidosis (NEJM 2009;361:62) and no hypocalcemia, but no convincing evidence HCO3 is superior to NS. Monitor for hyperK, hypoCa. Continue aggressive IVF until CK <5000; if adequately volume resuscitated, continue IVF with close monitoring and diuresis

# Nephrology Glomerular Disease

## NEPHROTIC SYNDROME (NS)

**Etiology**: ↓podocyte integrity → glomerular proteinuria (predominantly albumin). **Presentation**: Constitutional sx (fatigue, anorexia), 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), protein malnutrition, edema (often around ankles/legs)
**Diagnosis: spot urine PCR> 3000mg/g confirmed by 24h UPr >3.5 g/dL AND albumin <3.5** (distinguishes from nephrotic range proteinuria). Note that low and high muscle mass will over and underestimate proteinuria on spot ratios, respectively.
**Work up:** UA, Hgb a1c, ANA, anti-dsDNA, anti-PLA2R, THSD7A, SPEP/SFLC, HBV, HCV, HIV, syphilis, cryoglobulins, C3/C4, renal bx
**Treatment**: Edema: diuretics (loop first line, augment with thiazides if resistant) + low Na diet (<2g/d). HLD: statin. VTE risk: consider ppx (especially if membranous disease, SAlb <2 g/dL, proteinuria >10g/d, or BMI >35). ACE/ARB (↓glom pressure). Use of steroids or immunosuppression depends on disease but typically involves high-dose glucocorticoids. See KDIGO 2021 guidelines.

| Disease | Associations and Tx considerations | Biopsy Findings |
|---|---|---|
| **Diabetes** | T1DM and T2DM, retinopathy/neuropathy; very common cause of adult NS | Nodular glomerulosclerosis |
| **FSGS** | 1°: toxin or circulating permeability factor → podocyte effacement<br>2°: viral (HIV, parvo, EBV, CMV), drugs (NSAIDS, pamidronate, interferon, rapamycin, heroin, lithium, anabolic steroids, mTOR inhibitors), adaptive (2/2 nephrectomy, CKD, obesity, reflux, HTN), chronic hypoxemia (OSA, sickle cell) | Mesangial collapse & sclerosis. Collapsing variant (a/w HIV & SLE) rapidly progresses to ESRD |
| **Membranous** | 1°: Antibodies to PLA2R (75%) highly specific (NEJM 2009;361:11) or THSD7A<br>2°: SLE, HBV, syphilis, drugs (NSAIDs, penicillamine, gold), solid tumors<br>Tx: Rituximab, or cyclophosphamide + steroids (KDIGO 2021, Figure 30,31) | Thick BM w/dense subepithelial deposits & no cellular infiltrates |
| **Minimal Change** | Idiopathic; a/w NSAIDs, lymphoma (HL most commonly), children>adults, anti-nephrin auto-antibodies (NEJM 2024; 391:5) | Podocyte effacement (EM) |
| **MPGN** | **Immune complex mediated: Chronic Infxn** (HCV>HBV, endocarditis, abscess**); Autoimmune:** SLE> Sjogren's, RA; **Monoclonal gammopathies; Other:** Lymphoma, solid tumor cancers.<br>**Complement-mediated**: dense deposit disease or C3/C4-glomerulonephritis | Thick BM, mesangial proliferation, subendothelial ± subepithelial deposits |
| **Amyloidosis** | AL (myeloma) and AA (systemic inflammation, e.g. RA, IBD) | 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
**Presentation** : AKI (azotemia →oliguira), HTN, edema (often periorbital), proteinuria, hematuria, hypercoagulability. If systemic vasculitis, fatigue, fever, weight loss, small-vessel involvement of other organ systems (palpable purpura, DAH, mononeuritis multiplex), SLE sx.

- **Rapidly progressive GN (RPGN):** nephritic syndrome that progresses to renal failure in weeks-months: **↓GFR >50% in ~3 mo**, glomerular crescents on bx, 0.5-2.5 g/d proteinuria, dysmorphic RBC.

**Workup:** UA/sed (dysmorphic RBC; specific, less sensitive), RBC casts (rare, very specific), sub-nephrotic proteinuria (<3.5g/d, but 10-30% >3g/d). Consider serololgic work up as per below. Early renal consult for consideration of biopsy and steroids.
**Treatment:** Tx of etiology (abx, antivirals, removal of offending drug), BP mgmt, diuresis, low Na diet. Bx will guide immunosuppression, but if high index of suspision for RPGN or ANCA-vasculitis, consider empiric IV methylpred pulse (0.5-1 g x3 days) as you await bx followed by cyclophosphamide (CYC) or rituximab (RTX). **RPGN from ANCA vasculitis**: induction w/ steroids + RTX or CYC (NEJM 2010;363:221); maintenance w/ RTX > AZA (NEJM 2014;371:1771). Induction w/o PLEX and w/ ↓-dose steroids appears non-inferior and ↓ infx risk (NEJM 2020;382:622).

| Disease | Associations and Tx considerations | Labs |
|---|---|---|
| **Renal-Limited Immune Complex Deposition** | | |
| **Post-infectious GN** | ~1-2w post-pharyngitis, 3-6w post-cellulitis; ↓ C3 for >12w may be indication for kidney bx to exclude C3GN. No benefit in steroids | ⊕ASO, anti-DNAse B, anti-hyaluronidase antibodies, ↓C3 |
| **Fibrillary GN** | Idiopathic; cancer; autoimm (Crohn's, SLE, Graves', ITP) | Normal C3 (bx IF +DNAJB9) |
| **IgA nephropathy** | 1°: ~1-2d post-viral URI or GI infx. 2°: liver dx, Celiac, HIV<br>Tx: Sparsentan (Lancet 2023;401:1584) | +/- ↑IgA, nl C3; Biopsy for official diagnosis |
| **Systemic Immune Complex Deposition** | | |
| **SLE (Classes 3, 4)** | Photosensitivity, malar rash, sicca, pleuritis, cytopenias, arthralgias; Tx: See KDIGO 2024 Guidelines | ⊕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, ANCA (⊕can be induced) |
| **IgA Vasculitis (HSP)** | Post-URI, malignancy, nephropathy, purpura, arthritis, GIB | ⊕IgA, nl C3 (IgA does not fix complement) |
| **Pauci-Immune Glomerulonephritis aka ANCA-associated** | | |
| **Granulomatosis with polyangiitis** | Granulomatous sinusitis/otitis, other ENT sx, pulm sx (DAH, granuloma), arthritis, palpable purpura, RPGN | c-ANCA/anti-PR3 (80%)<br>p-ANCA/anti-MPO (10%) |
| **Eosinophilic granulomatosis w/ polyangiitis** | Multi-system, new-onset asthma, allergic rhinitis/sinusitis, mononeuritis multiplex | p-ANCA/anti-MPO (50%), eos ≥1500 |
| **Microscopic polyangiitis** | 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) |
| **GBM Diseases** | | |
| **Anti-GBM/Goodpasture** | RPGN (crescentic), DAH (Goodpasture: hematuria/hemoptysis) | Linear IgG along BM, ⊕anti-GBM IgG |
| **Alport** | Mutant COL4A (renal, hearing, eye dx), familial | EM w/ split GBM, ⊕COL4A3-5 testing |

# Nephrology — Chronic Kidney Disease

## Overview

- CKD definition: GFR <60mL/min OR kidney damage (albuminuria ≥30mg/d for ≥3mo) (JAMA 2015;313: 837)
- eGFR: extrapolated from endogenous filtration markers like Cr or cystatin C. Subject to under/over estimation when filtration rates change. (NEJM 2021;385:1737). Race in eGFR calc can lead to undertreatment and transplant inequity for Black pts (NEJM 2020;383:874)
- Role for Cystatin C: protein excreted by all nucleated cells, less affected by gender, age, body size, nutritional status than Cr (ExpRev 2020; 25:10) Recommend combined eGFRCr-Cys in situations where eGFRCr is not accurate (KDIGO 2024)
- Etiology: **DM (47%), HTN (28%)**, GN (7%), cystic kidney (3%), other (15%) (USRDS 2018)
- Epidemiology: 15% US adults; ESRD prevalence 4-fold higher in Black pts than White pts (USRDS 2021). 13% of Black individuals have a high-risk **apolipoprotein-1 (ApoL1)** genotype, which confers ↑CKD risk
- Disease Monitoring: Physiologic mean decline in eGFR with age is ~1mL/min per year per 1.73 m² from peak 120 ml/min attained during third decade of life (J, Nephrol 2014; 27:635). G1-G3a: risk factor reduction. G3a-G3b: evaluate & treat complications. G4 (or A3):nephrology referral, prep for RRT/transplant. G5: RRT (if indicated), transplant eval

**Prognosis of CKD by GFR and Albuminuria Categories**

| GFR categories (ml/min/1.73 m²) Description and range | | | Albuminuria categories Description and range: A1 | A2 | A3 |
|---|---|---|---|---|---|
| | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | <30 mg/g <3 mg/mmol | 30-299 mg/g 3-29 mg/mmol | ≥300 mg/g ≥30 mg/mmol |
| G1 | Normal or high | ≥90 | | | |
| G2 | Mildly decreased | 60-90 | | | |
| G3a | Mildly to moderately decreased | 45-59 | | | |
| G3b | Moderately to severely decreased | 30-44 | | | |
| G4 | Severely decreased | 15-29 | | | |
| G5 | Kidney failure | <15 | | | |

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

## Management

- BP control: goal <120/80 (KDIGO 2024) . Mortality benefit w/ intensive BP mgmt (SBP <120 mmHg) (NEJM 2021;384(20) Lancet 2024;404(10449)).
  - *If proteinuria*: ACEi; *if edema and eGFR <30*: loop diuretic, *if eGFR >30:* thiazide (consider chlorthalidone in select advanced CKD pts) (NEJM 2021;385:2507); *if resistant HTN or HF*: spironolactone.
- Proteinuria: Albuminuria independently predicts mortality and CKD progression. Tx goal as <300mg/d. Start w/ RAAS blockade (**ACEi or ARB**) up titrated as tolerated NEJM 2013;369:1892). If CKD w/ eGFR > 20 and T2DM OR UACR ≥ 200 mg/g, **add SGLT2-i** to ↓ CKD progression (NEJM 2022;388:117). If CKD a/w diabetic kidney disease w/ GFR ≥ 25, ACEI/ARB maximized + SGLT2i started + K ≤ 4.8 + continued albuminuria ≥ 30mg/d, consider **finerenone** (non-steroidal MRA shown to ↓ CV risk by ↓ in HF exacerbations)(NEJM 2020;383(23)).
- DM: goal HgbA1c <7%. Both **SGLT2i** (if eGFR > 20-30) and **GLP-1 agonists** (eGFR >30) ↓ rate of CKD progression (NEJM 2019;380:2295, NEJM 2017;377:839. **Metformin** safe at eGFR >30-45. **Insulin** safe at any eGFR, though must dose adjust as insulin clearance ↓ w/ ↓GFR.
- CVD: risk 2-4x general population. Statin if >50 y/o, eGFR <60, and no ESRD/tx (Kidney Int 2014;85:1303). SGLT2 inhibitors ↓ CKD progression/mortality/CVD outcomes. (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)
- Nephrotoxins: **Avoid** NSAIDs, chronic PPI's, contrast, select and dose meds renally (abx, tacrolimus, statins, opiate pain meds)
- Nutrition: nephrocaps (B-complex / C), Na <2 g/d, ↑ fruit/vegetable intake, maintain protein intake of 0.8 g/kg/d in CKD G3-5 (KDIGO 2024) not to exceed 1.3 g/kg/d, restrict K/Phos prn
- Monitoring: q4-12mo Cr & electrolytes, PTH, CBC, Fe studies. Annual UAlb/Cr & UProt/Cr ratios, 25-OH Vit-D. Renal U/S at dx
- Nephrology referral: GFR ↓30, sudden ↓ in GFR, severe proteinuria (Alb:Cr >300), UA w/ +blood/protein with ↓ GFR, resistant HTN
- Prognosis: Use Tangri risk score (JAMA 2016;315:164) especially in CKD G3-5 to estimate absolute risk of kidney failure

## Complications

| Hyperparathyroidism | | | | | |
|---|---|---|---|---|---|
| **Type** | **Ca** | **$PO_4$** | **PTH** | **Vit D** | **Pathophysiology** |
| 1° HyperPTH | ↑ | ↓ | ↑ | nl | Excess PTH production by parathyroid gland |
| 2° HyperPTH (2/2 ↓VitD) | ↓ | ↓ | ↑ | ↓ | Decreased Ca absorption stimulates PTH secretion |
| 2° HyperPTH (2/2 CKD) | nl/↓ | ↑ | ↑ | nl/↓ | ↓ PO 4 excretion increases PTH secretion |
| 3° HyperPTH | ↑ | ↑ | ↑↑ | nl/↓ | Longstanding 2° hyperPTH leads to PTH gland hyperplasia |

- Mineral and bone disorder: check Ca, $PO_4$, ALP, 25-OH vit D (1,25-OH vit D level will fluctuate) (Annals 2018;168:422).
  - PTH rising or 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 calcimimetic vs parathyroidectomy if non-responsive to medical therapy
- Anemia: Hgb < 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): Consider 1 gram IV iron empirically if Tsat <20% and/or ferritin <100ng/mL. If TSAT is 20-30% and ferritin <500, can consider challenging with iron or starting an ESA. Check q3m if on ESA. (Cochrane 2019;2:7857).
  - If Fe replete and Hgb <10, consider erythropoiesis stimulating agents (ESA) consider ESA, which ↓ transfusions, 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: $NaHCO_3$ starting at 650 mg 2-3x/day titrating up to 1300 mg TID for goal $HCO_3$ in normal range (23-29 mEq/L; avoid >29 mEq/L bc ↑ mortality). Slows progression of CKD, improves bone health (CJASN 2019;14:1011)
- Uremic bleeding: Treat depending on clinical context or if pre-procedure; can use DDAVP 0.3-0.4 mcg/kg x1 with max 40 mcg
- 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 IR small bore tunneled IJ. Prefer LIJ CVC in case need for HD

# Nephrology — Dialysis & Transplant

## Overview (NEJM 2022;386(10):964)

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): volume removal, removal of plasma water by hydrostatic pressure

**Emergent Indications for RRT (AEIOU)**

**A**cidosis: metabolic, pH <7.1
**E**lectrolytes: refractory/rapidly rising K or hyper $Ca^{2+}$
**I**ngestions: dialyzable toxins (eg: Li, ASA, methanol, ethylene glycol, metformin)
**O**verload: diuretic-refractory volume
**U**remia: encephalopathy, pericarditis, coagulopathy with uremic bleeding

## Timing of RRT

Timing: controversial. while early initiation may benefit certain subgroups, consensus is to avoid early initiation in the absence of the emergent indications above.

- ELAIN (JAMA 2016;315:2190): early RRT→↓duration RRT and LOS/mortality
- IDEAL-ICU (NEJM 2018;379:1431): no Δmortality w/ early RRT (pt w/ sepsis, AKI)
- STARRT-AKI (NEJM 2020;383:240): early RRT did not reduce 90d mortality vs. standard RRT (clinical indication) in critically ill pts.
- AKIKI-2 (LANCET 2021;397:1293): delaying RRT until clinical indications a/w ↑mortality (for pt w/oliguria >72h or BUN >112)

## Access for Hemodialysis

- Dialysis lines can only be accessed by dialysis/ICU RNs (except in codes); contact dialysis unit (x63700).
- PICCs: HD or future HD candidates should not receive PICC unless first cleared by Renal (to preserve options for vascular access)

| Types of access for HD | Durability | Benefits | Risks/Downsides |
|---|---|---|---|
| Non-tunneled double lumen central line, femoral or R IJ | Days-weeks | Can be placed and used immediately. | Infection. Can clot or kink. ONLY to be used for RRT while admitted. |
| Tunneled central line | Weeks-months, can be years | Can be placed by IR within hrs. Can be used as an outpt. | Infection and clot. ONLY to be used for RRT. Long term risk of central venous stenosis |
| AV fistula (pt A-V) | Years | Lowest infection and clot risk. Associated with increased survival | ~3-6 months to mature, 1° failure in ~40%. Limb edema, aneurysm/stenosis/clot, vascular steal, high output CHF |
| AV graft (synthetic graft connects A-V) | Years | Useable in days-wks. Lower infection and clot risk than central access. | Delayed failure (~25%) 2/2 stenosis/thrombosis. Risk of aneurysm. Infection requires surgical resection. |

## 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; $Ca^{2+}$ and $HCO_3^-$ move from dialysate to blood (diffuse via concentration gradients). Volume removal occurs via UF. Blood flow rate ~200-500mL/min. Usually three 4h sessions/wk.
- Intradialytic medications: erythropoietin, iron, vitamin D analogues, antibiotics, heparin or citrate (to prevent clotting of HD circuit)
- Complications: HoTN, arrhythmia/cardiac events, cramps, disequilibrium syndrome, dialyzer reaction, HIT, hemolysis, EtOH w/d

## Peritoneal Dialysis (PD) (NEJM 2021;385:1786)

Daytime: PD RN (617-726-0717)

- Mechanism: infusion of fluid rich in osmotic agent (e.g. dextrose) → use peritoneum as membrane→ solute removal via diffusion
- Benefits: preserves residual GFR longer than iHD, better middle molecule clearance; can be done at home.
- Modalities: (1) continuous ambulatory PD (**CAPD**) manual exchanges occurring day and night (2) nocturnal intermittent peritoneal dialysis (**NIPD**) w/ dwells only at night (3) automated PD (**APD**) multiple automated exchanges overnight w/ long daytime dwell
- Complications: Encapsulating peritoneal sclerosis, hernia, pleural effusion, leaking, hypoK (dialysate has no K). **Peritonitis** (dx 2/3: 1) abd pain/cloudy fluid 2) effluent fluid WBC >100 w/ >50%PMNs (after >1-2 hr dwell) 3) +effluent fluid culture (see ellucid). Treat after culturing w/ IP vanc/ceftazidime (use IV gram+&- coverage if septic). Remove catheter if no resolution w/in 5d or if fungal infxn.

## Continuous Renal Replacement Therapy (CRRT)

- Principles: continuous slow clearance, replacement fluid must be added back to restore volume, A/B balance + electrolytes. Less effective in toxin removal/volume overload compared w/ IHD. Not ideal for hyperK/toxins. Blood flow rate ~100-200mL/min.
  - **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 + diffusion to remove solute
- Indications: (1) **HD instability**/inability to tolerate iHD (2) persistent acidemia despite iHD (3) risk of cerebral edema w/ iHD.
- Volume management: run negative, even, or slightly positive. Replacement fluid w/ dextrose, bicarb, lactate, acetate or citrate.
- Anticoagulation: used to ↓risk of circuit clotting, use heparin OR citrate, citrate achieves regional AC by Ca chelation; follow iCa levels (will ↑ total Ca but ↓iCa), metabolized in liver → if $Ca_t$/iCa >2.5,↑AG with met alkalosis=possible citrate toxicity (avoid in liver failure).
- Complications: HoTN, arrhythmias, hypothermia, ↓iCa/K/PO4, bleeding, thrombocytopenia (mechanical destruction), 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**: years (HTN, CNI tox, BK virus, recurrence of original renal pathology, chronic allograft nephropathy)

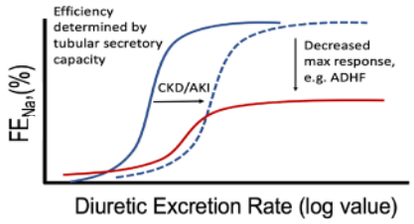
**Immunosuppression**

| Class | Examples | Mechanism of Action | Adverse Events |
|---|---|---|---|
| **Calcineurin inhibitor (CNI)** | Cyclosporine<br>Tacrolimus (FK506) | Inhibits calcineurin-mediated activation of NFAT → blocks T-cell cytokine production | Nephrotoxicity (long-term fibrosis), HTN, tremor, insomnia, hirsutism (Cyclosporine only) |
| **mTOR inhibitor** | Sirolimus (Rapamycin) | Inhibits mTOR → blocks IL-2 production | Pulm edema, poor healing, ↑TG, oral ulcer |
| **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 + fluid restriction 1.5-2L
- Loop diuretics have a sigmoidal dose-response curve (i.e. diuretic threshold effect), so double dose until adequate response is achieved
- If adequate UOP but volume not improving, Na/fluid restrict + increase diuretic freq
- Transient ↑ in serum Cr are common (~20% of cases in DOSE-AHF, ROSE-AHF), can be tolerated if effective decongestion. Diuresis did not worsen renal function; rather, associated with better outcomes in HF (Circ 2018;137:2016, JCF 2016;22:753).




| | **Loop Diuretics** (Diuretic>natriuretic) | | | **Thiazide Diuretics** (Natriuretic>diuretic) |
|---|---|---|---|---|
| **Examples** | **Furosemide** | **Torsemide** | **Bumetanide** | **Chlorthalidone, HCTZ, Metolazone (PO), Chlorothiazide (PO/IV)** |
| **Mechanism of Action** | Inhibit Na-K-2Cl transporter in asc. limb of loop of Henle to ↓Na reabsorption and "break" medullary concentrating gradient | | | Inhibit NaCl channel in DCT to ↓Na reabsorption and prevent urinary dilution |
| **PO Bioavail.** | 20-50% | 80-90% | 80% | Variable |
| **Duration of action** | ~6 hours | 6-8 hours | 4-6 hours | HCTZ: 6-12h; chlorthalidone: 24-48h metolazone: 24h; chlorothiazide (IV): 2h |
| **Dosing considerations** | 1mg Bumetanide IV/PO = 20mg Torsemide PO = 20mg Furosemide IV = 40mg Furosemide PO. Consider dosing BID-QID to avoid anti-natriuresis seen in QD dosing (see NEJM 2017;377:1964 Fig. 2C) | | | Administer metolazone 2.5-10mg PO or chlorothiazide 500-1000mg IV 30 min before loop diuretic to "disable" Na reabsorption in DCT (**sequential nephron blockade (SNB)).** |
| **Side effects** | **↑Na, ↓K, ↓Mg**, ↓Ca, ↑urate, ↑$HCO_3$, ototox, allergy, bumex - myalgias | | | **↓Na** (avoid if SIADH), **↓K, ↓Mg**, ↑Ca, ↑urate, ↑glucose, HLD, pancreatitis |

## Disease-Specific Considerations

| Condition | Mechanism | Treatment |
|---|---|---|
| **CKD/AKI** | ↓GFR → ↓delivery of diuretic to nephron → **higher** doses needed for effective diuresis<br>• Organic acids accumulate, damage PCT, and compete with diuretics → higher diuretic dose required | • High-dose loop ± thiazide augmentation *(prefer Furosemide in CKD given renal excretion, long ½ life)* |
| **Chronic Diuretic Use** | • "Braking phenomenon" of compensatory DCT hypertrophy leads to ↑ distal Na reabsorption | • Add metolazone or chlorothiazide |
| **CHF** | • In ADHF, GI edema leads to ↓absorption of PO diuretics<br>• High sympathetic tone → ↑RAAS, Na reabsorption | • Use IV. DOSE (NEJM 2011;364:797): in ADHF, no Δ sx or renal fx for pts receiving drip vs bolus dosing<br>• Consider **SNB** (see Stepwise Approach in CHF) |
| **↓ Albumin, nephrotic syndrome** | • Loop diuretic (needs to bind to albumin) leaks out of vasculature (↑$V_D$) resulting in ↓delivery to nephron | • Consider bumetanide (lower albumin-binding need)<br>• No evidence for benefit of albumin + loop diuretic |
| **Cirrhosis** | • Decreased delivery to nephron in setting of ↓ albumin<br>• Splanchnic vasodilation → ↓EABV → renal hypoperfusion<br>• SNS and RAAS → ↑Na reabsorption | • **Caution with IV diuretics** unless resp distress as causes rapid fluid shifts. 5/2 Spiro/Lasix ratio to promote eukalemia<br>• See *ESLD: Ascites* |
| **Loop/Thiazide Allergy** | • Loop and thiazide diuretics have large sulfonamide groups; however, data suggest limited cross reactivity between diuretics & other sulfa drugs | • If reaction, rotate to different loop/thiazide diuretic<br>• If sustained reaction→ **Ethacrynic Acid** (50 mg = bumetanide 1 mg) |

## Other Diuretics and Stepwise Approach in Heart Failure (NEJM 2017;377:1964)

1. IV loop diuretic. Starting dose: 2x-2.5x home dose as IV furosemide (CHF) (e.g. if home 80mg PO Lasix, give ~80-100mg IV) or Cr×40 as IV furosemide (e.g. if Cr 3, use lasix 120mg IV)
2. Reassess in 1-2 hrs and double dose Q1-2H until response achieved. Adequate dose causes brisk diuresis (Goal >100-150 cc/hr).
   a. Consider loop diuretic gtt: bolus when initiating gtt, then dose gtt based on goal daily dose, and re-bolus every time gtt increased. However, evidence suggests that it is not more effective in ADHF (NEJM 2011;364:797.
3. If insufficient UOP, consider augmentation to achieve SNB. Selection of agents should be tailored to severity of overload, clinical setting, long term benefits, labs, and ability to replete Mg/K.
   a. **Chlorothiazide**: short term augmentation or diuretic challenge is required inpatient, can help with hypernatremia
   b. **Metolazone:** when a longer duration of augmentation is required inpatient or outpatient, can help with hypernatremia
   c. **Acetazolamide**: **PCT blockade**. Acetazolamide IV 500 mg daily in addition to a loop diuretic, especially if metabolic alkalosis limiting diuresis. (↑HCO3, pH >7.45). ADVOR (NEJM 2022;387:1185) showed better decongestion when added to loop diuretics in ADHF compared to loop diuretics alone. Caution in COPD, acidosis, and sulfa allergies.
   d. **Aldosterone Antagonists**: Spironolactone: 12.5-200 mg / eplerenone 25-50 mg QD. Role in CHF/Cirrhosis. Causes ↑K, gynecomastia (10% pts, only spironolactone). Useful if need to raise K and minor augmentation needed.
   e. **SGLT2i:** Modest diuretic effect started closer to DC (Circ 2022;146:289). Maintenance diuretic may need to be ↓ when starting. Caution in pts w/ frequent UTIs, AUD, prior DKA, and ↓ PO intake.
4. Nephrology consult for consideration of short term UF/RRT as a bridge to renal recovery or advanced therapies
5. If starting maintenance loop diuretic at discharge, no strong evidence to prefer torsemide over PO furosemide (TRANSFORM-HF: JAMA 2023;329:214), but make sure to adjust the amount of maintenance diuretic if also discharging w/ MRA or SGLT2i.
6. Be conscious of K and Mg repletion during hospitalizations and discharge with standing K/Mg repletion or increased MRA if needed.

# Nephrology — Acid-Base Disorders

## Overview

- **ABG vs VBG**: VBG pH ~0.04 lower, $HCO_3$ ~2mEq lower (BMP more accurate), $CO_2$ ~3-8 mmHg higher. VBG can screen for hypercapnia w/ pCO2 cutoff ≥45mmHg (100% Sn) but does **NOT** accurately assess degree of hypercapnia. VBG $PCO_2$ non-correlative in severe shock. **When in doubt, check ABG** (AJEM 2012;30:896).
- Severe acidemia (pH <7.2) may precipitate systemic vasodilation, ↓inotropy/MAP, ↓response catechols/pressors, arrhythmia, ↑K, insulin resist., AMS
- Severe alkalemia (pH >7.6) may precipitate systemic vasoconstriction, ↓coronary/cerebral perfusion, SVT/VT, ↓K/Ca/Mg/Phos, AMS, seizure, hypoventilation

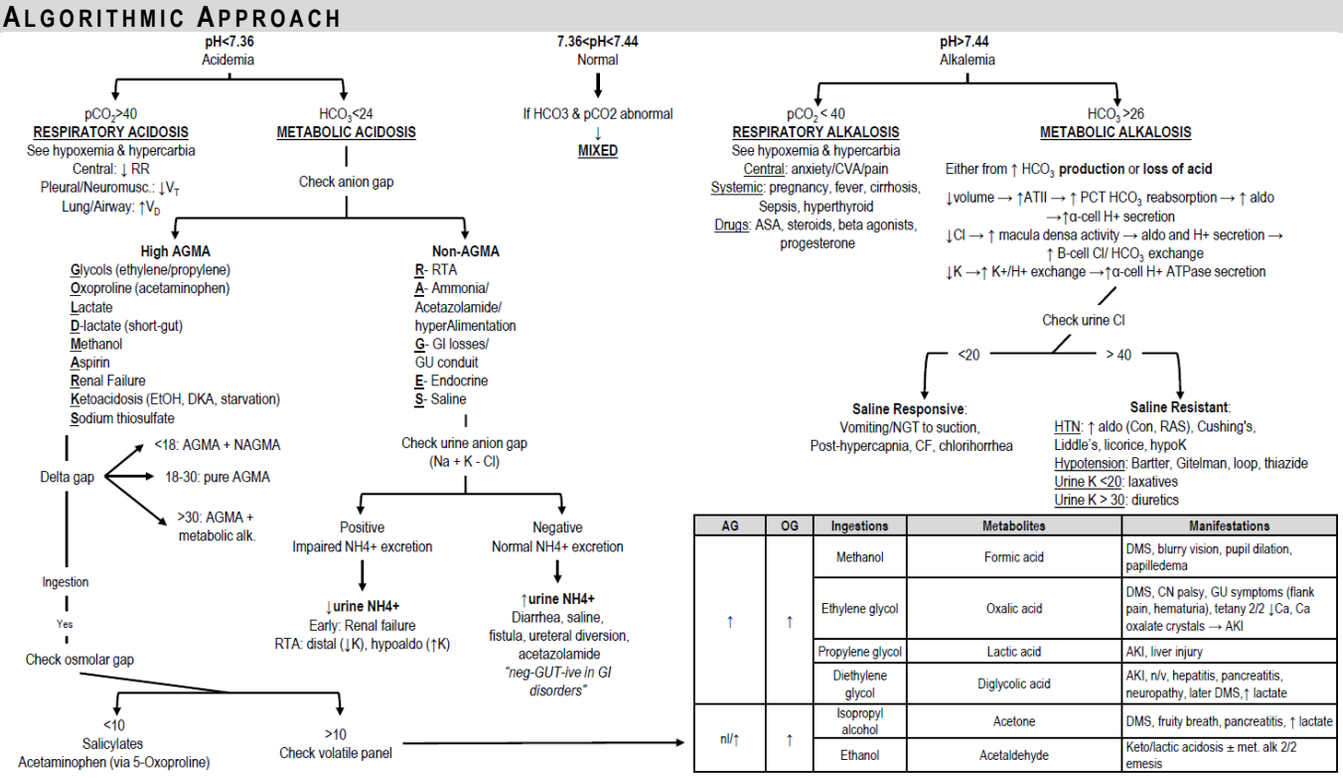
## Step-Wise Approach (NEJM 1998;338:26; NEJM 2014;371:1434)

1. Is there acidemia (pH <7.35) or alkalemia (pH >7.45)?
2. Is 1° disorder metabolic (↓bicarb with acidosis, ↑ bicarb with alkalosis) or resp (↑ pCO2 with acidosis, ↓ pCO2 with alkalosis)?
3. Is there an anion gap? Calculate regardless of pH or $HCO_3$
   **AG = Na – (Cl + $HCO_3$)** = unmeasured anions – unmeasured cations
   *Correct AG for albumin:* $AG_c$ = AG + 2.5(4 – albumin)
   *Negative AG:* ↑↑Na or other cations (Ca, Mg, Li), lipids (interfere with chloride), protein (multiple myeloma), bromide or iodine intox,
4. Is pt compensating? (see chart, respiratory takes min-hrs, renal 3-5d)
5. If there is ↑AG metabolic acidosis (AGMA), calculate "**delta-gap**"
   **Delta gap = (Albumin corrected AG-12) + $HCO_3$. If <18:** additional NAGMA present**, 18-30:** no additional disorder**, >30:** additional met alk
6. Consider Osm gap = [2(Na + K) + Urea/2.8 + glucose/18 + EtOH/4.6 – serum Osm] to screen for exogenous osmoles (e.g. toxic alcohols), also seen in pseudohyponatremia

### Expected Compensation (Kidney360 2022; 3(8)

Metabolic acidosis: 2-24h
Winter's formula: $pCO_2 = (1.5 \times HCO_3) + 8 \pm 2$
Metabolic alkalosis: start 30min, complete 24h
$PaCO_2 = 0.7 \times (HCO_3) + 20 \pm 5$
Respiratory acidosis:
Acute: # D $HCO_3$ = 0.1 x # D $pCO_2$ # 1
Chronic: # D $HCO_3$ = 0.35 x # D $pCO_2$
Respiratory alkalosis:
Acute: $ D $HCO_3$ = 0.2 x D $pCO_2$
Chronic: $ D $HCO_3$ = 0.41 x $ D $pCO_2$

## Algorithmic Approach




| AG | OG | Ingestions | Metabolites | Manifestations |
|---|---|---|---|---|
| ↑ | ↑ | Methanol | Formic acid | DMS, blurry vision, pupil dilation, papilledema |
| | | Ethylene glycol | Oxalic acid | DMS, CN palsy, GU symptoms (flank pain, hematuria), tetany 2/2 ↓Ca, Ca oxalate crystals → AKI |
| | | Propylene glycol | Lactic acid | AKI, liver injury |
| | | Diethylene glycol | Diglycolic acid | AKI, n/v, hepatitis, pancreatitis, neuropathy, later DMS,↑ lactate |
| nl/↑ | ↑ | Isopropyl alcohol | Acetone | DMS, fruity breath, pancreatitis, ↑ lactate |
| | | Ethanol | Acetaldehyde | Keto/lactic acidosis ± met. alk 2/2 emesis |

# Nephrology — Acid-Base Disorders

## 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 + electrolytes (K, iCa) and volume status. Bolus admin is controversial due to c/f CO2 accumulation → hypercapnia (acidosis), 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 $CO_2$
  - Special considerations:
    - Toxic alcohols: call poison control, NaHCO3, **fomepizole**, or HD (if vision Δ, AKI, HAGMA, methanol >50mg/dL, ethylene glycol >300mg/dL)
    - Salicylate poisoning: NaHCO3 to goal urine pH >6.5 and serum salicylate level <40 or HD (if level >80mg/dL, coma, AKI, hypervolemia, AMS), dextrose containing fluids if AMS. **Acetazolamide is contraindicated**
    - NAGMA and uremic acidosis are more responsive to HCO3 than lactic and ketoacidosis
  - Chronic: in CKD, replete with PO NaHCO3 for goal $HCO_3$ >22. See *CKD*
- **Metabolic alkalosis**: replete volume, K, & Cl
  - Treat both (1) underlying cause of metabolic alkalosis and (2) cause of renal retention of $HCO_3$
  - If saline responsive: **NS w/ KCl** until urine pH >7. For pts w/ CHF/cirrhosis & alkalosis 2/2 diuresis, consider Acetazolamide and/or K+ sparing diuretic. See *Advanced Diuresis*
  - If saline resistant: for mineralocorticoid excess → use $K^+$-sparing diuretic (**prefer amiloride, faster than spironolactone**) & consider surgical removal of adenoma
  - If pH >7.6 & persistently volume overloaded, give **acetazolamide** + loop diuretic with close $K^+$ monitoring. May need KCl
- **Respiratory acidosis**: treat underlying process; adjust vent settings if intubated. $NaHCO_3$ unlikely to be helpful, theoretically harmful if unable to ventilate subsequent $CO_2$ produced. For every 100mEq $HCO_3$ administered, 2.2L $CO_2$ 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 select pts w/ Hyperchloremic NAGMA or hyperK (Type IV). **R/o GI losses & ↑IV NS use before ordering UAG!**

**Pathophysiology**: inappropriate net retention of acid or inadequate reabsorption of bicarb
- In acidemia, kidney should ↑NH4+Cl- excretion and 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): decreased threshold for proximal tubule $HCO3^-$ reabsorption → more HCO3 spills into urine
  - Primary (rare): Na-HCO3 cotransporter defect
  - Acquired: **amyloidosis, MM**, post-renal transplant, bladder outlet obstruction, heavy metals, ↓Vit D, Wilson's disease, PNH
  - Meds: acetazolamide, cisplatin, tenofovir, aminoglycosides, topiramate
  - Often a/w Fanconi Syndrome: glucosuria (w/ serum gluc <180), hypouricemia, aminoaciduria
- Distal RTA (Type I): inability to secrete H+ in distal tubule. Various subtypes of distal RTA related to affected transporter/tight junction
  - 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, ibuprofen, codeine
- Type IV: effective hypoaldosteronism: ↓aldo secretion OR tubular resistance → ↑K → ↓$NH_3$ synthesis → ↓$NH4^+$ excretion
  - Hyperkalemia inhibits glutaminase enzyme, which generates NH3 ("ammoniagenesis"). Acidosis ensues as unable to fix and excrete H+ as ammonium.
  - 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
- VBG, BMP (AG, $HCO_3$, K), UA (pH), urine lytes. Consider urine Ca/Cr to differentiate proximal vs distal RTA
- Estimate of Urine $NH_4^+$: UAG = Na + K - Cl (less useful when ↑urine pH >6.5 or UNa < 25, high aldo state)

| | PROXIMAL RTA (TYPE II) | DISTAL RTA (TYPE I) | TYPE IV RTA |
|---|---|---|---|
| **Defect** | **↓Proximal $HCO_3^-$ resorption** | **↓Distal $H^+$ secretion** | **↓Distal K and acid secretion** |
| **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/ $NH4^+$ |
| **Urine AG = Na + K – CL** | ⊖ | ⊕ | ⊕ |
| **Additional dx testing** | Urine Ca/Cr nml, give bicarbonate and check urine pH | Urine Ca/Cr elevated | Renin, aldosterone, cortisol |
| **Complications** | Rickets, osteomalacia | CaPO4 urinary stones | Hyperkalemia |
| **Tx** (Goal HCO3 22-24) | **Challenging**. NaHCO3 (10-20 mEq/kg) or KCitrate. | NaHCO3 (1-4mEq/kg) | Treat hyperK: loop, low K diet<br>If hypoaldo, can give fludrocort |

# Nephrology — Sodium Disorders

## HYPONATREMIA: free water excess relative to serum sodium (JAMA 2022:328(3):280-291)

**S/Sx**: often asymptomatic; can present with AMS, HA, N/V, weakness, seizures, signs of increased ICP, salt cravings
**Workup**: (Consider if serum Na <130) H&P: symptoms, water intake hx, diet hx, urination frequency, etiology, chronicity, new meds, endocrine ROS, volume status, surg w/ irrigation (prostate/bladder/uterine)

- Studies: *Obtain prior to treatment* Serum: BMP, Osm. Consider uric acid, TSH, AM cortisol. Urine: **UA, Osm, Na, uric acid.**
- Determine if ADH is present (**UOsm** >100**). Can approx UOsm from UA: last 2 digits of SG x 30 (e.g., SG 1.010 ≈ UOsm 300)
- 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) ≥10-12% (small studies: 100% PPV for SIADH/thiazide hypoNa; FEUA ≤8% = 100% NPV for SIADH). ↓EABV: often sUA >5, BUN↑, FEUA <4%
  - IVF: SIADH: NS initially ↑SNa but then will ↓SNa (Na is excreted while $H_2O$ retained). Hypovolemia: NS will ↑SNa

*Note: Serum osm may be misleading and not reflective of serum tonicity if ineffective osms are present (BUN or ethanol)*

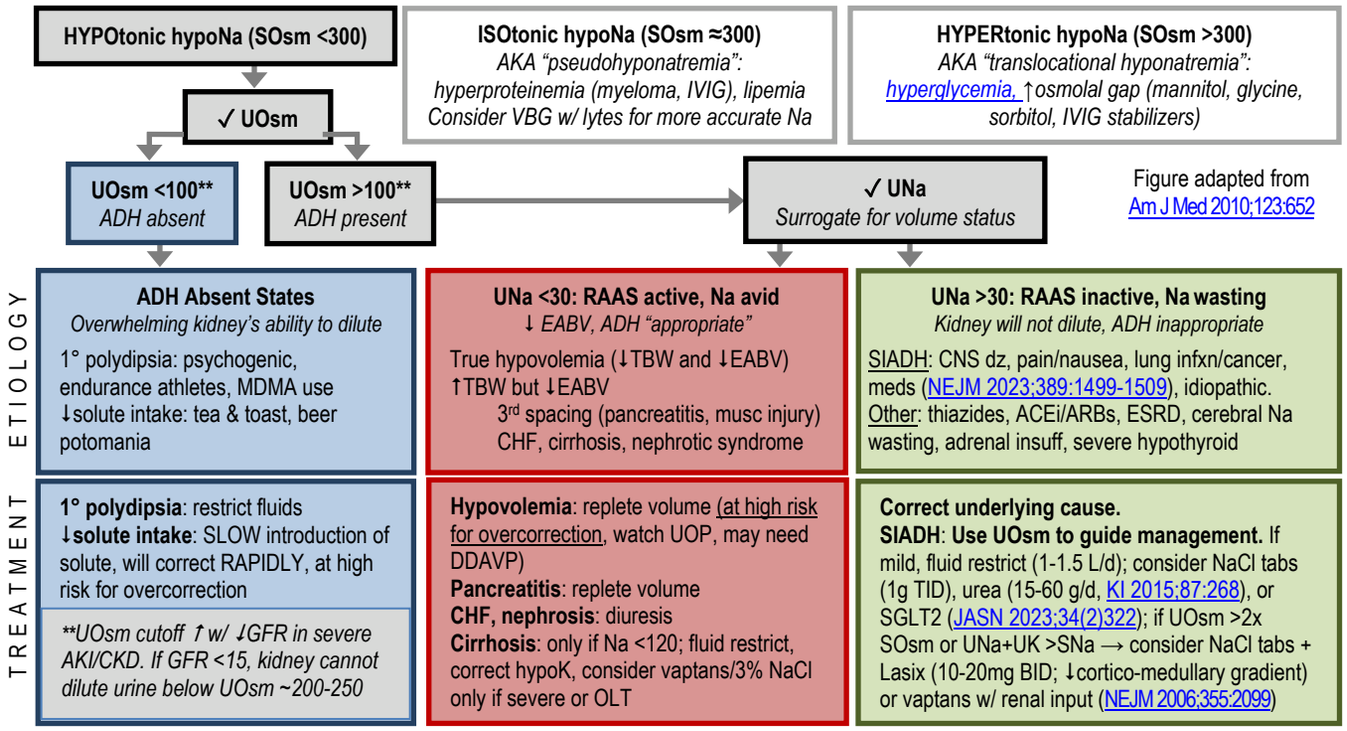



Figure adapted from Am J Med 2010;123:652

**Treatment**: depends on acuity, severity, and etiology (JASN 2017;28:1340). **Renal c/s if patient needs 3% NaCl and/or DDAVP clamp**

- **Rate/goal**: ↑Na 4-6 mEq/L per 24h, to short-term goal ≥125; typically ↑Na 4-6 will alleviate sx
- **Severe symptomatic** (sz, AMS): 3% NaCl via 100mL bolus over 10 min; up to 3x until sx resolve or Na ↑5 (max 8-10 / 24h)
- **Severe asymptomatic** (Na <120): 3% NaCl at Na Correction Rate, usually 15-30mL/h, until Na ≥125; Na <120 a/w 6-10% in-hosp mortality (Clin J Am Soc Nephrol 2018;13:641). Consider proactive DDAVP clamp in high ODS risk (see **Risk Factors** below)
- **Mild/mod** (Na 130-134/Na 120-129): etiology-specific treatment (e.g., fluid repletion, fluid restriction, diuresis, hold diuresis). Slow correction may be associated with increased mortality (JAMA Intern Med 2025; 185(1):38-51).

**Overcorrection**: Na ↑ >8 in 24h or >18 in 48h. *In high ODS risk patients, some guidelines say ΔNa >4-6meq/24h is overcorrection*
Osmotic demyelination syndrome (ODS): delayed onset (2-6d) dysarthria/dysphagia, paresis, behavior∆/AMS, locked-in synd. Dx with MRI ~4w after sx onset. **Risk Factors**: starting Na ≤110 (ODS unlikely if starting Na >120, Hosp Pract 1995;37:128), malnutrition, EtOH use, cirrhosis, ↓K

- Be aware that rapid correction more likely in hypovolemic hyponatremia and low solute hyponatremia (CJASN 2018;13:984). Monitor for water diuresis post fluids (presents with rapid increase in UOP (>100ml/h)) and consider DDAVP clamp.
- If Na trajectory *predicts* overcorrection, consider DDAVP clamp (AM J Kidney Dis 2022;79(6):890)
  - 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, urgently ↓Na to within previous goal (i.e., ΔNa < 8 mEq/L/24h or <4-6 mEq/L/24h in high ODS risk):
  - D5W 6mL/kg IBW over 2h (↓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. 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
**Work-up: history (water and diet hx, urinary hx, meds – especially lithium, recent brain surgery, malignancy), labs: BMP, serum osm, urine osms. If urine osm <300, consider AVP deficiency or resistance. If urine osm <700, consider extra renal water loss**
**Treatment**: BMP q12-24h, strict I/O. Aim to ↓SNa by 12 mEq/L 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 ↑ if burns, fever, diarrhea (cannot measure, so ↑ 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

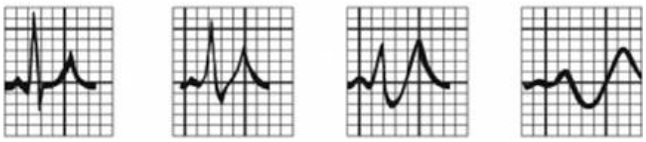
# Nephrology — Potassium Disorders

## Normal Potassium Handling/Homeostasis (NEJM 2015;373:60)

- Ingested $K^+$ absorbed in intestines → taken up and sequestered by liver/muscle cells via insulin & β2 receptors → ↑Na-K ATPase
- 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 (macula densa). ↑Na+ delivery → K+ excretion; ↓Na+ delivery → K+ retention

## Hyperkalemia

- S/S: Muscle cramps, weakness (ascending), 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 (note: lab only checks for RBC hemolysis and NOT WBC lysis), or infusion of $K^+$-containing IVF; consider blood gas $K^+$
- ECG: peaked T waves → ↓QT→ ↑PR interval ± AVB, flat p → wide QRS ± BBB → sine wave pattern → PEA/asystole/VF
  - *ECG does not correlate w/[$K^+$]*(Clin J Am Soc Neph 2008;3:324)



- Etiologies: **A**cidosis, ↓**A**ldosterone; **B**-blocker, **B**lood; **C**ell lysis/turnover; **D**rugs, **D**M, **D**ecreased GFR
  - **Redistribution**: cell lysis (hemolysis, rhabdo, TLS), acidosis, ↓insulin, hyperosm, meds (digoxin, β-blockers, minoxidil), hyperK periodic paralysis, post-hypothermia
    - Usually transient unless impaired renal $K^+$ excretion
  - ↓ **Renal K excretion**: required for persistent hyper$K^+$
    - ↓ Aldo production/action: ACEi/ARBs, NSAIDs, $K^+$-sparing diuretics, calcineurin inhib, 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
  - **Elimination is key**, other measures are temporizing. Address reversible factors (optimize volume status, low $K^+$ diet, meds). Of note, hyperK-related sine waves can be misinterpreted as VT. Do **NOT** use amiodarone if suspected hyperkalemia (deadly)

**Hyperkalemia Treatment**

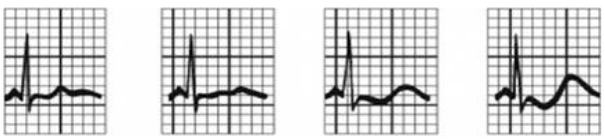
| Strategy | Treatment | Onset | Duration | Notes |
|---|---|---|---|---|
| Stabilize | **Calcium**: calcium gluconate or $CaCl_2$ (central line) 1-2g IV, can repeat q5 min PRN | 1-3m | 30-60m | 1st line if **any ECG Δs**. Stabilizes cardiac membrane. **Avoid if on dig** |
| Redistribute | **Bicarb** (sodium bicarbonate 1-2 amps IV vs gtt) | 5-10m | 1-2h | Drives $K^+$ into cells. **Consider especially if ↓↓ pH** |
| | **Insulin** (5U IV) + **D50** 25g (if BS<250) | 10-30m | 4-6h | Drives $K^+$ into cells. ↓$K^+$ 0.5-1.5mEq/L |
| | **Albuterol** (10-20mg neb) (Avoid w/ active ACS or significant tachyarrhythmias) | 15-30m | 15-90m | |
| Eliminate | **Furosemide** ≥40mg IV; can approx. as 40xCr if K>6 (Can give with NS to provide volume to diurese) | 30m | Variable | Urinary $K^+$ excretion If ↑↑ volume can + thiazide |
| | **Lokelma** (10g TID) > **Patiromer** 8.4 g daily prn (avoid GI binders if SBO/constipation/ileus) | 1h; 7h | 24h | Swaps $K^+$ for $Ca^{++}$ or $Na^+$ in gut |
| | **HD** lowers K immediately | N/A | 3h | Removes $K^+$, may rebound d/t shifts |

Note: Kayexalate use has ↓↓ in favor of Lokelma given issues w/ efficacy and risk for GI complications (JAMA Intern Med 2019; 179:1023)

## Hypokalemia

Signs and symptoms: usually with $K^+$<3 → cramps, ileus, weakness (ascending, can involve respiratory muscles), rhabdo, paralysis, worsened HE in cirrhosis (Nat Rev Neph 2010;7:75)

- ECG: flat T waves, ST dep, U waves, ↑QT, atrial or ventricular ectopy → VT, VF (esp if $K^+$<2.5, 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), antipsychotics, hypokalemic or thyrotoxic 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, ifosphamide, cisplatin, gent)
    - Acidemia: DKA, RTA (proximal [Type II] and some distal [Type I])
    - 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 artery stenosis, renin-secreting 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 (e.g. periodic paralysis)
  - Oral KCl (ER = pill, IR = powder) preferred for tx as safer, quick acting, and many pts are $Cl^-$ depleted
  - IV formulation KCl if unable to take PO → max 10mEq/h (floor), 20mEq/h (ICU)
  - Always replete Mg, otherwise $K^+$ repletion ineffective due to K+ wasting via ROMK (JASN 2007;18:2649)
  - Avoid dextrose-containing solutions → can acutely worsen hypokalemia (dextrose ↑insulin secretion → $K^+$ shifts into cell)

# Nephrology Magnesium & Phosphorus Disorders

## HYPOMAGNESEMIA (Med Sci (Basel) 2019;7:56; AJKD 2024;803:815)

- S/Sx: lyte disturbances (↓K, ↓Ca, alkalosis), hypoparathyroidism, lethargy, muscle weakness; severe: delirium, coma, neuromuscular hyperexcitability (e.g. hyperreflexia, tetany, seizures), cardiovascular (↑QRS, peaked T waves, later ↑PR, ↑**QTc**, U waves, VT/TdP), accentuation of digoxin toxicity
- Etiologies:
  - **GI**: ↓intake (AUD), ↑loss (diarrhea, pancreatitis, malabsorption, small bowel resection, **PPIs**), cellular shift (refeeding syndrome)
  - **Renal wasting**: Meds (thiazide, loop diuretics, ampho-B, aminoglycosides, foscarnet, tacro/cyclosporine, cisplatin, digoxin, pentamidine), inherited (e.g. Gitelman syndrome), T2DM, EtOH
    - Use **FEMg** to distinguish renal vs GI loss (>3% suggests renal wasting)
- Treatment: oral (slow) vs. IV (fast, typically used inpatient), slow repletion better for sustained correction
  - IV: $MgSO_4$ 1-2g over 2-15min x2 if unstable. If stable, 1-2g over/30-60min; favor IV if sx, reduce dose if CrCl<30
  - PO: $MgCl_2$ 4-8 tabs/day, causes less diarrhea than Mg oxide 800-1600mg/day, **always use in divided doses**
  - If hypoMg due to renal wasting, can add K-sparing diuretic or SGLT2i to decrease Mg excretion

## HYPERMAGNESEMIA (AJKD 2024;803:815)

- S/Sx (typically only if Mg > 4): mild: nausea, flushing, HA, lethargy, drowsiness; severe: neuromuscular depression (hyporeflexia [first sign], weakness, resp failure), cardiovascular (HoTN, bradycardia, conduction defects [↑PR, ↑QRS, ↑QTc, CHB, arrest]); hypocalcemia (hyperMg can suppress PTH)
- Etiologies: Mg intake exceeds renal clearance. Rarely pathologic w/o renal insufficiency
  - Med overdose (Epsom salts, laxatives, Maalox, Mg enemas) → avoid these agents in ESRD, pre-eclampsia/eclampsia treatment
  - Gastritis/PUD/colitis (increased Mg absorption in these states)
  - Misc - DKA, hypercatabolic states (TLS), lithium, adrenal insufficiency, milk-alkali syndrome, iatrogenic (repletion)
- Treatment (symptomatic only): Ca gluconate 1g IV over 10 min vs gtt to counteract resp depression/cardiac toxicity; **IV fluids** + loop diuretics to enhance renal excretion. If ESRD, HD for removal

## HYPOPHOSPHATEMIA (AJKD 2024;250:253; JCEM 2012;696:706)

- S/Sx: (typically if phos <1.0 mg/dL, esp. if acute): ↓intracellular ATP →global cellular dysfunction→ muscle weakness, AMS/encephalopathy, paresthesia, seizures, CHF, resp depression, proximal myopathy, rhabdo, dysphagia/ileus, hemolysis, bone and dental demineralization (bone pain, hypercalciuria, rickets/osteomalacia) (JASN 2007;18:1999)
- Etiologies:
  - **Redistribution (into cells)**: ↑insulin (DKA/HHNK tx, **refeeding**), acute resp alkalosis (↑pH → ↑glycolysis), hungry bone syndrome (deposition of Ca and phos in bone immediately following parathyroidectomy)
  - **↓GI absorption**: poor PO, chronic diarrhea, ↓vit D, antacids or phos binders (e.g. aluminum, Mg, sevelamer)
  - **↑Renal excretion**: ↑PTH (1° or 2° hyperPTH), Fanconi syndrome (multiple myeloma, tenofovir), ↑FGF-23 (genetic/paraneoplastic), meds (e.g. acetazolamide, metolazone, IV iron) (QJM 2010;103:449), osmotic diuresis (glycosuria), CVVH (esp at high bicarb dose), post-kidney transplant (response to residual ↑FGF-23 and PTH)
  - Use **$FEPO_4$** to distinguish GI/redistribution vs renal (>5% suggests renal wasting)
- Treatment: address underlying cause such as medications
  - **Severe** (<1 mg/dL or 1-2 mg/dL and at high risk of becoming severe e.g. refeeding) **or symptomatic**
    - IV Na or K phos 30mmol q6h with frequent levels (can give 15, 30, or 45mmol doses at MGH). Change to PO once >1.5mg/dL. Give ½ dose in CKD/ESRD.
    - Aggressive IV tx can cause Ca precipitation, hypocalcemia (tetany, seizures, arrhythmia, HoTN), AKI
  - **Asymptomatic** (<2 mg/dL and not at high risk): Na or K phos 1mmol/kg/d PO in 3-4 divided doses (max 80mmol/d)
    - 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
    - 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 → hypocalcemia (muscle cramps, tetany, tingling, perioral numbness)
- Etiologies:
  - **Acute phos load** (TLS, rhabdo, exogenous/phosphate-containing laxatives, fosphenytoin)
  - **Acute extracellular shift** (DKA, lactic acidosis, severe hyperglycemia)
  - **Acute kidney injury** or **CKD** 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), HD. Consider low phos diet, phos binders (sevelamer), renal consult if refractory/profound

# Nephrology IV Fluids & Electrolyte Repletion

## IV FLUIDS (NEJM 2013;369:1243)

Types: **crystalloid** (e.g. NS or LR), **free water** (e.g. D5W), and **colloid** (e.g. albumin, blood products)

- Fluids can be isotonic (NS more isotonic than LR), hypotonic (D5W, 1/2 NS, 1/4 NS), or hypertonic (3% saline)
- **Bolus fluids** = volume expansion in distributive/hypovolemic shock, GI losses, burns
  - Rate: 1L over 30min-2h. If concerned about volume overload, start w/ smaller volume (250-500cc).
  - LR has **minor** quantities of K & lactate, ↑K & lactate are **NOT** contraindications to LR (JEM 2018;55:313).
  - NS in large volumes can cause hyperchloremic non-AG metabolic acidosis (NAGMA) and ↑need for RRT (NEJM 2018;378:829; NEJM 2018;378:718) however no Δ mortality when compared to LR (JAMA 2021;326:818).
- **Indications where NS likely > LR**: ↑ICP (LR is slightly hypotonic and may ↑cerebral edema), hyperkalemia with kidney impairment (due to K in LR), and advanced liver disease (due to lactate in LR) (CJASN 2022;17:588).
  - Colloid is NOT superior to crystalloid for volume resuscitation in shock (JAMA 2013;310:1809)
- **Maintenance fluids** = goal to replace daily losses while preserving electrolyte balance +/- supplying a sugar source. **Always order with time limit.**
  - Rate 60 – 100 mL/h: guided by comorbidities, insensible losses (intubated/burns/fever via skin and lungs), oliguria, or ADH excess.
  - Daily losses = urine output (800-1500mL) + stool (250mL) + insensible losses (600-900mL). Increase insensible losses by 2.5mL/kg/d for each degree above 98.6F. Intubation/humified ventilation decreases insensible losses
  - D5NS or LR are typical maintenance fluids (NEJM 2015;373:1350). Consider NS in oliguric AKI w/ ↑K (↑distal Na delivery and K excretion) (CJASN 2022;17:588). Consider isotonic bicarb in high output GI fistulas/ostomies.

**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 typically for volume resuscitation

- **SBP**: improves renal outcomes. Dosing: 1st dose albumin 25% at 1.5g/kg w/in 6h (max 100g), 2nd dose 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**: ECMO chatter, mechanical circulatory support, burns, nephrotic syndrome, acute hemorrhagic shock, intra-dialysis
- NOT helpful in decompensated cirrhosis unless for the above indications (NEJM 2021;384:808)

## ELECTROLYTE REPLETION

| | Potassium | Magnesium | Phosphorus | Calcium |
|---|---|---|---|---|
| **Goal and Route** | - CAD/arrhythmia: ≥4<br>- Everyone else: ≥3.5<br>- Do not replete if on HD unless <3.0<br>**PO > IV** | - CAD/arrhythmia: ≥2<br>- Everyone else ≥1.7<br>**IV > PO** | - Replete if phos <2<br>**PO preferred**<br>**IV if <1 or <1.5 + symptoms**<br>Symptoms: weakness, MKS pain, SOB/resp failure, CHF, Δ neuro | - Replete if sx, long QTc, Ca <7.5, iCal <1.15mmol/L<br>**PO > IV unless iCal <1.0** |
| **PO repletion** | - KCl IR (powder): q4-6h<br>- KCl ER (pills): giant pills<br>- If K <3.5, ≥20 mEq KCl IR<br>- see Lexicomp for dosing | - Mg oxide 400mg (240mg elemental Mg) TID x1d | - Phos-Nak: 1 packet QID (7 mEq K, 7 mEq Na)<br>- K-Phos-Neutral: 1 packet QID (1 mEq K, 13 mEq Na) | - Ca carbonate 1250mg PO BID |
| **IV repletion** | - Peripheral: 10mEq/h<br>- Central: 20mEq/h w/ telemetry monitoring | - Mg sulfate 2g IV | Give 15-45mmol Phos over 6 hr<br>- K-Phos (1.5mEq K/mmol Phos)<br>- Na-Phos (1.3mEq Na/mmol Phos) | - Ca gluconate 1-2g IV;<br>- $CaCl_2$ used in codes, 0.5-1g q2-5min |
| **Comments** | - **10mEq K ↑serum K by 0.1 (in normal kidney function)**<br>- re-check K every 40mEq unless on stable daily dose<br>- **Correct hypoMg** | - **2g ↑serum Mg by 0.5**<br>- ↓Mg can cause ↓K/Ca | - IV Phosphate can precipitate Ca → causing hypocalcemia<br>- **Reduce/halve dose in CKD** | - Correct for low Alb & hyperphos first<br>- OK for lower iCa in TLS as high Ca x Phos product can precipitate in tubules<br>- **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)<br>**SG <1.010**: post-ATN (concentrating defect), diuretics, DI, polydipsia, hypovolemic hypoNa *after resuscitation*<br>**SG 1.010 – 1.025**: normal; **SG >1.025**: prerenal, ↓EABV, SIADH<br>Nb: presence of large molecules like contrast, glucose, proteins can cause ↑SG esp >1.030) despite isosmotic/dilute urine.. |
| **pH** | Normal 4.5 - 8, but strongly depends on serum pH and dietary intake<br>Urine pH should be <5 in the presence of acidemia. Acidemia + urine pH>5, suggests RTA(kidney not secreting $H^+$ ions)<br>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, steroids |
| **Blood** | Detects heme (glomerular, renal, or urologic); **FP**: hemoglobinuria (hemolysis), myoglobinuria (rhabdo), semen, drugs (rifampin, chloroquine, iodine), peroxidase producing bacteria. FN: vit C intake |
| **Protein** | Only detects albumin, not LMW proteins or light chains. + Protein when excretion >300mg/d.<br>Falsely elevated by high SG, heavy hematuria (heme protein), and iodinated contrast (w/in 24h). Falsely underestimated by very dilute urine. Persistent dipstick protein should be quantified with alb:Cr ratio. |
| **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<br>PCT failure (glycosuria w/ normal serum glucose " consider Fanconi's syndrome 2/2 MM, heavy metal, drugs, etc.). FN: vit C intake |

**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, 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 RBCs). |
| **WBCs** | UTI/cystitis (>10/microL expected for true infxn), pyelonephritis, AIN, atheroembolic, glomerular injury, renal/bladder TB, stones |
| **Epithelial Cells** | Tubular (ATN), transitional (proximal urethra to renal pelvis), squamous (contamination by genital secretions) |
| **Casts** | Hyaline, RBC, WBC, Muddy brown, Granular, Waxy, Fatty. ↑urine conc, stasis, ↓pH favor cast formation |
| **Crystals** | Struvite- urease producing organisms, Oxalate- ethylene glycol, uric acid-TLS. *Meds:* Acyclovir, Tenofovir, MTX |

| CONDITION | UA | CELLS | CASTS/CRYSTALS | COMMENTS |
|---|---|---|---|---|
| **Pre-renal azotemia** | SG >1.010 | | Hyaline, granular | ↓ FENa (if oliguric), ↓ FEUrea |
| **Nephrotic syndrome** | 3+ protein | | Oval fat bodies, hyaline | |
| **Glomerulonephritis** | + heme, +protein | Dysmorphic RBCs | RBC casts, WBC, granular | |
| **ATN** | SG ~ 1.010 ("isosthenuria") | Hallmarks: renal tubular epithelial cells (RTECs) and muddy casts (CJASN 2008;3:1615) PPV for ATN ~100% if ↑pre-test prob and any RTECs and/or muddy casts present. | | |
| **Rhabdomyolysis, hemolysis** | 3+ heme w/o RBCs on sediment | NO cells | Acellular hyaline casts with red or brown pigmentation | ↓ FENa, red/brown urine |
| **AIN** | Sterile pyuria | WBCs | WBC casts, granular | Urine eos NOT sens or spec |
| **Renal infarct** | Sterile pyuria | + RBCs, WBCs | | ↑urine LDH (↑serum LDH) |
| **Cholesterol emboli** | Sterile pyuria | | Cholesterol | |
| **Myeloma kidney** | | Bland | Bland | Proteinuria NOT detected by UA |
| **CKD** | +/- protein | | 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**: non-con CTAP > 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, hypomagnesuria, hypercystinuria, urea splitting bacteria, high sodium intake, acidic urine (urate, cysteine), or basic urine (calcium phosphate, struvite), drug-induced (guaifenesin, triamterene, sulfa drugs, protease inhibitors), toxic ingestion (ethylene glycol ® Ca oxalate stones)
**Acute management**: IVF, pain management (ketorolac preferred to opioids), alpha blockers (>5 mm and <10mm); urologic intervention if >10mm, concern for infected stone, AKI, unremitting pain/n/v, or anuria. See: Ureteral obstruction. See AAFP algorithm. OP urology input if no stone passage 4 weeks s/p alpha blocker.
**Chronic management**: fluid intake >2.5L/d, low Na diet, ↑ K diet, ↓oxalate diet (no nuts, chocolate, green leafy veggies, etc.), ↑Ca intake, avoid excess vitamin D, allopurinol if hyperuricosuria, thiazide diuretics if calcium stones- data inconclusive (NOSTONE trial: no difference in recurrence rate between HCTZ and placebo, but Ryan et al found ↑ thiazide dosage → ↓↓ urine Ca and ↓symptomatic stone events.)
**Citrate supplementation**: used for inhibition of Ca and uric acid stone formation. Leads to metabolic alkalosis. ↓new stones, stone size. 26% lower recurrence risk compared to no pharmacological tx (CJASN; 2024 19(5):p 565-572).

# Infectious Disease — Empiric Antimicrobials

## PRINCIPLES OF ANTIBIOTIC SELECTION (IDSA Guidelines, Sanford Guide, Johns Hopkins Abx Guide)

Consider the *substrate*:
- Is the patient **immunocompromised**? Age, DM, meds (e.g. ≥ 20 mg pred QD x 2 weeks), HIV, neutropenia, ESLD, ESRD.
- Is the patient **at risk** for any particular kind of infection? Think about prostheses, lines, altered anatomy, behaviors, and recent hospitalizations.

Consider the *tempo/severity*:
- Is the patient **unstable**? If so, start broad spectrum antibiotics quickly; *time to antibiotics correlates with mortality in septic shock.*

Consider the *syndrome:*
- What **evidence** is there of infection? *e.g.,* fever, localizing symptoms, leukocytosis, hypotension, inflammatory markers
- What is the likely **source**? *e.g.,* PNA, UTI, SSTI, bone & joint infection, CLABSI, GI
- If a source is evident, what are the **most common pathogens**?
- Might there be **metastatic foci of infection**? *e.g.,* blood, CSF, valves, bones, joints

Other considerations:
- If safe, **cultures before antibiotics** to improve diagnostic yield.
- Review the patient's **prior microbiology** to assess for history of resistant bugs
- **Broader ≠ better**. We routinely overcover for MRSA, *Pseudomonas*, and anaerobes.
- **Longer ≠ better**. Emerging studies show shorter duration is noninferior in a number of infections.
- **Fever ≠ infection.** Don't forget to consider inflammation, thrombus, medications, *etc.*
- **Narrow** and **convert to PO** when able (if indicated). Use the MGH antibiogram and, eventually, the susceptibility report.
- **Inadequate source control** is a common cause of treatment failure. Remove the line, drain the abscess, etc.

Antibiotic pharmacokinetic properties:
- Good **CNS penetration** *(not exhaustive and dose-dependent)***:** PCN, ampicillin, oxacillin, CTX, imipenem, mero, metronidazole, doxy (Lyme only), LZD. Vanc moderate but improves with severe meningeal inflammation. MGH Antibiotic penetration tip-sheet
- High **oral bioavailability** (*i.e.*, PO=IV) *(not exhaustive)*: metronidazole, linezolid, doxy, FQs, azithro, clindamycin
- High **urinary accumulation** (*not exhaustive*): PCN, amoxicillin, cefazolin, cipro/levoflox, aminoglycosides, vancomycin

Additional resources:
- For up to date MGH Antibiogram & Guidelines for Empiric Therapy for Inpatients (VPN needed for MGB handbook links)
- Surviving Sepsis Campaign – 2021 Adult Guidelines
- MGB dosing guidelines for antimicrobials

General spectrum of coverage for common IV β-lactams

| *Gram positives* | *Gram negatives* | *Anaerobes* | *Pseudomonas* |
|---|---|---|---|
| penicillin / cefazolin | | | |
| ampicillin | | | |
| ceftriaxone / cefotaxime | | | |
| cefepime | | | |
| ampicillin-sulbactam | | | |
| piperacillin-tazobactam / meropenem | | | |

Commonly encountered Bugs & Drugs

| Microbe | Antibiotics | Notes |
|---|---|---|
| *Staphylococcus aureus* | MSSA: IV nafcillin, cefazolin, oxacillin<br>PO cephalexin, cefadroxil | -Cefadroxil is BID, cephalexin is QID<br>-β-lactam >>>> vancomycin |
| | MRSA: IV vancomycin, daptomycin, ceftaroline<br>PO doxy, TMP-SMX, LZD, clinda<br>Long-acting dalbavancin, oritavancin | -Dapto is inactivated in lung by surfactant<br>-LZD highly bioavailable if PO and well tolerated for short course (<2wk) |
| Group A streptococci | -penicillins | -Add clinda if concern for TSS |
| Enterococci | -ampicillin, vancomycin, daptomycin, linezolid<br>-fosfomycin, nitrofurantoin (UTI only) | -MGH antibiogram shows good *E. faecalis* susceptibility to ampicillin<br>-If *E faecium*, more likely to harbor resistance |
| *Pseudomonas aeruginosa* | -IV cefepime, ceftazidime, piperacillin-tazobactam, imipenem, meropenem, aminoglycosides<br>-PO ciprofloxacin, levofloxacin | -Ertapenem does not cover PsA<br>-MGH defines resistant PsA as R to ceftaz and may need ID guidance for abx choice |
| MDR GNRs (AmpC inducers and ESBL producers) | -IV cefepime, imipenem, mero, aminoglycosides<br>-PO fluoroquinolone, TMP-SMX | -AmpC inducible resistance: *HECK YES: Hafnia alvei, Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes, Yersinia enterocolitica*<br>-Cefepime success highly-dependent on MIC |
| Cell wall-deficient ("atypicals") | -doxycycline, azithromycin, levofloxacin | -*Mycoplasma, Chlamydia, Legionella* |
| Anaerobes | -IV pip-tazo, amp-sulbactam, carbapenems<br>-PO metronidazole, clinda, amox-clav | -Think twice if anaerobic coverage needed<br>-Vanc+cefe does NOT cover anaerobes |

| Suspected Process | Microbiology | Empiric Antimicrobial Therapy | Notes |
|---|---|---|---|

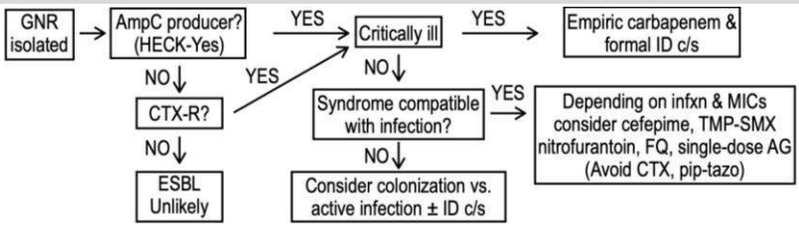
# Infectious Disease — Empiric Antimicrobials

| | | | |
|---|---|---|---|
| **Meningitis** (CID 2004;39:1267; CID 2017;64:e34) | -Generally: *S. pneumoniae*, HSV, other viral > *N. meningitidis*<br>-If >50 y, immunocompromised, EtOH: *Listeria monocytogenes*<br>-If hardware or nosocomial: Staph, PsA; *C. acnes* if VP shunt | -vancomycin+ CTX 2g Q12<br>-Age>50yrs: add ampicillin<br>-HSV: add acyclovir<br>-Healthcare-assoc, hardware, VP shunt, PWID: vancomycin + cefepime or meropenem | -If *S. pneumoniae*, add dexamethasone (reduces neurologic sequelae)<br>-Remove hardware if possible (*e.g.,* place external ventricular catheter in place of shunt) |
| **Community Acquired Pneumonia (CAP)** (AJRCCM 2019;200:e45) | -viral > bacterial<br>-*Legionella*, *Mycoplasma*, *Chlamydia* ("atypical")<br>-*S. pneumoniae* (classic lobar PNA), *H. influenzae*, *Moraxella catarrhalis*<br>-*S aureus* or *Legionella* (usually very sick)<br>-*Klebsiella* (EtOH) | -Healthy outpt: amox > azithromycin or doxy<br>-Outpt with comorbidities: Amox-clav+azithro or doxy, cefpodoxime+azithro or doxy, or levoflox alone<br>-Most inpatients: CTX+azithro, or levo alone<br>-Prior MRSA/PsA OR IV abx in past 90 d: vancomycin+cefepime+azithromycin | -Send influenza and viral testing<br>-Consider local azithromycin resistance<br>-Can substitute doxycycline for azithro<br>-Levofloxacin preferred for structural lung disease outpatient<br>-If postviral, consider *S aureus*<br>-If empyema, **needs drainage**<br>-Add anaerobic coverage if there is an abscess or empyema. Aspiration is not an indication for anaerobic coverage |
| **Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP)** (CID 2016;63:e61) | -CAP organisms, *S aureus*, GNRs including PsA, *Stenotrophomonas*<br>-Viruses | -cefepime or ceftazidime<br>-If received abx in last 90 days: vanc+cefepime | -Consider local MDRO prevalence<br>-Send viral and influenza testing |
| **Endocarditis** (Circ 2015;132:1435) | -Native: *S aureus*, strep, enterococci, few GNRs, HACEK<br>-Prosthetic: *S aureus*, *S. epidermidis* most likely; others above rarely | -Native: vancomycin+ceftriaxone<br>-Prosthetic: vancomycin+gentamicin+rifampin, but ask ID | -Early ID consult improves mortality and can help guide empiric therapy early based on patient characteristics!!<br>-MSSA: β-lactam >>> vancomycin |
| **Cholecystitis/ Cholangitis** (CID 2010;50:133) | -*E. coli*, *Klebsiella*, enterococci, anaerobes<br>-Often polymicrobial | -CTX+MNZ, cipro+MNZ<br>-Nosocomial/severe: cefepime+MNZ, piperacillin-tazobactam, imipenem, meropenem | -Source control is key (e.g. ERCP)<br>-Vanc or pip-tazo if c/f enterococci<br>-Often polymicrobial → broad abx for 48 h even if BCx growing only 1 organism |
| **Other Intra-abdominal** (CID 2010;50:133) | -Abscess: GNRs, anaerobes, enterococci, *Candida*, polymicrobial<br>-Diverticulitis: GNRs, anaerobes, rarely enterococci, polymicrobial | -CTX+MNZ, ciprofloxacin+MNZ if low risk<br>-Nosocomial/severe: cefepime+MNZ, piperacillin-tazobactam, imipenem, meropenem | -Prompt source control is critical. Drain if abscess. Surgical evaluation if peritonitis, perforation, fistula, recurrent diverticulitis<br>-clindamycin avoided if *B fragilis* due to resistanxce |
| **Spontaneous Bacterial Peritonitis (SBP)** (Hep 2021;74:1014) | -Enteric GNR, streptococci, enterococci; rarely anaerobes | -ceftriaxone, cefotaxime | -Ciprofloxacin reserved for patients w/ β-lactam allergies and used for ppx<br>-Initiate ppx after first episode of SBP |
| **UTI** (non-pregnant) (CID 2011;52:e103; CID 2010;50:625) | -Uncomplicated: *E.coli*, *Klebsiella*, *S. saprophyticus*, *Proteus*<br>-Complicated (*i.e.* systemic infxn, pyelo): above + enterococci, PsA, *Serratia, Providentia*<br>-CAUTI: above + other GNRs | -Uncomplicated: nitrofurantoin, TMP-SMX, fosfomycin<br>-Complicated: CTX, ciprofloxacin/levofloxacin<br>-CAUTI: vancomycin+ceftriaxone<br>-Cefepime if c/f PsA, carbapenem if c/f ESBL | -Do not treat asymptomatic bacteruria in nonpregnant immunocompetent patients<br>-Exchange Foley, consider repeat UA/UCx 48 h later if CAUTI |
| **Osteomyelitis** (CID 2023;ciad527; CID 2015;61:e26) | -Hematogenous source: *S aureus*<br>-Direct inoculation/vascular: *S aureus* > strep, PsA, GNR, enterococci, *Eikenella* (human bite), *Pasteurella* (animal bite) | -No abx if HDS, no signs c/f cord compression, and awaiting bone biopsy<br>-Vanc+CTX; cefepime if DM/PAD ulcer or direct inoculation | -Dx: CRP, ESR, MRI, bone biopsy<br>-Debride w/ bone bx+cx<br>-Amp-sulbactam if originated from bite |
| **Septic Arthritis** (Infect Dis Clin North Am 2017;31:203) | -staph, strep, *N. gonorrhoeae*, PsA (PWID), Lyme | -vancomycin+ceftriaxone (consider cefepime if PWID or other risk factor for PsA)<br>-If gonorrheal: ceftriaxone+doxycycline | -Dx: fluid aspirate with >50k WBC<br>-Consult ortho for joint washout asap<br>-Blood+joint fluid cx prior to abx |
| **Skin/Soft Tissue (SSTI)** (CID 2014;59:e10) | -Impetigo: *S aureus* > strep<br>-Cellulitis/Erysipelas: strep > staph<br>-Nec fasc: strep, *C. perfringens*, MRSA | -Purulent: vancomycin<br>-Non-purulent: cefazolin<br>-Bite: ampicillin-sulbactam<br>-Nec fasc: vanc+ [pip-tazo or mero] ±clinda<br>-DM/PAD ulcer: vanc + [CTX or cefe] | -If abscess, drain<br>-If nec fasc (rapid spread, crepitus, pain out of proportion), URGENT SURGICAL EVAL<br>-If nec fasc, clinda meant to inhibit exotoxin production |
| **Septic shock**, no source (Intensive Care Med 2021;47:1181) | -GNRs, *S aureus,* streptococci, PsA, anaerobes<br>-Consider TSS | -vanc+CTX or cefe, vanc+pip-tazo<br>-Concern for MDRO: carbapenem<br>-Critical illness: consider 1 dose aminoglycoside<br>-TSS: add clindamycin | -Start antibiotics within 1 h of recognition<br>-Amikacin generally the aminoglycoside of choice for critical illness |
| **Febrile Neutropenia** (T≥100.4F & ANC<500) (CID 2011;52:e56) | -Source not identified ~70% of time<br>-When source is identified, 60% GPCs (CoNS > *S aureus*, streptococci, enterococci), 40% GNRs (*E. coli*, *Klebsiella* > PsA) | -cefepime per MGH FN pathway<br>-Suspect CLABSI +SSTI, PNA, mucositis: add vancomycin<br>-HDUS, GPCs on BCx: add vancomycin<br>-Persistent fevers >4-7 d: consider micafungin | -Start antibiotics within 1 h of fever<br>-If afebrile x 72 h or ANC > 500, consider de-escalation<br>-Oral ppx: consider levo or amox-clav + cipro for prolonged neutropenia |

# Infectious Disease — Multidrug Resistant Organisms

## MDR GNRs (CID 2024:ciae403)

**AmpC β-Lactamase (cephalosporinase)**




- Mechanism: Inactivate 3rd gen cephalosporins & pip-tazo. Can be constitutive or inducible (turned on by accumulating cell wall fragments due to β-lactam inhibition of PCN binding proteins).
- Pathogens: Inducible AmpC producers include: **HECK-Yes: H**afnia alvei, **E**nterobacter cloacae, **C**itrobacter freundii, **K**lebsiella aerogenes, **Y**ersinia enterocolitica
  - Organisms don't equally produce AmpC: *E. cloacae*, *K. aerogenes* (formerly *E. aerogenes*), & *C. freundii* (highest risk, 20% resistance rate), *S. marcescens*, *M. morganii*, or *Providencia* spp. (5% resistance rate, treat based on AST) (CID. 2024:ciae403).
- Treatment**:** Don't treat *E. cloacae*, *K. aerogenes* & *C. freundii* w/ 3rd gen ceph (*e.g.,* CTX), even if reported as "susceptible"
  - *Uncomplicated cystitis*: **TMP-SMX** or **nitrofurantoin;** alt: Fosfomycin (*E. coli*), single-dose aminoglycoside, or FQ.
  - *Complicated UTI/non-UTI*: ***Cefepime*** if MIC ≤ 2 µg/mL, TMP-SMX, FQ; Alt: carbapenem, aminoglycoside.
  - *Critically ill*: carbapenem. Cefepime noninferior to meropenem when source control achieved (CID. 2013;57:781).

**Extended-Spectrum Beta Lactamases (ESBL)**

- Mechanism: Plasmid-mediated, inactivate most β-lactams (penicillins, cephalosporins, aztreonam).
- Pathogens: *Klebsiella spp.* (#1), *E. coli* (#2), *Proteus mirabilis* (#3), other GNR
- Risk Factors: Abx w/in past 6 mo, long hospitalization, nursing home, >65 yo, lines/catheter/tubes/ventilator, TPN, HD
- Laboratory detection: MGH infection control defines potential ESBL as a GNR resistant to ceftriaxone.
- Treatment: Avoid PCNs and cephalosporins (including pip-tazo) even if "susceptible" (JAMA 2018;320:984)
  - *Uncomplicated cystitis*: **TMP-SMX** or **nitrofurantoin**; alt: Fosfomycin (*E. coli*), single-dose aminoglycoside, or FQ.
  - *Complicated UTI*: **TMP-SMX** or **FQ**; alternative: Carbapenems
  - *Non-UTI*: empiric **imipenem-cilastatin** or **meropenem**. Avoid ertapenem in critical illness and hypoalbuminemia

**Carbapenem Resistant Enterobacteriaceae (CRE)**

- Mechanisms: Inactivating carbapenemase, porin loss (limits penem entry), efflux pump extrusion, or combination of factors
- Risk Factors: Cephalosporin or carbapenem use in past 3mo (**penem exposure not required**), medical care in India/Pakistan
- Laboratory detection: Suspicious when MIC > 2 µg/mL for imipenem, meropenem, or ertapenem
- Treatment: Preferred option is usually ***ceftazidime-avibactam*** (+aztreonam if care in India/Pakistan); **C/s ID**
  - Meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also active
  - Alternatives may include extended-infusion meropenem (if MIC ≤ 1 µg/mL*)*, aminoglycoside, or tigecycline [not for UTI/bacteremia]**.**
  - *Uncomplicated UTI*: FQ, TMP-SMX, or single-dose aminoglycoside if susceptible. If complicated, FQ or TMP-SMX

**Carbapenem resistant *Acinetobacter baumannii* (CRAB)**

- Treatment: Preferred sulbactam-durlobactam + mero or imipenem-cilastatin; Alt: high-dose amp-sulbactam + 2nd agent

**Difficult-to-Treat Resistance *Pseudomonas aeruginosa* (DTR-PsA)**

- Definition: Non-susceptible to pip-tazo, ceftaz, cefepime, aztreonam, fluoroquinolone, meropenem, AND imipenem-cilastatin
- Treatment: ***Ceftolozane-tazobactam*** usually preferred but other options (e.g. ceftaz-avibactam, cefiderocol, etc.); **C/s ID**

## METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

**Community-associated MRSA**: no healthcare exposure, SSTI in young & healthy patient
Risk Factors: HIV, PWID, prior antibiotic use; outbreaks: incarceration, military, sports, sharing needles/razors
**Healthcare-associated MRSA:** occurs >48h following hospitalization or within 12mo of healthcare exposure

- Risk Factors: recent hospitalization/surgery, HD, LTC facility residence
- Nasal swab: NPV in CAP = 96.5% (CID 2018;18:1) if ⊖ consider d/c MRSA coverage. MGH use Antimicrobial De-escalation Guidelines in HAP/VAP; emerging evidence that NPV for Staph infection at other sites is also high (CID 2020;71:1142).

**Treatment**

- Check the vanc MIC: Vanc susceptible if MIC ≤2 µg/mL (though ↑tx failure and mortality when MIC = 2 µg/mL), Vanc-intermediate (VISA) if 4 µg/mL ≤ MIC ≤ 8 µg/mL, Vanc-resistant (VRSA) if MIC ≥16 µg/mL
- Serious infections (*i.e.* bacteremia): **vancomycin** (consider AUC dosing, trough ~15-20) and **ID consult** (J infect. 2016;72:19). If persistent bacteremia or MIC ≥ 2 µg/mL, consider switching to **daptomycin** (**not in PNA** or meningitis), adding ceftaroline (Antimicrob Agents Chemother. 2018;62:01554), or both (Open Forum Infect Dis 2019;7:538).
- Mild infections (*e.g.,* SSTI): TMP-SMX, doxycycline >> clindamycin (increased resistance at MGH); linezolid

## VANCOMYCIN RESISTANT ENTEROCOCCI (VRE)

- *E. faecium*: often resistant & generally less virulent. *E. faecalis*: more virulent but highly Amp$^S$ at MGH.
- Definition: common resistance to ampicillin & vancomycin
- RFs: prior abx, Foley, indwelling lines; proximity to other VRE pts; long hospitalization/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): daptomycin, linezolid; **ID c/s**
  - Uncomplicated UTI: fosfomycin x1 (consider repeat dose on days 4 and 7) or nitrofurantoin

## COMMUNITY ACQUIRED PNEUMONIA (CAP) (AJRCCM 2019;200:45)

- **Definition**: PNA acquired in the community, including patients from nursing homes, dialysis, or outpatient clinic exposure
- **Diagnosis**: new infiltrate on chest imaging AND signs/sx (e.g. fever, cough, leukocytosis, Δ sputum, hypoxemia)
  - Elderly at ↑risk of blunted signs/sx but also ↑prevalence of atelectasis/aspiration
  - Radiographic consolidation/infiltrate NOT specific for bacterial vs viral PNA. Neutropenic patients may not have CXR findings.
- **Triage**: CURB-65 (Confusion, BUN>19, RR>29, SBP<90 or DBP <60, age≥65) → outpatient if score 0-1. Pneumonia Severity Index (PSI) more comprehensive → outpatient if <70, inpatient if >90
- **Severe CAP (ATS/IDSA Criteria)**: **1 Major**: pressor need or mech vent, OR **3 Minor**: RR≥30, P:F≤250, multilobar infiltrates, confusion, BUN>19, WBC<4 (not due to chemo), plt<100, T<36°C, HoTN requiring aggressive fluid resuscitation
- **Micro**: S. pneumo, respiratory viruses > S. aureus (common in severe CAP) H flu, GNRs, Legionella. Severe CAP: S. pneumo, S. aureus, PsA, Legionella (NEJM 2015;358:415; CritCareMed 2022;50(7))
- **Work-up (inpatient)**:
  - **Sputum cx and Gram stain** (ET aspirate if intubated): Obtain if inpatient + severe CAP or resistance risk. Adequate sample if >25 PMN and <10 SEC. NOTE: "abundant squamous cells" or squamous cells count > polys suggests the sample is saliva
  - **Blood cultures**: controversial benefit, positive <10-20% of inpatient PNA
    - Obtain Sputum cx and Bcx if: severe CAP, empiric treatment for MRSA/PsA, prev. MRSA/PsA, or hosp. w/ IV abx ≤90d
  - **Procalcitonin (PCT)**: ↑ in acute resp. infxn from bacterial causes. No validated threshold to distinguish bacterial vs. viral infxn. (ATS 2019;200:45). No clear role in guiding whether to start abx (CID 2020;70:538).
  - **Legionella urine Ag** (Sn 70%, Sp 99%); detects only serogroup 1 (80-90% in US). Check 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 *(see URI page for tx indications)*
- **IDSA/ATS CAP Empiric Treatment** (NOTE: additional considerations for immunocompromised; Chest 2022;158:1896)

| Outpatient | Preferred | Alternative/Other info |
|---|---|---|
| **No Comorbidities or MRSA/PsA RFs** | Amox 1g TID OR doxy 100mg BID OR macrolide (azithro OR clarithro) (**if local resistance <25%**) | **NOTE: U.S. has high rates of macrolide- and doxy-resistant S. pneumo** |
| **Comorbidities*** | [Amox-clav BID *AND* azithro] OR levofloxacin monotherapy | Cefpodoxime or cefuroxime can replace amox-clav; doxy can replace azithro |
| **Inpatient** | **Preferred** | **Alternative/Other info** |
| **Non-Severe** | (β-lactam [CTX] *AND* macrolide [azithro]) *OR* levofloxacin monotherapy | Amp/sulb can replace CTX; doxy can replace azithro if macrolide or fluoroquinolone not tolerated |
| **Severe/ICU** | β-lactam (CTX 1-2g QD) *AND* (azithro OR levofloxacin) | **In ICU, azithro >> levofloxacin (anti-inflamm. effect)**; consider other agents for drug-resistance (see below) |
| **MRSA/PsA RFs** | Vancomycin *AND* cefepime | 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. | | |

- **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**: cefepime, ceftazidime, pip-tazo, mero/imipenem; double coverage usually not necessary
  - MRSA: GPC clusters on gram stain, recent flu-like illness, necrotizing PNA/cavitation/empyema, ⊕ nasal swab, risk factors for colonization (ESRD, PWID, prior abx [esp. fluoroquinolones]). Tx: vancomycin or linezolid
- Anaerobic coverage: only if suspicion for empyema or lung abscess, (see HAP/VAP & Aspiration Pneumonia)
- Steroids: Recent RCT showed benefit in severe CAP (NEJM 2023;388:1931). Meta-analysis showed steroids may lower risk of MV, no sig. impact on mortality (Chest 2023;163:484). IDSA/ATS do not have rec for steroids. **AVOID** steroids 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 no clinical stability, extend course & evaluate for resistant pathogen, complication (empyema, abscess), alternative 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 older adults, 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 (if RFs)
- **Parapneumonic effusion**: exudative, develops adjacent to a pneumonia, 20-57% of PNA hospitalizations (CID 2007;45:1480). Appropriately sized effusions need diagnostic thora for evaluation esp if concern for infxn + need for extension of abx course.
  - **Definitions:** Uncomplicated (~pH >7.2/glucose >60, ⊖ GS/Cx) → complicated (requires drainage, pH <7.2/glucose ↓, still ⊖GS/Cx) → empyema (requires drainage, frank pus, + GS/Cx).
  - **Management**: Uncomp. effusions ok for abx alone if <1/2 hemithorax & free flowing; consider therap. thora if symptoms. Chest tube after diag. thora if: empyema, loculation, >1/2 hemithorax, thickened parietal pleura, sepsis w/ suspected pleural source (Chest 2000;118:1158; Ann Thor Surg 2018;105:1589)
  - 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 | |

***Ddx also includes non-infectious ventilator-associated events (VAEs) such as atelectasis, ARDS, pulmonary edema, and pulmonary embolism (Ann Transl Med. 2018; 6: 425; Infect Control Hosp Epidemiol. 2017; 38:867)

**Common microbiology**: enteric GNRs, MRSA/MSSA, *PsA*, *Acinetobacter*. 1/5 cases viral (SRCCM 2022 43:295)
**Workup**: CXR, sputum Cx, BCx, viral testing, 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
- Pulmonary toilet (oral hygiene including daily tooth brushing > oral and subglottic suctioning, mucolytics, etc.) (JAMA 2024; 184:131, Cochrane Database 2020; 12: CD008367)
- For patients on vent ≥72 hrs, 3 days of inhaled amikacin may decrease rate of VAP (NEJM 2024; 2052-202)

| Antipseudomonal β-lactams | Antipseudomonal non-β-lactams | Anti-MRSA agents* |
|---|---|---|
| - Cefepime<br>- Ceftazidime<br>- Pip-tazo<br>- Meropenem<br>- Aztreonam (only if severe PCN allergy: see MGH handbook) | - Levofloxacin/ciprofloxacin (PsA only ~70% susceptible to levo and ~80% to cipro at MGH as of 2024)<br>- Tobramycin 5-7mg/kg IV x1, then dose by level (contact pharmacy, Ellucid)<br>- Polymyxin B (call ID) | - Vancomycin<br>- Linezolid |
| Check MGB antimicrobial dosing guidelines to renally dose *Dapto cannot be used for MRSA coverage in pulmonary infections | | |

- **Tailoring therapy**:
  - Improvement after 48h or pathogen ID'd: narrow abx based on cx data and d/c MRSA+PsA coverage if possible. ⊖ MRSA swab w/ 96% NPV for MRSA infection, most evidence comes from swab on admission (CID 2018;18:67; CID 2020;71:1142). VAP: ⊖ tracheal aspirate NPV 94%, consider d/c abx after 72h (IJID 2010;14:18)
  - No improvement after 48h: consider broadening to cover MDROs and consider other sites of infection/abscess or non-infectious causes of clinical syndrome
  - MGH Antimicrobial De-Escalation and Time-Out Guidelines
- **Duration**: **7d**. Consider serial procalcitonin → d/c abx when <0.25ng/mL (ERJ 2009;34:1364; Cochrane Rev 2011;10)

## ASPIRATION PNEUMONIA (NEJM 2019;380:651)

- **Definition**: pneumonia secondary to excessive secretions, particulate matter, or fluid into airways. Micro-aspirations are common and aspiration pneumonia as a distinct clinical entity remains unclear. Aspiration PNA/pneumonitis are often result of larger volume/frank aspiration events
- **Predisposing factors**: AMS/dementia, esophageal dysmotility, post-bronchial obstruction, post extubation, gum disease/poor dentition, seizure, tube feeding
- **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, Sputum Cx (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 if not severely ill, pip-tazo if severely ill, amox-clav if outpatient; *alternative*: (CTX+MNZ) *OR* clindamycin. If failure to improve on normal therapy; consider imaging to assess for abscess/empyema; may need source control.
  - **Duration**: **7d** unless complicated by cavitation/abscess/empyema
- No clear clinical benefit for abx for ppx after aspiration (CID 2018;67:513)

## ASPIRATION PNEUMONITIS

- **Definition**: aspiration of chemical substances into the airways *without* associated 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**: no mortality benefit in initiating antibiotics in a patient with aspiration pneumonitis. It is clinically difficult to distinguish from PNA in the acute setting (as pneumonitis can cause fever & transient hypoxemia), so frequent reassessment required to determine whether antibiotics needed for an aspiration-related pneumonia

# Infectious Disease Viral Respiratory/Head & Neck Infections

## VIRAL RESPIRATORY INFECTIONS (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 select immunocompromised hosts, consider reactivation of latent viruses (e.g. CMV) if not on antiviral ppx
  - Transmission: hand contact, small droplets that become airborne, large droplet, peak viral shedding at 2-3d of illness
- **Presentation**
  - Symptoms: nasal congestion, rhinorrhea, dry/sore throat, cough, fever, conjunctivitis, myalgias w/ sx peaking at 3-5d and lasting 10-14d (if significant systemic illness consider influenza, COVID-19 >> measles, Hantavirus)
  - Complications: bacterial PNA (occurs in ~1/800 w/ initial improvement → worsening after ~7d, micro: S. pneumo, S. aureus), asthma/COPD exacerbation, secondary bacterial sinusitis (occurs ~1/50), otitis media, ARDS
- **Diagnosis**
  - Clinical diagnosis that generally does not require microbiological testing except for influenza and COVID-19
  - Resp. viral panel: at MGH NP swab PCR for COVID-19, Flu A/B, RSV; can help avoid unnecessary abx; collect within 5d of sx onset. Consider extended resp viral panel for immunosupp or high clinical suspicion with negative limited viral panel
  - Influenza testing: (IDSA: CID 2019;68:895)
    - RT PCR most sensitive and specific; can differentiate A, B and subtypes
    - Rapid Ag test 62% Sn, 98% Sp (<15min); during season ⊖ test does not exclude, not sufficient to stop tx
- **General Viral URI Treatment**
  - Sx management with decongestants, nasal sprays, anti-inflammatory agents, humidified air. NO role for ppx abx
  - COVID-19 specific treatments: remdesivir (NEJM 2020;383:1813), nirmatrelvir-ritonavir (NEJM 2022;386:1397), etc. in select patients. If using nirmatrelvir-ritonavir, ensure to check drug-drug interactions before initiating therapy. See MGB 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: hospitalized pts and outpts w/ severe or progressive dz regardless of illness duration, ↑risk (age >65, long-term care facility resident, pregnant, <2 wks post-partum, immunosuppressed, cirrhosis, DM, CHF/CAD, CKD, COPD, SCD, asthma, BMI >40, neuro dz) also regardless of illness duration
    - Consider: outpts with sx <48h or those with high-risk household members
  - Prophylaxis: oseltamivir 75mg qd x7d if ≤48h post-exposure (x14d ± additional 7d after last case if outbreak at long-term care facility); switch ppx → treatment dosing if sx develop (IDSA: CID 2019;68:895)

## HEAD AND NECK INFECTIONS (Principles of Crit Care. Chow AW. 5th edition. 2023)

- 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 PWID
- Diagnostics: blood cultures, **CT neck w/ contrast**, MRI (consider to evaluate for osteo), IR or ENT for tissue or abscess culture
- Empiric Treatment: varies based on likely source; odontogenic – amp-sulbactam or CTX+MNZ, otogenic - cefepime+MNZ, sinogenic - vancomycin+CTX+MNZ. **Involve ENT early** for drainage and airway monitoring
  - **Submandibular space** (Ludwig angina): sources- periodontal infection, peritonsillar abscess, parotitis; p/w mouth pain, "double tongue," drooling, dysphagia can rapidly progress to airway compromise; polymicrobial esp viridans strep
  - **Internal jugular septic thrombophlebitis** (Lemierre syndrome): pharyngitis and septic emboli (esp lungs). Most commonly *Fusobacterium necrophorum* or viridans strep. Treat with (pip-tazo OR CTX+MNZ) ± anticoagulation
  - **Deep neck space**: involving retropharyngeal, "danger," or 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 Ophthalmia 2018;63:505)

| | Preseptal/Periorbital | Orbital |
|---|---|---|
| Definition | Infection of anterior eyelid (not orbit or ocular structures) | Infection of orbit contents (fat, ocular muscles) but not the globe |
| Pathogenesis | Local trauma (e.g. scratch or insect bite) | Rhinosinusitis, oral abscess, dacryocystitis, local trauma, direct inoculation, ophthalmic surgery |
| Organism | Staph aureus, Strep spp. | Generally polymicrobial. Staph aureus, Strep spp; in immunosuppressed pt, consider Mucor and Aspergillus |
| Symptoms | Eyelid pain, edema, erythema ± chemosis & fever | Preseptal sx + pain with eye movement, proptosis, ophthalmoplegia w/ diplopia, fever & chemosis common |
| Diagnosis | Clinical; CT orbit & sinus to r/o orbital cellulitis | Clinical + CT orbit & sinus, blood cx; LP if c/f CNS extension, MRI if c/f cavernous sinus thrombophlebitis |
| Empiric Treatment | Augmentin 875mg q12h. If hx of skin trauma or no improvement in 24 hrs, add Bactrim 1-2 DS q12h for MRSA coverage. Clinda not recommended. | Vancomycin + CTX; add MNZ if c/f CNS involvement or odontogenic/sinogenic origin, involve ophtho early |
| Complications | Rare: eyelid necrosis, amblyopia | Vision loss, orbital/subperiosteal abscess, CNS spread |

# Infectious Disease — Urinary Tract Infections

## Asymptomatic Bacteriuria

**Definition**: bacteriuria (≥$10^5$ CFU/mL) w/o sx referable to a UTI, irrespective of pyuria

- **Treatment**: asymptomatic bacteriuria or pyuria should NOT be treated [*exceptions*: pregnancy, <1-2mo s/p renal transplant (controversial; OFID 2024 11:ofae342), rx prior to urologic procedures which traumatize mucosa] (IDSA: CID 2019;68:1611)

## UTI

**Clinical features**: frequency, urgency, dysuria (premenopausal), incontinence, nocturia, suprapubic tenderness in otherwise healthy nonpregnant women. In men w/ UTI sx, consider a dx of prostatitis +/- DRE for prostatic tenderness

↓

**Complicated UTI?** Acute UTI + any of: fever, chills/rigors/sx of systemic illness, CVA tenderness/flank pain, pelvic or perineal pain (evidence of infection outside of bladder), pregnancy, or renal transplant. Otherwise, not automatically complicated.

### No ↓

**Uncomplicated UTI (Cystitis)** (JAMA 2014; 312:1677)

- **Diagnosis**: clinical; UA can be used to confirm; pyuria (>10 WBC); nitrite and LE both ⊕ on dipstick → Sn 68-88%
  - Women: dysuria + ↑frequency w/o vaginal discharge/irritation → >90% likelihood of UTI. Outpatient, UA unnecessary unless immunocompromised or RFs for complicated UTI
  - Absence of pyuria *strongly argues against* cystitis
  - Nitrite: ⊕ w/ Enterobacterales (convert nitrate → 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. Saprophyticus*, *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, Cefpodoxime) x7d, single dose aminoglycoside if c/f MDRO (Antimicrob 2019;63:e02165)
  - Avoid NFT if CrCl <40
  - Avoid empiric T/S if resistance >20% (*E. coli* resistance ~30% at MGH in 2024)
  - Avoid T/S and NFT in 1st trimester and term for pregnancy

### ↓Yes

**Complicated UTI**

- 30% w/ UTI **and** fever are bacteremic [usually older, flank / suprapubic pain, ↑CRP, HoTN (NEJM 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: **cipro** 500mg BID OR **levo** 750mg x5-7d OR **T/S DS** BID x7-10d. Can give 1x IV CTX prior to oral tx.
  -Inpt: **CTX** OR **cefe**; penem if prior ESBL. Narrow to oral if improving. Duration for inpt: depends on clinical course & oral agent chosen (5-7d for FQ; 7-10d for T/S; 10-14d for β-lactam), consult ID and IR for associated abscesses
  - Avoid **NFT** & **fosfomycin** (poor for upper GU track)
  - Remove/replace coated urologic devices
  - Prostatitis: **FQN** preferred for better penetration (can also consider TMP-SMX); tx duration up to **6w**

## Catheter-Associated UTI (CAUTI) (IDSA: CID 2010; 50:625)

- **Definition**: leading healthcare-assoc. infection; requires: (1) s/sx of UTI 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 >2d) *OR* midstream voided specimen from pt whose catheter was removed within previous 48h
  - In pts w/ neurogenic bladder and ↓ sensation, other signs of UTI include new onset incontinence, autonomic hyperreflexia, malaise, lethargy, bladder pain
- **Prevention**: restrict catheters (see appropriate indications), remove catheters ASAP; consider straight cath. See Ellucid Policy
- **Dx**: do not screen asx patients; pyuria, turbidity, odor cannot differentiate asymptomatic bacteriuria from CAUTI
  - **Remove/Replace** catheter ASAP, obtain repeat UA/UCx from new catheter PRIOR to abx (only if CAUTI – not for asx bacteriuria screening). Catheters may have biofilm that acts as a reservoir for microorganisms
  - Purple urine bag syndrome: occurs due to byproducts from bacterial enzymes in urine; benign and ≠ UTI
- **Micro**: same as complicated UTI, with addition of *Candida* (see below); can be polymicrobial
- **Treatment**: If recent catheterization/instrumentation, h/o MRSA in urine, add vanc, then narrow pending culture results. Duration: 7d if improving; 10-14d if delayed response

## Candiduria (IDSA: CID 2016;62:e1)

- Asymptomatic colonization common; only treat if symptoms present OR neutropenic OR before urologic procedure
- Tx: **Fluc** 200-400mg (if susceptible) PO qd x14d *OR* for resistant *C.glabrata* or *C. krusei*, **Amphotericin** x1-7d

## Recurrent UTI

- Behavior Δs: 2-3L water intake daily, post-coital voiding, avoid spermicide use, wiping front to back for pt. w/ female anatomy
- 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 if no temporal relation to sexual activity (Cochrane Rev 2004).
- Other inventions include: Vaginal estrogen for post-menopausal women, methenamine (Pharm. 2023;44:197), and cranberry products (Cochrane Rev 2023). D-mannose not shown to decrease UTIs (JAMA 2024;184:619)
- 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, often poorly demarcated. May have lymphangitis, LAD, vesicles/bullae, fever (variable), leukocytosis (variable)
- **Risk Factors**: trauma, venous stasis, chronic edema (esp. lymphedema), immunosuppression (DM, HIV), obesity, PWID, neutropenia, inflammation (eczema, psoriasis, radiation therapy), prior surgery/biopsy, toe web abnormalities
- **Diagnosis**: CLINICAL**.** Can use ALT-70 score to avoid abx. Cannot use if prior abx. (data req to calc: location, age, WBC, HR) (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 (low yield, pos in <10%). Obtain if: systemic tox, extensive involvement, immunosuppression, surgical wounds, special exposures (bites, water), recurrent/persistent cellulitis, extremes of age. 20-30% skin bx return pathogen.
- **Differential diagnosis:** (if "bilateral cellulitis," strongly consider alternative diagnosis)
  - Non-infectious: *inflammatory* (contact derm, drug rxn, Sweet syndrome, gout, bursitis, EN, pyoderma gangrenosum, GVHD); *vascular* (stasis dermatitis, DVT, superficial thrombophlebitis, calciphylaxis), *neoplastic* (leukemia cutis, lymphoma)
    - *Unilateral*: contact derm, gout, drug rxn, vasculitis, insect bite, DVT, vaccine site rxn, erythema ab igne
    - *Bilateral:* stasis derm, lipodermatosclerosis (often heavily pigmented, thickened subq tissue), lymphedema
  - Infectious: abscess, erysipelas (well demarcated, superficial cellulitis involving upper dermis & superficial lymphatics), nec fasc, septic joint/bursa, osteomyelitis, herpes zoster, HSV, Orf virus, erythema migrans, toxic shock syndrome, mycotic aneurysm
    - If abscess present, ddx includes: folliculitis, cyst, hidradenitis suppurativa (often intertriginous skin), lymphangitis

**Treatment**: based on **1) purulence** and **2) severity**. Elevate affected limb. **Erythema may worsen initially**; should improve w/ 72h of abx. **Document daily photos & draw margin lines**. Duration: 5d; up to 14d if delayed signs of improvement

| Severity | Purulent (abscess or fluctuance) | Non-purulent° |
|---|---|---|
| | MRSA >> MSSA > Strep | Strep >> *S. aureus* > aerobic GNRs |
| **Mild** | I&D only | PO: cefadroxil, cephalexin, dicloxacillin, pen VK , amox-clav |
| **Moderate**: systemic signs of infxn OR abscess >2cm | I&D+Cx. Empiric: TMP-SMX *OR* doxy<br>MSSA: diclox *OR* cephalex MRSA: TMP-SMX | IV*:* cefazolin, CTX, pen G<br>Severe ß-lactam allergy: vanc, telavancin |
| **Severe**: systemic signs of infxn *AND* HoTN, immunocomp., rapid evolution, deeper infection, or failed PO tx | I&D+Cx. Empiric: vanc *OR* LZD *OR* dapto *OR* ceftaroline. MSSA: nafcillin *OR* cefazolin | Vanc+(pip-tazo *OR* cefepime+MNZ). Nec fasc or TSS: add clinda for toxin inhibition |
| °Non-purulent w/ **MRSA risk factors*** (prev. MRSA infx/colonization, hosp./surgery/abx in prev 8wks, PWID, penetrating trauma, hemodialysis, HIV, athletes, prisoners, military, LTC facility residents): add empiric PO/IV MRSA coverage (TMP-SMX or doxy)<br>*MRSA incidence increasing and many patients with MRSA infection do not have any risk factors (Med. Clin 2021; 4:723-725) | | |

- **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, burns, macerated ulcer, post-op)
- **Specific associations**: gas gangrene → *C. perfringens;* dog/cat bite → *Capnocytophaga*, *Pasteurella*; animals NOS → *Erysipelothrix*; human bite/PWID → *Eikenella*; freshwater → *Aeromonas*; saltwater→ *Vibrio vulnificus* (esp. cirrhosis)
- **Sporotrichoid spread ddx**: sporotrichosis, Nocardia, NTM (e.g. *M. marinum*), Bartonella, tularemia
- **PWID**: **infxn sources ($H_2O$, syringe, cotton filter, skin flora)**, share safe injection practices/PrEP (resources: CDC 1; CDC 2)

- **Prevention:** Compression therapy: ↓recurrence of cellulitis. Patients should be advised to wear compression stockings daily to shift fluid away from the lower leg (NEJM 2020;383:630)
  - PCN ppx effective for reducing recurrent cellulitis over 6 & 12 month periods, but not once ppx stopped (NEJM 2013 368:1695)

## NECROTIZING SOFT TISSUE INFECTIONS (NEJM 2017;377:2253)

- **Micro**: *Type I*: polymicrobial (mixed aerobes/anaerobes); *Type II*: monomicrobial (usually GAS > *Strep*, *Staph*, *Vibrio*, *Aeromonas*), associated with TSS; *myonecrosis* (i.e., gas gangrene): caused by *C. perfringens*, p/w tissue gas, severe pain, toxin-mediated shock
- **Risk Factors**: immunosupp., DM (e.g. Fournier gangrene), cirrhosis, neutropenia, EtOH, trauma, skin/mucosal breach, PAD
- **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**: CLINICAL. early suspicion and involvement of a **surgeon for surgical exploration** and **ID** is critical
  - LRINEC score ≥6 high suspicion for nec fasc (uses CRP, WBC, Hgb, Na, Cr, glucose); 90% Sn, 95% Sp (CCM 2004;32:1535)
- **Treatment**: urgent surgical debridement + abx: vanc + (mero or cefepime/MNZ or pip-tazo) + clinda (LZD also inhibits toxin production, use if clinda resistant). Adjunctive clinda may improve outcomes (Lancet Infect Dis. 2021;21:697)

## DIABETIC FOOT INFECTIONS (IWGDF/IDSA: CID 2023;ciad527)

- **Severity**: mild (≥2 items: swelling/induration, erythema >0.5 but <2cm around wound, pain, warmth, purulence); moderate (no systemic signs AND erythema ≥2cm from wound margin or deeper than skin involvement); severe (systemic symptoms present)
  **Diagnosis**: Tissue specimen for cx >>> wound cx (only culture after deep debridement; surface cx unhelpful and reflects colonization) - often polymicrobial w/ GPCs>GNRs, anaerobes. If c/f **osteomyelitis** *(see osteo)*
  - Probe-to-bone (to assess for osteo), ESR/CRP, X-ray. MRI if clinical ambiguity despite prior tests. Check pulses/sensation, ABIs (40% have PAD).
- **Treatment**:
  - Mild (rx 1-2wk): oral → target GPCs only (cephalexin, cefadroxil, amox-clav, diclox, levoflox); TMP-SMX or doxy for MRSA
  - Moderate/severe (rx 2-4wk): IV → No complicating features (amox/clav or CTX), recent abx (pip/tazo or erta depending on prior therapy and cx data), macerated ulcer/warm climate (pip-tazo), ischemic limb/necrosis/gas (see necrotizing SSTI), if concern for MRSA (vanc/linezolid/daptomycin)
  - If improving, may de-escalate IV to highly bioavailable PO regimen to complete course of 1-2wk, up to 4 if slow to improve/PAD

# Infectious Disease — Osteomyelitis

## Clinical Manifestations

- **Acute**: <2wk of sx & absence of necrotic bone or sequestrum. *Sx:* localized, dull pain & diminished function, evidence of inflammation (fever/chills/night sweats/erythema). Patients may be afebrile
- **Chronic**: previously failed tx, >3wk sx, presence of bony sequestrum, persistent drainage or sinus tract. *Sx:* pain (absent if neuropathy), erythema, swelling, poorly healing ulcers; *hallmark is necrotic bone.* Fever may be absent
- **Etiologies**: hematogenous seeding (usually monomicrobial) from bacteremia (↑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 PWID) (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
  - Sternoclavicular: anterior chest wall swelling, pain, tenderness; may be mistaken for abscess or atypical cellulitis; can occur via hematogenous spread or post-CT surgery ± mediastinitis
  - Mandibular: usually contiguous spread of oral flora/odontogenic infection; often w/ anaerobes
  - Foot: toe osteomyelitis or osteo a/w ulcer common in DM (IWGDF/IDSA: CID 2023;ciad527); PAD also risk factor

## Diagnostic Approach (JAMA 2008;299:806)

- **Exam**: probing to bone sufficient for dx only in patients w/ DM for foot OM (83% Sp, 87% Sn) w/o need for further imaging (CID 2016;63:944)
- **Blood Cx**: often ⊕ with hematogenous infxn involving vertebra, clavicle, pelvis (**always obtain BCx x2 before starting antibiotics**)
- **Labs**: ESR/CRP (if high can use for monitoring response) ± leukocytosis
- **Imaging**:
  - **>2wk of sx**: obtain plain XR first. If XR non-diagnostic and concerning story, obtain advanced imaging (MRI)
  - **<2wk of sx, suspected vertebral OM or DM**: start w/ advanced imaging (MRI), contrast preferred for vertebral OM
  - MRI: study of choice for further assessment after plain films; Sn 90%, Sp 82%, high NPV in foot osteo (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 ⊕ if soft tissue inflamm.); option if hardware precludes MRI
- **Bone biopsy**: **gold standard diagnostic test – obtain prior to empiric abx unless HDUS or neurologic compromise**
  - If diabetic foot infection, c/s vascular surgery, otherwise c/s ortho. If they decline, consult IR. Open Bx preferred to percutaneous (CID 2009;48:888). If perc. Bx ⊖ and suspicion high, repeat vs. obtain open biopsy
  - Bone Cx may be ⊕ even on abx; need 2 specimens: GS/Cx (aerobic, anaerobic, mycobacterial, fungal) + histopath
  - If evidence of OM on imaging or ⊕ probe to bone, bone biopsy ⊕ up to 86% of cases (CID 2006;42:57). Biopsy not required if ⊕ 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, has no neurologic compromise or e/o epidural abscess
  - Common organisms: **MSSA/MRSA**, CoNS, Strep, Enterococci, aerobic GNRs > Brucella, mycobacteria, fungi
  - Can consider adding rifampin if Staph + hardware (for biofilm) (Antimicrob Agents Chemother 2019;63;e01746)
  - 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 (RIF monotherapy not rec'd due to low barrier to resistance). Longer durations needed if prosthetic joint infection (NEJM 2021;384:1991; NEJM 2023;388:251) and ID should be involved. Retained hardware may require suppressive abx
  - No residual infected bone (i.e. amputation): abx 2-5d → up to 10-14 if associated SSTI
  - Consider trending ESR/CRP; if elevated at end of abx, consider further w/u. Routine MRI not recommended for all cases as radiographic 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 (See MGB handbook for dosing) | |
|---|---|
| Vancomycin + GNR coverage (typically CTX 2g q24h). Include PsA coverage (cefepime) for PWID | |
| **Organism-Specific Tx** | |
| MSSA | Nafcillin; cefazolin |
| MRSA or CoNS | Vanc; dapto; dalbavancin (OFID 2018;6:ofy331) |
| PCN-S Strep | Pen G, amp, CTX, vanc |
| Enterococci | Pen G, amp, vanc, dapto |
| GNR | CTX, cipro, levoflox, cefepime 2g q12h (q8h if PsA) |

# Infectious Disease — Bloodstream Infections & Endocarditis

## BLOODSTREAM INFECTIONS (BSI)

**Evaluation** (JAMA 2012;308;502)

1. Sources: lines, procedures, meningitis, endocarditis, osteomyelitis (OM), septic arthritis, PNA, UTI, SSTI, abscesses
2. 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) | High risk: septic shock (38-69% ⊕ BCx), meningitis (53%)<br>Medium risk: pyelonephritis (19-25%)<br>Low risk: cellulitis (2%), CAP (7%), other community-onset fever (13%) | Immunocompromised (neutropenia, HIV); hard-to-isolate source (OM, septic arthritis) |

3. 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 with growth & no systemic sx, certain organisms (e.g. CoNS, GPRs), time to positivity >3-5d
4. Further testing:
   - Staph aureus and Staph lugdunensis: very sticky and *never* contaminants. **Daily surveillance cx** (generally not needed for GNRs) (CID 2017;65:1776), **remove lines/hardware**, **TTE/TEE** to r/o endocarditis, consider imaging or arthrocentesis if joint swelling/pain.
   - Consider TTE for high grade Strep spp. No routine TTE for GNRs
   - Yeast: **TTE**, **ophthalmology c/s** to r/o fungal endophthalmitis, **remove lines**

**Antimicrobial selection**:

| GS | Empiric abx | Other considerations |
|---|---|---|
| GPCs | Vanc+CTX | S. aureus: **ID c/s** ↓mortality. Adding β-lactam (cefazolin/nafcillin) *may* improve outcomes (CID 2013;57;1760)<br>MSSA: β-lactam >>> vanc (CID 2015;61;361) |
| GPRs | Call ID | More likely true infection in immunocomp hosts, multiple bottles, hardware, or known GPR infection |
| GNRs | Cefe/ceftaz/Zosyn | If MDRO, see IDSA guidelines. Can often de-escalate to orals (e.g. FQ) (JAMA IM 2019:179:3; CID 2019;69:7). |
| Candida | Micafungin | **ID c/s** ↓mortality (Lancet ID 2019;19:1336); ALWAYS treat as true infection in blood |

## ENDOCARDITIS (AHA/IDSA: Circ 2015;132:1435; ESC: EHJ 2023;44:3948)

- Etiology: cutaneous (40%), oral (29%), GI (23%) – source often unknown
- Clinical manifestations: BSI s/sx; valvular complications → 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 hemorr)
- Diagnosis: **Duke criteria** → 2 major OR 1 major + 3 minor OR 5 minor
  - **TTE** in all; **TEE** if: ⊖ TTE w/ high susp; PVE; intracardiac device; suspected complications (AHA/ACC: JACC 2014;63:e57)**; consult ID**
- Monitoring: **repeat BCx** q24h until sterile x48h **& serial ECGs** for: new AV block (prolonging PR most common); p mitrale; low QRS voltage
- Micro: **NV**: Strep, Staph, CoNS/Enterococc., 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 ECG); **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: JTCS 2017;153:1241); **can c/s surgery for all PVE** (± streptococcal)
- AC/antiplatelet: 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. Not a substitute for initial ID c/s
- IV → PO may be non-inferior to IV in **carefully selected** L-sided IE pts (POET, NEJM 2019;380;415)
- Ppx: if prior IE, PV, unrepaired cyanotic CHD, or w/in 6mo of CHD repair, give amox. 2g or clinda. 600mg x1 (if PCN allergy) w/in 30-60 min pre-dental procedure (Circ 2007;116:15)

| Modified Duke Criteria (CID 2023;77:518) |
|---|
| **MAJOR CRITERIA** |
| **Micro: ⊕ BCx (typical org.* in 2 separate Cx, non-typical org. in 3 Cx) or ⊕*PCR C. burnetii, Bartonella* spp, *T. whipplei* or *C. burnetii, B. henselae, B. quintana* IgG titer 1:800 or IFA** |
| **Imaging: Endocardial involvement on echo, cardiac CT, or PET/CT** |
| **Surgical: evidence of IE on intraoperative inspection** |
| **MINOR CRITERIA** |
| **RFs**: valve dz, IVDU, prior IE, CIED, prosthetic, CHD |
| **Temperature >38C or 100.4F** |
| **Vascular phenomena**: septic arterial/pulm emboli, mycotic aneurysm, ICH, conjunctival hemorrhages, Janeway lesions, cerebral/splenic abscess |
| **Immunologic phenomena:** GN, Osler, Roth spots, ⊕RF |
| **Micro (not meeting major criteria):** ⊕ BCx, ⊕PCR or other nucleic acid based test from non-cardiac sterile body site |
| **Imaging: FDG-**PET/CT w/ abnormal metabolic activity w/in 3 mo of prosthetic cardiac implant |

***S. aureus, S. lugdenesis, E. faecalis, all Strep spp (except S. pneumoniae, S. pyogenes), Granulicatella spp, Abiotrophia spp, Gemella spp, HACEK.**

| Organism | Therapy | Notes |
|---|---|---|
| ***Streptococci*** (viridans; *gallolyticus* [*a/w colon cancer*]; *Abiotrophia* [treat as ↑MIC]) | **- PCN** OR **CTX** x4w (some infxns may have 2w options)<br>- may add gent based on PCN MIC, severity, or PVE | -Vanc inferior to beta-lactam**Vanc inferior to beta-lactams** |
| ***Staphylococci*** (*aureus; lugdunensis*; CoNS [often methicillin-resistant]) | - MSSA: oxacillin (better for CNS penetration), nafcillin (nephrotox risk), cefazolin x6w; MRSA: vanc or dapto x6w<br>- PVE: may add gent for first 2w and rifampin for 6w | -Vanc inferior to beta-lactam for MSSA-**Vanc inferior to beta lactams for MSSA** |
| ***Enterococci*** (*faecalis*, *faecium*) | - **Amp** AND **CTX** x6w, may add gent or streptomycin<br>- Vanc if amp-resistant. VRE: dapto + amp OR linezolid | - 4w amp+gent sufficient if NVE and <3mo sx; 6w if >3mo or PVE |
| **Gram** ⊖ (HACEKs mostly, PsA, other GNRs possible) | - HACEK: **CTX** OR **amp** OR **cipro** x4w (6w for PVE)<br>- GNRs: β-lactam + (AG or FQ) x6w | - Rare etiology, minimal data to firmly direct treatment modalities |
| **Fungi** (*Candida*, *Aspergillus*) | - Candida: **ampho B** 3-5 mg/kg/d (± **flucytosine** 25mg/kg q6h) OR **Micafungin** 150mg q24. **C/s surgery** (CID 2016;62:4)<br>- Aspergillus: **vori** (6mg/kg q12h x2 dose load then 4mg/kg q12h) or **ampho B** (CID 2016;63:4) | - Risk factors: TPN, lines, PPM/ICD, prosthesis, injection drug use |

# Infectious Disease — Meningitis & Encephalitis

## BACTERIAL MENINGITIS

**Clinical Features**

- History: 95% have ≥2 of: fever, neck stiffness, AMS, HA (NEJM 2004;351:1849). Lethargy, hypothermia may be common in elderly. Abd pain, peritonitis can be seen w/ VP shunts. Can also cause seizures, stroke (infectious vasculitis), hydrocephalus, CN deficits (esp TB and fungal) (Continuum 2021;27:836).
- 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 J EM 2013;31:1601). May be absent if >65 yo, immunocompromised, taking analgesics. Meningococcemia may be suggested by petechiae or palpable purpura

**Diagnosis** (CID 2004;39:1267; CID 2017;64:6)

- Blood cultures **STAT – BEFORE** antibiotics (positive in 70% patients); **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 (Clin Neuroradiol 2022;32:857)
  - Obtain opening pressure with simple column manometer (normal 200mm $H_2O$; mean 350mm $H_2O$ in bacterial meningitis)
  - For a list of studies to send and CSF analysis/interpretation, see **Procedures: Fluid Analysis**
  - Repeat LP if: no clinical improvement after 48h of appropriate antibiotics, evidence of antimicrobial resistance of cultured organisms, or ongoing fevers > 8 days w/treatment

**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%)<br>N. meningitidis (35%)<br>H. influenzae (7%)<br>GBS (6%)<br>Listeria (2%) | S. pneumoniae (75%)<br>N. meningitidis (10%)<br>GBS (7%)<br>H. influenzae (5%)<br>Listeria (3%) | S. pneumoniae (76%)<br>GBS (8%), Listeria (7%),<br>H. influenzae (6%)<br>N. meningitidis (5%)<br>Aerobic gram neg bacilli | Gram neg bacilli (40%)<br>S. aureus (10%)<br>Coag neg Staph, particularly w/presence of foreign material (10%)<br>C. acnes (prolonged growth time) |

**Empiric Treatment** (Lancet 2021;398:1171)

| 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 + mero** 2g q8h OR moxi 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/confirmed S. pneumococcal meningitis w/ GCS 8-11 (↓mortality/hearing loss, & 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
- Prevention: MenACWY/MenB, Hib, pneumococcal vaccines. Post-exposure ppx: All close contacts of patients w/ **suspected** *N. meningitidis* or close contacts (w/ increased risk factors) of patients w/ Hib.

## ASEPTIC MENINGITIS: meningeal inflammation with negative bacterial cultures

**Clinical Features**: similar to bacterial, usually less toxic. LP: **lymphocytic pleocytosis,** low CSF lactate (J Infect 2011; 62(4):255)
**Etiology**: *Infectious*: enteroviruses (most common), HSV2>1 (Neurology 2006;66:75-80), VZV, partially tx'd bacterial meningitis (usually days-wks), any stage of syphilis, Lyme, leptospira, mumps, Nocardia, TB, HIV (primary infxn), LCMV, fungal, brain/parameningeal abscess; *Non-infectious*: autoimmune (Behcet's, sarcoid, SLE, SJS, Sjogren, GPA), neoplastic (leukemia, lymphoma), drugs [NSAIDs, antimicrobials, IVIG, immune checkpoint inhibitors – can cause neutrophilic pleocytosis (AIM 1999;159:1185)], pituitary apoplexy
Additional Dx: WNV IgM (June – Oct), VDRL, Lyme Ab, serum HIV, HSV swabs of concurrent oral/genital lesions
**Treatment**: HSV, VZV → acyclovir 10-15 mg/kg IV q8h; tx underlying cause (if possible) & supportive care. **If suspect TB**, **c/s ID**

## FUNGAL MENINGITIS: see *Invasive Fungal Infections*

**Causes**: *Primary (immunocompetent)*: Crypto, Blasto, Histo, Cocci, other dimorphic fungi; *Secondary (immunocompromised)*: Cryptococcus, Candida, Aspergillus, other molds; intermittent healthcare related outbreaks
**Diagnosis**: CSF CRAG, (1,3)-B-D-glucan, fungal wet prep, fungal culture, large volume (40-50mL) for Cx (J Clin Microbiol 2013;51:1285)
**Treatment**: ID to guide. *See* Invasive Fungal Infections.

## ENCEPHALITIS [(IDSA: CID 2008;47:303) (CID 2023:77:5)]

**Presentation**: abnormal brain function (vs. normal cerebral function in meningitis): AMS, focal neuro deficits
**Etiology**: *Infectious*: **HSV1>>2,** VZV, arbo (**WNV**, WEE/EEE, St Louis, JEV), enteroviruses (Coxsackie, echoviruses, polioviruses), HIV, CMV (rare), JC, adeno, influenza, Powassan, Zika; *Non-infectious*: post-infectious demyelination (ADEM), autoimmune, paraneoplastic (anti-Hu [SCLC], anti-Ma2 [testicular], anti-CRMP5 [SCLC/thymoma], anti-NMDAr [ovarian teratoma, idiopathic])
**Diagnosis**: send CSF for HSV, VZV PCR; other viruses less common. If clinical suspicion ↑ (West Nile IgM, JC, CMV/EBV [extremely rare]); autoimmune-Mayo ab panel; 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 (Neurol Clinic 2021;39:197). If sx recur s/p tx, consider viral relapse vs. autoimmune encephalitis – high rates of autoimm. dz wks later (Lancet Neurol 2018;17:760)

# Infectious Disease — *C. difficile* Infection

## OVERVIEW (IDSA: CID 2021;73:1029; CID 2018;66:987)

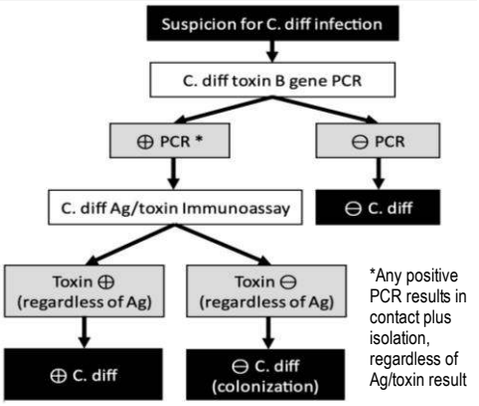
- Definition: C. difficile infection (CDI): acute-onset sx (usually ≥3 episodes/d of watery diarrhea) + e/o toxin-producing C. difficile or histopathology c/w pseudomembranous colitis
- RFs: **abx w/in 3mo** (particularly associated with penicillins, 2nd/3rd/4th gen ceph, FQ, carbapenems, clinda), ↑age (≥65yo), recent hosp or ↑LOS, severe comorbid illness, IBD, chemo/immunocompromise, GI surgery, tube feeding, PPI/H2RA
- Pathogenesis: fecal-oral via spores, 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 in pt w/o hospitalization in last 12 wks. *Potential sources*: contam. food/$H_2O$, pets, colonization or CDI in family, babies, outpt visits (AJG 2012;107:89; JAMA IM 2013;173:1359)

## CLINICAL MANIFESTATIONS

- Features: **watery diarrhea** (≥3 loose stools in 24h) +/- mucus/occult blood; ileus, fever, abd pain, nausea, ↑WBC
- 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, leukocytosis (WBC >15), lactic acidosis; fulminant colitis characterized by hypotension/shock, ileus, toxic megacolon w/ ↑↑mortality

## DIAGNOSIS

- **See MGB handbook.** Simplified algorithm to right.
  - Toxin B gene PCR: High Sn but can be ⊕ without active infection (strain may have toxin gene but not produce it)
  - GDH Antigen: Enzyme produced constitutively by all C. diff strains; sensitive but cannot distinguish toxigenic & non-toxigenic strains
  - Toxin A/B: Assay detects toxin production, high Sp but poor Sn
- **DO NOT** retest within 7d w/o significant clinical change
- **DO NOT** test for "cure" (may remain ⊕ 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 2021;73:1029; CID 2018;66:987)

| Category | Criteria | Treatment |
|---|---|---|
| **Non-severe** | WBC <15 AND Cr <1.5 | - **Fidaxomicin* 200mg PO BID x10d OR Vanc 125mg PO q6h x10d**<br>- Alternative: metronidazole 500mg PO q8h 10-14d (if Fidax & Vanc not avail)<br>- D/c antimotility agents, non-essential abx, cholestyramine (binds vanc) |
| **Severe** | WBC >15 OR Cr >1.5 | - **Fidaxomicin* 200mg PO BID x10d OR Vanc 125mg PO q6h x10d** |
| **Fulminant** | Hypotension/shock, ileus, megacolon | **- Vanc 500mg PO q6h** *AND* **metronidazole 500mg IV q8h**<br>- If ileus: can add **vanc PR** 500mg in 100cc NS as retention enema Q6H<br>- **Surgery c/s**; consider FMT if ileus, tx nonresponsive, or recurrent dz |
| **Duration**: **10d** for non-fulminant; if receiving concurrent abx duration may be **extended** 7d after completion of other abx | | |

***Fidaxomicin**: 1st line, ↓ recurrence vs vanc; currently cost prohibitive at MGH (Cochrane Rev 2017)

## RECURRENCE

- Recurrent CDI: resolution of sx w/ tx, reappearance of sx w/in 2-8 wks after abx completed. 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**: Fidax* 200mg PO BID x10d OR 200mg PO BID x5d then qod x20d OR Pulse-tapered PO vanc 125mg x6-8w AND **IV bezlotoxumab 10mg/kg x1 w/ fidax or vanc if w/in 6 mos of prior episode** (CID 2021;73:1029)
  **2nd recurrence**: Fidax* regimen (same as 1st recurrence) OR pulse-tapered vanc 125mg x6-8w *OR* vanc 125mg q6 x10d followed by rifaximin 400mg TID x20d AND **IV bezlotoxumab as above**. IDSA recommends evaluation for **fecal microbiota transplant** (**FMT**) after 2nd recurrence; more effective than vanc or fidax alone (NEJM 2013;368:407; CID 2019;68:1351; Gastro 2019;156:1324). Consult ID for FMT evaluation.

## OTHER CONSIDERATIONS

- **Infxn ctrl:** Contact precautions, wash hands with soap & water after contact (alcohol-based rubs won't eliminate spores)
- **Secondary ppx**: vanc 125mg PO qd for abx duration + additional 7d may ↓recurrence in pts w/ prior CDI receiving systemic abx (AJG 2016;111:1834; CID 2016;63:651; ICHE 2019;40:662). Practice patterns vary (NEJM 2023;388:654). May be effective as primary ppx in high-risk patients w/ 125mg daily dosing (CID 2020;71:1133; CID 2019;68:2003).
- **Probiotics**: Not recommended for prevention or treatment of CDI by society guidelines (CID 2018;66:987). Some evidence supports use w/ abx to reduce abx-associated diarrhea (JAMA 2012;307:1959).

# Infectious Disease — Invasive Fungal Infections

## Risk Factors

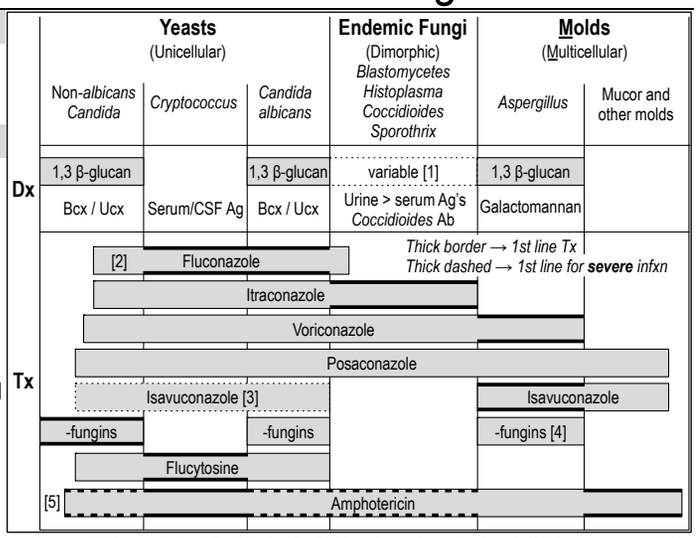
**Heme malignancy**, **HSCT** > Solid organ transplant, select biologics, HIV/AIDS, prolonged neutropenia, prolonged glucocorticoids, liver disease, burn patients, severe lung disease/prolonged intubation

## Diagnostic Testing

Gold Standard: Tissue biopsy with culture

Fungal markers:

- **1,3-β-D Glucan (BDG)** (CID 2021;72:S2): cell wall polysaccharide, detects *Candida, Aspergillus,* PJP, *Fusarium, Trichosporon, Histo, Cocci*. **CANNOT** detect Mucor, Rhizopus, Blasto, Crypto
  - **False** ⊕ w/ IVIG, albumin, HD, pip-tazo, unasyn, Strep, Pseudomonas (J Clin Microbio 2013;51:3478)
  - **False** ⊖ possible w/ candidemia (CID 2020;70:1925)
- **Galactomannan (GM)** (Cochrane Rev 2015): detects ***Aspergillus*** cell wall component; Sn (serum 65-80%, BAL 90-95%), Sp 88%
  - **False** ⊕ w/ some TPN formulations, IVIG, blood products
- **Histo Ag**: Urine Ag Sn 90% if disseminated (vs. serum Ag 80%); Sp limited by cross-reactivity (esp. with blasto)
- **Crypto Ag (CrAg)**: serum Sn&Sp >90% if disseminated, ↓ w/ pulm dz only, ↑Sn for pulm if HIV
- **Blastomycoses**: uAg > sAg; ↑Sn, modest Sp d/t cross-reactivity. Sn of uAg for pulmonary dz is ~80%.




**Notes**: [1] See left dx info [2] ~85% 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 most invasive fungi few exceptions, e.g., *C. lusitaniae, A. terreus, Lomentospora, Scedosporium.* Order amphoB w/ **pre hydration** *AND* **BMP, Mg** BID.
*Adapted from JA Freed and AJ Hale,* IDModules.com

| **Invasive Opportunistic Fungi** ****ID consultation is advised for these diagnoses**** *Aspergillus*, *Candida*, and *Pneumocystis* account for >80% of fungal infections diagnosed in hospitalized patients (OFID 2022;9:ofab593) | | |
|---|---|---|
| YEAST | **Candida** CID 2016;62:e1 | RFs: neutropenia, immunocompromised (heme malignancy, transplant, HIV/AIDS), TPN, PWID, CVC, prior abd. surgery, ICU<br>Spectrum of illness: sepsis (25% mortality), macronodular skin lesions (10%), endophthalmitis, endocarditis, osteomyelitis, UTI<br>Dx: **BCx** (**never contaminant,** grows slowly [BMC Infect Dis. 2013;13:486]), **c/s ophtho & ID, TTE**, repeat Cx daily. ↓Sn if deep tissue/hepatosplenic infxn; Ophtho c/s for dilated eye exam in non-neutropenic patients (if neutropenic, perform within first week of ANC recovery). Skin bx with cx if suspicious lesion. ***Candida score*** *if septic*<br>Tx: **BSI: echinocandins → azole** (amphoB for resistant strains); **remove CVCs**. **Endophthalmitis**: may need intravitreal amphoB/vori. **UTI**: see *UTI*. Duration: **BSI**: 2w after 1st ⊖ Cx w/ no dissemination, deep-seated infxn: longer, see *BSI* |
| YEAST | **Cryptococcus** Lancet ID 2024;9:s1473 | RFs: immunocompromise (**HIV/AIDS**, malignancy, transplant), ESLD, **can** occur in immunocompetent (*C. gattii* > *C. neoformans*)<br>Spectrum: asympt. → meningoencephalitis, (pulmonary [AHRF], skin nodules, liver abscesses); can be subacute<br>Dx: **serum/CSF CrAg (⊕ serum w/ ⊖ CSF = cryptoccal antigenemia)**, LP/CSF: OP >20 cmH2O, ↓gluc, ↑TP, lymphs, cryptococcomas on imaging, umbilicated skin lesions. Brain MRI and chest CT. Screen with serum CrAg if CD4<200 → LP if +.<br>Tx: CM: **amphoB + flucytosine (x2w) → fluc (≥8w),** serial LPs if OP≥20 or symptoms of ↑ICP, **fluc** for mild pulm dz/antigenemia<br>Ppx: fluc for HIV/AIDS (CD4<200) in high-risk, low-resource settings (in US not recommended unless positive serum antigen) |
| YEAST | **Pneumocystis** HIV.gov | RFs: immunocompromised (HIV/AIDS, heme malignancy, transplant), steroids equiv. to pred 20mg/day x4w<br>Spectrum of illness: pulm sx onset over days/weeks, PTX, hypoxemia out of proportion to CXR (diffuse GGO on CT)<br>Dx: **LDH >500** (Sn not Sp), **BAL > induced sputum** for silver stain/DFA **1,3-BDG** (Eur J Clin Micr ID 2014;33:1173)<br>Tx: **TMP/SMX (PO/IV 8-20mg/kg/d, divided q6-12h adjust PRN renal fxn).** Consider pred 40mg BID if severe hypoxemia (best evidence in HIV); Alternatives: TMP+dapsone, clinda + primaquine, atovaquone or pentamidine; Duration: 21d<br>Ppx: TMP/SMX (1 DS qD > SS qD, 1 DS MWF), atovaquone, dapsone (check G6PD), inhaled pentamidine |
| MOLD | **Aspergillus** CID 2016;63:e1 | RFs: neutropenia, steroids, transplant, COPD w/ prolonged ICU stay, anti-TNF, cannabis use, COVID19 with ARDS/ICU stay<br>Spectrum of illness: invasive pulm, aspergilloma, sinus, tracheobronchitis, CNS, endophthalmitis, disseminated, necrotic skin<br>Dx: **CT w/ halo sign**, **BAL**/sputum wet prep/fungal cx ± **biopsy**, serum **1,3-BDG** (not Sp), **GM** (Sp; trend serum in tx, BAL > serum)<br>Tx: **voriconazole** (monitor trough, drug-drug int), Posaconazole or isavuconazole ; debride if necrotic. Duration: >6-12w for pulm dz<br>Ppx: vori or **posa** [prolonged neutropenia, GVHD [NEJM 2007;356:348])] |
| MOLD | **Mucor** Lancet 2019; 19:e405 | RFs: DKA, iron overload, heme malignancy, prolonged neutropenia, immunocompromised (Semin Respir Crit Care Med 2015;36:692)<br>Spectrum of illness: rhino/orbital/cerebral invasion, pulmonary, GI, renal; black eschars over ulcers, rapidly progressive<br>Dx: **biopsy**, fungal wet prep/culture (broad **non-septate hyphae**), inform lab concerned for mucor, **CT w/ reverse halo sign**<br>Tx: **DEBRIDEMENT**, **amphoB**, consider posaconazole or isavuconazole (for salvage therapy or if renal dz) |
| **Select endemic Mycoses (Mycopathologia 2020;185:843)** | | |
| | **Histoplasmosis** CID 2007;45:807 | Endemic areas: Central/eastern US (Not limited to OH/MS River valleys), Central/South America, Asia, Africa<br>Spectrum of illness: PNA, meningitis, mediastinal disease, disseminated disease, pericarditis, arthritis<br>Dx: urine + serum Ag (improves sensitivity for detecting pulmonary infxn), histology, Cx. Chest imaging similar to sarcoid.<br>Tx: **itra or fluc or no tx** (mild-mod), **amphoB → itra** (severe); NSAID for extrapulm; Duration: variable<br>Ppx: for both Histo and Blasto (below), consider itraconazole for HIV (CD4 <150) in hyperendemic areas |
| | **Blastomycosis** CID 2008;46:1801 | Endemic areas: Eastern US & Canada<br>Spectrum of illness: fever, PNA (acute or chronic), ARDS, ulcerated skin lesions, osteomyelitis, prostatitis, CNS<br>Dx: wet prep (broad-based, budding yeast), Cx, uAg > sAg, **never a colonizer**<br>Tx: **itra** (mild-mod), **amphoB → itra** (severe); Duration: 6-12mo |
| | **Coccidiomycosis** CID 2016;63:e112 | Endemic areas: Desert regions: SW and S US, Mexico, Central & South America<br>Spectrum of illness: 40% symptomatic, pulm dz (self limiting), 5-10% chr pulm dz, 1% disseminated dz, PNA (+/- nodules), fever, rash (erythema nodosum), HA, eosinophilia, meningitis, osteomyelitis<br>Dx: serologies, Cx (if high concern, alert lab for biohazard), spherules on bx/aspirate, Ag for extrapulm (urine, blood, CSF)<br>Tx: **no tx** (mild-mod, immunocompetent); **fluc** or **itra**, consider **amphoB** (severe); Duration: 3-12mo<br>Ppx: fluc for 1° ppx for transplant in endemic areas; fluc ppx for HIV in endemic areas if CD4 <250, newly (+) serology w/o evidence of active disease; fluc for 2° ppx may be lifelong in meningitis cases |

# Infectious Disease — Tuberculosis

## Epidemiology and Risk Factors

- World: 1/4 infected; US: incidence 2.9/100,000, w/ ~4% HIV coinfection and ~1% MDR (CDC MMWR TB US 2023)
- Acquisition: homelessness, incarceration, PWID, healthcare work, immigration from, residence in, or frequent visits to high-prevalence area (eg, Africa, Asia, Eastern Europe, Latin America, Russia)
- Reactivation: risk 5% first 2y, 5-10% lifetime, higher if ≥1 risk factor: HIV, immunosupp, CKD (esp. RRT), DM, transplant, TNFα inhibitor, silicosis, malnutrition, tobacco, EtOH (NEJM 2011;364:1441); untreated HIV has 7-10% **yearly** risk

## Screening for Latent TB

Test based on likelihood of exposure & progression to active disease. **IGRA preferred** (TSPOT at MGH); **TST acceptable** (use TST/IGRA interpreter if BCG vaccinated). Both IGRA and TST are 80-90% Sn and >95% Sp in immunocompetent, ↓Sn in immunocompromised. Neither rules in/out active TB, can be **discordant ~30%** of the time. If ⊕ test w/ no risk factors, repeat either IGRA or TST prior to tx. If ⊕ test in ↑risk pt, proceed to tx (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, PWID |
| ≥15mm | No risk factors |
| Size reflects skin *induration*, NOT erythema | |

## Clinical Manifestations

- Primary TB: fever, chest pain, cough, arthralgia. CXR can be normal, have focal infiltrate, or ⊕ 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⊕) (J Clin Microbiol 2007:45:4064); more common than primary TB
- Extrapulmonary TB: meningitis with basilar predominance, Pott disease, GU involvement, intestinal TB, pericarditis, scrofula

## Diagnostics: Active Pulmonary/Extrapulmonary TB (ATS/CDC/IDSA: CID 2017;64:111)

| Site of Infection | | Diagnostic Tests |
|---|---|---|
| Lung | Sputum | Expectorated or induced, AFB smear/Cx x3 ≥8h apart (with one AM sample), add NAAT/PCR (Xpert) to one of the specimens; smear may be ⊖ 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 sensitivity but diagnostic if positive) |
| Pericardial fluid | | AFB, Cx, cell counts (typically exudative, ↑protein, 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 on pathology |
| 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 pulmonary TB (See Ellucid policy)

- When: cough, dyspnea, hemoptysis, >1 wk hoarseness, fever and/ or night sweats, unintentional weight loss, unexplained pleural/pericardial disease + ≥1 risk factor [HIV+, immigrant status (except Canada, Western Europe, Australia, NZ), PWID, homelessness, recent incarceration, prior TB/exposure]. First obtain CXR; if CXR normal (and HIV- or CD4>200), TB unlikely. If CXR abnormal/equivocal (or HIV+ and CD4<200), maintain isolation & obtain sputum x3 as above. Consider ID c/s
- Discontinue: use .TBorNotTB to see if TB risk status can be resolved or if infection control review needed

## Approach to Treatment (ATS/CDC/ERS/IDSA: Am J Respir Crit Care Med 2024;211:1)

- **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 drug-susceptible pulm TB: 4mo isoniazid(INH)-rifapentine(RPT)-moxifloxacin-pyrazinamide followed by 2mo INH-RPT-moxi equally efficacious as standard 6mo RIPE. Sputum AFB smear/cx monthly until 2 consecutive cx/smear negative.
  - Latent TB: INH+RPT qw x12 (3HP) ***OR*** rifampin 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. High mortality
  - ATS/CDC/ERS/IDSA 2024 Guidelines for Drug-resistant TB (Am J Respir Crit Care Med 2024;211:1)
- HIV co-infection: discuss timing of ART initiation w/ ID due to risk for IRIS
- 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)
- RIF/RPT remain widely used despite 2020 FDA announcement of nitrosamine impurities as perceived risk TB > cancer risk

# 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* AIDS-defining illness

## HIV Screening and Diagnostics

- **Screen** all 13-64yrs **once,** every **pregnancy**, dx of **another STI**, **PWID** annually, sex workers, MSM **>1 partner** since last test, partners of all ↑risk pts. MA: **verbal** informed consent req. See **Mass DPH site** for full details
- **Preferred**: 4th gen HIV 1/2 Ab/p24 Ag assay: mean detection limit **18d** (STD 2017;44:739). If +, f/u w/ HIV 1/2 Ab differentiation assay
- 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, inconsistent condom use, **PWID**, ↑risk sex (JAMA 2023;330:736). Transmission risk near zero if HIV+ partner has undetectable VL (JAMA 2016;316:171)
  - Prior to PrEP 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, wt gain, ↓renal/bone issues
    - *Injectable form (cabotegravir extended-release) also recently FDA approved (q2month) (NEJM 2021;385:595)
  - Event-driven PrEP: Truvada "2-1-1" for MSM: double dose 2-24h before sex, then 1 dose daily x 2d (not FDA-approved. See CDC). If discrete exposure (e.g. vacation), start Truvada qd 1w prior and for 1mo after (MSM only) (Lancet HIV 2019;7:113)
  - Monitoring: HIV q3mo, Cr q3-6mo (stop Truvada if eGFR <60, consider Descovy eGFR 30-60), STIs q3mo, pregnancy q3mo
- **Non-Occupational Post-Exp:** pts ≤72h after ↑risk exposure to HIV; case-by-case decision if HIV status of source unknown; check HIV Ab/Ag, HBV, HCV, STIs. Tx: 1) **Biktarvy,** 2)**Truvada** *or* **Descovy + doluegravir, x28d**; if ≥1 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, Hep A/B/C, MMR, VZV if nonimmune, hCG, cervical and/or anal Pap, ± HLA B*5701 (IDSA: CID 2020)
- **Initiate ART early** through referral at all CD4 levels to ↓mortality (NEJM 2015;373:795); exceptions: crypto meningitis & therapy for HIV/TB co-infection (NEJM 2014;370:2487). ART can often be initiated prior to genotype, even in ↑risk 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, DDIs, resistance, HLA B*5701 (abacavir hypersens.) (JAMA 2024)

- ART naive: 2 NRTI (typically TAF/FTC or TDF/FTC) + 1 of another class (often integrase inhibitor e.g. dolutegravir or bictegravir)
- Pregnancy: if new dx, 1st line TAF/XTC + dolutegravir; if prev well treated, cont existing regimen

## Hospital Management of People with HIV

- **Patient on ART**: determine regimen & adherence; **continue ARVs** (interruptions can ↑disease progression)
  - If ARVs must be held, hold **all** ARVs and **c/s ID**. Beware drug-drug interactions esp ritonavir boosted PIs (check DDI database)
  - ARVs historically a/w with lactic acidosis (AZT, ddI, d4T) rarely used nowadays. If elevated lactate, look for other causes.
- **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, crypto, 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 some forms of TB (e.g. CNS) or crypto meningitis]

**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. pneumo* (most common OI), TB | Vax: Flu; HAV, HBV, HPV, PCV20 or 21, PPSV23 after 8w; no live vax w/ CD4<200; LTBI: see *Tuberculosis* | None |
| **<200*** | *Pneumocystis jirovecii* (or hx of thrush) *screen for cryptococcus with serum CrAg | TMP-SMX DS qd (preferred) or 1 TMP-SMX SS qd *or* dapsone 100mg qd *or* atovaquone 1500mg qd | CD4 >200 x 3mo |
| **<150** | *Histo* (hyperendemic or exposure; not in Massachusetts) | Itraconazole 200mg PO qd | CD4 >150 x 6mo + VL suppressed |
| **<100** | *Toxoplasma* | TMP-SMX DS qd *or* dapsone 50mg qd + pyrimethamine 50mg qw + leucovorin 25 qw | CD4 >200 x 3mo + VL suppressed |
| **<50** | *Mycobacterium avium* complex (MAC) | Azithro 1200mg q1wk if not on ART | When ART initiated |

**Treatment of Specific OIs in Adults with HIV (review for dosing)**

| 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<br>CNS: LP + CSF PCR | Orolabial: acyclovir/valacyclovir x5-10d; Genital: tx 5-14d; CNS: acyclovir 10mg/kg IV q8h x3w |
| **Cytomegalovirus (CMV)** | Retinitis: ophtho exam; Colitis/esophagitis: bx; PNA: bronch w/ cytopath; Neuro: CSF PCR, brain Bx, Blood: PCR | Ganciclovir IV → valganciclovir 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) | Pyrimethamine 200mg x1; then by weight + sulfadiazine + leucovorin qd x6w; alternate is TMP-SMX |
| **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 200mg loading dose then 100-200mg PO/IV qd x14-21d |
| **MAC** | Cx (blood/sputum/bronch/marrow/tissue), AFB stain | (Clarithro 500mg BID > azithro 600mg qd) + ethambutol 15mg/kg qd |

# Infectious Disease



## 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**: check mumps/measles/rubella/VZV/CMV/EBV/HAV IgG, HBV (sAb, sAg, cAb), HCV, HIV, syphilis, Toxoplasma, TST/IGRA. Consider: endemic fungi (esp. Coccidioides), 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)**

| | Phase I: Pre-engraftment (0-30 days) | Phase II: Post-engraftment (30-100 days) | Phase III: Late Phase (>100 days) |
|---|---|---|---|
| **Immune System Defect** | Neutropenia, mucositis, catheters lines, acute GVHD | Impaired cellular immunity, acute GVHD | Impaired humoral and cellular immunity, chronic GVHD |
| **Virus** | HSV | | HSV |
| | | CMV | |
| | CRV (RSV, Influenza, Adenovirus) | | |
| **Fungal** | Candida | | |
| | Aspergillus | Aspergillus | |
| | | Pneumocystis | |
| **Bacterial** | Gram - | | |
| | Gram + (Staph, Strep) | | |
| | | | Encapsulated |
| | | | Nocardia |

**Infections After Solid Organ Transplant (SOT)**

| | <4wk. | 1-12mo. | | >12mo. |
|---|---|---|---|---|
| Viral | Donor-derived | | Adeno, BK | |
| | | EBV, HCV, HBV | | |
| | | HSV | | |
| | | HHV 6,7 | | HPV, JC/PML, PTLD |
| | | | VZV | |
| | | CMV, community-acquired | | |
| Fungal | | Aspergillus | | Aspergillus |
| | Candida | | Endemic fungi | Crypto |
| | | Mucor | PJP | Mucor |
| Bact | Surg.-related | | Listeria, Nocardia | |
| | | | | TB, NTM |
| Para. | | | Toxo, leishmaniasis | |
| | | | Strongy, T. cruzi | |

## HSCT Prophylaxis (JNCCN 2024;22:617)

- **Candida**: fluconazole 400mg daily (d0-365 at MGH)
- **HSV/VZV**: famciclovir 250mg BID, acyclovir 400mg q8-12h 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 or tenofovir
- **CMV**: pre-emptive monitoring of VL in high-risk pts & initiate tx (valganciclovir or ganciclovir) when ↑ in VL 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 *(ID c/s is advised)***

| Pathogen | Clinical Syndrome | Diagnosis/Treatment | Additional comments |
|---|---|---|---|
| **CMV** | Fever, malaise, leukopenia, +/- hepatitis, colitis/esophagitis, pneumonitis | **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). Alt Tx: foscarnet or maribavir (CID 2022;74:690) | Most common infxn s/p SOT. *Highest risk*: 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 |
| **PJP** | Subacute dyspnea, hypoxemia, fever | See *Invasive Fungal Infections* | 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 |
| **JC Virus** | Progressive multifocal leukoencephalopathy (ataxia, hemiparesis, VF deficits, cognitive Δ) | **Dx:** MRI brain w contrast, LP w JC PCR **Tx**: ↓immunosupp, optimize ART | Mainly in pts with HIV, but also w heme malignancies, organ tx, and pts receiving lymphocyte-targeted agents |
| **Strongyloides** | *Hyperinfection syndrome*: 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, low-threshold CT chest, induced sputum (GS/Cx, consider AFB and 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 (if exposure), early bronch w/ BAL. *NB*: engraftment syndrome, cryptogenic organizing PNA also on DDx |
| **Diarrhea** | Stool Cx, O+P (consider micro add-on for: *Cryptosporidium, Cystoisopora, Cyclospora,* Microsporidia), C. diff, CMV PCR. If high suspicion for viral colitis (e.g., CMV, adeno), c/s GI re: colo w/ Bx. In HSCT, consider typhlitis (NEC) and GVHD |
| **AMS+HA** | CT head, LP (opening pressure, GS/Cx, glucose, CSF protein, HSV PCR, CrAg, save for more tests). *NB*: fludarabine, cytarabine, calcineurin inhibitors also a/w encephalopathy |
| **Rash** | Low threshold for skin biopsy (path + cx). GVHD, medication allergy, HSV, cellulitis, local vs disseminated fungal infection |
| **Leukopenia** | CMV PCR, EBV PCR, consider tickborne illnesses during the correct season. Check med list |
| **Hepatitis** | If post-HSCT, consider viral (HAV, HBV, HCV, EBV, CMV, HSV, adenovirus & more rarely enterovirus and HHV6), *Candida* (if microabscesses), and non-infectious (GVHD, iron toxicity, DILI, hepatic sinusoidal obstruction syndrome) |
| **AKI** | UA, renal U/S, BK PCR if renal tx. Consider med toxicity and check levels (esp tacro, cyclosporine) |

# Infectious Disease — STIs & Travel Medicine

## Sexually Transmitted Infections; Routine STI testing in asymptomatic adults (CDC 2021)

| | Lesions | Symptoms | Diagnosis | Treatment (CDC 2021 for all STI) |
|---|---|---|---|---|
| Painless | Syphilis* (*T pallidum*) (CDC Updates) | **1°**: painless, firm, round ulcer(s)<br>**2°**: fever, condyloma lata of skin/mucus membranes, rash, LAD, uveitis<br>**3°**: aortitis/aneurysm, disseminated gummas, CN palsies, tabes dorsalis (impaired gait, sensation, reflexes)<br>**Latent** = by definition, asx (early <1y; late >1y or unknown). Highly infectious in 1°, *Neurosyphilis, otic, or ocular can occur at any stage* | 1st: **anti-treponemal CMIA** (Sn & Sp >98%); generally, remains ⊕ for life<br>**If CMIA⊕, lab reflexes to RPR.** RPR titer gives info on disease staging. Pregnany & anti-cardiolipin can cause false ⊕. CSF VDRL if c/f neurosyphilis<br>**If CMIA ⊕, RPR⊖**: send out test to state for 2nd treponemal test (TPPA) to confirm CMIA⊕ | **Prevention:** see DoxyPEP below**<br>**1°/2°/early latent**: benzathine PCN G 2.4milliU IM x1<br>**3°/late latent**: benzathine PCN G 2.4milliU IM qw x3<br>**Neuro**: IV PCN G 3-4milliU q4h or infusion x10-14d<br>**PCN allergy**: try to desensitize<br>Serologic cure = RPR falls by factor ≥4 |
| | LGV* (*C trachomatis* serovars *L1-3*) | **1°**: transient, painless anogenital lesion<br>**2°**: 2-6w later, painful inguinal LAD<br>**3°**: pelvic/abd LAD, inflamm diarrhea, abscess ("genitoanorectal syndrome") | Chlamydia NAAT via direct swab of lesion/aspirate detects LGV serovars. LGV-specific PCR available as sendout test | Doxy 100mg BID x21d + aspiration of buboes |
| | GI/Donovanosis (*K granulomatis*) | Painless progressive beefy red ulcerative genital lesions | Bx/tissue smear w/ Donovan bodies in phagocytes on staining | Azithro 1g qwk or 500mg qd x3w until healed<br>Relapses can occur 6-18 mo s/p tx |
| Painful | Genital herpes (HSV2>1) | Prodrome → painful vesicles → ulcers<br>1° infection: systemic sx ± LAD | Confirm clinical dx with PCR of vesicular fluid from unroofed lesion | Acyclovir/valacyclovir. Consider episodic vs. chronic suppressive tx based on frequency, severity, & risk of spread |
| | Chancroid* (*H ducreyi*) | Painful genital/perianal ulcer 5-7d post-exposure w/ inguinal LAD ± drainage | Clinical with negative syphilis & HSV; GS/Cx (Sn <80%) & PCR in some labs | Azithro 1g or CTX 250mg IM x1; often empiric PCN for syph; eval partners, re-assess in 3-7d |

| Discharge | Symptoms | Diagnosis | Treatment |
|---|---|---|---|
| Gonorrhea* (*N gonorrhoeae*), Chlamydia* (*C trachomatis*) | Vaginal/cervical: frequently asx, mucopurulent cervicitis, urethritis, PID<br>Penile: dysuria, purulent discharge, epididymitis<br>Pharyngitis or anorectal infxn possible | Vaginal/cervical: can self-swab, vaginal > urine NAAT (Sn >65%, >57%)<br>Penile: first-catch urine NAAT > urethra<br>Pharyngeal/anal swab based on hx (can self-swab) (BMJ Open 2019;9:e022510)<br>*NB:* Cx if c/f resistance | Prevention: see DoxyPEP below**<br>Gonorrhea: CTX 500mg IM x1, 1g if ≥ 150kg<br>Chlamydia: doxy 100mg BID PO x7d > azithro 1g PO x1<br>Concurrent infxn/empiric tx for both: CTX + doxy (azithro-R gonorrhea) (MMWR 2020;69:1911)<br>Eval partners, consider EPT† |
| *Mycoplasma genitalium* (*Suspect in pts who fail tx for GC/CT*) | Vaginal/cervical: cervicitis, PID, often asymptomatic<br>Penile: dysuria, purulent discharge<br>Anorectal: proctalgia, dyschezia | Vaginal/cervical: vaginal swab PCR<br>Penile: urine or urethral swab PCR (send out test) | Empir: Doxy 100mg BID x7d followed by moxifloxacin 400mg QD x7d (CDC 2021) |
| Trichomoniasis (*T vaginalis*) | Vaginal/cervical: asx, purulent malodorous discharge, pruritus, dysuria, dyspareunia<br>Penile: usually asymptomatic | Urine/ vaginal/ cervical/ urethral NAAT (Sn & Sp >95%) > wet mount for vaginal/cervical | Vaginal: Metronidazole 500mg BID PO x 7d<br>Penile: Metronidazole 2g PO x 1<br>(Alt: Tinidazole 2g PO x 1)±GC/CT tx; eval partner. Retest after 3 months (CDC 2021) |

| Virus | Risk factors | Screening | Prevention |
|---|---|---|---|
| HIV* | Bacterial STI, inconsistent condom use, HIV+ partner, PWID | See CDC | PrEP (*see* HIV); condom use |
| HPV | Rectal HPV: receptive anal intercourse<br>Cervical HPV: vaginal intercourse | Rectal: anal Pap, anoscopy<br>Cervical: Pap per USPSTF | HPV vaccine series; condom use |
| Hepatitis B | MSM, PWID, >1 partner in 6 m, HBV+ partner, HCV, HIV, other STIs | HBs Ag (can have false + if recent HBV vaccine), HBs AB, HBc Ab | HBV vaccination series; condom use. |
| Hepatitis C | MSM, HIV+, group / chem-sex, PWID, intranasal cocaine, non-professional tattoo parlor | HCV Ab (remain + after tx), HCV VL if Ab+ | Condom use, needle exchange, professional tattoos |

*Reportable to public health department (617) 983-6801 Mass.Gov. Requirements for reporting other STIs may differ by state.
**DoxyPEP: Consider for trans women and MSM w/ + test for GC/CT or syphilis w/in 1yr. Doxycycline 200mg PO x1 within 72hrs of unprotected sex (oral, anal, or vaginal). Can reduce reinfection risk by >50% (NEJM 2023;388:1296). Not yet shown to be effective for other demographic groups (NEJM 2023;389:2331).
†In MA: After making a new chlamydia dx, offer treatment for any partner w/i 60d without exam- EPT (instructions). Laws differ by state (CDC 2023).

## Travel Medicine

**Pre-Travel Counseling (refer to travel medicine clinic if requested or immunocompromised)**

- Patient: medical conditions (especially immunocompromise), pregnancy, med supply, dosing schedule changes for travel (e.g. insulin), supplemental O2 needs, allergies, immunization history, prior malaria exposure
- Trip: duration, season, purpose of trip, itinerary, exposures (e.g. urban v rural, cruise ship, animals, cave or water exposure, altitude, diving)
- General Counseling: consider travel insurance, keep medications in carry-on bags, contingency planning if ill, food and water sanitation, hand hygiene, animal avoidance, safer sex, sunscreen, sunglasses, seatbelt/helmet. Enroll in STEP via state.gov
- Arthropod bite avoidance: ↓exposed skin, insect repellant (DEET, picaridin, etc.), permethrin-treated clothing, mosquito nets

**Immunizations**: Ensure routine vaccinations are UTD, then use CDC site for country-specific recs; common travel vaccines: Influenza, Yellow Fever, Meningococcal, Typhoid, HAV, HBV, Japanese encephalitis, pre-exposure Rabies, Cholera. No live-attenuated vaccines in immunosupp.
**Malaria Prophylaxis** (typically S/SE Asia, Africa, Central/S America): See CDC. Rx options based on resistance patterns. ~1w pre-travel, up to 4w after. Daily: atovaquone-proguanil (Malarone), doxy, primaquine Weekly: mefloquine (a/w bad dreams; avoid if psych hx), chloroquine
**Traveler's Diarrhea** (CDC Yellow Book) Pathogens: ETEC, C. jejuni, Shigella spp, Salmonella spp, Vibrio spp, norovirus, rotavirus, Giardia, etc.
Tx: *mild*: loperamide; *severe* (fever, dysentery, travel interference, age>70): azithro 1g x1 > rifaximin > FQ, avoid loperamide
**Infections in a Returning Traveler:** Broad ddx; consider presenting sx, geography, exposures, 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 for ticks)

**Approach to tick bites and prevention**:
Physical prevention: daily tick check, shower after outdoors, check pets, clothing and gear, walk in center of trails
Chemical prevention: DEET, picaridin, IR3535, lemon eucalyptus oil, para-menthane-diol, 2-undecanone; 0.5% permethrin for fabrics
Removal: ASAP, pull **straight out w/o twisting or jerking** w/ clean tweezers, then wash area w/ soap/water or rubbing alcohol
**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 zoonoses to consider: tularemia (rabbits), leptospirosis (rats), brucella/coxiella (cows/sheep), though much less common
**Tick identity and geography (expanding due to climate change)**
*Amblyomma americanum* (lone star tick): **Ehrlichia**, STARI, tularemia; widely found in eastern US, more common in the south
*Dermacentor variabilis* (American dog tick): **RMSF**, tularemia; East of Rocky Mtns. (particularly southeast), northern Mexico (EID 2024;30:2288)
*Ixodes scapularis* (black-legged tick): Lyme, Anaplasma, Ehrlichia, Babesia, Powassan, relapsing fever. **NE**, Mid-Atlantic, central Midwest

| Disease | Presentation | Diagnosis | Treatment |
|---|---|---|---|
| **Lyme Disease** (IDSA: CID 2021;72:e1; Curr Op Rheum 2020;32:3; NEJM 2014;370:1724) | Early localized (days to 1 month): erythema migrans (3-30 d of bite, red ovoid lesion ± central clearing, 80% of pts), ± fever, fatigue, myalgia, arthralgia, HA, neck stiffness, regional LAD. Asx in 30% cases<br>Early disseminated (wks-mos): multiple EM lesions, sx above ± migratory arthralgias 60%; neuro 15%: CN palsies, meningitis, mononeuritis, radiculopathy; cardiac 1%: heart block, myopericarditis; LAD; conjunctivitis, keratitis, retinal vasculitis<br>Late disseminated (mos-yrs): **arthritis 60%** (mono- or polyarthritis of large joints, esp. knee), **neuro** (mild encephalopathy, peripheral neuropathy)<br>Post-treatment syndrome (yrs): nonspecific sx; fatigue, MSK pain, cognitive dysfunction; NOT a "chronic infection" and no evidence of dysregulated immune response so no role for abx or IVIG (CRAI 2022:62:264) | **Avoid serologic testing w/o specific objective s/sx and endemic area/exposure**<br>Early: can dx w/ clinical suspicion only (seronegative early on)<br>Early & Late disseminated<br>1. Screening ELISA IgM/IgG<br>2. Western blot (WB) if screen ⊕ or **equivocal**<br><br>IgM⊕ = 2 of 3 bands detected<br>IgG⊕ = 5 of 10 bands detected<br><br>IgM⊕ IgG⊖ at 6-8w: **false ⊕** | Early: doxy 100mg PO BID x10d OR Amox 500mg TID x14d OR Cefuroxime 500mg BID x14d<br><br>Disseminated (neuro, cardiac involvement, arthritis): CTX 2g q24h x14-28d based on severity<br><br>Ppx: doxy 200mg PO x1 **IF** (1) confirmed Ixodes tick (2) attached ≥36h (3) in highly endemic area *AND* ≤72h after tick removed |
| **Babesiosis** (IDSA: CID 2021;72:e49; Inf Dis Clin North Am 2022: 36:3) | Asymptomatic: 20% adults; no tx unless smear ⊕ > 1 mo.<br>Mild-to-moderate: 1-4 wks after bite or 1-6 mos. from blood transfusion; **fever,** fatigue, chills, sweats, myalgias, anorexia, HA, n/v, cough – can be subacute (up to 6mo)<br>Severe (usually immunosupp, malignancy, HIV, asplenic, >50yo): sx above w/ pronounced n/v, diarrhea,<br>Complications: **severe hemolysis**, DIC, ARDS, multiorgan failure, CHF | Labs: DAT⊖ **hemolytic anemia**, ↓PLT, ↑ALT/AST<br>Blood smear: ring forms in RBC (Maltese cross rare); parasitemia = %infected RBCs; monitor in immunosupp pts until neg smear<br>PCR: very Sn & Sp, not widely available | Mild-mod: 7-10 d of atovaquone 750mg q12h + azithro 500mg x1 -> 250mg qd<br>Severe: **c/s ID;** Azithro 500mg IV qd + atovaquone 750mg q12h; consider exchange transfusion if parasitemia > 10% or severe hemolysis or organ failure |
| ***Borrelia miyamotoi*** (Lancet Microbe 2022;10:e772) | **Relapsing fever**, HA, AMS, photophobia, chills, myalgias; ↓**WBC**/PLT, ↑ALT/AST (mimics anaplasmosis); rash usually absent; meningoencephalitis possible in immunocompromised (NEJM 2020;383:1578) | PCR > serology<br>*NB*: EIA cross-reacts w/ Lyme | Mild: Doxy 100mg BID x14d<br>Hospitalized: CTX 2g qd x 14-28d |
| **Powassan virus** (CID 2016;62:707) | Fever, chills, malaise, somnolence, n/v, **neuroinvasive dz** w/ high morbidity and mortality (CID 2024;78:1)<br>MRI: T2/FLAIR hyperintensities (esp. basal ganglia)<br>CSF: lymphocytic pleocytosis (can also be neutrophilic) | Serum/CSF serology (send-out to state lab): IgM ELISA, if + then neutralizing antibody testing | Supportive care, no antivirals known to be effective |
| **Anaplasmosis** | Common: fever, malaise, myalgias, HA, n/v, arthralgias, cough; rash is less common (<30%)<br>Labs: ↓**WBC**/PLT, ↑ALT/AST, ↑LDH, ↑ALP, ↑CK | PCR; morulae in neutrophils on smear in 20-80% of pts | Doxy 100mg BID x 7-10d<br><br>**(IDCNA 2022; 36:3)**<br>**(PLoS NTD 2024;18:8)** |
| **Ehrlichiosis** | | PCR; morulae in mononuclear on smear in 1-20% of pts | |
| **Rocky Mountain Spotted Fever** MMWR Recomm Rep. 2016;13:1 | 3-5d prodrome (fever, malaise, myalgias, HA, n/v) → progressive macular rash → petechial rash (limbs → trunk, spares face, end stage on palms and soles characteristic)<br>Severe: meningoencephalitis, shock, ARDS, DIC, organ failure<br>Labs: WBC variable, ↓PLT, ↓Na, AKI, ↑LFTs, ↑INR | Clinical dx: start empiric tx<br>Serology: undetectable until 7-10d after sx onset; repeat 14-21d after sx onset to confirm<br>PCR: special send out<br>Skin biopsy: 70-90% Sn | Doxy 100mg BID x5-7d minimum + ≥3d after afebrile (tx for all ages)<br><br>Can consider load 200mg x1 if critically ill |

# Infectious Disease — Mpox & Ectoparasites

## Virology and Epidemiology

Caused by **monkeypox virus**, an orthopoxvirus closely related to smallpox. **Two clades**: Clade I (Central Africa, ~10% mortality rate; also has subclades); Clade IIa (Western Africa, 0.1% mortality rate); Clade IIb (2022 global outbreak, low mortality). (NEJM 2022;387:1783; Lancet Infect Dis 2023;23:273).
**Animal-to-human transmission**: Bites, infected animal fluids, preparation of bush meat. Rodents are likely reservoir.
**Human-to-human transmission:** Direct contact with infectious lesions; respiratory secretions; transplacental; viral DNA found on fomites and bodily fluids (semen, feces, urine, saliva), but unknown if these are mechanisms of transmission
**2022 global outbreak**: 98% cases in MSM and close sexual contacts. 40% pts HIV+ (likely more severe in uncontrolled HIV but confounded by delays in tx), 40% on HIV PrEP. Up to 30% associated with concomitant STIs. (HIV Med 2022;BMJ 2022;378:72410;Lancet 2022;400:661;MMWR Morb Mortal Wkly Rep 2022;71:1412).
2024 global outbreak: 50k Clade I cases in Eastern/Central Africa, with rare travel-associated cases. Transmission via animal contact, household contact, and sex. Low risk to US as of 1/2025, slightly higher risk for US MSM with multiple partners (CDC 2024).

## Clinical Manifestations

**Incubation period**: mean 13 d, range 3-34 d
**Prodromal phase**: associated with viremia; 1-4 days with high fever, headache, fatigue, **lymphadenopathy**
**Eruptive phase**: 14-28 days with **mucocutaneous lesions** (including **palmoplantar**), progress from macules → papules/vesicles → pseudopustules (filled w/ debris rather than pus) → crusting and desquamation, may scar. Lesions **well circumscribed, umbilicated** a/w pain/pruritus. Clinical images: National STD Curriculum. 2022 outbreak commonly w/ **anogenital lesions** (NEJM 2022;387:679).
**Complications: Proctitis** (Associated with receptive anal sex. Anoscopy not routinely performed), **pharyngitis/tonsillitis** (may limit PO intake), **ocular** (conjunctivitis, keratitis, blindness), **CNS disease** [demyelinating encephalitis/encephalomyelitis/transverse myelitis. LP c/w viral meningitis (MMWR Morb Mortal Wkly Rep 2022;71:1212)], **Superimposed cellulitis** (most common complication)

## Diagnostics

Consider testing in patients with consistent rash and epidemiological risk factors → **c/s infection control/ID**; co-test for STIs, HIV.
**Orthopoxvirus PCR:** vigorously swab lesions to collect cells (do not attempt to unroof), collect 2 swabs/lesion and can swab multiple lesions. PCR of throat swabs and blood used for epidemiological, but not clinical testing.
**Serologic testing**: CDC IgM and IgG test → positive 5 and 8 days after rash onset
**Lumbar puncture**: if c/f encephalitis/myelitis → cell count, glucose, protein, orthopoxvirus PCR, IgM
**Biopsy**: may be helpful if multiple concomitant infections present (e.g. in immunocompromised patients). Lesions are positive for orthopoxvirus and histologically distinct from herpesvirus lesions.

## Therapeutics

Most patients have mild disease, supportive care only. Hospitalization for complications and/or severe pain.
**Tecovirimat (TPOXX)**: 14d course studied in PALM007 trial for clade I and STOMP trial for clade II did not reduce time to resolution of mpox lesions (CDC 2025). Discuss TPOXX use under CDC EA-IND with ID for immunocompromised patients or patients with severe manifestations. Most common side effects: fatigue, nausea, HA.
**Cidofovir/brincidofovir**: Consider in immunocompromised patients in combination with tecovirimat. Renal & hepatic toxicity. (Lancet Infect Dis 2022;22:1153; CDC 2024).
**Trifluridine/vidarabine eye drops**: use w/ tecovirimat for ophthalmic infections, q4h 7-10 d, c/s ophtho. (Arch Ophthalmol 2003;121:715).
**CNS involvement**: c/s neurology, high dose corticosteroids for demyelinating encephalitis/myelitis (JAMA Neurol 2022;79:1180)

## Prophylaxis

**Vaccination**: JYNNEOS → attenuated nonreplicating vaccinia virus, also confers smallpox immunity. Safe in immunocompromised patients (ACAM2000 is C.I.). Involves two doses, the 2nd dose given four weeks after the first. **Post-exposure prophylaxis:** Vaccination within 14d of close/sexual contact with infected patient or presumed exposure (MSM who have had sex in areas where mpox is spreading).
**Pre-exposure prophylaxis:** Offer vaccination for MSM/trans/nonbinary patients who have had at least one STI or >1 sex partners in last 6 mo, or any patient who has had sex at a commercial/public sex venue in last 6 mo. Limited data suggests breakthrough infections rare and mild (NEJM 2019;381:1897;NEJM 2022;387:2477).

## Common Ectoparasites (Am Fam Physician 2019;99:635; NEJM 2020;382:2230; CDC Yellow Book)

- **Scabies**: Initial infxn w/o sx then intense pruritis 2-6wk after inoculation (1-4 days if 2nd exp). Classically worsen at night. Exam w/ excoriated papulovesicles +/- burrows in interdigital spaces, intertriginous skin, wrists, shoulder blades or inguinal region. Clinical **Dx**.
  - **Rx:** 5% permethrin cream from neck down w/ removal after 8-14hr (reapply 7d later) **OR** ivermectin 200 ug/kg PO, repeat in 14d; treat household + close contacts
  - Clothing/bedding needs hot water (>130°F) + high heat drying **OR** 1wk isolation in sealed plastic bag
- **Lice**: Pruritis from saliva of lice. **Dx** Live lice should be visualized. Nits ≠ infestation. W/o human blood meal, lice die ≤2d
  - **Rx:** head lice - 1% permethrin shampoo (re-apply 7-10d later since not ovicidal); pubic lice - 1% permethrin cream (reapply 9-10d later if persist + test for STIs + rx partners); body lice - laundry and hygiene +/- permethrin
  - Use high-heat (>130°F) laundering/drying exposed items + vacuuming **OR** 2wk isolation in sealed plastic bag
- **Bedbugs**: Suspect if recent travel. Crops of bites on exposed skin not covered by sheets or clothing. "Breakfast, lunch, and dinner" sign. Feces leave black debris on bedding + furniture. W/o blood meal, bedbugs can *still* live **70d**
  - **Rx:** Resistant to insecticides. Use mechanical methods. Clothing/bedding needs washed at high heat (>140°F). Can expose items to -4°F for 2hr. Physical removal via vacuum. Isolate items in plastic bags for prolonged periods

# Infectious Disease — Fever of Unknown Origin

## DEFINITION (NEJM 2022;386:463; CCM 2008;36:1330; historical review Medicine 1961;60:1)

- Classically T>38.3C on multiple occasions for ≥3w, persisting w/o diagnosis despite ≥3d of inpatient investigation or 3 ambulatory visits (Curr Clin Top Infect Dis 1991;11:35; Br J Hosp Med 1996;56:21); newer recommendations call for T > 38 C (AMJMED 2022)

*Special subpopulations:* nosocomial (first fever > 24h of hospitalization), immunodeficient, neutropenic (current ANC<500 or expected in 1-2d), HIV-associated, travel-associated. **More often an atypical presentation of a more common disease than very rare disease.**

## WORKUP (AJM 2015:128;1138e1; CCM 2023, 51: 1570)

- **Ddx**: In US, most commonly **infectious** > **rheumatologic** > **malignant** > **other**
  - In up to 50% of cases, no source is identified (Am J Med Sci 2012;344:307)
- **History**: fever pattern, B symptoms, PMH (incl. dental hx, immunocompromise), valvular dz, exposures (travel, birthplace, animal, arthropod, food, blood products, sick contacts, sexual contact, drugs, occupation), TB risk factors, meds, vaccine hx, procedures/hospitalization, family hx
- **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, BMP, LFTs, ESR/CRP, UA/UCx (from fresh cath), BCx x2 (diff. sites, min 5 d incubation), CXR, HIV
  - 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, syphilis Ab, LDH, TFTs, SPEP/SFLC, ANA, ANCA, RF/CCP, cryo, CK/aldolase, EBV serologies, CMV PCR, ferritin, blood smear, HBV/HCV, viral NAAT, procalcitonin, organism-specific testing, BCx from at least 2 lumens of CVC if one in place
- **Imaging** (Arch Intern Med 2003;163:545): CT C/A/P (71% Sn, 71% Sp), LENIs, TTE/TEE**, FDG-PET/CT** (Sn 86%, Sp 52%, 58% yield, vertex to toes and IV contrast recommended J Nucl Med 2016;57:1913, AJR 2023;221), maxillofacial CT, POCUS

| Etiologies of FUO | |
|---|---|
| ***bold** = common causes (OFID 2020;7:ofaa132) | |
| **Infectious** | Abscess (perianal, brain, dental), HIV, **EBV**, **CMV**, HHV6-8, HBV, HCV, **endocarditis** (fastidious/HACEK, nutritionally variant *Strep*), nosocomial infection, hardware/graft infection, **osteomyelitis**, septic arthritis, sinusitis, complicated UTIs, **TB (extrapulmonary),** tick-borne infections, endemic fungi (e.g. cocci/histo/paracocci), **malaria** (#1 cause in returned traveler), cat-scratch disease, toxoplasmosis, Q fever, brucellosis, bartonellosis, salmonella, typhus, melioidosis, schistosomiasis, visceral leishmaniasis, Whipple's disease, lymphogranuloma venereum, leptospirosis |
| **Malig.** | **Lymphoma**, **leukemia**, MM, myeloproliferative disorders, **RCC**, HCC, CRC, **melanoma**, pancreatic, cervical, gastric, Castleman's, atrial myxoma, CNS metastases |
| **Rheum.** | Cryo, **PMR**, **GCA**, RA, **Adult Still's**, **(JRA)**/MAS, **SLE**, dermato/polymyositis, sarcoid, HSP, PAN, Kikuchi's, Takayasu's, Behcet's, GPA/MPA/EGPA |
| **Other** | **Drug fever**, serotonin syndrome, NMS, **DVT/PE/hematoma**, hypothalamic dysfunction, pheo, **hyperthyroidism**, alcoholic hepatitis, **cirrhosis**, **IBD**, factitious, HLH, familial periodic fever syndromes (FMF, Hyper-IgD Syndrome, Schnitzler's, TRAPS) |

## TREATMENT

- **Avoid empiric antibiotics** unless hemodynamic instability or immunocompromised
- D/C possible offending meds
- If ↑suspicion for GCA, 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 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$^3$; Immune reconstitution syndrome |
| **Neutropenic** & refractory to abx (NEJM 2002;346:222) | Fungal infx 45%, bacterial infx 10-15% (resistant, biofilms), GVHD 10%, viral infx 5%, misc 25% |
| **Returned traveler*** (AJTMH 2013;88:397) | Falciparum malaria (77%), typhoid fever (12%), paratyphoid fever (6%), leptospirosis (2%), rickettsiosis (2%), dengue (1%) |

*Only considers infectious etiologies, returned from Central or South America, Africa, Oceania, tropical and subtropical parts of Asia

## 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, thrombophlebitis 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, or CNS masses (JAMA Neurol 2013;70:1499)

# Infectious Disease

# Rare Diseases at MGH

| | Epi & Transmission | Symptoms | Labs | Diagnostic Tests | Treatment (c/s ID) |
|---|---|---|---|---|---|
| **Malaria** (*Plasmodium* spp) | Africa, Latin Am, Asia, Mid East, Eastern Europe<br>*Anopheles* spp. | 12-35d incub (up to yrs if *P. vivax*); fever, HSM, AMS, jaundice, petechiae | Anemia, ↓PLT, AKI, ↑LFTs, ↓**glucose**, acidemia | **BinaxNOW** (RDT) + thick/thin blood smear w/ Giemsa | Variable, c/s ID; *(see Travel Medicine)* Promising vaccine candidates |
| **Misc. Arthropod-borne Diseases**: Dengue, Chikungunya, and Zika often indistinguishable; consider testing for all 3 if concerned | | | | | |
| **Dengue fever** (DENV serotypes 1-4; *Flavivirus)* | India, Asia/Pac, Africa, Lat Am, Southern USA<br>*A. aegypti* & *A. albopictus* | Fever, retro-orbital HA, arthralgia "**break bone fever"**, petechiae, shock | Lymphopenia, thrombocytopenia, ↑**Hct** | <7d sx onset = NAAT; IgG/IgM (cross-rxn w/ Zika); tourniquet test | Rest, fluid; **avoid NSAIDs** due to ↑ hemorrhagic sx. Dengvaxia vaccine in US for children |
| **Chikungunya fever** (*Alphavirus*)<br>**Zika virus** (*Flavivirus*) | Africa, Asia/Pac, **Caribbean**, Lat Am, Southern USA<br>*A aegypti* & *A albopictus* (diurnal feeders); STI (Zika) | Fever (>102 in chik), HA, rash, polyarthralgia, conjunctivitis; Guillain-Barré syndrome + fetal microcephaly (Zika) | Chik: lymphopenia, thrombocytopenia, ↑LFTs, AKI<br>Zika: labs freq. nml | Chik: PCR if <7d sxs; serology if ≥7d<br>Zika: serology/plaque reduct.; serum/urine PCR if <7d of sx, serology if ≥7d of sx | Rest, fluid; avoid NSAIDs unless definitely not dengue. Chik: Rheum referral if pain >3 mo. Vaccine immunocompetent traveler for Chik (IXCHIQ) if age 18+. |
| **West Nile virus** (*Flavivirus*) | Africa/MEast, Europe, Americas<br>*Culex* spp. *(nocturnal)* | Asx; fever, HA, myalgia, 1% develop neuroinvasive disease | CSF pleocytosis (lymphs) | **Serum + CSF Abs >** CSF PCR only for immunocomp. (c/s ID) | Rest, fluid |
| **Leishmaniasis,** cutaneous/visceral (*Leishmania* spp) | C/S America, S Europe, Mid East, E Africa, S Asia<br>*Lutzomyia*/*Phlebotomus* | CL: painless ulcer(s), regional LAD<br>VL: fever, HSM, ↓wt | VL: cytopenias, ↑LFTs | Clinical dx, skin bx PCR/smear/cx; rarely Ab | Variable, species/region specific, c/s ID; abx if superinfected lesions |
| **Bacterial Zoonoses**: *Coxiella*, *Bartonella henselae* (or *B quintana*), and *Brucella* are important causes of **culture-negative endocarditis** | | | | | |
| **Cat scratch disease** (*B henselae*) | Worldwide<br>Cat bite/scratch, fleas | Fever, LAD 1-3w, neuro, ocular | ↑ESR/CRP,↑LFT | Ab 1-2w; histology | Variable, c/s ID |
| **Leptospirosis** (*Leptospira* spp.) | Worldwide; tropics > temp.<br>Water contaminated by animal urine/sewage | Fever, HA, myalgia, jaundice, conjuc. suffusion | **AKI,** ↑LFT **w/ very high bili,** rhabdo, anemia, hypoK | Serology if 3-5d sx | Outpt: doxy 100mg BID x7d; inpt: PCN G, doxy, or CTX |
| **Q fever** (*Coxiella burnetii*) | Worldwide (except N.Z.)<br>Aerosolized ungulate fluid | Fever, HA, myalgia, **PNA**, **endocarditis** | ↑AST/ALT, ↑Bili, ↓PLT, ↑CK | Serology ≥7d | Variable, c/s ID |
| **Brucellosis** (*Brucella* spp) | Worldwide<br>Dairy products, ungulate contact, lab exposure | Fever, HA, myalgia, spondylitis, endocarditis, orchitis | ↑AST/ALT, ↓WBC w/ relative ↑lymph, ↑ESR/CRP | Serology if 7-10d sx | Doxy 100mg BID x6w + gent/streptomycin or rifampin |
| **Tularemia** (*Francisella tularensis*) | N America, Europe > Asia<br>Arthropod bite, animal contact (rabbit), food/water, airborne | **Regional LAD**; 6 syndromes: ulceroglandular, glandular, oculoglandular, pharyngeal, PNA, & typhoidal | Nonspecific; ↑ESR/CRP; ↓PLT | Serology if sx ≥2w; GS, Cx (cysteine + media) | Streptomycin or gent 7-10d if severe disease; cipro or doxy 10-21d if mild disease |
| **Rickettsia**: in general, rickettsial diseases with eschars are scrub typhus, African tick-bite fever, RMSF, Mediterranean spotted fever, and rickettsialpox | | | | | |
| **Murine typhus** (*Rickettsia typhi*) | SE Asia, N Africa, N America<br>Feces of infected rat fleas | Fever, **centrifugal rash**, HA, myalgia | ↓Plt, ↑AST/ALT | Serology 2w apart | Doxy 100mg BID x7-14d |
| **Scrub typhus** (*Orientia tsutsugamushi*) | India → E Asia; Pacific, Chile<br>Bites from infected mite larvae (AKA chiggers) | **Eschar**, fever, lymphadenopathy, centrifugal rash, HA | ↓Plt, ↑AST/ALT, ↑Bili, AKI, WBC usually wnl | Serology 2w apart; consider eschar bx | Doxy 100mg BID x7d; azithro if tetracycline-R; combined IV doxy & azithro for severe disease |
| **Helminths**: if concerned about intestinal worms, albendazole is an effective and safe medication to give empirically while awaiting lab results | | | | | |
| **Schistosomiasis** (*Schistosoma* spp) | Africa, Brazil, MidEast, Asia<br>Fresh water with free cercariae from infected snails | Acute (3-8w): fever, urticaria, HA, swimmer's itch. Chronic: HSM, portal HTN, GN, hematuria, neuroschisto | ↑**Eos** (30-60%) in acute, ↓Plt; LFTs usually wnl | Serology 6-12w; stool/urine microscopy for speciation | Acute: pred 20-40mg x5d + praziquantel<br>Chronic: 40-60 x1 of praziquantel |
| **Trichinellosis** (*Trichinella* spp) | Worldwide, esp. Europe<br>Undercooked meat, esp. pork and bear | 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 |
| **Strongyloidiasis** (*Strongyloides stercoralis*) | Rural tropics/subtropics; Appalachia, SE USA<br>Skin contact w/ soil w/ human feces, fecal-oral, autoinfection | Skin rxn, epigastric pain, diarrhea, resp. sx; fever, n/v, sepsis/shock if hyperinfection | ↑**Eos**, ↑WBC; hyperinfection & disseminated dz (in immunosupp.) w/ **normal eos** | Serology Sn > stool, but ↓ Sp. ✓ BCx, may have GNR bacteremia (gut translocation) | Ivermectin 200 mcg/kg/day x2d; for 5-7d if disseminated. If from endemic region scr. for loiasis prior to tx. If RFs, scr. or tx prior to immunosuppression. |
| **Other Infections** | | | | | |
| **Enteric fever** (*Salmonella enterica* serotype Typhi or Paratyphi) | India, SE Asia, Africa<br>Fecal oral; asymptomatic carriers | Fever, lethargy, abd pain, 'rose spots', diarrhea (>50%), constip. (30%), HSM | ↓HR, ↑LFTs, ↓WBC (↑WBC sign of intest. perf.), anemia, abnormal coags | Stool/blood Cx. BMBx 90% Sn. Serology effective in non-endemic regions | Azithro/ciprofloxacin<br>Severe: CTX (consider meropenem if Pakistan or India) |
| **Melioidosis** (*Burkholderia pseudomallei*) | SE Asia, Aus, US Gulf Coast<br>Soil; aspiration, inhalation, percutaneous inoculation | Fever, PNA, disseminated abscesses, (particularly skin & lung) | ↑WBC; other nonspecific values c/w organ failure | Blood Cx on Ashdown's agar, GS | Variable, c/s ID |
| **Hantaviruses** | SW US, Lat Am, Eur., Asia<br>Aerosolized rodent excreta | Hemorrhagic fever, renal failure, ARDS | ↑PTT, ↓Plt, AKI, **proteinuria** | Serology via state department of health | Supportive care |
| **Toxoplasmosis** (*Toxoplasma gondii*) | Worldwide<br>Cats; cont. meat/water | Mono-like symptoms | Atypical lymphs, ↑AST/ALT | Serology 1-7d; CSF 2-5d | Tx if CNS, chorioretinitis, or pregnant (consult MFM) |

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, JAMA 2022;328:460; Dengue: NEJM 2012;366:1423, Nat Microbio 2019;4:1508; Zika: NEJM 2016;374:1552; Chikungunya: NEJM 2015;372:1231; West Nile: JAMA 2013;310:308; Cat scratch disease: Am Fam Physician, 2011;83; Brucellosis: NEJM 2005;352:2325; Rickettsia: NEJM 2023;388:792; Schistosomiasis: NEJM 2002;346:1212; Typhoid: NEJM 2002;347:1770; Melioidosis: NEJM 2012;367:1035; Leishmaniasis: Am J Trop Med Hyg 2017;96:24; Coxiella: MMWR 2013;62.3:1; Strongyloides: Am J Trop Med Hyg 2017;97:645.



Suggest an Edit

# Infectious Disease — Infection Control

**Resources**: Infection Control websites on Sharepoint and Ellucid for the most up-to-date MGH policies and list of diseases/conditions requiring isolation. For additional support, work with unit-specific nursing leadership and contact Infection Control (x62036)

**Standard Precautions**: apply to *all* patients. **Hand hygiene (HH) is the most important action to stop the spread of infection. Please stay up-to-date re: source control for masking/hospital-approved eyewear.**

- 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** according to instructions on label after patient contact/use

**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 | ○ Hand hygiene + nonsterile gloves + isolation gowns<br>○ **Do not touch** phones, beepers, notes while in room<br>○ Remove gown and gloves *together* only touching *inside* of PPE with bare hands, dispose of PPE inside or immediately outside the room<br>○ Dedicate the use of equipment (stethoscope, BP cuff) to avoid sharing w/ other pts. All equipment w/in the room is presumed contaminated<br>○ Disinfect reusable non-critical equipment (stethoscope) using hospital-approved disinfectant wipes for pathogen of concern | MRSA<br>VRE<br>MDROs<br>CRAB<br>CRE<br>Disseminated HSV |
| **Contact PLUS** | Spore forming & alcohol-resistant orgs transmitted by indirect/direct contact | ○ Contact precautions + hand wash soap/water + ABHR + private room<br>○ After doffing PPE; wash hands with soap/water x15-20sec, dry, then apply ABHR; use bleach wipes for equipment<br>○ Isolate pt empirically while awaiting results | *C. diff*<br>Norovirus<br>*C. auris*<br>Cutaneous anthrax |
| **Enhanced** | Cystic Fibrosis (bidirection protection) | ○ Contact precautions + private room and limitations on use of shared spaces | |
| **Droplet** | Large respiratory droplets (coughing, sneezing, talking) | ○ Surgical mask + eye protection + private room<br>○ Isolate pt empirically while awaiting results | *N. meningitidis*<br>Influenza<br>Rhinovirus<br>Adenovirus<br>Pertussis<br>Mumps |
| **Enhanced Respiratory** | COVID-19 | ○ N95/PAPR + eye protection + private room (may cohort known with known COVID-19)<br>○ 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 | ○ Standard precautions + N95/PAPR + AIIR | Tuberculosis<br>Varicella<br>Disseminated VZV |
| **Strict** | Highly pathogenic organisms | ○ Contact precautions + N95/PAPR + eye protection + AIIR. If suspected, isolate, contact Biothreats (Non-COVID) Pager #26876 | SARS/MERS<br>Avian Influenza<br>Variola (smallpox)<br>Mpox |

**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, gloves, and surgical mask for healthcare workers
  - Note: Plants and flowers should not be allowed in immunocompromised host rooms due to risk of fungal infection

**How Infection Statuses are Resolved and Transmission-Based Precautions Discontinued**:
Use .Resolve (previously CORAL/NEMO) for all COVID-related infxn statuses. For screening for resolution of prior MRSA, VRE, MDRO status, please review MGH Resolution Policy and use .Resolve. Discuss resolving any other infection status w/ Infection Control

**Bloodborne Pathogen Exposure**: (needlestick, splash to eyes, mouth, nose, open cut), see *Exposures & Needle Sticks*

1. Immediately wash affected area
2. Normal business hours: call MGH OHS (6-2217). Outside business hours: page on-call OHS clinician, pager #21272. Can also page MGH needlestick consultant, pager #36222.
3. Notify supervisor. Floor charge nurse can help with paperwork and expediting any necessary patient labs

**Pregnant Health Care Workers and Infectious Disease**

# Hematology — Pancytopenia & Anemia

## PANCYTOPENIA

| Etiologies | |
|---|---|
| **Infection** | **Viral** (HIV, HBV/HCV, CMV/EBV, parvo), **bacterial** (brucella, TB), **fungal** (histo), **parasitic** (leish, malaria, schisto) |
| **BM infiltration** | **Malignant:** leukemia*, MPN, MDS, MM, metastasis. **Non-malignant**: myelofibrosis, infection (TB, histo), storage dz |
| **BM failure** | **Nutrition**: ↓B12/folate/Cu/Zn, EtOH, anorexia. **Marrow suppression** from infxn (see above). **Immune destruction/suppression**: aplastic anemia, PNH, drugs, LGLL, SLE/RA, sepsis, HLH. **Ineffective hematopoiesis**: MDS |
| **Destruction / sequestration** | **Consumption**: autoimmune, DIC/TMA. **Splenomegaly**: portal HTN/cirrhosis, infection, autoimmune (SLE/RA), **others** |
| **Congenital** | Wiskott-Aldrich, Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, GATA2 deficiency, HLH |
| **Work-up** | |
| **History** | Time course, prior treatments/transfusions, autoimmune/onc hx, social, travel, occupational, infection hx, constitutional sx |
| **Initial labs** | **CBC/diff**, **retic**, **special slide**, **T&S**, LFT, TSH, Iron Studies, B12, folate, ESR/CRP, INR/PTT/fibrinogen<br>**Also consider**: Cu, Zn, Vitamin E, LDH, haptoglobin, SPEP/SFLC, DAT, uric acid, ANA, HIV/HBV/HCV/CMV/EBV/Parvo |
| **Review meds** | NSAIDs, PPIs, sulfas, antihistamine, chemo, anticonvulsants, antiprotozoals, heavy metals, **many others** |
| **Hematology** | **Consult for**: unexplained significant neutropenia/thrombocytopenia, Blasts* on Diff, DIC/TMA, HLH, heme malignancy |

Always consider the possibility of multiple independent cytopenias in addition to a unifying diagnosis
*Blasts first show up as 'Others' on a diff with a comment from the lab on their morphology until confirmed

## ANEMIA (Williams Hematology 2021)

**S/Sx**: ↓O2 delivery → fatigue, lightheaded, DOE, pallor, angina (if CAD), claudication, cramps, abd pain, N/V; compensatory mechanisms → ↑RR, ↑CO (↑HR, palpitations, flow murmur, later: high-output HF), ↑erythropoiesis (bone pain)
**Other findings**: dark urine/jaundice (hemolysis), glossitis (folate/B12/Fe def), motor/sensory deficits (B12 def), pica/koilonychias/angular cheilitis/RLS (Fe def), splenomegaly (cirrhosis, infxn, thalassemia, malignancy, chronic hemolysis), constipation/bone pain (myeloma), melena (GIB), heavy menstrual bleeding, unusual thromboses (PNH), petechiae/purpura (coagulopathy, pancytopenia), family hx (thal/SS)
**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, review prior CBC
  - If unrevealing/otherwise indicated by history: ± SPEP/SFLC, Hgb electrophoresis, AM testosterone, EPO, BMBx
- **RI >2% → "Hemolysis labs" vs recent bleeding**: 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 μm³) | **Normocytic** (MCV 80-99 μm³) | **Macrocytic** (MCV ≥100 μm³) |
|---|---|---|
| **Iron deficiency anemia (IDA)**<br>• ↓Fe, ↑TIBC, ↓ferritin (<30 high Sp; <15=⊘Fe in BM), Fe/TIBC <16%, <20% with inflammation, ↑RDW<br>**Thalassemias**<br>• Fe studies nml, MCV ↓↓ (often <70), Mentzer index (MCV/RBC <13; high Sp); Hb electrophoresis<br>**Sideroblastic anemia**<br>• ↑ferritin, Fe/TIBC nml; smear: basophilic stippling (Pb); BMBx: ringed sideroblasts | **Anemia of inflammation/chronic disease**<br>• ↓Fe,↓/nl TIBC, ↑ferritin (>100), Fe/TIBC ↓/nl (<20%)<br>**Mixed:**<br>• IDA & ↓folate/B12 (dimorphic: nml MCV w/ ↑RDW)<br>**Organ-specific**:<br>• **Renal** (CKD/ESRD): ↓Epo (should ↑10x per 10% Hct drop)<br>• **Endocrine** (thyroid, pituitary, adrenal, parathyroid, testosterone; ↓metab rate→↓O2 demand) ->↓Epo secretion<br>• **Marrow** (red cell aplasia, aplastic anemia, MDS, myelofibrosis, myelophthisis, PNH, MM): check SPEP, serum FLC, BMBx | **Megaloblastic**: *smear shows hyper-seg PMNs and macro-ovalocytes*<br>• ↓**Folate**: ↑homocysteine, nl MMA<br>• ↓**B12**: ↑homocysteine, ↑MMA (↑anti-IF Ab, ↑gastrin if pernicious anemia; falsely nml B12 possible)<br>• Copper deficiency<br>• **Early myeloproliferative d/o**<br>**Non-megaloblastic**: MCV usually <110<br>• **Cirrhosis, EtOH**<br>• **Reticulocytosis**: lysis or bleed<br>• **Hypothyroidism**<br>• **MDS** (refractory anemia) **& MM**<br>**Meds**: antifolates, pur/pyr analogs, AEDs, HAART, AraC, Hydrea, others |

### DESTRUCTION/LOSS (RI >2%)

| **Extrinsic** (to RBC) | **Intrinsic** (to RBC) |
|---|---|
| **MAHA (-DAT, +schisto)**: see *Thrombocytopenia*<br>• Smear (≥2 schisto/HPF), plt ~25K, ↑LDH, ↑indirect bili, ↓hapto<br>**Immune (+DAT, +spherocytosis)**: Antibody and/or complement-mediated<br>• **Warm autoimmune** (CLL, HIV, lymphoma, SLE): +DAT anti-IgG/C3<br>• **Cold autoimmune** (EBV, lymphoid malig, mycoplasma): +DAT anti-C3<br>• **Drugs** (PCN, cephalosporins)**, alloimmune** (hemolytic transfusion rxn)<br>**Non-immune (-DAT)**:<br>• **Infection**: Babesia, Malaria, Carrión disease, C. perfringens, H. flu (type B)<br>• **Toxin**: lead, copper (Wilsons), insect/spider/snake bites, hypotonic infusion<br>• **Hypersplenism**: many; massive SM usually heme malig or infection<br>• **Vitamin E deficiency**<br>• **Mechanical trauma**: mechanical valve, aortic stenosis | **Hereditary**:<br>• **Hb** disease (SS, HbC, thal): Hb electrophoresis<br>• **Enzyme deficiency** (G6PD, PK): *G6PD levels often nml in attack*; check 4w later & repeat in 3mo if ⊖<br>• **Membrane defect:** spherocytosis, elliptocytosis<br>**Acquired (new onset)**:<br>• **PNH** (paroxysmal nocturnal hemoglobinuria): flow cytometry ± FLAER for GPI anchor, smear nml, UA (Hgb/hemosiderin), thrombosis (intra-abd/cerebral)<br>**Acute blood loss**: GI blood loss, hematoma |
| **Intravascular**: ↑↑LDH, ↓↓hapto, hemoglobinemia & -uria; **Extravascular**: ↑indirect bili ± ↑LDH ± ↓hapto (if free Hb escapes spleen) | |

# Hematology — Pancytopenia & Anemia

## 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 disease (esp. if not responsive to PO iron), menorrhagia hx. Calculate Fe deficit with Ganzoni equation (can also use .irondeficit in EPIC)
- **Treatment**:
  - **PO 325mg $FeSO_4$ QOD** (QOD ↑ absorption: Lancet Haematology 2017;4:e524). ~6w to correct anemia, ~3-6mo to replete stores. ↑ absorption on empty stomach, VitC may ↑absorption, ↓ absorption w/ $Ca^{2+}$ rich foods, antacids.
    - GI SE: constipation, epigastric pain, N/V
  - IV iron if ongoing heavy bleeding, CKD, malabsorption, IBD, intolerant to PO, or chronic CHF (NEJM 2009;361:2436). IV Iron at d/c following ADHF ↓risk of future HF hospitalizations (Lancet 2020;396:1895). Typical dose: **iron sucrose 100 – 300 mg per dose, repeated until total iron req met**.
    - SE: n/v, pruritus, flushing, myalgia/arthralgia, CP. Anaphylaxis rare with modern products. Pt with inflammatory arthritis may have flare from IV infusion.

## Anemia Of Inflammation/Chronic Disease (NEJM 2019;381:1148; Blood 2019;133:40)

- **Etiology**: autoimmune, infection, malignancy, CHF, CKD, obesity, DM, aging, critical illness
  - inflammatory cytokines (IL-1, IL-6 & TNFα) → ↑hepcidin → ↑ ferroportin internalized / degraded → ↓intestinal Fe absorption, ↓Fe & hepatic Fe mobilization
- **Time course**: usually 1-2mo to develop, but can ↓Hgb 2-3g/dL in 1-2d in acute illness
- **Treatment**: tx underlying disease and concomitant deficiencies (Fe, folate, B12, Vit E)
  - **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 ≥20%, ferritin ≥100 for EPO therapy

## Macrocytic / Megaloblastic Anemia (MCV ≥100μm³)

- Review meds, if without megaloblastic changes (hyperseg PMN): consider thyroid, liver, nutritional causes, MDS, reticulocytosis
- ↓**Folate** ("foliage"), **3mo** stores
  - Etiology:**↓intake** (EtOH, elderly), **↓absorption** (Celiac, jejunum), **↑demand** (pregnancy, hemolysis, malignancy), **meds** (MTX, TMP, AEDs). When severe, can be a/w hemolysis & pancytopenia.
  - Labs: ↑homocysteine, MMA normal
  - Tx: 1-5mg PO qd (can worsen B12 deficiency and associated neurologic complications if not replete)
- ↓**B12** ("beef"), **3y** stores
  - Etiology:**↓intake** (EtOH, vegan), **pernicious anemia** (Ab to intrinsic factor (IF), gastric parietal cells), **↓absorption** (gastrectomy, Celiac, Crohn's, PPI, chronic pancreatitis), **↑competition** (SIBO, tapeworm); when severe a/w pancytopenia & **subacute combined degeneration** (dorsal columns, corticospinal tract) w/ dementia, ataxia, paresthesia
  - Labs: B12 lvl, check homocysteine/MMA if B12 borderline (200-350). Consider anti-IF Ab if homocysteine/MMA ↑ or if B12 <200
  - Tx: 1-2mg PO B12 qd vs IM dosing (depending on if symptomatic anemia, neuro sx, malabsorption). Post-tx, neuro sx start to improve 3mo-1y (NEJM 2013;368:149)

## Autoimmune Hemolytic Anemia (AIHA) (NEJM 2019;381:647; Blood 2017;129:2971)

- **Warm AIHA**:
  - Etiology: antibody-mediated, often **idiopathic**, less common CLL/lymphoma/MM, ALPS, SLE, HIV, EBV, HCV, SARS-CoV-2, babesia, meds. Extravascular > intravascular hemolysis. Rule out other causes of hemolytic anemia
  - Dx: +DAT anti-IgG and/or C3d (typically IgG and pan agglutinin)
  - Tx: transfusion for symptomatic anemia or Hgb <7, steroids, d/w blood bank. 2nd line: rituximab, splenectomy, mycophenolate
- **Cold agglutinin disease**:
  - Etiology: **Often associated with lymphoproliferative process, EBV, mycoplasma, autoimmune**. Hemolysis mediated by complement.
  - Dx: +DAT anti-C3d only and cold agglutinin titer
  - Tx: Tx underlying process, workup clonal lymphoproliferative disorder. If symptomatic, warm transfusions, plasmapheresis, rituximab, sutimlimab. Steroids/splenectomy not indicated.
- **Drugs**: both Ab & non-Ab-mediated; abx (PCN, cephalosporins, sulfa); NSAIDs; rasburicase (G6PD), anti-cancer meds, others
  - If +DAT but no hemolysis, think **drugs**, ↑↑**IgG** (IVIG/Rho(D)/myeloma), **CTD** (e.g., controlled SLE)
- **Other etiologies**: paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria (PCH; anti-C3).

## Hemophagocytic Lymphohistiocytosis (HLH)

- Excessive inflammation/tissue destruction secondary to abnormal immune activation of macrophages and lymphocytes & cytokine storm. Can be **primary** (genetic mutations; most often in children) vs **secondary** (malignancy, infection or autoimmune dz).
- **Workup: molecular testing or dx with** 5 of 8 clinical features: 1) fever, 2) splenomegaly, 3) bicytopenia (2/3 cell lines), 4)↑TG OR ↓fibrinogen, 5) ferritin ≥500 (usually >3k), 6) ↑sIL-2R, 7) hemophagocytosis in BM, spleen, or LN, and 8) low/no NK activity. Also ↑LFTs, hepatomegaly, ↑LDH, ↑D-dimer, ↓ fibrinogen, ↓ESR, ↑CXCL9. **H-score** for probability.
- **Evaluate for trigger**: infection (pan-culture, viral titer/PCR: EBV, CMV, hepatitis, HSV, VZV, HIV, HHV-8, HHV-6, parvo, bartonella, leishmaniasis), malignancy, CAR-T, rheum, neuro (brain MRI, LP), genetic
- **Tx**: Treat underlying etiology. If acutely ill: dexamethasone (crosses blood-brain barrier) + etoposide (+/- intrathecal therapy for CNS involvement). Consider emerging therapies (ruxolitinib, anakinra). Allogeneic HCT indicated for some (primary HLH, relapsed/refractory, significant CNS involvement) ( Blood 2019;133:2465)

# Hematology — Sickle Cell Disease

## OVERVIEW (JAMA 2022;328;570)

- **Definitions**:
  - Sickle Cell allele: autosomal recessive βglobin gene A->T (Glu6Val) missense mutation
  - Sickle Cell Trait (SCT): heterozygous for HbS w/o aberrancy in partnered βglobin gene
  - Sickle Cell Anemia (SCA): homozygous for HbS (HbSS)
  - HbSC disease: heterozygous for HbS & HbC (HbSC): generally milder than SCA, with less severe anemia and hemolysis
  - Sickle Cell Disease (SCD): umbrella term for inherited hemoglobinopathies with at least one HbS allele
- **Epidemiology**: ~300K born with SCD per year worldwide. ~100K w/ SCD in U.S, 1.2K families in Boston area. ~7-8mil worldwide
- **Pathophysiology**: deoxygenated HbS polymerization → sickle shaped RBCs impact RBC membrane integrity & adherence to vascular endothelium → hemolysis-related endothelial dysfunction and vaso-occlusive episodes (VOE).
- **Diagnostics**: baseline Hb electrophoresis and HPLC: tests to separate HbS from other variants (HbA, HbF, HbC)
- **Mortality**: average life expectancy for SCD is ~50 years; ↑ socially vulnerability → ↑ mortality (JAMA 2024;7(9):e2440599)

## CLINICAL MANIFESTATIONS

- **Vaso-Occlusive Episode**: caused by sickled RBCs adhering to vascular endothelium → microvascular occlusion which can lead to tissue ischemia and pain (Transl Med. 2021;19:397). Complication for which patients most commonly seek medical attention; frequency peaks between ages 19-39.
  - Sx: severe pain, swelling, tenderness, HTN, N/V. ↑risk when Hb >8.5 and ↓HbF.
  - Triggers: dehydration, infection, changes in the weather, stress, menses, EtOH. Over 50% of VOE w/o clear etiology.
  - Dx: no objective signs or lab values, patient report is the criterion standard
- **Acute Chest Syndrome**: new imaging infiltrate + pulmonary symptoms in a patient with SCD, including: dyspnea, fever, chest pain, cough, or hypoxemia (NEJM 2000; 342: 1855-1865). #2 cause of hospitalization. Pulmonary arterial circ ↓O2 tension → ↑risk VOE. Complications include PNA, thromboses, fat embolism. NB: 50% preceded by or a/w acute pain episodes
  - Dx: CXR, ↑WBC, r/o PE & MI
  - Tx: O2 goal >95%, antibiotics (CTX+azithro or FQ), adequate analgesia is critical to prevent splinting-sickling cycle, transfusions (simple vs exchange), bronchodilators
- **Multisystem involvement:**
  1. Splenic sequestration: 20% pts; acute 2g/dL ↓Hb
  2. Infection: given functional asplenia/hyposplenism, ↑risk of encapsulated org, defects in alternative complement pathway. If febrile, send BCx and cover empirically w/ CTX (+azithro if c/f acute chest; +vanc if HDUS or c/f meningitis)
  3. CV: major cause of death, CM (secondary to chronic anemia, hemosiderosis), ↑MI risk (even in absence of atherosclerosis)
  4. Neurologic: stroke (~1/4 of pts with SCA with experience a stroke by age 45) → neurocog impairment, epilepsy
  5. Hepatobiliary: hepatic VOE, intrahepatic cholestasis, iron overload from frequent transfusions, pigmented gallstones
  6. Bone: ↑rate Vit D def & osteoporosis, osteonecrosis
  7. Heme: chronic compensated anemia, aplastic crisis, & hyper-hemolytic episode: rare; pain, fever, ↓Hb w/in 7-15d of transfusion; Tx: notify blood bank, hydration ± steroids, IVIG, rituximab, eculizumab
  8. Vascular/cutaneous: priapism, leg ulcers, pulmonary HTN, renal insufficiency, proliferative retinopathy

**Severe complications of disease requiring urgent hematology consult to discuss red cell exchange**: severe acute chest syndrome, stroke, multiorgan failure syndrome, myocardial infarction

## MANAGEMENT

**Contact Sickle Cell Team (p28439) for every admission.** Consult inpatient hematology for severe SCD-related complications (as above)

- Workup: CBC/diff, BMP, LFTs, coags, reticulocyte count, BCx, UA/UCx; CXR; special slide (polychromasia., sickle cells, Howell-Jolly)
- **All inpatients: VTE ppx, pain control,** O2 (SpO2 <92%), often IVF for acute pain episodes. **See Acute Care Plan**. Utilize Epic Order Set ("General Adult Sickle Cell Crisis").
  - **Pain control**: IV opioids within <1hr of ED arrival (see MGH ED protocol) ± fluids at 100-150 mL/hr IV ± NSAIDs (5-7 days; ketorolac ≤ 5 days; Blood Adv 2020;4:2656). If unknown prior dose, ask patient and consider IV morphine 0.1-0.15mg/kg ≤10mg or Dilaudid 0.02-0.05mg/kg (max 1.5mg). Once admitted, discuss transition to PCA with patient and pharmacy. Do NOT hold long-acting PO opioids unless on a PCA with a basal rate. Avoid steroids (↑ rebound pain). Give aggressive bowel regimen ± methylnaltrexone. If uncontrolled, contact chronic pain for high dose PCA titration and to consider ketamine (MGH policy).
  - **Pruritis**: chronic (non-sedating antihistamine or 5-$HT_3$RA), inpatient consider continuous infusion ↓dose naloxone gtt (0.25 mcg/kg/hr), compatible for simultaneous admin w/ morphine. *Note: Avoid IV Benadryl in favor of PO*
- Neutral language: misperceptions interfere with management, biased language a/w poor pain control and ⊖ attitude to pt (JGIM 2018;33:685). Avoid stigmatizing terms, eg: "sickler, freq. flyer, pain seeking" which ↑ bias and bidirectional mistrust (JAMA 2022;328;570).
- Transfusions: *Indicate Sickle Cell on Epic transfuse order for more extensive match.* Mechanisms of benefit include: dilute HbS, ↓Epo reducing production of new HbS cells, ↑SpO2. Indicated in stroke, multiorgan failure, acute chest, sequestration, peri-op. symptomatic or severe anemia (drop of hgb >2 from baseline). No e/o benefit in acute pain episode (Br J Haematol 2015;171:288). Exchange > simple (risk of hyperviscosity). Judicious w/ transfusion (alloimmunization; risk of clinically sig. iron overload if >15-20 RBC units) (Blood Adv 2020;4:327).
  - Iron chelators: deferoxamine (subcutaneous and IV), deferiprone and deferasirox (PO, poorly tolerated, toxic). Initiated ~1-2 years of chronic transfusions or ferritin >1000-1500 ng/mL.
- Outpatient: hydroxyurea (↑HbF; continue inpatient), folate/MVI, L-glutamine (↓ RBC oxidative stress; NEJM 2018;379:226) Vaccines for encapsulated bacteria (Mening, HiB, Pneumo), HBV, flu, COVID. Consider prophylactic transfusions in patients with multiple episodes of acute chest despite maximal therapy. Consider SNRIs, amitriptyline, and pregabalin for chronic pain (Blood Adv 2020;4:2656).
- Other therapies: allogeneic BMT only curative option. Gene therapy targeting BCL11A (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 |
|---|---|---|
| - Infection: sepsis, HIV/HCV, VZV/CMV/EBV, parvo, tickborne<br>- Nutrition: EtOH, ↓B12, ↓folate<br>- Drugs: abx, chemo (ASH Edu 2018;2018:576)<br>- Neoplasm: MDS, BM infiltration, 1° heme<br>- Other: hereditary, cirrhosis, aplastic anemia, some vWD | - Immune: ITP, SLE/APLS, RA, lymphoma, post-transfusion<br>- Drugs: heparin, MTX, abx, AEDs, anti-GPIIb/IIIa, quinine<br>- MAHA: DIC, TTP, HUS, mHTN, preeclampsia/HELLP<br>- Mechanical: CVVH, bypass, ECMO, IABP, valves | - Hypersplenism<br>- Hemangioma<br>- Massive transfusion<br>- Hypothermia<br>- 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, BMP, LFTs, coags, special slide, T+S, HIV, HCV, pregnancy test, citrated plt count (r/o pseudo-thrombocytopenia)
- If asymptomatic, mild (100-150k): history of risk factors (i.e. alcohol use), routine exam, CBC for other cytopenias, special slide, HIV/HCV testing, B12, folate (common cause of over-testing)
- 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: consult Hematology, consider BM biopsy

## IMMUNE THROMBOCYTOPENIA (ITP) (Blood Adv 2019;3:3829; Blood 2017;129:2829; NEJM 2019;381:945)

Antiplatelet antibodies cause plt clearance and bind to megakaryocytes, resulting in apoptosis and near-normal rate of platelet production. Can be primary (80%, no clear associated condition), secondary (eg. SLE, APLAS, CVID, CLL, Evan's, HCV, HIV, drug-induced ITP, etc).
**Presentation**: **Precipitous and sudden decline in platelet.** Asx or mucocutaneous bleeding; 10% of ITP has AIHA. Consider thrombopoietin level (may predict responsiveness to TPO receptor agonists (Am J Hematol 2018;93:1501-1508)).
**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-plts, upcoming procedures, & plt near 30k
- Plt 10k-29k: steroids ± IVIG, RhoGAM if RhD+; if not bleeding, DO NOT give plts (destroyed & ↓ Plt further) (Blood 2015;125:1470)
  - Steroids (takes 4-14d to work): dexamethasone 40mg/d x4d, methylpred 1g/d x3d, or prednisone 60mg/d x3w w/ taper
- Plt <10k: steroids + IVIG, consider romiplostim, do not give plts unless c/f bleeding
- Severe bleeding: Plt, IVIG, steroids (pulse-dose methylpred & dex), Amicar (0.1g/kg/30min→gtt 0.5-1g/h)/TXA, romiplostim
- Refractory/recurrent: ↑romiplostim dose, ritux, fostamatinib; last resort (>12m after dx) splenectomy (>50% effective, risk of relapse)

## HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) (Blood Adv 2018;2:3360; Blood 2017;129:2864; NEJM 2015;373:252)

IgG anti-PF4-heparin complex binds & activates plts→ hypercoagulable state. Can occur with any heparin (UFH, LMWH, heparin flushes)
**Types:** HIT Type 1 (mild platelet drop no lower than 100k 1-2d from heparin exposure, not clinically significant) vs. HIT Type 2 (see below)
**Presentation**: 5-10d after exposure, ↓plt >50%, nadir 40-80k, thrombosis in 30-50% (skin necrosis, DVT/PE, arterial), GIB (~3%)

- Consider rapid-onset HIT if <24h with prior heparin exposure within 100d; delayed-onset can present up to 3w after last heparin

**Diagnosis/Management**: Calculate 4Ts Score. (If incomplete information, may be prudent to err on side of higher 4T score. Recalculate for change in clinical picture). 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). 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
3) Screen for DVT with upper/lower extremity ultrasound

- Duration of AC: if no thrombosis, until plt >150k (at least 4 weeks); if thrombosis, at least 3mo. Non-heparin AC options:
  - **Fondaparinux** (SQ): for stable non-surgical patients, contraindicated if GFR <30, irreversible
  - **Argatroban** (IV): preferred in renal failure & surgical pts (short half-life), monitor w/ chromogenic Xa (goal 20-40%)
  - **Bivalirudin** (IV): only approved for HIT undergoing PCI, preferred in liver failure
  - **DOACs:** can be used for patient with average bleed risk, **warfarin** not until plt >150K for 2 consecutive days
- Add heparin to allergies, avoid in future & use other VTE ppx. If strong 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). **Resolution of ↓Plt expected in ~7d**

## THROMBOTIC MICROANGIOPATHY (TMA) (NEJM 2014;371:654)

Microthrombi → **MAHA** (↓Hb, ↑LDH, ↓haptoglobin, +schistos, -DAT), **↓↓plt** (consumption), **end-organ injury** (vascular occlusion)

- **Drug-induced (DITMA):** gemcitabine, oxaliplatin, quetiapine, quinine, tacrolimus, cyclosporine, bevacizumab, opioids
- **TTP** (Plt <30K): inherited/acq. *ADAMTS13* def. →vWF multimers →formation of plt microthrombi. S/Sx: purpura, GI sx, neuro sx; fever, AKI. Dx: PLASMIC score mod/high, lab testing of ADAMTS13 activity. Tx: **plasma exchange/FFP,** steroids, ritux. DO NOT transfuse to correct Plt unless severe bleed, though transfusion not a/w ↑ risk of mortality/CNS comp (Transfusion 2009;49:873).
- **HUS** (plt >30K)
  - **Shiga-toxin-mediated** O157:H7 *E. coli*, *Shigella* ("ST-HUS"). S/Sx: bloody diarrhea, severe AKI; severe neuro sx rare. 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, malignant HTN, HELLP, post-HSCT
- **Immediate Management:** if DITMA, d/c drug. Special slide (+schistos), c/s Heme if concerned and/or severe anemia/↓ Plt, monitor UOP (for renal impairment), consider complement (C3/C4) testing. 1st line: therapeutic plasma exchange, transfuse RBCs if symptomatic anemia, transfuse platelets for <20k or <50k with bleeding/pre-procedure.

# Hematology — Eosinophilia

## OVERVIEW (Am J Hematol 2022; 97:129; 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, rheumatologic dz, etc

| | |
|---|---|
| **Infections** | **Helminthic**: strongyloidiasis, toxocariasis, schistosomiasis, ascaris, filariasis, trichinellosis, hookworm, fascioliasis. **Fungal**: aspergillus (ABPA), coccidiomycosis, histoplasmosis. **Protozoal**: isospora. **Viral**: HIV, HTLV1/2 |
| **Malignancy** | Primary HES (platelet-derived growth factor receptor alpha-assoc.), eosinophilic leukemia, CML, NHL, HL, mastocytosis; less common with solid tumors |
| **Autoimmune** | EGPA (see *Vasculitis*), PAN, eosinophilic fasciitis, RA, IBD, EoE, IgG4, sarcoidosis, GVHD, blistering disease |
| **Allergic** | Drugs (i.e. penicillins, cephalosporins, NSAIDs, ranitidine, aspirin, allopurinol, phenytoin, tetracyclines), DRESS, asthma/atopy, ABPA, hyper IgE syndrome, AIN, episodic angioedema (Gleich syndrome) |
| **Misc** | Adrenal insufficiency, cholesterol emboli syndrome, acute arterial thrombosis, radiation exposure, familial (Chromosome 5q mutation), iatrogenic |

## 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, family hx
- **Exam**: assess for rashes, cardiac/pulmonary/GI 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, high-res CT Chest & PFTs if dyspnea, coughing, or wheezing
  - If AEC >1500, assess for HES: check U/A, CK, troponin, EKG, CXR, PFTs, CT C/A/P or PET (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 parasitoid/fungal serologies; ANCA if c/f EGPA; ANA, RF, CCP if c/f rheum dz; ACTH/cort stim if c/f AI; IgE levels, allergy testing if c/f allergy; imaging/bronch; endoscopy if c/f EoE/EGE; TTE/CMR if c/f cardiac dz; periph. flow ± BMBx if c/f MPD or >1500 & no obvious 2° cause
- **When to suspect drug reaction:** isolated ↑Eos or w/ systemic illness (e.g. DRESS, hepatitis, AIN). PCN/cephalosporins common culprits. Suspect DRESS if new drug 2-8w prior, fever, rash, facial edema, LAD, ↑ LFTs, ± organ involvement, atyp. lymphs.

## 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

## 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, restriction, intracardiac thrombi), cardiac MRI (+subendocardial LGE), endomycocardial bx
  - 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; Dx: BAL Eos ≥25%; Tx: steroids
- Chronic eosinophilic PNA: >4w fever, cough, SOB, wt loss; a/w asthma; Dx: BL mid-upper lobe infiltrate; BAL Eos ≥25%; Tx: steroids
- 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/small bowel/colon ± esoph.; Sx: n/v/d, abd. pain, malabsorption (mucosal dz), poor motility/obstruction/perforation (muscular layer dx), ascites (serosal dz); Tx: dietary Δs, PO steroids

## PRIMARY HYPEREOSINOPHILIC SYNDROMES (HES) (Am J Hematol 2022; 97:129; Hematology 2015;2015:92)

- **Myeloproliferative HES** (~20% of HES in US): acute/chronic eosinophilic leukemia; 80% pts have *FIP1L1-PDGFRA* fusion gene
  - Dx: anemia, thrombocytopenia, ↑tryptase, ↑B12, special slide (dysplastic eosinophils), BM Bx (fibrosis, hypercellularity)
  - Tx: if PDGDR+→ imatinib ± steroids (if cardiac sxs); if JAK2+→JAK2 inhibitor; if FGFR1+→chemo. 2nd line: sorafenib, midostaurin, or ponatinib.
- **Lymphocytic HES**: clonal T-cell expansion →↑IL-5 → ↑Eos. Often p/w skin/soft tissue involv., polyclonal hyper-IgG, ↑IgE. 5-25% progress to lymphoma (a/w chromosome 6p deletion).
  - Dx: flow cytometry for aberrant Th2 type CD4 cells; Tx: steroids; 2nd line: IFN-α, hydroxyurea, anti-IL-5
- **Idiopathic HES/Hypereosinophilia of Uncertain Significance ($HE_{us}$)**: eosinophilia w/o identified cause +/- organ involvement → consider ANCA-neg EGPA, suggested all pts get f/u to ensure no end-organ involvement even if asx at dx. Tx: Steroids only if sx.

# Hematology — Coagulation Disorders

## HYPERCOAGULABLE STATES (NEJM 2017;377:1177) (ASH 2023 Guidelines)

**Do not test at time of event or during anticoagulant therapy***. If performed, should be >**2 weeks *after* stopping anticoagulation.** Testing includes: Factor V Leiden, prothrombin gene mutation, protein C/S def, antithrombin deficiency, antiphospholipid Abs.

**Exception: may begin testing for APS in acute setting for pts with compelling history (will influence choice of AC)*

| | Do not test for thrombophilia | Test for thrombophilia |
|---|---|---|
| **Patients with established VTE** | - **Unprovoked VTE (warrants indefinite AC)**<br>- VTE provoked by surgery<br>- VTE provoked by other clear predisposing medical syndrome (nephrotic syndrome, MPN, HIT) | - VTE provoked by a major nonsurgical transient risk factor (e.g. admission for PNA) or OCP/peri-pregnancy *(controversial)*<br>- Cerebral/splanchnic VTE (+ test JAK2, PNH in hepatic/PVT)<br>- VTE in patient < 45y **or** with 1st deg relative w/ VTE < 45y<br>- Recurrent or multiple thromboses<br>- Arterial thrombosis (test for APS)<br>- Warfarin-induced skin necrosis (test for protein C deficiency) |
| **Patients without VTE – special situations** | - Females considering OCP/HRT without FHx thrombophilia<br>- Patients with cancers at high risk of VTE (Khorana score) → thromboprophylaxis | - Females considering OCP/HRT or planning pregnancy **if + FHx high-risk thrombophilia**<br>- Patients with cancer at low/intermediate risk of VTE and undergoing tx **if +FHx VTE** |

| INHERITED CONDITIONS | | |
|---|---|---|
| **Condition** | **Clinical Pearls** | **Testing** |
| **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 (PTG) mutation** | - 2nd most common cause; ↑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<br>- A/w warfarin-induced skin necrosis (screen if hx) | - Free protein C/S functional assays: levels are↓ by acute thrombosis, VKA, liver dz, DIC, chemo, uremia (Prot C), pregnancy/OCP/nephrotic sx (Prot S); levels are↑ by DOAC (Prot C/S), HLD and nephrotic sx |
| **Antithrombin III deficiency** | - More commonly inherited; may be acquired from drugs (L-asparaginase) → ↓level or function<br>- Heparin works via ATIII to inactivate FIIa and FXa; if ATIII defic., will be heparin-resistant & require ↑doses | - ATIII functional assay assessing FXa inhibition<br>- levels are↓ by acute thrombosis, UFH/LMWH, liver dz, nephrotic syndrome, and levels are↑ by DOAC, direct thrombin inhibitors |
| **ACQUIRED CONDITIONS** | | |
| **Antiphospholipid syndrome (APS)** | - **Primary** or **secondary** to SLE/other autoimmune dz<br>- **S/Sx**: Unexplained venous/arterial thrombosis (esp. in young pts), adverse pregnancy outcomes, livedo reticularis/racemosa, valvular dz, ↓ platelets<br>- **Tx**: **VKA** (warfarin)<br>- **Catastrophic APS:** ⊕ aPL w/ 3+ organ thromboses in <1w, mortality ~50%. Tx: AC + steroids + TPE or IVIG | - Clinical criteria: thrombosis, pregnancy loss<br>- Lab criteria: ⊕ lupus anticoagulant (LA), RVVT, anti-cardiolipin, anti-β2 glycoprotein, twice **12w apart**<br>- LA unreliable on AC (false ⊕) and acute thrombosis (false ⊖); anti-CL and β2GP not affected<br>- ⊕ aPL Ab can be seen in infx, rheum, malig, meds<br>- False ⊕ VDRL (NEJM 2018;378:2010) |
| **Heparin-induced thrombocytopenia (HIT)** | - **S/Sx:** See "Thrombocytopenia" page. Drop in plt count (≥50%) 5-10s after heparin initiation<br>- **Tx**: STOP heparin and start alternative AC (e.g. fondaparinux, Argatroban) while awaiting results | |
| **Other** | **Malignancy** (pancreatic, MPN), pregnancy, **drugs** (OCPs, HRT), nephrotic syndrome, obesity, autoimmune disease (IBD, RA), CVCs | |

## 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). Should also consider diseases affecting vascular function (e.g. HHT, scurvy, EDS)
- If prolonged PT/PTT and etiology are 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 inhib (VIII, V>>IX, XI; autoimmune d/o, malig), nonspecific inhibitor (e.g. LAC)
  - 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

**Hemophilia: most common severe bleeding disorder,** X-linked. Caused by Factor VIII (Hemophilia A) or Factor IX (Hemophilia B) deficiency→ ↓clot formation and stabilization → bleeding (joint damage from recurrent bleeds common cause of morbidity)

- Dx: **↑PTT** (can be normal in mild def) → 1:1 mixing study (if PTT corrects = factor def)→factor specific assay to distinguish A and B
- Tx: Concentrates of FVIII/FIX ppx for bleeding events or on-demand w/ bleeds. Emicizumab (bispecific ab which functions like Factor XIII) approved for prophylaxis in Hemophilia A. Multiple novel gene therapies currently under investigation (Blood 2019;133:389).

**Disseminated Intravascular Coagulation (DIC)**: massive activation of coag. cascade from various inflammatory etiologies (sepsis, CA, obstetric complications, trauma, pancreatitis). Consumption of coag. factors → **bleeding**, microvascular **thrombosis**, MAHA, organ dysfunction (kidneys, lungs, CNS, adrenal)

- Dx: **↑PT/PTT, ↑D-dimer, ↓fibrinogen, ↓plts, +schistocytes, ↑LDH, ↓haptoglobin** (often normal coags in chronic DIC). Can differentiate DIC from liver dz w/ ↓FVIII (FVIII present in endothelium, not liver), DIC score
- Tx: treat underlying cause, transfuse plts if <10k, cryo if fibrinogen <100, FFP if INR >2. Amicar generally contraindicated.
  - If severe bleed: transfuse for plts <30 or 50 and Fibrinogen <150

| Coagulation Defect | Normal aPTT | Prolonged aPTT |
|---|---|---|
| **Normal PT** | **Platelet dysfunction** (VWD, other platelet disorders), ↓Factor XIII | **Intrinsic pathway**: ↓VIII, IX (hemophilia), XI (Ashkenazi); VWD; ↓XII, PK, HMWK (no bleeding); LAC (prothrombotic) |
| **Prolonged PT** | **Extrinsic pathway**: ↓Factor VII, warfarin, liver disease, Vit K deficiency | **Common pathway**: liver disease, DIC, Vit K deficiency, warfarin. Rarely common pathway deficiency/inhibitor |

# Hematology — Anticoagulation Agents

## Oral Agents (ASH: Blood Adv 2018;2:3257; CHEST: Chest 2021;160:2247, AHA: JACC 2020;143:e72)

| Agent | Dosing | Bridging, Switching, or Reversal |
|---|---|---|
| **Warfarin** (Coumadin)<br>- Vitamin K antagonist: inhibits vitamin K-dependent gamma-carboxylation of Fs II, VII, IX, X, & Protein C+S<br>- $t_{1/2}$ 40h (variable)<br>- CYP2C9 interactions | - Initiation: 5mg qd x2d; frail, HF, kidney/liver dz: consider 2.5mg; BMI >40: consider 7.5mg<br>- Adjust by INR, which lags 48h behind dose Δ<br>Monitoring: (UW Dosing Nomogram)<br>**- INR < goal**: ↑by 5-15% or consider booster dose<br>**- INR at goal**: no change<br>**- INR between 0.1 and 1.0 above goal**: ↓by 5-15%, consider holding a dose<br>**- INR >1 above goal**: hold until INR at goal, restart but ↓ by 10-20%<br>**If overlap with direct thrombin inhibitor**: check chromogenic FXa: goal 20-40% | **Bridging**: (see below to bridge from parenteral AC):<br>To parenteral AC: start IV w/o bolus when INR <2<br>**Reversal for life-threatening/intracranial bleeding:**<br>1) Vit K 5-10 mg IV over 10-20m<br>2) 4-factor PCC/Kcentra over 10m if INR >2 (≥1.5 in ICH)<br>*MGH dosing*: Kcentra 1500u, follow INR q30m w/ pharm<br>*Non-MGH dosing:* INR 2-4: 25u/kg (max 2500u), INR 4-6: 35u/kg (max 3500u), INR >6: 50u/kg (max 5000u)<br>*If Kcentra not available, give 2U FFP by rapid infusion.*<br>**Reversal *without* active bleeding:**<br>INR >10→ Vit K PO 2.5-5mg<br>INR 4.5-10→ Vit K PO 1-2.5mg if ↑risk of bleeding<br>INR <4.5→ no reversal, hold warfarin |
| **Dabigatran** (Pradaxa)<br>- Direct thrombin (IIa) inhibitor, $t_{1/2}$ 12-17h<br>- 80% renal clearance<br>- P-gp substrate<br>- S/e: ↑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<br>- **VTE**: 150mg PO BID *after 5d UFH/LMWH* (RE-COVER, NEJM 2009;361:2342)<br>- **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 warfarin and start dabigatran when INR < 2<br>**Reversal if life threat.**: can be dialyzed, lipophilic<br>- Idarucizumab 5g (RE-VERSE, NEJM 2017;377:431) |
| **Rivaroxaban** (Xarelto)<br>- Direct Xa inhibitor<br>- $t_{1/2}$ 5-9h; 11-13 in elderly<br>- 66% renal clearance<br>- Avoid with CYP3A4 and P-gp dual inhibitors | - **Non-valvular AF**: 20mg PO QD if GFR >50, 15mg if GFR 15-50 (ROCKET AF, NEJM 2011;365:883)<br>- **VTE**: 15mg PO BID x21d, then 20mg QD. After 6mo, consider ↓ to 10mg QD if ongoing risk for VTE (NEJM 2010;363:2499; NEJM 2012;366:1287; NEJM 2017;376:1211)<br>- **PPX**: 10mg PO QD (NEJM 2013;368:513) | **Bridging/switching**: (J Thromb Thrombolysis 2016;41:206)<br>- To parenteral AC: start when next DOAC dose due<br>- From LMWH/fonda: start w/in 0-2h of next dose<br>- From UFH: start immediately after drip stops (for *edoxaban*, start 4h after stopping UFH)<br>- From warfarin:<br>• Start rivaroxaban when INR <3<br>• Start apixaban when INR <2<br>• Start edoxaban when INR ≤2.5<br>- To warfarin: (Note: all ↑INR)<br>• Rivaroxaban/apixaban: stop, start warfarin, and use parenteral agent until at therapeutic INR<br>• Edoxaban: cut edoxaban dose by ½ and begin warfarin, stop edoxaban once INR ≥2<br>- DOAC to DOAC: start when next dose due<br>**Reversal if life-threat.**: not dialyzed off, protein-bound<br>- Andexanet alfa (recombinant FXa): bolus → 2h gtt (NEJM 2015;373:2413; NEJM 2019;380:1326) |
| **Apixaban** (Eliquis)<br>- Direct Xa inhibitor<br>- $t_{1/2}$ 12h<br>- lower renal clear. (25%) (*can use in ESRD*) | - **Non-valvular 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 (NEJM 2011;365:981)<br>- **VTE**: 10mg BID x7d, then 5mg BID x6mo; after 6mo, consider ↓ to 2.5mg BID (NEJM 2013;369:799 & 368:699)<br>- **PPX**: 2.5mg BID (NEJM 2009;361:594) | |
| **Edoxaban** (Savaysa)<br>- Direct Xa inhibitor<br>- $t_{1/2}$ 10-14h<br>- 50% renal clearance<br>- Avoid if CrCl >95 or <15<br>- P-gp substrate | - **Non-valvular AF**: 60mg PO QD; 30mg if CrCl 15-50 or wt ≤60kg; do not use if CrCl>95 (NEJM 2013;369:2093)<br>- **VTE**: 60mg QD *after 5d UFH/ LMWH*, 30mg QD if CrCl 15-50, ≤60kg, or taking P-gp inhibitor (NEJM 2013;369:1406) | |

## Parenteral Agents

| Agent | Dosing/Monitoring | Bridging/Switching | Reversal | Other |
|---|---|---|---|---|
| **Heparin** (UFH)<br>- Binds & activates ATIII → inactivates Xa & IIa<br>- $t_{1/2}$ 60-90min | - **ACS**: 60U/kg → 12U/kg/h; PTT 63-83<br>- **VTE**: 80U/kg → 18U/kg/h; PTT 70-100<br>- **PPX**: 5,000U SC q8-12h<br>- Monitoring: PTT; anti-Xa (goal 0.3-0.7) if baseline ↑PTT or high doses; ACT if ↑↑) | - To LMWH: give LMWH & stop UFH at same time<br>- To warfarin: stop 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<br>- **Do NOT give FFP**: has ATIII, which potentiates AC effect | - Preferred in renal failure (CrCl <30), peri-procedure, poor absorption, pregnancy |
| **Enoxaparin** (LMWH, Lovenox)<br>- Binds & activates ATIII→inact. Xa>>IIa<br>- $t_{1/2}$ 4.5-7h | - **ACS/VTE**: 1mg/kg BID; QD if GFR <30<br>- **PPX**: 40mg SC QD; 30mg BID if ↑↑risk; ↑30% if BMI ≥40; 30mg QD if GFR <30<br>- Monitoring: not routine; can check anti-Xa 4h after 4th dose, goal 0.5-1.0 | - To UFH: ⦸ LMWH & start UFH w/o bolus 1-2h before LMWH dose due<br>- To warfarin: ⦸ LMWH once therapeutic INR ≥2d | | - Acute VTE: LMWH > UFH (Cochrane Rev 2017)<br>- Prolonged $t_{1/2}$ in renal failure |
| **Fondaparinux** (Arixtra)<br>- Binds & activates ATIII→inact. Xa only<br>- $t_{1/2}$ 17-21h | - **VTE**: <50kg → 5mg QD \| 50-100kg → 7.5mg QD \| >100kg → 10mg QD<br>- **PPX**: 2.5mg SC QD<br>- CrCl <30: contraindicated<br>- Monitoring: not routine; can check 4h anti-Xa | - To warfarin: stop fonda. once therapeutic INR ≥2d<br>- To UFH: start UFH (no bolus) 1-2h before due<br>- From UFH: start 1h after UFH stops | - No reversal agent | - ↑aPTT at therapeutic doses<br>- If CrCl 30-50, consider Δ agents |
| **Argatroban**<br>- Direct IIa (thrombin) inhibitor<br>- $t_{1/2}$ 45min | - **HIT**: 1-2mcg/kg/min<br>- Monitoring: PTT, goal 1.5-3x baseline<br>- Caution in critically ill, cardiac dysfunction, liver disease | - To warfarin: stop once chromogenic factor Xa 20-40% (argatroban ↑INR) | - No reversal agent | |

**Factor XI/XII inhibitors under investigation** (Blood 2022;1:495): antisense oligonucleotides (ASO), antibodies (abelacimab NEJM 2021;385:609, osocimab, small molecules (milvexian, asundexian)

# Hematology — Anticoagulation Management

## Choosing An Anticoagulation Agent

**Guidelines**: CHEST for VTE: Chest 2021;160:2247, 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 2021;77:e25

| | | |
|---|---|---|
| VTE | Obesity | **Avoid DOAC** if BMI ≥45 or wt ≥150kg, use warfarin (Circulation 2024;149). If use, check peak/trough (ISTH: JTH 2021;19:1874) |
| | Active Malignancy | **Apixaban** (NEJM 2020;382:1599), **edoxaban** (NEJM 2018;378:615), **rivaroxaban** (JCO 2018;36:2017), **LMWH** > warfarin (NEJM 2003;349:146). Prefer apix or LMWH in GI/GU CA w/ intraluminal lesions (edox/rivarox ↑bleeding risk).<br>**DOAC > LMWH** for **short-term** VTE tx, **either for long-term**. Apix/rivarox **ppx** ↓VTE in high-risk outpts, suggest in mod-risk: consider if Khorana ≥2 (NEJM 2019;380:711; NEJM 2019;380:720). LMWH ppx OK in high-risk outpts |
| | Recurrent | **If on non-LMWH**: switch to LMWH. **If on LMWH**: increase LMWH by 1/4-1/3 of current dose and check Xa level |
| | All Others | **DOACs** > warfarin > LMWH. Treat SVT if high risk features (eg. Hx of VTE, surgery, active CA, clot w/in 3cm to saphenofem. jxn (Lancet. 2017:e105-e113). Acute, prox. DVT/severe distal DVT → 3 mo DOAC>VKA. IVC filter only if contraindications to AC. |
| AF | Non-valvular | **DOACs** > warfarin for stroke risk, mortality, and bleeding risk |
| | Valvular | **Warfarin** if mod/severe MS (regardless of CHADS2VASC) w/ INR goal 2-3 |
| | + PCI | **Dual** (P2Y12i+OAC) v **triple therapy** (+ASA): dual w/ ↓bleeding, likely no ↑events (Annals 2020;172:474; EHJ 2019;40:3757) |
| | | Dual therapy: **OAC + clopidogrel** x6-12mo. OAC options: *Rivaroxaban*: 15mg qd (some use 20mg) (NEJM 2016;375:2423). *Dabigatran:* 150mg BID (NEJM 2017;377:1513). *Apixaban:* 5mg BID (or 2.5 mg BID) (NEJM 2019;380:1509). *Edoxaban:* 60mg QD (*though didn't ↓bleeding v VKA) (Lancet 2019;394:1335). *Warfarin* + clopi/ticag can also be used. (Lancet 2013;381:1107). Ticag. may be used in-hospital or if very high thrombotic risk. After 12mo, can likely Δ to OAC alone (NEJM 2019;381:1103) |
| | | If triple therapy chosen (high thrombotic/low bleed risk), typically d/c ASA & transition to P2Y12i+OAC therapy at 1-4 wks |
| Valve | Mechanical | **Warfarin (+ASA for aortic On-X valve)**. DOACs not approved. INR goal for AVR = 2.5 (3 if +AF, VTE, etc.); MV/TV = 3 |
| | 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 (Blood 2018;132:1365; AIM 2019; 171:685) |
| 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 lose dose rivaroxaban (2.5mg BID) + ASA → better CV outcomes vs. ASA alone; ↑major bleeding but no Δ in ICH or fatal bleeding (NEJM 2017;377:1319). Can consider if high risk for events & low bleeding risk |
| | s/p PCI | **12 mo DAPT**, new research w/ 1-3 mo DAPT+12 mo clopi non-inf to 12 mo DAPT (JAMA 2019;321:2414); can integrate DAPT score into clinical decision making |

## Anticoagulation Bridging

**Guidelines**: ACC: JACC 2017;69:871; ASH: Blood Adv 2018;2:3257; CHEST: Chest 2022;162:E207

| Indication | AF | | VTE | | Mechanical Valve | |
|---|---|---|---|---|---|---|
| Thrombotic Risk | Risk Factors | Bridge? | Risk Factors | Bridge? | Risk Factors | Bridge? |
| High | - $CHA_2DS_2$-VASc ≥7 (or CHADS2 5-6)<br>- CVA/TIA, or systemic embolism <3mo<br>- Rheumatic valvular dz | Yes, unless major bleed/ICH <3mo | - VTE <3 mo<br>- Severe thrombophilia: protein C/S or ATIII def, APLAS, multiple abnormalities | Yes | - Any mechanical MV<br>- Caged ball/tilt disc AVR<br>- Any mechanical valve w/ CVA/TIA <6mo | Yes |
| Moderate | - $CHA_2DS_2$-VASc 5-6 (or CHADS2 3-4)<br>- CVA/TIA or systemic embolism >3mo | Likely bridge if prior CVA/TIA and if no ↑risk of bleeding | - VTE 3-12mo<br>- Recurrent VTE<br>- Active malignancy<br>- 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 against risk of procedural bleeding (UpToDate table) |
| Low | - $CHA_2DS_2$-VASc ≤4 (or CHADS2 0-2)<br>- No prior CVA/TIA or systemic embolism | No | - VTE >1y & no other risk factors | No | - Bileaflet AVR w/o AF or CVA risk factor | No |

- **BRIDGE** trial (NEJM 2015;373:823) demonstrated no difference in arterial embolism but ↑risk of bleeding w/ bridging in pts with AF undergoing invasive procedure requiring interruption of VKA (*NB*: excluded pts w/ mech. valves, stroke/TIA <3mo, major bleeding <6w, CrCl <30, plt <100k)
- Bridging Vitamin K Antagonist (VKA) w/ UFH or LMWH (prefer LMWH if kidney function allows):
  - 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

| Drug | 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) |

*For bleeding risk stratification use procedural bleeding risk + HAS-BLED score.

- If low bleeding risk, can resume 24h after procedure. If high bleeding risk, wait 48-72h. If NPO or more procedures: UFH/LMWH.

****See Peri-Procedural DOAC Management for MGH-specific peri-procedural guidance for cardiac cath. lab & IR procedures****

# Hematology — Transfusion Medicine

## 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" **x3d**
- **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<br>Processing<br>1. Leukocyte reduction<br>2. Irradiation<br>3. Washing (rarely) | - Hgb <7 (NEJM 2014;371:1381; NEJM 2013;368:11)<br>- Hb < 7.5 if cardiac surgery (JAMA 2023;1892:1902)<br>Hgb <8 if CAD, ortho surgery (JAMA 2021;325:552)<br>- Hgb <10 if acute MI (NEJM 2023;389:2446)<br>- Acute hemorrhage (>15% intravascular volume)<br>- AIHA (no specific Hgb threshold)<br>- Sickle cell disease (see *Sickle Cell Disease*) | - Each unit: Hct ~55%<br>- **1U ↑Hgb ~1**<br>- Rate: if active hemorrhage, give over 60-90min |
| **Platelets** | 1U = 6pk = 300cc<br>Types<br>1. Apheresis platelets derived from 1 donor<br>2. Pooled platelets from multiple donors<br>Processing<br>1. Leukocyte reduction<br>2. Irradiation | - <10k: PPX spont bleeding (NEJM 1997;337:1870), antifibrinolytics in refractory thrombocytopenia in CA<br>- <50k: active major bleed, intra- or post-op bleed, ppx prior to invasive procedures (<30k bedside procedures)<br>- <100k: post-bypass bleed, ICH/ophthalmic (no data)<br>- ITP: only if life-threatening CNS/GI/GU bleed (often preceded by wet purpura, mucus membrane bleeding) | - Response at 30-60m: **1U ↑PLT ~30K**<br>- No evidence that apheresis > pooled plts<br>- No evidence that platelets reverse anti-platelet agents (Lancet 2016;387:2605)<br>- CI: TTP/HUS, HIT |
| **Fresh Frozen Plasma** | 1U = 250cc<br>Typical starting dose 2U<br>Non-cellular portion of blood containing all coag factors; separated and frozen after collection | - Active bleed d/t deficiency in one or more coag. factors<br>- ALF: consider for ↓plt or ↑INR only if bleed or pre-op<br>- Cirrhosis: **cryo preferred**, treating INR w/ FFP ↑bleeding due to ↑portal pressures, has prothrombotic effect (J Thromb Haemost 2021;19:664)<br>- Warfarin reversal: Vit K>PCC>FFP (Circ 2012;125:2944)<br>- Trauma, DIC, congenital TTP (for ADAMSTS13)<br>- Ppx prior to bedside invasive procedures for INR >2.0 (low quality evidence [Cochrane 2019:11:CD012745]) | - Response: **2U ↑coag activity ~10%**<br>- Max correction: **INR 1.7**<br>- Effect <6h due to short $t_{1/2}$ of FVII<br>- Potentiates effect of heparin with ATIII |
| **Cryo-precipitate** | 10U = 150cc<br>Contains factor VIII, factor XIII, VWF, and fibrinogen | - Fibrinogen <100-150: 50-100mg/dL give 10U; <50 give 20U<br>- Massive transfusion w/ ↓fibrinogen or abnl ROTEM/TEG<br>- Complex cardiac surgery (JAMA 2017;217:738)<br>- Postpartum hemorrhage (Br J Anaesth 2015;114:623)<br>- DIC, uremia if DDAVP ineffective, FVIII deficiency, VWD<br>- Cirrhosis: fibrinogen <100-120 or c/f dysfibrinogenemia | - 10U cryo should ↑fibrinogen ~85mg/dL<br>- Fibrinogen $t_{1/2}$ 3-5d<br>- FVIII or vWF replacement: cryo is last resort therapy |
| **Coagulation Factors** | VIII, IX, rFVIIa, ATIII; combo: II+IX+X (Profilnine); PCC = II+VII+IX+X (Kcentra), FEIBA (anti-inhib. complx), vWF/FVIII (Humate-P) | - Coagulation factor deficiency/inhibitor<br>- Von Willebrand's disease (Humate-P, NovoSeven)<br>- VKA reversal (IV Vit K first, for severe bleed PCC > FFP) | - Blood Transfusion Service approval required<br>- S/E: allergic rxn, thrombosis |
| **Antifibrinolytics** | Contain Lysine derivatives that bind to plasminogen to ↓fibrinolysis and ↑hemostasis<br>Types (topical, PO, IV): Aminocaproic acid (Amicar), Tranexamic acid (TXA) | - Trauma (Health Tech 2013;17:1)<br>- Postpartum hemorrhage (Lancet 2017;389:2105)<br>- Cardiac surgery (NEJM 2017;376:136; J Thor C Surg 2019;157:644), ECMO<br>- Cirrhosis: when hyperfibrinolysis suspected (see *ESLD)*<br>- Major ortho surgery, plt refractoriness in HLA alloimmunization, closed space bleeding, coag factor inhibitor | - Amicar: load 4-5g over 1h → 1g/h for 8h or until bleeding controlled<br>- TXA: load 1g over 10min → 1g over 8h cont. infusion<br>- S/E: risk of seizures w/ high dose TXA |
| **Albumin** | Types<br>1. 5% (iso-oncotic)<br>2. 25% (hyper-oncotic)<br>Both contain 12.5g albumin & 154mEq Na (isotonic) | **5% if hypovol/intravasc depl., 25% if fluid/Na restricted**<br>- Cirrhosis: HRS, SBP, LVP (see *ESLD*)<br>- Shock: 4% albumin similar to 0.9% NS for IVF resuscitation (when alb. >2) (SAFE, NEJM 2004;350:2247)<br>- ARDS: 25% albumin (25g) q8h x3d + Lasix gtt x3d → ↑O2, neg. TBB (when alb. <2) (Crit Care 2005;33:1681) | - C/I: traumatic brain injury<br>(Also see *IV Fluids and Electrolyte Repletion*) |
| **IVIG** | Types<br>Polyclonal IgG and trace plasma contaminants<br>Dose adjust for obesity | - Immunodeficiency: hypogammaglobulinemia IgG <400<br>- Immunosuppression in autoimmune disease (e.g. ITP, AIHA, post-transfusion purpura, acquired VWS)<br>- Neuro: CIDP, myasthenia gravis, GBS<br>- ID: toxic shock syndrome, Kawasaki disease | - SE: infusion reactions, aseptic meningitis, hyperosm renal tubular injury, thrombosis |

# Hematology — Transfusion Medicine

## 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 and Emergency Blood MGH Policy

Call **Blood Bank (x63623 – main; x85280 - Lunder).** Run down w/ patient sticker and pick-up slip to **Gray/Bigelow 2** to pick up cooler(s)
**Emergency Release Blood**: 4u of uncrossmatched whole O blood (for men & women >50y). For women <50y, 6u group O pRBCs (Rh-neg), 3u plasma, and one dose of platelets. Only **ONE** cooler, sufficient for most bleeding.
**Massive Transfusion Protocol**: One cooler of 4u whole O blood **followed by coolers** of 6u O pRBCs, 3u plasma, and 1 dose platelets released q15min until the blood bank is called to stop. MUST have a blood bank sample sent before 3rd cooler or plasma/platelets will NOT be released.

- Activate MTP when anticipate transfusing one TBV (70cc/kg) or >4u immediately, continued hemorrhage >250cc/hr, or clinical judgement
- Occurs most commonly in trauma, GI bleeding, cardiac surgery, obstetric complications, rupture of major blood vessel
- Access: Ideal = short and stubby: ≤18g PIV, MAC/Cordis. Take off clave (blue cap) and pressure bag blood vs Belmont.
- **No universally accepted ratio**: 1:1-2:1 (1u pRBC:1-2u FFP:1u plt) transfusion protocol is most common ideal. FYI: 1 bag/dose plt ~6u plts
  - Goals: Hb >7-10, INR <2.5 (unless ESLD), PLT >50k, fibrinogen >100-150
  - Cryo does NOT come in MTP, must be ordered separately based on either fibrinogen levels or empirically (1-2 pooled Cyro:7-8 pRBC)
  - Excessive FFP a/w ARDS in pts not requiring massive transfusion.
- Correct coagulopathy → IV vit K/PCC, AC reversal agents, platelet dysfunction (ASA, Plavix, uremia) → DDAVP 0.3mcg/kg
- Consider IV Amicar or IV TXA (especially in obstetric, surgical, or trauma. Not helpful in GIB (HALT-IT). Dosing on previous page)
- **Complications**: hypothermia (cover pt w/ Bair hugger, use blood/fluid warmers), hypo-$Ca^{2+}$ (2/2 citrate, administer CaCl2 to target an iCal of 1-3 mM or consider empiric 1-2g per 6 units pRBC), dilutional coagulopathy esp. w/ IVF, metabolic alkalosis (citrate metabolized to bicarb), hyper-$K^+$, shock liver (AST/ALT >800, give additional anti-fibrinolytic), females of reproductive age may need rhogam post resuscitation.

## 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**; consider using a checklist of blood product types
- **Acceptable products**: hematinics (iron, folate, B12, recombinant human EPO), non-blood volume expanders (IVF), 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

**Discuss scheduling with either MGH Dialysis Center (if pt already on iHD) or Transfusion Medicine (p21829)**

- **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. Patients will need access with tunneled dialysis line or non-tunneled HD line
- **Cytapheresis**: removes abnormal or excessive # blood cells. Indications: leukapheresis for hyperleukocytosis (goal WBC <100k, controversial); RBC exchange for sickle cell patients with acute decompensation (organ failure, acute chest, etc.), severe babesiosis (high grade parasitemia >10, severe hemolysis, or pulm/liver/renal dz); platelet removal for thrombocytosis rarely done (goal plts <1k)

# Hematology — Transfusion Reactions

**INITIAL EVALUATION**: Blood Bank (**x63623**, **p21829**) (Br J Haematol 2023;201;832)

**S/Sx**: fever/chills/rigors, hives/flushing/pruritis, infusion site pain, shock/oliguria, SOB, wheezing, crackles, hypoxia, angioedema, bleeding diathesis, nausea/vomiting

1. STOP transfusion, ABCs, VS q15min, notify blood bank
2. If only urticarial sx or isolated T ≤39C → treat sx, resume once symptoms resolved
3. Initial workup to consider: CBC, BMP, LFTs, 'Transfusion Reaction' Epic Order Set
   - High suspicion for hemolysis: DAT, Bili, LDH, hapto, crossmatch, UA, smear
   - High suspicion for sepsis: GS/BCx of both pt & blood product
   - High suspicion for TRALI/TACO: JVP, NT-proBNP, ABG, portable CXR

| | Acute | Delayed |
|---|---|---|
| **Immune-mediated** | AHTR, FNHTR, Urticaria/hives, Anaphylactic, TRALI, IgA def | DHTR, TA-GVHD, post-tx purpura |
| **Non-immune mediated** | Cold toxicity, citrate toxicity, sepsis, TACO | Viral infection |

| Reaction/Per-Unit Risk | Presentation/Diagnosis | Pathophysiology | Treatment/Prevention |
|---|---|---|---|
| **ACUTE TRANSFUSION REACTIONS (<24H)** | | | |
| **Acute Hemolytic (AHTR)**<br>1/76,000-137,000 | **Sx**: 15min to 2-4h; fever/chills, nausea, tachycardia, HoTN, back/flank pain, bleeding, DIC<br>**Dx**: +Hemoglobinuria, +DAT, +Bili/LDH, +smear (spherocytes) | - ABO/Kidd incompatibility (preformed Abs) → intravascular hemolysis (IgM), cytokine/complement activation<br>- Rh/Kell/Duffy incompatibility → less severe extravascular hemolysis | **Tx**: IVF ± diuresis for goal UOP >100cc/hr x24h<br>- Monitoring: HoTN, AKI, DIC, mortality ∝ volume transfused<br>**PPX**: careful crossmatch |
| **Febrile Non-Hemolytic (FNHTR)**<br>1/14 (PLT)<br>1/200-2,500 (RBC) | **Sx**: 1-4h; low-grade fever, chills/rigors, HA, flushing<br>**Dx**: hemolysis workup negative, also send BCx (results would be negative) | - Donor WBCs produce TNFα, IL1, IL6<br>- RBC: donor WBCs activated by recipient anti-HLA Abs<br>- PLT: donor WBCs make cytokines before transfusion | **Tx**: auto-CPAP ± meperidine<br>**PPX**: leukoreduction, little evidence for pre-medication |
| **Sepsis (Bacterial Contamination)**<br>1/75,000 (PLT) | **Sx**: 15-60min; high fever, rigors, abd sx, HoTN/shock<br>**Dx**: GS/BCx of both pt & bag | - Bacteria >> viruses in donor blood<br>- RBC: Yersinia, PsA (endotox-GNRs)<br>- PLTs: Staph epi (GPCs) | **Tx**: antibiotics, quarantine all other similar products<br>**PPX**: routine screening |
| **Urticaria/Hives**<br>1/33-100 | **Sx**: anytime during/after transfusion; localized or diffuse hives & redness<br>**Dx**: no work-up necessary | - IgE-mediated hypersensitivity to donor plasma proteins | **Tx**: pause → 2nd gen. antihistamine→ resume if urticaria resolves<br>**PPX**: washed products, no evidence for pre-medication |
| **Anaphylactic/ Anaphylactoid**<br>1/20,000-50,000 | **Sx**: within min; acute HoTN, angioedema, urticaria, wheezing, GI symptoms<br>**Dx**: clinical; consider IgA def., serial mast cell tryptase | - IgE-mediated hypersensitivity in recipient lacking IgA or haptoglobin<br>- Bradykinin-mediated flushing/HoTN in pt taking ACEi or neg charged filters (e.g. plasma exchange w/ albumin) | **Tx**: ABCs, O2, IVF ± pressors, epi IM Q15min, methylpred 125mg, IV/PO diphenhydr. 25-50mg, $H_2$ blocker<br>**PPX**: washed products |
| **Transfusion-Related Acute Lung Injury (TRALI)**<br>1/12,000 (RBC)<br>1/38,000 (PLT) | **Sx**: 1-6h; dyspnea ± fever<br>**Dx**: NT-proBNP nl, bilateral CXR infiltrates w/o CHF, noncardiogenic pulm edema (ARDS) | - Pre-transfusion stress activates lung endothelial cells & primes PMNs<br>- Donor anti-HLA Abs/bioactive factors attack primed PMNs of recipient | **Tx**: ABCs, O2, contact blood bank, intubation<br>**PPX**: male donor plasma (fewer anti-HLA, anti-PMN Abs); defer donors w/ prior assoc. TRALI |
| **Transfusion-Assoc. Circulatory Overload (TACO)**<br>1/100 (RBC) | **Sx**: 1-6h; dyspnea<br>**Dx**: elevated NT-proBNP, CXR w/ cardiogenic pulm. edema 2/2 vol. overload | - Infusion rate or volume that cannot be effectively processed by recipient<br>- Highest risk in elderly, HF, CKD, chronic anemias | **Tx**: O2, IV diuretics, ± nitrates, NiPPV<br>**PPX**: slower rate (1cc/kg/hr) |
| **IVIG Transfusion Reactions**<br>5-15% of infusions | - Inflammatory rxn: fever, chills, flushing, headache, myalgias<br>- Anaphylactoid rxn: urticaria, flushing, chest pain, N/V, HoTN | - Inflammatory rxn: Ab/Ag interaction i/s/o concurrent infxn<br>- Anaphylactoid rxn: unknown, potentially kinin-mediated, rare | **Tx**: IVF, sx mgmt<br>**PPX**: slow & space out infusions |
| **DELAYED TRANSFUSION REACTIONS (>24H, <28D)** | | | |
| **Delayed Hemolytic (DHTR)**<br>1/2,000 | **Sx**: ~3d; fever, anemia, jaundice, flu-like illness, hemoglobinuria<br>**Dx**: +DAT, +DBili/LDH, +smear w/ spherocytes, low haptoglobin | - Anamnestic IgG against previously exposed antigen (Kidd/Duffy/Kell) → extravascular hemolysis | **Tx**: supportive<br>*NB*: delayed serologic transfusion reaction is the same except w/o hemolysis |
| **TA-GVHD**<br>Rare (typically immunosuppressed) | **Sx**: 2-30d; fever, rash, mucositis, diarrhea, hepatitis, pancytopenia | - Donor T cells attack non-HLA matched recipient organs in s/o immunosuppression or 1st degree relative donor | **PPX**: irradiation |
| **Post-Transfusion Purpura (PTP)**<br>Rare (women>>>men) | **Sx**: 3-14d; purpura, mucocutaneous bleed<br>**Dx**: PLT <10,000, anti-HPA-1A | - HPA-1A (common in donor PLTs) HPA-1A neg women develop Abs | **Tx**: 1st line: IVIG \| 2nd: PLEX<br>**PPX**: HPA-1A negative PLTs |

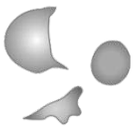
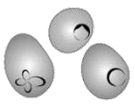
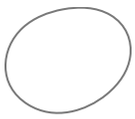
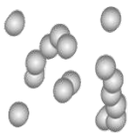
# Hematology — Peripheral Smear Interpretation

## General Approach (NEJM 2005;353:498; Blood smear basics)

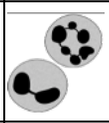
- Special slide: 5th floor Bigelow building, first left off elevators, then another left, proceed down the hall past the Core lab, then second door on your left is the heme lab. Inside heme lab, second enclave on the right has the microscope and special slides next to it.
- Low power (20x): Scan slide for WBC distribution. Find the monolayer within the "feathered"/thin edge where RBCs are just apart.
- Med power (40x): Examine monolayer/feathered edge for rouleaux, parasites, abnormal WBCs, platelet aggregation/microsatellites
- Oil Immersion (100x): Examine monolayer to assess the size, shape, and morphology of major cell lineages:
  - **RBC**: Assess size (compare to a lymphocyte nucleus for scale), morphology (membrane irregularities, fragmentation), color (pallor, reticulocytes), inclusions (i.e. basophilic stippling, Heinz bodies), patterns (agglutination, rouleaux)
  - **WBC**: Examine at edges and thin end of film. Assess distribution of normal WBC, size, shape, cytoplasm (including granules and vacuolation), and inclusions (i.e. Dohle bodies). Evaluate neutrophils for nucleus segmenting (average is 3).
  - **Platelet**: Assess for appropriate number (1 plt per HPF [high-powered field] = 20K platelets in CBC), giant platelets, 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/HPF (normal 3-5/HPF) + absent alt diagnoses suggests TMA (Int J Lab Hematol 2012;34:107) | - Correlate with CBC, haptoglobin, LDH<br>- Assess for clinical causes of TMA, valve hemolysis. Consider calculating PLASMIC score if concern for TTP |
| 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) | - Thick and thin smears for confirmation/parasite burden<br>- Babesia, Lyme, Anaplasma testing |
| Evidence of iron deficiency? | Hypochromic, microcytic cells; "pencil" cells |  | >5% hypochromic cells is gold standard for functional IDA, incl in pts with active inflammation (Clin Chem 2002;48:1066) | - Iron studies if not yet sent (supplementation if no contraindication)<br>- Consider thalassemia and sickle cell anemia if clinically suggestive |
| Are there rouleaux? | Linear aggregations of RBCs throughout smear (may be artifact at edges) |  | Associated with inflammatory, infectious, and malignant conditions. Sn but not Sp for MM (Arch Int Med 2002;162:1305). Reflects presence of ⊕ charged proteins, incl. Ig & fibrinogen (Blood 2006;107:4205) | - Correlate for causes of elevated Ig/decreased albumin, incl. infection, inflammation, cirrhosis<br>- 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) | - Assess for causes of hyposplenia; 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) | - Check folate/B12, consider supplementation (hyper); MDS workup (hypo) |
| Are lymphocytes atypical? | Large lymphocytes, extra cytoplasm, prominent nucleoli | | ≥10% atypical lymphs ⊕LR for infectious mononucleosis (JAMA 2016;35:1502); part of RegiSCAR score for DRESS | - Apply to RegiSCAR; consider EBV/CMV, HIV, Toxoplasma infection |

**Platelet Lineage**

| Question | Findings | Clinical Significance | Next Steps |
|---|---|---|---|
| Are giant platelets present? | Large platelets ≥ size of RBC | Suggests marrow response to destruction; incr. plt turnover (ITP); or proliferation (myeloproliferative dz); clumps suggest pseudo-thrombocytopenia | - Consider peripheral causes of thrombocytopenia incl drug-induced, hemolysis, sequestration<br>- Consider MYH9 and other hereditary plt disorders |

## Other Common Findings And Implications (Harrison's 18th Ed.)

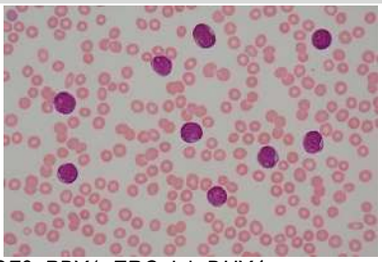
| Target Cells | Acanthocytes (Spur Cells) | Echinocytes (Burr Cells) |
|---|---|---|
| Membrane redundancy due to liver disease, thalassemia, HbC disease | Irregular, dense membrane projections present in severe liver disease | Small, uniform membrane projections present in uremia and MAHA |

# Oncology — Acute Leukemia

## General Admission Approach

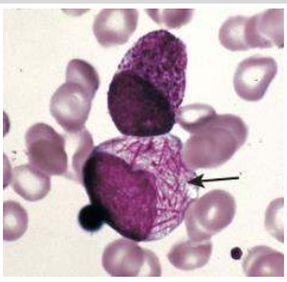
- **History**: sibling status (for donor search), family history (for inherited syndromes), and if pre/peri menopausal, obtain date of LMP
- **Peripheral smear**: anemia, thrombocytopenia, variable WBC, circulating **blasts** ("other cells"), Auer rods (*indicates myeloid origin*)
- **Peripheral flow cytometry**: Collect in yellow top. In Epic, order "Flow cytometry labs (blood)" → fill in Clinical hx; select "Leukemia Panel." To **RUSH case (e.g. for new dx),** send page to Pager 21867: - *Hematopathology Team* . Sample is sent to BWH and interpreted by MGH Hemepath. FYI **Routine (non-rush)** are sent to Mayo
- **Screening**: LFTs, lipase, B12, folate, HBV/HCV/HIV serology, CMV IgG, T&S, G6PD, urinalysis, quantitative bHCG (if applicable)
- **Monitoring** (initially q8h):
  - **TLS**: BMP (if ↑WBC, use blood gas K), LDH, uric acid, iCal, Phos, Mg. Cairo-Bishop criteria requires 2 lab (↑uric acid, ↑K, ↑phos, ↓Ca) + 1 clinical (AKI, arrhythmia, seizure); see *Oncologic Emergencies* | **DIC**: PT/INR, PTT, fibrinogen, D-dimer
- **BMBx**: aspirate+core, flow, cytogenetics (+/- FISH), molecular diagnostics (e.g. BWH Rapid Heme Panel, MGH Heme Fusion Assay)
- **Imaging**: **CXR**, **TTE** (prior to induction due to cardiotoxic chemotherapies), **CT head** (if CNS sx)
- **Access**: Coordinate with attending: double-lumen **Hickman** vs. triple-lumen **PICC** if induction anticipated, not needed for venetoclax
- **LP ± intrathecal chemo**: indications for LP → all ALL, AML w/ CNS or ocular symptoms, APL with systemic relapse
  - CT or MRI before LP: AMS, focal neurologic signs, papilledema, seizure within the last week
- **HLA typing**: Initiate allo-HCT work-up if ≤80 yo. In Epic, order "HLA Lab" → select "Specimen Type: Blood," "Patient: Recipient," "Test: Bone Marrow/HSC, Allotransplant – Initial workup." Coordinate w/ RN, as it is difficult to tell if HLA typing is pending in Epic.
- **Use Leukemia Admission Order Set**: Neutropenic precautions | **TLS ppx**: allopurinol 300mg qd (*HLA-B*5801* ↑prevalence in Southeast Asian, black populations, ↑risk of SJS/TEN, consider testing (ACR guidelines) | **GI ppx**: omeprazole 20mg qd | **HSV/VZV ppx**: acyclovir 400mg bid or famciclovir 500mg qd | Hibiclens daily | Peridex mouthwash | **No VTE ppx** (thrombocytopenia)

## Acute Lymphoblastic Leukemia (ALL)



- Epi: Bimodal. Peak incidence in children, but another peak in >45yo (68% 5y survival)
- S/Sx: pancytopenia sx (pallor, petechiae/bruises, infections), bone pain, B symptoms, masses (LAD, HSM; anterior mediastinum 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
  - LBL = lymphoblastic lymphoma → pts w/ extramedullary mass(es) w/ <20% BM blasts
- Risk stratification for AYA and Adults (Lancet 2020;395:1146; Blood 2021;138;948):
  - **B-ALL/LBL** (subtyped by clinical/molecular features):
    - **Favorable**: WBC<30k, <35yrs, hyperdiploidy (>50 chromosomes), *ETV6-RUNX1, TCF3–PBX1, ERG* del, *DUX4*-rearrange
    - **Unfavorable**: ↑WBC, older, CNS/testicular involvement, hypodiploidy (<44 chromosomes), various rearrangements
  - **T-ALL/LBL**: **Favorable**: *NOTCH1*/*FBXW7* mut. **Unfavorable**: WBC >100k, CNS disease, complex karyotype, *RAS*/*PTEN* mut.
  - **Measurable residual disease (MRD)**: search for leukemic cells using flow cytometry, NGS or RT-PCR of gene fusions. MRD-positivity correlates w/ risk of relapse. MRD evaluation → dynamic risk assessment, therapy decisions (e.g. allo-HCT)
- Treatment (NEJM 2006;354:166; JCO 2011;29:532):
  - *General*: no single best regimen. Incorporate (1) induction (2) consolidation (3) intensification [if needed] (4) CNS therapy [if needed] (5) maintenance (6) allo-HCT [for relapse or unfavorable-risk disease]
    - If pt is AYA (age 15-39), pediatric-inspired regimen often used (usually incorporating asparaginase + ↑corticosteroids)
      - Asparaginase toxicities: hypersensitivity, pancreatitis, hepatotoxicity, thrombosis (Blood 2020;135:987)
    - If *BCR-ABL1*-positive, TKI is used in conjunction w/ chemo (e.g. R-HyperCVAD plus dasatinib) (Blood 2019;133:130)
    - 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 (POMP); TKI maintenance if *BCR-ABL1*-positive
  - Relapsed/refractory B-ALL: **blinatumomab** (CD19 BiTE), **inotuzumab ozogamicin** (CD22 ADC), **CAR T-cells**, allo-HCT

## Acute Promyelocytic Leukemia (APL)



- Subtype of AML with distinct biology and excellent prognosis (>80% 5y survival) (NEJM 2013;369:111)
- S/Sx: pancytopenia sx (fatigue, anemia, ecchymoses, infection); very high risk for DIC and bleeding
- Smear: **atypical promyelocytes** (large, "dirty" granular, bilobed nuclei), **+Auer rods** (see right)
- Cytogenetics: **t(15;17) → *PML-RARα* (>97%)**, rarely t(11;17), t(5;17)
- Treatment (JCO 2017;35:583):
  - **Immediately start ATRA** (all-*trans* retinoic acid) if **any** suspicion for APL given early mortality from coagulopathy and low toxicity. Dose: 45 mg/m$^2$ in 2 divided doses daily. Target plts >50, fibrinogen >150
- *Induction*: if low-risk (WBC ≤10K): ATRA + arsenic trioxide (ATO)*. If high-risk (WBC >10K): ATRA/ATO + anthracycline or gemtuzumab ozagamicin (CD33 ADC). *Consolidation*: ATRA/ATO or gemutzumab ozagamacin. *Monitor qtc
- Complications of ATRA:
  - **Differentiation syndrome**: fever, rising WBC, hypoxemia (pulmonary infilitrates, effusions), peripheral edema, weight gain, AKI → high-dose steroids (dexamethasone 10mg q12h), supportive care, temporary cessation of ATRA if severe +/- cytoreduction
  - **Hyperleukocytosis**: see *Oncologic Emergencies*
  - **Idiopathic intracranial hypertension**: HA, vision loss, papilledema → hold ATRA, pain control ± steroids/acetazolamide

## ACUTE MYELOID LEUKEMIA (AML)

- Pathophysiology: clonal disorder of hematopoietic progenitor cells w/ infiltration of BM, blood, & other tissues. Significant heterogeneity in underlying molecular abnormalities (*see* Risk Category table)
- Epi: most common leukemia in adults (80%). Median age 68 at dx. 5-10% w/ familial syndrome.
- S/Sx: **pancytopenia** (fatigue, petechiae, ecchymoses, infections), 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 pain/swelling (leuk. infiltration, gout), **leukostasis** (AML > ALL; typically WBC >50-100K; SOB, HA, blurry vision, stroke), spurious ↑K (check blood gas K); falsely low $PaO_2$
- Dx: ≥20% blasts in BM or characteristic translocation (e.g. t(8;21)(q22;q22.1)) or myeloid sarcoma (extramedullary tumor of AML cells). Recent schism in classification (ICC vs. WHO 5th).

| Risk Category (5y OS) | Genetic Abnormality (NCCN 2024 AML Guidelines) |
|---|---|
| Favorable (55-65%) | t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*<br>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*<br>Biallelic mutated *CEBPA*<br>Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low}$ |
| Intermediate (24-41%) | Mutated *NPM1* and *FLT3*-ITD$^{high}$<br>Wild-type *NPM1* without *FLT3*-ITD or with *FLjkmT3*-ITD$^{low}$<br>t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*<br>Any other cytogenetic abnormalities not favorable or adverse |
| Poor/ Adverse (5-14%) | t(6;9)(p23;q34.1); *DEK-NUP214*<br>t(v;11q23.3); *KMT2A* rearranged<br>t(9;22)(q34.1;q11.2); *BCR-ABL1*<br>t(8;16)(p11.2;p13.3)/KAT6A::CREBBP<br>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2-EVI1*<br>-5 or del(5q); -7; -17/abn(17p)<br>t(3q26.2;v)/MECOM(EVI1)-rearranged<br>Complex karyotype, monosomal karyotype<br>Wild-type *NPM1* and *FLT3*-ITD$^{high}$<br>Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2<br>Mutated *TP53* |

- Complications: (1) **DIC** → keep fibrinogen >150, INR <1.5, plt >30-50, add ATRA if any c/f APL (2) **febrile neutropenia** (3) **TLS** → allopurinol, IVF, rasburicase if uric acid >10 (4) **leukostasis** → hydroxyurea, IVF, leukapheresis, avoid transfusions (can ↑viscosity, worsen). Single dose cytarabine may also be considered if uncontrolled w/ hydroxyurea.
- Subtypes: t-AML (therapy-related from prior chemo, RT), s-AML (secondary from preceding heme disorder, e.g. MDS, MPN, PNH) - both of which are generally considered harder to treat than de novo AML
- Risk stratification: based on cytogenetics, mutations, performance status (Karnofsky/ECOG), gero assessment (Blood 2013;121:4287)
- Tx: intensive (see below, NEJM 2009;361:1249) vs. non-intensive (**HMA±venetoclax [BCL2 inhibitor]**, NEJM 2020;383:617)
  - Many factors influencing choice: cytogenetics, mutational profiling, performance status (Am J Hematol 2021;96:493)

**1) Induction**: standard regimen for "medically fit" pts: **"7+3"** →cytarabine (aka "ara-C") continuous infusion days 1-7 + ida/daunorubicin (bolus/short infusion) on days 1-3.
Additional/alternative agents for pts with certain subtypes of AML:
- Midostaurin (TKI) added to 7+3 in AML with *FLT3* mutations (NEJM 2017;377:454)
- Liposomal cytarabine/daunorubicin (Vyxeos): ↑survival in t-AML & s-AML, but longer neutropenia (JCO 2018;36:2684)
- Gemtuzumab ozogamicin added in CD33-positive core-binding factor AML (*RUNX1 or CBFB* translocations, (Blood 2017;130:2373)
- Venetoclax + HMA (azacitidine or decitabine) instead of 7+3 if older and/or adverse risk (e.g. *TP53*). (NEJM 2016;375:2023)

↓

**2) Day 14 BM Biopsy**: check for residual leukemia

→ **3a) Residual Leukemia**: if residual leukemia cells, **re-induction chemo** (e.g. **5+2**) may be given

**3b) No Residual Leukemia**: if BM is "ablated" (i.e. sufficiently acellular w/o evidence of leukemia), check again for complete remission (CR) at day 28

↓

**4) Day 21-25 Count Recovery**: await count recovery (may be delayed w/ addition of experimental therapies)

← **5) Day 28 BM Biopsy**: check for CR (<5% blasts in BM, nl CBC); 70-80% if <60 yo; 50-60% if >60 yo

↓

**6) Consolidation**: initiated soon after first CR. Goal to eradicate residual disease for sustained CR. Options include chemo and/or allo-HCT. In general, allo-HCT preferred in poor-risk disease if patient is candidate and has suitable donor. Chemo alone is used in lower-risk disease or if not allo-HCT candidate.
**Risk stratification determines management** (Blood 2017;129:424):
- Favorable risk: **HiDAC (high dose ara-C)** x3-4 cycles
- Intermediate risk: chemo (HiDAC) vs. allo-HCT
- Poor/adverse risk: **allo-HCT** vs. clinical trial

→ **7) Surveillance**: CBC q1-3mo for 2y, then q3-6mo up to 5y

↓

**8) Survivorship**: cardiac, psychosocial, vaccines, etc.

**Salvage :** If residual disease on surveillance (relapsed) or persistent disease after induction (refractory), initiate salvage therapy with goal of inducing complete remission and bridging to allo-HCT or clinical trial (Blood 2024;143:11).. ***IDH1* mutated** → Ivosidenib (NEJM 386(16):1519) or Olutasidenib (Blood Adv 2023;7:3117) | ***IDH2* mutated** → Enasidenib (Blood 2017;130(6):722) | ***FLT3* mutated** → Gilteritinib (NEJM 2019; 381:1728) | **Chemotherapy** → 7+3 (esp. if earlier durable response), HiDAC, mitoxantrone + etoposide + araC (MEC), fludarabine + araC + G-CSF + idarubicin (FLAG-Ida), others | **HMA ± venetoclax**

# Oncology Lymphadenopathy & Lymphoma

## Evaluation of Lymphadenopathy (AFP 2016;94:896)

- Generalized LAD (≥2 regions): infection (HIV, EBV/CMV/toxo, syphilis, mycobacteria) vs autoimmune (SLE, sarcoid) vs malignancy (lymphoma, metastatic disease) vs benign (Castleman's, Kikuchi dz, IgG4) vs meds (e.g. phenytoin) Localized LAD: cervical [URI/SSTI/dental infection, malignancy (lymphoma, H&N)], supraclav. (malignancy), axillary (infection, breast), inguinal (STI)
- Malignancy signs: Age>40, >4wk, hard or matted nodes, B symptoms. Painful nodes less likely malignancy but doesn't rule out
- Hx: chronicity, exposures, travel, meds, B symptoms (fever, night sweats, >10% unintentional wt loss in 6mo), infxn/malignancy ROS
- Exam: localization (consider nodal drainage), size (abnormal >1cm), consistency, fixation, tenderness (inflammation)
- Labs: CBC/diff, LDH, HIV, HBV, HCV. Depending on pre-test prob: T-spot, syphilis, ANA, EBV/CMV/toxo serologies
- Imaging: CT C/A/P w/ contrast, PET/CT for size, distribution, ideal bx site, monitoring of response/progression (w/ Deauville scoring)
- Biopsy: consider if large (>2cm), persistent 4-6w, or increased size, w/ immunophenotyping & cytogenetics. Empiric steroids may decrease yield of biopsy. **Excisional** (cells & nodal architecture) > core needle (tissue for molecular studies) > FNA (high false neg.)

## Lymphoma General Principles

**Lymphoma Staging**: if Hodgkin lymphoma (HL), add "B" if B Sx. PET Deauville score (1-5): 1 = no FDG uptake; 5 = markedly FDG-avid

Stage I: 1 LN region, or single extralymphatic organ — Stage III: LN groups above and below diaphragm
Stage II: ≥2 LN groups on same side of diaphragm — Stage IV: disseminated ≥1 extralymphatic organs

**LN region**: cervical (R/L), axillary (R/L), subpectoral (R/L), mediastinal, hilar (R/L), celiac, paraaortic, mesenteric, iliac (R/L), inguinal (R/L)
**Workup**: PET/CT, HBV/HCV/HIV serology, G6PD, quantitative bHCG (if applicable), PFTs (+DLCO), TTE (prior to anticipated chemo)
**Fertility Preservation**: sperm/oocyte/ovarian tissue cryopreservation prior to tx. Menstrual suppression: GnRH agonists if ↓plt expected

## Hodgkin Lymphoma (NCCN; 2024)

Bimodal age distribution (Lancet 2012;380:836). Reed-Sternberg cells (**CD15+ CD30+** CD20- CD45- PAX5+ PD-L1+) in inflammatory milieu
**S/Sx**: neck LAD, mediastinal mass, pruritis, B sx, ↑Eos. Rare: burning pain w/ EtOH, nephrotic syndrome (i.e. MCD), liver abn, skin lesions
**WHO classification**: nodular sclerosis (70%), mixed cellularity (25%), lymphocyte rich (5%), lymphocyte depleted (<1%)

**Treatment**: note long-term risk of cardio- and pulm-toxicity, 2° malignancy (t-AML)

- **Stage I-II**: ABVD ± XRT. **Stage III-IV**: ABVD vs. BV-AVD (NEJM 2018;378:331) vs. BEACOPP ± XRT. Interim PET/CT for escalating vs. de-escalating tx. **Relapsed/refractory**: salvage chemo (ICE vs GVD) + auto-HCT; brentuximab vedotin (BV); PD1 inhibition (pembro or nivo), bendamustine, allo-HCT

## Non-Hodgkin Lymphoma

Most common blood cancer, a/w immunosupp., autoimmunity, infection (EBV, H. pylori, HCV, HIV, HHV8, HTLV1) (Lancet 2012;380:848)
**Indolent (e.g. FL)**: incurable, but better prognosis (monitor for transformation) vs. **Aggressive (e.g. DLBCL)**: curable, but worse prognosis

| Diagnosis | % of NHL | Clinical Features | Treatment |
|---|---|---|---|
| **Diffuse Large B-cell** (DLBCL) | ~35% | Aggressive, rapid growth, nodal/extranodal *BCL2*, *BCL6*, or *MYC* translocations common<br>Prognosis: **IPI**, cell-of-origin (GCB > ABC)<br>**Double-hit lymphoma (DHL)**: more aggressive subtype w/ *MYC* + either *BCL2* or *BCL6* translocations. Triple-hit = ultra-HR. | - Stage I-II: R-CHOP + RT; Stage III-IV: R-CHOP; if DHL, consider more aggressive Tx (i.e. R-EPOCH); if old/frail, R-mini-CHOP<br>- IT MTX CNS ppx for high CNS-IPI **controversial**<br>- Relapsed/refractory: CD19 CAR T-cells preferred (Lancet 2022;399:2294, NEJM 2022;386:640) vs. chemo + auto-HCT vs Ab-drug conjugates (using polatuzumab) (NEJM 2022;386:351) |
| **Follicular** (FL) | ~25% | Generally indolent; occasionally aggressive **t(14:18) BCL2+.** High grade = more centroblasts. **FLIPI** score prognostic | - Stage I/contiguous II: Observe; RT preferred; Stage II-IV: observation, anti-CD20 ± bendamustine (BR), lenalidomide (LR), CHOP, or CVP; R/R: CAR-T, PI3K inhibitors (JNCCN 2023;21-11)<br>- Monitor for transformation (rapid LN growth, ↑LDH, B symptoms) |
| **T-cell lymphoma** | ~15% | Diverse varieties. Peripheral T-cell (**PTCL**) NOS most common. Cutaneous T-cell (**CTCL**) i.e. Mycosis fungoides, Sezary syndrome (disseminated). Anaplastic large cell (**ALCL**) a/w *ALK*, breast implants. Adult T-cell leukemia/ lymphoma (**ATL**) a/w HTLV-1, geography (e.g. Caribbean). Enteropathy-associated T-cell (**EATL**) a/w celiac disease | |
| **Marginal Zone** (MZL) | ~10% | **Extranodal MZL (MALT)**: a/w sites with chronic inflammation, e.g. stomach w/ **H. pylori+ t(11;18)**, salivary glands (Sjogren's), thyroid (Hashimoto's), small intestine, etc.<br>**Splenic MZL**: often HCV+, cryoglobulinemia<br>**Nodal MZL**: generally indolent, similar to FL | - Gastric MALT: if H. Pylori+, quad Tx can cure; if H. Pylori-, RT<br>- Nongastric extranodal localized: RT, observation<br>- Advanced nodal: observe, rituximab + chlorambucil/bendamustine<br>- Splenic MZL: if HCV+, HCV Tx can lead to regression. If HCV-, Rituxumab (preferred) or splenectomy (definitive for diagnosis to differentiate from splenic diffuse red pulp small B-cell lymphoma) |
| **Small or chronic lymphocytic** (SLL/CLL) | ~5% | Often indolent, painless LAD, **IgM M-protein**<br>No risk of leukostasis unless WBC >400k<br>Prognosis: **Rai/Binet**, IGHV unmutated (HR), ZAP70+ (HR), CD38+ (HR), FISH (del17p = HR), genetics (*TP53* mut. = HR) | - Only treat when "active" (Blood 2018;131:2745), i.e. cytopenia, bulky disease, progressive lymphocytosis w/ increase >50% over 2mo, autoimmune dz (AIHA, ITP), significant constitutional symptoms<br>- Evolving combinations with BTKi (zanubrutinib, acalabrutinib, ibrutinib), anti-CD20 (obinituzumab, rituximab), and venetoclax |
| **Mantle Cell** (MCL) | ~5% | Wide clinical spectrum, can involve spleen, GI, BM. Leukemic (SOX11-) often indolent **t(11;14),** cyclin D1+. MIPI score prognostic | - Stage I/non-bulk II: BR, VR-CAP, R-CHOP, or LR + R maintenance<br>- Stage II-IV: RDHAP ± R-CHOP, NORDIC, or R-B ± R-HiDAc + BTKi vs auto-HCT w/ R maint (Blood 2022;140:1). R/R: BTKi, CAR T |
| **Burkitt** (BL) | ~1% | Aggressive, extranodal sites (jaw if African). ↑spont. TLS. **t(8:14), cMYC+**, EBV/HIV | - More aggressive than DLBCL treatment: R-EPOCH, R-CODOX-M/IVAC, R-HyperCVAD. Relapsed: chemo + auto- or allo-HCT |

**ABVD** = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
**BEACOPP** = Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
**CHOP** = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
**CODOX-M/IVAC** = Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide, Cytarabine
**CVP** = Cyclophosphamide, Vincristine, Prednisolone
**DHAP**= Rituximab, Dex, Cytarabine and Carbo-, -Cis- or Oxali-platin
**EPOCH** = Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
**HyperCVAD** = Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, alternated w/ methotrexate & cytarabine, followed by maintenance POMP
**R-B ± R-HiDAc** = Rituximab/Bendamustine x3 + Rituximab/High-Dose Cytarabine x3
**VR-CAP** = Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone

# Oncology — Plasma Cell Disorders

## Evaluation of Plasma Cell Disorders (Leukemia 2009;23:215)

**When to evaluate:** Elevated total serum protein, hyperCa, unexplained peripheral neuropathy, restrictive CM, recurrent infections, osteopenia, osteolytic lesions, spontaneous frx, anemia, nephrotic syndrome, kidney impairment with bland urine, Bence Jones proteinuria, immunoglobulin deficiency, elevated ESR, unexplained orthostasis

| Evaluation | Purpose | When to Send |
|---|---|---|
| **Ig Levels** | **Quantify** immunoglobulin (Ig) levels in blood (IgG, IgM, IgA, IgD, IgE). Will not discern monoclonal vs. polyclonal | If suspecting a 1° (e.g. B cell deficiency) or 2° humoral immunodeficiency<br>*Consider IVIG if IgG < 400 mg/dL & infections* |
| **SPEP** | **Detect/quantify** M-protein (monoclonal protein = M-spike = paraprotein), Ig from an abnormally expanded B/plasma cell | If suspecting a monoclonal B-cell or plasma cell disorder, **send SPEP & FLC**. FLC ↑sensitivity. "SPEP panel" order contains quantitative IgG/A/M, total protein, SPEP & reflex IF. **Serum FLC is separate order**. *At MGH lab, cannot force SIFE if no M-spike on SPEP (FLC assay should be sufficient in most of these cases)* |
| **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) | |
| **Serum FLC Assay** | **Identify** light chain abundance (outside normal κ/λ ratio 0.26-1.65)<br>Normal ratio w/ ↓LC = immunosuppression<br>Normal ratio w/ ↑LC = infection/inflammation or ↓renal clearance | |
| **UPEP** | **Detect/quantify** Bence Jones Protein (BJP, i.e. urine monoclonal protein, which is typically κ or λ LC). UA/dipstick will miss BJP | **Not** needed unless high suspicion (+M-prot/abnl FLC). If UPEP+, can use 24h UProt to quantify |
| **Urine IF** | **Identify** the type of BJP (κ or λ) | If UPEP+ for BJP (reflex) |

## Classifying Plasma Cell Disorders (Lancet Oncol 2014;15:e358)

| Diagnosis | Presentation | Diagnosis | Risk Stratification | Treatment |
|---|---|---|---|---|
| **Multiple myeloma (MM)** | **CRAB:** Ca >11mg/dL, Renal dz (Cr >2), Anemia (Hgb <10), Bone lesions (≥1 focal lytic lesion). | ≥10% bone marrow involvement; M-protein ≥3. | R-ISS staging, cytogenetics | See below. |
| **Smoldering MM** | Asymptomatic, no CRAB. Prog. to MM 10%/yr for 5yr, then 3%/yr for 5yr and then 1-2%/yr for 10yr. | 10-60% bone marrow involvement, M-protein ≥3. | High risk: BM PC >20%, M-prot >2, FLC ratio >20. | If high-risk, use daratumumab; otherwise observe. |
| **MGUS** | Asymptomatic. Incidentally diagnosed. | <10% bone marrow involvement, M-protein <3. | (1) M-protein, (2) non-IgG M-protein and (3) abnl. FLC ratio. | Observation, frequency informed by number of risk factors |
| **Waldenstrom Macroglobulinemia** | LAD/HSM, anemia, hyperviscosity (HA, vertigo, dizzy, Δ vision, AMS), bleeding (acq VWD), cryoglobulins, cold agglutinins. | IgM monoclonal gammopathy, ≥10% BM involvement, infiltrate immunophenotype. | Modified Staging System for WM (J Clinical Onc:42:2527) | Bendamustine+α-CD-20, BTKi, plasmapheresis |
| **Solitary Plasmacytoma** | Skeletal pain or pathologic fracture of affected bone. No CRAB. | Biopsy-proven solitary bone tumor w/ evidence of clonal PC, no BM involvement. | Risk of progression to MM higher if M-protein persists post RT. | Primarily radiation therapy (RT); may require surgery for bone instability. |
| **AL Amyloidosis** | Cardiomyopathy, purpura, nephrotic syndrome, polyneuropathy, orthostasis, HSM, macroglossia, bleeding. | Congo-red stain (apple-green birefringence) on bx. Send for mass spec. | Stage using BNP, troponin and FLC. FLC nadir <20 after tx is a/w better response. | Daratumumab-CyBorD; early auto-HCT if candidate. |
| **POEMS syndrome** | Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin | MGUS and polyneuro-pathy are required. | Albumin at diagnosis | Limited dz: RT; advanced dz: ~MM. |

## Multiple Myeloma Workup and Management (Am J Hematol. 2024:99:1802; NCCN 2024 MM Guidelines)

- **Workup**: ↓Albumin/Globulin, ↑globulin, ↑ESR, peripheral smear (rouleaux), ↑LDH, ↑β2M, whole body low-dose CT ± PET/MRI. BMBx (IHC, flow, cytogenetics/FISH, rapid heme panel). 10% w/ concurrent amyloid. 10-30% w/ extramedullary dz.
- **High-risk factors**: t(4;14), t(14;16), t(14;20), del17p, gain1q, del1p. Any 2 or 3 high risk factors = double hit or triple hit, respectively.
- **Treatment agents**: Induction includes combination of proteasome inhibitor [bortezomib (Velcade – V, Bor), carfilzomib (K), ixazomib (Ix)], immunomodulator [lenalidomide (Revlimid – R), pomalidomide (Pom), thalidomide (T), iberdomide], steroids/chemo [dexamethasone (low dose = d), prednisone (P), melphalan (M), cyclophosphamide (Cy), doxorubicin (dox)], and monoclonal antibodies [anti-CD38 daratumumab (D, Dara) & isatuximab (Isa); anti-SLAMF7 elotuzumab (Elo)].
- **Induction & consolidation**: NOT curative. Standard risk median overall survival (OS) approaching 10y. High risk median OS ~3y
  - Induction: triple w/ VRd most common; CyBorD if renal failure at diagnosis; DaraRd if frail; quad (DaraVRd) ↑use, esp. if HR
  - If candidate for autoHCT, usually performed early, but can delay until relapse w/o detriment in OS (NEJM 2017;376:1311)
  - Maintenance (e.g. **R** +/- **V**) following auto-HCT, or after induction if no HCT. 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); measurable residual disease-negative (<1 PC in $10^5$ cells on flow/VDJ sequencing)
- **Relapsed/refractory MM**: CAR-T (BCMA, GPRC5D), BiTE (teclistamab, elranatamab, talquetamab), belantamab, bendamustine-based regimen, venetoclax if t(11;14), chemo, salvage autoHCT.
- **Other Tx**: Bisphosphonates, denosumab, XRT for bone lesions; opportunistic infection ppx; VTE ppx; EPO-analog for anemia.

# Oncology MDS & MPN

## MYELODYSPLASTIC NEOPLASMS/SYNDROMES (MDS)

- Diagnosis: 1+ cytopenia, BMBx with dysplasia >10% of cells in at least one lineage and <20% blasts, cytogenetics
  - Initial eval: CBC/diff, blood smear, BMBx w/ aspirate, EPO, broad work-up to rule out other causes of bone marrow failure and peripheral cytopenias (nutritional, infectious, autoimmune, endocrine, drug-related)
  - Classification systems categorize MDS subtypes according to genetic changes, degree of dysplasia & BM blast %
- Pathophys: clonal mutation → ineffective/dysmorphic hematopoiesis → cytopenias, risk of transf. to AML, and reduced survival
- Presentation: median age 65-75; s/sx include fatigue (55%), fever/infection (15%), and bleeding (8%)
- RF: old age, male, exposures (benzene, tobacco, chemotherapy, XRT), autoimmune disorders (rheumatic heart dz, RA), PNH
- Prognosis: IPSS-M > IPSS-R predicts progression to AML and survival. *TP53* multi-hit (not monoallelic), *FLT3*, etc. confer risk
- Treatment: based on IPSS-R, performance status & age
  - *Low risk:* No intervention shown to improve survival (JAMA 2022;328:872). Supportive care if asx or mild cytopenias. ESA for anemia (JCO 2008;26:3607), TPO-RA for thrombocytopenia. Hypomethylating agents (azacitidine/decitabine) or ATG if multiple cytopenias. alloHCT in select, younger pts. Targeted tx: lenalidomide for del(5q), luspatercept for ringed sideroblastic
  - *High risk*: If alloHCT candidate, transplant +/- induction or hypomethylating prior (alloHCT improves outcomes even up to age 75, per JCO 2021;39:3328). If not alloHCT, azacitidine or decitabine. Ongoing trials with venetoclax plus azacitidine.

Clonal hematopoiesis (CH) is increasingly identified in patients without frank myeloid malignancy; categories of CH include:

- **Clonal Hematopoiesis of Indeterminate Potential (CHIP)**: risk factor for MDS/AML and cardiovascular disease, variant allele frequency (VAF) ≥2% of leukemia-associated gene, no cytopenias, <5% BM blasts, rate of progression to AML 0.5-1%/yr
- **Clonal Cytopenia of Unknown Significance (CCUS):** unexplained cytopenia + CHIP
- **Idiopathic Cytopenia of Unknown Significance (ICUS)**: unexplained cytopenia, but not CHIP (either VAF <2% or no mutation)

## MYELOPROLIFERATIVE NEOPLASMS (MPN): clonal expansion, 1+ myeloid lineages, often involve activation of JAK-STAT

Sequelae vary; PV/ET can progress to 2° MF (~10-20%) or straight to AML (<5%). MF progression to AML is more common (10-20%).
Tx goals: improve QOL (e.g. constitutional symptoms,), prevent thrombosis (aspirin, hydrea), prevent progression to AML (alloHCT)

| | Polycythemia vera (↑Hgb +/-↑WBC ↑Plt) | Essential thrombocythemia | Primary myelofibrosis (↓Hgb ↓or↑WBC ↓or↑Plt) | Chronic myeloid leukemia (↓Hgb ↑WBC ↑Plt) |
|---|---|---|---|---|
| **Sx** | VTE, aquagenic pruritus, erythromelalgia, splenomegaly, ruddy complexion, GI (epigastric pain, ulcers), HA, dizziness, Δ vision, gout flare | Thrombosis, bleeding (acquired vWF, consider if plt >1 mil), vasomotor sx, HA, syncope, Δ vision, CP, paresthesia erythromelalgia, livedo | Fatigue, night sweats, weight loss, bone pain, massive hepatosplenomegaly, abdominal pain, early satiety, thrombotic/hemorrhagic events | Fatigue, weight loss, night sweats, bleeding, splenomegaly, abdominal pain (LUQ), L shoulder pain (Kehr's sign), gout flare. 20-50% are asymptomatic at diagnosis |
| **Dx** | **Major WHO criteria**:<br>- Hgb >16.5 (♂), Hgb >16 (♀)<br>- BMBx showing trilineage proliferation<br>- Mutations: *JAK2* V617F (95-97%) or *JAK2* exon 12 mut.<br>**Minor WHO criteria**:<br>- Low Epo (below reference) | **Major WHO criteria**:<br>- Plt >450k<br>- BMBx w/ enlarged megakaryocytes with hyperlobulated nuclei<br>Mutations: *JAK2* 60-65%, *CALR* 20-25%, *MPL* 5%<br>**Minor WHO criteria**:<br>- Other clonal markers | **Major WHO criteria**:<br>- BMBx w/ "dry" tap showing reticulin or collagen fibrosis<br>- Mutations: *JAK2* 65%, *CALR* 25%, *MPL* 5%, others<br>**Minor WHO criteria**:<br>- Leukoerythroblastic smear (left-shift, nucleated and teardrop RBCs), ↑LDH, anemia, splenomegaly | **Mutation**: ***BCR-ABL1* fusion** (by FISH, RT-PCR), CBC with ↑ granulocytes (myelo, metamyelo, bands), basophilia, eos. Phases: **chronic**, **accelerated** (10-20% blasts), or **blast** (>20% blasts). Blast phase can be consistent with AML (80%) or ALL (20%) |
| **Tx** | **All**: phlebotomy (goal HCT < 45), ASA81 (if no bleeding), allopurinol, antihistamine<br>**If >60, ↑risk thrombosis**: Hydroxyurea (HU) or IFN-α, **2nd line**: ruxolitinib (JAK2-inhib, NEJM 2015;372:426) | **All**: ASA81 (unless vWF syndrome). **If age>60 or ↑risk thrombosis**: HU > interferon-α > anagrelide (PDE inhib, blocks plt production) (NEJM 2005;353:33) | AlloHCT (only cure), transfusion, hydroxyurea, ruxolitinib [JAK2 inhibitor, primary benefit is symptom reduction, splenomegaly (NEJM 2012;366:787)]. Momelotibin/fedratinib for relapsed/refractory. | **Chronic phase:**<br>TKI: imatinib, dasatinib, nilotinib. 2nd gen TKI (ponatinib > asciminib) if T315I mutation. Consider alloHCT if TKI intolerant, resistance.<br>**Blast phase:** Tx as AML/ALL w/ induction + TKI, alloHCT |
| **DDx** | ↑**Epo**: hypoxemia-induced (heart/lung dz, carboxy-Hb, smoking) vs. Epo-producing tumor (rare). ↓Epo: activating epo receptor mutation (rare) | Infection, inflammation, iron deficiency, splenectomy, bleeding, other MPN (PMF), MDS (e.g. 5q-), solid cancers | AML, CML, ET, PV, MDS/MPN overlap syndromes, MDS, hairy cell leukemia, other malignancies (e.g. w/ bone metastases) | Leukemoid rxn (↑LAP), drugs (steroids, GCSF, ATRA), infection (C. diff, mono), bleeding, splenectomy, DKA, organ necrosis, other MPN |

## OTHER MYELOID DISORDERS: Variety of conditions ranging from aggressive to indolent

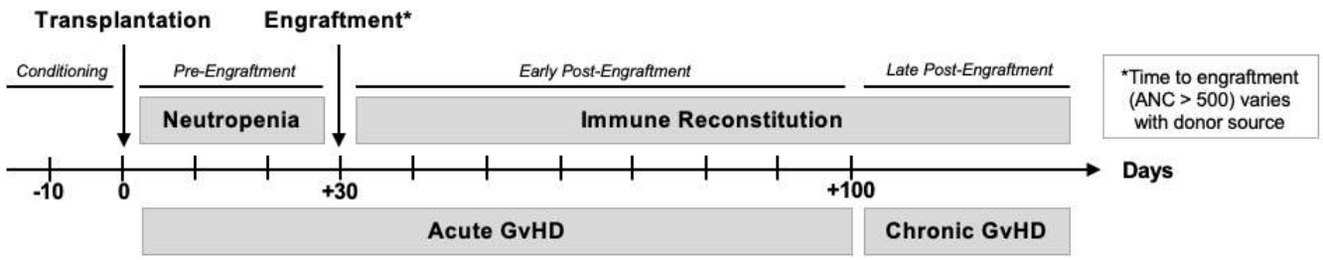
- **MDS/MPN syndromes:** Chronic myelomonocytic leukemia (CMML; see below); MDS/MPN with SF3B1 mutation/ring sideroblasts & thrombocytosis; MDS/MPN with neutrophilia ("atypical CML")
  - **CMML:** characterized by peripheral blood monocytosis (≥1x10⁹/L or ≥10%) and MDS/MPN features. Proliferative (WBC ≥13k) vs. dysplastic (<13k). Prognosis: Mayo Molecular. ↑Prog. to AML. Tx: supportive, hydroxyurea, alloHCT
- **Blastic plasmacytoid dendritic cell neoplasm (BPDCN):** skin lesions, w/ or w/o marrow involvement and leukemic dissemination
- **Mastocytosis**: includes cutaneous and systemic mastocytosis. Associated w/ *KIT* D816V. +Darier's sign. Recurrent anaphylaxis

# Oncology Hematopoietic Stem Cell Transplantation

## Types of Transplant

| | Allogeneic Transplant | Autologous Transplant |
|---|---|---|
| **Definition** | Transplant of **non-self (donor)** hematopoietic cells | Transplant of **self (patient)** hematopoietic cells |
| **Goals** | **Reconstitute hematopoiesis** after conditioning chemo and **graft-versus-tumor (GVT) effect** to kill malignant cells. Also used for bone marrow failure syndromes. Always curative intent. | **Reconstitute hematopoiesis after high-dose chemotherapy**. Intent generally curative except in plasma cell disorders, where goal is to prolong remission |
| **Indications** | ↑risk **AML** (40-60% 5YS), **ALL** (40-50% 5YS), **MDS** (45% 5YS), ↑risk **myelofibrosis**, TKI-resistant **CML**, **relapsed lymphoma**, **aplastic anemia,** thalassemia, sickle cell disease, primary immunodeficiency (SCID), inborn errors of metabolism | **1st relapsed lymphomas** (40-50% 5YS), **MM** (35% 5YS); relapsed **Waldenström**, **AL amyloidosis**, select solid tumors (germ cell, neuroblastoma, Ewing sarcoma), autoimmune disease (MS, SS, Crohns, SLE) |
| **Source of cells** | Mostly **peripheral blood**, but some centers use more **bone marrow** given lower risk of chronic GVHD. Umbilical cord blood is occasionally used | Usually **peripheral blood** given less invasive harvest, more rapid engraftment |
| **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<br>***Acute*** (within 100 days)<br>***Chronic*** (>100d, morbidity/mortality mo/yrs later) | **No**, but rare "GVHD-like" syndrome occurs in ~0.5% of auto-transplants (BMT 2020;55:1879) |
| **Graft-versus-tumor (GVT)** | **Yes**, major therapeutic goal is 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) |
| **Pharmacologic Immunosuppression** | **Yes** (usually 3-6 months; sometimes for 1-2y if GVHD develops) | **No** |

## Allogeneic Hematopoietic 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)**: compatible siblings, matched at 10/10 HLA alleles
  - **Matched-unrelated donor (MUD)**: 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)

| Cell Source | Collection | Engraft | GVHD Risk | Notes |
|---|---|---|---|---|
| **Bone marrow (BM)** | Aspirated from iliac crest | 18-21d | (Reference) | Less often used despite lower cGVHD risk, due to slower/less effective engraftment |
| **Peripheral blood (PBSC)** | Mobilization and peripheral apheresis | 12-15d | Higher risk | Generally preferred source due to faster engraftment (Cochrane Rev 2014) |
| **Cord blood (CB)** (Blood 2013;122:491) | Immature cells from umbilical cord at delivery | 28d (variable) | Lower risk | ↑txp-mortality compared to MUD; allows for more HLA disparity |

- **Conditioning regimens** (Blood 2014;124:344): determined by underlying condition, disease status, and 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, ↑immunosuppression, ↑txp-mortality, ↓relapse
  - **Reduced intensity conditioning** (**RIC**): tumor debulking & allows for engraftment
    - Permits transplant in elderly w/ co-morbidities; ↓toxicity, ↓txp-mortality, ↑relapse (JCO 2017;35:1154)
  - Conditioning agents: chemo (e.g.,fludarabine, 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), **cell source** (BM, PBSC, CB), **GVHD prophylaxis** regimen (e.g. tacro vs. cyclosporine, methotrexate, etc.)
- Example one-liner: 35M w/ AML (FLT3-mutated) who is now day +4 from his **myeloablative** (Bu/Cy) matched related donor (**MRD**) peripheral blood hematopoietic-cell transplant (**PBHCT**) with tacrolimus/methotrexate GVHD prophylaxis (day 0 = 1/1/21).

# Oncology Hematopoietic Stem Cell Transplantation

**INFECTIOUS COMPLICATIONS**: 2/2 chemo-related pancytopenia & immunosuppression (ASBMT/IDSA: BBMT 2009;15:1143)

| MGH Ellucid | 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)<br>Neutropenic enterocolitis (**typhlitis**) | GPCs & GNRs | **Encapsulated bacteria** (SHiN)<br>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 mimic 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, pneumatosis
  - Tx: pip/tazo vs cefepime/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 BID (day -1 to +365 [auto]; 1y minimum & until off IS [allo])
  - **CMV**: **letermovir 480mg qd** (dose-reduced w/ cyclosporine) used in CMV-seropositive recipients (day +7 to +100)
    - Alternative: weekly CMV VL (day -1 to +100), with pre-emptive therapy for viremia with IV ganciclovir or PO valganciclovir
  - **Fungal***: **fluconazole 400mg qd**, vori 200mg BID, posaconazole 200mg TID (day -1 to ANC>500 [auto] or 3-6mo [allo])
    - Anti-mold (vori-, posa-, isavu-conazole) prophlyaxis is considered in patients with AML, lengthy neutropenia
  - **PCP/Toxo***: **Bactrim SS qd** (start after engraftment as outpatient for 6mo [auto], >1y or off IS [allo])

## GRAFT-VERSUS-HOST DISEASE MGH Ellucid

- **Acute GVHD**: D0 to +100. ~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, donor parity, TBI-myeloablation, PBSC > BM > CB
  - Cause: (1) Short-lived donor T cells react immediately; (2) Post-engraft, chronic infl → DAMPs/PAMPs → organ damage
  - 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). Grading here.
  - 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). Trial enrollment for cell therapies (MSCs, Tregs) (Blood 2020;136:410)
- **Chronic GVHD**: 30-70% of patients s/p allo-HSCT (humoral immune response, $T_H2$ cell-mediated) (NEJM 2017;377:2565)
  - Cause: Pro-inflammatory environment iso graft-vs-tumor response, infx → iatrogenic thymic dysfx in training new T cells + Treg depletion → chronic inflammation w/ T/B cells → aberrant tissue repair after multiple injurious cycles → fibrosis
  - 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 & belumosudil (ROCK2 inhibitor) have shown responses in steroid-resistant disease; cell therapies (BBMT 2020;26:835)
- **GVHD PPX**: day **-3 to indefinite (tapered over months to years)**, *goal to prevent graft rejection & acute/chronic GVHD*
  - **T cell depletion regimens**: (ATG, decreased T-cell dose) no longer favored; ↓chronic GVHD but no effect on survival
  - **Post-transplant cyclophosphamide**: combined with tacro/MMF, previously used most widely for haplo and MMUD, now considered standard of care for all donor types ↓a/cGVHD, ↑infections

| 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)** | Expands Treg, limits allo-reactivity (JCI 2019;129:2357) | Given days +3 and +4, particularly for haploidentical | **Hemorrhagic cystitis**, mucositis, cardiac toxicity |

# Oncology Hematopoietic Stem Cell Transplantation

**NON-INFECTIOUS COMPLICATIONS**: immune-mediated organ damage, toxic effects of chemo, or immunosuppression

| QUICK REFERENCE: MGH ELLUCID (day -8 conditioning to day +30 engraftment) | | | |
|---|---|---|---|
| **Monitor S/Sx** | **DDx fever** | **DDx abdominal pain** | **DDx dyspnea/hypoxemia** |
| • **Chemo toxicity**: mucositis, N/V/D, S/Sx of infection<br>• **GVHD**: rash, jaundice, diarrhea (24h volume)<br>• **SOS**: RUQ pain, jaundice, ascites, edema<br>• **Engraftment syndrome**: fever, dyspnea, edema | • Infection (bacterial, viral, fungal, parasitic)<br>• Drug reaction<br>• Engraftment syndrome (day 7-9 for auto, day 14-21 for allo)<br>• Tumor (initial lysis & cytokine release)<br>• Immobility (aspiration, DVT/PE)<br>• GVHD | • Neutropenic enterocolitis<br>• Colitis: *C. difficile*, CMV<br>• SOS<br>• GVHD<br>• Obstruction, ileus, constipation | • Existing disease: CHF, COPD, asthma<br>• PNA: bacterial, fungal, aspiration<br>• Volume (often on mIVF, transfusions)<br>• Drug: chemo-induced lung injury or cardiotoxicity<br>• Engraftment (pulmonary edema from capillary leak)<br>• Pneumonitis<br>• Alveolar hemorrhage<br>• PE, TRALI, GVHD |

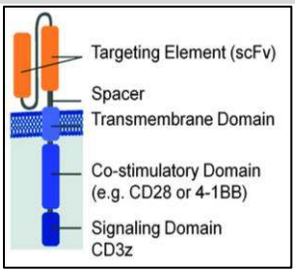
- **Pre-Engraftment (day 0-30):** common to have mucositis, nausea/vomiting, alopecia, rash, diarrhea
  - **Mucositis**: most HSCT patients get some degree of mucositis; duration & severity are worse in allogeneic HSCT. Treatment is focused on pain & caloric intake. **WHO grade**: (1) erythema (2) ulcer, 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): might reduce duration & severity with 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)
  - **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 for INR<1.5, maintain plt >50k; limited data for recombinant FVIIa
  - **Liver – sinusoidal obstruction syndrome (SOS)** (previously called **veno-occlusive disease** [VOD]):
    - Cause: direct cytotoxic injury to hepatic venules leading to hypercoagulable 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 (<21d post-HCT), hepatomegaly/RUQ pain, sudden weight gain (fluid) >2-5% baseline body weight (see criteria and grading: Br J Haematol 2021;190;822)
    - 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 (CD34 boost); transfusions with irradiated & leukoreduced products

**DISEASE RELAPSE**: #1 cause of death post-HCT. **Mechanisms**: immune escape, resistant clones that survive conditioning

- Treatment: post-transplant maintenance (e.g., gilteritinib in FLT3-ITD AML) (Blood 2023;141:1), donor lymphocyte infusion (DLI), salvage chemo, then second allo-HCT, clinical trials for novel therapies
- Hospice and/or palliative approach is appropriate in select cases

# Oncology CAR T cell Therapy

## MECHANISM OF ACTION (NEJM 2018;379:64)




- **Chimeric antigen receptor T cells** autologous cell therapy whereby T cells are collected from patient, genetically modified with construct encoding a chimeric antigen receptor (CAR) that directs T cells against a tumor antigen. CAR T cells are infused into patient, where they persist *in vivo*
- **CAR**: transmembrane engineered protein consisting of extracellular immunoglobulin (antibody)-derived domains (ScFv), which binds a tumor antigen (e.g. CD19). The ScFv is fused to signaling (CD3z) and costimulatory domains (CD28 or 4-1BB) that cause T cell activation and proliferation

## SELECTED FDA-APPROVED CAR T CELL THERAPIES

- **Yescarta** (axicabtagene ciloleucel - "axi-cel"; anti-CD19, CD28 co-stim domain)
- **Kymriah** (tisagenlecleucel - "tisa-cel"; anti-CD19, 4-1BB co-stim domain)
- **Tecartus** (brexucabtagene autoleucel - "brexu-cel"; anti-CD19, CD28 co-stim domain)
- **Breyanzi** (lisocabtagene maraleucel – "liso-cel"; anti-CD19, 4-1BB co-stim domain, 1:1 ratio of CD8+:CD4+ CAR T cells)
- **Abecma** (idecabtagene vicleucel - "ide-cel"; anti-BCMA, 4-1BB co-stim domain)
- **Carvykti** (ciltacabtagene autoleucel - "cilte-cel"; anti-BCMA, 4-1BB co-stim domain, 2 anti-BCMA camelid nanobody domains)

## TOXICITIES (JNCCN 2024; BBMT 2019;25:625) MGH Ellucid

- In general, the anticipated management approach of disease specific treatment-related adverse events should be discussed with the attending of record as case-specific considerations are common
- **Cytokine-release syndrome (CRS)**
  - At least Grade 1 occurs in majority of patients, <10% Grade 3. Typically 1-3d (up to 10-15d) post-infusion, lasts ~7d. Caused by cytokine release (IL-2, sIL2R, IFNγ, IL-6, GM-CSF) triggered by CAR T cell engagement of antigen and *in vivo* expansion. ↑risk: bulky disease, baseline ↓platelets, ↑CRP. Axi-cel > Tisa-cel
  - **Signs/Sx**: fever, ↓BP, ↑HR, ↓$SpO_2$, malaise, rigors, anorexia, myalgia. Can affect any organ (CV, lung, GI/liver, renal, CNS), arrhythmias, capillary leak syndrome, HLH
  - **Dx**: monitor for 7d post infusion for FDA-approved therapies (inpt or possibly close outpt); VS, basic labs, ferritin, coags, CRP, TLS labs. When suspicious, make sure to rule-out infection
  - **Tx**: **See table.** Tocilizumab (anti-IL6R) 8mg/kg over 1h (≤800mg); siltuximab (anti-IL6) and/or anakinra (anti-IL1R); 2nd line: steroids. If plan to treat CRS with steroids or anti-IL6, ****always discuss with the treating attending of record** (even if overnight)**
  - Broad-spectrum antibiotics (cefepime) if fever + neutropenia

| ASTCT CRS Grade | | General Treatment** |
|---|---|---|
| 1 | **Fever** (≥38C) | Tylenol, supportive. If >3d, consider tocilizumab |
| 2 | Fever & **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, IV fluids |
| 3 | Fever + ↓BP requiring **pressor** or ↓$SpO_2$ requiring **HFNC, NRB** | **Tocilizumab** as above, **dexamethasone** 10mg IV q6h (or equivalent) |
| 4 | Fever + ↓BP requiring **multiple pressors** or ↓$SpO_2$ requiring **BIPAP, MV** | **Tocilizumab + dex** as above. If refractory, consider **methylpred** 1g/d IV x3d w/ taper |

- **Immune effector cell-associated neurotoxicity syndrome (ICANS)**
  - **Etiology**: unclear; cytokine diffusion into brain (IL-1, IL-6, IL-15 a/w neurotoxicity), BBB disruption, CAR T cell trafficking to CNS
  - **Timing**: typical onset 4-10d post-infusion, duration variable (14-17d). Can occur w/ or after CRS, but CRS is not req. for ICANS.
  - **S/Sx**: aphasia, impaired fine motor skills, seizure, motor weakness, toxic encephalopathy (see ICE & ICANS grade), rare parkinsonism w/ BCMA CAR T cells (Nat Med 2021;27:2099)
  - **Dx**: neuro c/s, ICE score, ICANS grade. If grade ≥3: MRI brain w/ w/o contrast, EEG, LP (r/o infection), fundoscopy
  - **Tx: See table.** Seizure prophylaxis starting on day of infusion (levetiracetam 500-750 mg q12h for 30d). Generally, dexamethasone +/- anakinra, treat CRS if present, but ****first discuss with the attending** (even if overnight)**
  - **Prognosis**: generally reversible, rare fatal cases

| Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool | |
|---|---|
| Max score: 9 | A&Ox3 [+ hosp] (4 pts), naming [clock, pen, button] (3 pts), follows commands (1 pt), writes sentence (1 pt), serial 10s from 100 (1 pt) |

| ASTCT ICANS Grade | | General Treatment** |
|---|---|---|
| Grade 1 | ICE = 7-9, awakens spontaneously | Supportive |
| Grade 2 | ICE = 3-6, awakens to voice | Dex 10mg IV x1 |
| Grade 3 | ICE = 0-2, awakens to tactile stimulus, or focal edema on neuroimaging, or brief seizure | Dex 10mg IV q6h or methylpred 1mg/kg IV q12h |
| Grade 4 | ICE = 0, unarousable, seizure >5min or w/o return to b/l, or deep focal motor deficit, or diffuse cerebral edema, or raised ICP | Methylprednisolone IV 1g/d x3d or equivalent w/ taper. Can add anakinra if no response |

- **Persistent Hematologic Toxicity**
  - Can cause grade ≥3 anemia, neutropenia, thrombocytopenia, and B-cell aplasia that persists months-years
  - Mechanism unclear, a/w with decreased baseline hematopoietic reserve and inflammation (Blood 2021;138: 2499)
- **Hemophagocytic Lymphohistiocytosis Like Syndrome (IEC-HS):** Rare, 1% develop (see Anemia) (TCT 2023 HLH guidelines)

# Oncology — Solid Organ Malignancies

| Organ | Risk factors/screening | Diagnostics | Treatment |
|---|---|---|---|
| Breast<br>▪ Infiltr. ductal (70-80%)<br>▪ Invas. lobular (5-10%)<br>▪ Mixed ductal/lobular (7%)<br>▪ Inflammatory Breast Cancer (1-5%)<br>▪ Mucinous (2%)<br>▪ Tubular (1.5%)<br>▪ Medullary (1%)<br>▪ Papillary (1%) | Risk factors:<br>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, DES exposure<br><br>Screening:<br>▪ USPTF: q2y mammo 40-74<br>▪ NCCN: q1y mammo >40 or 10y before earliest FHx if >30 or 10y after RT if >30 | ▪Dx bilateral mammogram (Bi-RADS), US, FNA or core Bx (> excisional Bx), breast MRI if young or to assess extent (good Sn, but Sp 72%)<br>▪Path review<br>▪FH, ± germline genetic testing & counselling | Early stage (I, IIA, IIB through T2N1):<br>▪ Breast Conserving Surgery ± RT (NEJM 2023;388:585) vs. mastectomy ± RT, HR tx, HER2 tx, or chemo if high risk<br>Locally advanced (Stage IIB T3N0, IIA-IIIC):<br>▪ Surgery + RT w/ (neo)adj. chemo & HR/HER2 tx<br>(Neo)adjuvant therapy:<br>▪ ER/PR+, HER2-: tamoxifen or aromatase inhibitors (AI) (anastrozole, letrozole, exemestane); no AI if premenopausal; ± ovarian suppression if high risk. Chemo: AC-T (doxo, cyclophos [CYC], paclitax.) or TC<br>▪ HER2+: TCH(P) (trastuzumab, carboplatin, docetaxel, ± pertuzumab) or ACTH(P) (doxorubicin, CYC, paclitaxel, trastuzumab ± pertuzumab) + ER/PR tx if HR+<br>▪ Triple Neg: if early stage adjuvant chemo + PARPi (BRCA1/2), stage II/III neoadj chemo +/- pembro (PDL1), w/ adjuvant capecitabine +/- pembro +/- chemo.<br>Metastatic/recurrent (Stage IV):<br>▪ ER+: as above ± fulvestrant (ER antagonist); ± CDK4/6 inhibitor or everolimus (mTOR inhibitor)<br>▪ HER2+: THP (1st line) or T-DM1 (trastuzumab-drug conjugate), trastuzumab+lapatinib<br>▪ BRCA mutation: olaparib or talazoparib<br>▪ Triple neg: systemic tx |
| Colorectal<br>▪ AdenoCa (98%)<br>▪ Neuroendocrine<br>▪ Lymphoma | Risk factors:<br>▪ FHx, genetic, IBD (UC>CD), obesity, tobacco, red/processed meat, EtOH, adenomat. polyps, age<br><br>Screening (45-75yo):<br>colo (q10y), flex sig (q5-10y), CT colo (q5y), FIT (q1y), Cologuard (q3y), FOBT (q1y) for 50-75yo | ▪ Colonoscopy<br>▪ CT C/A/P, CEA<br>▪ MRI for liver mets<br>▪ Pelvic MRI or endorectal US for rectal CA<br>▪ Molecular testing: MSI/MMR status in all, K/N-RAS, BRAF, HER2, POLE, POLD1, RET amp. | Colon:<br>I-IIA: surgery + observation, or capecitabine or 5-FU/leucovorin (IIA)<br>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 pembro<br><br>Rectal:<br>low anterior (LAR) v abdominoperineal resection (APR) ± neo v adj chemoRT. Chemo as in colon cancer |
| Lung<br>▪ NSCLC (84%): adeno, large>SCC<br>▪ SCLC (13%) | Risk factors (Nat Rev Ca 2007;10:778):<br>▪ Age, male, tobacco, asbestos, occup. exposures, lung fibrosis or COPD, exposure to infectious agents (TB, fungal), FH<br><br>Screening:<br>▪ USPSTF: Annual low dose CT chest for 50-80 yo current smokers with ≥20 pack-year hx OR quit within last 15 yrs (Annals 2014;160:330) | ▪ CT C/A/P, FDG-PET/CT, brain MRI<br>▪ PFTs<br>▪ Evaluate pathologic LNs with biopsy<br>▪ Molecular testing for NSCLC (EGFR, ALK, ROS1, NTRK1/2/3, MET exon14 skipping, RET, PD-L1) before systemic tx | NSCLC: IA: surgery ± RT; IB-IIIA: surgery if able ± adjuv chemoRT ± osimertinib or atezolizumab. IIB/IIIA unresectable, IIIB: definitive chemoRT + adjuvant durvalumab IV: systemic tx as below:<br>▪ ChemoRT: cisplatin + docetaxel/etoposide/ pemetrexed; carboplatin + pemetrexed/paclitaxel/ gemcitabine/docetaxel<br>▪ Targeted inhibitors: EGFR (osimertinib 1st line, erlotinib); ALK/ROS1 (alectinib, brigatinib, lorlatinib); BRAF/MEK (dabrafenib/trametinib); TRK (larotrectinib, entrectinib)<br>▪ Immunotherapy (PD-L1+) pembro ± chemo. ipi/nivo, atezolizumab+ platinum+ taxane + bevacizumab<br>SCLC:<br>▪ Limited: surgery + chemo ± mediastinal RT<br>▪ Extensive (NEJM 2018;379:2220): chemo & atezolizumab v durvalumab (maintenance immunotherapy) ± RT for lobar obstruction, SVC syndrome, bone/brain mets<br>▪ Chemo: platinum agents, etoposide, irinotecan |
| **Organ** | **Risk factors/screening** | **Diagnostics** | **Treatment** |
| Melanoma<br>▪ Superficial spreading (75%)<br>▪ Nodular (15-30%)<br>▪ Lentigo maligna (10-15%)<br>▪ Acral lentiginous (<5%)<br>▪ Amelanotic (2-10%)<br>▪ Ocular (5%)<br>▪ Mucosal (~1%) | Risk factors:<br>▪ Sun exposure (UVB > UVA), atypical nevi, high nevi count, FHx or personal hx, immunosupp.<br>▪ Familial melanoma with germline CDKN2A, CKD4, POT1 mutations<br>Most common somatic mutations:<br>▪ BRAF (V600E, V600K) 50%, NRAS 15-20%, KIT 10-15% (acral). Genetic testing for stage II-IV disease | ▪ Biopsy of primary tumor (Breslow depth prognostic), LN sampling, CT C/A/P, brain MRI, & serum LDH for active surveillance and treatment response<br>▪ Liver MRI for ocular/uveal melanoma – liver most common metastatic site | Localized disease: 0-I wide excision of primary tumor ± sentinel lymph node biopsy. Ib-II Topical wide excision +/- pembro/nivo (IIb/IIc) +/- RT, if surgery contraindicated or as adjuvant tx topical thx.<br>Metastatic disease: Systemic therapy ± excision (if feasible) ± RT (for sympt. localized disease, e.g. brain mets) ± talimogene laherparepvec (T-VEC, intralesion injection of HSV " tumor cell lysis & GM-CSF expression)<br>Systemic therapy: Immunotherapy (NEJM 2015;373:23; NEJM 2015;372:2521): anti-PD-1 (pembro/nivo); anti-CTLA4 (ipilimumab), ipi+nivo (NEJM 2019;381:1535). Targeted tx (NEJM 2014;371:1867): If BRAF/MEK mutated, combo inhibitors(dabrafenib+trametinib, vemurafenib+cobimetinib, encorafenib+binimetinib). If KIT mutant, imatinib. |

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Suggest an Edit

| | | | |
|---|---|---|---|
| Pancreas<br>▪ Exocr./adeno (~95%)<br>▪ Endocrine (<5%) | Risk factors:<br>▪ Tobacco, EtOH, obesity, DM, chronic pancreatitis, age, male, FHx, HNPCC, chemical/heavy metal exposure, germline mut. (BRCA1/2, TP53, STK11, MLH1, MSH2/6, PMS2, CDKN2A).<br>Genetic mutations:<br>▪ KRAS, TP53, SMAD4, TGFbR1/2, CDKN2A, MLL2/3, KDM6A, ATM, NTRK, ALK, ROS1, BRAF, HER2, PALB2 | ▪ CT C/A/P pancreas protocol, EUS+Bx, MRCP ± ERCP, MRI for indeterminate lesions, PET/CT in high risk patients<br>▪ CA19-9, LFTs<br>▪ Germline testing +molecular profiling of tumor tissue<br>▪ Bx metastatic site if metastatic disease | ▪ Resectable/Borderline: surgery ± systemic tx: 1st line FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin), modified-FOLFIRI, gemcitabine+nab-paclitaxel, gem+capecitabine, ± chemoRT<br>▪ Locally advanced: systemic tx as above or stereotactic body radiation (SBRT)<br>▪ Metastatic: systemic tx ±:<br>• BRCA1/2: olaparib (NEJM 2019;381:317);<br>• NTRK fusions: larotrectinib, entrectinib<br>• MSI-H/dMMR/TMB-H: pembrolizumab (NEJM 2015;372:2509)<br>• BRAF V600E: dabrafenib + trametinib |
| Prostate<br>▪ Adenocarcinoma (95%)<br>▪ Transitional, basal cell, intraductal carcinomas; neuroendocrine, carcinosarcoma, lymphoma, stromal sarcoma | Risk factors:<br>▪ Age, black race, genetic factors (BRCA1/2, PALPB2, CHEK2, P53, MSH/MLH, FANCA) and family history), smoking<br><br>Screening with PSA:<br>▪ 40-75 high risk, q1-2 yrs if PSA <3, normal DRE<br>▪ 55-69: avg risk individual risk-benefit discussion, PSA <1 (q2-4 yrs)<br>▪ 70 and above: no testing (JAMA 2018;319:1901)<br>USPTF: 55-69, individual risk-benefit per above. | Diagnosis: Bx<br><br>After diagnosis:<br>▪ TRUS, MRI, biomarkers, CT C/A/P, bone scan<br><br>Germline testing:<br>▪ High/very high NCCN risk<br>▪ Any risk level if +FHx or intraductal histology | Very low risk: surveillance (PSA, DRE ± Bx) if > 10 yr expected survival, if < 10 yr no intervention.<br>Low risk: surveillance vs external beam radiation therapy (EBRT) ± brachytherapy (BT) vs radical prostatectomy, if < 10 yr survival observe.<br>Intermediate/high risk: combination of EBRT, BT ± prostatectomy w/ lymph node dissection, and androgen deprivation therapy (ADT):<br>Orchiectomy, Androgen R blocker: enzalut-, apalut-, darolut-, flutamide. Androgen synthesis inhib: abiraterone (very high risk). GnRH agonist: leuprolide, gose-, hist-, triptorelin, GnRH antagonist: degarelix, relugolix.<br>Metastatic/recurrent: ADT, if fail, ADT+doxetaxel. Bone mets: radium-223 or denosumab/zoledronic acid, palliative RT. MSI-H/dMMR/highTMB: pembro if fail ADT. |
| Cancer of Unknown Primary<br>▪ Adenocarcinoma or carcinoma not otherwise specified (85%)<br>▪ Squamous cell carcinoma (5%)<br>▪ Undifferentiated carcinoma (5%)<br>▪ Neuroendocrine tumors (5%) | Pathologic Diagnosis:<br>▪ Core needle biopsy (preferred) and/or FNA from accessible site<br>▪ MSI/MMR testing<br><br>Initial Evaluation:<br>▪ Immunohistochemistry<br>▪ Gene expression profiling<br>▪ Tumor serum markers: β-hCG (testicular), AFP (testicular, hepatocellular carcinoma), CEA (CRC), CA-125 (ovarian) | Workup:<br>▪ Complete H&P (breast, GU, pelvic, rectal, skin exams)<br>▪ Routine labs (CBC, electrolytes, LFT, Cr)<br>▪ Occult blood stool testing<br>▪ CT C/A/P with IV contrast +/- PET<br>▪ Endoscopy, UA, LDH (if indicated) | Adenocarcinoma: paclitaxel + carboplatin ± etoposide; gemcitabine + cisplatin or docetaxel; capecitabine + oxaliplatin (CapeOx); fluorouracil + leucovorin + oxaliplatin (FOLFOX) or irinotecan (FOLFIRI); docetaxel + carboplatin or cisplatin<br>Squamous cell carcinoma: Paclitaxel + carboplatin or cisplatin; gemcitabine + cisplatin; docetaxel + carboplatin or cisplatin; cisplatin + fluorouracil; docetaxel + cisplatin+ fluorouracil (DCF)<br>Adenocarcinoma and SCC: capecitabine, fluorouracil, pembrolizumab, selpercatinib<br>Neuroendocrine tumors: paclitaxel + carboplatin + etoposide; cisplatin + etoposide; temozolomide ± thalidomide. |

# Oncology Immune Checkpoint Inhibitors

## IMMUNE CHECKPOINT INHIBITORS (ICI)

- **Mechanism of Action**: Block receptors that suppress T cell activation → CTLA-4, PD-1, LAG-3 (on T-cell) or its ligand e.g. PD-L1 (on cancer cell) → ↑antitumor immune response (Cell 2023;186:1652)

**Indications**: ~10 drugs approved for 15 cancers. Prior autoimmunity not absolute C.I., but can cause flares (Cancer 202012:738)

## IRAES: DEFINITION, DIAGNOSIS, GRADING, AND MANAGEMENT (ASCO: JCO 2021;39:4073; NCCN Guidelines 2024)

- **Definition**: Immune related adverse events (irAE) are systemic autoimmune/inflammatory events 2/2 ICIs, involving any organ system w/ variable timing. Some data show irAEs a/w improved survival, even if hospitalization (JAMA NetwOpen 2024)
- **Most common irAE sites**: skin, liver, colon, renal, CNS, peripheral neuro, endocrine (hypoT), MSK, heme, pulm
- **Inpatient Mgmt**: ***Consult SIC*** *(Severe Immunotherapy Complications) service for inpatient questions regarding concern for IRAEs. Phone Directory → Hematology/Oncology on Call → Cancer Center On Call → Ellison 16 Onc Team 2 + SIC.*

**Select IRAEs: COMPRHENSIVE GRADING AND MANAGEMENT GUIDELINES (**JCO Oncology Practice 2022; 18:6).

**1. Skin toxicity**: Common, 30-40% of pts (CTLA-4 > PD-1/L1 blockade). Rash, pruritis, bullous derm, lichen planus, psoriasis, rarely SJS/TEN/DRESS. Vitiligo seen in melanoma, rarely in other cancers, a/w response to immunotherapy (JNCCN 2024; 22:9).

- **Timing**: Early, within the first few weeks after tx initiation
- **S/Sx**: Four types (1) Inflammatory (2) Immunobullous (3) Keratinocyte alteration (4) Immune reaction mediated
- **Dx**: exam; r/o other etiologies (infection, DRESS, SJS/TEN); grading based on BSA (<10% Gr 1, 10-30% Gr 2, >30% Gr 3)
- **Tx**: topical steroids, oral antihistamines for inflammatory/pruritic reaction. If severe, consider systemic steroids + derm c/s

### irAE Severity and Grading

| Severity | General Approach |
|---|---|
| Grade 1 | • Continue Checkpoint Inhibitor (**if no CNS / heme / cardiac irAE)**<br>• Increased freq. of monitoring |
| Grade 2 | • Delay Checkpoint Inhibitor<br>• PO steroids OP (0.5 – 0.1 mg/kg), taper 2-4 weeks<br>• Re-challenge w/ ICI if returns to Grade 1 or resolved<br>• Increased freq. of monitoring |
| Grade 3 | • Delay Checkpoint Inhibitor<br>• PO steroids OP (1 – 2 mg/kg), taper 4-6 weeks, IV if symptoms persist 48-72 hrs<br>• Consider organ specialist consult |
| Grade 4 | • Discontinue checkpoint inhibitor **(except endocrinopathies managed w HR)**<br>• Inpatient IV steroids w/ taper<br>• Consult organ specialist |

**2. Colitis**: More common w/ anti-CTLA-4; grade 3/4 colitis is higher with ipilimumab (<10%) than with anti-PD-1 agents (1-2%). (JITC 2018; 6:95).

- **Timing**: 6-8w after initiation of therapy
- **S/Sx**: Diarrhea, weight loss, abdominal pain/urgency/rectal bleeding if severe
- **Dx**: Lactoferrin/calprotectin; r/o other etiologies (*C diff.*, stool Cx, etc.). 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.

**3. Pneumonitis**: More common w/ anti-PD-1, serious toxicity rare. Higher risk w/ combination therapy.

- **Timing**: Highly variable, can be later in therapy. (Immunother Cancer 2020; 8:e000840)
- **S/Sx**: Dyspnea, cough, fever, acute interstitial pneumonia/ARDS; 1/3 asymptomatic (JCO 2017;35:709; Clin Cancer Res 2016;22:6051)
- **Dx**: Rule out other etiologies (e.g. PCP), workup w/ CT though often non-specific can show GGOs and/or nodular infiltrates. Consider BAL +/- biopsy if suspect Grade 2 or higher.
- **Tx**: Oxygen, glucocorticoids w/ taper (4-6 wks), diuresis, infliximab, mycophenolate mofetil or IVIg if severe or refractory.

4. **Hypophysitis** (JAMA Oncol 2018;4:173): Primarily w/ anti-CTLA-4 (3%), rarely w/ anti-PD-1/PD-L1 (0.5%). Mechanistically distinct from other irAEs; possibly by direct binding of ipilimumab to CTLA-4 on normal cells of anterior pituitary (Sci Transl Med 2014;6:230).

- **Timing**: Median onset ~8w
- **S/Sx**: HA (common, can be severe), fatigue, n/v, dizziness, weight changes, hot flashes, cold intolerance, hyponatremia (anterior hypopituitarism), vision changes; usually 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)**.** **Central hypothyroidism**: levothyroxine. **Hypogonadism**: consider testosterone replacement. **GH deficiency**: GH theoretically contraindicated due to active malignancy, although little clinical evidence

**5. Myocarditis** (JACC 2018;71:1755): Rare but serious AE a/w high mortality (46% in severe myocarditis); risk higher w/combo tx

- **Timing**: Generally within 3mo (Oncologist 2018;23:874; Lancet 2018;391:933)
- **S/Sx**: Heart failure, arrhythmia (new afib, high grade AV block, ventricular tachycardia)
- **Dx**: CK, EKG, **troponin**, NT-proBNP, TTE, MRI and EMG ± endomyocardial Bx
- **Tx**: Discontinuation of ICI; high dose or pulse-dose steroids (1g IV, then PO pred 1mg/kg) (J Am Heart Assoc 2020;9:2); 2nd-line consider ATG/IVIg or infliximab/MMF/tacro (Oncologist 2018;23:879). GDMT for HFrEF. Potential PPM need (pending prognosis)

**Other irAEs** (JCO 2019;36:1714): Inflammatory arthritis/myositis, PMR/GCA, **nephritis,** pancreatitis/DKA, adrenal insufficiency, **hepatitis**/cholestasis, myasthenia gravis, GBS, peripheral/autonomic neuropathy, aseptic meningitis, encephalitis/ADEM, optic neuritis, transverse myelitis, AIHA, ITP, TTP/HUS, aplastic anemia, acq. hemophilia, pericarditis, uveitis/iritis, episcleritis, blepharitis.

# Oncology — Oncologic Emergencies

## TUMOR LYSIS SYNDROME (TLS) (NEJM 2011;364:1844; JCO 2008;26:2767)

- **Pathophys**: 2/2 tx initiation or spontaneous in cancers w/ high turnover → release of intracellular metabolites (i.e. uric acid, K+, phos) → AKI (uric acid causes renal vasoconstriction, precipitates in tubules), seizure, CaPhos crystal deposition (↑phos → ↓Ca)
- **Presentation**: ↓UOP, weakness/cramps/tetany/perioral numbness, seizure, arrhythmia
- **Risk factors: high risk (>5%):** ALL/AML (WBC ≥100k), CLL (on venetoclax & bulky disease), Burkitts, stage 3/4 lymphoblastic NHL, bulky TCL/DLBCL; **intermediate risk (1-5%):** ALL (WBC <100k), AML (WBC 25-100k or <25k & ↑LDH), Burkitt, DLBCL, CLL (chemo-specific & ↑WBC), rare chemo-sens bulky solid tumor (e.g. germ cell tumors**); low risk (<1%):** HL, indolent NHL, CML, CLL (on alkylating tx & WBC <50k), MM, MDS, all other solid tumors.
  - **High risk substrate**: WBC >50k, LDH >2x ULN, bulky disease (>10cm), old age, hypovolemia, uric acid >7.5, AKI/CKD, mediastinal mass, BM involvement, HSM**. High risk agents**: venetoclax (highest), CAR-T, daratumumab, rituximab, etc.
- **Labs/workup**: BMP (electrolytes, Cr, iCal), Mg, phos (calculate Ca-phos product), uric acid, LDH, CBC/diff, ECG
- **Diagnosis (Cairo-Bishop criteria)**:
  - Laboratory diagnosis: ≥2 criteria within 3d before or 7d after cytoxic therapy: uric acid ≥8mg/dL, K ≥6mEq/L, phos ≥4.5mg/dL, or Ca ≤7mg/dL. Criteria also satisfied if 25% change from baseline.
  - Clinical diagnosis: laboratory dx & ≥1 clinical criteria: Cr 1.5x ULN, arrhythmia, or seizure
- **Prophylaxis**: **Low risk** → Oral fluids. Daily labs. **Medium risk** → Continuous IVF (NS) at 2-3L/m²/d. Allopurinol 2-3d before chemo until Day +1. BID labs. **High risk** → Medium risk measures + telemetry & q6-q8 Labs. Consider rasburicase
- **Treatment**:
  - **Hydration**: D5-1/2NS or NS if hypoNa/hypovolemic @ 2-3L/m²/d. Maintain **UOP ≥100cc/hr** for excretion of uric acid and phos; diuretics PRN (prefer loops to ↓K) to maintain UOP and treat hypervolemia
  - **Treat abnl electrolytes**: hyperK tx (e.g. lokelma), sevelamer, **delay tx of hypoCa** until phos normalizes or hypoCa is severe (tetany/arrhythmia) to avoid ↑CaPhos precip
  - **Allopurinol**: 300-600mg/day (adjust dose if renal dysfunction). Can use febuxostat if hypersensitivity or advanced CKD.
    - ↓ clearance of other meds (cyclophosphamide, MTX, 6-MP, azathioprine, ampicillin)
    - *HLA-B*5801* ↑prev. in East Asian, Southeast Asian, Black pts ↑**risk of SJS/TEN**, consider alternative tx
  - **Rasburicase** (↑uric acid clearance; discuss w/ attending & MGH Ellucid Policy): 0.2mg/kg IV (but 3-6mg IV usually effective), administer if high risk, baseline renal failure, ↑baseline or rising uric acid >7.5/Cr despite allopurinol/saline, or volume overlaod
    - Risk of anaphylaxis, methemoglobinemia. **Contraindicated in G6PD deficient** (can cause hemolysis); **check G6PD early**
  - **Renal replacement therapy**: **generally** indicated if Ca-phos product ≥70mg²/dL² (albumin-corrected Ca × phos)
  - **Other:** Urinary alkalinization w/ NaHCO3. Contraindicated in hyperphos (↑CaPhos precip). Not common at MGH.

## HYPERVISCOSITY SYNDROME/LEUKOSTASIS (Blood 2018;132:1379)

- **Etiology**: (**1**) ***hyperproteinemia*** from monoclonal gammopathy (e.g. Waldenström's macroglobulinemia) or polyclonal (e.g. cryoglob) (**2**) ***hyperleukocytosis/leukostasis*** seen in AML/ALL with blasts >50k (rare in CLL unless >400k WBC) (**3**) *other:* PV, sickle cell
- **S/Sx**: pulm (SOB, infiltrates) & CNS (blurry vision 2/2 retinal vein engorgement, HA, dizziness, ataxia, confusion, coma), fever, epistaxis → page **Heme/Onc fellow** & **Clin Path resident** for **emergency viscosity study**, notify attending to discuss pheresis
- **Diagnosis**: serum viscosity (↑Ostwald tube), SPEP, SFLC, **WBC (often >100k, but can be lower if AML/ALL blast crisis)**
  - Lab artifacts from hyperleukocytosis: **spurious ↑K** (use blood gas K), **falsely low arterial paO₂** (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** (↑viscosity)

## METASTATIC EPIDURAL SPINAL CORD COMPRESSION (Seminars in Neurology 2010;30:245; Lancet Neurology 2008;7:459)

- **Primary CA**: prostate, lung, breast > NHL, renal cell, multiple myeloma, Hodgkin's
- **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) → gait instability/ataxia → sensory deficits (ascending numbness, saddle anesthesia in cauda equina), bowel/bladder dysfunction (urinary retention, incontinence)
- **Exam**: pain precedes other sx by ~8w, weakness/ataxia, paresthesia, ↑reflexes, ⊕ Babinski, ↓anal sphincter tone
- **Diagnosis**: STAT total spine MRI with cord compression/metastasis protocol, CT myelography if MRI not possible
- **Treatment**: after imaging, STAT page **Spine Surgery** AND **Radiation Oncology**
  - Neuro deficits/pain: generally **dexamethasone 10mg x1 IV**, then 16mg PO daily (divided), taper once definitive tx

## 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 > melanoma > RCC > breast > head and neck, thyroid, esophageal, non-esophageal metastatic GI
- **S/Sx**: HA (40-50%), focal neuro deficits (20-40%), cognitive dysfunction (30-35%), new onset seizures (10-20%), stroke (5-10%)
- **Diagnosis**: MRI w/ contrast > non-enhanced MRI or CT with contrast.
- **Treatment**: control vasogenic edema (**dexamethasone 10mg IV x1, then 4-8mg IV/PO BID**), consider AED (usually not for 1° ppx); avoid AC if concern for active hemorrhage; definitive treatment will ↓local recurrence: for multiple mets, stereotactic radiosurgery > whole-brain XRT (↑neurocognitive impairment can be mitigated w/ hippocampal avoidance/memantine) > surgery (JCO 2022;40:492)

## SUPERIOR VENA CAVA (SVC) SYNDROME (NEJM 2007;356:1862; CA Cancer J Clin 2022;72:570)

- **Etiology**: external compression of SVC from mediastinal mass (commonly lung CA or NHL) causing ↑upper body venous pressure
- **Sx**: raised ICP, narrowing of larynx/pharynx (dyspnea, stridor), head/neck swelling (visually striking), hemodynamic instability
- **Diagnosis**: CT venography (SVC syndrome protocol), **obtain/ensure tissue diagnosis ASAP to guide definitive tx**
- **Treatment**: secure airway, RT/chemo, intravascular stent (emergent if refractory sx), steroids (resp distress only, d/w attending)

# Oncology — Febrile Neutropenia

## Definitions and Etiology (J Oncol Pract 2019;15:19)

- **Definition**: **T ≥100.4 (**≥1hr or oral >100.9) with **ANC <500 cells/mL** or <1000 cells/mL with predicted decrease to <500 over 48hr
- **Microbiology**: **ONLY** ~40-50% cases have infectious source identified; others attributed to translocation of intestinal bacteria
  - When organisms identified: 40% GNRs (E. coli, Klebs > PsA); 60% GPCs (CoNS > MSSA/MRSA, strep, enterococcus/VRE) esp w/ indwelling lines or mucositis; fungal (Candida, molds) more likely w/ prolonged ↓ANC, broad-spectrum abx use, or TPN

## Evaluation

- **H&P**: comorbidities, type & time since last chemo, prior micro data, recent antibiotic therapy/ppx, medications, vascular devices
- **Exam**: mouth (mucositis), skin, perineum/rectal (**visual inspection**, **avoid DRE**), indwelling lines/port (erythema/tenderness)
- **Studies**: BCx x2+ sites (≥1 periph, 1 per CVC lumen), UA/UCx, CXR, SCx/GS, resp viral panel, CMV PCR (if HSCT)
  - Fungal markers: LDH, β-D-glucan; galactomannan if high risk for Aspergillus (HSCT, GVHD, neutropenia >10-14d)
- **Further symptom-directed studies to consider**:
  - GI symptoms: CT A/P (evaluate for neutropenic colitis/typhlitis); stool culture, O&P, C. diff if diarrhea
  - Pulmonary symptoms: CT chest ± bronch/BAL (especially if prolonged F&N), SCx/GS, MRSA nasal swab, RVP, urine legionella, and consider testing for endemic mycoses if characteristic CT chest findings + exposure hx
  - Headache/sinus pain: CT face/sinus
- **Risk stratification**:
  - **MASCC Risk Index** (JCO 2000;18:3038) and **CISNE** (JCO 2015;33:465) can measure risk of F&N-related complications
  - **High risk**: anticipated ANC ≤100 for ≥7d, inpt status at time of fever, co-morbidities/infections (renal/hepatic impairment, PNA, central line infxn), allogeneic HCT, mucositis grade 3-4, alemtuzumab use or CAR-T within past 2mo → inpatient management
  - **Low risk** (JCO 2018;36:1443): short anticipated ANC ≤100 (<7d), no co-morbidities, good performance status (ECOG 0-1), strong home social support → treated with PO antibiotics after brief inpatient stay versus strictly outpatient

## Treatment/Prophylaxis

- **MGH Guideline**; **Alternate** guidelines: (Clin Infec Dis 2011;52:e56, J Oncol Pract 2018;14:250)
- **Empiric abx**: within 1h; higher mortality for each hr of delayed abx (Antimicrob Agents Chemother 2014;58:3799)
  - **Gram-negatives (PsA dosing)**: Initial antimicrobrials SHOULD target gram-negative pathogens, including PsA
    - **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 - both share the same side chain) + levofloxacin
    - High-risk ESBL: meropenem 1g q8h (2g q8h if meningitis)
    - Low risk: IV -> PO regimen (discuss w/ attending); cipro/levoflox + amox-clav vs clinda (if PCN allergy); avoid if prior FQ ppx
  - **Gram-positives**: **NOT a standard part of FN empiric regimen** (Clin Infect Dis 2011;52:56)
    - Select indications: HoTN/severe sepsis, GPC bacteremia, catheter-related infxn (rigors with infusion, erythema on exam), SSTI, radiographic PNA, severe mucositis + prior FQ ppx + GNR coverage with ceftaz
    - First line: vanc; if there is concern for VRE then daptomycin (unless pulmonary process) or linezolid
  - **Anaerobes**:
    - Indications: intra-abd source, C. diff, oral ulcer/periodontal infxn, post-obstructive PNA, necrotizing ulceration
  - **Fungi**:
    - Indications: **F&N >4-7d** despite abx, ⊕ fungal biomarkers, ⊕ CT chest (circumscribed, air crescent, cavity), ⊕ BAL Cx
    - Micafungin 100mg q24h or Amphotericin 5mg/kg q24h (admin after 500cc NS). Consult ID if high suspicion
- **Modification/duration**: Recommended duration of empiric therapy varies between guidelines (Ther Adv Infect Dis 2022;9)
  - **Resolution of fever**:
    - Documented infxn: narrow abx and tx for recommended course, then consider 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), discuss w/ ID
    - Clinically worsening: broaden abx ± fungal coverage, consider CT chest ± bronch to evaluate for fungal infxn
  - **Catheter-associated infection**: also see *Bloodstream Infections & Endocarditis*
    - Coag-negative staph, non-VRE Enterococcus: generally can keep line if IV abx + abx lock x2w
    - Staph aureus, PsA, fungi: must remove line. For gram negative, d/w ID/attending, consider line removal vs. lock therapy
    - Complicated infxn (e.g. endocarditis, septic thrombosis, bacteremia/fungemia >72h post removal): remove line, abx x4-6w
- **Prophylaxis**:
  - **Anti-microbial ppx**: refer to NCCN guidelines for more specific indications
    - Antibacterial (FQs): high-risk pts (heme malignancy) and attending discretion for intermediate-risk pts
    - Antifungal (azole vs echinocandin): select heme malignancies during neutropenia and early post-HCT
    - PJP (TMP-SMX, atovaquone): if ≥20mg prednisone daily for ≥1mo, purine analog, CD4≤200, or post-HCT/CAR-T
    - HSV/VZV (acyclovir vs famciclovir): heme malignancy on therapy, post-CAR T, or post-HCT (1-2 years)
  - **G-CSF**: ppx reduces incidence and duration of FN when risk >20% but does NOT decrease mortality (JCO 2015;33;3199); consider adding if critically ill, anticipated prolonged neutropenia, PTLD, or HIV. Caution if leukemia (d/w attending)

# Oncology Inpatient Chemotherapy Regimens

| Regimen* | Protocol | Supportive Care |
|---|---|---|
| | **Leukemia** | |
| **7 + 3**<br><br>7d of **cytarabine** and 3d of **anthracycline** | **Induction for AML**<br>Idarubicin 12 mg/m2 daily x3days or<br>Daunorubicin 60-90 mg/m2 daily x3 days<br>Cytarabine 100-200 mg/m2 continuously, days 1- 7 | **Premedication:** TTE given cardiotoxicity risk<br>**Emetic Risk:** High<br>**Neutropenia Risk**: High<br>**Growth Factor:** Filgrastim or Pegfilgrastim |
| **Decitabine (5-aza-2'-deoxycytidine, Dacogen)**<br><br>28-day or 42-day cycle until disease progression or toxicity | **MDS/AML:** 20 mg/m$^2$ IV over 60 min daily on Days 1-5<br><br>**AML with unfavorable cytogenetic and/or *TP53* mutation:** 20 mg/m$^2$ IV over 60 min daily on Days 1-10<br><br>**MDS**: 15 mg/m$^2$ over 90 min q8h on Days 1-3 OR 20 mg/m$^2$ over 60 min daily on Days 1-5 | **Premedication:** anti-diarrhea med PRN, IVF and/or electrolyte replacement<br>**Emetic Risk:** Minimal-to-low<br>**Neutropenia Risk**: Moderate<br>**Growth Factor:** Filgrastim or Pegfilgrastim |
| **5-Azacytidine (5-Aza, Vidaza, Azadine, Onureg)**<br><br>28-day cycle until disease progression or toxicity | **AML:** 300mg PO qday on D1-14<br><br>**MDS:** Cycle 1: 75mg/m$^2$/day for D1-7; Subsequent Cycles: 75 mg/m$^2$/day q4weeks (Dose may be increased to 100 mg/m$^2$/day if no benefit after 2 cycles) | **Premedication:** For first 2 cycles, antiemetic 30 min prior to each dose then PRN after 2 cycles if no n/v; neuro-monitoring for CNS tox<br>**Emetic Risk:** Moderate, Cycle 1-2<br>**Neutropenia Risk**: Moderate<br>**Growth Factor:** Filgrastim or Pegfilgrastim, Epoetin alfa |
| **HiDAC (High-Dose ara-C)**<br><br>**(ara-C, Cytarabine)** | **Consolidation:**<br>**HiDAC:** 1.5-3 g/m$^2$ over 3h q12h on Day 1, 3, 5 -OR- Day 1, 2, 3 for 3-4 cycles<br>*5 + 2*: ara-C + anthracycline OR mitoxantrone<br>*5 + 2 + 5:* ara-C + anthracycline + etoposide | **Premedication:** Corticosteroid eye drops throughout consolidation<br>**Emetic Risk:** Moderate<br>**Neutropenia Risk**: Moderate<br>**Growth Factor:** Filgrastim or Pegfilgrastim |
| **Hyper-CVAD**<br><br>Dose-intensive phase:<br>8 cycles of Hyper-CVAD alternating with High-Dose Methotrexate and Cytarabine (HD MTX-ara-C)<br>+ intrathecal (IT) PPx each cycle for 16 IT treatments.<br><br>Maintenance phase:<br>Dependent upon clinical response | **Hyperfractionated Cyclophosphamide (CP):** 300 mg/m$^2$ IV over 3h q12h for 6 doses on days 1-3, given with Mesna 600 mg/m$^2$ as continuous infusion ending 6h after last dose<br>**Vincristine:** 2 mg IV Days 4 and 11<br>**Doxorubicin:** 50 mg/m$^2$ IV on Day 4<br>**Dexamethasone:** 40 mg daily on Days 1-4; 11-14<br><br>**HD MTX-ara-C:**<br>**MTX:** 200 mg/m$^2$ IV over 2h followed by 800 mg/m$^2$ IV over 24h on Day 1; Leucovorin rescue starting 24h after completion MTX; dose according to MTX level<br>**ara-C:** 3 g/m$^2$ over 2h q12h x 4 on Days 2-3<br>**Methylprednisolone:** 50 mg IV twice daily Days 1-3<br><br>**CNS PPx:**<br>*Risk-stratified CNS ppx with alternating intrathecal (IT) high-dose methotrexate (MTX) and cytarabine (Ara-C)*<br>**MTX:** 12 mg IT on Day 2<br>**ara-C:** 100 mg IT on Day 8 | **Premedication:** NS 100mL/hr prior to chemotherapy. Continue through cyclophosphamide<br>**Emetic Risk:** Day 1-5, high<br>**Neutropenia Risk**: High; Median times to granulocyte and platelet recovery were 18 and 21 days, respectively<br>**Growth Factor:** Filgrastim or Pegfilgrastim on Day 5 (24h after chemotherapy) |
| **ATRA/ATO**<br>Induction: ATRA should be continued until CR is achieved. Restage with BM aspirate and biopsy on Day 28 | **Induction:**<br>**All-Trans Retinoic Acid (ATRA):** 45 mg/m$^2$ in divided doses daily, starting Day 1. S*tart ATRA upon first suspicion of APL*<br>**Arsenic trioxide (ATO):** 0.15 mg/kg IV daily, starting after cytogenetics confirmation<br><br>**Consolidation:**<br>**ATRA:** 45 mg/m$^2$/d for 2 weeks q4wks for a total of 7 cycles<br>**ATO:** 0.15 mg/kg IV 5d/wk for 4 weeks q8wks for a total of 4 cycles | **Premedication:** None<br>**Emetic Risk:** Moderate<br>**Neutropenia Risk**: High<br>**Differentiation Syndrome:** maintain a high index of suspicion (fever; WBC >10k; SOB; hypoxemia; pleural or pericardial effusions). Discuss steroid use with attending, supportive<br>**Growth Factor:** Myeloid growth factors should not be used during induction. May be considered during consolidation for life-threatening infection |
| **Hydroxyurea (Hydrea; HU)** | **HU:** Starting dose 500 mg BID or 1000 mg QD; dose adjusted to ANC 500-1000; cytoreduction and WBC count goal based on disease and therapy regimen | **Premedication:** None<br>**Emetic Risk:** Minimal-to-low<br>**Neutropenia Risk**: Moderate<br>**Growth Factor:** count recovery within days |

# Oncology Inpatient Chemotherapy Regimens

| Lymphoma | | |
|---|---|---|
| **R-CHOP**<br><br>14-day cycle, restage after 2-4 cycles, total 3-6 cycles +/- radiation | **Rituximab**: 375 mg/m$^2$ IV Day 1<br>**Cyclophosphamide**: 750 mg/m$^2$ IV over 30 min Day 1, combined oral and IV hydration 2-3L on day of chemo<br>**Doxorubicin**: 50 mg/m$^2$ IV Day 1<br>**Vincristine**: 1.4 mg/m$^2$ (max 2 mg) IV over 15-20 min Day 1<br>**Prednisone**: 100 mg PO Days 1-5<br>**CNS PPx:** 4-8 doses of IT MTX and/or cytarabine or high-dose MTX during the course of treatment | **Premedication:** Diphenhydramine and acetaminophen prior to rituximab, hydration for hemorrhagic cystitis risk<br>**Emetic Risk:** Day 1, high<br>**Neutropenia Risk**: High<br>**Growth Factor:** Filgrastim or Pegfilgrastim on Day 6 or 3-4 days after completion of chemotherapy until count recovery |
| **Dose-Adjusted R-EPOCH**<br><br>21-day cycle, 6 cycles (dose adjustments based on ANC counts from BID CBC during previous cycle) | **Rituximab**: 375 mg/m$^2$ IV Day 1<br>**Etoposide:** 50 mg/m$^2$ infusion over 24h daily on Days 1-4<br>**Doxorubicin:** 10 mg/m$^2$ continuous infusion over 24h daily on Days 1-4<br>**Vincristine:** 0.4 mg/m$^2$ continuous infusion over 24h daily on Days 1-4<br>**Cyclophosphamide:** 750 mg/m$^2$ IV over 30 min Day 5, combined oral and IV hydration 2-3L on day of chemo<br>**Prednisone**: 60 mg PO BID Days 1-5<br>**CNS PPx:** 4-8 doses of IT MTX and/or cytarabine or high-dose MTX during the course of treatment | **Premedication:** Diphenhydramine and acetaminophen prior to rituximab<br>**Emetic Risk:** Days 1-5, high<br>**Neutropenia Risk**: High<br>**Growth Factor:** Filgrastim or Pegfilgrastim after completion of chemotherapy until count recovery |
| **R-ICE**<br><br>14-day cycle, 3 cycles | **Rituximab**: 375 mg/m$^2$ IV Day 1<br>**Ifosfamide:** 5,000 mg/m$^2$ IV continuous infusion over 24h on Day 2 with NS at 1.5-3 ml/kg/hr beginning 2h prior and ending 2-4h after infusion<br>**Mesna:** 5,000 mg/m$^2$ IV infusion over 24h on Day 2<br>**Carboplatin:** Dose AUC 5 mg/mL IV over 30 min on Day 2<br>**Etoposide:** 100 mg/m$^2$ daily on Days 1-3 | **Premedication:** Diphenhydramine and acetaminophen prior to rituximab<br>**Emetic Risk:** Day 1, 3 – Low; Day 2 High<br>**Neutropenia Risk:** High<br>**Growth Factor:** Filgrastim or Pegfilgrastim on Day 4 or 3-4 days after completion of chemotherapy until count recovery |
| **ICE** | See **R-ICE** above, hold rituximab | |
| **R-DHAOx**<br><br>21-day cycle | **Rituximab:** 375 mg/m$^2$ IV Day 1<br>**Dexamethasone:** 40 mg PO daily on Days 1-4<br>**Cytarabine:** 2,000 mg/m$^2$ IV Day 2 (2 doses)<br>**Oxaliplatin:** 130 mg/m$^2$ IV over 2h on Day 1 | **Premedication:** Diphenhydramine and acetaminophen prior to rituximab<br>**Emetic Risk:** Moderate<br>**Neutropenia Risk:** High<br>**Growth Factor:** Filgrastim or Pegfilgrastim on Day 5 or 3-4 days after completion of chemotherapy until count recovery |
| **R-Bendamustine**<br><br>28-day cycle, 6 cycles | **Rituximab:** 375 mg/m$^2$ IV Day 1<br>**Bendamustine:** 90 mg/m$^2$ IV over 10 min **or** IV over 30 min daily on Days 1-2, CVC recommended for administration | **Premedication:** Diphenhydramine and acetaminophen prior to rituximab<br>**Emetic Risk:** Moderate, Day 1-2<br>**Neutropenia Risk**: High |
| **High-dose Methotrexate (MTX)**<br><br>Dependent on chemotherapy regimen and count-recovery for 1-8 cycles | **CNS Disease PPx and Tx:**<br>**IV MTX:** doses of 500 mg/m$^2$ or higher at varying times based on disease<br>**Intrathecal MTX**: 12-15 mg q2-7 days; continue for 1 dose beyond CSF cell count normalization<br>**Leucovorin:** 25 mg IV over 15 min **or** PO on Day 2 starting 24h from initiation of MTX and q6h until MTX < 0.05 uM | **Hydration:** Alkaline hydration with 5% Dextrose in sodium bicarbonate 100 mEq/L at 150 cc/hr 4h prior until 72h after MTX infusion<br>**Emetic Risk**: Days of MTX, moderate<br>**Neutropenia Risk:** High<br>**Growth Factor:** Filgrastim or Pegfilgrastim on Day 4 or 3-4 days after completion of chemotherapy until count recovery |
| **Solid** | | |
| **FOLFOX, FOLFIRI, FOLFOXIRI, FOLFIRINOX**<br><br>(FOL) Folinic Acid 1d<br>(F) 5-Fluorouracil 1-2d<br>(IRI) Irinotecan<br>(OX) Oxaliplatin 1d | **Folinic Acid:** 200 mg/m² IV Day 1<br>**Oxaliplatin**: 85 mg/m² IV Day 1<br>**Irinotecan** 180mg/m² IV Day 1<br>**Fluorouracil**: 400 mg/m² IV bolus followed by 2400 mg/m² for 2 days | **Toxicities:** If acute cholinergic syndrome appears use atropine. Can also have laryngospasm and rarely, coronary artery vasospasm spasm (5-FU). Send *DPYD* gene test to screen for DPD deficiency.<br>**Emetic Risk:** High<br>**Neutropenia Risk**: High<br>**Growth Factor:** Filgrastim or Pegfilgrastim on Day 6 or 3-4 days after completion of chemotherapy until count recovery |

*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 (WHO Guidelines; CDC guidelines; DFCI Pink Book

- A comprehensive pain hx is essential to guiding therapy. Goal is to maximize level of functioning and quality of life.
- Step-wise approach to pain management:
  - Mild to moderate pain: non-opioids and adjuvants
    - Acetaminophen: max dose 4g daily, 2-3g safe in liver disease (Br J Clin Pharmacol;2016;81:210)
    - NSAIDs: celecoxib best if ↑GIB risk, ketorolac if severe pain [10 –15 mg recommended, no added analgesia with higher doses (Am Fam Phys 2017;96:262), use with caution in recent GIB, CAD, renal disease, IBD
  - Moderate to severe pain: schedule non-opioid options, try topicals, then consider short-acting opioids PRN
  - Severe pain: requiring round-the-clock opioids. Discuss w/ attending, consider adding extended release (ER) meds
    - Avoid ER opioids if pain source is expected to resolve (e.g., bone fracture, hematoma, abscess, post-procedural)
- "Basal-bolus" strategy: Obtain basal level of pain control throughout the day with scheduled oral doses + PRNs for breakthrough pain

## 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 (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 (systemic or topical), steroids*
- Neuropathic: burning, stinging, allodynia, hyperalgesia
  - Topical: capsaicin, camphor/menthol, lidocaine, diclofenac gel. POs in chart below (start low & go slow in older adults)
- Non-pharmacologic: PT/exercise/activity, heat or ice, CBT, treating comorbid psych dx, massage, acupuncture, other integrative therapies (note: for inpatient, massage and acupuncture currently only available for heme/onc patients including sickle cell)

*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

## Neuropathic Pain and Opioid-Sparing Analgesia (*R – dose adjustment needed for renal function)

| Drug | Initial Dose | Titration | Dose range | Notes |
|---|---|---|---|---|
| **Gabapentin** | 100 mg po TID *R | Inc 100 mg TID q3 days | 300 – 3600mg/day | Dose adjust for renal function; may take a few weeks to see effect |
| **Pregabalin** | 75 mg BID or 50 mg TID *R | Can ↑ by 50-150mg/day within 1 wk if tolerating | 300 mg / day in 2-3 divided doses | |
| **Duloxetine** | 20 mg daily *R | Inc by 20-30 mg per week | 20-60 mg / day | Common side effect sweating (6%); avoid if CrCl<30ml/min |
| **Venlafaxine** | 37.5-75mg daily *R | Inc by 75 mg q 4 days | 75 – 225 mg /day | Allow 4-6 wks for effect; Risk of withdrawal syndrome when stopped (need taper) |
| **Amitriptyline** | 25 mg at bedtime, 10 mg in frail/elderly | Titrate dose every few days | 25-100 mg at bedtime | Allow 2-4 wks for effect. Less side effects with nortriptyline |
| **Nortriptyline** | | | | |

## KETAMINE (General Guidelines on Ketamine for Acute Pain, MGH Ketamine Use Policy)

Initiation of ketamine, and adjustment of dose requires consultation with either **Palliative Care or Chronic Pain Service**

**Consider in:** 1) Expected severe post-operative pain (abdominal/thoracic surgery, orthopedic surgeries) 2) Opioid tolerant pts presenting for surgery or acute pain exacerbations. 3) Pts at increased risk of opioid-related respiratory depression (OSA)

- **Adverse effects**: rare at sub-anesthetic dosing (HTN, tachycardia, arrythmia, hallucinations, increased ICP, increased bronchial secretions, N/V). Psychomimetic effects may be treated w/ 0.5-1 mg IV haloperidol or 1-2 mg IV lorazepam.
- **Avoid in**: poorly controlled cardiac disease, pregnancy, active psychosis/hospitalization hx (<3 yrs), severe liver dz, elevated ICP/IOP

## Opioids (CDC guidelines; 2022;11; DFCI Pain Management Pocket Resource; 2024;3)

- **Below chart is** for opioid naïve patients in moderate or severe pain.
- Opioid-tolerant defined as total daily dose (TDD) x7d: morphine 60mg/oxycodone 30mg/hydromorphone 8mg/ equianalgesic dose of another opioid. If opioid tolerant, consider home PO breakthrough dose or 10-20% of ER dose; if concern for hepatic or renal metabolism, would use wider dosing intervals and be more cautious with uptitration
- Patients on buprenorphine/methadone for OUD, or active non-Rx OUD → treat pain w/ full agonists if needed(See OUD & Withdrawal) . Can consult ACT if needed for assistance.
- Avoid using combo pills (limits titration flexibility). See Opioid Pharmacokinetics Chart below for sample initial dosing

| | Route | Sample Initial PRN Doses | Onset (min) | Peak Effect (min) | Duration of Effect (hr) | Clearance/Metabolites |
|---|---|---|---|---|---|---|
| **Morphine** | IV | 2-4mg q3-4h prn | 5-10 | 10-30 | 3-5 | AVOID in renal disease |
| | PO | 7.5-15mg q3-4h prn | 15-60 | 90-120 | 4 | |
| **HYDROmorphone** | IV | 0.2-0.4mg q3-4h 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 | 2nd 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 | |

| Methadone:* | Fentanyl Patch:* |
|---|---|
| ○ Beneficial in neuropathic pain (TID dosing for pain)<br>○ Cannot be converted linearly from other opioids<br>○ **Safety concerns**: bimodal short and long half-life (up to 150 hours), QTc prolongation (monitor K, Mg)<br>○ Takes days to reach steady state. Typically titrated q72 hours | ○ Safer in both liver and renal dysfunction<br>○ Less effective in cachexia (less subq fat for absorption)<br>○ **Safety concerns:** if febrile, reduce or remove patch (cutaneous vasodilation → faster absorption)<br>○ Requires 18-24h to reach therapeutic level |

*Initiate with Chronic Pain/Palliative Care consult. Must ensure that there is an outpatient prescriber at discharge (PCP or subspecialist)

## Opioid Up-titration/Rotation (CDC Guidelines; 2022;)

- If pain only moderately controlled with scheduled doses (not in pain crisis, no side effects), ↑ total daily dose by 30-50%. Use 'Pain' summary tab in Epic to trend daily morphine milligram equivalent (MME) usage; use caution if patient is taking methadone (long half-life).
- If taking ER opioid and needing >3-4 rescue doses daily, ↑ ER dose by 50-100% of total rescue dose used in past 24h
- Rotate opioids if side effects, dose reduce by 25-50% when rotating (see box below and DFCI Pink Book, pg10)
- If pain persists, repeat pain hx, consider total pain, and involve an interdisciplinary team (eg, palliative care, chronic pain, etc)

**Step 1)** Calculate total daily opioid requirement
**Step 2)** Convert TDD to equivalent dose of new opioid using opioid conversion table
**Step 3)** Reduce dose by 25-50% to account for incomplete cross-tolerance
**Step 4)** Select new long-acting opioid. Divide TDD into doses (depending on agent)
**Step 5)** Add breakthrough dose, should be 10-20% of TDD of ER opioid

**Opioid Equianalgesic Doses**

| Drug | PO/PR (mg) | SQ/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 |

*Caution w/ conversion to fentanyl (short duration of action). Expanded opioid common conversion table available (DFCI Pink Book)

## 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 at least 50%**. In sickle cell VOE, **follow patient's guidance**/Acute Care Plan; if not showing improvement, engage SCD team early and adjust medication dosing as clinically indicated while awaiting their input.

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:
   - No pain relief and no side effects → increase dose by 50-100%
   - Minimal relief and no side effects (<50% reduction in pain score) → repeat the same dose
   - Pain reduced >50% and no side effects → reassess in 2-3h, use this dose as new breakthrough dose
   - Side effects with no pain relief → rotate to different IV opioid (no dose reduction if uncontrolled pain).

## Patient-Controlled Analgesia (PCA) (DFCI Pain Management Pocket Resource; 2024; 19)

- Appropriate for patients who are alert & oriented and able to use equipment. Families may NOT use PCA by proxy
- Requires daily delirium assessment (ie, CAM/4AT). Unrecognized delirium can obscure pain hx/medication use.
- Enables frequent administration of pain meds (vs max q1-2hr)
- Order "General PCA" (opioid-naïve pts) or "High Risk PCA" (BMI >40, hx OSA, RASS -2 to -5, age >65). If pt is opioid-tolerant, requires basal rate, consult Palliative Care/ Pain
- Increases in basal rate takes ~12 hrs to reach steady state: adjust basal rate q24hrs

**General Opioid-Naïve PCA Dosing**

| | Morphine | Hydromorphone | Fentanyl |
|---|---|---|---|
| **Patient Administered Dose** | 1.5 mg | 0.2 mg | 20 mcg |
| **Lockout Interval (per min)** | 10-15min | 10-15min | 10-15min |
| **One-Hour Dose Limit** | 6mg | 1.4mg | 215 mcg |
| **RN/Clinician Bolus (for breakthrough)** | 2mg q30min PRN | 0.3mg q20min PRN | 25 mcg q20 min PRN |
| **Continuous Infusion Rate** | 0mg/hr | 0mg/hr | 0mg/hr |

## Adverse Effects of Opioids and Management (DFCI Pain Management Pocket Resource; 2024; 20)

- **Respiratory depression**: Follows sedative effects. Hold opioid, consider low dose naloxone but CAUTION if on high dose ER opioids
  - Dilute 0.4mg naloxone (1ml) in 9ml saline, give 1-2ml q2min until ↑RR or mental status improves. Naloxone half-life is 30-120min, **watch for recurrence** of resp depression and consider naloxone gtt. All patients d/c'd on opioids need a naloxone script
- **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/cramping; avoid if any concern for GI obstruction). (See Constipation, IBS, & Colonic Disorders)
- Opioid-induced hyperalgesia: generally seen w/ high doses (or lower doses in CKD), consider rotating opioids and involving pall care
- Myoclonus: reduce dose or rotate opioid, increase hydration; can give low dose BZD, or baclofen. If persists, c/s pall care
- Nausea/vomiting: tolerance to N/V may develop, start antiemetic on a fixed schedule for a few days. Suggest prochlorperazine, metoclopramide, haloperidol, avoid ondansetron (constipating). (See Nausea & Vomiting)
- Pruritus: mediated by mu receptor (not histamine – **Benadryl ineffective unless rash/allergic reaction**); consider opioid rotation, nalbuphine 5mg IV q6h prn, or low dose naloxone gtt
- Sedation: occurs prior to resp depression. Hold sedatives/anxiolytics/opioids, reduce dose, if persistent consider CNS stimulant (increased caffeine intake, dextroamphetamine or methylphenidate 2.5-5.0 mg PO daily, modafinil 100-200 mg PO daily), discuss w/ Pall Care team.
- Delirium: reduce dose or rotate opioid; IV Haldol 1-2.5mg BID-QID or IV/PO Zyprexa 2.5-5mg PO QD-BID

# Geriatrics & Palliative Care Adv Care Planning & Code Status

## SERIOUS ILLNESS CONVERSATIONS MGH CONTINUUM PROJECT

*When?* Conversations can be planned or may happen spontaneously in any setting (NEJM 2014;370:2506). Should discuss early in disease course as outpatient, or:

- New, progressive (eg, increasing hospitalizations/ED visits, intolerance of guideline-directed therapies), or life-altering 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). Can use Walter Index 1 year mortality calculator. Life expectancy <6mo ( JAMA 2001;285: 2987; J Palliat Med 2012;15:175)
- Age >80 and hospitalized if no previous documentation (See Geriatric Assessment & Frailty)

*Why?* Longitudinal SICs help explore illness understanding, hopes/worries, and what matters most. Involves pt-centered recommendation regarding a care plan that aligns with pt goals. Can be used for the purposes of Advanced Care Planning, discussion of transition to hospice/CMO, or referral to palliative care (more than just code status)

*How?:* Preparation for planned meetings:

- Consider consulting **Palliative Care** prior to the formal meeting if complex decisions/psychosocial issues/family conflict.
- Consider involving hospital ethics, **the Optimum Care Committee (OCC)**, if you have concerns about the family's preferences for patient care that do not align with the wishes of the patient or reality of the medical situation.
- Identify time and location to accommodate the patient and their loved ones, RN, SW, primary team, and consultants as applicable. Can be helpful to see if any long-term provider (PCP) is available to join.
- **Prior to the patient and their loved ones joining, meet** with the health care team 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 (in alignment w/ pt stated goals)**

MGB Serious Illness Conversation (SIC Guide, Educational Videos): The script below can be adapted depending on whether you are talking directly to the patient vs the patient's family.

| Step | Suggested Prompts |
|---|---|
| Open the conversation | "I'd like to talk about what is ahead with your health. Would that be ok?" |
| Assess prognostic awareness | "What is your **understanding** of your health?"<br>"Looking to the future, what are your **hopes** about your health? What else?" "What are your **worries**? Tell me more." |
| Share worry | "Would it be ok if we talked more about what may lie ahead?"<br>"I **hear** you're hoping for ____ and I worry the decline we've seen will continue" or "I **worry** something serious may happen in the next few wk/mth/yrs."<br>"It can be difficult to predict what will happen with your health." |
| Respond to emotion | **NURSE mnemonic** to respond to patient's/loved one's emotions (CA Cancer J Clin. 2005; 55:164):<br>**Acronym** / **Example**<br>**N**ame: "It sounds like you are frustrated."<br>**U**nderstanding: "I cannot imagine what it would be like to be in this situation."<br>**R**espect: "You're asking all the right questions and doing an amazing job advocating for your husband."<br>**S**upport: "I will be around to answer any of your questions."<br>**E**xplore: "Tell me more about what you are thinking." |
| Align | "I wish we didn't have to worry about this." |
| Explore what's important | "What gives you strength as you think about the future of your health?"<br>"If your health worsens, what is **most important** to you?"<br>"How much do your family or friends know about your priorities and wishes?" |
| Make a recommendation | "It **sounds like** ____ is very important to you."<br>"Given what's important to you, I would **recommend**_____" |

**Document Serious Illness Conversation: (Refer to Advanced Care Planning Module 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
- Consider filling out ACP forms if not already filled out. See Advanced Care Planning Forms below

## 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. Filling out this form is a priority for all patients but more urgently for older adults, those with emerging cognitive impairment, and those with multimorbidity and/or complex life-limiting illnesses.
  - *If no HCP*: 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): medical orders for patients with multimorbidity 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
  - Pink form available on all medical units. Remember that you **do not** have to fill out or discuss everything on the back page (clinical discretion). When filling out a new form, provide patients with a copy and scan into Epic for future documentation.
  - Remember that these decisions **can be changed** (fill out a new MOLST if decisions change)

# Geriatrics & Palliative Care Adv Care Planning & Code Status

- **Links to existing MOLST/HCP** forms are found in Advance Care Planning Activity tab or scanned into the Media tab

## CODE STATUS DISCUSSIONS

General Considerations

- 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 appears discordant with the clinical setting, Do **not** need to routinely readdress on admission if has been recently addressed by outpatient providers
- Code status ≠ ACP. Code status is a medical procedure for which harms/benefits should be weighed iso clinical context.
- Many procedural teams (i.e. cards, surgery) require temporary reversal of DNR/DNI periop, often 30d (JAGS2022;70(12):3378-3389):
  - If changing code status pre-op, **ensure your discharge documentation includes changing status back**/date of conditional code status end
  - If changing code status during early post-procedure or during chemotherapy, **notify procedural team/primary oncologist**

Survival Outcomes (Circulation 2019;139:e56; JAMA 2019; 321:1200)

- *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, acceleration of physical and cognitive frailty/disability

Code status options:

| | |
|---|---|
| Full Code | The patient would want all resuscitative measures to be used |
| DNR/Ok to Intubate | The patient would not want cardiac resuscitation but would want to be intubated in the event of impending respiratory failure |
| DNR/DNI | In the event of a pulseless cardiac arrest or respiratory failure, the patient would not want cardiac resuscitation or intubation |
| DNR/DNI/LLST Comfort Measures Only (CMO) | The patient would want their care team to orient care around comfort only, and care not oriented around comfort may be withdrawn while still treating the patient's symptoms |
| **Do not offer "Full Code Except Do Not Intubate."** Cardiopulmonary arrest requiring CPR nearly always necessitates intubation, and thus this is not an appropriate code status. | |

Conducting Code Status Discussions (JAMA 2012;307:917)

- Suggested opener: "Have you ever discussed CPR and intubation with your medical team? I want to make sure that I understand whatever decisions you've made regarding those two interventions."
- Suggested framing: "Resuscitation is a medical procedure we would perform if your heart were to stop and you died. What have you heard about resuscitation?"
- Many people would prefer a natural death. If you prefer a natural death, then we would protect you from these procedures and ensure your comfort." Approaches to discussion of code status based on scenario (NEJM 2020;382:2450):

| Scenario/Indication | Approach/Goal | Example |
|---|---|---|
| The patient has a stable condition and is likely to benefit from CPR/Intubation | Make sure the patient does not strongly prefer to avoid | "Right now, if your heart were to stop, you would receive CPR. Is this consistent with your goals?" |
| The patient already has a preference to limit CPR and intubation that needs confirmation | Confirm an already established preference | "Your records show that you made an emergency plan with your 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." |
| The patient has an advancing illness, and it is unclear whether the benefits of CPR and intubation would outweigh the burdens (the decision depends heavily on the patient's values and goals) | Shared decision-making | "If an emergency were to occur and your heart were to stop, it is difficult to predict what would happen if you received CPR or a breathing tube. Recognizing this uncertainty, if your heart were to stop and you were to stop breathing, what would you want your medical team to know about what is important to you?"<br>"Given what's important to you, I would recommend_____" |
| The patient is at risk for decompensation/death, unlikely to benefit from CPR and intubation | Informed Consent | **Introduce/assess:** If urgent: "I wish we were meeting under different circumstances."<br>**Share information:** "Given all that's happened, I worry that your health has worsened. What are your thoughts about how things have been going?"<br>(Discuss medical situation, share concerns using hopes/concerns)<br>**Explore goals: "**Given where we are, what is most important to you?" **Make a recommendation:**<br>-"I recommend we make a plan to help you meet your goals and avoid treatments that are unlikely to help." |



Suggest an Edit

# Geriatrics & Palliative Care — End of Life & Pronouncement

## Anticipated Inpatient Death

- Involve family, chaplaincy (available 24/7), social work services, longitudinal providers (e.g. PCP, subspecialists) in/during EOL care
- Ask about religious/cultural traditions, final wishes, and/or any specific preferences/experiences to keep in mind
- Do not broach topic of potential organ donation with family (see Organ Donation section below); New England Donor Services is specifically trained for this and will coordinate consent and donation process
- When passing off a patient who may pass away, prep "**Post-Mortem**" section under "Discharge as Deceased" Epic Tab (see below)
  - Consider asking families about autopsies in advance if/when appropriate
- Assess whether you will need to notify the medical examiner's office. Common reasons listed below. Comprehensive list here.
  - Any death associated with acute or chronic use of alcohol or drugs (including alcohol-related cirrhosis)
  - Death associated with diagnostic or therapeutic procedures
  - Death by accidental/unintentional injury (including falls, fires), violence, suicide, or uncertain circumstances

## Organ Donation

- Eligibility: IF family & medical team elect to discontinue medical support in any ventilated patient with a non-recoverable injury/condition, team should then complete a New England Donor Services e-referral form (see below) **prior** to any of the following:
  - Initiating therapeutic hypothermia, initiating brain death testing, transitioning from FULL to either DNR, DNE, or CMO status
- DO NOT broach topic of potential donation with family; NEDs is specifically trained for this and will coordinate consent & donation process which can take up to 24hrs
- 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 Prep: Death paperwork must be done by declaring MD (prep in advance). After vent withdrawal (usually extubation in OR), MD/RN coordinate sx management until time of death, declare death based on irreversible cessation of circulatory/respiratory function

## Withdrawing Ventilatory Support (palliative extubation, discontinuation of NIPPV)

- Prior to extubation, refer to MGH MICU Policy & ATS Guidelines (AJRCCM 2008;177:912). Review plan with the following people:
  - Family: ask if they want time privately w/ pt prior to extubation. Review expected signs of dying process (agonal breathing/'rattle' of pooled secretions, mottled extremities), expected timeline (usually min to hrs [Chest 2010;138:289]), and plan for sx control
  - RN: ensure adequate PRNs for air hunger/pain (IV opioids), anxiety (IV Haldol or benzos), and secretions (glycopyrrolate) are at bedside (see *Comfort Focused Care*); may need continuous infusions depending on requirements; can use CMO order set. Stop paralytics though can continue any prior sedative and/or opiate infusion(s) utilized for comfort while mechanically ventilated
  - RT: determine plan for immediate withdrawal vs down-titration of vent support
- Do not withhold appropriate sx management because of concern for hastening death or concern for increased sedation
  - *"The Rule of Double Effect"* (NEJM 1998;338:1389): focus on managing sx. If in doubt, ask for help
  - The goal is adequate pain, dyspnea, and anxiety relief; dose based on ongoing symptoms and prior dose effectiveness

## Death Pronouncement

- **PRONOUNCEMENT:** Introduce yourself to the family, express condolences, and explain what you are doing
  - **FEEL** for pulse, **LISTEN** for heart/breath sounds (>60 sec), **SHINE** light to assess for absence of pupillary reflex, and **NOTE** time at the end of your exam which becomes official time of death (do **NOT** need to say out loud)
- **QUESTIONS FOR NEXT OF KIN:** (**Order: HCP** (unless the proxy form specifically prohibits them from consenting to autopsy), Spouse > Adult child > Parent > Adult sibling > Adult grandchild > Grandparent > Other family).
  - Would they like to be connected with MGH Decedent Affairs Office (new service; provide support re: final arrangements; connecting family with spiritual care, social services, bereavement groups, and even financial resources for burial)
  - Would they want an autopsy? (consent NOK in order listed above)
  - If yes, ask about organ disposition (i.e. do they want MGH to retain organs for further testing, education, research?). See below for further instructions.
  - Are there any other family members whom they would like you to inform?
  - Is anyone else coming to view body prior to transport to morgue? (have 4hrs; can't see body at morgue but can at funeral home)
  - **What you can tell family:** body is kept at MGH morgue until the funeral home they select calls MGH and arranges for pickup. Family should select and contact funeral home directly (Decedent Affairs office can assist with this)

> **Autopsies** are **free** & do not delay funerals (can still have open casket). They help determine cause of death & can be instrumental in advancing research.

- **ONCE YOU LEAVE THE ROOM:**
  - **Notify ATTENDING and PCP** (Email acceptable if death was expected)
  - **Electronic Documentation:** No longer paper form (except at NWH), now section under Epic Discharge Tab called 'Discharge as Deceased', similar to standard floor discharge navigator layout – **NOTE: items CAN be prepped & saved ahead of time.**
    - In **"Cause of Death"** section: don't write "cardiac arrest" or "respiratory arrest"; Fill out as many **underlying causes** as applicable - do not need to fill in ALL the lines but be as specific as possible. See CDC guide for examples.
    - If family **consented to an autopsy**, a *separate paper form* needs to be completed and delivered to Warren 049 (office beside the morgue) during business hours. If filling out the form after business hours, discuss with unit coordinator who will drop off the form. **Mark "Autopsy Consent Form Completed" section as "In progress" unless you are delivering the completed form to the Warren building.**
    - Call **Medical Examiner** if necessary (see above *"Prior to Death"*); document first name of said staff member.
    - Click on **New England Donor Services** referral link: replaces initial screening phone call
      - Opens separate online tab within Epic with patient's demographic info prepopulated/filled in; will need to answer several additional questions (cause of death, vent hx, whether + for HIV/HBV/HCV, if active cancer & what type if so);
      - Will still need to subsequently call **NEDS** coordinator (800-446-6362) to confirm above referral outcome
    - Call **Admitting Office** (x6-3393) to inform them of death. Will ask cause/time of death, Med Examiner, NEDS info;
  - **Document a brief "note of patient death"**: SmartPhrase ".MGHDOMDEATHNOTE"
  - Complete short **discharge summary** within the Discharge as Deceased Navigator tab discussed above
  - **Debrief** process and death with team or Night Teach

# Geriatrics & Palliative Care — End of Life Care & Hospice

## End of Life Care General Principles

- The focus of EOL care is to enhance patient's comfort, optimize symptom management, and ensure alignment with what matters most to patient. Code status change to DNR/DNI or CMO (Comfort Measures Only) is **not a requirement**.
  - Note that EOL is a medical state while code status reflects patient goals/values. If code status appears discordant with medical state, close communication among team members is essential for clear understanding of GOC.
  - EOL care should involve all members of the interdisciplinary team (clinicians, SW, chaplains) so that a patient's physical, emotional, social, and spiritual domains of care are adequately assessed and comfort maximized. Additionally, allowing time with family and respecting cultural and/or religious rituals if feasible is important.
  - Communicate expected signs of dying and time course to loved ones. **Any clinical provider** (MD, NP, RN, SW, chaplain) **can request an EOL visitation policy exception with RN leadership irrespective of code status** if passing is expected.
- Prepare paperwork and logistical planning as feasible prior to death (see *End of Life and Pronouncement*)
- If encountering a difficult family dynamic around the time of death, do not hesitate to involve the attending even overnight

## Best Supportive Care: Management Considerations in CMO

- Comfort-focused Care (also called Comfort Measures Only or CMO): Approach to care with the goal to maximize comfort. **Does not mean all treatments are stopped** (e.g., pts may benefit from thoracentesis, paracentesis, or venting G tube if within pt's goals)
- Lines/tubes: Maintain PIV access as possible, d/c central line if feasible.
- Supplemental $O_2$**:** Not shown to have benefit if not hypoxemic. Instead, offer fan therapy, HOB elevation, IV/PO opioids (AJHPC2020;37:294)
- Foley: Can maintain for comfort; discuss w/ RN.
- Stop labs/routine VS unless it is helpful in managing comfort. Reassure loved ones that we can use RR, temp, & appearance as guide
- Medications: Continue meds contributing to patient comfort, those that will prevent uncomfortable events (e.g., rate control, diuretics, inhalers, nitrates, anticoagulation for stroke ppx, AEDs for seizure control), or that have a withdrawal syndrome (e.g., SSRIs).
- Tube feeds, TPN/PPN, IVF: Generally avoid; may cause volume overload without meaningful benefit (JCO 2013;31:111). Instead, encourage good mouth care and food/drink for comfort as able. Reassure loved ones that appetite/thirst declines at EOL (Fast Facts).

| **Example PRN Orders: if questions or concerns, consult Palliative Care for support**<br>*Always treat acute symptoms with boluses rather than changing drip rate. Drips effectively act as long-acting meds<br>**If uncontrolled acute symptoms despite IV bolus, can repeat after 20-30min at same dose or doubled dose and change PRN dose | | |
|---|---|---|
| | **IV access** | **PO only (No IV access)** |
| **Analgesia/Dyspnea** | Opioids: see *Pain Management*. Can dose more frequently (uptitrate dose q30 min PRN for uncontrolled air hunger/pain) at EOL when goal is for aggressive symptom management (discuss w/ RN).<br>Dyspnea: Start with 2-5mg IV morphine equivalents for the opioid naive | |
| **Secretions**<br>*Stop TF, lay on side, pharm trial, reassure fam | Glycopyrrolate 0.2-0.4mg IV/SC q4-6hrs PRN | Glycopyrrolate 1mg PO q4-6hrs PRN *or* atropine 1-2 drops SL q6hrs PRN (of note, atropine crosses BBB & may contribute to delirium) |
| **Delirium, Anxiolysis** | Haloperidol 0.5-1mg IV q4-6hrs PRN | Haloperidol 0.5 mg PO q4-6 hrs PRN *or* Olanzapine 2.5-5mg SL q6h PRN |
| **Anxiolysis associated with dyspnea** | Lorazepam 0.5-1mg IV q4-6hrs PRN (increase as needed) | Lorazepam 0.5-1 mg PO q4-6hrs PRN (increase as needed) |

**Resources**: Palliative Care Network of Wisconsin Fast Facts and app; DFCI resources: Pink Book for pain, Green Book for N/V

## Hospice Overview

- Hospice: multidisciplinary care for patients with advanced illness and life expectancy <6mo with goal of providing best supportive care when disease modifying therapy is no longer effective. Paid through Hospice Insurance Benefit (most often through Medicare)
- **Can be provided in multiple locations,** including home (most common), SNF, hospice house, or acute care hospital depending on patient's care needs and caregiver support
- Services include intermittent nursing care (~1-2 visits/week 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, 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. More complex palliative or comfort interventions such as XRT, TPN, or advanced IV pain therapies (ketamine, lidocaine), are covered by hospices on a case by case basis.

## General Inpatient Hospice (GIP)

- GIP Hospice: hospice level of care for pts who have short-term symptom mgt needs that cannot be provided adequately in any other setting (e.g., high flow O2, uncontrolled sx requiring IV medications, high RN needs for wound care/suctioning). Most appropriately offered at hospice house & this DC plan should be prioritized if pt can be transported.
- Consider GIP at MGH for pts who are actively or imminently dying and/or cannot safely transport. If admitted to GIP at MGH, pt will be "Discharged to Hospice" and Pall Care becomes primary team.
- Discuss w/ floor CM team (for insurance benefit screen and coordinate w/ hospice liaison), hospice agency (ie, Good Shepard, Care Dimensions, Norwell Home Health & Hospice), and Pall Care if pt is appropriate for GIP Hospice and, if so, which location

## Supportive Care Unit (SCU)

Supportive Care Unit: 10 bed unit on Phillips 20 & 21 for patients with serious illness who have acute symptom management or goals of care needs. Care teams include palliative care attending, NP/MDs, SW, spiritual care, and specialized CM**. Transfer to SCU may be appropriate if pt symptoms are not well controlled despite aggressive management on the gen med floor, though beds are limited.** To discuss possible transfer to SCU, page 27228 to discuss with SCU attending

# Geriatrics & Palliative Care — Geriatric Assessment & Frailty

## General approach to the comprehensive geriatric assessment

- Overview: The comprehensive geriatric assessment (CGA) systematically identifies medical and psychosocial factors that lead to functional limitations for older adults and should be approached by an interprofessional team. One widely accepted framework is the "Geriatric 5Ms" (mind, mobility, medications, matters most, multicomplexity) (JAGS 2017;9:2115).
- Outcomes: CGA associated with increased likelihood that inpatients will be alive and in their own homes 3-12 months following discharge (Cochrane 2017;9:CD006211) & predicts operative/procedural risk (JAGS 2020;68(6):1235; EJSO 2016;42:1890-7). Outpatient, serial CGA provides opportunity to tailor care to the evolving needs of patients (JAH 2021;33:469).

| Topic | Examples | Tools |
|---|---|---|
| Mind | Vision, hearing, mood, sleep, memory | PHQ-2 or Geriatric Depression Scale (English, Spanish)<br>*Cognitive Tests (suggested stepwise approach):*<br>1. Mini-Cog (English, non-English languages)<br>2. RUDAS (minimizes effects of educational level, cultural learning, and language in assessing cog fxn)<br>3. MOCA (English, Spanish) |
| Mobility | Pain, feet, falls/fear of falling (BMC Geriatr 2021;21:350) | Timed up and go test (<12s)<br>Gait speed test (4m/5sec = 0.8m/sec)<br>30 sec Chair-to-Stand test (>8 stands in 30 sec) |
| Medications | High risk meds, polypharmacy, immunizations | See *Polypharmacy & Elder Abuse* |
| Matters most | Social history, HCP, code status | Massachusetts HCP<br>Resources for patients: Prepare for your care (5-step program for patients), The Conversation Project<br>See *ACP & Code Status* for further info |
| Functionality | Appetite/nutrition/weight<br>Dentition/swallowing<br>Constipation/incontinence<br>Sexual history<br>Substance use<br>ADLs: bathing, dressing, toileting, transferring, feeding, etc<br>iADLs: cleaning, finances, engaging w/ technology, etc | Mini-Nutritional Assessment (English, Spanish)<br>Home Safety Assessment |

Effective interventions to reduce falls:

- Home safety assessments: referral to PT/OT should explicitly request fall reduction program as well as home safety evaluation
- Repair of single cataract decreased risk of hip fracture in the year following repair (refer pts for ophthalmologic exams)
- Discourage use of progressive lenses (older adults often less able to adjust to changes in depth perception with these lenses)
- Assess for orthostatic hypotension and completing comprehensive medication review. *See Polypharmacy*
- Multicomponent exercise programs (strength/resistance training, aerobic, & balance) done in groups superior to programs done alone
- Sit-to-stand repetitions both while hospitalized and at home

## Frailty

**Frailty** is an identifiable clinical state in which an individual is more vulnerable to stressors due to reduced physiologic reserves. This increased vulnerability leads to increased risk of falls, hospitalization, loss of independence, iatrogenic harm and death from otherwise minor illnesses or low burden interventions (JAMDA 2013;14:392). ***Reframe "failure to thrive" as frailty.***

- Community prevalence ranges from 11% (age 50-59) to 51% (age 90+). Age is a RF, but not necessary/sufficient for diagnosis
- **Importance:** Frailty predicts outcomes and can facilitate patient-centered care. The benefit of routine screening has been shown in high-risk contexts (oncology and surgery) and management should aim to increase physiologic reserve. (NEJM 2024:391:538)
- Two concepts of frailty: **1) *Fried Frailty Phenotype Model* ->** physical manifestations of reduced physical reserves (self-reported exhaustion, unintended weight loss, low grip strength/weakness, slow walking speed, physical inactivity) (J Geront 2001;56:M146; BMC Geriatr 2013;13:64); **2) *Deficit Accumulation Model* ->** a concept in which 30 or more factors from the 5M domains and/or variables known to diminish over time is used to construct a Frailty Index (J Geront 2007;67:722)
- Frailty is ***dynamic***: individuals can move between different states of frailty over time.
- Frailty is ***potentially reversible***: modifying RFs can improve QoL and reduce morbidity and mortality (JAGS 2007;55:11)
- Frailty Tools (In Epic: Rarely Used→Additional Tools→Geriatrics→Frailty Index) are commonly based on brief screening tools (guide available at efrailty.org)

**Interventions for frailty** (Age Ageing 2017;46:383)

- Screen for and treat high-risk comorbidities (e.g. urinary incontinence, osteoporosis, vision/hearing impairment, driving risk)
- 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)
- Consults: for complex patients, refer for nutrition assessment (weight loss, concern for micronutrient deficiencies); out-patient Geriatric Clinic for follow-up CGA and longitudinal care; MGB Home-Based Palliative Care for severe frailty and limited life expectancy.
- Cognition: inpatient: cognition screening, delirium precautions (limiting overnight VS/interventions, labs, lines/tethers, physical/chemical restraints); outpatient: OT and/or SLP consult (cognitive training, info processing, problem-solving, driving eval)
- Environment Modifications: consider SW consult, PT/OT consult, iCMP referral, Home Health (includes PT, OT, Speech, & SW)
- Address advanced directives/HCP/Code Status

# Geriatrics & Palliative Care — Polypharmacy & Elder Abuse

## Polypharmacy: Prescribing and Deprescribing Medications

**Medication Reconciliation**: confirm meds w/ pt & family; ask about medication administration system (eg, blister packs, pill boxes)

- Review prior notes, d/c summaries, & paperwork from SNFs for med changes
- Look up pharmacy dispenses in Epic: Chart Review → Misc Reports → Medication Dispense History; or call 24/7 pharmacies: CVS 781-391-2668 (dial 1, 2, "staff"); Walgreens 781-321-1765 (dial 2, #, "other question")
- Ask about OTC meds, herbal/dietary supplements (including CBD/THC), which can be easily missed culprits of drug-drug interactions
- 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), MGH Home Health

**Deprescribing Medications:**

- **Use tools** like Medication Appropriateness Index (med importance overview); MedStopper (prioritize discont.); deprescribing.org (gen guidelines))
- **Confirm eGFR with cystatin C:** Creatinine-derived eGFR can often overestimate CrCl in older adults due to sarcopenia
  - Renal adjustment of medications important for mitigating side-effects/complications (enoxaparin, apixaban, rivaroxaban, dabigatran, antibiotics, antiepileptics)
- **Classes to AVOID in geriatric patients**: See Beer's list (JAGS 2023;71:2052) and STOPP-START for further details
  - Anticholinergics: delirium, falls, blurred vision, urinary retention, tachycardia. Avoid antihistamines (fexofenadine>cetirizine; avoid 1st gen), TCAs, MAOIs, antimuscarinics (oxybutynin), muscle relaxants (cyclobenzaprine), prochlorperazine. *Long term use linked to increased risk for dementia* (JAMA IM 2015;175:401)
    - Anticholinergic Risk Scale: additive effect of multiple meds w/ minor anticholinergic effects can be significant.
  - Benzodiazepines: delirium, falls, cognitive impairment, etc. (also risk w/ non-BZD hypnotics e.g. zolpidem)
  - Antipsychotics: inc mortality with antipsychotics in the elderly with underlying cognitive impairment (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 (do NOT use nighttime SSI in older adults)
  - PPIs: *C. diff (Innov Pharm 2021;12)*, bone loss/fracture (not confirmed w/ data) - taper or switch to H2 blocker as able.
  - 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) (NEJM 2018;379:1509)
  - Tramadol: multiple drug interactions and receptor activity
  - Serotonergic medications: serotonin syndrome can present as anxiety or agitation w/ initiation or titration of meds in older adults
  - Parkinson's disease: ondansetron is antiemetic of choice. **Avoid** antipsychotics, metoclopramide, prochlorperazine

## Common Signs of Elder Abuse

- Generally includes persons 60 years or older (although this definition is state-dependent).
- Definition (CDC): "An intentional act or failure to act that causes or creates a risk of harm to an older adult."
- Includes physical, emotional, sexual, neglect, abandonment, and/or financial abuse. Can present as:
  - Withdrawn affect, deferring to others to answer
  - Unwashed hair, dirty clothes, appearing unkempt (don't forget to look at feet and nails!)
  - Dirty or unsafe living conditions, mismatch in level of social supports/services vs needs based on physical or cognitive disability, tension w/ family around financial planning to help with care needs
  - Worsening of pressure ulcers, skin tears, weight loss
  - Lack of necessary medical aids (walkers/canes, adult briefs)
  - Unpaid bills, eviction notices, inability to hire more services/help or transition to a new level of care etc. despite adequate financial resources
- Risk Factors (NCEA): advanced age, female sex, non-white race, disability, cognitive impairment
- Screening
  - AMA recommends regular screening but USPSTF did not identify sufficient evidence (Screening tools validated in various settings are available for use, consider using comprehensive geriatric assessment above)
  - Concerns should prompt cognitive testing, functional assessment, and obtaining collateral to screen for unrecognized dementia as an underlying cause of these signs and symptoms (See "*Dementia*")
- **Guardianship** (Gerontology 2007;47:591-603): legal process that gives a guardian permission to take care of and make decisions for an incapacitated adult who does not have a pre-designated HCP. Consider guardianship in situations where the patient does not have capacity regarding **high-risk decisions** and no HCP identified. Pt may be determined to lack **competence** (legal status) by a court.
  - **If concern for abuse/neglect from HCP, obtain collateral from longitudinal providers and consider OCC consult before proceeding with guardianship process.**

## Reporting Logistics

General, Caretaker, Facility

- Making a report through the Massachusetts Executive Office of Elder Affairs (can be made by any member of the healthcare team)
- Report can be made online or via phone: (800) 922-2275
  - If you make a report via phone, must submit a mandated reporter form to the local Protective Services agency within 48h
  - To report abuse of a patient by nursing home or hospital staff, reach out to the other providers/institutions first to discuss and obtain collateral and understand greater clinical/social context. If continued concern, can contact the Massachusetts Department of Public Health: (800) 462-5540
- Similar to DCF reports, this is an ask to an objective, multi-disciplinary team to investigate concerns rather than a condemnation
- Documentation: No template currently available in Epic. Document findings as part of a progress note or in a separate encounter. Remember to be detailed but not inflammatory/derogatory in describing subjective & objective findings suggestive of abuse or neglect.

*Leanna Travis, Jade Connor*



Suggest an Edit

# Rheumatology — Approach to Rheumatologic Disease

**OVERVIEW**: rheumatologic diseases may be roughly separated into 4 categories

| Category | Inflammatory Arthritis | Connective Tissue Disease | Vasculitis | Other |
|---|---|---|---|---|
| Major Diseases | RA, seronegative spondyloarthropathy, crystalline arthritis | SLE, Sjögren's, systemic sclerosis (diffuse/limited), MCTD, UCTD, myositis (DM, PM) | Small (GPA, MPA, EGPA, CryoVas, IgA, anti-GBM), med (PAN), large (GCA, Takayasu), or variable vessel (Behcet's) | Autoinflammatory diseases, sarcoid, IgG4-related disease, VEXAS |
| Initial work-up | RF, anti-CCP, ANA, Xray, ultrasound | **ANA first, if + then**: SLE: dsDNA, C3/4, Sm, APLS Sjogren's: Ro/La, SSc: Scl70, RNApol3, centromere, MCTD: RNP, Myositis: CK, aldo, Jo-1 | **Small**: ANCA, ANA, cryo (sent warm), C3/C4, UA, anti-GBM if DAH/GN **Large**: imaging, ±ophthocs, TA bx (GCA) | Sarcoid: Ca, vit D, limited role for ACE. IgG4: IgG subclasses, C3/C4 |

**Treatment** (Severity ↓)

- *Glucocorticoids (aim to minimize steroid exposure)*
- *Hydroxychloroquine*
- *DMARDS (MTX, SSZ)* | *DMARDS (MTX, AZA, MMF)*
- *Most Biologics, JAK inhibitor* | *RTX, belimumab, voclosporin, anifrolumab* | *RTX, TCZ, anti-C5a*
- *Cyclophosphamide (CYC)*

DMARD = disease-modifying antirheumatic drug
MTX = methotrexate
SSZ = sulfasalazine
AZA = azathioprine
MMF = mycophenolate mofetil
Biologics = Ab/protein-based Rx (anti-TNF, anti-IL17, anti-IL12/23, CTLA4-Ig, anti-IL1, RTX, TCZ, etc.)
RTX = rituximab (anti-CD20)
TCZ = tocilizumab (anti-IL6)

**Nuances of treatment not encapsulated by this figure – see following pages

## CLASSIC SYMPTOMS BY DISEASE CATEGORY

**General**: Fevers, arthritis, rashes, alopecia, nail Δ, sicca, conjunctivitis, uveitis, episcleritis/scleritis, headaches, Raynaud's, acrocyanosis, oral/genital ulcers, polychondritis, enthesitis, serositis, thromboses, neuropathy, pregnancy loss
**CTD:** SLE (arthritis, oral ulcers, Raynaud's), Sjogren's (sicca), Systemic sclerosis (Raynaud's), Myositis (lung, skin, muscle)
**Vasculitis**: Small (DAH, GN, mesenteric ischemia, mononeuritis multiplex, palpable purpura), Med/Large (generalized sx)
**Inflammatory Arthritis**: joint pain and stiffness (prolonged in AM >60 min), joint swelling, +/- rashes

## LABS

CBC/diff, BMP, LFTs, UA, ESR/CRP, TSH. Target serological testing to positive items on rheum ROS

## DDX

Consider malignancy (including paraneoplastic phenomenon) and infectious syndromes as alternative diagnoses

## WHEN TO CONSULT RHEUM

1. Concern for new inflammatory arthritis, connective tissue disease, or vasculitis
2. Guidance on interpretation/further work-up of positive rheumatologic serologies (e.g., positive ANA (>1:80), +RF, etc.)
3. Patients with history of rheum disease p/w exacerbation, new infection/malignancy (guidance on immunosuppression), or complication of either therapy or disease
4. Work-up/management of new interstitial lung disease (in conjunction with pulm), inflammatory eye disease, or FUO

## HEALTHCARE MAINTENANCE FOR RHEUM PATIENTS

**If prolonged steroids:** $Ca^{++}$/vitD (for bone health), pneumocystis ppx (generally if ≥20mg prednisone for ≥4 weeks), PPI (GI ulcer ppx), early osteoporosis (bone density screening), and A1c check
**General HCM:** Consider reproductive planning (many meds teratogenic), immunizations, skin exam/sun protection if anti-TNF or MTX (↑skin cancer), increased pap frequency (J Low Genit Tract Dis 2019 Apr;23(2):87-101), and optimizing CV risk w/ primary prev (↑risk w/ chronic inflammation (Lancet Rheumatol 2021;3:e58). Safety labs q3-6 months for most DMARDs (CBC diff, CMP).

## Acute Arthritis Syndromes

| Arthritis | Joint pattern | Presentation | Diagnosis | Treatment |
|---|---|---|---|---|
| **Gout** | - Often acute, hot, swollen, and painful joint<br>- Mono > poly<br>- 1st MTP joint (also called podagra; 1st sx in 50% pts)<br>-hindfoot, fingers, ankle, knee, wrists<br>- Most common cause of inflammatory arthritis | - Rare in men <25 and pre-menopausal women<br>- Triggers: diuretics, meat, seafood, EtOH, HTN, DM2, CKD, initiation of urate lowering therapy, illness<br>- Acute flares → chronic arthropathy (tophi)<br>- Urate nephrolithiasis, chronic nephropathy | Gold standard: Arthrocentesis: **neg birefringent needle-shaped crystals**, WBC 10k-100k/uL<br>- ACR-EULAR Criteria for Gout can help in absence of joint aspiration<br>- At first dx, obtain plain films to evaluate for erosions/tophi<br>-Hyperuricemia (>6.8 mg/dL) may be seen but is NOT required for diagnosis<br>- US or dual energy CT if dx uncertain | Acute: **colchicine** (1.2mg x1, 0.6mg 1h later, 0.6mg 1-2x daily until 2-3d after resolved) *or* **pred** (40mg QD until resolved then taper) *or* **NSAIDs** (naproxen 500mg BID, indomethacin 50mg TID for ~5-7d), *or* **intra-art steroids** (if 1-2 joints). Choice driven by pt and side effect profile. **Anti-IL1 if above contraindicated.** If already on allopurinol, should continue in acute attack. Renally dose if AKI.<br>Chronic: (**urate lowering tx indicated** if ≥2 attacks/yr, disabling attacks, tophi, or erosions)<br>Check uric acid outside of flare as it can be falsely low during flare (goal of <6 mg/dL during therapy).<br>Start urate lowering therapy ~2 wks after flare or w/ colchicine ppx 3-6 mo to ↓ flare risk<br>**Allopurinol** 1st-line; start low to ↓ hypersens risk, Check HLA-B*5801 if Korean, Han Chinese, Thai, African descent before starting allopurinol (Clin Pharm Ther. 2013;93:153). Can also consider febuxostat (increased risk of CV death), probenecid, or pegloticase in patients with C.I. to allopurinol |
| **CPPD** (pseudo-gout) | - Mono > poly<br>- Knee > wrist, shoulder, ankle<br>- Neck stiffness and painful ROM<br>"crowned dens syndrome" | - Commonly asymptomatic<br>- Can coexist with gout, OA<br>- Age often >50<br>- Joint trauma may be RF | - Arthrocentesis: **small pos birefringent rhomboid crystals,** WBC 10k-100k/uL<br>- Plain films looking for chondrocalcinosis; US or dual energy CT if dx remains uncertain | - Acute: if ≤2 joints → **intra-art steroids** (1st line). 2nd line same as gout (**colchicine** w/in 24h sx onset, NSAIDs, oral steroids)<br>- Chronic (consider prophylactic meds if >3 flares per year): NSAIDs, colchicine, HCQ, low-dose pred, MTX. Anti-IL1 if refractory<br>- Screen for 2° causes: hyperPTH, hypoMg, hemochromatosis |
| **Pyogenic bacterial septic arthritis** | -Mono (50% knee), >1 joint (20%)<br>- Gonococcal: mono or oligo | - Hematogenous spread most common<br>- ↑risk in RA<br>- Gonococcal: fever ± tenosynovitis & skin lesions | - Arthrocentesis: **WBC 50-150k/uL, ↑PMNs,** GS/Cx; blood cx -staph>strep>GNR<br>- Gonococcal: GU NAAT, often ↓ synovial WBC + neg cx<br>- XR ± CT/MRI | - **Antibiotics** for 3-4w (CTX x7-14 d for gonococcal)<br>- Joint drainage/**urgent washout** (ortho c/s)<br>- If prosthetic joint infection, involve ID |
| **Viral arthritis** | - Often symmetric poly small joint (e.g. parvo) ± large joint; often similar to RA | - Fever & fatigue | - Ddx: parvo, HBV, HCV, HIV, rubella, chikungunya, dengue, enterovirus<br>- Obtain travel history | - NSAIDs<br>- Antivirals if available<br>- Many etiologies self-limited |

## Chronic Arthritis Syndromes

| Arthritis | Joint pattern | Presentation | Diagnosis | Treatment |
|---|---|---|---|---|
| **Osteoarthritis** | - Poly > mono<br>- Asymmetric<br>- Knees, hips, MTP, CMC, PIP, DIP, C-spine, L-spine | -Pain and stiffness in one or few joints worsen with use<br>- Age >45<br>- AM stiff <30min, slow progression, no warmth, muscular wasting | - Clinical dx<br>- Bony swelling, joint deformity, limited ROM<br>- XR joint space narrowing, osteophytosis, subchondral sclerosis | - PT, braces, weight loss, Tai Chi<br>- Topical **NSAIDs**, acetaminophen, PRN NSAIDs, duloxetine<br>- **Intra-articular steroids**<br>- If severe, refer to ortho, PM&R<br>- Not recommended: glucosamine, bisphosphonates, PRP (ACR Guideline 2019) |
| **Miscellaneous infectious** | - Mono (Lyme, TB), oligo/poly (*T. whipplei*) | - Lyme: arthritis can be first sign of disease<br>- immunocx or RFs: fungal, TB (indolent monoarthritis)<br>- *T. whipplei:* arthralgias > arthritis, diarrhea, ↓weight | - Arthrocentesis, Lyme serology, mycobacterial cx, fungal cx, SI biopsy (*T. whipplei*) | - Lyme: 4w of doxy or amox<br>- TB, fungal: involve ID<br>- *T. whipplei*: 2w CTX + 1y TMP/sulfa (involve ID) |

| | | | | |
|---|---|---|---|---|
| **Rheumatoid Arthritis** | - Mono in early stage, then poly<br>- Small peripheral (MCP, PIP, wrists, MTP)<br>- Symmetric | - F>M, age 35-65<br>- AM stiff >30min<br>- Joint deformity<br>- RA nodules | -ACR-EULAR classification criteria, w/ 6/10 defining RA (Rheumatology (Oxford) 2012;51:vi5)<br>- Synovitis on exam<br>- **RF, anti-CCP**<br>- Joint XR for erosions<br>- ESR/CRP can be normal | - Acute: **prednisone** or **NSAIDs**, initiate DMARD if not on already<br>- Chronic: **DMARD** (MTX > HCQ, SSZ, leflunomide); 2nd line: combo therapy, **biologic** (infliximab, abatacept, TCZ), or JAKi (baricitinib) (Ann Rheum Dis 2017;76:960) |
| **Spondylo-arthritis (SpA):**<br><br>**-Ankylosing spondylitis (AS)**<br><br>**-Psoriatic arthritis (PsA)**<br><br>**-IBD-assoc. (IBDa)** | **AS:** mostly axial (spine, SI)<br>**PsA:** can be distal (DIPs), asymm oligo, symm poly, arthritis mutilans, axial<br>**IBDa:** distal oligo or poly arthritis > axial | - AM stiff >30min<br>- Extra-articular: tenosynovitis, enthesitis, dactylitis, uveitis, pyoderma gangrenosum<br>**AS:** Pain in low back, buttock<br>**PsA:** nail pits/onycholysis, 70% with psoriasis<br>**IBDa**: oligo varies with IBD activity, poly or axial has independent course | - Clinical dx<br>- ↑ESR/CRP (not Sn)<br>- HLA-B27<br>**AS:** ↓spine mobility, bamboo spine + **sacroiliitis** (XR or MRI)<br>**PsA:** CASPAR criteria (91% Sn, 99% Sp), pencil-in-cup DIPs | - **NSAIDs** (1st line)<br>**AS: TNFα inhibitor** (2nd line), anti-IL17, JAKi<br>**PsA:** If mod, **MTX** > SSZ or leflunomide, apremilast (PDEi).<br>- If severe/erosive**, TNFα inhibitor.** If non-response, anti-IL17 or anti-IL12/23. Anti-IL17 can worsen IBD<br>**IBDa:** SSZ > MTX or AZA, TNFα inhibitor, anti-IL-12/23 |
| **Reactive arthritis** | - Oligo > mono > poly (small joints)<br>- Asymmetric<br>- LE > UE | - 1-4w post-infxn*:<br>- Conjunctivitis, urethritis, cervicitis, oral ulcers, circinate balanitis, keratoderma blennorrhagica, SpA sx<br>-Enthesitis or dactylitis | - Preceding infection*<br>- Arthrocentesis<br>- Stool cx (if diarrhea)<br>- G/C NAAT | - If GU infxn, treat. If GI infxn, may not need to treat<br>- Acute: **NSAIDs** > intra-articular steroids > prednisone<br>- Chronic: if >6mo, **MTX** or SSZ |

* Causes: Enteric: *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C. diff*; GU: *Chlamydia*, *E. coli, Ureaplasma*, *Mycoplasma*

**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 arthritis, 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 | Complication |
|---|---|---|---|---|
| **SLE** | - F>M, 15-40yo, Afr./Latinx/Asian descent > White<br>- **Constitutional** sx (fever, wt loss, fatigue, myalgia), **malar** rash (spares NL fold), **discoid** lesions, **photosensitivity**, oral/nasal **ulcers** (often painless), **cytopenias**, serositis, **nephritis**, pneumonitis/DAH/ILD, seizure/CVA/neuropsych, vasculitis<br>- **Arthritis/arthralgia**: migratory, polyarticular (knees, carpal joints, PIPs > other), symmetric, nondeforming. ⊕Morning stiffness. | ⊕ANA (>95%; Sn not Sp)<br>⊕ **anti-dsDNA** (~70%; 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%)<br>⊕ antiphospholipid Abs (40%)<br>- CBC/diff, BMP, +DAT, C3/4, ESR/CRP, UA/UPCR; consider RF, CCP if sig. arthritis, (2019 EULAR/ACR Criteria) | **- All (including pregnant): HCQ (↓flares, clots, death)**<br>- Lifestyle: sun protection, tobacco<br>- **steroids** (goal to taper and d/c if possible).<br>- Lupus nephritis: 2024 KDIGO Guidelines<br>- If flare/active dz: add immunosuppressive rx (MTX, MMF, CYC, RTX, belimumab, anifrolumab), (Ann Rheum Dis 2024) | - CVD (Semin Arthritis Rheum 2013;43:77); ↑ risk **VTE/ATE** (APLS)<br>- Pregnancy (neonatal death, pre-eclampsia, prem delivery)<br>-ESRD<br>-Osteonecrosis (2/2 SLE and steroids) |
| **Drug-induced lupus** (DIL) | - Fever, arthralgias/arthritis, myalgias, rash, serositis. Nephritis uncommon. ~1/3 of isolated cutaneous lupus drug-induced (Br J Dermatol 2012;167:296)<br>- **Months-years** exposure (Ann NY Acad Sci 2007;1108:166)<br>- High risk: **procainamide** (15-20% per y), **hydralazine** (5-10% / y). Mod: quinidine. Low: TNFi, penicillamine, carbamazepine, methyldopa, others | Serologies/clinical features often **unique** to the **offending drug**.<br>⊕ **ANA** (almost all cases)<br>⊕**Anti-histone** (Sn but not Sp for DIL, also in up to 80% idiopathic SLE) ⊖ **anti-dsDNA** (exc. TNFi, IFN) ⊕ **anti-SS-A/Ro** (not Sp) Others: ANCA, anti-RNP | Treat sxs, not antibodies<br>- **Withdraw** offending agent: resolution may take weeks-months<br>- Occasionally NSAIDs, HCQ, steroids for sx<br>- Avoid common DIL drugs in patients with known dx SLE | - Generally good prognosis; life threatening disease is rare and should prompt workup for SLE or other CTD |
| **Sjogren's** | - F>M, 40-60y. **Sicca** (dry mouth/ eyes), caries, parotid enlargement, vag. dryness. Extraglandular: fatigue, myalgia, vasculitis, nephropathy, neuropathy, cytopenias, pulm, RA/SLE w/ 2° Sjogren's | ⊕ ANA ⊕ **anti-SS-A/Ro**<br>⊕ **anti-SS-B/La**<br>- Schirmer test, parotid US, salivary gland bx, (2016 EULAR/ACR Criteria) | - Sicca only: sx mgmt.; regular eye, dental care<br>- Extraglandular: immunosuppression rx depends on symptom/organ involved | - 5-10% lifetime risk of NHL, MALT lymphoma<br>- head/neck cancers (Head Neck 2023;45) |
| **Inflammatory myopathies** [polymyositis, dermatomyositis (DM), immune mediated necrotizing myopathy, statin induced] | - F:M (2:1), 40-50yo. Symm proximal>distal weakness. dysphagia, constitutional sx, arthralgias, ILD<br>- DM skin findings: heliotrope rash, poikiloderma (chest: V-sign; back: shawl; thigh: Holster), scalp rash, Gottron's papules, mechanic's hands | CK/aldolase, myositis panel<br>Often thigh MRI → muscle bx<br>⊕ **ANA** (50%), lookup Ab phenotypes: anti-Jo1 (anti-synthetase), anti-Mi2, anti-MDA5, anti-SRP, anti-HMGCR.<br>LDH and AST/ALT (can be normal in amyopathic type DM) | - Induction: **prednisone**<br>- Maintenance: **AZA, MTX**<br>- Resistant/severe: pulse steroids, AZA, MTX, MMF, IVIG, ritux, CYC | - **Malignancy** in DM (25% w/ new cancer dx w/in 3 years of myositis onset,<br>- ILD in 10% |
| **Mixed CTD** | - 80% Female<br>- Overlap of SLE, SSc, polymyositis; Raynaud's; non-erosive arthritis | ⊕ ANA (often **speckled**)<br>⊕**anti-U1 RNP** (100%, not Sp) | - SLE fts.: **steroids**, ritux<br>- If scleroderma sxs, less responsive to steroids | - Main cause of death is **PAH** |
| **Systemic Sclerosis** (scleroderma, SSc) | F:M 4:1, 30-50yo. +Raynaud's (almost all), skin thickening, telangiectasias, sclerodactyly, calcinosis cutis, esophageal dysmotility, arthralgia<br>Other systemic sx: renal crisis, ILD (>70%), PAH (10-40%), digit ischemia<br>Subtypes:<br>**Limited cutaneous** (acral skin involvement, freq. PAH)<br>**Diffuse cutaneous** (diffuse skin thickening, freq ILD).<br>**Systemic sclerosis sine scleroderma –** no skin involvement, + multiorgan involvement | ⊕ **ANA** (95%)<br>⊕ **anti-centromere*** (a/w limited)<br>⊕ **anti-Scl-70*** (a/w diffuse)<br>⊕ **anti-RNA pol I,II, or III*** (a/w diffuse, is risk factor for scleroderma renal crisis)<br>- HRCT, PFT, TTE (ILD, pHTN)<br>*Ab are >99% specific (Arthritis Rheum 2013;11:2737) | - **ILD**: MMF, CYC (AZA or TCZ) induc. → MMF, AZA, TCZ maintenance. If progressive: anti-fibrotic, rituximab<br>- **PAH**: CCB, riociguat, PDEi, prostacyclin ag<br>- **MSK**: HCQ, MTX<br>- **Raynaud's**: CCBs<br>- **Skin**: MMF, MTX<br>- **GI**: PPI & promotility | ⬆cancer risk<br>**Renal crisis** (<20%): ***avoid steroids if at risk (can trigger).*** AKI, abrupt HTN; a/w anti-RNA-pol III; tx with **ACEi** (captopril) |
| **UCTD &** Overlap Synd | - Early Raynaud's, incomplete SLE | Dx of exclusion; not meeting criteria for dx of specific ds | Per 1° features | Per 1° features |

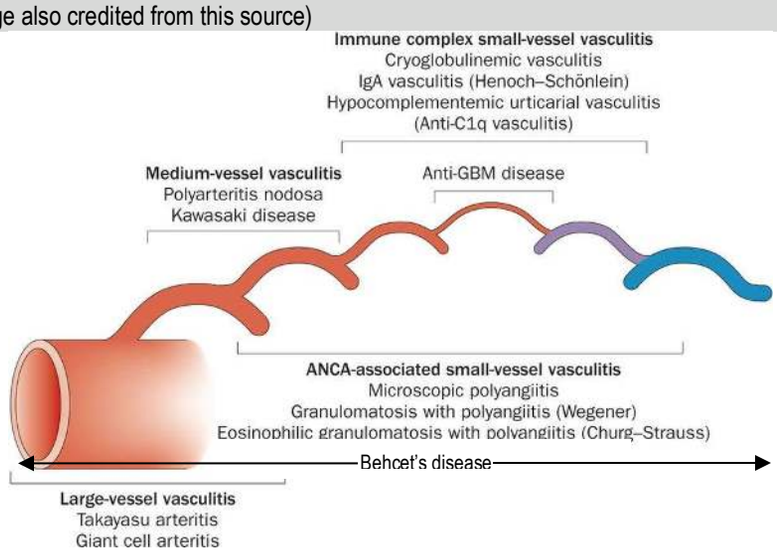


Suggest an Edit

# Rheumatology Vasculitis

## DIAGNOSTIC OVERVIEW (Arthritis Rheum 2013;65:1, image also credited from this source)

- Classified by size and type of blood vessel involved. Large vessels (aorta + branches) vs. medium-sized vessels (named visceral arteries) vs. small vessels (vessels w/o names)




**STEP 1** – SUSPECT VASCULITIS

- No "typical" presentation, consider in constitutionally ill pt w/ multisystem organ involvement & evidence of inflammation
- **LARGE** vessel: aorta/branches, e.g. ext. carotid, temporal, ophthalmic → limb claudication, bruits, asymmetric BP, absent pulses, HA, vision 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, mesenteric ischemia
- **SMALL** vessel: vessels of skin, small airways, glomeruli→petechiae, palpable purpura, glomerulonephritis, alveolar hemorrhage/ hemoptysis, mononeuritis multiplex, scleritis

General work-up:

- **Inflammation**? → CBC/diff (anemia of chronic disease, thrombocytosis, neutrophilia, eosinophilia), ESR, CRP
- **Organ involvement**? → BMP, LFTs, UA + sediment, CXR, brain MRI/MRA (if neurologic symptoms)
- **Suspected large vessel**? →if c/f GCA (HA, jaw claud.,vision Δ), see below. If other sx (GI, limb claud.), consider CTA/MRA C/A/P
- **Suspected medium vessel?** → consider CTA/MRA C/A/P, deep biopsy of cutaneous findings (derm c/s)
- **Suspected small vessel?** → ANCA (will reflex to MPO/PR3 ELISA if ⊕), immune complex w/u (C3/C4, RF, cryo), rash biopsy (derm c/s) (*Note*: ANA/RF not ⊕ in 1° vasculitis; ⊕RF may suggest cryoglobulinemia/endocarditis; ↓C3/C4 in cryo, SLE, 25% of PAN)

**STEP 2** – RULE OUT MIMICS and assess for SECONDARY CAUSES: based on presentation (Int J Rheumatol. 2020:8392542)

- **Infections:** endocarditis, chronic osteomyelitis → immune complex deposition; HBV → PAN; HIV, HBV, & HCV → cryoglobulinemia; syphilis, salmonella, *S aureus*, BCGosis, TB → aortitis
- **Inflammatory ds:** sarcoidosis, amyloidosis, Susac Syndrome (Encephalopathy, branching retinal artery occlusions, SNHL)
- **Malignancies/lymphoproliferative:** lymphoma, myeloma, MGUS, IgG4-Related Disease (see *Misc Rheum* page)
- **Coagulopathy/vasculopathy:** APLAS, TTP. If skin necrosis of lower ext., consider cholesterol emboli, calciphylaxis, pyoderma gangrenosum. If renal/internal carotid/vertebral art. involvement/dissections, consider fibromuscular dysplasia.
- **Meds/drugs:** hydralazine, PCN, sulfa, PTU, levamisole in cocaine, immunotherapy, post radiation
- **W/u**: BCx, HBV (med-v), HCV/HIV (small-v), syphilis/Tspot (large-v), SPEP/SFLC, tox screen. Consider IgG4, TTE, APLAS panel

**STEP 3** – CONFIRM DIAGNOSIS

Tissue biopsy: may be required to secure diagnosis. Sites: skin, sural nerve, and muscle (PAN, ANCA), temporal artery (GCA), kidney (ANCA, IgA), lung (ANCA). Less common: testicle (PAN), rectum/gut, liver, heart, brain (1° CNS vasculitis), sinus (GPA)
Additional imaging: may help support med/large vessel involvement if CTA/MRA non-dx and/or tissue bx infeasible. Generally PET (GCA, Takayasu) or catheter-based angiogram [celiac/SMA, renal (PAN), chest (Takayasu, GCA), limbs (Buerger), brain (1° CNS vasculitis)]

## LARGE-VESSEL VASCULITIS (NEJM 2003 ;349 :160, Arth Rheum 2021 ;1349-1365, Ann Rheum Dis. 2020 ;19-30)

**GIANT CELL ARTERITIS**: inflammation of aorta & extracranial branches (i.e., spares ICA), often temporal artery (TA). Most common primary systemic vasculitis. Age >50, 3:1 F:M. If <50 yo, rare → consider alternative dx

- **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 specific; fatigue with chewing, NOT PAIN), h/o PMR, ischemic stroke
- **Exam**: asymm BP/pulse; tender/thickened/pulseless TA; bruits; limb/jaw/tongue claud.; formal eye exam; neuro exam
- **Dx**: suspicion should prompt temporal art US & Rheum c/s. ↑ESR (<50 in 10%), ↑CRP. **Gold standard = temporal artery biopsy** w/ granuloma (c/s surg). Unilateral false ⊖ in 30-45% (skip lesions, bx length, laterality, lack of TA involvement, steroids), consider bilateral (↑yield 5%). If c/f large-vessel GCA or bx neg: vessel imaging (PET, CTA/MRA, US w/ similar sens/spec)
- **Rx**: 1st line: High-dose steroids (PO pred 40-60mg qd; if c/f vision Δ, higher dose/IV immediately if ↑suspicion; NEVER delay for Bx) Steroid-sparing: TCZ > MTX=LEF=TNFi > abatacept (Arthritis Care Res 2021;73:1349). ↑ sust. remission w/ TCZ (NEJM 2017;377:317).
- **Polymyalgia rheumatica (PMR):** seen in 50% of GCA pts; 10% pts with PMR develop GCA.

**TAKAYASU ARTERITIS**: "pulseless disease," granulomatous inflamm. of thoracoabd. aorta & branches. Age <40, 8:1 F:M, Asian descent

- **Sx**: constitutional (fever, arthralgias/myalgias, wt loss, night sweats), vessel inflammation (carotidynia, limb claudication), vascular dz (TIA/stroke/dizziness/syncope, MI/angina, HF, mesenteric ischemia). **Exam**: ↑BP, **unequal pulses/BPs** (LE>UE), ↓pulses, **bruits**
- **Dx**: MRA or CTA; arteriography w/ occlusion, stenosis, aneurysms; consider carotid US/Doppler studies, PET-CT
- **Rx**: prednisone 1mg/kg/d; 50% of patients will need 2nd agent for chronic sx (MTX, AZA, TNFi > tocilizumab)

## MEDIUM-VESSEL VASCULITIS

**POLYARTERITIS NODOSA**: systemic necrotizing vasculitis that primarily affects the kidneys, skin, muscles, nerves, GI, joints, but **almost always spares lungs**. Age 40-60, a/w HBV (Arthritis Care Res. 2021;73(8):1061-1070). Can have single-organ or cutaneous-only

- **Sx**: constitutional symptoms (fever, fatigue, weight loss); mononeuritis multiplex (~70% of pts); GI distress (mesenteric ischemia), myalgias; AKI (though GN suggests alternate etiology); gonadal pain (>10%), seizures
- **Exam**: HTN, skin lesions (erythematous nodules, purpura, livedo reticularis, ulcers, bullous eruption, palpable purpura), neuropathy
- **Dx**: gold standard = biopsy (⊖ granulomas; inflammatory infiltrates of vessel wall and fibrinoid necrosis); HBV/HCV, C3/C4, CTA/MRA w/ focal stenosis or microaneurysm (renal/mesenteric)
- **Rx**: prednisone 1mg/kg/d ± MTX or AZA (IV steroids and CYC if severe); antivirals if HBV-related

**THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)**: segmental inflammatory nonatherosclerotic occlusive intravascular thrombi of small-med arteries and veins of extremities. Age ≤50, 70-90% ♂, strongly a/w tobacco use. (Cochrane Syst Rev. 2016(3): CD011033)

- **Sx:** claudication (arch of foot, calf); Raynaud's (40%), ulcers and digital gangrene; livedo reticularis (hands, feet, & digits); typically ischemic symptoms start in distal vessels and progress more proximally.
- **Dx**: biopsy (rarely) or dx criteria: age, tobacco, distal ischemia (+ABI, thrombophlebitis), ⊕ angiogram/CTA/MRA (segmental dz, abrupt cutoffs, corkscrew collaterals), r/o mimics (PAD, systemic sclerosis, APLAS, thromboembolism)
- **Rx**: **smoking cessation** (↓amputation rates), IV iloprost ($PGI_2$ analog), PCBs for pain, CCB for Raynaud's, PDE3 inhibitors

## ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS (AAV)

**PR3-ANCA+** = cytoplasmic staining (proteinase 3 [PR3]; c-ANCA), **MPO-ANCA+**= perinuclear staining (myeloperoxidase [MPO]; p-ANCA)

**GRANULOMATOSIS WITH POLYANGIITIS (GPA):** necrotizing granulomatous vasculitis commonly affecting the upper respiratory tract upper and lower airways (90%), kidneys (80%), ± cutaneous leukocytoclastic vasculitis (LCV).

- **Sx:** upper respiratory: (sinusitis/crusting rhinitis, subglottic stenosis, saddle nose, otitis media, mastoiditis, hearing loss); lower respiratory: (alveolar hemorrhage, large pulmonary nodules); kidney involvement (crescentic necrotizing glomerulonephritis)
- **Dx**: sinus CT (± bone erosions), Bx w/ **granulomatous inflammation** of vessel walls, PR3-ANCA+ 90%. R/o anti-GBM
- **Rx**: limited disease: MTX + prednisone; severe disease: induction w/ steroids + RTX > CYC (NEJM 2010;363:221; Arthritis Care Res 2021;73(8):1088). Adding avacopan allows ↓ steroids (NEJM 2021;384:599). Maintenance w/ RTX > AZA.

**MICROSCOPIC POLYANGIITIS (MPA)**: necrotizing vasculitis of small vessels without granulomas. All ages (mean 50-60). Similar sx to GPA w/o ENT/upper airway dz; most common cause of pulmonary-renal syndrome (NEJM 2012;367:214)

- **Dx**: MPO-ANCA+ 70%, PR3-ANCA+ rare; BAL; gold standard = skin/renal bx; r/o HIV, cryo, anti-GBM, HBV, HCV**. Rx**: as for GPA

**EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS** (**EGPA**): necrotizing granulomatous inflammation of vessels in lungs, skin, nerves, heart (major cause of mortality); ↑**asthma/allergic rhinitis** (asthma precedes vasculitis)

- **Dx**: ≥4 of: asthma, >10% periph. eos, neuropathy, migratory lung infiltrates, paranasal sinus dz, consistent Bx. 50% ⊕ MPO-ANCA
- **Rx**: steroids ± CYC or RTX (if severe disease) or mepolizumab (anti-IL5, if not severe, NEJM 2017;376:1921). Do not delay Rx if c/f mononeuritis (risk of nerve infarction). Screening TTE for all new dx (Arthritis Care Res 2021;73(8):1088)

**RELAPSING DISEASE:** Recurrence of any sx in any organ after remission, cannot have other cause (ACR 2021;73(8):1088). 5-50% on maintenance therapy. Dx: often presents as recrudescence of initial sx; new organ involvement/sx possible but uncommon

## IMMUNE COMPLEX-ASSOCIATED SMALL-VESSEL VASCULITIS (Arth Rheum. 2019:1904-1912, N Engl J Med. 2021:1038-1052)

**IgA VASCULITIS (HSP)**: 90% in children; ♂>♀; preceding URI; in adults, ↑severity (↑ nephropathy) and ↑ a/w meds or malignancy

- **Sx**: classic **tetrad** of **1) palpable purpura** (100%, LEs/buttocks = dependent areas, without thrombocytopenia or coagulopathy), **2)** colicky abdominal pain (50-65%, adults w/ ↓ intussusception), **3)** arthritis (75%), **4)** renal involvement (50%, proteinuria, microscopic hematuria, RPGN) (AFP 2020;102 (4):229)
- **Dx**: clinical dx in children; in adults, preferably confirm w/ biopsy (leukocytoclastic vasculitis w/ vessel wall IgA dep.)
- **Rx**: children: usually self-limited; adults: may require immunosuppression (orchitis, cerebral vasculitis, pulmonary hemorrhage, severe abd pain/ bleeding) w/ 1-2 mg/kg/day of prednisone or dapsone. (Rheumatology (Oxford). 2019 Sep 1;58(9):1607-1616)

**CRYOGLOBULINEMIA**: 2/2 antibody that precipitate at ↓temp & dissolve w/ rewarming. Common extrahepatic HCV manifestation.

- **Type 1**: monoclonal (usually IgM or IgG), a/w MGUS, Waldenstrom's, MM. S/Sx:↑ hyperviscosity (↑ in cold) → acrocyanosis, digital ischemia, livedo reticularis, HA, transient CN sx; peripheral neuropathy, GN. Consider sending serum viscosity.
- **Type 2:** "mixed" monoclonal IgM against polyclonal IgG (IgM w/ RF activity), a/w infx (**HCV**/HIV/HBV, endocarditis), autoimmune dz
- **Type 3:** "mixed" polyclonal Ig (IgM or IgG) against polyclonal Ig (IgM or IgG), a/w autoimmunity (CTDs, RA, PAN), HCV. S/Sx (type 2 +3): immune complex dep. → **Metzler triad** (palpable purpura, arthralgias, weakness), mononeuritis multiplex, GN.
- **Labs/Dx:** Send C3, C4, RF, HCV, HBV, CBC diff ± infx/rheum labs per sx above**.** Note: blood samples for serum cryoglobulins need to be received warm by lab, wrapped w/ hot pack, within 30 min of collection.
- **Rx:** avoid cold in type 1. Tx underlying cause (e.g. HCV, malign.); prednisone ± RTX/CYC; consider plasma exchange in Type 1

## VARIABLE-VESSEL VASCULITIS

**BEHCET'S DISEASE:** vasculitis affecting vessels of all sizes, both venous and arterial; characterized by recurrent oral and genital ulcers and skin/GI/neuro/joint/ocular sx. Age 20-40, more common in Turkey, Middle East, and Asia, a/w HLA-B51

- **Dx:** clinical dx - recurrent painful oral ulcers and ≥2 of: painful genital ulcers (specific), ocular dz (uveitis, retinitis), skin lesions (pustules, folliculitis, papules, erythema nodosum), ⊕ pathergy test (small needle prick elicits red pustule). May have: GI sx (similar to IBD), neurologic sx (migraine, CN abnormality, venous sinus thrombosis), vascular dz (ATE/VTE, aneurysms), arthritis (nonerosive/asymmetric). R/o HSV as cause of ulcers.
- **Rx**: (Ann Rheum Dis. 2018;77:808) Mild (arthritis, ulcers): **topical steroid**, topical sucralfate (mouthwash) low dose pred. Colchicine > apremilast for prevention (NEJM 2019;381:1918); Severe: **pred** 1mg/kg/d, ±: AZA, TNFi, IFN, CYC, MTX; organ failure (esp ophth.): IV pulse steroids

# Rheumatology Autoantibodies

| Antibody | Antigen (ANA pattern if +) | Disease | Comments (Consider relevant symptoms before ordering)) |
|---|---|---|---|
| **Inflammatory polyarthritis** | | | |
| **RF (IgM)** | Fc gamma | RA (26-90%), Sjogren's (75-95%), Cryoglobulinemia (40-100%), others | - Not Sp despite name: RA, CTD, cryoglobulinemia, chronic infxn (e.g. HCV, subacute bacterial endocarditis)<br>-⊕ in 10% of healthy patients<br>- RA: "seropositive", a/w erosive & extraarticular manifestations (nodules, scleritis, ILD, pleuritis, rarely rheumatoid vasculitis) |
| **CCP** | Citrullinated peptides | RA (50-75%) | - Most Sp test for RA, a/w erosive dz & extraarticular manifestations. Used for dx only, *NOT* marker of disease activity |
| **Connective tissue diseases (SLE, Sjogren's, SSc, MCTD, UCTD, DM/PM)** | | | |
| **ANA** | **When to order**: clinical suspicion for SLE or other ANA-⊕disease (**not** a screening test given high prevalence of false ⊕; **not** to track disease activity). In populations with low prevalence of SLE (e.g. elderly), PPV low given high false ⊕ rates<br>- ANA = antinuclear antibodies (**ENAs** "extractable nuclear antigens" specify Ag and are a subset of ANAs). Low titer ANA ≤1:160 often false ⊕. If ANA ⊕, order specific autoantibodies guided by clinical presentation; 5% healthy people test ⊕<br>- ⊕ ANA: MCTD (100%), SLE (98%), scleroderma (90%), drug-induced lupus (DIL, 90%), Sjogren's (60%), PM/DM (50%)<br>- Ddx for ⊕ ANA: *Autoimmune:* autoimmune hepatitis, PBC, IBD, myasthenia gravis, Graves', **Hashimoto's**; *ID:* malaria, SBE, syphilis, HIV, HSV, EBV, HCV, parvo-B19; *systemic inflammation:* lymphoproliferative d/o, IPF, asbestosis*; Medications* | | |
| **dsDNA** | ds/mtDNA (homogenous) | SLE (40-60%) | - Sp for SLE, a/w SLE ***activity*** (follow titers) & lupus nephritis, consider DIL |
| **Histone** | Histones (homogenous) | SLE, drug-induced lupus (90%), Felty's syndrome | - Sn but not Sp for DIL<br>- Common meds: **procainamide, hydralazine**, minocycline, phenytoin, lithium, INH, quinidine, terbinafine, TNFi |
| **Smith** | snRNP (speckled; ENA) | SLE (30%) | - Sp for SLE, not indicative of dz activity |
| **RNP** | U1-snRNP (speckled; ENA) | MCTD (100%), SLE (30%) | - MCTD: high-titer anti-U1 RNP. Also seen in systemic sclerosis (20%) |
| **SS-A/Ro** | Ro52, Ro60 (speckled; ENA) | Sjogren's (75%), SLE (40%) | - Can be seen with myositis, PBC, SSc, MCTD. A/w neonatal lupus syndrome, cutaneous lupus. **2% SLE pts have ⊖ ANA but ⊕ anti-Ro** |
| **SS-B/La** | La (speckled; ENA) | Sjogren's (40%), SLE (10-15%) | - Sp for Sjogren's, SLE. Usually seen w/ ⊕ anti-Ro. A/w neonatal lupus syndrome |
| **ACA** | CENP A-F (centromere) | lcSSc (15-40%) | - A/w limited systemic sclerosis, ↑risk of PAH, ↓risk of ILD, esophageal disease |
| **Scl-70** | Topo-I (speckled) | dcSSc (10-40%) | - A/w diffuse systemic sclerosis; ↑risk of ILD, scleroderma renal crisis |
| **RNA pol III** | RNA pol. III (nucleolar) | dcSSc (4-25%) | - A/w scleroderma renal crisis, 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, ↓risk of pulm. & renal dz, ↑risk inflamm. myositis |
| **APL** | Phospholipids (on plasma membranes) | SLE (10-44%) | - Lupus anticoagulant (affected by current AC), ELISA for anticardiolipin, anti-B2-glyoprotein. APLAS classification criteria |
| **Myositis** | | | |
| **Jo-1*^** | tRNA synthetase (His) (cytoplasmic) | PM/DM (30%), anti-synthetase syndrome (~20%) | - Antisynthetase syndrome: myositis (DM/PM), ILD (70%), polyarthritis, mechanic's hands, Raynaud's, fever |
| **Mi-2*** | Mi-2 HDAC factor (homog., speckled) | DM (15-20%) | - More likely in acute DM, good prognosis, a/w disease activity |
| **MDA-5*^** | MDA-5 dsRNA binder | DM | - Clinically amyopathic dermatomyositis, rapidly-progressive ILD |
| **TIF1g*** | TIF1γ (fine speckled) | Juvenile DM | - A/w malignancy in adult DM |
| **SRP*** | Signal recog. particle (cytoplasmic) | PM | - Immune-mediated necrotizing myopathy (degenerating, regenerating, and necrotic cells on bx), rapidly progressive disease course |
| **HMGCR** | HMG CoA reductase | myositis | - Immune-mediated necrotizing myopathy, 70% with statin exposure (at any time in past), ≠ 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<br>- Antibody frequency lower in GPA without renal involvement |
| **MPO (p-ANCA)** | Myeloperoxidase | MPA (70%), EGPA (20%), Renal-Limited, DIV (95%) | - Poor correlation of titer with disease flare/remission<br>-More likely to present with renal-limited disease (J Inter Med 1998;244:209)<br>- Drug-induced vasculitis (DIV): high-titer ⊕ MPO (hydral, PTU, minocycline) (Arthritis Rheum 2022;74:134)<br>- Levamisole vasculitis secondary to cocaine use: MPO or PR3/MPO |
| **Cryo-globulins** | Fc gamma | Cryoglobulinemic vasculitis | - HCV > HBV, HIV, CTDs, lymphoproliferative disease, endocarditis<br>- A/w low C4, glomerulonephritis, +RF |

* ordered as part of "myositis panel 3"; panel also includes other less common myositis antibodies
^ order separately for faster results if desired



Suggest an Edit

# Rheumatology Miscellaneous Rheumatologic Diseases

## Polymyalgia Rheumatica

- Inflammatory condition characterized by proximal muscle aches and AM stiffness. Exclusively in pts >50yrs, peak 70-80yrs, 2:1 F:M.
- **Sx:** abrupt onset symmetrical aching and AM stiffness, most commonly in the shoulders, followed by hip girdles, neck, & torso. Stiffness with inactivity is severe. Can also have fever, malaise, weight loss. Often have limitation of active shoulder abduction.
- **Dx:** Nearly all pts have ↑CRP±ESR. Autoantibodies are negative. EULAR/ACR classification criteria (Ann Rheum Dis 2012;71:492).
- **Tx:** prednisone 12.5-20 mg/d w/ slow taper, consider addition of MTX or TCZ if refractory (Ann Rheum Dis. 2022;838-844). Sarilumab (IL-6R) sustained remission in relapsing dz and reduced glucocorticoids (NEJM 2023:389:1263).**10% of patients with PMR will be diagnosed w/ GCA at some point, and 50% of patients with GCA will have PMR.** Screen at initial dx and routinely at f/u visits

## IgG4-related Disease (Ann Rheum Dis. 2015;74:14; Arth Rheum 2020;72:7)

- Fibro-inflammatory condition involving pancreas, biliary tree, salivary/lacrimal glands, RP, thyroid, & orbits. Mean age ~60. M>F
- **Sx**: **pancreatitis** (w/ otherwise unclear etiology); sclerosing **cholangitis**; sialadenitis; lacrimal gland hypertrophy**; retroperitoneal fibrosis**; orbital pseudotumor; enlargement of pancreas, lungs, kidneys, or any of above organs. Often insidious.
- **Dx**: tissue **biopsy** [storiform ("strawlike") fibrosis, lymphoplasmacytic infiltrate (↑IgG4+ plasma cells), obliterative phlebitis, tissue eosinophilia]; ↑serum IgG4 levels (90% Sn, 60% Sp, NPV 96%, can track with disease activity). May have ↑ serum IgE and ↓ C3/C4
- **Tx**: if sx and/or progressive imaging, **steroids (0.6mg/kg qd)** ± biologics (**RTX**) to induce remission. RTX often for maintenance

## Sarcoidosis (Int Emerg Med 2018;13:325; Lung 2016:194:91; Am J Resp Crit Care Med 2020;201:e26)

- Systemic inflamm disorder characterized by granulomatous inflammation of virtually any tissue, most commonly **hilar LN**, pulmonary parenchyma, skin, liver, eyes. F>M, young adults. ↑ in Northern European, ↑ in Black patients
- **Sx**: fever, arthralgias, ↓ wt, fatigue; dyspnea, cough; rash; HSM, LAD; uveitis; cytopenias (BM involvement); pHTN; restrictive CM; arrhythmias (AVB; ventricular>atrial; sudden death); nephrolithiasis; neurosarcoid (CNopathy, periph. neuropathy, meningitis, seizures, hypothalamic dysfn); Lofgren syndrome (↑ Sp) = acute hilar adenopathy, arthritis, erythema nodosum
- **Dx**: definitive dx usually requires **non-caseating granulomas on bx** (skin, LN, EBUS), compatible clinical findings, **r/o of mimics** (TB/NTM, fungal, lymphoma, GPA, IgG4, CVID, Berylliosis/Silicosis). Obtain CXR (CT if atypical). No need to bx isolated asx incidental hilar LAD or if classic syndrome w/ ↑ pretest prob of sarcoid (e.g., Lofgren). ↑serum ACE 41% Sn, 90% Sp. Check Cr, alk phos, $Ca^{2+}$ ± 1,25-/25-vitD (granulomas can produce 1,25-vitD), CBC, baseline eye exam & EKG if new dx.
- **Tx**: many do not need tx and can be monitored. If sx, oral **steroids** ± MTX ± TNFi (Eur Respir Rev 2020;29:55).

## Adult Onset Still's Disease (AOSD) (J Rheumatol 1992;19:424; Rheumatol 2023;00:1)

- Rare disorder w/ fevers, arthritis, rash diagnosed after 16yr. Monophasic, intermittent, or chronic. F=M, bimodal (15-25, 36-46 yo)
- **Sx**: fever (often spikes 1-2x daily); arthralgias; evanescent **salmon-colored maculopapular rash** coinciding w/ fever, often truncal, trauma may precipitate (Koebner phenom.); pericarditis; pleuritis; can be c/b **HLH/macrophage activation syndrome**
- **Dx**: **Yamaguchi criteria (**J Rheumatol 1992;19:424), (require **≥5 features,** including **≥2 major criteria**
  - Major: fever ≥39ºC for ≥1w; arthralgias/arthritis ≥2w; salmon-colored rash; ↑WBC (≥80% PMN)
  - Minor: sore throat; LAD; HSM; ↑AST/ALT, ↑LDH; negative ANA/RF
  - Other labs (non-criteria): ↑ESR/CRP; **ferritin >3000** (if >10,000, **consider HLH/MAS**, see *Hematology*); ↑plt; ↓Hgb
- **Tx**: Mild: **NSAIDs** 1st line, then steroid/DMARD Severe: **anakinra, pred** 0.5-1mg/kg/d +/- MTX, TNFi, anti-IL6

## Relapsing Polychondritis (Rheumatol 2018;57:1532; Clin Exp Rheumatol 2022;40:81)

- Rare immune-mediated dz a/w inflammation of cartilaginous structures (ears, nose, trachea, joints) & other tissue (eyes), a/w VEXAS
- **Sx:** bilateral auricular chondritis (can impair hearing), nasal chondritis (saddle-nose), arthritis, laryngeal/tracheal chondritis, valvulopathy; eye inflamm; cochlear/vestib dysfunction. **Dx:** ↑ESR/CRP; eval resp/card (CXR/CT ± bronch, PFTs, ECG/TTE)
- **Tx: steroids** first-line; NSAIDs for arthritis; MTX, AZA, biologics for steroid-sparing; CYC if organ-threatening

## VEXAS Syndrome (NEJM 2020;383:2628)

- **V**acuolated myeloid/erythroid cells; **E**1 enzyme loss of fnx; **X**-linked (M>F); **A**utoinflammatory; **S**omatic mutations in *UBA1*
- **Sx:** recurrent fever (92%); alveolitis; auricular/nasal chondritis; neutrophilic dermatosis; small to medium vessel vasculitis; cytopenias, macrocytic anemia; thromboses. 60% meet criteria for relapsing polychondritis. Strong a/w myelodysplastic syndrome and MM.
- **Dx:** Genetic testing, consider BMBx. **Tx:** High-dose steroids and DMARDs. Emerging data for TCZ, JAKi, HSCT. Poor prognosis

## Familial Mediterranean Fever (Ann Rheum Dis 2016;75:644)

- Autoinflammatory disorder of recurrent fever & serositis. ↑ in Mediterranean descent, onset <10 yo (65%), <20 yo (90%)
- **Sx**: recurrent acute attacks (1-3d, resolve spontaneously) of fever a/w peritonitis (often mistaken for surgical abdomen); unilateral pleuritis; arthritis (monoarticular); skin lesions (erysipelas-like); exertional myalgia; pericarditis; testicular pain; aseptic meningitis.
- **Dx**: During attack: ↑ WBC, ↑ ESR/CRP. Check UA for secondary AA amyloidosis (proteinuria). Genetic testing for definitive dx
  - Diagnostic criteria: requires 1 major or 2 minor criteria (Arthritis Rheum 1997;40:1879)
- **Tx**: **colchicine** (to prevent acute attacks and secondary amyloidosis). 2nd line: anti-IL1 (Ann Rheum Dis. 2016;4:644)

## Fibromyalgia (JAMA Intern Med. 2021; 181(1):104-112)

- Central pain processing disorder manifesting as chronic widespread MSK pain, often w/ fatigue, sleep disturbance, and multiple somatic sx. F>M, 20-55 yo. Can coexist with other inflammatory dz like SLE, RA. Often psych. comorbidities.
- **Sx**: widespread MSK pain; fatigue; cognitive disturbance; psych. sx; HA; paresthesia; IBS. "Pan-positive" ROS not uncommon
- **Dx**: clinical: >3 mo of sxs; multiple tender points. Revised 2016 criteria. Labs: normal (ESR, CRP, TSH, CBC, BMP)
- **Tx**: Initial: patient education; CBT for pain; graduated **exercise program;** sleep hygiene. Pharmacologic: 1st line amitriptyline, duloxetine, milnacipran; may consider cyclobenzaprine, gabapentin, pregabalin (monotherapy > combo). Avoid opioids

# Rheumatology — Rheumatologic Medications

| DRUGS | INDICATIONS | COMMON TOXICITIES/NOTES |
|---|---|---|
| **Ibuprofen**, **indomethacin** (short act.)<br>**naproxen** (long acting)<br>**celecoxib** (COX-2 selective inhibitor)<br>**diclofenac** (topical) | OA, SpA, RA, gout, CPPD, SSc, SLE | **Gastropathy** (RFs: age, DAPT/AC/steroids; ↓ w/ PPI/misoprostol ppx, celecoxib), **kidney injury** (AKI, AIN, papillary necrosis), **CV mortality** (naproxen may ↓ risk, celecoxib noninferior, NEJM 2016;375;2519) |
| **Colchicine**; microtubule inhibitor | Gout/CPPD, FMF, Behcet's | **Diarrhea**, **myopathy**, myelosuppression, neutropenia, **med interactions,**↓ dose if ↓ GFR/CTP class C liver dz |
| **NON-BIOLOGIC DMARDS** | | |
| **Hydroxychloroquine** (HCQ, *Plaquenil*) | SLE, RA, Sjogren's, APLAS | N/V, **retinopathy (baseline & q1y retinal exam)**, dizziness, rash, alopecia, myelosupp., ↑QTc, cardiomyopathy (rare); note that HCQ is not immunosuppressive |
| **Methotrexate*** (MTX, *Rheumatrex*); DHFR inhibitor (antifolate) | RA (first line), Psoriatic Arthritis | **Myelosupp. (add folate)**, **↑LFTs, pneumonitis** (baseline CXR), GI, stomatitis, HA, rash, teratogen. Monitor: CBC + LFTs q12w |
| **Azathioprine*** (AZA, *Imuran*); purine synthesis inhibitor | DM/PM, SLE nephritis, vasculitis (maintenance), RA | GI, ↑LFTs; myelosupp., lymphoproliferative d/o, bruising. Check **TPMT** deficiency and avoid xanthine oxidase inhibitors (allopurinol) as can ↑toxicity |
| **Mycophenolate*** (MMF, *CellCept*); purine synthesis inhibitor | AAV, DM/PM, PsA, Scleroderma, SLE | Cytopenias, ↑LFTS, nausea, diarrhea, HA, insomnia, rash, **teratogen**, lymphoma/skin cancer, med interactions |
| **Leflunomide*** (*Arava*); pyrimidine synthesis inhibitor | Psoriatic Arthritis, RA | N/V, alopecia, rash, diarrhea, HTN, **hepatotoxicity**, URI, dizziness/HA, **teratogen,** peripheral neuropathy |
| **Sulfasalazine*** (5-ASA, SSZ, *Azulfidine*) | AS, IBD, JRA, Psoriasis, RA | Sore throat, stomatitis, rash, HA, N/V, myelosuppression, delayed hypersensitivity rxns; **check G6PD** |
| **Cyclosporine*** (CsA);<br>**Voclosporin*** - calcineurin inhibitor | SLE nephritis (voclosporin); RA | **HTN, AKI**, HA (both); N/V, GI, gum hyperplasia, hirsutism, edema, tremor (CsA); ↓ HTN & AKI and no level monitoring w/ voclosporin |
| **Cyclophosphamide*** (CYC, *Cytoxan*); DNA alkylation | **Severe organ-threatening dz** (SLE nephritis, ANCA) | Myelosuppression, lymphoma, **hemorrhagic cystitis** (MESNA ppx), bladder cancer, **infertility** (cumulative dose, leuprolide ppx), teratogen, <1% pneumonitis |
| **Apremilast** (*Otezla*); PDE4 inhibitor | Psoriasis, Behcet | N/D, URI, HA, depression, weight loss |
| **Tofacitinib***(*Xeljanz*); JAK1&3 inh.<br>**Upadacitinib*** (*Rinvoq*); JAK1 inh.<br>**Baricitinib*** (*Olumiant*): JAK1&2 inh. | RA, Anklyosing spondylitis, psoriasis | **Malignancy and CV events** (NEJM 2022; 386:316). Infection, cytopenias, ↑LFTs, diarrhea, **↑VTE**, **death (black box warning**) |
| **BIOLOGICS** | | |
| **Adalimumab*** (*Humira*); anti-TNF<br>**Infliximab*** (*Remicade*); anti-TNF<br>**Golimumab*** (*Simponi*); anti-TNF<br>**Certolizumab*** (*Cimzia*); anti-TNF<br>**Etanercept*** (*Enbrel*); sol. TNF-R | AS, IBD, Psoriasis/PsA, RA | **CHF (contraindicated in HF)**, HA, infusion rxn, nausea, rash, infection, **drug-induced lupus, skin cancer.** Can develop anti-therapeutic Ab -> loss of clinical response. Monitor: CBC, LFTs q3-6 mo**.** Safe w/ HCV (Expert Opin Biol Ther 2012;12:193) |
| **Rituximab*** anti-CD20<br>**Obinutuzumab*** (Gazyva); anti-CD20 | APLAS, ANCA, IgG4, Scl-ILD, SLE | Infection, HTN, **infusion reaction,** PML, fever, rash/pruritus, LE edema, neutropenia/hypogammaglobulinemia (ritux) |
| **Belimumab*** (*Benlysta*); anti-BAFF | SLE | **Depression**, HA, infusion reaction, PML, GI |
| **Abatacept*** (*Orencia*); soluble CTLA4 | PsA, RA | Infection, HA, nausea, dizziness, HTN, dyspepsia |
| **Tocilizumab*** (*Actemra*); anti-IL6R<br>**Sarilumab*** *(Kevzara*); anti-IL6R | GCA (toci), RA, PMR | Infection, **hepatotoxicity**, HLD, GI perforation (h/o diverticulitis -> contraindicated), neutropenia, thrombocytopenia |
| **Anakinra*** (*Kineret*), anti-IL-1R;<br>**Canakinumab*** (Ilaris); anti-IL1β | Gout/CPPD, AOSD/MAS | Myelosupp./neutropenia (anakinra), rash/injection site rxn/pain, HA, arthralgia, fever |
| **Secukinumab*** (*Cosentyx*);<br>**Ixekizumab*** (*Taltz*); anti-IL17A | AS, Ps/PsA, GCA (secu) | Infection, IBD flare (secu), diarrhea; neutropenia (ixekizumab), derm rxn (secu) |
| **Ustekinumab***(*Stelara*); anti-IL-12/23<br>**Guselkumab***(*Tremfya*); anti-IL23<br>**Risankizumab*** (*Skyrizi*); anti-IL23a | Ps/PsA, IBD | Infection; seizures (ustekinumab); HA, diarrhea |
| **Anifrolumab***; anti Type I IFN-R | SLE | Infection, bronchitis/URI, heme malignancies, hypersensitivity |
| **Mepolizumab*** (*Nucala*); anti-IL5<br>**Benralizumab*** (*Fasenra);* anti-IL5R | EGPA | Injection site rxn, HA |
| **Avacopan*** (*Tavneos*); anti-C5aR | ANCA (GPA, MPA) | HA, N/V/D, HTN, rash, ↑LFTs |
| **Intravenous immunoglobulin** | APLAS, DM/PM, IMNM, Kawasaki's | Transfusion reactions/anaphylaxis, hemolysis, aseptic meningitis, thromboembolism, HA |

*Can ↑ **HBV/TB reactivation** and chronic infection risks **(check HBV/HCV serologies, HIV, and IGRA or PPD prior to starting)**

# Endocrinology — Outpatient Type 2 Diabetes Mellitus

## SCREENING (Diab Care 2025:48;S35)

ADA recs: Begin at ≥35 years, repeat q3y if normal. Repeat q1y if pre-DM. Adults at higher risk = 1) BMI ≥25 (≥23 in Asian-Americans) + RF (1st degree relative with T2DM, nonwhite, history of CVD, HTN, HDL<35, triglycerides >250, PCOS, sedentary lifestyle, acanthosis nigricans, MASLD) *or* 2) History of gestational DM (screen q1-3y) *or* pancreatitis *or* 3) HIV prior to starting/switching ART. (ADA 2025).

## PRE-DIABETES (Diab Care 2025:48;S35)

- 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; at initiation of second-gen antipsychotics & repeat 12-16 weeks after; prior to starting HIV ART, switching ART, & 3-6 months after.
- Treatment: **lifestyle Δ** most effective; **metformin** also effective, esp. if BMI ≥35, age <60, or GDM hx (Cochrane Rev 2019)

## DIABETES (Diab Care 2025:48;S27)

- Diagnosis: A1c ≥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 at the same time or promptly after**.
  - For **T1DM**, check TSH at dx and q1y. Screen for thyroid dz and celiac at dx, and again if signs/sx develop. (Diab Care 2025;48;S63)
  - Use plasma blood glucose criteria and not A1C if high RBC turnover: sickle cell disease, 2nd/3rd trimester of pregnancy, ↓G6PD, HD, HIV, recent blood loss/transfusion, EPO tx.
  - A1c less reliable post-partum, with certain HIV drugs, thalassemia and sickle cell (high cell turnover), and anemia (UTD list)
- Tx: goal A1c <7%; can liberalize to <8-8.5% if life expectancy ≤10 years or high risk for hypoglycemia (e.g., ESRD)

| Healthcare Maintenance for Diabetic Patients (Diab Care 2024:47;S56) (Diab Care 2024:47;S116,S182) (Diab Care 2025:48;S59-85 ) | |
|---|---|
| Every visit | • Review blood sugar log: **goal AM FPG 80-130**, postprandial (1-2h) <180; eval for **hypoglycemia frequency, causes, and timing**<br>• Review medication regimen and medication-taking behavior. Screen for tobacco, EtOH, and substance use. Counsel.<br>• Blood pressure: **goal <130/80**. ACEi/ARB first line. Can target <120/70 in pts w/ multiple CV RFs (if it can be safely attained).<br>• Weight, BMI: weight center referral if BMI ≥40 or ≥35 with poor control; nutrition referral for all (JAMA 2023))<br>• **Foot exam** (inspect skin, joints, pulses, sensation) esp. if known neuropathy or PVD; ABIs/vascular referral if PVD<br>• Skin exam (acanthosis nigricans, insulin injection/insertion sites, lipodystrophy) |
| Q3-6mo | • A1c **q6mo** if controlled and stable regimen; q3mo if ↑ target, recent tx change, hypo/hyperglycemia, or change in health status |
| Annually | • Lipids: Age 20-39 consider statin if additional risk factors (RF). Age 40-75: moderate-intensity **statin for all DM pts regardless of lipid panel.** If ≥1 ASCVD RF, then high intensity statin w/ target LDL-C<70. Pts with clinical ASCVD (ACS, TIA), target LDL-C<55 with statins + other agents<br>• Urine mAlb/Cr, Cr/eGFR; ACEi/ARB if hypertensive w/ proteinuria *or* GFR <60; refer to renal if GFR <30<br>• Neuropathy exam: 10g monofilament (+ if no sensation at 4/10 sites, see PCOI); pinprick, vibration, or reflexes<br>• Retinopathy screen w/ dilated eye exam or retinal photography; can consider q2-3y if normal exam(s)<br>• LFTs: consider elastography and/or hepatology referral if elevated to evaluate for MASLD<br>• Other: B12 for those on metformin. T1DM – yearly TSH. |
| Vaccines | • Influenza annually, COVID-19, HBV series if age <60 and not immune, Zoster (age >50), TDAP, Pneumococcus, RSV (CDC) |

| Basal Insulin Management (Diab Care 2024:47;S158) (Diabetes Care 2025;48;S181–S206) | |
|---|---|
| Criteria for initiation | • Consider if **A1c ≥9%,** random BG ≥300, fasting BG ≥250, or symptomatic; suspicion for T1DM or LADA/insulin deficiency; <65yo on two agents with A1c >8% (or ≥65yo and A1c >8.5%) on two occasions >3mo apart; or A1c rising quickly.<br>• Able to perform self-monitoring with glucometer; consider referral to DM educator |
| Initial dose | • Starting dose: A1c <8%: 0.1-0.2 U/kg/d, A1c>8%: 0.2-0.3 U/kg/d<br>• Choice of agent: choose long-acting (glargine/detemir/degludec qd), preferred over intermediate-acting (NPH BID) to reduce risk of hypoglycemiaRoute: pen (easier to use, more expensive) vs needle/syringe |
| Titration | • Increase by 2-4U or 10-15% q2-3d until AM fasting BS is 80-130 without hypoglycemia; savvy patients can self-titrate.<br>• If hypoglycemia occurs or FPG <80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater. |
| If patients required additional control beyond basal insulin, the ADA recommends considering a GLP-1 receptor agonist or dual GIP/GLP-1 RA before initiation prandial insulin to minimize the risks of hypoglycemia and weight gain associated with insulin therapy. | |

| Prandial Insulin Management | |
|---|---|
| Criteria | • Consider if A1c still not at goal with basal insulin >0.5U/kg/d and fasting glucose within target range (80-130). |
| Initial dose | • Strategy 1: add 1 rapid-acting insulin before largest meal → start w/ 4U or 0.1U/kg or 10% basal dose<br>• Strategy 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. Confirm w/ pt they eat 3 meals regularly if choosing this. |
| Titration | • Increase dose by 1-2U or 10-15% q3d until target glucose reached (pre-prandial: 80-130; 1-2h post-prandial <180)<br>• If A1c still not controlled: add rapid-acting insulin to another meal and titrate as above<br>• If hypoglycemia occurs or FPG <80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater |

## INSULIN SUPPLIES

- Needles: Pen needles for pts on insulin pen or 2) needle+ syringe 32G 4mm is less painful (higher gauge = thinner and shorter needle), but larger patients and high insulin doses often require longer/wider needle.
- Syringes: boxes of 100. Choose smallest syringe that will hold the dose (smaller barrel → clearer scale markings)
- Alcohol swabs (or patients can wash hands/skin with soap and water)

| Use this barrel size… | With this dose range… |
|---|---|
| 3/10 mL | 30U or less |
| 1/2 mL | 31-50U |
| 1 mL | 51-100U |

- Glucometer & test strips: Many choices, each with own strip brand. Most test strips come in boxes of 50-100. Some glucometers can read BG aloud (helpful for visually impaired). Tip: MassHealth only covers FreeStyle. Otherwise OneTouch Verio usually covered.
- **** All durable medical equipment including test strips and glucometers requires an ICD-10code on the script itself****

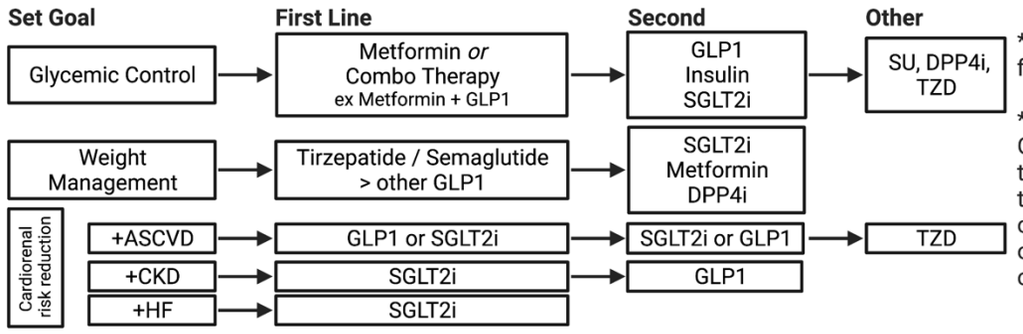
*Emily Stephens & Anika Agarwal*



Suggest an Edit

# Endocrinology — Outpatient Type 2 Diabetes Mellitus

## Algorithm for Oral Anti-Diabetic Therapy (Diab Care 2021;44:S111) (PCOI)




*Lifestyle modifications are first line for all w/ DM.

*New guidelines emphasize GLP1/SGLT2 as first line therapy for many due to their weight loss and cardiorenal benefits. Choose order based on goals/ comorbidities.

## Non-Insulin Agents (Dual Combination therapy when A1c ≥1.5% above goal)

| Drug/Dose Range | %↓ A1c | Indications/Benefits | Contraindications | Side Effects/Considerations |
|---|---|---|---|---|
| **Metformin**: 1st line anti-diabetic medication; many effects, primary mechanism is decreasing hepatic glucose production | | | | |
| **Metformin** (Glucophage) 500-1000mg BID | 1-2 | **First line therapy**<br>Minimal weight loss<br>Improvement in lipids | GFR cutoffs:<br><45mL/min don't initiate<br><30mL/min discontinue<br>Metabolic acidosis | **Nausea, bloating, diarrhea**<br>B12 deficiency<br>**Lactic acidosis** in severe liver/renal disease or hypoperfusion state |
| Metformin pearls: discuss GI sx (decrease over time). Minimize by advising slow titration (250-500mg/wk), taking WITH food, or switching to XR formulation. Benefits/side-effects are dose-dependent – maintain highest dose tolerated. | | | | |
| **SGLT-2 Inhibitors**: block renal glucose reabsorption, increase glucosuria | | | | |
| **Canagliflozin** (Invokana) 100-300mg qd<br>**Empagliflozin** (Jardiance) 10-25mg qd<br>**Dapagliflozin** (Farxiga) 5-10mg qd | 0.8-0.9 | **↓CV events, ASCVD mortality, CHF** hospitalization, **CKD** progression (NEJM 2019;380:2295)<br>**Weight loss**<br>↓risk of hypoglycemia<br>↓BP 3-5mmHg | GFR cutoffs:<br>Start if eGFR ≥20 mL/min<br><20 mL/min discontinue<br><br>History of DKA | UTI & GU **fungal infections**<br>Small risk of **euglycemic DKA** (hold in pts 3-4 days prior to surgery & post-op until take PO)<br>Risk of dehydration/HoTN<br>Risk of fracture (canagliflozin)<br>May ↑LDL cholesterol<br>? ↑ risk amputation w/ canagliflozin |
| SGLT2i pearls: Discuss diuretic effect, replace water loss to avoid euglycemic DKA. Initiate 1 mo low dose, then titrate to effective dose. For potency, empagliflozin > canagliflozin > dapagliflozin. HF benefit is probably not a function of A1c lowering. | | | | |
| **GLP-1 Receptor Agonists**: stimulate glucose-dependent insulin release from beta cells. Slow gastric emptying, promote satiety and w/l | | | | |
| **Liraglutide** (Victoza) 0.6-1.8mg qd<br>**Dulaglutide** (Trulicity) 0.75-4.5mg qwk<br>**Semaglutide** (Ozempic) 0.25-2.4mg qwk | 0.5-2 * | **↓CV events, ASCVD**<br>**Weight loss**<br>First line injectable therapy (before basal insulin)<br>↓risk of hypoglycemia<br>↑dose↑efficacy (wt/A1C) | **FDA Black Box Warning**: ↑risk medullary thyroid ca. in rodents, not yet demonstrated in humans. Avoid if hx MTC/MEN2<br><br>GFR 30-45: avoid exenatide | **GI**: **n/v, diarrhea**<br>**Injection site reactions**<br>Delayed gastric emptying<br>↑risk of pancreatitis<br>Low starting dose is to avoid GI side fx.<br>Up titrate for effective wt loss/ A1C lowering |
| Tirzepatide (Mounjaro) GLP1/GIP 2.5-15 mg qwk | 2.6 | | | |
| GLP-1 RA pearls: for weight loss, semaglutide > dulaglutide > liraglutide > others. Up-titrate to effective dose in 1mo intervals. | | | | |
| **DPP-4 Inhibitors**: inhibit degradation of endogenous GLP1, ↑glucose-dependent insulin secretion and ↓glucagon secretion. | | | | |
| **Sitagliptin** (Januvia) 25mg-100mg qd<br>**Linagliptin** (Tradjenta) 5mg qd | 0.5-0.8 | Linagliptin preferred if CKD/ESRD<br>↓risk of hypoglycemia<br>Weight neutral | No contraindications, but very weak | Saxagliptin, alogliptin: **↑hosp for CHF**<br>Joint pain |
| **Insulin Secretagogues**: stimulate release of insulin from pancreatic beta cells, thus only effective in pts who still have beta cell function | | | | |
| Sulfonylureas:<br>**Glipizide** 2.5-20mg qd<br>**Glimepiride** 1-8mg qd | 1-2 | Affordable | T1DM, DKA<br>Low cross-reactivity in pts with sulfa allergy | **Weight gain**<br>**Hypoglycemia** (esp. glyburide)<br>Possible ↑CV mortality |
| Meglitinides: **Repaglinide** (Prandin) 0.5-4mg qAC | 0.5-0.7 | Use like bolus insulin (short-acting)<br>**CKD**<br>↓nocturnal hypoglycemia | Severe liver disease<br>Concurrent gemfibrozil therapy | **Weight gain**<br>**Hypoglycemia**<br>↑serum conc. w/ clopidogrel<br>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<br>Possible benefit in NASH | Hx of bladder cancer, renal impairment<br>NYHA Class III/IV HF | **FDA Black Box Warning**: **↑risk of CHF (2/2 ↑ fluid retention)**<br>**Weight gain;** ↑risk of fracture |

## Considerations for DM in pregnancy (Diabetes Care 2024;47:S5-S10)

- Tighter glycemic control required in pregnancy to prevent maternal & fetal complications; goal HbA1C <6.0-6.5% and FBG <95mg/L
- Discontinue GLP-1s. Metformin and glyburide should not be used as first-line agents due to concerns about efficacy and safety. Insulin is the preferred tx for hyperglycemia in pregnancy. Insulin requirements may be higher.
- Weight loss is not recommended due to the risk for small-for-gestational-age infants
- Encouragement of breastfeeding is recommended for all postpartum individuals

*Emily Stephens & Anika Agarwal*



Suggest an Edit

# Endocrinology — Inpatient Diabetes Mellitus Management

## Insulin Nomenclature

| Type (Onset) | Formulation | Peak | Duration |
|---|---|---|---|
| Rapid (10min) | lispro (Humalog) aspart (Novolog) glulisine (Apidra) | 30-60 min | ~4h |
| Short (30min) | Regular insulin (Humulin R, Novolin R) | 2.5-5h | ~6h |
| Intermediate (1-2h) | Insulin NPH (Humulin N, Novolin N) | 4-12h | ~12h |
| Long (3-4h) | glargine (Lantus) qD detemir (Levemir) qD degludec (Tresiba) qD | none | 24h |

**Basal insulin**: standing (NOT PRN) fixed intermediate/long-acting for basic metabolic requirements
**Nutritional insulin**: standing (NOT PRN) rapid/short-acting to cover meals
**Correctional insulin**: sliding scale (can be standing or PRN depending on pt) rapid/short-acting to correct hyperglycemia from prior meal
**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. Always overlap with SC insulin by 2-3h ***before*** stopping insulin gtt

## Inpatient Management (Diabetes Care 2024;47:S295-S306)

- Glycemic targets: Floor: fasting 100-140mg/dL, random <180 mg/dL. ICU: 140-215mg/dL (NOT stricter) (NEJM 2023(13):1180)
- Check BG in: (1) diabetics (2) non-diabetics with gluc >140mg/dL (3) pt w/ therapies a/w hyperglycemia (glucocorticoids, octreotide)
- How to check: **FSBG qAC** (at least for 24-48h) initially OR **FSBG q6h if NPO** or on **continuous** TF or TPN. FSBGs less accurate in hypotension (esp. on pressors), hypothermia, edema, anemia, and Raynaud's/altered blood flow to skin. Confirm with BMP.

**Admission Orders** (NEJM 2006;355:1903)

1. Hold home oral antihyperglycemic agents when patients are acutely ill (***NEVER hold basal insulin for T1DM***)
2. **Check A1c** in all patients with DM/hyperglycemia if not done in last 3 months
3. If on insulin at home: 25-50% reduction given expected change in diet while hospitalized and initiate ISS for correction and **then adjust basal-bolus dosing over the hospitalization** (Diabetes Conversion Guidelines) (goal 50:50 basal:bolus)
4. If **not** on home insulin:
   a. Well-controlled: start with **lispro** ISS **and change to basal-bolus** once TDD established. Prolonged use of ISS as only anti-hyperglycemic tx is **discouraged (SSI-only reg. suboptimal unless pt well-controlled on orals)** (J Hosp Med 2019;2;114)
   b. Not well-controlled (BG >180mg/dL): start w/ **basal (0.25U/kg/day)**, use 0.15U/kg in pts with ESRD, elderly, and low BMI. Then add prandial insulin (0.05-0.1U/kg) qAC PLUS correctional insulin qAC.
5. **If NPO**: 50% dose reduction or 0.1U/kg/day for basal. Hold prandial & change correctional ISS and FSBG from TID qAC to q6h
6. Correctional insulin sliding scale: use low-dose if insulin-sensitive/ESRD/ESLD/frail, always do TID qAC and MAKE SURE no HS

**Adjusting Insulin Dosing**: in general, adjust insulin requirement by no more than **20%**. ↓insulin if fasting <100 (hypoglycemia risk).

| | | |
|---|---|---|
| Fasting/AM BG ↑ (or ↓) from qHS glucose | → | ↑ (or ↓) basal insulin dose* |
| Fasting BG high + qHS BG high but are the same | → | ↑ dinner prandial insulin dose (no Δ basal) |
| BG rises with each meal over the course of the day | → | ↑ prandial insulin dose at each meal |
| Pre-lunch or dinner BG high (w/ other BGs in range) | → | ↑ prandial insulin dose of preceding 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

1. **Glucocorticoids**: NPH 0.1U/kg/d for every 10mg pred (or equivalent), up to 0.4U/kg/d (dose BID); if dexamethasone or continuous glucocorticoid use, use glargine qD
2. **Tube feeds**: if not on insulin, 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 would have been due, and ↓NPH dose by 50% or more based on pre-TF insulin requirements. **TPN**: regular insulin can be added to TPN (discuss w/ nutrition)
3. **Insulin pumps:** consists of basal rate (units/kg/h) which replaces glargine, bolus dose based on carb ratio (units insulin:gram carbs), and correctional insulin based on the sensitivity factor (units insulin:mg/dL above target glucose). Complications: site infection, pump failure, interrupting infusion. **Endocrine/DM consult required** to develop contingency plan in case of pump failure. **IF CONCERN FOR AMS, TRANSITION TO SUBQ BASAL/BOLUS REGIMEN** (the pump is run ***completely*** by the patient).
4. **Patient's Home CGM:** Can be used to titrate insulin while inpatient but note that often the BG reading is 20-30 minutes delayed and should be cross-checked with FSBG initially. Should not be used in ICU. **Can consult endocrine for help with this.**

**Discharge**: If oral meds are held inpatient, resume 1-2 days before d/c (ADA, 2023). If poorly controlled DM on insulin PTA: increase home regimen. If new home insulin: nutrition c/s + floor RN teaching and outpatient f/u. Discharge order set: rx for glucometer, test strips, lancets, syringes/vials or pens/needles to MGH outpatient pharmacy and bring up to floor for RN teaching (MGH video link).

## Inpatient Hypoglycemia

↑**Risk**: T1DM, brittle DM, malnutrition, emesis, ↓body weight, ↓PO intake, ↓steroid dose, AKI (↓insulin clearance), CKD (esp. dialysis)

***Beware of hypoglycemia unawareness in T1DM and longstanding T2DM***

**Manifestations**: BG<70: Adrenergic component: shakiness, anxiety, diaphoresis, acute hyperphagia. Neuroglycopenic component: AMS, malaise. <55 with risk of seizure, coma. If possible, correlate with BMP (esp if concern for poor peripheral vasculature) in pt w/o overt reason for hypoglycemia.

**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. Consider dextrose infusion if persistent despite amp/PO or if cannot tolerate PO well. If sulfonylurea OD: 50-75mcg octreotide SQ. **Review and adjust insulin**

| Insulin | Pro-Insulin | C-Peptide | Ddx |
|---|---|---|---|
| ↑ | ↑ | ↑ | Insulinoma, oral hypoglycemic, autoimmune |
| ↑ | ↓ | ↓ | Exogenous insulin admin |
| nl | nl | nl | Non-islet cell tumor, e.g. IGF-2-secreting tumor |

**Ddx:** *If ill/medicated*: drugs (insulin [secretagogues], EtOH), sepsis, ESLD, ESRD, HF, adrenal insufficiency, non-islet cell tumor
*If well-appearing*: post-gastric bypass (post-prandial, or "reactive", hypoglycemia), insulin or insulin receptor antibodies, insulin (secretagogues), insulinoma (particularly if fasting hypoglycemia)

**Workup**: must meet **Whipple's Triad** to merit eval! Triad of 1) sx c/w ↓BG, 2) reliably ↓BG when sx present, 3) sx relief once euglycemic

1. Mixed-meal with postprandial eval (q30min labs for 5h post-meal, or fasting eval with admission for 72h fast)
2. Check: serum glucose, insulin level, C-peptide, βOHB, proinsulin, sulfonylurea/meglitinide screen at time 0

# Endocrinology DKA/HHS

## 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 (acetoacetate, β-hydroxybutyrate, acetone)
- *Acidosis*: ↑β-hydroxybutyrate and acetoacetate, and contraction alkalosis with total body $HCO_3$ 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, HCO3 < 18, 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 (if serum bicarb reduced or hypoxemic). Consider hs-trop, EKG, BCx/UCx, CXR, lipase/amylase
  - UA ketone **does not** test for β-hydroxybutyrate, which is the predominant ketone in DKA (must measure from **serum**)
- **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).

**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<250 (DKA) or <300 (HHS)**

Step 2: **Potassium repletion** (200-400 mEq total body K defecit due to extracellular shift, osmotic diuresis, and lack of insulin; may be normal / elevated at presentation but total body K+ is low – aggressive K+ repletion is critical as hypokalemia will limit ability to administer insulin)

- K < 3.3, give 20-40 mEq KCl IV per hour. **DO NOT START INSULIN UNTIL K > 3.3**
- K 3.3≤K≤5.3: add 20 mEq K to IVF
- K >5.3: continue to monitor q2h

Step 3: **Insulin therapy,** see MGH DKA/HHS Guidelines: Floor vs ED/ICU. The #1 goal of insulin in DKA is to stop ketogenesis and close the AG

- **Don't start insulin until you have control of K (>3.3meq/L)**
- **Don't stop the insulin gtt** unless true hypoglycemia (<70 mg/dL) or hypokalemia (<3.3 mEq) occurs
- **Initial**: bolus 0.1U/kg regular insulin (max 10U), then start 0.1U/kg/h IV regular insulin gtt (max 10U)
  - For mild DKA, subcutaneous insulin regimens may be used instead of IV (Cochrane Rev 2016)
- **Titrate insulin drip based on Ellucid Policy linked above.** FYI: MICU general insulin gtt protocol is NOT for DKA.
- Once BG **<250**, discontinue prior mIVF and start D5W at 100-250 cc/hr and reduce insulin to ½ current weight-based rate. Based on every 1-hour BG checks, adjust insulin infusion and D5W-containing fluids using table below to maintain BG between 140-249 mg/dL until resolution of ketoacidosis

**Other electrolytes**:

- $HCO_3$: no proven benefit w/ pH > 6.9. **If pH <6.9**, give 2 amps $HCO_3$ dissolved in 400mL sterile water w/ 20mEq KCl over 2h
- Phos: total body deficit but serum phos may be ↑/nml; will ↓ w/ insulin; **only replete if <1.0** to prevent cardiac dysfunction
- **Transitioning to SQ insulin**: criteria: (1) BG **<200** *and* (2) **AG <12** *and (3)* **HCO3 ≥15** or **pH >7.3 Basal** regimen w/ either: home glargine dose *OR* glargine at 0.25-0.4 U/kg/d *OR* glargine 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). **Ensure 2hr overlap between IV insulin gtt and SQ basal** (abrupt discontinuation of insulin gtt coupled with a delayed onset of SC insulin regimen may lead to ketone formation and rebound hyperglycemia)
- **Bolus** regimen w/ either: 0.25-0.4U/kg/d divided (if T1DM or unknown) *OR* ISS only (if T2DM).
- **Continue dextrose containing fluids** until pt able to eat at least ~50% of meals (D5W or consider increase to D10W if NPO)

**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 (Addison's disease)**: **↓all adrenal hormones → ↑ACTH**. Lesion localizes to bilateral **adrenal glands**

- Causes: autoimmune (80-90% cases in developed countries; anti-21-hydroxylase Ab+ in 86%, autoimmune polyglandular syndromes) >> infection (TB, HIV, CMV, meningococcus, histo > all fungi except *Candida*; most common cause worldwide), bilateral adrenal hemorrhage (infection, DIC, APLAS), infiltration (hemochromatosis, primary amyloidosis), malignancy (mets), genetic, drugs (mitotane, abiraterone, ketoconazole, etomidate, rifampin, anticonvulsants).

**Secondary AI**: **↓ACTH → ↓adrenal hormone (glucocorticoids only).** Lesion localizes to **pituitary gland or hypothalamus**

- Causes: Abrupt cessation of chronic supraphysiologic glucocorticoids, meds, genetics, pituitary/hypothalamic lesions (see *Pituitary Disorders*)

## CLINICAL MANIFESTATIONS (Lancet 2003;361:1881)

**Primary AND Secondary**: Signs/symptoms: weakness, fatigue, anorexia, myalgia, nausea, vomiting, abdominal pain, fever, psychiatric sx, orthostasis, ↓wt, amenorrhea

- Lab abnormalities: **hyponatremia**, hypoglycemia, hypercalcemia, non-AG acidosis, anemia, eosinophilia, lymphocytosis

**Primary only** (↓serum aldo): **hyperK (only 65%)**, salt craving, **hyperpigmentation** (↑MSH), n/v, abdominal pain, ↓BP, ↑HR, shock
**Secondary only** (RAAS intact): ± hypopituitarism, hypoglycemia (more common than in primary AI)

## 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) high-dose 250 µg IV → repeat serum cortisol **60min later**
  - Normal response: serum cortisol >18µg/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
- **Second line:** If cort stim is not possible, check AM cortisol and ACTH as a preliminary test to suggest AI
  - 6-8 AM cortisol: highly suggestive of AI if ≤3µg/dL (<5µg/dL suggestive); AI ruled out if ≥15 µg/dL (18 µg/dL on older assays).
    - Falsely low: **↓albumin** (cirrhosis, nephrotic syndrome, critical illness; ↓bound and total cortisol, but free cortisol may be nml); PM testing (cortisol level is highest in morning)
    - Falsely high: pregnancy, estrogen tx (↑cortisol binding globulin, ↑bound/total cortisol, free cortisol may normal)
- Testing for **primary** AI: ↑ACTH >2x ULN; ↓aldo, ↑plasma renin, 21-OHase Ab; TB test, VLCFA (males). Consider CT A/P/FNA
- Testing for **secondary, tertiary** AI: ↓ or normal ACTH, normal aldo. Consider MRI pituitary

## ADRENAL CRISIS

- Acute-onset AI with distributive shock in s/o major stressor (infxn, trauma, major surgery, critical illness). ***Consult endocrine.***
- **No known AI**: draw ACTH/cortisol; 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; NEJM 2019;381:852)

- **Adrenal crisis** " **stress dose steroids** (**hydrocort 100mg IV x1**) & **>2-3L NS or D5NS** (if hypoglycemic). BMP, cortisol & ACTH. Follow w/ hydrocort 50mg IV q6-8h. Start fludrocortisone 0.1mg QD when off IV fluid (in primary AI & hydrocort dose <50mg in 24h).
  - **Consider in any patient taking glucocorticoids** (>5 mg pred eq/day for ≥4 wk or >40 mg pred eq/day for ≥1 wk)
  - May taper once patient's clinical status improves and *underlying precipitant is adequately addressed*
- **AI** " glucocorticoid: hydrocortisone 15-25mg/day PO (2/3 AM, 1/3 early PM) > prednisone 3-5mg/day (QD or BID) >> dexamethasone (significant Cushingoid side effects). 1º AI: add fludrocortisone 0.05-0.1 mg PO QD (n.b. hydrocortisone has mineralocorticoid activity; dose adjust appropriately); Dose monitoring: hypoK, HTN, edema → reduce dose; New dx: use plasma renin activity (PRA), goal upper normal range; Liberal salt intake, esp. with exercise or exposure to temps >85 ºF (>29 ºC). Consider ↑fludrocortisone dose in summer; Consider DHEA replacement for 3-6 mo trial in women with impaired mood 2º AI: assess other pituitary hormone deficiencies (treat AI before hypothyroidism to ↓risk adrenal crisis)
  - **If minor illness (e.g., URI) or minor surgery → sick dose:** "3x3 rule" = 3x daily glucocorticoid dose for 3 days
  - **If severe illness → stress dose:** emergency hydrocortisone injection (as below)
  - Supply patients with medical alert bracelet + card and glucocorticoid injection kit (100 mg hydrocortisone) for emergency use
  - Consider screening for AI diseases (unknown optimal frequency) including DM, thyroid dz, premature ovarian failure, celiac dz

## STEROID PEARLS

- Taper: **not necessary if steroid use <3w** (independent of dose) → low risk of HPA suppression. Usually the patient's **specialist** prescribing the steroid a slow taper if underlying disease might flare with an abrupt decrease in steroid dose. Otherwise can drop steroid dose to 5mg pred equivalent and perform a cort stim. If AI present, continue pred 5 mg for 6-8 weeks then repeat cort stim
- Ppx: **PJP**: if taking pred ≥20mg for ≥4w + 2nd reason for immunocompromise; **PUD**: if taking aspirin/NSAIDs; **osteoporosis**: calcium 1200mg/d + vitamin D 800IU/d if on any dose >3mo (consider bisphosphonates for pts at intermediate/high risk of fracture); **DM2**: monitor glucose/A1C, consider insulin dosing (cover with NPH 0.1 U/kg per 10 mg prednisone equivalents up to 40 mg)

| 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, LCH, lymphocytosis), TBI, genetic, tumors (1°: pituitary tumors, mets; 2°: external stalk compression [e.g., craniopharyngioma, meningioma, mets]), autoimmune hypophysitis

- 1° only: Sheehan's (infarction), apoplexy (hemorrhage), meds (immune checkpoint inhibitors)

**Clinical Manifestations & Diagnosis**:

| Hormone Deficiency | Signs/Symptoms | Laboratory Tests |
|---|---|---|
| Prolactin (rarely isolated) | Reduced lactation | PRL |
| ACTH (2° adrenal insufficiency) | Weight loss, anorexia, nausea, dizziness | AM cortisol, cort stim test, ACTH |
| GH | Low energy, central obesity, ↓bone mineral density, ↓exercise performance, psych (depression, immaturity) | IGF-1, insulin tolerance test |
| TSH (2° hypothyroidism) | Weight gain, bradycardia, hair loss, dry skin, hyporeflexia | TSH, free T4 |
| LH/FSH | amenorrhea/oligomenorrhea, decreased libido, ED, infertility | LH, FSH, estradiol, AM testosterone |

**Treatment**: replace deficient hormone (JCEM 2016;101:3888) and **endocrine consult**. Cortisol/thyroid replacement is most important: if deficiencies of both, **treat AI before hypothyroidism** (can precipitate adrenal crisis). For central hypothyroidism, target free T4 (not TSH)

## HYPERPITUITARISM

**Definition**: excess of any of the hormones secreted by the anterior pituitary gland (PRL, ACTH, GH, TSH, LH/FSH)
**Causes**: hyperfuctioning pituitary adenoma ***
**Clinical Manifestations & Diagnosis**: if pituitary adenoma → headaches, visual field deficits (bitemporal hemianopia)

- **Imaging:** MRI brain w/ and w/o contrast (ask rads for pituitary protocol)

| Hormone Excess | Signs/Symptoms | Laboratory Tests |
|---|---|---|
| Prolactin (Prolactinoma) | Infertility, amenorrhea, galactorrhea (F>M), erectile dysfunction | PRL*** (often > 100 ng/ml) |
| ACTH (Cushing's disease) | Weight gain, depression, insomnia, easy bruising, poor wound healing, central obesity, acne, hirsutism, wide violaceous striae, prox muscle weakness, HTN, osteoporosis, DM | Overnight 1 mg dex suppression test, late-night salivary cortisol, or 24h urinary free cortisol excretion |
| GH (Acromegaly) | Arthralgias, paresthesias, hyperhidrosis, OSA, CHF, HTN, enlarged jaw/hands/feet, coarse features, deep voice, skin tags | IGF-1, confirm with GH level after glucose tolerance test |
| TSH (2° hyperthyroidism) | Tremor, palpitation, heat intolerance, weight loss, ↑BMs, SOB | TSH, free T4, total T3 |

*** Prolactin elevation can also be due to stalk compression (often mild, < 100 ng/ml) and other physiologic causes (pregnancy, exercise, stress, eating) vs. pathologic causes (hypothyroidism, cirrhosis, renal failure, meds [e.g. dopamine antagonists])

**Treatment**:

- **Prolactinoma**: if >1cm or symptomatic, first-line treatment is **dopamine agonist** (cabergoline > bromocriptine [less tolerated and less effective]); side effects include GI upset, dizziness, headaches, and mood changes (mania, depression). If <1cm and asymptomatic, can monitor closely with MRI and prolactin levels (JCEM 2011;96:273). In pregnancy, normally stop tx unless growing adenoma.
  - Use lowest dose possible to restore prolactin to normal (men and post-menopausal women: <20 ng/mL, pre-menopausal women: <30 ng/mL); TTE **not required** prior to initiation (JCEM 2016;101:4189)
- For all other hypersecreting pituitary adenomas, treatment is **transsphenoidal pituitary surgery** ± radiation therapy; after surgery, treat patients with empiric steroids until cort stim test 4-6 weeks post-op to evaluate for adrenal insufficiency
- For GH secreting adenomas in pts who are poor surgical candidates or w/ persistent dz, can tx with somatostatin analog (octreotide)

## AVP DEFICIENCY (AVP-D) AND RESISTANCE (AVP-R)

**Definition**: formerly known as diabetes insipidus (DI); polyuria (>50mL/kg/day) in setting of deficiency of (central) *or* resistance to (nephrogenic) arginine vasopressin (AVP), also known as antidiuretic hormome (ADH)
**Causes**: AVP Deficiency (central): trauma, surgery, hemorrhage, infarction, neoplasm, infiltrative (sarcoidosis, histiocytosis), infection, autoimmune, drugs (EtOH, phenytoin) || AVP Resistance (nephrogenic): drugs (lithium, cisplatin), hypoK/hyperCa, infiltrative (sarcoidosis, amyloidosis, MM), sickle cell
**Diagnosis**: confirm polyuria (24h urine volume >3 L) prior to referral/evaluation; ensure urine dipstick negative for glucose

- **Water deprivation test**: normal physiology: water restriction → ↑SOsm → ↑ADH → ↑UOsm (JCEM 2012;97:3426)
  - Check Na, SOsm, UOsm, UVol q2hr. If UOsm > 700 mEq/kg, appropriate ADH response (dx: primary polydipsia)
  - Once (1) **SOsm > 295** mEq/kg, (2) **Na ≥145** mEq/L (adequate ADH stimulus) → administer **desmopressin 4 mcg IV**, then check UOsm, UVol q30min x 2hr. Judge reponse:
    - UOsm ↑ to <300 mEq/kg → ↑ by <15% **complete AVP-R** || ↑ by 15-45% → **partial AVP-R**
    - UOsm ↑ to >300 mEq/kg → ↑ by >100% **complete AVP-D** || ↑ by 15-100% → **partial AVP-D**

**Treatment**: correct hypernatremia (see *Sodium Disorders*). **Allow patient to drink to thirst. PO preferred to avoid rapid Δ in serum Na**.

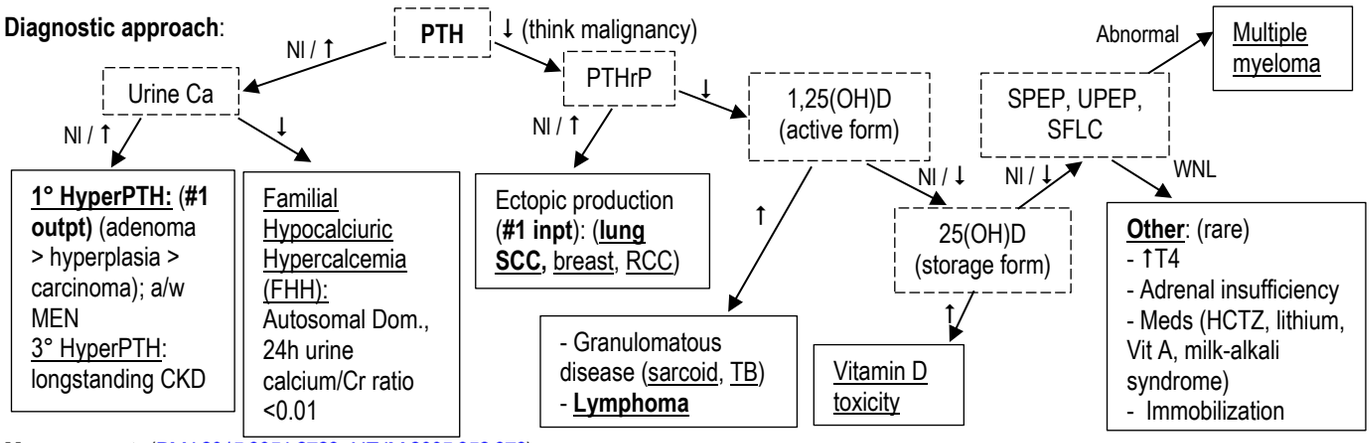
- AVP-D (central): **desmopressin** (exogenous ADH) given intranasal (5mcg qhs + 5mcg qd to tid) or PO/SC, can also add adjunctive meds; dosing frequency also depends on if thrist drive is present. If **impaired thirst** or no access to water, high risk of hypernatremia.
- AVP-R (nephrogenic): if partial, 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 → ↑proximal Na/water reabsorption →↓ distal Na delivery where ADH acts), **amiloride** (similar to HCTZ, beneficial in Li-induced AVP-R by blocking Li entry across ENaC), **NSAIDs** (enhance renal response to ADH), **chlorpropamide** (enhances renal response to ADH)

# Endocrinology — Calcium Disorders

## HYPERCALCEMIA

**Definition**: mild (Ca 10.5-12 mg/dL; iCa 1.3-3mM); moderate (Ca 12-14 mg/dL; iCa 3-3.5 mM); severe (Ca >14 mg/dL; iCa >3.5 mM)
*If unsure of validity of total Ca measurement due to hypoalbuminemia or major acid-base disturbances, obtain an iCa (correction algorithms for albumin are no longer supported [Things We Do for No Reason])*
**Clinical signs/symptoms**: **MSK ("bones")**→osteitis fibrosa cystica (1° hyperPTH), arthralgias, osteoporosis/fractures, weakness; **Renal ("stones")**→polydipsia, polyuria, nephrolithiasis, Type 1 RTA, AKI; **GI ("groans")**→n/v, anorexia, constipation, ileus, pancreatitis, ulcers; **Neuropsych ("overtones")**→fatigue, depression, anxiety, AMS, stupor, coma; **CV**→bradycardia, short QTc, AV block, calcification, HTN

**Diagnostic approach**:



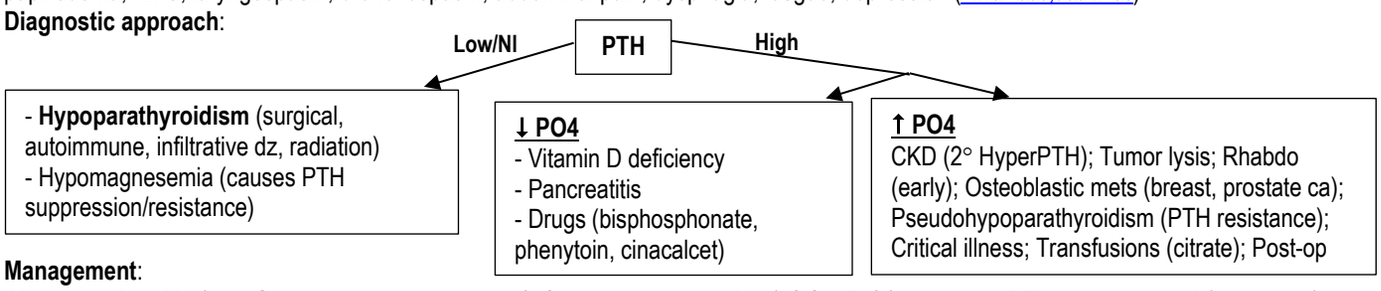

**Management**: (BMJ 2015;305:h2723; NEJM 2005;352:373)
**Mild-moderate**: avoid contributory meds (thiazides, lithium, Ca supp.); PO hydration; oral PO4 repletion to 2.5-3.0 (IV may cause hypoCa)
**Symptomatic** or **severe** (Ca >14): **should be admitted** for treatment and have an endocrine +/- renal consult to assess HD needs

- 1st line treatment: IVF and subQ calcitonin (faster but transient) + IV zoledronic acid (for delayed but sustained effect after 2-4d)
  - Volume resuscitation: pts are typically very dehydrated, which decreases renal clearance of Ca; bolus NS then gtt @ 200-300cc/h with goal UOP 100-150cc/h.
  - Calcitonin: 4-8U/kg subQ BID x 48 hrs (substantial Ca reduction within 12-24h). Possible tachyphylaxis within 48-72h.
  - Bisphosphonates: Zoledronate preferred. Takes 2-4d for effect. SE: hypoCa (check vit D, replete prior if < 20 ng/dL), hypoPhos, flu-like illness, impaired renal fxn. Reduce rate or dose if CKD (Cr>4.5). Avoid if CrCl <30.
- Other treatments:
  - Denosumab: monoclonal Ab against RANKL → blocks pre-osteoclast maturation. Good option in patients with CKD. May be favored over IV bisphosphonates in hypercalcemia of malignancy, but both can be used if refactory. Requires careful monitoring as hypocalcemia risk >> than with bisphosphonates esp at low GFRs. Check 25(OH)D + replete prior to admin.
  - Loop diuretics: **ONLY** if concurrent HF, CKD (once volume replete), elderly; otherwise avoid 2/2 worsen dehydration
  - Glucocorticoids: for calcitriol mediated etiologies [i.e. granulomatous diseases], takes 2-5 days to take effect.
  - HD: if life-threatening or Ca >18 at onset AND neuro sx.

**Special considerations for 1° hyperPTH**: surgery = curative. Indicated if (1) symptomatic *OR* (2) asymptomatic with Ca >11.5, osteoporosis/vertebral fracture, CrCl <60, nephrolithiasis, 24-hr urinary Ca > 250-300 mg/day, *or* age <50. Consider surgery if life expectancy > 10 years (Clin Endo 2024;100(1):3-18) If poor surgical candidate, consider **cinacalcet**, bisphosphonate, HCTZ, raloxifene (JAMA Surg 2017;152:878; JCEM 2014;99:3607)

## HYPOCALCEMIA

**Definition:** Ca < 8.5 mg/dL or iCal < 1.12 mmol/L
**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,** papilledema, AMS, laryngospasm, bronchospasm, abdominal pain, dysphagia, fatigue, depression (BMJ 2008;336:1298)
**Diagnostic approach**:




**Management**:
**Always replete Mg** (hypoCa can be hard to correct w/o first correcting hypoMg (<0.8 mEq/L) → causes PTH resistance and ↓ secretion)
IV Ca repletion: if severe (**Ca <7.5/iCa <0.8 or seizures, ↑QTc, bronchospasm**) or no PO access. Not indicated for asymptomatic hypoCa in CKD.

- 1-2g IV **Ca gluconate** (preferred) or $CaCl_2$ (in codes: via central line, risk of skin necrosis if extravasates) over 10-20 min (slowly to mitigate cardiac risk)-> can repeat in 10-60 min if no effect; **Trend iCa q4-6h** (more reliable given frequent changes in pH in ICU)
- IV therapy ↑serum levels for only 2-3h, chase with gtt or PO; can do sliding scale repletion in ICU

PO Ca repletion: if Ca >7.5 (iCa>0.8) or asx: 1-2g *elemental* Ca QD in split doses (Ca citrate better absorbed vs CaCO3 esp. if pt on PPI)
Vitamin D repletion: *See Vitamin D;* often need to give calcitriol for primary hypoparathyroidism.

# Endocrinology Osteoporosis & Vitamin D

## OSTEOPOROSIS

**Definitions**: fragility fracture or BMD T-score ≤-2.5 on DXA. **Osteopenia**: T-score -2.4 to -1.1. BMD threshold based on fracture risk in postmenopausal white females, applicable to postmenopausal women and men ≥50 yo (ISCD 2019).

- T-score: SD compared to mean for young, healthy adults of same sex and race
- Z-score: SD compared to mean for age, sex, ethnicity-matched population (preferred younger patients)
- Fragility fracture: occurring spontaneously or from minor trauma (e.g. fall from standing height); fractures of hands, feet, ankles, cervical spine, face, skull typically do not count.

**Etiology**: (Osteoporos Int 2022;33:2049)

- 1° osteoporosis most common. RFs: age (women ≥65, men ≥70), low body weight (<57.6 kg), FHx of hip fracture, smoking, early menopause, excessive EtOH use
- Many 2°causes, including: kidney and liver dz, hyperthyroidism, hyperPTH, ↓vit D, hypogonadism, hypercalciuria, myeloma, malabsorption, RA, SLE, COPD, drugs (e.g. glucocorticoids, PPI, AED, heparin, aromatase inhib, MTX, GnRH agonists)

**Diagnosis**:

- FRAX score estimates 10-year fracture risk with or without BMD data. In the US, clinical dx of osteoporosis when FRAX 10-year risk of major osteoporotic fracture ≥20% or hip fracture ≥3% (Endocrine Practice, 2020;26:1).
- **Indications for DXA Scan** (spine and hip +/- forearm): all women age ≥65 (USPSTF) and men ≥70; younger if RFs; fracture and age ≥50; hx condition or meds assc. with ↓bone mass or bone loss (Osteoporos Int 2022;33:2049)
- **Initial labs for 2° causes**: CBC, BMP/Ca/Mg/Phos, LFTs, 25(OH)-vitD, PTH, testosterone (men), 24h urinary Ca and Cr
  - Consider TSH, SPEP+sFLC, tTG-IgA, iron/ferritin, homocysteine, prolactin; Urine (UPEP, free cortisol, histamine)

**Management**: (JCEM 2012;97:1802; JCEM 2019;104:1592; Osteoporos Int 2022;33:2049)

- **Lifestyle measures:** all patients with ↓BMD: weight-bearing exercise 3-4x/wk, smoking cessation, fall prevention measures, ↓EtOH intake, Ca 1200mg qd (diet+supplement, divided doses ≤500 mg/dose). Replete Vit D to goal 30-50 ng/ml (usually 800-1000 IU/day).
- **Pharmacologic therapy**: initiate in postmenopausal women with hip/vertebral fracture; those with osteoporosis; or those with osteopenia and FRAX 10y risk ≥20% for any fracture, ≥3% for hip; or males >50 yrs with above features & males w/ prostate cancer receiving androgen-deprivation therapy who are high risk of fracture.
  - **Bisphosphonates**: normal Ca, Vit D >20 prior to initiation. Reasses fracture risk and consider drug holiday after 3 years of IV and 5 years of oral bisphosphonates in patients with improved T-score ≥ -2.5 & no new fractures. (JCEM 2019;104:1592)
    - **PO alendronate** 70mg or **PO risedronate** 35mg weekly. Avoid if GFR <30, esophageal dysmotility or h/o bariatric surgery. Strict instructions: 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, hx bariatric procedures (Roux-en-Y) or otherwise unable to tolerate PO. Can experience flu-like symptoms after infusion.
  - **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. Side effects: ↑risk endometrial ca (tamoxifen only), ↑risk DVT/PE, edema, hot flashes, muscle cramps
  - **Referral to Endocrine** for advanced therapies, refractory disease, severe osteoprosis (T score ≤-3.0 or ≤-2.5 with fragility fracture) or age< 50: **denosumab** (RANKL mAb; if discontinued should be started on antiresorptive, preferably a bisphosphonate) (NEJM 2009;361:756; JCEM 2020;106:264), teriparatide and abaloparatide (recombinant PTH and PTHrP analog, respectively) (Lancet 2018;391:230), romosozumab (sclerostin inhibitor)
- **Inpatient** following **fragility fracture**: assess need for surgical treatment and **consult Fracture Liaison Service (p25656).** Bisphosphonates decrease rate of new clinical fracture and mortality post-hip fx (NEJM 2007;357:1799)

**Monitoring**: variable recommendations; can repeat follow-up DXA hip/spine after 2 years; if stable, can space out scans

## VITAMIN D

**Definitions:** Measured by **25[OH]D (calcidiol)** in serum (JCEM 2019;104:234). No consensus cutoff but most groups use: Vit D Sufficiency: >20ng/mL; Insufficiency: 12-20ng/mL; Deficiency: <12ng/mL; Risk of toxicity >100ng/mL +↑Ca intake

**Diagnosis**:

- Population screening not recommended, only screen high-risk patients (Choosing Wisely; JCEM 2011;96:1911): Rickets, osteomalacia, osteoporosis, hyperPTH, inadequate PO, ↓ cutaneous synthesis (↓sunlight i.e., institutionalized or northern latitudes, sun pigmentation, aging), malabsorption (gastrectomy, IBD, CF, celiac, pancreatobiliary disease), ↓synthesis (ESLD, CKD), change in catabolism (AEDs, steroids, HAART, immunosuppressants)
- If deficient, obtain PTH, BMP/Phos, ALP, TTG. Consider if insufficient AND concern for secondary cause e.g., IBD

**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
  - <12ng/mL: 50,000IU weekly x6-8w followed by 800-1000IU qd; 12-20ng/mL: 800-1000 IU qd
  - Calcium citrate may be preferred if patient has constipation, is at risk of renal stones or is taking a PPI or H2 blocker.
- For patients ≥65y at high fall/fracture risk: Vit D ≥1000IU + Ca 1200mg qd from all sources with goal serum 25(OH)D >30ng/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 (poor conversion of 25(OH)D): calcitriol 0.25-1.0 µg qd
- Intermittent, high dosing of Vit D associated with increased falls in older adults and is generally avoided (JAMA 2010;303:18)

# Endocrinology Thyroid Disorders & Male Hypogonadism

## Inpatient TFTs

**Testing:** If thyroidal illness suspected, TSH alone is inadequate; should also test for FT4 & T3. TSH reflects changes within 4-6 wks. *Routine screening on admission not indicated*. Only send if related to CC or suspect thyroid disease (J Hosp Med 2020;15:560)
**Hyperthyroidism:** Undetectable TSH (<0.01)**, Hypothyroidism:** TSH >20 + low T4.
**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)

- Pattern: (1) acute illness: ↓↓↓T3, ↓T4, ↓/nl FT4, ↓/nl TSH. (2) recovery phase: ↑TSH → T4/T3 recovery, takes 2-4 weeks.
- 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.

**Pitfalls:** Heparin, lasix (>80mg/day), aspirin, NSAIDs, and phenytoin displace TH binding proteins and can distort free TH measurements (Best Practice & Research Clinical Endocrinology & Metabolism, 2013;27:745).

## Hypothyroidism (Endocrine Practice, 2012;18:988)

**Definition**: elevated TSH with low T4 (primary) or inappropriately low/normal TSH with low T4 (2°/central)
**Signs/symptoms**: general (fatigue, cold intolerance, constipation, dry skin, myalgias, weight gain), neuro (depression, cognitive dysfunction, 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

| | TSH | FT4 |
|---|---|---|
| **Primary** | ↑ | ↓ |
| **Central** | ↓/Normal | ↓ |
| **Subclinical** | ↑ | Normal |

**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 (Hashimoto's, granulomatous, postpartum), drugs (lithium, amio, ICIs, TKIs, contrast), iatrogenic (thyroidectomy, radiation), iodine deficiency
- **2°:** see *Pituitary Disorders*
- ↑ **T4 requirement**: pregnancy, estrogen (↑THBG), weight gain, malabsorptive (e.g., celiac disease), nephrotic syndrome (↑ excretion), rifampin, phenytoin, carbamazepine, phenobarbital

**Tx**: levothyroxine (T4) starting dose ~1.4mcg/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 calcium, aluminum hydroxide, iron, cholestyramine
- **Check TSH q4-6 weeks and adjust by 12-25mcg** until normal TSH. If pituitary insufficiency/2° hypothyroidism, track FT4s as TSH is not an accurate reflection of thyroid function. **Once on stable dose**, check TSH q6-12 months

| TSH | Age<65 | Age>65 |
|---|---|---|
| **5-6.9** | Consider RFs to guide tx | No tx |
| **7-9.9** | Tx | Tx only if sx |
| **≥10** | Tx | Tx |

**Subclinical hypothyroidism**: elevated TSH with normal FT4 (biochemical dx)

- Dx: can check anti-TPO Ab (if ⊕, monitor TFTs because at ↑ risk for Hashimoto's)
- Treatment: tx all patients with **TSH ≥10**. If TSH>7 and age<65 OR if age>65 and symptomatic, tx. If TSH 5-6.9, consider risk factors (e.g., CV disease, HLD) to guide tx. Lower doses are of levothyroxine are sufficient (25-75mcg) (Endocrine Practice, 2012;18:988)
- Elderly patients often have higher TSH levels, can be nl, tx if symptomatic.

## Myxedema Coma

**Definition**: Manifestation of severe hypothyroidism, **STAT endo consult**; mortality >30%, commonly 2/2 hypercarbic resp failure
**Precipitants**: infection, MI, cold exposure, surgery, sedative drugs (esp. opioids) in a poorly controlled hypothyroid patient. Most common in older women with hypothyroidism
**Signs/symptoms**: **AMS** (**lethargy**/obtundation, +/- 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, ↑TSH
**Treatment**: **do not wait for lab confirmation to start tx!**

- **Test and empirically treat adrenal insufficiency**: **hydrocortisone** 100mg q8h until AI ruled out. Give steroids **BEFORE T4** (if concomitant AI, replacing thyroid first will catabolize residual cortisol and cause HoTN/death). Draw serum cortisol prior to rx.
- **Levothyroxine (T4)** Loading dose 200-400 mcg IV followed by 50-100 mcg IV QD until able to take T4 orally. Favor low end of range if elderly or at risk of cardiac complications (MI, arrhythmia).
- **Liothyronine** (**T3)** Loading dose 5-20 mcg followed by 2.5-10 mcg q8h, given in rare cases as it is more arrhythmogenic and causes rebound hypermetabolism.
- Monitor FT4 and T3 Q1-2 days, avoiding very high T3 levels.
- Patients are **hypometabolic**: use lower drug doses at lower frequency, avoid mental status-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. Can occur at any time between administration to 18 months later.
**Amiodarone-induced hypothyroidism:** due to Wolff-Chaikoff or thyroiditis
**Amiodarone-induced hyperthyroidism**

- Type 1: ↑synthesis of T4/T3 d/t ↑iodine, usually seen in pts w/ latent Graves' or goiter and early after amio Rx. **Tx:** methimazole
- Type 2: direct toxicity of drug → thyroiditis; stored hormone release w/o synthesis. Seen late/after amiodarone Rx. **Tx:** 40-60 mg prednisone/day x 1-3mo followed by taper
- If unknown: tx with methimazole and prednisone. Rapid response → Type 2, taper methimazole. Poor response → Type 1, taper steroid
- Okay to continue amiodarone, esp. if Type 1 (amiodarone prevents T4 → T3 conversion)

# Endocrinology Thyroid Disorders & Male Hypogonadism

## HYPERTHYROIDISM (Thyroid 2016; 26:1343)

**Definition**: low TSH with high T3/T4 (primary) or high/normal TSH with high T3/T4 (secondary/central)
**Signs/symptoms**: general (↓weight, ↑appetite, heat intolerance, tremor, weakness), CV (palpitations, afib, systolic HTN), diarrhea, dyspnea, sweating, anxiety, emotional lability, urinary frequency, abnormal menses, osteoporosis

- Exam: goiter +/- thyroid bruit, lid lag, exophthalmos and pretibial myxedema (Graves' only), hyperreflexia and tremor
- Apathetic thyrotoxicosis: depression, weakness seen in elderly

**Labs**: ↑HDL, ↓LDL, normocytic anemia, ↑Ca, ↑AlkP, ↑Glu
**Workup**: 1) TSI and TBII (⊕ in Graves'), 2) RAIU (not for amio-induced or if recent IV contrast), 3) thyroid US w/ Doppler

| | TSH | FT4 | Total T3 |
|---|---|---|---|
| **Primary** | ↓ | ↑ | ↑ |
| **Central** | ↑/nl | ↑ | ↑ |
| **Subclinical** | ↓ | nl | nl |

**Causes**:

- **1°**: **Graves' disease** (most common, **positive TSI or TBII establishes diagnosis**), toxic adenoma (TA), toxic multinodular goiter (TMG), 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, though PTU preferred in 1st trimester of pregnancy), radioiodine (risk of ophthalmopathy), thyroidectomy (watch for hypoparathyroidism). Monitor total T3 and fT4 q6wks.
- If using thionamides: obtain baseline CBC w/ diff (10% of patients have neutropenia that resolves with tx (Clin Endo 2021;94:473)); *risk of agranulocytosis*: routine ANC monitoring not recommended but CBC w/ diff recommended at earliest sign of febrile illness + discontinue drug until result available
- Toxic adenoma or multinodular goiter: radioiodine, surgery, radiofrequency ablation, less commonly thionamides

## THYROID STORM (Thyroid 2016; 26:1343)

**Definition:** Extremely rare manifestation of thyrotoxicosis, **STAT endocrine consult**. Mortality rate 10-30%, 2/2 cardiovascular collapse
**Precipitants**: surgery (any), trauma, infection, iodine load (incl. amiodarone), irregular use/cessation of antithyroid drugs
**Signs/symptoms**: **AMS** (**agitation**, delirium, psychosis, coma), **hyperpyrexia**, **tachycardia**, atrial arrhythmias, CHF

- Exam: goiter, tremor, warm/moist skin, exophthalmos (Graves')

**Labs/dx**: ↑T4/T3, ↓TSH, Burch-Wartofsky Point Scale (BWPS) ≥ 45 highly suggestive
**Treatment**: Patients are hypermetabolic and will clear drugs quickly

- **Beta blocker**: e.g., **propranolol 60-80 mg PO Q4-6H** (only propranolol decreases T4→T3 conversion), doses up to 2g/d. Titrate to sx and HR (i.e., <80). Can also use esmolol gtt for rapid titration (esp. pts who may not tolerate propranolol, e.g., HF)
- **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→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 to prevent use as substrate for new hormone synthesis in TA/TMG; can cause Jod-Basedow (iodine-induced hyperthyroid) in toxic adenoma and Wolff-Chaikoff (iodine-induced hypothyroid) in Graves
- **Hydrocortisone** (100mg q8h) to reduce T4→T3 conversion
- **Cholestyramine** (4 g PO qid) to reduce enterohepatic recycling of thyroid hormone
- **Plasmapheresis** for those unable to take thionamides and urgently being prepared for thyroidectomy

## 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 (Low T, High FSH/LH): Klinefelter, cryptorchidism, testicular radiation, orchitis, myotonic dystrophy, HIV
- 2° causes (Low T, Low FSH/LH): hyperprolactinemia, obesity, Fe overload, opioids, glucocorticoids, androgens (e.g. supplementation), progestins, GnRH agonists
- 3° causes (rare): impaired GnRH signaling due to tumors, radiation to the brain, Kallmann, severe malnutrition.

**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, osteoporosis
**Diagnosis**:

- Measure 8am-10am fasting total testosterone x2 (nl total T range ~ 300-800)
  - Measure free testosterone only if c/f Δ in SHBG (obesity, nephrotic syndrome, steroids, HIV, cirrhosis, thyroid dz)
- 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 (see *Pituitary Disorders*); for 1° consider karyotype.

**Management**:

- **Testosterone therapy** is the mainstay of treatment to induce/maintain 2° sex characteristics and address symptoms
  - Formulations: intramuscular (weekly, q2w, and monthly), transdermal gel, patches, tablets
  - SE: site reactions, acne, oiliness of skin, no large RCT to study cardiovascular risk/MACE or VTE
  - Contraindications: prostate ca, breast ca, erythrocytosis, severe BPH, untreated OSA, severe LUTS, planning fertility

**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, re-initiate 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 (NEJM 2023)

# Allergy & Immunology — Common Allergy Problems

| Diagnosis | Symptoms | Work-Up | Treatment |
|---|---|---|---|
| **Rhinitis**:<br>- Allergic<br>- NARES<br>- Vasomotor<br>- Atrophic | IgE mediated/histamine induced nasal congestion, rhinorrhea (anterior/posterior), sneezing, and itching in response to an inhaled allergen<br>- Intermittent: <4 days/week or <4 consecutive weeks/year<br>- Persistent: ≥4 days/week and ≥ 4 consecutive weeks/year | Usually not needed, though skin allergen testing can be helpful | Allergen avoidance<br>Pharmacotherapy:<br>- Intranasal corticosteroids: fluticasone<br>- Oral Antihistamines: cetirizine, fexofenadine<br>- Intranasal antihistamines<br>JACI 2020; 146:721 |
| **Allergic Conjunctivitis** | Exposure to allergens → b/l ocular itching, redness, swelling, & clear watery discharge<br>- Acute: sxs develop in <30m and resolve w/in 24h<br>- Seasonal: days/weeks; corresponding to various pollen seasons & assoc. w/ rhinitis<br>- Perennial: mild, waxing/waning course related to year-round indoor allergens | | Allergen avoidance & rhinitis treatment if systemic sxs<br>Pharmacotherapy:<br>- OTC olopatadine (0.1 and 0.2%) 1 drop/eye BID (0.7% 1 drop/eye daily)<br>- OTC alcaftadine (0.25%) 1 drop/eye daily<br>- can also use OTC Visine short term iso rebound hyperemia<br>Ophthal. 2024;131(4):P134-P204 |
| **Chronic Urticaria** | Spontaneous appearance of wheals, angioedema, or both for >6 weeks | CBC, ESR, CRP, TPO IgG, IgE | Step wise approach:<br>- 2nd generation antihistamine<br>- increase dose of 2nd gen antihistamine<br>- Antihistamine + omalizumab (Xolair)<br>- Antihistamine + omalizumab (Xolair) + cyclosporine<br>JACI 2022; 150:1249 |
| **Atopic Dermatitis** | Intermittent flares of scaly, pruritic, red, inflammatory rash on flexural surfaces, driven by impaired skin barrier and inappropriate immune response to allergens, infections, and stress<br><br>Often associated with allergic rhinitis and asthma | Clinical diagnosis that **must** include:<br>- Chronic /relapsing history<br>- Pruritis<br>- Typical rash morphology (flexural surfaces in adults with axillary and groin sparing)<br>Clinical features supporting dx:<br>- Atopy<br>- Early age at onset<br>- IgE reactivity<br>- Xerosis | Treatment depends on severity<br>- Scored using SCORAD calculator<br>All patients should use emollients at least 2x/day and after warm (not hot) showers or handwashing as maintenance therapy.<br>- Mild: maintenance therapy + low to medium potency topical steroids BID for 2-4 weeks<br>- Moderate: mild therapy + BID topical calcineurin inhibitor +/- crisaborole +/- twice weekly dilute bleach baths, +/- wet wrap therapy<br>- Severe: moderate therapy + systemic biologics and specialty referral<br>AAFP 2020; 101(10):590-598 |
| **Oral Allergy Syndrome** | Itching, burning, and swelling of lips, mouth, and tongue after ingestion of certain fruits, vegetables, +/- nuts<br>- Typically resolve after a few minutes<br>Caused by cross-reaction to certain proteins found in pollens | Skin testing<br>Clinical symptoms | Avoidance to foods that lead to reaction - cooking the food often improves the symptoms<br>Systemic reactions are rare<br>JACI 2024; 12 (3); 599-604 |
| **Food Allergy** | IgE mediated reactions **are rapid onset** and present with urticaria/angioedema, lower respiratory tract symptoms, nausea, abdominal pain/cramping, vomiting, diarrhea<br>See *Anaphylaxis* | Clinical hx and tempo of symptoms<br>Skin testing has good NPV, but not good specificity | - Avoid causal foods<br>- Oral immunotherapy if age appropriate<br>- Referral for biologics (omalizumab, dupilumab)<br>ANAI 2023; 131(1); 29-36 |
| **Stinging Insect Reactions** | Reaction most often to venom of insects in *Hymenoptera* order (bees, wasps, hornets)<br>- Local: pain, redness, swelling confined to tissues contiguous w/ sting site. Large local rxn are often >10cm. Can last from 3-10d<br>- Systemic cutaneious: widespread pruritus, erythema, urticaria, and/or angioedema & involves skin that is NOT contiguous w/ sting site<br>- *Anaphylaxis* | Clinical hx of sting that led to systemic allergic reaction (systemic cutaneous and anaphylaxis)<br>+ skin testing to venom specific IgE | - Removal of stinger<br>- for local rxns: NSAIDs, cetirizine, & hydrocortisone 0.1% cream<br>- if anaphylaxis → 0.3-0.5 mg IM epinephrine. Can repeat q5-15 min PRN<br>- Referral for venom immunotherapy if anaphylaxis<br>JACI 2025;13(1):61-65 |

# Allergy & Immunology — Angioedema & Anaphylaxis

## ANGIOEDEMA (Allergy 2014;69(5):602) | (Int J EM 2017)

- **Definition**: localized non-pitting swelling of skin or mucosal tissue due to interstitial edema; Usually affects areas of loose connective tissue including face, throat, lips, extremities, genitals, bowels. Often asymmetric. Occurs in min-hrs after exposure and resolves within 1-3d. **Common triggers**: food, insect bites, drugs, temp, delayed pressure, solar, vibratory, cholinergic, contact, and aquagenic

| Type | Symptoms | Triggers |
|---|---|---|
| **Histamine (mast cell mediated)** | Localized swelling<br>**Urticaria/pruritis**<br>Bronchospasm<br>+/- hypotension | Common allergens, ASA, NSAIDs, CCB, opioids, contrast dye, tPA, platinum-based chemo, β-lactams, metoprolol, sirolimus/everolimus, risperidone, idiopathic/spontaneous |
| **Bradykinin** | Localized swelling w/in 24-36h exposure<br>Abd cramping/pain (typically without emesis)<br>**NO urticaria**<br>Usually longer w/ worse symptoms | **ACEi**: 0.1-0.7% pts; may occur any time during treatment and recur 4-6 wks after cessation. Consider also in ARBs, DPP-4 inhibitors.<br>**C1 inhibitor deficiency:** Either due to AD inheritance (present at early age) or acquired (usually lymphoproliferative disorder). Screen: ↓C4, normal C3.<br>**Hereditary Angioedema:** begins in childhood, worsens in puberty (estrogen), stress. Prodromal sxs include erythema marginatum (Allergy 2022;77(7):1961)<br>**TPA mediated angioedema**: tPA activates complement system and leads to ↑ histamine release and ↑ bradykinin levels. |

- **Work up:** CBC w diff, BMP, LFTs, CRP, ESR, C4 level, C1 inhibitor level, C1 inhibitor function, & tryptase (see below)
- **Treatment**: in ALL patients **ABCs: secure airway**; involve ENT for awake **nasotracheal** intubation
  - **If urticaria, multisystem involvement, or underlying illness/infection**: remove exposure → treat like anaphylaxis (see below)
  - **If no urticaria/pruritis**: **1 gram TXA** (bradykinin-mediated angioedema does not respond to epinephrine or steroids)**:**
    - On ACEi**:** stop ACEi, add to allergy list → supportive care (if severe, consider treating similar to HAE [mixed evidence])
    - Known hereditary or acquired angioedema**:** page Allergy for C1-inhibitor (ecallantide, **icatibant)**. **FFP** 2nd line.
    - Not on ACEi; no known disorder**:** H1 antihistamines + methylpred → PO pred (5-7 d taper) + H1 antihistamine
- **Follow-up**: Place Allergy/Immunology referral on discharge; long preventive therapy for HAE: lanadelumab (kallikrein inhib)

## ANAPHYLAXIS (AAAI 2023,132(2):124-176) | Anaphylaxis Treatment Protocol

| 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 |
| | Non-IgE mediated | NSAIDs, HMW dextrans, 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 |

- Anaphylaxis is a life-threatening systemic allergic reaction that includes a range of clinical **s/sxs including**: (1) Cutaneous = angioedema, urticaria, flushing, pruritis; (2) Respiratory = dyspnea, wheeze, upper airway angioedema, rhinitis; (3) GI = nausea, vomiting (most common), diarrhea; (4) Cardiovascular = hypotension**. Can have biphasic reaction**: resolution w/ return of symptoms 1-72h (usually <12) after initial symptom resolution despite no further exposure to trigger (4-20% pts)
- **Diagnostic criteria**: **1 of 3** must be met*
  1) Acute onset (min-hr) of **skin ± mucosal** involvement AND either **respiratory sx** *OR* **hypotension (age appropriate)**
  2) Two or more of the following after exposure to **LIKELY allergen**: skin/mucosa swelling, respiratory sx, HoTN, persistent GI sx
  3) **Low BP** (SBP<90 or >30% drop from baseline) after exposure to **KNOWN allergen** for patient

**There are multiple definitions of anaphylaxis that lead to diagnostic uncertainty. General consensus found in Fig 2 of AAAI 2023,132(2):124-176.*

- **Labs**: **tryptase** (within 15min-3h of symptom onset & 24h after sx resolve to establish baseline). Values ≥1.2x baseline + 2ng/dL = mast cell activation. Normal levels do not rule out anaphylaxis (normal in 37%). Consider plasma histamine (peaks in 5-15 min).
- **Treatment**: **Establish and maintain airway**, administer oxygen/IVF (1-2L) and lie pt flat/Tberg for hypotension, remove trigger (consider all clothing). **Epinephrine**: **1st line**. **(1mg/mL) 0.3-0.5mg IM** in mid/outer thigh**.** ONLY medication that *reverses* airflow obstruction & prevents cardiovascular collapse. May repeat **q5-15min**; if >3 doses required, consider epi gtt (1-10mcg/min). If on beta blockers AND resistant to epinephrine → glucagon (1-5mg bolus → gtt @ 5-15mcg/min)
  - Adjunctive agents: **Albuterol** (stacked nebs x 3) PRN wheezing/cough/SOB; **H1 antihistamines**: Benadryl 25-50mg or fexofenadine 360 mg PRN for pruritis/urticaria. *Does NOT treat airway obstruction/hypotension!* **H2 antihistamines**: famotidine 20mg IV or PO; **Methylpred. IV or IM:** 40mg if weight <120kg, 80mg if weight >= 120 kg. No evidence to prevent biphasic rxn. May be beneficial if (1) severe sx requiring hospitalization (2) known asthma (3) significant/persistent bronchospasm.
- **Monitoring:** Should be observed until complete sx resolution. ~5% of pts have biphasic reaction, those at ↑ risk p/w hypotension, severe presentation, or require 2 or more IM epi injections. Hospitalize pts with severe anaphylaxis. Admit to ICU if on epi drip.
- **Make sure to discharge home with EpiPen (at least one in hand, or Rx for two) & refer to Allergy**
- If h/o anaphylaxis to stinging insect, refer for skin testing. If +, consider SQ venom immunotherapy, which ↓ risk of subsequent anaphylaxis from 50-60% to 2-3% (NNT = 2) (NEJM 2014;370:1432)

# Allergy & Immunology — Drug & Contrast Allergy

## ADVERSE DRUG REACTIONS (ADRs) (Allergy 2019; 74: 1457)

**KEY History:** Drug, date, dose, route, doses/days into course, co-administered meds, coinciding infections, sx, severity (home, office, ED, hospital, or ICU), treatment given, exposures since
**Document appropriately in EPIC allergy section. Include rxn, date, intolerance vs reaction, other meds tolerated**

ADRs defined by WHO as any noxious/unintended/undesired drug effect that occurs at doses used for prevention, diagnosis, or treatment.

- **Type A =** predictable (85-90%): dose-dependent reactions related to a 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 (10-15%): dose-independent, unrelated to pharm action, occurs only in susceptible pts
  - **Drug intolerance**: undesirable effect that occurs at low and sometimes subtherapeutic doses w/o abnormalities of metabolism/excretion/bioavailability (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): direct release of mediators from mast cells and basophils rather than IgE antibodies (e.g., flushing during vancomycin infusion, exacerbation of asthma/rhinitis w/ aspirin in AERD, opiate pruritis)
  - **Drug allergy** (5-10% of all ADRs): immunologically-mediated hypersensitivity reactions, including IgE mediated

## HYPERSENSITIVITY REACTIONS (Gell and Coombs Classification) (Allergy 2023;78(11):2851)

| Type | Reaction | Mechanism | Presentations | Timing |
|---|---|---|---|---|
| I | IgE-mediated | Ig-E mediated degranulation of mast cells due to antigen binding and cross-linking of IgE<br>Anaphylaxis Pathway | Anaphylaxis, allergic rhinitis, allergic asthma, urticaria, angioedema, hypotension | Min-hrs (usually 1 hour) |
| II | Antibody | IgM/IgG antigen interactions on target cell surfaces | Drug-induced cytopenia | Varies |
| III | Immune-complex | Immune complex formation & deposition in tissues → complement activation → local/systemic inflammation | Serum sickness, vasculitis, drug induced lupus | 1-3 wks |
| IV | Cell-mediated, delayed | Ag activates T cells → Ag later binds to activated T cells → cytokine release → macrophage & cytotoxic T cell accumulation | Contact dermatitis, SJS/TEN, DRESS, AGEP | Days to weeks |

## CLINICAL MANIFESTATIONS OF DRUG ALLERGY (AACI 2018;14:60)

| Organ | 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* | | |
| Blood | Hemolytic anemia, thrombocytopenia, leukopenia | | Varies, but in general:<br>-Hemolytic anemia: acute<br>-Drug-induced TMA: acute or subacute | PCN, sulfa drugs, AEDs, cephalosporins, quinine, heparin, thiazides |
| Liver | Hepatitis, cholestatic jaundice | | Varies, can be acute or chronic | Sulfonamides, phenothiazines, anti-TB drugs, carbamazepine, erythromycin, allopurinol |
| Kidney | Interstitial nephritis, glomerulonephritis | | Varies, days to months | PCNs, sulfonamides, allopurinol, PPIs, ACEi, NSAIDs |
| Multi-organ | Anaphylaxis | Urticaria, angioedema, bronchospasm, GI, hypotension | Immediate (usually within 1 hr) | Abx, NM blockers, anesthetics, contrast, recombinant proteins (e.g., omalizumab) |
| | DRESS | Rash, fever, eos, hepatic dysfunction, LAD | 2-8 weeks | AEDs, sulfa drugs, minocycline, allopurinol, mAB (monoclonal Ab) |
| | Drug induced lupus erythematosus | Arthralgias, myalgias, fever, malaise | Months to years | Hydralazine, procainamide, INH, quinidine, minocycline, abx, anti-TNF |
| | Serum sickness | Arthralgias, urticaria, fever | 1-2 weeks | Heterologous Ab, infliximab, mAbs, allopurinol, thiazides, abx, bupropion |
| | Vasculitis | Cutaneous or visceral vasculitis | 1-3 weeks | Sulfa abx and diuretics, mAbs, hydralazine, levamisole, PTU |

# Allergy & Immunology — Drug & Contrast Allergy

## DIAGNOSIS (JACI 2022;150(6):1333)

- **Labs** (sometimes helpful): CBC w/ diff (eos), LFTs, Cr, 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 ¼ of rx dose for oral meds)
  - If **no reaction**: 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 ⊕ **reaction**: Anaphylaxis pathway: Epi 1:1000 IM (0.3 mg), Benadryl 50mg IV/PO, page allergy fellow, & complete a Medication Safety Report.

## DRUG DESENSITIZATION (JACI 2010;125:S126) | Ellucid-Drug Desensitization and Test Dose Administration

- **Indications**: ⊕skin test, ⊕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., chemo, aspirin)
- **If patient discontinues medication**: procedure must be performed again if pt stops medication for >2-3 half-lives

## PENICILLIN & CEPHALOSPORIN ALLERGY | Handbook-Penicillin and Cephalosporin Hypersensitivity Pathway

- 10% of pts report a PCN allergy, but **90%** of patients with a h/o PCN allergy can tolerate PCN (JACI 2010;125:S126)
- 80% of pts with IgE-mediated allergy to penicillin will lose their penicillin sensitivity over 10-year period (AAAI 2019; 321:188)
- Patients with 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)
- Allergic determinants of cephalosporins can be derived from the **beta-lactam structure**, but in later (3rd/4th gen) cephalosporins, they are most commonly derived from the R-group.
- Refer for outpt PCN skin testing if (Allergy Referral): unclear reaction and likely requirement for that drug in the future
- See Penicillin Cephalosporin Hypersensitivity Pathway for guidance on inpatient test dose procedure in pts reporting PCN allergy

## OTHER COMMON DRUG ALLERGIES

- **Taxanes/platinum-based Chemotherapy**: differentiate *infusion reaction* (SIRS response) from anaphylaxis (type I HSR). Platinum agents assoc with IgE HSR. Taxanes generally non-IgE mediated, premed usually effective (AAAAI 2009;102:179)
- **Allopurinol hypersensitivity syndrome**: rash, fever, hepatitis, AKI usually within 4-8 wks. Testing for *HLA-B5801* in pts at ↑ risk (patients of Southeast Asian descent and African American) recommended prior to starting (ACR Guideline 2020)
- **Aspirin/NSAIDs** (JACI 2021;148:283): 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 (ie aspirin for ACS), 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**: Avoidance of NSAIDs, desensitization and daily uninterrupted therapy, leukotriene-modifying drugs, or biologics (omalizumab, mepolizumab, dupilumab) (JACI 2021; 148:283)

## IV CONTRAST MEDIA (ACR Guidelines 2024) | Ellucid -Allergy Premedication | *See Contrast* for details on contrast reactions

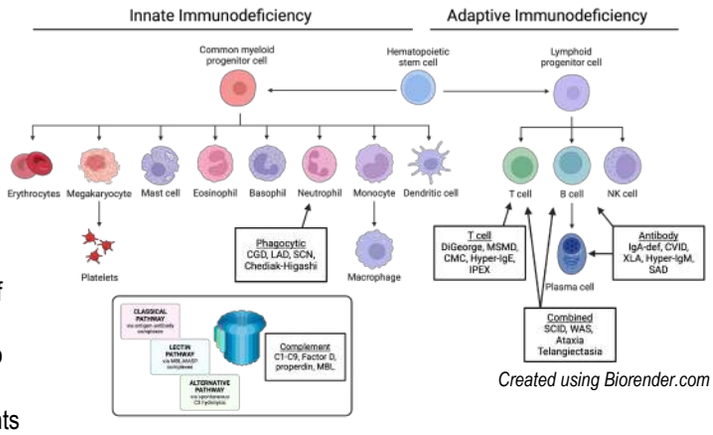
| Type/Path | Epidemiology | Presentation | Clinical pearls | Pre-Treatment (MGH protocol) |
|---|---|---|---|---|
| **Pseudoallergic**<br>Direct stimulation of mast cells / basophils | Mild rxn: 0.6% pts<br><br>Severe rxn: 0.04% pts | Immediate pruritus, urticaria, angioedema, airway obstruction, HoTN, abd pain.<br>Called pseudoallergic bc not immune rxn -can still cause danger. | **Seafood allergy is NOT** a contraindication.<br>**Oral contrast is NOT** contraindicated in a patient with IV contrast allergy, very rare pseudoallergic reactions. | ***Elective*** (13h protocol)<br>Prednisone 50mg PO at 13, 7, & 1h prior AND Benadryl 50mg PO 1h prior<br>***Urgent*** (4-5h)<br>Methylprednisolone 40mg IV now & q4h until scan AND Benadryl 50mg IV 1h prior<br>***Emergent (no data)*** (1h)<br>Methylpred 40mg IV AND Benadryl 50mg IV @ 1h prior |
| **Delayed**<br>T cell-mediated | 0.5-14% of patients | >1h - 1 wk. Usually mild, skin eruption. Can be more severe | **Tx**: Supportive care | Unknown efficacy to steroid/antihistamine ppx. Not specifically advocated |

# Allergy & Immunology — Primary Immunodeficiency

## Primary Immunodeficiency Disorders (JACI 2015 ;136(5):1186)

Definition: inherited deficits of immune system → ↑ incidence/severity/frequency of infections.
Prevalence: 1/1200-2000 pts
Warning signs in adults: 1) ≥4 infxn requiring antibiotics/y (ear, sinusitis, bronchitis, PNA), 2) infxn not responsive to antibiotics, 3) ≥2 severe infxn (osteo, septic arthritis, meningitis, sepsis), 4) ≥2 PNA w/in 3y, 5) chronic diarrhea, 6) recurrent deep abscesses, 7) persistent fungal infxn, 8) persistent thrush, 8) infnx w/ benign mycobacteria, 9) relevant Fam Hx
H&P: developmental hx, fam hx, age at onset, frequency & type of infections, syndromic features, autoimmune disease

- Most severe forms are on MA newborn screen; mild forms go undetected into adulthood (e.g. antibody def)



*Created using Biorender.com*

Rule out 2° causes of immunodeficiency: HIV, immunosuppressants (rituximab and other mAbs, chronic glucocorticoid use), malignancy, radiation, cirrhosis, diabetes, nephrotic syndrome, SLE, RA, asplenia
General principles of management: vaccination, abx ppx, ↑risk of malignancy, immunoglobulin replacement, HSCT

| | Disorder | Presentation | Infectious Organisms | Testing (JACI 2022 42: 1508-1520) |
|---|---|---|---|---|
| INNATE | **Complement** (5%) | Any age<br>- Sinusitis, PNA, meningitis (recurrent nisserial infections) → think late complement def (C5-C8)<br>- Lupus-like syndrome → early complement def C1/C1s/C2/C4a/b<br>- Rheumatoid disorders<br>- Atypical AUS<br>- Protein losing enteropathy | Bacteria: encapsulated esp. Neisseria, gonococcal infections | Complement levels:<br>C1q, C1s, C2, C3, C4, Factor H, Factor I, Thrombomodulin, CD46, C1 inhibitor, CD59, CD55<br>CH50+AH50 (alt pathway) |
| INNATE | **Phagocyte abnormalities** (10%) | Infancy/childhood<br>- Oral, lymphadenitis, skin and soft tissue, liver, lung, bone, anorectal<br>- Unusually severe infections<br>- Granulomas, poor wound healing | Bacteria: S aureus, PsA, Serratia, Klebsiella, non-TB mycobacteria, nocardia<br>Fungi: Candida, Aspergillus | ANC (↓SCN, ↑LAD), ELANE gene in SCN, Oxidative burst via DHR/NBT test for CGD, Other tests to order for: SCN gene abnormalities, WAS, CSF3R, MKL1, G6PD, GATA2, CYBB, NCF1,<br>*On outpt Invitae genetic panel |
| ADAPTIVE | **T cell subset defects** (5%) | Infancy<br>- Oral thrush<br>- Diarrhea (enteropathy)<br>- Respiratory Infections<br>- ILD<br>- pancytopenia | Bacteria: Mycobacteria<br>Viruses: CMV, adenovirus<br>Fungi: Candida, PJP | Flow cytometry<br>Anergy/proliferation tests<br>STAT1, AIRE if chronic mucocutaneous candidiasis or APECED, FOXP3 (IPEX), IL2RA, CTLA4 |
| ADAPTIVE | **B cell / Antibody** (65%) | >6 mos, can present in adulthood<br>- Recurrent sinusitis, otitis media, PNA, bronchiectasis<br>- Chronic GI malabsorption, diarrhea<br>- Autoimmune disease (29% in CVID) (Blood 2012;119:1650)<br>- Anaphylaxis to blood products (IgA deficiency) | Bacteria: H flu, Strep, Staph, Moraxella cat, PsA, mycoplasma pneumoniae<br>Virus: Enterovirus (esp. with IgA deficiency)<br>Parasites: Giardia | SPEP (IgG, IgA, IgM), IgG subclasses, flow cytometry<br>**Vaccine response**<br>Polysaccharide PPSV23 titers:<br>≥70% of serotypes ≥1.3 = adequate. If not, give PPSV23 & repeat titers in 4-6 wks<br>Protein: tetanus, diphtheria IgG<br>Conjugated: Hib IgG |
| ADAPTIVE | **Combined B & T cell** (15%) | <6 mos old, FTT<br>- Oral thrush, viral infections<br>- Chronic diarrhea<br>- Absent thymus<br>- Active disease to live vaccines<br>- Autoimmune cytopenias | Bacteria: Salmonella, Listeria, non-TB mycobacteria<br>Viruses: CMV, EBV, VZV<br>Fungi: Candida, Aspergillus, cryptococcus, histoplasmosis<br>Parasites: PJP, toxo, Cryptosporidium | B Cell Enumeration (CMF)<br>As above for B & T cell deficiencies<br>Adenosine deaminase deficiency<br>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
- **Replaces antibodies** and is **anti-inflammatory** through multiple mechanisms.
- Starting doses: 400-800 mg/kg q3-4 wks for trough level >500-600 mg/dL (higher in pregnancy & bronchiectasis)
- Consider HBV serologies prior to IVIG: can't check for 3-4mo after IVIG. If patient already got IVIG, consider HBV PCR
- **IVIG in infection** depends on host & infection. If CVID w/ infection, can check IgG levels. Beneficial in CMV pneumonitis in solid organ tx recipients, rotaviral enterocolitis & bacterial infections in lymphoproliferative dz (e.g., CLL)

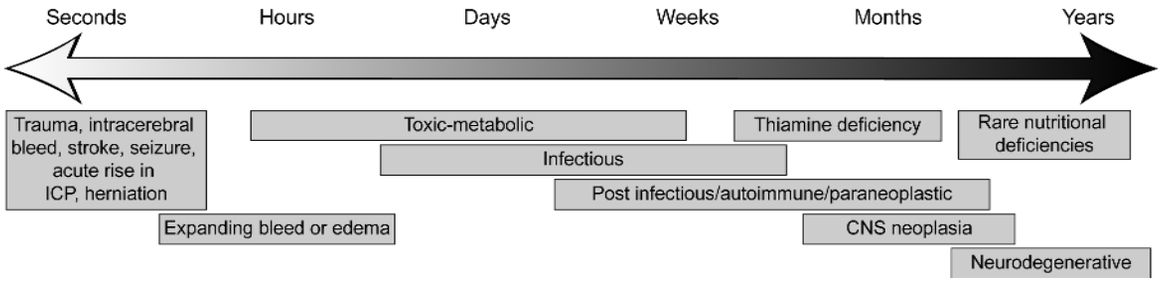
## Therapeutic Use of Vaccines in Patients with PID (JACI 2018;141:474)

- **ALL** patients with PID can receive **INACTIVATED** vaccines according to routine schedule. Prioritize flu, HPV, PNA. 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.

# Neurology — Altered Mental Status

## CAUSES OF AMS

**AMS is an umbrella term** for (1) altered level of arousal (i.e. awake at rest to coma), (2) altered level of attention and/or (3) altered content of consciousness (i.e. confused, disoriented, agitated, awake but hypoactive).This is opposed to **delirium** which is a syndrome of fluctuating inattentiveness presenting due to 1° neurological disorders, medical diseases and environmental factors such as hospitalization, disruption of sleep-wake cycle and pain. Duration of various etiologies listed in graphic below.
**Major categories**: (1) 1° neuro. disorder (2) or *medical* condition: (metabolic, infection/sepsis, drug/toxin, pain, constipation/urinary reten.)
**AEIOU TIPS**: **A**lcohol (intox, HE, withdrawal/DTs, Wernicke's*)/**A**rrythmia, **E**lectrolyte (↑/↓ Na, Ca, Mg, K)/**E**ndocrine (glucose, pituitary, thyroid, parathyroid, adrenal), **I**nfection (sepsis vs 1° CNS: encephalitis, meningitis, abscess), **O**xygen (hypoxia, hypercarbia)/**O**verdose (opiate), **U**remia/**U**rine retention, **T**rauma/**T**umor/**T**TP/**T**emp, **I**atrogenic (see MAR below), **P**sych/**P**oison**, S**eizure (+post-ictal) /**S**troke/**S**yncope. **note: Wernicke's rarely presents with full diagnostic triad, if suspicious→ high dose Thiamine*




## APPROACH TO ACUTE AMS

**ABCs & vitals**: call **Rapid Response** if appropriate (+/- **RICU** if concern for airway, +/- **Code Stroke** if focal exam change w/ last known well or last *seen* well <24h or high risk for head bleed/clot)

- **Hx**: baseline functional status, **last known well**, time course, previous AMS, recent clinical events, past medical history (i.e. neurogenerative disease/dementia, hx CVA, seizure disorder, cranial mets), use of antipsychotics/AC (and time of last dose given).
  - **MAR**: (stopped/started, withdrawal/overdose) insulin, benzo, opioid, steroid, anticholinergic, antihistamine, antiHTN, AED, anti/dopaminergic, digoxin, Li, ASA, OTCs, MSK relaxers, abx (Beta-lactams > FQs, sulfonamides, macrolides) (Scientific Reports 2024;14:8747). Consider: *Catatonia, NMS, & Serotonin Syndrome*
- **Neuro Exam**: Start with level of arousal, avoid "stuporous, lethargic"; *describe* what you're seeing: i.e. "asleep but able to wake up after calling name or sternal rub." If not arousable, proceed with coma exam (below). If arousable, test level of attention (DOW backwards, backward digit span etc). If attentive, proceed with detailed neurological exam. If not, perform neuro exam that does not rely on patient contribution.
  - Coma exam: pupils, corneal, vestibulo-ocular reflex, facial symmetry, cough/gag, limb movements (spontaneous vs response to nox stim: localizing to pain vs voluntary complex withdrawal vs reflexive stereotypical withdrawal vs triple flexion vs mute, pay attention to symmetry between R and L) (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 **toxidromes, incontinence/tongue laceration** (seizure)

| NEUROLOGIC EXAMINATION | | |
|---|---|---|
| **Arousal/Mentation** | **Brainstem Functions** | **Motor/Sensory** |
| Arousal level ("what you see"): "AVPU scale"<br>1) Alert<br>2) Verbal stimuli<br>3) Painful stimuli<br>4) Unresponsive<br>Orientation<br>Attention (days of week/months of the year backwards, serial 7s)<br>Language: comprehension, fluency, repetition, naming | Pupils (CN 2→3):<br>- Absent light reflex (upper brainstem injury, excessive sedation)<br>- Bilateral fixed, dilated (upper brainstem injury/compression)<br>- Unilateral fixed, dilated (herniation w/ CN III compression)<br>- Pinpoint (opioids, pontine injury)<br>Blink to threat (CN2/7) or visual field testing if able (CN 2)<br>Corneal reflexes (CN 5→7): absent (upper brainstem injury, deep sedation), normal, or forceful closure<br>Extraocular eye movements (CN 3/4/6):<br>- Conjugate lateral deviation (destructive or irritative lesions)<br>- Vertical disconjugate ("skew deviation"; structural)<br>- Roving eyes (esp. if conjugate suggests metabolic cause)<br>Facial symmetry (CN 7): test at rest and on activation (smile)<br>Vestibulo-ocular reflexes (CN 8→6→3 for horizontal VORs): eye mvmnt w/ horizontal head turn<br>Cough/gag (CN 9/10): q-tip to the back of throat for gag; if intubated, suction for cough | Motor: asterixis? (aka negative myoclonus?) Response to noxious stimuli (nares/sternal rub/extremities) (localizing > withdrawal (voluntary vs reflexive > extension > none)if mental status allows (i.e. awake/alert/full effort), perform confrontational testing<br><br>Sensory: compare sensation to light touch |

- **If arousal impaired → emergent w/u; if attention impaired but arousal intact → same w/u, but non-emergent**:
  - **Workup:** FSBG, CBC/diff, BMP, LFTs, TFTs, INR, lactate, VBG, UA, EKG, CXR, bladder scan, B1, B12, TSH
  - Based on initial assessment: ± cultures, toxicology, drug levels, cortisol, CK, CTH ± CTA head/neck, MRI, EEG, LP etc.

## APPROACH TO SUBACUTE AMS: consider Neurology consult prior to further extensive work-up

- Hx/Exam as above. **DDx** also includes: infection (HIV, Lyme, syphilis), autoimmune (paraneoplastic/anti-NMDA, sarcoid, CAPS/SLE, Sjogren's, ADEM, autoimmune limbic encephalitis, vasculitis), metabolic (thyroid, B1, B3, B12, Wilson's), medications, toxidromes, HTN encephalopathy, hepatic encephalopathy, PRES (tacro/cyclosporine), adrenal insufficiency/Cushing's, porphyria (urine PBG)
- **Helpful diagnostic tests**: rEEG: for non-convulsive status epilepticus (NCSE); LTM: for intermittent seizures. MRI with contrast: for stroke, malignancy, infxn/inflammatory process, Wernicke's. Lumbar puncture:(CTH to r/o herniation first): see *Lumbar Puncture*, discuss advanced testing with Neurology

## TREATMENT OF AMS: **diagnose and treat underlying cause**; see disease-specific pages.

# Neurology — Dementia

**INITIAL EVALUATION: should almost always be in the outpatient setting,** can assess over time without acute illness or delirium

**Dementia** (chronic cognitive impairment) w/u is an outpatient task and should NOT be performed while inpatient, as concurrent medical issues might confound the cognitive assessment. Inpatient eval considered for 1) any rapidly progressing dementia syndrome, or 2) new dementia diagnosis in pts <55yo or with new focal deficit (eval stroke)

- 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 screen, syphilis, Lyme, HIV, UA, metals, ESR, LFT, folate, B1 (AFP 2005;71:1745)
- Imaging: NCHCT or **MRI brain (preferred)** to r/o structural lesion (tumor), assess **atrophy pattern** and vascular dementia
- **Outpt 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)

****Clinical phenotypes often overlap and may require years to differentiate****

| Syndrome | Presentation | Exam | Imaging | Treatment |
|---|---|---|---|---|
| **Gradually Progressive** | | | | |
| Alzheimer Dementia (60-80%, mild cognitive impairment (MCI) as precursor) | • **Short term memory loss early;** language & visuospatial deficits<br>• Apraxia in later stages | • Nml neuro exam (excluding mental status)<br>• Neuropsych: amnesia w/ short memory span, alexia, agraphia | Hippocampal (± global) atrophy; ventriculomegaly, ?microhemorrhages (cerebral amyloid angiopathy (CAA)) | • AChE-inhibitors (mild-severe dz)<br>• NMDA-inhibitors (mod-severe dz)<br>• Anti-amyloid abs |
| Lewy Body and Parkinson's Dementia | • **Fluctuations** in attention/alertness<br>• **Visual hallucinations (LBD)**<br>• **REM behavior disorder**<br>• Falls/syncope<br>• Neuroleptic intolerance<br>• Memory problems late | • Parkinsonism: resting tremor (can be absent), cogwheel rigidity, bradykinesia, stooped/shuffling gait<br>• Parkinson's dementia if motor sx >1y before dementia<br>• Neuropsych: fluctuations w/ intrusions and confabulation, visuospatial impairment | Global volume loss | • AChE-inhibitors (esp. rivastigmine) for memory sx<br>• Carbidopa/levodopa trial for motor sx<br>• Sx management of **autonomic dysfxn**<br>• Avoid typical antipsychotics |
| Frontotemporal Dementia | ***Behavioral type***<br>• Personality Δ (disinhib., apathy, poor insight)<br>• Stereotyped behaviors<br>**1° prog aphasia type**<br>• Dysnomia, dysfluency, poor comprehension | • May have **frontal release signs** (non-specific)<br>• 15-20% get motor neuron dz<br>• Neuropsych testing: poor impulse control, difficulty in organization | Atrophy predominantly in **frontal and temporal lobes** | • Management of behavioral sx (consult psych)<br>• AChE-inhibitors not helpful<br>• **Avoid** NMDA-inhibitors |
| **Stepwise Progressive** | | | | |
| Vascular Dementia | • **Abrupt focal sx, stepwise progression**<br>• Depression common<br>• Hx: CVA, HTN, HLD, AF | • Focal deficits (depend on stroke location), can include: weakness, dysarthria, ataxia, gait changes | Cortical or subcortical **punctate lesions, white matter disease**, and **volume-loss** | • 2° stroke prevention and RF modification<br>• AChE-inhibitor for memory deficits |
| **Rapidly Progressive** (Ann Neurol 2008;64:97) | | | | |
| Prion Diseases (Sporadic, Variant Creutzfeldt-Jacob Disease) | • **Rapidly progressive** sx in memory, concentration, judgment<br>• Mean onset age ~60 for sporadic, 28 for variant<br>• Younger→ ↑psych sx | • **Myoclonus, exaggerated startle response**<br>• EPS (bradykinesia, nystagmus, ataxia), UMN (hyperreflexia, Babinski, spasticity)<br>• **LP: RT-QuIC>>14-3-3** | **MRI: cortical ribboning and BG** diffusion rest, subcortical hyperintensity on FLAIR<br>**EEG**: 1-Hz periodic epileptiform discharges | • No tx<br>• Death w/in 1y (median disease duration 6mo) |
| Limbic Encephalitis (Autoimmune, Paraneoplastic) | • Sx evolve days-weeks (more indolent possible)<br>• **Short-term memory sx**<br>• **Psych sx:** agitation, delusions, hallucinations<br>• **Focal seizures** | • Prominent psych features<br>• Dyskinesias, rigidity<br>• Autonomic instability<br>• **LP**: lymphocytic pleocytosis, oligoclonal bands, **autoantibodies** (CSF + serum) | **MRI: FLAIR hyperintensity or contrast enhancement** (esp. in temporal lobe)<br>**EEG**: extreme delta brush very specific | • Immunotherapy: **steroids, IVIG, PLEX,** rituximab, cyclophosphamide<br>• **Tumor resection** |

**TREATMENT:** can treat symptoms, but treatment does not slow the progression of disease (**Lancet Neurology 2023;23:13-15**)

- Inpatient Considerations: For patients with Parkinson's, **do NOT stop/change** home medications (NGT if needed). Stopping Sinemet can cause NMS. If patient has LBD, avoid antipsychotics. If necessary, atypicals (olanzapine, quetiapine) or trazadone preferred
- AChE (acetylcholinesterase) inhibitors: donepezil (first line), rivastigmine (patch), galantamine. Small effect on decreasing rate of cognitive decline, 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)
- Anti-amyloid Abs: In pts w/ MCI or mild dementia + amyloid (confirmed by LP or PET), lecanemab (NEJM 2023: 388; 9-21) and donanemab delayed clinical progression (JAMA. 2023;330(6):512-527). Amyloid-Related Imaging Abnormalities (ARIA) (edema -E or hemorrhage -H) seen in ~20% (Brain. 2023 6;146(11):4414–4424). CMS reimburses for FDA-approved anti-amyloid abs. AC and intravenous thrombolysis contraindicated for pts on anti-amyloid antibodies due to risk of ARIA-H.

# Neurology — Headache & Vertigo

## HEADACHES (Lancet Neurology 2023;23(1),17-19)

**Approach**: distinguish **primary** HA (tension, migraine, etc.) from **secondary** HA (tumor, ICH/SAH, ↑ICP, etc.)
**Red Flags (consider neuro c/s or neuroimaging):** new onset HA (in pt with c/f trigeminal autonomic cephalgia, hx of SCD, or >50 yo); positional or sudden+severe onset HA; headache with maximal intensity at onset, PMH immunocompromised, TB, cancer, or VPS; abn neuro exam, fever/nuchal rigidity
**Tension HA**: ~40% population, ♀>♂, band-like, forehead radiating to occiput, mild-mod severity, duration 30min to 7d (NRDP 2021;7,24)
**Migraine HA**: >3/5 "POUND" criteria: **P**ulsating, 4-72h h**O**urs, **U**nilateral (*although ~1/2 of migraines are bilateral despite classical teaching of unilateral HA*), **N**ausea, **D**isabling (JAMA 2006;296:1274)

- Migraine with aura: 1 unilateral/reversible sx [visual/retinal (scintillating scotoma, visual field deficit), sensory (tingling, numbness), speech/lang (aphasia), motor (wkness), brainstem (dysarthria, vertigo, ataxia, diplopia)] lasting minutes, usually followed by HA

**ED/Inpt Management:** for migraine/tension HA **w/o red flags**

**Step 1**
1) 1L IVF (adjust volume per comorbidities); 2) 2g Mg; 3) 1g acetaminophen OR NSAIDs (15mg ketorolac, 500mg naproxen, 400mg ibuprofen, 25mg indomethacin); 4) 6mg sumatriptan; 5) Chlorpromazine 25 mg OR prochlorperazine 10 mg OR metoclopramide 10 mg; 6) Diphenhydramine 25mg (to prevent extrapyramidal SE of antiemetics + promote sleep which helps w/

→ 60 min, If not improved →

**Step 2**
1) VPA 500-750 mg IV (after negative pregnancy test); 2) Consider droperidol 2.5-5mg IV/IM OR haloperidol 5mg IM (after EKG)

- For recurrent migraine attacks resulting in ED presentations can use dexamethasone 10 mg once followed by Medrol dosepack to decrease recurrence after successful abortion of the ongoing attack

**Outpatient Management:**

| Migraine HA | |
|---|---|
| **Preventatives** (if >4 days/mo, long duration, or disability) | **Rescue** (max 2 doses/week, treat early) |
| **BB/CCB**: propranolol 20mg BID up to 160mg/d; metoprolol 25mg BID up to 200mg/d; verapamil 80mg TID, ↑ gradually<br>**Antidepressants**: amitriptyline/nortriptyline 10mg qhs, ↑ to 150mg; venlafaxine 37.5mg qd, ↑ to 75-150mg<br>**Anticonvulsants**: topiramate 25mg qd, ↑ gradually to 100mg BID; VPA 500-1500mg qd (avoid both in young ♀)<br>**CGRP antagonists:** erenumab 140mg monthly sc, oral atogepant (Lancet 2023;402: 775-785)<br>**Supplements**: Mg 400mg qd, riboflavin 400mg qd, melatonin, feverfew<br>**Botox**: referral to HA clinic | **NSAIDs/APAP**<br>**Triptans:** sumatriptan [5-20mg q2h (max 40mg/d) intranasal, 4-6mg q1h (max 12mg/d) SC, 25-100mg q2h (max 200mg/d) PO]; zolmitriptan [5mg q2h (max 10mg/d) intranasal, 1.25-2.5mg q2h (max 10mg/d) PO]; ***C/I**: CAD/PAD;* risk of vasospasm, liver dz, basilar migraine, MAOIs w/in 2w; risk of serotonin syndrome<br>**CGRP antagonists:** ubrogepant 50-100mg q2h (max 200mg/d) PO |

- Tension HA: prevention - smoking cessation, treat OSA, TCA, SSRI; rescue - NSAIDs *OR* acetaminophen +/- antiemetic, max 2 doses/week to prevent development of medication overuse headache; medication overuse headache is associated with use of acute abortive treatments or analgesics for more than 10-15 days of the month (or >2-3 days/week)
- Menstrual migraine: before/during menstruation → NSAIDs or sumatriptan (Neurology 2008;70:1555). Consider preventive tx perimenstrually w/ longest-acting triptan - frovatriptan 2.5mg QD/BID (begin 2d premenstrually, for total 6d/month)
- In pregnancy: NO gadolinium contrast, NSAIDs, VPA. C/s OB/Neuro if ? re: med safety/efficacy (Continuum 2022: 28: 72-92)

## VERTIGO

**Definition**: illusion of motion of self or world secondary to vestibular dysfunction; a/w n/v, postural/gait instability
**Approach**: **distinguish central vs peripheral** (AFP 2017;95:154); MGH ED Approach to Acute Dizziness Flowchart

- Hx/Exam: ensure actually experiencing vertigo and NOT lightheadedness, duration of sx, episodic/persistent, triggers (position Δ, loud sounds), prior sx, assoc sx (5D's for brainstem: dysarthria, diplopia, dysphagia, dysphonia, dysmetria), otologic sx (ear pain, tinnitus, ear discharge, hearing loss, ear fullness sensation). Obtain orthostatics. Perform Dix-Hallpike. **HINTS exam video.**
- HINTS exam: each test *must be c/w peripheral to be reassuring*, test must be performed *while the patient is symptomatic with vertigo.* In **acute, ongoing** vertigo, Sn 97%, Sp 85% for stroke (*Superior to MRI within the first 72h of presentation for differentiating acute posterior circulation ischemic stroke from peripheral causes of vertigo*)
  **H**ead **I**mpulse (pt looks at your nose, passively rotate head ~20°. No saccade = ambiguous. Catchup saccade = peripheral)
  **N**ystagmus (unidirectional e.g., always left-beating = peripheral; direction changing = central, any vertical = central)
  **T**est of **S**kew (cover one eye, then other, any vertical skew/correction = central) (Acad Em Med 2013;20:986)
- If ordering MRI: order w/ thin cuts through brainstem and coronal DWI sequences to improve the sensitivity of MRI

**Tx (peripheral)**: metoclopramide, prochlorperazine, meclizine (≤2w, vestib suppression), lorazepam, or diazepam, **AND vestibular PT**

| | 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 (vestibular schwannoma, ependymoma, brainstem glioma, medulloblastoma), NF, MS, vestibular migraine | MRI brain w/ contrast (coronal DWI and thin cuts thru brainstem), MRA head & neck |

# Neurology

# Stroke & TIA

## Acute Stroke Activation (In-House Stroke Pathway)

1) If **sudden-onset focal neuro symptoms** within past 24h, activate the stroke team pager by **calling the operator at 6-3333.** This will notify the stroke resident and nursing supervisors.
2) **BE AT BEDSIDE. This a code equivalent.** Obtain 18g PIV in R AC. Place on travel monitor.
3) **ABC/VS,** check **EKG**, **telemetry**, **FSBG. NPO.** HOB at 0° if c/f LVO (ZODIAC, 2024), but HOB >30° if c/f ↑ ICP (e.g. mass effect, ICH, LVO > 24h LKW), significant aspiration risk, or orthopnea. **Do not treat HTN** unless BP >220/120, c/f ACS, or ICH (see below). Confirm weight/MRI contraindications.
4) Be ready to provide the following information:
   a) **Last seen/known well (LSW/LKW) time.** This is NOT when symptoms were noticed but when pt was last witnessed to be at their neurological baseline.
   b) AC/AP (and time of the last dose administered), CrCl, allergies, code status.
   c) Contraindications to tPA/TNK.
   d) Physical exam findings: most predictive findings incl. facial paresis, arm drift/weakness, and abnormal speech (JAMA 2005;293:239).
   e) Premorbid disability (e.g., walks w/ assistance, bedridden, dependence on iADLs/ADLs),
5) **Order STAT CTA Head/Neck** (only need to order CTA; includes NCHCT). If unable to receive contrast, stroke team may consider STAT MRI ± MRA.
6) **Obtain STAT Labs**: **FSBG**, **CMP**, **CBC, PT/PTT/INR**, **type and screen**, **d-dimer,** VBG, trop, UA/UCx, tox screen, & AED levels (if appropriate), b-HCG (<50 years). +/- Factor Xa (on DOACs and last dose unknown). If wnl, might be eligible for tPA/TNK.
7) Neurology will perform **NIHSS** at bedside and may activate stroke group pager (pharmacy, radiology, NSGY, IR, ICU RN).

**IV thrombolysis (tPA/TNK)**

**Inclusion**:
1. Severe or disabling neuro deficit
2. Age ≥18
3. LSW <4.5h or 'wake-up' sx (might be eligible for IV thrombolysis per WAKE-UP trial, NEJM 2018;379)

**Exclusion**:
History: stroke/head trauma <3mo; head/spine surg <3mo; prior ICH; intracranial malignancy, AVM, aneurysm; incompressible arterial puncture <7d; GI onc or GIB <21d
Clinical: **BP ≥185/≥110 (must bring it below 185/110 before giving tPA/TNK)**; BG <50; active internal bleeding, bleeding diathesis
Heme: plt <100K, PTT > 40s, PT > 15s; current AC (warfarin w/ INR >1.7; therapeutic heparin use w/in 48h w/ ↑PTT; DOAC w/in 48h)
Head CT: hemorrhage or already established infarct

**Mechanical thrombectomy (IAT)**

**Inclusion**:
1. Clinical: **NIHSS ≥6, LSW ≤24h**, age 18-90, baseline mRS ≤2, life expectancy >12mo
2. Radiological: ICA or MCA M1/2 occlusion, basilar/vert occlusion, small infarct core volume and/or favorable penumbra-to-core mismatch ratio

Note: *Proven* benefit w/ these inclusion crit; *probable* benefit w/ NIHSS ≥4, mRS ≤3, prox occlusion w/ ASPECTS ≥ 5. Discuss all cases w/ Neuro, may opt for IAT

**Exclusion**: Anaphylaxis to contrast, acute ICH

Stroke Mimics: **"MINT": M**etabolic (*Gluc, Na, uremia, TME, thyroid disorders, MELAS, hypoxia, hypercarbia*), **I**nfection (*Bell's Palsy, meningitis, encephalitis, vestibular neuronitis*), **N**eurological (*migraines, Todd's paralysis/post-ictal, FND, MS, MOG, NMO*), **T**oxins/**T**rauma.

## Acute Stroke Initial Management (MGB Guidelines)

### 1. ISCHEMIC STROKE

**IV thrombolysis: TNK is now the preferred agent over tPA at MGB**: 0.25mg/kg (max 25mg).

- LSW 0-3h: goal to start IV tPA/TNK w/in 60min of ED arrival (AHA/ASA: Stroke 2018;49:e46).
- LSW 3-4.5h: IV tPA/TNK recommended but w/ relative exclusion criteria of: age >80, AC (regardless of INR), NIHSS score >25, & h/o both stroke & DM2 (NEJM 2008;359:1317).
- Wake-up or Unknown Onset: consider IV tPA if DWI lesion <70mL w/o FLAIR changes (NEJM 2018;379:611).

**Mechanical thrombectomy:** Considered for patients with disabling deficits & proximal LVO with **LSW <6h** (NEJM 2015;372:11). May extend time to **LSW 6-24h** based on perfusion imaging (NEJM 2018;378:708, NEJM 2023;388:1259) or clinical mismatch. No benefit in medium/distal occlusions (NEJM 2025).

**BP control**: low SBP (<150) a/w poor outcome (Arch Intern Med 2003;163:211)

- If tPA/TNK candidate: goal BP **≤185/110** prior to thrombolysis **(treat STAT if higher! 1st line: IV labetalol/nicardipine)**; continue BP goal **≤180/105** after TNK/tPA for 24h
- If no tPA/TNK: goal BP **≤220/120** (allow auto-regulation) for 1d, then gradually ↓ BP goal.
- If anticoagulated: goal SBP **≤180 to prevent hemorrhagic transformation.**
- If active cardiovascular disease (ACS) & requires tighter BP control, discuss w/ neuro.
- **Monitor neuro exam:** sx worse at low BP c/f BP dependent hypoperfusion/ongoing ischemia → **lay bed flat, give IVF bolus, STAT page neuro.**

### 2. HEMORRHAGIC STROKE (see *CNS Emergencies*)

## Inpatient Post Stroke Care

Frequent **neuro checks** q1-2h x 24h if unstable/ICU and 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).

- Post tPA/TNK: No AC/AP for 1st 24h. **NCHCT 24h post-tPA→** if no e/o hemorrhage and etiology cryptogenic, start DVT ppx.
- If did NOT receive tPA/TNK: **ASA 325mg x1**, followed by long-term antiplatelet or AC (may delay antiplatelet and/or AC for large ischemic strokes). Start DVT ppx if ischemic stroke (unless large volume hemorrhagic conversion).

**General Work up: Labs**: In addition to STAT Code Stroke labs, obtain lipids, A1c, TSH, ESR, CRP, CYP2C19 genotype. If cryptogenic stroke and/or stroke in young person: consider syphilis, HIV +/- bloodstream or CNS infectious w/u +/- hypercoagulability (d/w Neuro) (STROKE 2021;52:364). **Imaging**: MRI brain w/o contrast; H&N CTA or MRA (TOF if low GFR); carotid U/S PRN (CTA/MRA > US carotid to view intracranial pathologies). ***For more detailed/tailored workup and management, please see table on text page.***

**2° PREVENTION PLAN: Discuss w/ Neuro** (depends on suspected etiology, size of infarct, NIHSS, ABCD$^2$, etc.). **Typically, no need** for both antiplatelet (AP) & anticoagulation (AC) for 2° stroke prevention. In general, prioritize AC if there is an indication, and DAPT>AP monotherapy in preventing recurrent stroke if started within 24-48h of LSW (see indications below). Benefits seen within first 3 wks.

- Start **high-intensity statin** (e.g. atorvastatin 40-80mg) with LDL goal <70 (NEJM 2006;355 and NEJM 2020;382:9)
- **Long-term 2° antiplatelet therapy:**
  - ASA monotherapy: ASA load (325 mg) → 81mg qd (50-325mg/d effective; ≤200mg/d ↓ risk of major bleed) (Am J Cardiol 2005;95:1218). Used for non-minor stroke/cryptogenic. Highest risk of recurrence in first few days after index event.
  - Clopidogrel monotherapy: 75mg qd, may be superior to ASA for atherosclerotic vascular dz. (Lancet 1996;348:1329)
  - DAPT (ASA/clopidogrel *OR* ASA/ticagrelor): If **high-risk TIA (ABCD$^2$ >3) or minor stroke (NIHSS <4)**: ASA 81mg + clopidogrel 300-600mg load → ASA 81mg + clopidogrel 75mg for **3w** → by clopidogrel or ASA alone (NEJM 2013;369:11 and NEJM 2018;379). May replace clopidogrel with ticagrelor. Ticag has faster onset & does not require metabolization from pro-drug by

CYP2C19. LoF in CYP2C19 →↓ efficacy of clopidogrel; common in Han Chinese descent. Can send genotype with initial workup. (NEJM 2020; 383:207 NEJM 2021;385)
  - **Intracranial atherosclerosis**: ASA 325mg/clopidogrel 75mg for **3mo** → ASA 325 qD (NEJM 2011;365:993)
  - **Recurrent stroke on ASA or clopidogrel alone + significant athero**: no clear evidence & higher bleed risk with long-term DAPT (NEJM 2006;354:1706; Lancet 2004;364:331), consider ASA + low-dose rivaroxaban (NEJM 2017;377).
- **Long term 2° anticoagulation therapy:** embolic infarcts from AFib, paradoxical embolus, LV thrombus, VST, or hypercoag state
  - DOAC>warfarin for non-valvular AF and warfarin *only* for valvular-AF (moderate-to-severe MS). OK to restart immediately for TIA, wait 1-2d for small infarct, 3-4d for moderate-sized and 5-7d for large infarcts; NEJM 2023;388-2411). Discuss duration of hold w/ neuro if hemorrhagic transformation. Consider endovascular left atrial appendage occlusion if anticoagulation is contraindicated or not tolerated (JACC 2020(76):23:2795-2796).

| Suspect When: | Diagnostic Workup: | Acute Management Concerns |
|---|---|---|
| **CARDIOEMBOLIC STROKE** | | |
| - ACA/MCA/PCA occlusion w/o sig vascular dz<br>- Infarcts in multiple vascular territories<br>- Known risk factors (LA/LV thrombus, AF, LVEF<35%, aortic arch atherosclerosis, LA dilation, R→L shunt)<br>- Hypercoagulability/hyperviscosity (malignancy, HbSS, cryo, clotting d/o) | **- TTE (w/ bubble if <60yo):** if PFO, r/o venous thrombus (LENIs/ MRV pelvis), consider closure (NEJM 2017;377:1022)<br>- If no hx of AF: **tele followed by 30d MCOT vs. LINQ** at d/c to uncover more AF, but the clinical significance of this is unclear (NEJM 2014;370:2478; JAMA 2021;325:2169). | - Unless c/f hemorrhagic transformation, transition to long-term AC in 2-7d (NEJM; 2023;388). |
| **SYMPTOMATIC CAROTID STENOSIS** | | |
| - H/o amaurosis fugax<br>- Ipsilateral >50% stenosis per NASCET criteria or <50% stenosis with high-risk features (intraplaque hematoma, ulceration) (Stroke 2020;311-314) | **- CTA** vs. **MRA** head & neck, **carotid US** typically needed prior to carotid endarterectomy (CEA) | - If **stroke/TIA and either stenosis >50% or high-risk plaque features,** consider revascularization (stent/angioplasty/CEA) ideally w/in 2w of sx (NEJM 1998;339:1415 ).<br>- Discuss temporary **anticoagulation** w/ neurology<br>- Consider ***induced* HTN** if symptoms fluctuate with BP |
| **INFECTIVE ENDOCARDITIS** | | |
| - Unexplained fever w/ stroke or pt with valvular dz | **- Blood cultures**<br>**- TTE** followed by **TEE or PET** if neg<br>**- CTA head +/- conventional angio** to ID mycotic aneurysms (↑bleeding risk) | **- Immediate antibiotics; tPA contraindicated**<br>- Early cardiac surgery if small non-hemorrhagic stroke; delayed cardiac surgery (2-4w) if large or hemorrhagic stroke<br>**- Avoid AC or AP** w/o a separate indication (↑ **risk** for hemorrhagic conversion and ↑ mortality Stroke. 2011;42:1797-1798). |
| **CAROTID AND VERTEBRAL DISSECTIONS** | | |
| **-** <60yo or posterior circulation stroke in pt w/o RFs<br>- Neck pain, HA, or Horner's syndrome<br>- Trauma (vertebral fx), chiropractor, coughing spells | **- CTA** vs. **MRA with T1 fat saturation**<br>- Consider connective tissue disease (Marfans/FMD) | Goal of tx is to prevent stroke: ↑↑ risk in first few days<br>**- AC vs AP** (Stroke 2024;91-106): Prefer AC if intraluminal thrombus or occlusive dissection in pt w/o high hemorrhage risk); prefer AP if intracranial extension (risk of SAH), large infarct size, or high hemorrhagic risk otherwise.<br>- High rate of recanalization → tx 3-6mo then re-image |
| **CEREBRAL VENOUS SINUS THROMBOSIS** | | |
| **-** Positional HA, vomiting, papilledema, vision Δ<br>- P/w seizure (common, may be difficult to control) | **- NCHCT**: ↑density in torcula (dense delta sign)<br>**- CTV** vs. **MRV** to assess intracranial venous system<br>- Consider **hypercoagulable workup** | **- Immediate anticoagulation (heparin or LMWH) even in presence of hemorrhage**<br>- AEDs if seizures (not indicated for ppx)<br>- IV fluids, avoid dehydration, modify risk factors (smoking, OCPs)<br>**- Long term anticoagulation (warfarin/DOAC)** for 3-6 months, then reimage (JAMA Neurol 2019;76:1457) |

## TRANSIENT ISCHEMIC ATTACK (TIA)

**Definition**: *transient* neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia w/o imaging evidence of acute infarction. Risk factors for TIA are the same as those listed for stroke above.

- **Imaging**: CT/CTA head and neck emergently to assess vessels, bleeds and established infarcts. Consider outpatient MRI if presenting to ED (TIA pathway at MGH, discuss w/ neuro).
- **Cardiac w/u**: TTE (w/ bubble if age <60yo or age>60yo w/o vascular risk factors) to evaluate for thrombus or PFO. MCOT vs. LINQ monitoring to exclude AF if suspected embolic TIA
- **ABCD²** score (**A**ge, **B**P, **C**linical features, Sx **D**uration, **D**iabetes): used to identify pts w/ high risk of ischemic stroke w/in **1w** of TIA
- **Management**: immediate intervention ↓ the risk of recurrent stroke (1.5-3.5% risk w/in 48h), see 2° Prevention above – prefer DAPT over AP monotx in the absence of indication for AC for high-risk TIA (aka ABCD2 ≥4).

## POST-DISCHARGE STROKE/TIA CARE

**Work up:** f/u pending labs (e.g. hypercoag panel), repeat APLAS labs after 12w if pos, f/u MCOT/LINQ, order repeat imaging as noted.
**Management:** d/c short term meds as appropriate (e.g. d/c ASA or Clopidogrel after 21d); start AC per neuro if indicated, ask about depression (Br J Psychiatry 2013;202:14), consider treating w/ fluoxetine for enhanced motor recovery (Lancet Neurol 2011;10:123); remind pts that deficits may continue to improve for >1yr, behavioral modifications (smoking cessation, diet and exercise, weight reduction), and consider sleep study if concern for OSA.

# Neurology CNS Emergencies

## INTRACRANIAL HEMORRHAGE (ICH): epidural (EDH), subdural (SDH), subarachnoid (SAH), intraparenchymal (IPH)

- **Causes**: trauma (all), ruptured aneurysm/AVM (SAH, IPH), IPH also caused by HTN, cerebral amyloid, tumor (most common w/ met breast, lung, melanoma, RCC, choroid, thyroid), cortical vein/venous sinus thrombosis, hemorrhagic transformation of ischemic stroke
- **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**: MGH ICH Guideline; mortality benefit to care in neuro-specific ICU or stroke unit (2022 AHA ICH Guidelines)
  - STAT Neurosurg (p21111) if SAH/SDH/EDH or lobar IPH w or w/o sxs of herniation (minimally invasive hematoma evac in lobar IPH improves outcomes (NEJM 2024;390:1277) otherwise, Neuro (inpatient: p20202; ED: p20000)
  - **Elevate HOB** to 30-45° to ↓ICP and prevent aspiration. **Obtain labs**: PT/INR, CBC, CMP, fibrinogen, type and screen
  - **BP control**: **strict SBP <140 with arterial line monitoring** (studied in SAH or ICH due to ruptured aneurysm/AVM, to prevent re-bleeding, A-line not appropriate for floor level care), use **IV labetalol, nicardipine, clevidipine, or esmolol** (Lancet Neurol 2008;7:391); consider less restrictive BP goal for pts presenting with SBP 180-220 (ie. target SBP <160) or 25% reduction if SBP >220 (NEJM 2016;375:1033). For aneurysmal SAH → PO nimodipine. (Stroke. 2022;53(6):1993-2005)
  - **Correct coags if**: warfarin/**INR**>1.5: vitamin K 10mg IV x1 AND 3-5U FFP or 4-factor PCC/KCentra; **↓plt**: transfuse, goal >50; uremia/antiplatelet use: consider DDAVP 0.3mcg/kg IV; heparin/LMWH: protamine sulfate, consider heme c/s; s/p tPA: check fibrinogen, give cryo, ± amicar 4-5g → 1g/hr; rivaroxaban/apixaban: 4-factor PCC/KCentra OR Andexanet alfa, page pharmacy
  - **Venous sinus thrombosis (VST)**: AC w/ LMWH/UFH despite ICH (Stroke 2011;1158-92). Manage seizures (see *Seizures*) & ↑ICP.
  - 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 **48h after** last stable NCHCT, confirm w/ Neurology
  - Start prophylactic levetiracetam 500mg BID **x7d** for **traumatic** SDH or SAH (Neurocrit Care 2010;12:165)

## ELEVATED INTRACRANIAL PRESSURE (ICP)/HERNIATION: ICP > 20mmHg

- **Etiologies**: mass (tumor, abscess, hemorrhage), cerebral edema (infarction, inflammation, hyperammonemia, DKA), hydrocephalus (tumor, intraventricular hemorrhage, leptomeningeal disease, meningitis), PRES, VST. High ICP may cause compression/ischemia. Severe local swelling or CSF drainage with large space-occupying lesions causes herniation (displacement & compression of brain).
- **Signs of ICP**: nausea, vomiting, headache, diplopia somnolence/confusion, or limited upgaze; flexor/extensor posturing; ipsilateral hemiparesis (uncal herniation); **fixed/dilated/asymmetric pupil, Cushing's triad (bradycardia, ↑SBP, irreg. breathing)**
- **Tests**: STAT head CT, blood gas, BMP, CBC
- **Management**: MGH ICP Guideline
  - STAT Neurosurgery for ICP monitor/EVD placement/decompressive hemicraniectomy, Neurology to discuss need for Neuro ICU
  - Secure ABCs, elevate HOB to 30-45˚, keep head midline (to secure venous drainage), treat pain/agitation, maintain BP to avoid CPP <50mmHg (CPP=MAP-ICP).
  - If c/f herniation, **hyper**ventilate to PaCO2 ~ 30-35 mmHg (transiently reduces ICP)
  - **Hyperosmolar therapy**: **Check BMP, serum Osm to calculate Osm gap q6h**. **Start with 23% saline boluses**, then use mannitol, or both staggered 3h apart (discuss with Neuro) (Emerg Med J 2014;31(8):679-83)
    - 23% saline 30cc q6h requires central line → better option for patients with AKI/CKD; caution in HF, hold if Na >160;
    - IV mannitol 1g/kg q6h (max 100g, caution in pts on HD). **Hold** if Osm gap >10-12, Na >160, serum Osm >340
  - If edema 2° to **malignancy or bacterial infection**, give 10mg IV dexamethasone x1, then 4-8mg BID
  - **Complications during LP**: **if sx of herniation or opening pressures >40cm $H_2O$ w/ space occupying lesion**, consider STAT head CT. Immediately replace stylet into needle, only drain CSF from manometer, STAT Neurosurgery consult.
  - **Do not** use **HYPO**tonic fluids (LR) for resuscitation as this can worsen edema. Use NS instead. J Neurosurg 1995;83(6):949-62).

## HYPERTENSIVE ENCEPHALOPATHY AND PRES (POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME)

- Dx of exclusion w/ (sub)acute onset, varied neuro sx, vasogenic edema, & severely elevated BP. (J Neurol 2017; 264(8): 1608–16).
- **Associated symptoms**: severe HTN, but also relative HTN in setting of eclampsia/pre-eclampsia, cytotoxic/immunosuppr meds (cyclosporine, tacro, cisplatin, bevacizumab), acute/chronic renal failure, uremia, sepsis, vasculitides, TTP due to impaired cerebral autoregulation and endothelial dysfunction, hypoMg (NEJM 1996;334:494)
- **Symptoms**: thunderclap HA, confusion, decreased consciousness, visual disturbances, seizures, ICH and ↑ICP
- **Tests**: **MRI brain w/ contrast**: FLAIR w/ vasogenic edema w/in white matter in the posterior cerebral hemispheres; DWI/ADC typically nl (though can have strokes); additional regions can be affected incl. brainstem, cerebellum, basal ganglia, frontal lobes
- **Management**: ICU if severe, strict BP control (goal SBP <140, reduce by 10-15% 1st hour then 5% daily, if severe use nicardipine or labetalol drip), treat seizures (does not typically evolve into seizure disorder), $Mg^{2+}$ (esp. in eclampsia), remove inciting factor (i.e stop medication, dialyze if needed, treat infx)
- **Prognosis**: often fully reversible; complications include progressive cerebral edema, ICH, stroke, death

## CORD COMPRESSION: high level of suspicion in cancer or in IVDU with back pain, urinary sx or LE weakness

- **Etiologies**: subacute (tumor/mets, abscesses) vs acute (disc herniation, trauma, hemorrhage)
- **Symptoms**: back pain (worse at night/Valsalva), motor weakness, **hyper**reflexia below lesion if chronic (**hypo**reflexic if acute, cauda equina), ⊕Babinski, loss of sensation ("sensory level"), bowel/bladder incontinence OR retention, loss rectal tone, saddle anesthesia
- **Imaging**: **STAT MRI C/T/L w/ contrast** (cord compression protocol), call ED (x63050) or inpt MRI (x64226) to prioritize
- **STAT page** NSGY/Ortho spine for decompression ± Rad Onc for possible XRT if tumor related (see *Oncologic Emergencies*)
- **Dexamethasone**: 10mg IV x1 then 4mg IV Q6H, esp in malignancy (Cochrane Database Syst Rev. 2015 Sep 4;2015(9):CD006716)

# Neurology Seizures

## DEFINITIONS Epilepsia 2017;58:522 Continuum 2019;25:306 Continuum 2022;28:230 Lancet Neurology 2023;23:19

- **Classification of seizure (sz)**: describe onset and semiology
  - *Focal onset:* **unilateral**, occurring in one hemisphere, ± impaired awareness, may evolve to bilateral tonic-clonic
  - *Generalized onset:* occurring in & rapidly engaging bilateral distributed networks, **impaired awareness** (exception: frontal seizures-preserved awareness despite being bilateral)
  - *Motor:* limb stiffening (tonic), limb jerking (clonic), brief muscle contraction (myotonic), loss of tone (atonic), or automatisms
  - *Non-motor:* autonomic changes, staring/behavioral changes, cognitive changes, sensory phenomena
- **Epilepsy**: ≥2 unprovoked sz >24h apart or 1 unprovoked sz + recurrence risk ≥60% over the next 10y or dx of an epilepsy syndrome
- **Status epilepticus**: ≥ 5min of continuous sz or 2+ sz w/ incomplete recovery of consciousness in between (Epilepsia 2015;56:1515)
- **Non-convulsive status epilepticus**: electrographic sz or EEG & clinical improvement w/ tx (Epilepsy Behav 2015;49:158)
- **Psychogenic non-epileptic sz (PNES)**: most prevalent phenotype of fxnl neuro disorder (FND). Long & fluctuating course, asynchronous/side-to-side mvmts, closed eyes, preserved awareness, memory of spell. No pathology. changes in brain physiology.

## ETIOLOGY: provoked vs unprovoked?

- **Causes/RFs**: 1° epilepsy, vascular (ischemia/hemorrhage), withdrawal (EtOH/BZD), masses (tumor, abscess), trauma, metabolic (↓BG, ↑CO2, ↓O2, ↓Ca, ↓/↑Na), meds, infxn (systemic, CNS), HTN/HoTN, high fever, eclampsia, PRES. Bupropion IR (not sustained release form.) >300 mg ↓ sz threshold. (FDA, 2023)
- **Ddx**: syncope, TIA, migraine, PNES (~30% have epilepsy, Brain Behav 2022;12), myoclonus, dystonia, cataplexy, tremor, catatonia
- **H&P**: sz history, prodrome (headache, confusion, anxiety, irritability), med list (↓sz threshold, e.g. penicillins, opioids, antipsychotics), triggers (exertion, pain, fatigue, stress, cough, urination/defecation, infxn), tongue biting (lateral), incontinence, lateralizing signs, EtOH/BZD. GET COLLATERAL. If witnessing, CAPTURE VIDEO for neurology.
- **Labs**: **FSBG, Utox & Stox, UA, CXR, AED lvls, BMP/Na**, Mg/Phos, CBC, LFT, VBG, CK, INR, lactate, b-hCG. Do NOT order prolactin, limited studies show elevation likely 10-20 minutes *after* event, nl prolactin cannot rule out seizure or epilepsy.
- **Monitoring**: tele (↑risk for ictal bradycardia/aystole), pulse O2 (NEJM 2013;368:2304-12)
- **Neuroimaging**: epilepsy protocol MRI w/ contrast for **unprovoked 1st sz** (Continuum 2022;28:230-260), **focal sz,** focal neuro exam, h/o trauma, malignancy, or HIV. 10% found to have relevant structural lesion (Neuro 2007;69:1996).
- **LP/BCx**: if febrile, HIV/immunocompromised, 2° autoimmune encephalitis (anti-NMDA) (Epilepsia 2020;61:1341)
- **EEG**: within 24-48h if not seizing, **emergent if seizing**. **DO NOT wait for EEG to manage**. If emergent, contact EEG fellow (p16834). Sens. of rEEG is ~50% if obtained w/in 1st 24h after sz. Negative EEG cannot r/o sz if convincing clinical presentation.

## SEIZURE PPX Neuro 2015;84:1705 Neuro 2006;67:s45 Cochrane 2008;CD004424 Neurosurg Focus 2008;25:E3 Stroke 2016;47:2666

- **No AED in 1st sz unless** prior TBI, abnml EEG, or abnml imaging. Early AED ↓short term recurrence (<2y), not remission (3+y).
- **ETOH seizure**: ppx **not indicated** for intox/withdrawal, **ICH**: only if clinical sz or traumatic etiology, levetiracetam 500mg BID x7d
- **Brain tumor**: no ppx. If sz, levetiracetam > lacosamide (fewer chemo interactions), **Severe TBI**: levetiracetam 500-750mg BID x7d
- **PNES**: Outpatient, CBT & Psychiatry. Inpatient, educate about functional neurological sx, c/s social work.
- In MA, **no driving** (for LOC event) until 6mo event free. Counsel pt, include in d/c summary. Restrictions vary by state.

## 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. Discuss AED load with Neurology.
- Treatment of **status epilepticus** (MGH Status Epilepticus Protocol)
  - **Lorazepam 4mg IV q5min x1-2** and order 2nd line agent → persists >5min→ **call Neurology,** give 2nd line agent: **levetiracetam 60mg/kg x1 (max 4500mg/dose)** vs. valproate 40mg/kg x1 (max 3000mg/dose) vs. fosphenytoin 20 PE/kg (over 10 min) → persists >20min → intubation w/ propofol/midazolam/(3rd-line) ketamine. Avoid etomidate. (NEJM 2019;381:2103).
  - If no IV access, **midaz 10mg IM**/nasal/buccal or diazepam 20mg PR. 2nd line medications require PIV.
- Suspected preeclamptic sz: 4mg IV Mgx1, consider infusion at 2g/hr. Page OBGYN.

| 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** (aggression, anxiety/depression, psychosis) |
| Valproic acid (Depakote)† | 20-40mg/kg Max 3g | 1:1 PO:IV | 50-100mcg/mL (>1h post load) | ↑**weight**, **hepatitis, N/V**, tremor, alopecia, encephalopathy (↑NH3), ↓platelets. **Good w co-morbid mood disorder.** |
| Phenytoin (Dilantin)†, Fosphenytoin† | 20 mg/kg Max 1.5g | 1:1 PO:IV | 10-20mcg/mL, correct for alb, (2h post load) | **HoTN/arrhythmia** (if run >50mg/min; fosphen. has ↓cardiotox), gingival hypertrophy, nystagmus/ataxia/slurred speech, blood dyscrasia, DRESS, **rash (TEN/SJS)** |
| Lacosamide (Vimpat) | 200-400mg | 1:1 PO:IV | 10-20mcg/mL | HA, diplopia, dizziness, ataxia, nausea. Get EKG before & after load (**PR prolongation, flutter/fib**). |
| Lamotrigine (Lamictal)* | No Load | Only PO | 3-15mcg/mL | **Rash (TEN/SJS)**, DRESS, nausea, drowsiness, ↓PMNs, HLH, aseptic mening. **Good w co-morbid mood disorder.** |
| Topiramate (Topamax)† | No Load | Only PO | N/A | ↓**weight**, **drowsiness**, glaucoma, NAGMA→nephrolith., cognitive dysfxn, aggression, anxiety/depression |
| Carbamazepine (Tegretol) | No Load | Only PO | 4-12mcg/mL | SIADH, N/V blood dyscrasia, ataxia, blurred vision, DRESS. Screen for **HLA-B*1502** if Asian descent for **↑risk of TEN/SJS** (Epilepsia 2019;60:1472). |
| Clobazam (ONFI) | No Load | 1:1 PO:SUSP | N/A | **Drowsiness**, resp. depression (BZD), ataxia, URI, UTI sx, fever |
| Perampanel (Fycompa) | No Load | 1:1 PO:IV | N/A | **Aggression/irritability**, dizziness, drowsiness, weight gain |

Others: Brivaracetam, Cenobamate (effective in highly active & ultra-refractory focal epilepsy), Ethosuximide (absence), Phenobarbital (historical), Vigabatrin, Zonsiamide. Aerosolised alprazolam as rescue medication (Epilepsia 2023;64:374-85).
**Preferred in pregnancy, †Teratogenic*

# Neurology Weakness & Neuromuscular Disease

## CHARACTERIZATION OF A PERIPHERAL PROCESS

- Weakness: ask about **function** (rising from a chair, stairs, brushing hair, tripping while walking, opening jars, zippers/buttons) and onset/ tempo. Clarify vs. generalized fatigue or systemic symptoms (i.e. of anemia, infection, electrolyte abnormalities, thyroid/adrenal issues)
- **UMN signs**: spasticity, increased tone, hyperreflexia, ⊕ Babinski; **LMN signs**: fasciculations, atrophy, decreased tone, hyporeflexia
- **Patterns**: UMN (UE extensors, LE flexors), LMN (length dpdnt, myotomal), myopathy (proximal), bulbar (dysphagia, dyspnea, dysarth.)
- **Sensory sx**: negative (↓ temp/pin [small fibers]), vibration/proprio [large fibers], imbalance) or positive (tingling, allodynia, hyperalgesia)
- **Autonomic sx**: orthostasis, constipation/diarrhea, urinary retention/incontinence, sexual dysfxn, ↓/ ↑sweating, nausea, early satiety
- **Exam**: 0/5 - no mvmt, 1/5 - flicker, 2/5 - mvmt if no gravity, 3/5 - mvmt vs. gravity only, 4/5 - dec. power vs. resistance, 5/5 - nml
- **EMG/NCS**: localization (radicular, nerve, junction, muscle), motor vs. sensory, axonal vs. demyelinating process (guides tx), severity (guides prognosis). **Higher yield if sx for ≥2-3w (do as outpatient).**

| Localization | Associated Signs/Sx | Diagnostics | Important/Common Causes |
|---|---|---|---|
| **Brain** | Cortical (lang., visual field, neglect), cerebellar, UMN | **MRI Brain** (with contrast if c/f cancer, infection, demyelinating dz) | **Vascular** (hemorrhage, ischemia)**, tumor, trauma,** demyelinating dz |
| **Spinal Cord** | Truncal sensory level, bowel/bladder dysfxn, UMN (if chronic) | **MRI Spine** (level from exam, contrast if c/f cancer, infxn, demyelinating dz); **CSF** if c/f inflammatory or infxn | **Transverse myelitis** (MS, NMO, sarc/Sjo/SLE), infxn (viral myelitis, abscess, TB, AIDS, HTLV, syph.), paraneoplastic cause, neoplasm, ↓**B12/Cu**, vascular, **trauma,** toxic, myelopathy |
| **Anterior Horn Cell** | LMN; if motor neuron dz, UMN & LMN | **NCS/EMG** ± MRI brain and spine | **ALS,** SMA, poliomyelitis, acute flaccid myelitis |
| **Radicular** | Motor/sensory corresponding to nerve root. Radiating pain. | **MRI Spine** (nerve root from exam)<br>**LP** if polyradiculopathy<br>**NCS/EMG** can aid in localization if sx >3w | Nerve root compression 2/2 disc hernation, spondylosis; polyradiculopathy→DM (thoracic, lumbosacral), AIDP/CIDP, infxn (Lyme, HIV, CMV), malignancy (leptomeningeal, chemo) |
| **Peripheral Neuropathy** | Motor/sensory; autonomic dysfxn. Often symmetric/ length dependent. | **Labs**: A1c, B12/MMA, S/UPEP<br>**Consider**: Lyme, syphilis, HIV, B1, B6, vit E, B3, Cu, ANCA, ANA, ESR, CRP, RF, TSH, C3/C4, celiac w/u<br>**NCS/EMG**: localization & pattern (not for eval of small fiber dz) | Symmetric, length dependent: toxic/ metabolic/nutritional (DM, chemo, EtOH, ↓B12, critical illness), hereditary (CMT), **AIDP/CIDP**, paraprotein-related<br>Mononeuropathy: compression/trauma Multiple mononeuropathy: **vasculitis**, DM, amyloid, RA/SLE/sarcoid/Sjogren, leprosy |
| **NM Junction** | Motor only; weakness fluctuates with use; a/w ptosis, diplopia. | **Ice pack test**<br>**Labs**: MG panel (below)<br>**NCS/EMG**: repetitive stim, single fiber EMG**. CT chest** if above c/w MG | **Myasthenia gravis**, Lambert-Eaton, botulism, tick paralysis, meds (ICI, penicillamine, aminoglycosides), snake/spider venom |
| **Myopathy** | Proximal weakness most common. Pain uncommon. | **Initial labs**: CK/aldolase, LDH, LFTs, TSH/fT4, PTH, ESR/CRP<br>**EMG**: e/o muscle irritability, chronicity<br>**May need muscle biopsy** | **Critical illness**, meds (**steroids**, **statins**, colchicine, cyclosporine, NRTI), **inflammatory** (inclusion body, dermatomyositis, polymyositis) |

**Sx tx:** Pain: gabapentin, pregab, TCA, SNRI; Dysautonomia: compress. hose, abd binder, fludrocort, midodrine, droxidopa, pyridostigmine

## ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (GUILLAIN-BARRÉ)

- **Symmetric, progressive** numbness & weakness, **hypo/areflexia**, bulbar weakness (50%), autonomic dysfxn, **acute resp failure (10-30%)**
- Causes: recent infxn (***C. jejuni [25%]***, flu A/B, HIV, COVID, CMV, EBV, *Zika*), vaccine (rare), meds (TNF-alpha antag, tacro, ICI)
- Dx: **LP** w/ albuminocytologic dissociation (↑protein, nml WBC), **NCS/EMG (2-4 wks after symptom onset), RT consult for mechanics**
- Tx: **IVIG** or PLEX; monitor resp with NIF/VC (RT) q2-4h until stable; tele for dysautonomia, glucocorticoids not effective
- **Elective intubation 20-30-40 Rule**: VC <20mL/kg, NIF weaker than -30cm H2O, MEF <40cm H2O, or ≥20% decline in ~24h
- Mimics: CIPD, myelopathy, trans. myelitis, ALS, polio, myositis, tick paralysis, vasculitis, paraneop, toxin/vit def, hexacarbon expos., AIP
- **AIDP less likely**: persistent asymmetric weakness, bowel/bladder dysfxn at onset, >50 CSF PMN, sensory lvl, severe pulm dysfxn w/o limb weakness at onset, fever at onset, nadir of weakness in <24h or >4w, purely sensory

## MYASTHENIA GRAVIS/LAMBERT EATON (MG/LEMS)

Weakness of voluntary muscles that typically involve ocular (ptosis, diplopia), bulbar, respiratory, neck, proximal>distal limb muscles.
MG: **worse w exertion**, repetitive mvmts, & in the evening. LEMS: transient improvement w activity.

- Cause: auto-Ab against postsynaptic ACh-R in skeletal muscle (MG) or voltage-gated calcium channels (LEMS); **ICI therapy.**
- Exam: **ptosis w up-gaze** after 2min. Ice pack test: after observing ptosis, place ice on eyes for 1min, ptosis will improve (sens 80%). Fatiguable diplopia. (Historical: tensilon test, requires atropine at the bedside. Only improves MG not LEMS).
- **Monitor for respiratory failure**: track number counting in single breath, worry if <20, assess cough/swallow. Trend mechanics with RT: NIFs/VC as above (*20-30-40 Rule*). Aggressive pulm toilet. HOLD pyridostigmine if bulbar sx and/or intubated (2/2 ↑secretions)
- Dx: **Ach-R Ab** (80-90% pos in generalized dz, 40% in ocular dz, ~100% sp); if ⊖, check anti-MuSK & LPR4. **EMG/NCS** w **repetitive stim**: decremental response (MG) or potentiation (LEMS). **Chest CT**: r/o thymoma. TFTs. Find **underlying malignancy** in LEMS.
- Tx: sx (pyridostigmine); immune: rapid (IVIG, plasmapheresis), chronic (steroids ±AZA/MMF); thymectomy (thymomatous MG or <65yo)
- **Myasthenic crisis:** exacerbation requiring intubation or noninvasive vent. Triggers include surg, infxn, pregnancy, **meds** (abx incl FQs, macrolides, AGs; AEDs; antipsychotics, BBs, CCBs, Mg, glucocorticoids, statins, iodinated contrast rarely). AVOID succinylcholine.

# Neurology — Neuroprognostication

**Neurological prognostication** refers to the recovery from a consciousness disorder after severe brain injury; Neuroprognostication is critical, complex and uncertain (Semin Neurol 2017;37:40). The introduction of targeted temperature management (**TTM**: see *Cardiac Arrest & TTM*) can alter the timeframe for neurological recovery and the interpretation of prognostic markers. It is important to use the following as a framework to conceptualize neuroprognositication in conjunction with active GOC conversations and close interactions with Neurology.

## Cerebral Performance Category (CPC)

- Original CPC scale (NEJM 1986;314(7):397-403) is commonly used, though does not always reflect patient/family values(Resusc 2016;100:6-10). *Note: Previously high-functioning patients and/or family may not feel CPC 1-2 is a good outcome*
- 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.

## Post-Cardiac Arrest Diagnostics

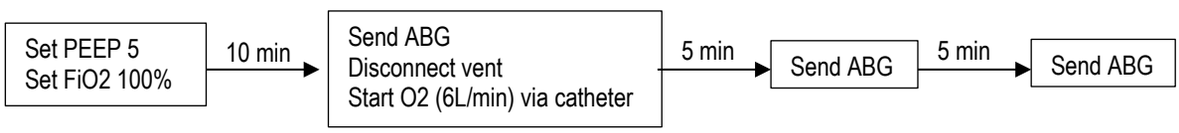
**Critical Caveat:** each of the below tests has a FPR > 0 (i.e. will be "positive" for prediction of poor outcome in some patients who would have a good outcome); FPRs are likely underestimated due to "self-fulfilling prophecy" bias; use of prognostic indicators in combination may reduce FPRs and withdrawal of life sustaining treatment in patients who otherwise would have had a good outcome (MGH Neuroprognostication Guidelines)

- Clinical exam:
  - Poor prognosis: **status myoclonus** (spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs, axial musculature ± EEG correlate) < 48h post arrest or rewarming. **Absent brainstem reflexes** (esp. bilateral pupillary/corneal) 3-7d post arrest or rewarming. At 72h ~20/30% sens & ~99/95% spec. At 96h ~100% spec.
- Electroencephalography (EEG): started immediately post arrest, continued for 24h post rewarming
  - Poor prognosis: absence of EEG reactivity, seizures/status, discharges, voltage attenuation, alpha or delta coma patterns, burst suppression (Neurology 2013;80:339)
- Neuron specific enolase (NSE): check serially at 24, 48, 72h post arrest
  - Non-specific marker of neuronal injury (also found in RBC and platelets)
  - Poor prognosis: >70mcg/L at 24-48h, >59mcg/L at 48-72h (Neurology 2022;98:e62)
- Somatosensory evoked potentials (SSEP): 48h post cardiac arrest or rewarming
  - Measurement of brain activity in response to somatosensory stimulation
  - Poor prognosis: bilateral absence of N20, which reflects the integrity of thalamocortical projections
- CT head: 48h post cardiac arrest or rewarming
  - Poor prognosis: widespread hypodensity in combination with poor clinical exam
- Brain MRI: 2-6d post cardiac arrest or rewarming (not useful < 48h post arrest/rewarming)
  - Poor prognosis: extensive restriction of diffusion in combination with other poor prognostic signs

## Brain Death

- Variability exists in prerequisites, clinical evaluation, apnea/ancillary testing to evaluate for brain death across hospitals.
- Prerequisites: irreversible CNS catastrophe; absence of severe acid-base, electrolyte, or endocrine abnormality; neg tox screen, clearance of CNS depressants (i.e., 5 half-lives since last dose or subtherapeutic level), absence of neuromusc blockade, eucapnia, euvolemia
- In principle, brain death = **coma** + **absence of brainstem reflexes** + **apnea** with irreversible etiology (NEJM 2021;385:2554-61)
- **Death by neuro criteria confirmed when all prerequisites met PLUS**
  - Consistent coma and brainstem reflex exams and positive apnea test OR
  - Incomplete brainstem reflex exams due to patient factors, positive apnea test, and one supporting ancillary test OR
  - Consistent coma and brainstem reflex exam, inconclusive/aborted apnea test, and one supporting ancillary test
- Clinical exam (by Neuro/NSGY attending or Neurocrit care fellow): coma exam (i.e. absence of response to nox stim in extremities & head (incl. absence of decorticate/decerebrate posturing), absent brainstem reflexes (pupils, oculocephalic [doll's eyes], VORs [cold calorics], corneals, cough, gag)

**Apnea testing** (Separate Protocol for ECMO)




Always perform in presence of RT AND Neurology/Neurosurgery Attending OR Neurocritical care fellow
Stop test and draw ABG for spontaneous respiration, ectopy, SpO2 <90% x30 sec, SBP <100
**Test pos if resp movements absent at PaCO2 >60 (or >20 inc from baseline if chronic retainer)**

- Ancillary tests (only if clinical exam/apnea test inconclusive): conventional angio, nuclear flow study, SPECT, EEG, TCDs
  - For EEG, order evoked potentials and ensure electrodes are tested (touched) at beginning of epoch (ask techs)

# Psychiatry — Consent & Capacity

## Three Elements of Valid Informed Consent (NEJM 2007;357:1834; NEJM 2017;376:856-867)

1. Relevant clinical information: at minimum: diagnosis, proposed intervention, its purpose, its basic risks/benefits, alternatives, and risks/benefits of alternatives (including no intervention)
2. Voluntary decision: decision is voluntary and w/o coercion from hospital staff or family/friends (advice/discussion are NOT coercion)
3. Capacity: confirm patient is able to make a decision about the ***specific question*** being addressed at the time it is being asked

## Exceptions to Informed Consent

1. Emergency in incapacitated patient: 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 (p26831) if time allows. If not, need to make a team-based clinical judgment of emergency.
2. Lack of capacity or competency: turn to the appropriate HCP/surrogate decision-maker; note **only a court-appointed surrogate can override an incapacitated patient's verbal refusal** or physical resistance in a non-emergency situation

## 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. When deemed lacking, the judge may make a global determination or define time and domain-based parameters within which a legally appointed surrogate can make decisions on the patient's behalf.
- **Any physician can determine capacity**. Psychiatry should be consulted only for complex cases (e.g. neuropsychiatric illness impairing decision-making, disagreement between patient/family/medical team.) Be ready to tell consult: Specific decision the pt is asked to make, the decision pt offers, risk/benefit of intervention. Be prepared to accompany consultant during evaluation if needed to provide info to pt re: proposed dx test/tx/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 consistent choice** | Ask pt to indicate a choice. Inability to express one or to participate in assessment is equivalent to incapacity in a sufficiently high stakes situation. Frequent reversals of choice may also indicate lack of capacity. |
| **Understand relevant information** | Ask pt to describe understanding of the information given by the physician (dx, proposed intervention, purpose, risks/benefits, risks/benefits of alternatives including no intervention). Some cueing is OK here. Do not overestimate what is reasonable to expect from a lay person. |
| **Appreciate the situation and its consequences** | Ask pt to describe views of diagnosis, interventions, and likely outcomes. Is patient aware of their illness? Its seriousness? Consequences? What are the patient's non-medical priorities that factor into their decision? |
| **Able to manipulate info in a rational fashion** | Ask patient to compare treatment options, consequences, and reasons for choice. Does the patient weigh the risks and benefits logically? A rational choice may not be the same as a "good" one. |

## Surrogate Decision-Makers

- Encourage each pt to sign legal HCP form specifying surrogate. "Confirmed" (by court procedure) when pt lacks capacity and retains ability to refuse/resist medical activities. Confirmation of HCP is not needed if pt is incapable but agreeing, assenting, or unconscious.
- Surrogate's job is, ideally, to make the decision pt would have made for themself if able — **not** what the surrogate wants. If a pt's wishes cannot be known, the surrogate should make the decision in the "best interests" 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 where MA Probate Court grants a guardian the authority to make decisions on behalf of someone who 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 have capacity to designate a HCP*. For help: 'Guardianship Team'
- Emergency guardianship is not required to provide lifesaving treatment & should not delay care (see above).

## 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, NP, psych RN, psychologist, SW, or police officer uses to apply for involuntary psych eval and possible hospitalization of pt who, based on MD's exam & opinion, requires hospitalization to avoid likelihood of serious harm by reason of primary mental illness. Authorizes transport to psych facility and, if necessary, restraint of the pt to maintain safety
- Issued when likelihood of serious harm to self and/or others is imminent (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 *intoxication, withdrawal, delirium, dementia, 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 they are unable to protect themself in the community.
- **Section 12b** (reverse side of the "pink paper,"): completed by evaluating psychiatrist, authorizing involuntary psych hospitalization

## Safety (Medical) Hold

- Order that can be placed that empowers staff to prevent pt from leave AMA when the following criteria are met: (1) Patient lacks capacity to leave the hospital and is attempting to do so (2) There is imminent risk of harm to self and/or others from leaving AMA (3) Pt does not meet S12 criteria (4) Physical restraint or chemical tranquilization would be excessive
- Staff may prevent a pt under a safety hold from leaving AMA using non-physical methods (e.g. verbal redirection, standing in a doorway or exit, preventing an elevator door from closing) but should not place themselves at risk or physically hold a patient.
- If the pt should escalate or become physically aggressive, consider involving security and then providers should follow restraint/seclusion protocols

# Psychiatry Agitation

## AGITATION MANAGEMENT 101

- Goals: 1) Safety of pt & staff; 2) Help pt manage distress (promote calm); 3) Avoid restraints; 4) Avoid coercive interventions
- General Considerations:
  - Take early notice of anger/fear, yelling, pacing/restlessness, sweating, aggressive body language. LISTEN to RN and PCA
  - Address any easily/quickly reversible issues: hunger, thirst, pain, communication breakdowns. Consider urinary retention, & constipation as sources of discomfort. Work up/treat any other contributors (delirium, psych d/o, substance intox/withdrawal).
  - Offer PO medications early in escalation process. Think about standing medication if recurrent concerns.
  - If pt requires restraints, should **always** receive med to help ease/lessen time in restraints. Monitor for ongoing need and discontinue restraints ASAP. Restrained pts are at risk of aspiration, rhabdomyolysis, MSK injury, delirium. **Restraints/seclusion may be traumatizing, are a/w morbidity/mortality, and result from treatment failures.**

## APPROACH TO VERBAL DE-ESCALATION: DEFUSE (NUEMBLOG) (West J Emerg Med 2012;13:1)

**D**ecide if situation is appropriate for verbal de-escalation. Clues include a patient who is responsive, engageable, not an active threat to safety. Multiple staff should be available as de-escalation team, but only 1 verbally interacts with patient.
**E**nsure safety. Ensure adequate backup. Clear area of potential weapons (loose objects, supplies). Respect personal space (two arm's length between you and patient). Be aware of body language and positioning (hands visible, stand at angle to patient).
**F**orm relationship. Introduce yourself by name and title. Ask what they like to be called. If they are responsive in conversation, consider asking, "Will you allow us to help?". Use short sentences and simple vocabulary and give patient time to process.
**U**tilize interests. Identify patient's wants and feelings. Agree as much as possible, either in truth, principle, odds, or to disagree. Reinforce that you will let no harm come to the patient.
**S**et limits. Speak matter-of-factly about consequences for bad behavior. Offer choices for behavior, even if it's between oral or IV meds. Use repetition as needed until you are heard by patient.
**E**nforce/Evaluate. If aggression escalates and violence seems imminent, withdraw and mobilize help. Once the situation is defused, by either verbal de-escalation or medication, debrief staff and/or patient.

## CHOOSING MEDICATIONS – CHART REVIEW:

- Consider current standing medications. Can any of these be used for acute agitation?
- Allergies/adverse reactions
- Major medical comorbidities (heart conditions, h/o arrhythmia, OSA, COPD, Parkinson disease, fall risk)
- MAR: previous medications for agitation, medication burden (is patient near max daily dose for an agitation medication?)
- QTc: be mindful of borderline QTc or heart disease. If no recent EKG, do not defer giving meds to obtain one – obtain when next able.

## MEDICATION OPTIONS & SPECIAL POPULATIONS: *always offer PO option 1st if pt able to safely take PO* (ELLUCID POLICY)

- General principle: Treat exacerbations of the underlying condition with the agent intended for it, within medical reason:
  - GABA withdrawal, catatonia, stimulant intoxication → benzodiazepines
  - Psychosis → antipsychotics
  - Mania → antipsychotics/mood stabilizers/benzodiazepines
  - AVOID antipsychotics in patients with catatonia and NMS
- Medication options: (MDD = Max Daily Dose, ODT = Oral Disintegrating Tablet)
  - Consider consulting psychiatry for pts requiring IM meds
  - **Quetiapine** (PO) 12.5-100mg. Can lead to orthostatic hypotension.
  - **Trazodone** (PO) 12.5-100mg. Good for elderly; limited delirium risk. Can precipitate mania in bipolar disorder.
  - **Olanzapine** (PO, ODT, IM, IV) 2.5-10mg. MDD 20mg. NOTE: **do not** co-administer parenteral benzos with parenteral olanzapine within 4 hours (risk of lethal respiratory depression).
  - **Haloperidol** (PO, IM, IV) 2.5-10mg. MDD 30mg. IM haloperidol has greatest risk for EPS side effects. IV haloperidol has greatest QTc-prolonging potential (check if QTc >550), esp in medically ill populations (Psychosomatics 2018;59:105).
  - **Diphenhydramine** (PO, IM, IV) 12.5-50mg. Sedating, often not used alone but as an adjunct w/ IM Haldol to decrease EPS risk. Used with haloperidol and lorazepam with caution in cases of very severe agitation/physical aggression ("5-2-50").
  - **Hydroxyzine** (PO) 25-50mg. Antihistamine with anxiolytic effects, rapid onset. Delirium risk. Possible QTc prolongation.
  - **Risperidone** (PO, ODT) 0.5-2mg. MDD 8mg. NOTE: highest risk of EPS among second generation antipsychotics.
  - **Chlorpromazine** (PO, IM, IV) 25-100mg. Can lead to HoTN. Can also lower seizure threshold. Avoid in pregnancy.
  - **Lorazepam** (PO, IM, IV) 0.5-2mg. Use caution with older adults due to delirium and COPD/OSA due to hypercarbia. NOTE: **do not** co-administer parenteral benzos with parenteral olanzapine within 4 hours (risk of lethal respiratory depression).
- Special populations
  - **Geriatric:** PO: consider trazodone 12.5-25mg or quetiapine 12.5-25mg. If cannot take PO: olanzapine 2.5-5mg IM/IV.
  - **<18 years of age:** If <35kg, can do clonidine 0.05mg PO. If >35kg, can do clonidine 0.1mg PO. If severe and unable to take PO, can do olanzapine (<25kg: 1.25mg olanzapine IM, 25-70kg: olanzapine 2.5mg IM, >70kg: olanzapine 5mg IM).
  - **Parkinson's/Lewy Body Dementia:** PO: quetiapine 12.5-50mg. If cannot take PO: lorazepam 0.5-1mg IV/IM. First-gen antipsychotics + 2nd-gen antipsych (olanzapine, risperidone) avoided 2/2 dopaminergic blockade, which could worsen EPS
  - **Substance withdrawal: (**See Alcohol Use Disorder & Withdrawal, Opioid Use Disorder & Withdrawal)
- Consider APS consult when: 1) Agitation is severe and refractory to initial pharmacological treatments and/or non-pharmacological interventions have been exhausted; 2) There is need for specialized interventions such as ECT; or 3) There are risks of severe complications from escalating doses of PRNs (NMS or prolonged QT).

# Psychiatry — Delirium

## DELIRIUM: definition per DSM-V-TR

1) Disturbance of consciousness (i.e. reduced ability to focus, sustain, or shift attention);
2) Additional disturbance in cognition (memory, orientation, language, visuospatial ability, or perception);
3) Change from baseline, develops over a short period of time (usually hours to days) & tends to fluctuate;
4) Not better explained by another neurocognitive disorder and does not occur in the context of severely reduced arousal/coma.

Complications: a/w ↑mortality (JAMA 2010;304:433), ↑institutionalization (Lancet 2014;383:911), ↓cognition (NEJM 2012;367:30)

## RECIPE FOR DELIRIUM = VULNERABLE BRAIN + ACUTE INSULT

- Risk factors: older age, stroke, dementia, TBI, vascular disease/ HTN, SUD, visual/hearing impairment, psychiatric disease
- Acute insult: Life-threatening etiologies (**WWHHHHHIIMMPS**): **W**ithdrawal (from EtOH or benzodiazepines); **W**ernicke's; **H**ypoxia (i.e. MI, CHF, anemia); **H**ypoglycemia; **H**ypoperfusion of CNS (esp. in patients w/ vascular disease, common after surgery); **H**yper/hypothermia; **H**ypertensive encephalopathy; **I**ntracerebral hemorrhage; **I**nfection; **M**eningitis/encephalitis; **M**etabolic disturbances (renal/hepatic failure, DKA, acid-base, adrenal); **P**oisoning (heavy metal, anticholinergics, drug-drug); **S**eizures/Status Epilepticus
  - Other considerations: states of inflammation such as infection (↑ permeability of the blood brain barrier), disturbances or big swings in HR/BP (esp. in pts w/ vascular disease, ↓ cerebral perfusion, common after surgery), intoxication (including iatrogenic), withdrawal, metabolic disturbance, endocrinopathy, vitamin deficiencies, toxins

## DELIRIUM EXAM

- **4AT tool** (available in MDcalc)- Sp/Sn 80-89% (AAG 2021; 50:733)
- Tests level of consciousness, attention, orientation and acuity

## AVOID DELIRIUM BY PREVENTION

- **Minimize deliriogenic meds**: anticholinergics, antihistamines, benzodiazepines, opioids
- **Preventative meds:** suvorexant (more robust evidence than trazodone)
- **Ensure:** no urinary retention, regular bowel movements, & adequate pain management
- **Precautions**: frequent reorientation, mobilize with PT/OT, OOB to chair, **glasses/hearing aids**, minimize lines/telemetry/catheters, early volume repletion if c/f hypovolemia. **Avoid** room changes or physical restraints (JAMA 2017;318:1161)
- **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

**Most important step**: identify **UNDERLYING CAUSE** w/ special attention to life-threatening conditions (see Recipe for Delirium, above)**:**

- Maintain IV access if possible
- Behavioral management: implement delirium precautions, modified deliriogenic medications, treat circadian dysfunction
- **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)

Behavioral/environmental management >> 1:1 sitter (re-orients) >> meds >> restraints (deliriogenic)

**Medical Management** (NEJM 2017; 377:1456)

- **For HYPERactive delirium/AGITATION → start low + PRN, escalate to scheduled**
  - Haloperidol- least sedating, IV>PO as reduces EPS risk 0.25-0.5mg IV q30-60m PRN vs 0.5-1mg PO q4h PRN vs. IM q1h PRN
  - Olanzapine- most sedating, lowest EPS risk - 2.5-5mg SL/PO/IM qd-q4h PRN
  - Quetiapine- PO only, 12.5-25mg PO q1h PRN
- **If continued severe agitation or requiring > 2 doses antipsychotic → consider Psychiatry consult**:
  - Haloperidol PRN: double PRN dose q20 min until effective, ~5-20mg IV
  - 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. Prolonged antipsychotic use in older adults can increase mortality**
- **Avoid benzos as may worsen delirium**, though warrants risk/benefit as in some cases risk of withdrawal > risk of continuing
- For patients with prolonged QTc or symptoms refractory to medications, discuss with psychiatry

## WHEN TO CONSIDER PSYCHIATRY CONSULTATION

- **Escalating/persistent delirium**, underlying neurodegen, disorder (esp. PD), hx TBI, psych disorder, SUD
- Significant co-morbidities (CV disease/critical illness)
- **Know the following prior to calling:** workup done thus far to identify underlying cause and past/current medication list

## WHEN TO CONSIDER NEUROLOGY CONSULTATION

- New focal finding suggesting stroke: *Stroke* Neuro p*20202*
- Other concerning findings (convulsions, meningismus, e/o elevated ICP, abnl spot EEG/LP): *General Neuro p20702*
- **Know the following prior to calling:** last seen well, baseline deficits, anticoagulation

# Psychiatry

Psychosis

## MENTAL STATUS: document **daily** if new AMS or worsening psychiatric sx (AFP 2024;109:51)

**APPEARANCE/BEHAVIOR**: Grooming/hygiene, eye contact, attitude/cooperation, abnormal movement (fidgeting, tics, TD)
**SPEECH/LANGUAGE**: Mechanics: rate, volume, prosody, articulation, and fluency. Watch for speech latency, paucity of speech, mutism, echolalia (copying provider's speech), verbigeration (repeating meaningless phrase like a "broken record").
**THOUGHT PROCESS**: Linear, logical, goal-directed vs. disordered. Types of thought disorder: circumstantial (non-linear; initially veers off but still goal-directed) > tangential (nonlinear, not goal-directed; ultimately loses topic entirely) > flight of ideas (rapid jumps between somewhat-connected thoughts) > word salad (incomprehensible speech). Disorganization: deficiencies in logical organizing of thoughts needed to achieve goal. Thought blocking: interruptions in thought causing inability to respond.
**MOOD/AFFECT**: Mood: subjective description of emotional state. Affect: physical expression of emotional state.
**THOUGHT CONTENT/PERCEPTIONS**: SI/HI, delusions vs. overvalued ideas, hallucinations, obsessions, poverty of content
**COGNITION**: Level of consciousness, orientation, Luria sequence, MOCA
**INSIGHT/JUDGMENT**: Insight: pt recognizes sx as pathological/accepts dx. Judgment: pt's action based on insight.

## PSYCHOSIS WORKUP AND DIFFERENTIAL DIAGNOSIS

- **Characteristics**: delusions, thought/behavior disorganization, hallucinations: auditory > visual (often neuro/medical, esp. delirium, dementia, alcohol withdrawal) > tactile (rare; often substance-induced) > olfactory (rare; neuro/temporal lobe involvement)
- **Ddx**:
  - Psychotic/mood disorder: schizophrenia (no clinically significant mood episodes), schizoaffective (primarily psychotic disorder w/ some mood episodes), mood disorder w/ psychotic fx (primarily mood disorder w/ some psychotic symptoms)
  - Neurocognitive disorder: intellectual disability, autism spectrum, dementia, and neurodegenerative disorders
  - Medical mimics: **delirium (visual hallucinations)**, migraine, steroid-induced, lupus encephalitis, porphyria, Wilson's, epilepsy, autoimmune/paraneoplastic encephalitis, Charles Bonnet syndrome, hepatic/uremic encephalopathy, neurosyphilis, prion dz
  - Substance-induced: Can exclude if hx of psychosis during sobriety. GABAergic (i.e. EtOH, benzo) withdrawal (VH, formication; 24hrs - 5d); cocaine/amphetamine intox (persecutory delusions, formication); cannabis intox (paranoia, persecutory delusions); hallucinogen intox (VH, paranoia). Note: isolated opioid intoxication/withdrawal does **not** typically include psychosis.
  - New-onset primary psychotic disorder in >50yo is rare. Medical causes (delirium, dementia, CNS pathology) more likely
  - **Refer to psych**: outpatient = always, inpatient = if decompensated ± safety concerns
- **Labs**: CBC, BMP, TSH, CRP, UA, tox screens (should include **separate order for urine cannabinoids** as these are no longer routinely tested for but critical for dx), med levels, delirium w/u (see *Delirium*). Consider treponemal ab, HIV, B12, ANA, pregnancy. Imaging not routinely indicated unless atypical presentation or neuro/medical etiology suspected.

## TREATMENT BASICS

- **General principles:**
  - Confirm home antipsychotics/mood stabilizers early in admission & continue *only if* pt reliably taking; otherwise, dose reduce/hold pending psych consult. Ask if pt on long-acting injectable meds/date of last injection and which PRNs work well. Get collateral from DMH case manager, family, shelter, or Freedom Trail Clinic (if on clozapine). Hold if catatonia on ddx.
  - If on >1 standing antipsychotic, confirm before ordering (otherwise avoid). If on valproate, Li, clozapine, check level ASAP.
  - Continue home benztropine, benadryl, propranolol, clonidine (if prescribed) to reduce EPS. Note: lamotrigine has SJS risk, if not taking for >2-3 days re-start at 25mg QD, uptitrate q2w (contact pharmacy/psych for questions).
- **Clozapine**: Uniquely effective, but many SE. Continue inpatient (withdrawal catatonia if stopped suddenly).
  - Neutropenia agranulocytosis in <1% of pts (84% w/in first 3mo); weekly CBC diff for first 6mo, biweekly for next 6mo, then monthly. May need to DC if ANC <1.5k. **Requires REMS training/monitoring, consult psych/pharmacy w/ questions.**
  - Risk for myocarditis, withdrawal catatonia, severe constipation/bowel obstruction. Infx can ↓ metabolism and ↑ levels.
  - On admission: continue med to avoid w/d catatonia, ensure bowel regimen, check levels if infection or tobacco use
- **Extrapyramidal symptoms (EPS)**:
  - Dystonia: muscle spasm incl. oculogyric crisis, torticollis, trismus, opisthotonos, laryngospasm. (**risk of rapid airway obstruction**), **Tx**: Benztropine 2mg IM/IV OR Benadryl 50mg IM/IV → repeat in 20 min if no effect → Ativan 1-2mg IM/IV
  - Pseudoparkinsonism: reversible; bradykinesia, tremor, rigidity, masked facies, shuffling gait. **Tx**: anticholinergics
  - Akathisia: subjective feeling of inner restlessness, inability to stay still. **Tx**: low dose BB (e.g. propranolol)
  - Tardive dyskinesia (TD): Involuntary, repetitive, arrhythmic movements: lip smacking, chewing, puckering, writhing. Occurs w/ long-term antipsychotic use, often irreversible. **Tx:** VMAT2 inhibitors

## ANTIPSYCHOTICS & SIDE EFFECTS (AFP 2010;81:617)

| | Anti-cholinergic | Prolong QTc | EPS | NMS | Prolactin ↑ | Postural hypoTN | Sedation | HLD | Wt gain | DM2 | Sexual dysfxn |
|---|---|---|---|---|---|---|---|---|---|---|---|
| haloperidol | + | + | ++ | ++ | +++ | + | + | + | + | + | ++ |
| chlorpromazine | +++ | ++ | + | + | ++ | +++ | +++ | ++ | ++ | + | +++ |
| aripiprazole | 0 | + | + | + | 0 | + | + | 0 | 0 | + | + |
| olanzapine | + | + | + | + | + | + | ++ | +++ | +++ | ++ | + |
| quetiapine | + | + | 0 | + | 0 | ++ | ++ | ++ | ++ | + | + |
| risperidone | 0 | + | ++ | + | +++ | ++ | + | + | ++ | + | ++ |
| ziprasidone | 0 | ++ | + | + | + | + | + | 0 | 0 | + | + |
| clozapine | +++ | + | 0 | + | 0 | +++ | +++ | +++ | +++ | ++ | + |

# Psychiatry — Catatonia, NMS, & Serotonin Syndrome

## CATATONIA

- Definition: *Behavioral syndrome due to underlying condition* that can occur in the context of many psychiatric, neuro, or medical dx; marked by inability to move normally despite full physical capacity; waxes/wanes; pathophysiology incompletely understood.
- **Subtypes**: stuporous: immobility, mutism, withdrawal; excited: hyperkinesis, stereotypy, disorientation; malignant (**medical emergency**): sx 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) > dissociative disorders
- Neuro/medical: seizures/NCSE, autism spectrum, PRES, CNS lesion, infection, TBI, delirium, anti-NMDAR encephalitis, SLE
- Drug: dopamine-blockers, dopamine withdrawal, sedative/hypnotic withdrawal, hallucinogens, synthetic marijuana, opiates

**Diagnosis**: (Psych Scand 1996;93:129;)

Bush-Francis Catatonia Rating Scale (BFCRS)– 14-item screening (positive when ≥ 2 items) and 23-item rating scales (Positive when ≥ 4 items) OR the presence of 2-4 of the below signs for several hours:

| Observed Signs | Elicited Signs |
|---|---|
| -Immobility: Hypo-akinetic, not influenced by external stimuli<br>-Stupor: Decreased alertness, diminished response to voice/painful stimuli<br>-Excitement: Impulsive, stereotypic behavior<br>-Mutism: Verbally unresponsive while awake<br>-Speech mannerisms: Robotic speech, foreign accent, palilalia<br>-Behavioral mannerism: Odd, purposeful movements<br>-Posturing: Voluntarily maintaining a posture for a long time<br>-Echophenomena: Echolalia/echopraxia (mimic sound/movement)<br>-Stereotypy: Awkward non-goal-directed repetitive movements.<br>-Staring: Fixed gaze | -Ambitendency: Stuck on hesitant movement when the examiner verbally contradicts own nonverbal signal (extend hand and say "do not shake my hand")<br>-Waxy flexibility: rigid tone that is gradually overcome<br>-Automatic obedience: "Stick out your tongue. I want to write on it with a pen." (pt will stick out tongue)<br>-Negativism: Opposite/no response to instruction.<br>-Stimulus-bound behavior: Behavior tied to certain stimuli |

- Vital signs (malignant catatonia): hyperthermia (T >100.4 F), tachycardia, labile BP, tachypnea, diaphoresis
- Lab findings (malignant catatonia): Leukocytosis (15,000 – 25,000), CK ≥ 1000, and ↓ serum iron
- Lorazepam Challenge: **2mg IV x1** (0.5-1mg in frail/elderly). Partial relief of signs after 5 -10 minutes after is consistent with a diagnosis of catatonia. Negative challenge test does NOT rule out catatonia.
- **Differential dx**: delirium, dementia, stroke, PD, stiff person & locked-in syndromes, NCSE, akinetic & elective mutism, anti-NMDAR encephalitis; If **malignant***:* NMS, malignant hyperthermia, serotonin syndrome, DTs, CNS infection/vasculitis, anticholinergic toxicity

**Treatment**: (Gen Hosp Psychiatry 2017;48-1)

- **Always consult psych. HOLD antipsychotics/other D2 blocking meds.** Trend CK, BMP; q4h VS; IVF, supportive care.
- Treatment: 2mg IV lorazepam q6-8h, uptitrate as tolerated, max 24mg/day based on BFCRS. Hold for respiratory depression only, NOT sedation (catatonia sx can mimic sedation). If no response → **ECT** → **amantadine/memantine** → **anticonvulsants** → **aripiprazole/clozapine + lorazepam**

## NEUROLEPTIC MALIGNANT SYNDROME (NMS) (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 medication change that causes decreased dopaminergic tone (med list: Neurohospitalist 2011;1:41)
- **Risk factors**: initiation/increase of dopamine-blocking med or withdrawal of pro-dopamine med (typically occurs within hours/days, but can be idiosyncratic), withdrawal from EtOH/sedatives, hx of NMS/catatonia, basal ganglia d/o, exhaustion, dehydration, agitation
- **Labs**: ↑WBC and CK>1000 (correlates w/severity) most common, ↓ serum iron, mild ↑ LDH/alk phos/AST/ALT, ↑↓ electrolytes
- **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

| Stage | Clinical Presentation | Intervention/Treatment |
|---|---|---|
| **Early** | Mild rigidity, confusion, T<100.4F, HR <100 | • Stop offending agent & contributors (serotonergics, Li, anticholinergics)<br>• Aggressive fluids/supportive care ± **lorazepam** 0.5-2mg IV q4-6h |
| **Moderate** (may require ECT) | Moderate rigidity, T100.4-104F, HR 100-120 | • Cooling measures ± ICU<br>• **Bromocriptine** 2.5mg PO q8h *or* **amantadine** 100mg PO q12h |
| **Severe** (may require ECT) | Severe rigidity, ± coma, T >104F, HR >120 | • ICU level of care (if intubation required, midaz > propofol for sedation)<br>• **Dantrolene** 1-2.5mg/kg IV q6h x48h |

## SEROTONIN SYNDROME (SS) (NEJM 2005;352:1112)

- **Overview**: Exposure to serotonergic agent(s) leading to 1) Δ mental status 2) neuromuscular hyperreactivity (tremor, clonus, hyperreflexia) 3) autonomic instability (tachycardia, tachypnea, diaphoresis, mydriasis, hyperthermia, shivering, sialorrhea, hyperactive bowel sounds, diarrhea). Watch for rhabdo/AKI. *Note:* n/v/d common in SS prodrome but rarely seen in NMS
- **Causative agents**: amphetamines, bupropion, buspirone, carbamazepine, carbidopa-levodopa, cocaine, cyclobenzaprine, diphenhydramine, ergotamines, fentanyl, linezolid, lithium, LSD, MAOIs, MDMA, meperidine, methadone, methylene blue, metoclopramide, mirtazapine, ondansetron, SNRIs, SSRIs, St. John's wort, TCAs, tramadol, trazodone, triptans, tryptophan, VPA
- **Diagnosis**: Hunter's Criteria 84% sensitive 97% specific (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 **cyproheptadine** 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.

# Psychiatry Depression

## MAJOR DEPRESSIVE DISORDER (MDD)

- Epidemiology: common in general population. U.S. lifetime prevalence ~20%, F>M (JAMA Psych 2018;75:336)
- Screening: USPSTF recommends **universal screening of adults; PHQ-2**: to begin; **PHQ-9** to complete screening (AFP 2012;85:139)
- DSM-5-TR criteria: (mnemonic SIGECAPS): must have depressed mood and/or loss of **I**nterest/pleasure + ≥4 of following sx: change in **S**leep, worthlessness/**G**uilt, fatigue/decreased **E**nergy, poor **C**oncentration, change in weight/**A**ppetite, **P**sychomotor agitation/slowing, thoughts of death (not just fear of death) or **S**I.
  - Sx must be present over same **2w period** & cause significant **impairment/distress**
  - Ddx: other psych (e.g. bipolar, adjustment disorder, personality disorder, prolonged grief, PMDD), drug intox/withdrawal, meds, OSA, hypothyroidism, stroke, TBI, delirium, vit def, Huntington's dx, dementia, MS, HIV
- Tx: psychotherapy ± medication; combination > either alone (pharmacology > therapy) (APA 2019; J Clin Psychiatry 2008;69:1675)
  - SSRIs are 1st line: All 2nd-gen antidepressants are roughly equivalent (consider starting with **sertraline or escitalopram** as they have best combination of efficacy and acceptability (Lancet 2009;373:746). Response time for SSRIs may vary between 1-2 weeks up until 8-12 weeks, with an average of 6-7 weeks (Am J Psychiatry 2006 163:28)
  - Other common options: bupropion, mirtazapine, & SNRIs. **Bupropion** lowers seizure threshold and is C.I. if risk of seizure (seizure disorder, eating disorder, etc.), may aid in smoking cessation; caution in pts with renal/hepatic impairment (↑ concentration) or with cardiovascular disease (↑ BP). **SNRIs** may also ↑ BP. Consider **mirtazapine** in older adults ( ↑ appetite).
  - Use Mayo Clinic Depression Medication Decision Aid to choose meds based on side effect profile
  - Risk of death in TCA overdose, advising caution when Rxing TCAs to patients with history of suicidality or serious attempts
  - In addition to meds/psychotherapy, consider intensive outpatient programs (psychotherapy, case management, and medication management, often ~3hr/day 3days/week), partial hospitalization programs (multidisciplinary tx option where patients live at home but receive treatment throughout the day, often 5days/week), and inpatient hospitalization
- **Pregnant pts:** In mild/moderate MDD, consider psychotherapy first. In severe, or if psychotherapy unavailable, consider medication. If prior successful med trial, consider using that same antidepressant. Increased risk of cardiovascular defects with paroxetine. Possible SSRI use after 20 weeks a/w newborn PPH (Gen Hosp Psychiatry 2009;31:403).

**Side Effect Profiles of Commonly Prescribed Antidepressants** (Can J Psychiatry 2016;61:540; NEJM 2005;353:1819)

| Class | Drug | Anti-Cholinergic | Drowsiness | Insomnia/ Activation | Nausea/ Vomiting/Diarrhea | Wt Gain | Sexual Dysfn | Orthostatic HoTN | ↑ QTc | Usual Daily Dose (mg) |
|---|---|---|---|---|---|---|---|---|---|---|
| SSRI | Citalopram | - | +/- | ++ | + | + | +++ | + | ++ | 20-40 |
| | Escitalopram | - | - | ++ | + | + | +++ | + | +/- | 10-20 |
| | Fluoxetine | - | - | ++ | + | +/- | +++ | + | +/- | 20-80 |
| | Paroxetine | + | ++ | ++ | + | ++ | ++++ | ++ | - | 20-50 |
| | Sertraline | - | - | ++ | ++ | + | +++ | + | + | 50-200 |
| SNRI | Duloxetine | + | + | +/- | + | - | + | - | - | 30-90 |
| | Venlafaxine | ++ | + | ++ | ++ | - | +++ | - | +/- | 75-225 |
| Atypical | Bupropion | + | - | ++ | + | - | - | - | - | 150-450 |
| | Mirtazapine | - | ++++ | - | - | ++++ | + | + | + | 15-45* |
| Serotonin Modulator | Trazodone | - | ++++ | - | ++ | - | $ | ++ | ++ | 150-600* |
| | Vilazodone | - | - | ++ | +++ | - | +/- | - | - | 20-40 |
| | Vortioxetine | - | - | + | + | + | + | - | - | 5-20 |
| TCA | Amitriptyline | ++++ | ++++ | - | + | ++++ | ++++ | +++ | + | 50-150* |
| | Nortriptyline | ++ | +++ | - | - | +++ | +++ | + | + | 75-150* |

$ Risk of priapism, *nighttime dosing

**Dosing of Antidepressants:**

- Start at low dose, titrate q1-2 weeks. Adequate trial is 6-12 weeks at full dose; if poor tolerance/response after 4-6 weeks, augment with psychotherapy or other medications; consider switching SSRIs
- Advise re: initial side effects that they will develop tolerance to (e.g. GI upset, dizziness). Physical sx (sleep disturbance, appetite changes) usually resolve first, within days-weeks. Mood sx may take weeks to resolve. Sexual side effects may persist. **Caution:** SSRI use in bipolar disorder can precipitate mania. Continue taking antidepressants for at least 6 months after symptom remission

**Discontinuing Antidepressants:**

- Stopping requires tapering off over 2-4 wks to prevent discontinuation syndrome (affective sx, flu-like sx, sleep disturbance, GI upset, dizziness/balance/sensory sx, electrical sensation or 'brain zaps'). MAOIs reduction may cause psychosis.
- Paroxetine (short half-life, most likely to cause discontinuation sx): taper down 5-10 mg weekly over 4+ weeks
- Fluoxetine (long half-life): taper may not be needed for doses < 40 mg daily; if ≥ 40 mg daily, taper over 2 wks. If pt develops discontinuation sx, restart antidepressant or increase dose, then taper more gradually over 6-12 weeks

**When to Refer to Psychiatry**: concern for bipolar, failure of ≥2 adequate rx trials, severe MDD with SI/HI, psychosis, or catatonia.

# Psychiatry — Anxiety Disorders

## Generalized Anxiety Disorder (GAD)

- Epi: US lifetime prevalence 8%, 2-3x more prevalent among F vs M. (AFP 2022;106:157). Excess worry a/w CAD (Nat Rev 2012;9:360)
- Screening: USPSTF recommends screening of adult primary care patients (Grade B). 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).
- DSM-5-TR criteria:
  - A) Excessive anxiety/worry occurring most days for ≥6mo re: multiple life domains, that is:
  - B) difficult to control, and
  - 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 disorders.
- Tx: 1st line therapy = **SSRIs/SNRIs** and/or CBT (meta-analyses have found effect sizes ≈ equivalent). No individual SSRI/SNRI more effective; SSRIs have lower risk of insomnia/activation over SNRIs. **Escitalopram, citalopram, and sertraline** generally preferred
- Advise pts that symptoms may take 4-6 weeks to resolve. For first few days, anxiety and activation may worsen as SSRI takes effect. See *Depression* for dosing recommendations.
- Adjunctive therapy: Consider buspirone 10 mg, increase by 10mg/day q1-2weeks (note: little efficacy as an acute anxiolytic); gabapentin 300- 900 mg TID; hydroxyzine 25-50 mg QID; lorazepam or clonazepam 0.5-1 mg PO BID PRN for 4-6 wks while SSRI takes effect. If refractory, psychiatry may start risperidone/quetiapine. Consider propranolol 10 mg TID in patients without history of asthma and normal vital signs. Counsel pt on dependence of BZD, and always consider non-BZD options first

**Refer to Psych**: need for CBT, failure of 2 adequate SSRI/SNRI trials, severe GAD w/ recurrent panic, SI

## Panic Disorder

- Epi: US lifetime prevalence ♀7.0% & ♂3.3% (AFP 2015;91:617)
- DSM-5-TR criteria: A) Recurrent unexpected panic attacks; B) >1 month of persistent worry about panic attacks or their consequences, or >1 month of significant maladaptive change in behavior related to attacks; C/D) sx not better explained by drugs/meds/other psych disorders (e.g. social anxiety disorder, specific phobia, OCD, PTSD)
- Workup for panic attacks: vitals, ECG, BMP, CBC, thyroid panel, HCG, tox screen. Consider testing for pheochromocytoma, seizures, OSA, asthma/COPD if any clinical suspicion.
- Treatment: 1st line = CBT and/or SSRI (equally effective). See GAD above for adjunctive therapies during SSRI initiation.

**Refer to Psych**: need for CBT, severe symptoms, failure of 2 SSRI trials, SI

## Post-Traumatic Stress Disorder (PTSD)

- Epi: US lifetime prevalence 6%: ♂4.1%, ♀8%; higher in combat/severe disaster survivors (AFP 2023;107:273)
- Screening: Primary Care PTSD Screen (PC-PTSD-5): screens for trauma exposure then for sxs based on DSM criteria; score >4 with Sn 100%, Sp 85.2% (J. Clin. Psychol 2022;78:2299), though cutoff of 3 may be more accurate for female pts due to higher false negative rates (JAMANTW 2021;4)
- DSM-5-TR criteria:
  - A) Exposure to trauma;
  - B) Intrusive sx (recurrent, 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);
  - F/G) Lasting **>1mo** & causing significant distress (If <1mo, the diagnosis is Acute Stress Disorder).
- Treatment: trauma-focused therapy + SSRIs/SNRIs; tx of psych/SUDs comorbidities; clonidine, atypical antipsychotics; prazosin 1mg nightly, increasing 3-15mg over few months for sleep disturbance. Counsel pt on risks of orthostasis and rebound HTN for prazosin/clonidine if discontinued abruptly.
- **All care/conversations should be trauma-informed, recognizing that not all patients are ready to discuss trauma (and avoid probing patients on their trauma if so).**

**Refer to Psych**: all should be referred for psychotherapy ± pharmacotherapy (depending on complexity of needs)

## Obsessive-Compulsive Disorder (OCD)

- Epi: US lifetime prevalence 2.3%. Mean age of onset ~19-20, rarely develops after early 30s (AFP 2015;92:896)
- DSM-5-TR criteria: A) presence of obsessions (recurrent and persistent thoughts/urges/images that are intrusive and unwanted, and that pt tries to suppress) and/or compulsions (excessive or unconnected repetitive behaviors/mental acts that pt feels compelled to perform in response to obsessions or rigid rules to reduce or prevent anxiety/distress); B) obsessions/compulsions are time-consuming or cause significant distress/impairment; C/D) sx not better explained by drugs/meds/other psych disorders
- Treatment: 1st line = ERP and/or SSRI depending on pt preference, severity of OCD, and presence of depressive sx. Combination tx is most effective (Curr Neuropharmacol 2019;17:710). Adequate trial of SSRI is maximum tolerated dose for 12 weeks. OCD pts typically require higher doses than for other indications. If good response to SSRI, duration of treatment should be *at least 1-2 years* with taper off over several months (AFP 2015;92:896). 2nd line = clomipramine, venlafaxine, or atypical antipsychotics.

**Refer to Psych**: need for CBT, severe symptoms, failure to respond to 2 high-dose SSRI trials, SI

# Psychiatry — Alcohol Use Disorder & Withdrawal

## Substance Use - General Principles

**Screening:** Ask all primary care pts & inpatients about current and lifetime substance use. USPSTF recs screening for *unhealthy* use.

- EtOH: AUDIT-C screens for unhealthy use, CAGE detects dependence
- Other substances: "How many times in the past year have you used a recreational drug or used a prescription medication for nonmedical reasons?" (Arch Int Med 2010)

**History**

- Most recent use, quantity, frequency, route of ingestion, triggers for use
- Benefits vs. harms of use; medical, psychiatric, and behavioral complications of use; harm reduction practices
- Age of first use, family hx of use disorders, periods of abstinence
- Treatment hx: Medications, structured treatment settings, mutual support groups. Current goals (↓ amt or freq of use vs. abstain)

**Diagnosis**

- **Use ≠ disorder.** Assess for use disorder of all substances reported by number of DSM-5-TR criteria met (impaired control, social impairment, risky use, and pharmacological criteria): 2-3 = mild, 4-5 = moderate, ≥6 = severe. Once criteria for use disorder is no longer met, can classify as early remission (>3 months but <1y) or sustained remission (>1y).
- Ask about 1° vs. 2° substances used. *"Of the substances you use, is there one you identify as the biggest problem?"*
- Avoid using PSUD ≠ DSM diagnosis = **stigmatizing while being diagnostically/therapeutically meaningless.**
- Tox screens alone should not be used to diagnose SUDs. False positives and negatives are possible. Use tox screen to check for concomitant substance use, monitor opioid use, and initiate conversations around use with patients.

| DSM-5-TR Criteria for SUDs |
|---|
| 1. Substance taken in **larger amounts** and/or over a longer period than intended |
| 2. **Unsuccessful efforts to cut down** or control use |
| 3. A **great deal of time is spent** to acquire, use the substance, or recover from effects |
| 4. **Craving** or strong desire or urge to use the substance |
| 5. Recurrent use resulting in a **failure to fulfill major role obligations** at work, school, or home |
| 6. Continued use despite **persistent/recurrent social or interpersonal problems caused by substance** |
| 7. Important social, occupational or recreational **activities given up** or reduced because of use |
| 8. Recurrent use in **physically hazardous situations** |
| 9. Use continued despite persistent or recurrent **physical or psychological problem** that is likely caused or exacerbated by the substance |
| 10. **Tolerance**, defined as ↑amount of substance to achieve desired effect; or ↓ effect w/ same amount |
| 11. **Withdrawal**, defined as characteristic withdrawal syndrome for the substance; or pt is taking substance to relieve or avoid w/d symptoms |

**Approach:** Person-first language and trauma-informed care. People w/ SUD experience bias and discrimination from healthcare providers. Address drivers of self-directed d/c: pain, agitation, discomfort, and allowing pts to leave the floor (MGH policy) (Subst Abus 2020;41:519). Involve ACT early. Consider risks of escalation before directly involving security (e.g. may have security in hall on standby).

**Treatment**: Medications: many can be prescribed by PCP. Counseling: MI, CBT; Peer support: recovery coach, AA/SMART recovery

**SUD Levels of Care** (Boston Area and MGH SUD Resources.)
Levels of care usually progress from hospitalization/"detox" " CSS " TSS " long-term residential tx " sober living

| Inpatient | | | Outpatient | | |
|---|---|---|---|---|---|
| Acute Treatment Services (ATS): Medically Supervised Withdrawal/ "Detox" | Clinical Stabilization Service (CSS)/Transitional Support Service (TSS) | Dual Diagnosis Units | Long-Term Residential Treatment ("Halfway Houses") | Partial Hospitalization Program (PHP) | Intensive Outpatient Program (IOP) |
| -Medical mgmt of acute w/d in a standalone detox center.<br>-Not best for pts with risk of severe alcohol withdrawal.<br>-LOS: 4-7d<br>-Patients cannot go to ATS once admitted to the hospital | -Inpt programs to transition from ATS/hospital to longer treatment; very structured with counseling.<br>-Usually go from CSS to TSS.<br>-D/c coord: ACT SW<br>-LOS: 14d (CSS), 30d (TSS) | -Inpt locked psych unit, address comorbid SUD + 1° psych disorders.<br>-Often reserved for pts w/ severe comorbid sx +/- acute safety concern. (i.e mania, psychosis, SI)<br>-D/c coord: Psych c/s<br>-LOS: 3-7d | -Covered by insurance<br>-Offer groups, counseling and attendance at outside mutual support<br>-Few offer meds esp in OUD (JAMA 2020;324:804).<br>-D/c coord: ACT SW<br>-LOS: 6-12mo | -Highly structured outpt treatment, 6-8h/d for 5d/w.<br>-Intensive group therapy; tx for both SUD and MH concerns.<br>-D/c coord: Psych<br>-LOS: 1-3w | -Outpt., less intensive than PHP; usually ~3h/d for 3d/w<br>-Provides psychoeducation/therapy.<br>-D/c coord: ACT SW<br>-LOS: 1-3mo |

## Alcohol Use Disorder (AUD)

**Diagnosis and Health Effects**

- Diagnose AUD w/ DSM criteria. Quantify use to counsel re: risks. 1 standard drink = 14g ethanol (5oz wine, 12 oz beer, 1.5 oz spirits)
- Risky use ↑ risk for health consequences (not part of SUD criteria). Includes drinking while pregnant; binge drinking: ≥5 drinks/occasion for men, ≥4 for women; heavy drinking: ≥15 drinks/wk for men & ≥8 drinks/wk for women or binge drinking 5 or more days the past month (NIAAA).
- Chronic use: Cytopenia (low Hb, WBC, Plt); low K/Mg/Ca/Phos/VitD (EtOH toxic to renal tubules and ↓GI absorp); ketoacidosis (↓ gluconeogenesis → rel. hypoglycemia → ↓ insulin → ketosis); lactic acidosis (↑ratio of NADH/NAD) (NEJM 2017;377:1368), GI effects including gastritis, gastric/duodenal ulcers, pancreatitis, hepatic injury & progression to cirrhosis.

**Treatments for Moderate-Severe AUD**

- Psychosocial: See above. 12 step program↑ rate of abstinence compared to other counseling methods (Cochrane Rev 2020)

- FDA approved *first line*: naltrexone, acamprosate; *second line*: disulfiram (JAMA 2018; 320: 815)
  - Naltrexone (↓reward/cravings through mu-opioid receptor blockade) PO can start at 50 mg (12.5-25 mg if risk of adverse effects)→50-100mg daily or IM (Vivitrol) 380mg q4w (CI: acute hepatitis/ALF, current opioid use or on bup or methadone). Side effects: nausea, fatigue, ↓appetite. Monitor liver enzymes q6mo. Naltrexone likely > acamprosate (JAMA 2006;295:2003)
    - Assess for OUD first as Naltrexone will block effects of opioids and precipitate withdrawal
  - Acamprosate (↓cravings) 666mg TID (Adjust dose to 333mg TID at CrCl <50, CI: CrCl<30, pregnancy)
  - Disulfiram (→ disulfiram-ethanol reaction: nausea, flushing, vomiting, sweating, hypotension, palpitations, rarely serious CV rxs): Start PO 125-250mg daily → 250-500mg/d maintenance dose (CI: psychosis, severe myocardial disease)
    - Only for patients in sobriety wishing to abstain. NOT advised to "reduce" active drinking (JAMA 2018; 320: 815)
- Non-FDA approved, consider when not responsive to naltrexone or acamprosate: topiramate (100-150mg BID), gabapentin (~600mg TID) (Addiction 2019;114:1547), baclofen (5mg TID -> 15mg TID) (Am J Psych 2018;175:86)
- Success can range from reducing heavy drinking days to abstinence. Utilize principles of harm reduction. Set goals with patient
- Risk of **malnutrition** with alcohol use. Assess lytes. Consider MVI w/ folic acid, thiamine daily (Drug Alcohol Depen 2017;179:229)

**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>IM 500mg TID x7d (*infuse over 30 mins to prevent anaphylaxis*) → 100mg qd until no longer at risk (Note: no consensus on dosing/duration; however, risk of excess B1 unclear while untreated W-E → irreversible W-K)
  - Ppx in those at risk: IV 200mg X1d > 200mg PO BID X4d (find under Alcohol Withdrawal Order set – Adjunctive Medications) 100mg qd at discharge until no longer at risk
- 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: ↑GABA stimulation → glutamate upregulation. After chronic stim, GABA receptors less sensitive & require more EtOH to balance increased glutamate. Abrupt cessation: ↓GABA → unbalanced glutamate → noradrenergic surge → ↑dopamine
- EtOH eliminated via approx 0th-order kinetics: approx. 15-20 mg/dL/hour. Blood EtOH clearance calculator.
- BAC effects vary widely by person and chronicity of EtOH use. For many, BAC can be approximated grossly as: <80 mg/dL: legal driving limit // 100 mg/dL: impaired judgment // 200 mg/dL: confusion/staggering // 300 mg/dL: stupor // 400 mg/dL: coma/death

**Evaluation:**

- H&P: Time of last drink, hx severe withdrawal & complications (withdrawal seizures, delirium tremens, alcoholic hallucinosis, ICU/intubation), co-ingestions (including BZD), EtOH use hx, recent changes in use, assess for active SI and concurrent psych dz
- Labs: CMP, CBC, serum osm if HCO3 <15 or AGMA (2/2 ketoacidosis), LFTs, CPK if found down (>5K = rhabdo), tox screen, serum EtOH (clear ~15-35 mg/dL/h, chronic = faster metab, higher tolerance) (J Forensic Sci 1993;38:104), pregnancy test if of childbearing potential > consult OB if in third trimester/at risk of pre-term delivery/concern for Fetal Alcohol Syndrome

**Subtypes and Management:** Sx vary by time after last drink, developing within hrs to days after cessation/reduction in use that has been heavy and prolonged (Diaphoresis, HR>100, hand/tongue tremor, insomnia, nausea/vomiting, transient visual/tactile/auditory hallucinations, agitation, anxiety, GTC seizures). Prediction of Alcohol Withdrawal Severity Scale: PAWSS

- Initial Tx for all EtOH withdrawal: IV/IM thiamine, D5-LR to fix ketoacidosis, replete lytes (esp Phos/K), folate 1mg qd, MVI, place on CIWA (q1-4h assessment, d/c once CIWA-Ar <8 for 24h or 6 consecutive scores less than 8), offer ACT c/s for AUD treatment
- **Mild withdrawal** (CIWA-Ar <10): Can be managed in ambulatory setting with supportive care (non-caffeinated fluids, MVI, thiamine 100mg PO 3-5D, RTC precautions) (ASAM 2020); or can consider taper of gabapentin>> PO BZD (Alcohol Clin Exp Res 2009:33:9):
  - Gabapentin 1200mg loading dose + 600mg q6h Day 1 or 1200mg/d 1-3D, tapered to 300-600mg/d up to 4-7D
- **Mild-moderate withdrawal** (CIWA-Ar: 10-18): Within 48h; tremors, sweats, ↑HR, ↑BP, HA, anxiety, intact orientation.
  - **Treat with EtOH withdrawal order set.** Typically BZD >> phenobarbital (unless contraindication to BZD or hx of comp. withdrawal). Some patients benefit from adjunct medication. Consider carbamazepine or gabapentin in addition to BZD.
- **Severe withdrawal** (CIWA-Ar >19): **ALWAYS TREAT, can be fatal. IV** BZD vs. phenobarb using EtOH withdrawal order set, as detailed below. Predictors: hx of DT/sz, comorbidities (especially TBI), age>65, ↑BP, ↓Na/↓K, Plt <150 (JAMA 2018;320:825).
  - **Seizures**: 6-48h; typically 1x GTC or burst of multiple GTCs in a short period. If status epilepticus, consider other etiologies. Should be immediately treated to prevent another seizure. Fast-acting BZD: lorazepam, diazepam
  - **Alcoholic hallucinosis**: 12h-48h; visual/tactile >> auditory (pt typically aware that hallucinations are not real), clear sensorium.
  - **Delirium Tremens (DT)**: 72h-3d, up to 2w; tremors, sweats, ↑HR, ↑BP, fever, disorientation, inattention, hallucinations (pt typically unaware that hallucinations are not real), agitation; usually CIWA >20.

| ALCOHOL WITHDRAWAL TREATMENT: *Use Epic Order Set & Reference Ellucid Guidelines* | | |
|---|---|---|
| | **Benzodiazepine** (BZD) | **Phenobarbital** (PB) |
| When to use | Generally 1st line. Mild-mod w/d sx, no recent (within last 2-3 years) complicated w/d (See Figure 2 of Ellucid guidelines) | Recent (within last 2-3 years) DTs, seizures, ICU admissions for w/d; patient preference for phenobarb; Resistant Alcohol Withdrawal (RAW)/ Refractory Alcohol Withdrawal: severe or complicated withdrawal or CIWA scores not improving despite high doses of BZD |
| Notes | CI: Acute angle closure glaucoma, AMS/delirium, Active DT, not responding to BZD (see resistance).<br>Resistance (>6mg lorazepam/h) or BZD toxicity (like DTs) w/ escalating dose.<br>Consider switch to phenobarb if CIWA scores not improving despite high doses of BZD.<br>Considerations: Diazepam, chlordiazepoxide: Longer half life, often preferred for smoother withdrawal course and breakthrough control<br>Lorazepam: (↑half-life, lower risk of oversedation if concerned for liver dx) | CI: hx SJS/TEN; hx AIP; unstable respiratory status<br>Relative CI: high likelihood of self-directed d/c, limited period of recent use (ex: completed withdrawal treatment in last 10 days)<br>Side effects: apnea, hypoventilation, ↓HR, ↓BP, laryngeal spasm<br>Medication interactions: CYP3A4 inducer – decreases conc. of many rx including apixaban. May enhance effects of anti-HTN meds. |
| Mech. | GABA-ergic. $t_{1/2}$ varies by BZD | GABA-ergic and anti-glutamate receptor. Auto-taper, long half-life (1-4d), predictable effect, wide therapeutic window. |
| Dose | **PO > IV** if able to take PO<br>No evidence showing superiority of effectiveness among BZDs<br>**PRN**: Use CIWA-Ar scale when patient can appropriately communicate. Avoid treating for subjective symptoms. mMINDS for patients who cannot communicate.<br>**Standing**: Generally not recommended unless significant difficulty in obtaining serial scores<br><br>**Lorazepam** shorter acting and preferred in liver disease or older adults. **Diazepam** and **chlordiazepoxide** are longer acting and have higher risk of over sedation in susceptible patients<br><br>Monitor CIWA score, what sx they are scoring for, and total daily BZD requirements. | **Loading dose:** Dosing should be based on **ideal body weight.** Standard 6-10mg/kg as 3 divided doses (several factors affect recommended dose – See Figure 3 for floor management). IV on medical floor requires pulse ox and tele (see Ellucid for specifics)<br><br>**↓dose** (6-8 mg/kg) if **sedation carries high risk**:<br><br>**Rescue dose:** 2mg/kg for CIWA >15 AND coarse tremor AND one of the following: SBP>165, HR>115, diaphoresis. DO NOT give for agitation, hallucinations<br><br>Consider discussion with ACT/Psychiatry if refractory to phenobarbital and adjunctive therapies. PO taper can be considered in high risk ICU patients |
| Other | Consult ACT team for assistance w/ pharmacologic and psychosocial mgmt of AUD, or if considering standing BZD taper and unsure of dosing sched. | Discharge: phenobarbital increases sensitivity to BZDs/EtOH; **drinking after IV/IM load can be fatal**. |

**Adjunctive Therapies (**See Table 4 of Ellucid guidelines**): NOT to be used as monotherapy**

- Clonidine can be used as an adjunct for autonomic hyperactivity and anxiety Beta-blockers can be used as adjunct in select patients for persistent hypertension or tachycardia
- Haldol can be used for agitations/hallucinations BUT might lower seizure threshold

# Psychiatry — Opioid Use Disorder & Withdrawal

## Opioid Use Disorder (OUD)

- Chronic, relapsing disorder of opioid use due to dysfunction of brain reward circuits (J Addict Med 2015;9:358)
- **Screen** all patients. Confirm diagnosis using DSM-5-TR Criteria for opioid use disorder. Use ≠ SUD
- 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/day or $ spent/day, recent withdrawal
  - Assess **treatment readiness**: treatment hx, social circumstances, patient's current goals (e.g. no change, safer use, 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 **HIV PrEP** for patients with high-risk injection practices
  - Assess **risk of overdose**: h/o OD, h/o psychiatric (i.e. mood) disorder or suicidality, ↓tolerance from recent incarceration or abstinence-based treatment, change in supplier/dealer, access to naloxone, high-dose Rx'd opioids and/or other sedatives (check PDMP), EtOH use, injection use, respiratory disease, severe chronic pain (Addiction 2015;110:996; Lancet 2019; 393: 1765)
- Labs: serum/urine tox (fentanyl now included in urine tox but may take days to result), LFTs, EKG. Consider HIV, HBV/HCV, syphilis
- Tx: agonist treatment with **buprenorphine** or **methadone** is 1st line tx for opioid withdrawal and OUD. Should be offered to **every patient with OUD**. Long-term agonist therapy for OUD decreases morbidity and mortality (BMJ 2017;357:j1550). When choosing bup vs. methadone consider long-term plan: methadone = daily observed administration at clinic. Buprenorphine = transmucosal TID vs. long acting injectable qmonth vs. subcutaneous injection q6mo prescribed by outpatient provider
- 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 total daily dose 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)

## 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: 0.4mg 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.
  - 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 (remember fever + patch → overabsorption). Consider naloxone gtt

## Acute Opioid Withdrawal

- S/Sx: dysphoria, restlessness/irritability, muscle twitching, yawning, piloerection, mydriasis, rhinorrhea, myalgia/arthralgia, lacrimation, n/v/d, abd cramping. Onset: 6-12h after short-acting opioids, 24-48h after last methadone, variable for fentanyl analogs (long half-life)
- 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 film). 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
  - Low-dose Induction: 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; consult ACT for protocol
- Methadone: **long-acting full agonist**. Check and trend ECG for QTc, use with caution with other QTc-prolonging meds.
  - Day 1 initial dose: 40mg x 1 (consider dose reduction for pt >60, c/f ↓tolerance, concurrent sedating meds/BZDs, or liver dz). F/u COWS q4h. If >2h s/p first dose and COWS >12 or pt reporting w/d, spot dose 10-20mg x1. MUST call ACT if ≥60 mg daily dose
  - Day 2: Continue dose if COWS <6; incr. by 10-20mg if COWS 6-12. If not pursing methadone maintenance, consult ACT
- If unable to initiate suboxone/methadone, or if in precipitated wd, offer symptomatic medications and short-acting opioids for pain:
  - Autonomic dysreg: clonidine 0.1-0.2mg TID PRN/lofexidine 0.54-0.72mg QID PRN; avoid w/1st bup/methadone dose, watch BP
  - GI upset: Bentyl 10-20mg q6h PRN abd cramps; ondansetron 8-16 mg q8-12 PO/IV PRN, promethazine 25-50mg IM PRN N/V; loperamide 2mg PRN diarrhea. Remain mindful of QTc
  - Anxiety: hydroxyzine 25mg q8h PRN or trazodone 50-100mg q8h PRN; if precip w/d, consider lorazepam 1-2 mg q6h 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
  - MGH Bridge Clinic: see website for hours + contact info, low-barrier immediate access SUD treatment both in-house & via mobile services in community

# Psychiatry — Other Substance Use

## TOBACCO (USPSTF: JAMA 2021;325:280, ATS: AJRCCM 2020;202:e5)

**Screening:** Tobacco: **5A's** framework: **A**sk about use, **A**dvise to quit, **A**ssess readiness, **A**ssist if ready, **A**rrange follow up.
**Treatment**: 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: **Varenicline** is first line and should be started even in patients not ready to quit (AJRCCM 2020;202:e5). For those patients planning to quit, start pharmacotherapy **1-2w prior to quit date**; continue for 3-6mo; monitor tobacco use to see decrease.
  - Varenicline: 0.5mg qd x3d → 0.5mg BID x4d → 1mg BID. SEs: nausea, insomnia/vivid dreams; avoid if hx PTSD/SI, but recommended in other comorbid psych conditions (AJRCCM 2020;202:e5); monitor for neuropsychiatric symptoms
  - Bupropion: 150mg qd x3d → 150mg BID. SEs: insomnia, agitation, HA, dry mouth. CI: seizure disorder. Relative CI: ↓GFR
  - Nicotine Replacement Therapy (NRT): long acting (patch) + short acting (lozenges/gum/nasal spray)

## CANNABIS

- **Intoxication**: Euphoria followed by relaxation; tachycardia; hallucinations (especially w/ high potency THC)
- **Drug interactions:** Research not definitive, cannabis may increase warfarin levels (Basic Clin Pharm Tox 2019;124:28)
- **Cannabinoid hyperemesis syndrome**: Dysreg of GI cannabinoid receptors → recurrent n/v, abd pain, sx relief w/ hot showers, mild leukocytosis. **Tx**: THC cessation, IVF, antipsychotic (haloperidol), BZD, capsaicin cream (Exp Opin Pharmacoth 2022;23:693).
- **E-cigarette or Vaping Associated Lung Injury (EVALI)**: Dx of exclusion in respiratory failure <90d after e-cig/vape use. b/l GGOs; BAL with lipid laden macrophages. Possibly due to Vit E acetate (NEJM 2020;382:903). Suspected cases must be reported to MA DPH.
- **Tx:** No FDA-approved meds. Topiramate, NAC, gabapentin, dronabinol, nabilone may help cravings (Pharmacotherapy 2016:511).

## SYNTHETIC CANNABINOIDS (SPICE/K2/BATH SALTS)

- **Intoxication**: Agitation/violence, hallucinations, paranoia, anxiety, tachycardia, arrhythmia, myoclonus, diaphoresis. Variable time to symptom onset and recovery based on synthetic used, quantity consumed, and route of ingestion
- **Tx**: Low stimulation environment, IVF, consider IV/IM BZD to reduce agitation and prevent seizure (Curr Psychiatry Rep 2016;18:52).

## BENZODIAZEPINES

- **Intoxication:** Memory impairment, disinhibition, psychomotor slowing, depression, amplified w/ EtOH.
- **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). **Can be lethal.**
- **Abstinence syndrome weeks after cessation**: Anxiety, tachycardia, restlessness.
- **Tx**: Manage severe w/d inpt. Consider prolonged taper w/ same BZD. Consider collaboration w/ outpt prescribers

| Commonly Used BZDs | ~ Equiv Dose | 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) |

## STIMULANTS: COCAINE, METHAMPHETAMINE, PRESCRIBED STIMULANTS

**Cocaine:**

- **Intoxication**: Euphoria, hyperactivity, grandiosity, anorexia, anxiety, psychotic sx (formication, paranoia, AH/VH). ½ life ~1h.
- **Withdrawal**: Depression, fatigue, nightmares, cravings, ↑sleep/appetite. Acute w/d tx: Supportive care, BZD if symptoms severe.
- **Complications**: *Acute*: vasospasm, HTN emergency (**Tx**: BZD, phentolamine if refractory, nitroglycerin; avoid βB), ACS (**Tx**: ASA, nitro, BZD), arrhythmia, ischemic bowel. *Chronic*: LVH, cardiomyopathy. Intranasal: nasal septum perforation, ulcers, chronic rhinitis. Inhalation: cough, SOB, hemoptysis, PTX. "Cocaine-Induced Lung Injury": syndrome of fever, hemorrhagic alveolitis, respiratory failure, eosinophilic infiltration thought d/t levamisole additive. Injection: discuss harm reduction practices, eg using vitamin C powder as acidifier over lemon juice (fungal infxn) or vinegar (damages veins), use PCOI guide and Grayken guide.

**Methamphetamine:**

- **Intoxication:** Similar to cocaine. Sympathetic activation, executive dysfunction, memory impairment, ↑libido. ½ life ~6-12h.
- **Complications:** HTN, hyperthermia, rhabdomyolysis, may exacerbate existing psych sx. **Tx for severe agitation**: BZD first line.

**Stimulant Use Disorder Tx:** Consult ACT. Limited psychosocial programs in community and mixed evidence for pharmacotherapy.

- **Psychosocial**: Contingency management is best supported; also consider CBT, community reinforcement, motivational interviewing.
- **Pharmacotherapy:** No FDA approved meds. Insufficient evidence for replacement therapy, opioid agonists or NAC across all stimulant use disorders (PLOS ONE 2020;15: e0234809). Replacement therapy may help sustain cocaine abstinence (Cochrane Review 2016). Consider topiramate and/or baclofen for cocaine cravings/dependence (Psychiatry 2005;2:44). IM ER naltrexone + PO ER bupropion may reduce meth use (NEJM 2021: 384;140).

## HALLUCINOGENS

**MDMA/Ecstasy: Intox**: Euphoria, HTN, hyperthermia, stimulant properties. ½ life ~2h. **Complications**: HypoNa, serotonin synd, seizure
**LSD: Intox**: Euphoria, synesthesia, depersonalization. **Complications**: Frightening imagery. Rare vital sign abnormalities.

## XYLAZINE

- **Intoxication:** α2 agonist found as adulterant, thus most overdoses are concomitant with fentanyl. Bradycardia, resp depression, hyperglyc, miosis, hypothermia, PVCs, transient HTN → sustained hypotension. ½ life ~23-50min **Tx:** No specific reversal agents for humans. Treat concomitant opioid OD. (Addiction 2024;119:606)
- **Xylazine wounds**: necrosis w/ black eschar. **Tx:** Standard wound care.

## 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 SUD treatment when there is immediate likelihood of serious harm as a result of the SUD. Petition must be filed by MD, blood relative, spouse, guardian, police officer, or court official.

# Psychiatry Drug Testing

## MGH Toxicology Screens

- **Basic serum toxicology screen**: Quantitative for EtOH, salicylates, APAP; qualitative for TCAs.
- **Urine drug screen** (VDAU): Qualitative screen for amphetamines, BZDs, cocaine, opiates, fentanyl, oxycodone. *Not included*: **THC,** bupe, barbituates, methadone, meperidine, LSD, PCP, propoxyphene. If a patient may need a THC test (often needed for transfers to facilities such as McLean or if ordering w/u for depression, mania, psychosis), please include in original utox order
- **SUD management panel** (VPP2): Same as VDAU + bupe, methadone (24h turn-around).
- **Oral drug screen**: Amphetamines, buprenorphine, benzos, cocaine & metabolite, opiates, methadone, oxycodone, 6-MAM, fentanyl

| Test | Turnaround |
|---|---|
| Serum tox | 2 hours |
| Urine tox | 2 hours |
| SUD | 2-24 hours |
| Oral tox | 2-3 days |

## Oral vs. Urine Tests

- **Oral drug mass spectrometry**: Used for outpatient testing for chronic opioids or buprenorphine. Differentiates BZD subtypes and opiates. Superior sensitivity/specificity of amphetamines, opioids and cocaine. More expensive than UTox screen.
  - ODS technique: Rinse w/ 40 mL water for 30 seconds and swallow prior to test, repeated twice. Wait 10 minutes (early testing → false negative), then place swab under tongue for 5 minutes
- **Urine drug screens:** Cheap, easy, noninvasive. Used more often on inpatient. Does not differentiate subtypes of BZDs or opiates. Superior sensitivity for BZDs but does not detect lorazepam. Superior sensitivity for buprenorphine (detects doses as low as 2mg/d). **THC, barbiturates, and 6-MAM must be ordered separately.**
  - Tampering: More common w/ UDS (eg synthetic urine, smuggling urine in bathroom)

Strategies to minimize UDS tampering: Specimen validity testing via checking Cr level, pH (Cr best marker for urine integrity), direct observ, check specimen cup temp, ask pts to leave belongings outside bathroom

| Detection Time of Drugs in MGH Toxicology Screens* | | |
|---|---|---|
| | **Urine** | **Oral** |
| **Urine Tox Panel (VDAU)** | | |
| Amphetamine, methamphetamine | 1-3 days | 3-6 days |
| *Benzodiazepines* | | |
| Alprazolam | 2-3 days | 1-2 days |
| Chlordiazepoxide | 10-20 days | 5-10 days |
| Clonazepam | 5-10 days | 5-10 days |
| Diazepam | 10-20 days | 5-10 days |
| Lorazepam | Not detected | 1-2 days |
| Cocaine | 2-5 days** | 2-7 days** |
| Opiates (morphine, codeine) | 2-4 days** | 2-4 days** |
| Hydrocodone, hydromorphone | 2-3 days | 2-3 days |
| Fentanyl | 2-3 days*** | 2-3 days*** |
| Oxycodone | -2-3 days | 2-3 days |
| **Urine SUD Panel** | | |
| Buprenorphine | 2-3 days | 6-10 hours |
| Methadone | 5-10 days | 5-10 days |

*Estimates updated 3/2023 from MGH laboratories Detection times are specific to MGH and are not hard cut-offs.
**Longer in chronic/high-dose users
***Best available estimates (detection time for chronic/high-dose fentanyl users over long period of time is unknown)

Source: MGH Toxicology lab and PCOI

| | | Drugs Detected | False Positive | False Negative | Comments |
|---|---|---|---|---|---|
| Urine Tox Panel (VDAU) | Amphetamines | Amphetamine, methamphetamine, ecstasy/MDMA | Beta blockers, ranitidine, bath salts, trazodone, bupropion | | Ritalin does not cause a false positive |
| | Benzos | Alprazolam, chlordiazepoxide, clonazepam, diazepam, triazolam | | Lorazepam, temazepam | Clonazepam detected even at 1mg/day |
| | Cocaine metabolites | Benzoylecgonine | | | |
| | Opiates | Morphine, hydromorphone, codeine, hydrocodone, heroin | Poppy products, rifampin, levofloxacin | Oxycodone, oxymorphone | Fentanyl, methadone, naloxone, naltrexone do not interfere |
| | Fentanyl | Norfentanyl (metabolite), fentanyl | | | |
| | Oxycodone | Oxycodone and metabolite oxymorphone | | Substances imparting color to urine (e.g., Flagyl) | |
| Urine SUD Panel | Buprenorphine | Parent drug and major metabolite | | | |
| | Methadone | Methadone | Quetiapine, tramadol, vortioxetine, chlorpromazine | | Does not cause false positive for opiates |

## Interpreting Results

Tox screens alone should not be used to dx SUDs as they do not give information on frequency or intensity of use. False positives and negatives are possible. It is not recommended to alter prescribing meds based on positive tox screens; instead, use these tests to check for concomitant substance use, monitor opioid use, and initiate conversations around use with patients. The best tox screen is eliciting a careful and respectful social hx.

# Primary Care — Health Screening & Maintenance

## General Screening Guidelines [Evidence Grade] ([a]USPSTF, [b]ADA, [c]AACE, [d]ACC/AHA, [e]ASCCP, [f]ACS,)

| 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 ≥10% prescribe a statin* [B][a] *If ASCVD risk 7.5-10% consider statin [C][a]. Insufficient evidence for/against statin for age >75 [I].[a] | | | | | | |
| | | | | | | PREVENT risk calc (30-79y) will soon replace the above. Provides 10yr and 30yr risk. Race free. Includes eGFR/UACR, BMI, A1c, and zip code (proxy for SDH) | | | | | | | | |
| **ASA for 1° ppx** | | | | | | | | | Consider in 40-59y w/ ASCVD risk ≥10% w/ no ↑risk of bleeding[δ] [C][a,d] | | | Not rec for adults >60 [D][a] | | | |
| **DM** | If HTN or BMI ≥25 (≥23 Asian) w/ ≥1 DM RF^, or GDM [B][b] | | | | | | Fasting plasma glucose or A1C [B][b] Screen minimum Q3y. ↓interval if abnl result or new RF (e.g. weight gain) [C][b] ✓ annually in pre-DM[b] | | | | | | | | |
| **HTN** | Q3-5y; Q1y if elevated BP reading, obese, AA [A][a] | | | | | | | | Q1y [A][a] | | | | | | |
| **HLD** | Insufficient evidence for screening [I][a] | | Men 20-45, women 20-55: screen Q5yr, ↑ if RF [C][c] Q1y in DM [B][c] | | | | | | | M >45, F >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 (see *Weight & Weight Loss*) [B][d] | | | | | | | | | | | | | | |
| **Diet** | Intensive behavioral counseling if CVD RF* [B][a] | | | | | | | | | | | | | | |
| **Exercise** | 150min/wk mod.-intensity exercise or 75min/wk intense-exercise & 2d of muscle strength. activity [A][d]; fall prevention in >65 [B][a] | | | | | | | | | | | | | | |
| **Universal Cancer Screening** | | | | | | | | | | | | | | | |
| **Colorectal CA** | Start 10y prior to age of affected family member at dx** | | | | | | 45-49 needs colo Q10y, flex sig Q5y,or FIT testing Q1y [B][a] ; if flex sig or FIT abnx, will need colo. If colo abnx, path determines f/u | | | | | | | | +/-** |
| **Lung CA** | | | | | | | | | | (Age 50-80) Q1y low-dose CT if 20 pack-yrs or more (regardless of quitting date) or if current smoker [B][a]*** | | | | | |
| **Infectious Disease Screening** | | | | | | | | | | | | | | | |
| **HIV** | Screen all age 15-65 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+, people who inject drugs , 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] | | | | | | | | | | | | | | |
| **Syphilis** | Screen in all individuals at increased risk of infection [A][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). Not enough evidence to recommend for or against screening for suicide [I][a] | | | | | | | | | | | | | | |
| **Anxiety** | Screen regularly in adults ages 19-64, various screening tools such as GAD-2 or GAD-7 [B][a] | | | | | | | | | | | | | | |
| **Alcohol** | Screen regularly with AUDIT-C [B][a] | | | | | | | | | | | | | | |
| **Tobacco** | Every encounter [A][a]. **A**dvise to quit, **A**ssist doing so (plan, quit date, QuitWorks, meds), **A**rrange f/u. Strong evidence to start varenicline (Chantix) over other tx options, despite psych comorbidities or readiness (AJRCCM. 2020;202:e5) | | | | | | | | | | | | | | |
| **Unhealthy Drug Use** | Screening [B][a] via asking questions about unhealthy drug use (not drug testing) is beneficial when services for accurate diagnosis, effective treatment, and appropriate care can be offered (JAMA 2020;323:2310) | | | | | | | | | | | | | | |
| **Inter-partner Violence** | Screen regularly in women of reproductive age [B][a]. Use HITS tool. Assess immediate safety & consider HAVEN referral. ↑ rates in LGBT population. | | | | | | | | | | Consider screening for ongoing IPV, elder abuse screening [I][a] | | | | |
| **Fall Risk** | | | | | | | | | | | | Yearly screening, PT, Vit D [B][a] | | | |

*If ASCVD borderline: (5%-7.5%), 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 CAC score to guide starting -stain (see *Outpatient CV Health*)
[δ]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, HTN, HDL<35 or TG>250, physical inactivity, conditions associated w/ insulin resistance (e.g. obesity)
**Begin at age 40 or 10y prior to earliest dx in fam (whichever comes first) for ≥1st degree relative dx<60 or two 1st degree relatives of any age; Age 40: ≥1st degree relative dx≥60; 75+: based on life expectancy. Early screening for special populations: hx of high-grade polyp, IBD, prior colon or rectal ca, hx prior pelvic/gut radiation, genetics.
***Consider screening cessation if limited life expectancy or screening would impede surgical candidacy.

## Additional Screening Guidelines for Men [Evidence grade] ([a]USPSTF, [f]ACS, [g]Endo, [h]PCOI)

| Age | 18-40 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75+ |
|---|---|---|---|---|---|---|---|---|---|
| **AAA** | | | | | | | If +tobacco hx [B][a] * | | |
| **Prostate CA**,*** | | Discuss risk-benefit if FHx** Q1-2y[δf] | Disc. risk-benefit if FHx***, AA Q1-2y[δf] | Discuss risk-benefit if Q1-2y[δ] if life expectancy ≥ 10y[f] | | | | | |
| | | | | | PSA 55-69y if pt preference [C][a], *recommend against* if >70y [D][a] | | | | |
| **Testicular CA** | *Recommend AGAINST* routine screening in all men[Σ] [D][a] | | | | | | | | |
| **Anal CA**[#] | In MSM: anal PAP Q1y starting at 35 if HIV+ (space to Q3y after 3 neg Paps); consider Q2-3y starting at 45 if HIV-[h] | | | | | | | | |
| **Osteoporosis** | | | | If RF^[g] | | | | DXA[g] | |
| **STIs** | In MSM: Q1y, Q3-6mo if multiple/anonymous partners or sex in conjunction w/ drug use; hx re: sexual practice can guide screening (pharyngeal, anal, urine). Prescribe PrEP to patient at risk of HIV acquisition [A][a] | | | | | | | | |

*Society for vascular surgery recommends screening in men and women **Inform all patients of uncertainties, risks, and potential benefits before starting PSA screening
***Discrepancy between societal guidelines, USPSTF: individual risk-benefits discussion for persons with prostates aged 55-69 [C], stop screening at age 70 [D]. ACS: for average-risk persons with prostate, start risk-benefits discussion at age 50, stop when life expectancy <10 years
[δ] Screening frequency varies based on level. PSA < 2.5ng/mL = Q2y. PSA ≥ 2.5ng/mL = Q1y[f]; Amer Urological Assoc recs Q2y interval
**>1 first-degree relative with history of prostate cancer at early age ***First-degree relative diagnosed with prostate cancer at age <65
^Low body weight, prior fracture, smoking [Σ]If higher risk (h/o cryptorchidism or orchiopexy, testicular atrophy, or sxs), evaluate, educate & consider periodic testicular exams
[#]Lacking evidence to inform screening initiation age & intervals. NYS DOH AI includes follow-up algorithm. Stop when life expectancy <10y

# Primary Care — Health Screening & Maintenance

## Additional Screening Guidelines For Non-Pregnant Women [Evidence grade] ([a]USPSTF, [f]ACS)

| Age | 18 | 19 | 20 | 21 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75+ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Breast CA*** | Consider BRCA counseling if +FHx. Screening tools available [B][a] | | | | | | | Q1-2y mammogram age 40-74. Stop if <10y life expectancy [a,f] | | | | | | | |
| **Cervical CA^δΣ** | | | | | Q5y 1° high risk HPV testing (preferred if available); if not available, Q5y cytology + hrHPV co-testing OR Q3y cytology alone[f] | | | | | | | | If neg adequate screening, stop[a] | | |
| | | | | Q3y cytology [A][a] | | Q5y 1° hrHPV testing (preferred)[f] OR co-testing (hrHPV & cytology) OR Q3y cytology alone [A][a,f] | | | | | | | | | |
| **Ovarian CA** | *Recommend AGAINST* routine screening in asx women [D][a] (Lancet 2021;397:2182) | | | | | | | | | | | | | | |
| **STIs** | ≤24: GC/CT annually [B][a] | | | | Screen based on risk assessment [B][a] | | | | | | | | | | |
| **Contraception** | Discuss with everyone including trans ♂ (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] (*see Osteoporosis*) | | | | | | | | | | | | DXA [B][a] | | |

*Discrepancy btw societal guidelines despite same evidence. USPSTF: 40-74 Q2y [B]; >75 no recommendation [I]. ACS: 40-44 option to start Q2y screening; 45-54 Q1y; ≥55 discuss transitioning to Q2y screening until life expectancy <10y. ACOG: offer mammography at 40; start screening at 50; discuss cessation at 75; screen Q1-2 years
^All screenng methods still accepted to promote access to adequate cervical cancer screening. USPTF recommends age 21 start whereas ACS recommends age 25. ACOG recommends start at age 21 due to underscreening in younger populations.
Σ Subsequent screening dictated by age, prior screening results, and other factors. Use ASCCP for algorithm of next steps.
δWomen w/ HIV require more frequent Paps & Paps preferred (HPV testing w/o cervical cytology is **not** approved). See NIH guidelines

## Additional Screening Guidelines For Transgender Individuals*

| Age | 18-40 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75+ |
|---|---|---|---|---|---|---|---|---|---|
| **CVD Risk** | As above; if patient has been on hormones for many years, use hormonal sex in the calculator | | | | | | | | |
| **Osteoporosis** | Consider at any age if s/p gonadectomy and >5y w/o hormone tx | | | Consider based on FRAX (no guideline on which sex to use) | | | DXA | | |
| **Breast CA** | | | | Trans ♀: Q2y *after* 5-10y hormone use | | | | | |
| | Trans ♂: if natal tissue present (incl s/p partial mastectomy), screen per guidelines for non-trans ♀ | | | | | | | | |
| **Cervical CA** | Trans ♂: if natal tissue present (incl s/p subtotal hysterectomy), screen per guidelines for non-trans ♀^ | | | | | | | | |
| **Prostate CA** | Trans ♀: screen per guidelines for non-trans ♂. Use lower ULN for PSA if on estrogen | | | | | | | | |
| **Anal CA** | Trans ♀: screen per guidelines for non-trans ♂. | | | | | | | | |

*See Transgender Health
^Cells 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, [a]NYS DOH AI)

| Immunizations | 19-21 | 22-26 | 27-49 | 50-64 | ≥65 |
|---|---|---|---|---|---|
| **COVID-19** | 1 or more doses of updated (2024-2025) formula. See CDC guidelines for unvaccinated and special populations | | | | |
| **Influenza** | Annual flu vaccine | | | | Annual high dose flu vaccine |
| | *No live (intranasal) if immunocompromised (or contact), pregnant, asplenia, cochlear implant, CSF leak, ≥50; OK for 65+ to get regular adult flu vaccine if high dose not available* | | | | |
| **Tdap/Td** | 1 dose Tdap then Td or Tdap booster every 10 years; extra Tdap dose during each pregnancy | | | | |
| **RSV** | Seasonal administration in pregnancy | | | | Recommended for adults 60+ |
| **MMR*** | 1-2 doses based on indication (if born 1957 or later) | | | | |
| | *1 dose in ♀ of childbearing age; 2 doses if HIV & CD4≥200, healthcare personnel, or college students* | | | | |
| **Varicella*** | 2 doses (if born 1980 or later) | | | | |
| **Zoster*** | Immunocompromised: 2 doses of RZV 1-2 mo apart | | | All: 2 doses of RZV 2-6 mo apart | |
| | *Administer RZV regardless of history of Zostavax (live, no longer available) administration* | | | | |
| **HPV**** | 2-3 doses | | 27-45y SDM*** | | |
| | 3 dose series to all people with HIV up to 45y[a] | | | | |
| **PCV15/PPSV23 OR PCV20** | Chronic heart, lung, kidney, or liver dz; DM; AUD; smoking; nephrotic syndrome; CSF leak; cochlear implant; immunocompromising conditions: PCV20 x1 OR PCV15 x1 followed by PPSV23 x1 ≥ 8 wks or 1 yr later | | | If never vaccinated, PCV20 x1 OR PCV15 x1 followed by PPSV23 x1 ≥1 yr later. If partially/fully vaccinated before age 50, may need to repeat vaccine. See CDC website for full details. | |
| **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****** | Universal vaccination for adults ages 19-59, as well as adults 60+ with risk factors for HBV (travel to endemic country, HCV, HIV, sexual exposure risk, IVDU, chronic liver dz, incarcerated, mucosal or percutaneous blood exposure (incl dialysis, DM, work exposure)<br>Recombivax HB: 3 doses (dose doubled if pre-dialysis or on HD); HEPLISAV-B: 2 doses | | | | |
| **Meningococcus**** (MenACWY/MenB) | Functional/anatomical asplenia, HIV, ↓complement (including by meds), travel to endemic country, freshmen in dorms, military recruits<br>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) | | | | |
| **Monkeypox** | Any person at risk of monkeypox (persons who are gay, bisexual, and other MSM, transgender or nonbinary people who in the past 6 mo. have had a new STD dx or >1 sexual partner): 2 doses | | | | |

*Hold live vaccines in pregnancy, malignancy, and immunocompromised (incl HIV w/ CD4 <200, cochlear implant). Ok if CD4 ≥200
**Wait until after pregnancy ***Shared decision making (SDM): most likely to benefit adults not yet exposed to HPV or w/ new sex partners
***Conduct complete serologic testing (HBsAg, anti-HBs, and anti-HBc) on all adults over 18 at least once in a lifetime. Boosters not recommended for most people who have been vaccinated. For patients on HD, if anti-HBs <10 mIU/mL, a booster should be administered. For other immunocompromised people (HIV, stem-cell transplant recipients, chemotherapy) the need for booster doses is undetermined. Also consider booster in patients with anti-HBs levels <10 mIU/mL with an ongoing risk for exposure.

# Primary Care — Women's Health

## Breast Concerns PCOI – Breast Concerns)

Most breast concerns seen in primary care are benign (~90%); evaluation should focus on ruling in/out malignancy.

- Nipple Discharge: **Bilateral/milky:** eval bHCG, prolactin, Cr, TSH, med review. **Unilateral, bloody** (associated with mass)**:** <30y U/S, ≥30y dx mammo and U/S. Surgery referral for concerning imaging, MRI vs surgery referral if imaging negative
- Palpable Mass: All palpable masses require imaging. <30y U/S; ≥30y diagnostic mammo and U/S. Next steps pending imaging. Common ddx: fibroadenoma, cyst, galactocele, breast CA, fat necrosis
- Breast Pain: If **palpable mass** → image. **Cyclical:** wait two cycles. **Focal**: <30y U/S, ≥30y U/S and BL dx mammo; **Diffuse**: unlikely malignant, <30y sxs management (APAP, NSAID, hot/cold, eval for extramammary causes), ≥30y BL dx mammo

## Vulvar/Vaginal Concerns (Obstet Gynecol 2020;135:e1; Obstet Gynecol 2020;136)

| | Presentation | Dx | Tx |
|---|---|---|---|
| Vaginitis | **Bacterial vaginosis (BV)**: most common; malodorous discharge, often asx; RF = sexually active, douching<br>Recurrent vaginosis defined as: ≥3x/yr | Wet prep or "Genital culture female" (collect vaginal swab w/ rayon swab); Gram stain: Nugent score 7-10 = BV<br><br>Amsel's criteria (≥3): 1) homogeneous, thin, grey-white discharge 2) >20% clue cells 3) +KOH test 4) pH >4.5 (less reliable if post-menopause) | **Metronidazole** PO 500mg BID x7d or vaginal 0.75% x5d, clinda PO 300mg BID x7d or vaginal 2% x7d<br>Recurrent: Metrogel x7d, followed by 2x/w maintenance for 4-6 mos |
| | **Candida**: curd-like discharge, no odor, pruritus, vulvar erythema ± edema, dysuria, dyspareunia<br>Complicated: severe sx, pregnancy, non-*C. albicans*<br>Recurrent defined as: ≥4x/yr | "Genital culture female" or yeast culture for fungal sensitivity if recurrent. pH normal (3.5-4.5), KOH microscopy<br>Recurrent: test for DM2, HIV, fluconazole resistance, non-*C. albicans* infect | **Fluconazole** 150mg PO x1, miconazole 2% x7d if pregnant<br>Complicated: Fluc 150mg q72h x3 doses<br>Recurrent: Fluc 150mg q72h x3 doses + maintenance or fluc 150mg x 7-14d |
| | Other infections: Trichomonas, Gonorrhea, Chlamydia, HSV; See *STI.* If + STI, consider expeditated partner treatment.<br>**If collecting samples at MGH, at least 3 separate swabs should be sent: G/C, genital culture (rayon), trichomonas** | | |
| Painful | **Vulvodynia**: general or local pain, provoked or unprovoked, >3-6mo | Q-tip test to localize pain, exclude other etiology | Pelvic PT, TCA, gabapentin, lidocaine 5% before sex, steroid/lidocaine inj., sitz bath |
| | **Genitourinary Syndrome of Menopause**: vaginal dryness; pain w/ intercourse; thin, pale mucosa | Wet Mount/ Gram stain: Vaginal pH >4.5, parabasal cells | Topical vaginal estrogen, lubricants, Replens moisturizer, ospemifene |
| Dermatoses | • **Contact dermatitis**: erythema, swelling, fissures, erosions → r/o candida, remove offending agent<br>• **Lichen simplex chronicus**: intense pruritis + lichenified plaque → antihistamines, topical corticosteroids; stop itch/scratch cycle<br>• **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<br>• **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 (Obstet Gynecol 2015;126; PCOI)

- Types: **stress** (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.), comorbid conditions (DM, CHF), bowel habits (constipation), caffeine/EtOH use, voiding diary, multiparity is RF
- Exam: check for prolapse, vulvar/vaginal atrophy, cough/valsalva stress test; rectal exam (fecal impaction, sphincter tone); neuro exam; Dx: UA/Cx, PVR (abnl >150cc); urethral mobility assessment and urodynamic studies if etiology unclear
- Initial tx: 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): Systemic hormones (estrogen + progestin, estrogen mono-Rx if hysterectomy) first line 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, +smoking. Side effects: breast tenderness, vag bleeding; ↓CRC, fracture risk; ↑breast CA, CVD, VTE (equivocal if ↑risk attenuated with topical Tx); no mortality risk after 5-7y on therapy (JAMA 2017;318:927). See PCOI for specific formulations/considerations. If not eligible/desiring systemic hormones: SSRI/SRNIs (paroxetine best), gabapentin, clonidine.
- **Vaginal/vulvar sx** (now called **genitourinary syndrome of menopause**): see above; oral therapy not effective, use topical
- **Psych sx**: sleep disturbance, poor concentration**,** new-onset depression. May improve with Rx for vasomotor sx

## 2° Amenorrhea (AFP 2019;100:39)

- Definition: 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 progestin challenge: medroxyprogesterone acetate 10mg x10d. If no withdrawal bleed, suggests uterine abnl

## Polycystic Ovary Syndrome (PCOS) (Obstet Gynecol 2018;131)

- Affects 5-10% of women of reproductive age; often comorbid w/ CVD, DM, HTN, MASLD, 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], PRL, TSH); DHEAS, total testosterone, SHBG to confirm if dx unclear
- Tx: wt loss, exercise, **C-OCP** (2nd line = oral progesterone or levo-IUD), spironolactone, metformin (if insulin resistant), fertility referral
- Screening for CVD/DM: at time of diagnosis followed by q1y BP check, q2y lipid panel, q1-3y 2h 75g OGTT>fasting glucose, A1c

## Preconception Counseling/Infertility (Fertil Steril 2021;116)

- Preconception counseling (PCOI): multivitamin qd w/ 400-800mcg folic acid; review immunizations (Rubella, Varicella, HepB, COVID-19, RSV at 32-26 wks of pregnancy); optimize mgmt of wt, thyroid (TSH goal 0.5-2.5, recheck after conception), HTN (avoid ACEi/ARB, check b/l Cr, spot Ur protein/Cr), DM (↑risk birth defects; metformin/insulin first-line), mood (avoid paroxetine; SSRI safety debated, engage Psych/MFM), VTE (LMWH preferred), asthma, OUD (methadone & suboxone safe in pregnancy); avoid tobacco, EtOH, drugs; review medications and check for teratogens
- Infertility: evaluate after 12mo unprotected intercourse in <35yo, 6mo in ≥35, sooner if >40; fertility tx covered by insurance in MA
- Hx: prior OB/GYN hx (menstrual hx, pregnancies, PID, fibroids/polyps, abnl Pap, endometriosis, contraceptive use), sexual hx (timing, frequency, sexual dysfunction), hx chemo/XRT, meds, substance use, FHx. Ddx: see amenorrhea above
- Dx: ovarian reserve tests, pelvic/transvaginal U/S, PCOS w/u, STI & fallopian tube patency testing, TSH, PRL, **semen analysis**
- Tx: fertility awareness (intercourse qod cycle d9-14, or from 5d before and day of ovulation); refer to Repro-Endo for other w/u, induction of ovulation, IVF, or donor oocytes

## Contraception (CDC USMEC 2016; CDC 2020 Summary; [a]Society of Fam Planning), 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%) | Pros: ↓menses, PMS, cramps, acne, endometrial/ovarian CA<br>Cons: n/v, breast tenderness, can ↑HTN/TGs, ↓libido, spotting, cannot start if <21d post partum) | **A**: Hx VTE, thrombogenic mutation; Breast or liver CA w/in 5y; Migraine w/ aura or >35yo & any migraine; >35yo & >15 cig/d; hx CVA; Uncontrolled HTN; DM w/ vascular dz, CAD, CVD,valvular dz, ESLD;<br>**R**: Obesity (↓efficacy of some rings/patch) |
| **Vaginal Ring** | 3w in, 1w out | 9% (0.3%) | | |
| **Patch (e.g. Xulane, Ortho Evra)** | Weekly x3w, 1w off; apply to arm, torso, or buttock | 9% (0.3%) | | |
| **Progestin-only** | | | | |
| **IUD (hormone content: Mirena/Liletta > Kyleena > Skyla)** | M/L q8y<br>Kyleena q5y<br>Skyla q3y | 0.2% | Pros: long-acting, lighter periods, may reduce cramping/anemia, discreet<br>Cons: irregular bleeding, requires removal, physical complications (rare)<br>Pt preference: amenorrhea (~18%) | **A** (all): active breast CA or w/in last 5y<br>**A** (IUD): abnl uterine cavity; unexplained vag bld; active STI, PID, endometritis at insertion; endometrial or cervical CA<br><br>**R** (all): APLAS, ESLD, liver CA, breast CA >5y ago<br>**R** (implant): unexplained vag bld<br>**R** (injection): unexplained vag bld, CV RF, ischemic heart disease, PVD, uncontrolled HTN, DM w/ end-organ damage, CVA<br>**R** (pill): malabsorption |
| **Implant (Nexplanon)** | q3y to upper arm (q5y efficacy[a]) | 0.05% | | |
| **Injection (Depo-Provera)** | q3mo IM/SQ to arm, thigh, or buttock | 6% (0.2%) | Pros: long-acting, discreet<br>Cons: irregular bleeding; temp ↓BMD; prolonged return to fertility (~1y); may worsen HA, acne, mood | |
| **Pill (e.g. Micronor, Slynd, OTC Opill)** | Daily | 8% (0.3%) | Pros: no effect on breastfeeding<br>Cons: irregular bleeding, HA, acne, mood sx, timing[Σ] | |
| **Hormone-free** | | | | |
| **Copper IUD (Paragard)** | q10y (12-20y efficacy) | 0.8% (0.6%) | Pros: long-acting, safe in ESLD<br>Cons: heavier bleeding, cramping | **A**: Same as progestin IUDs above; copper allergy, Wilson's dz |
| **Male condom** | Every encounter | 18% (2%) | Pros: STI prevention<br>Cons: requires pt adherence | **R:** Oil-based lubricant w/ latex condom |
| **Tubal Ligation Vasectomy** | Permanent | 0.5%<br>0.15% | Pros: available to men and women<br>Cons: irreversible, surgical | **R**: Surgical risk<br>**R**: Pt unsure of decision |

* Typical use: % women who will have pregnancy in 1 year on this method (perfect use in parentheses); [Σ]Newer formulations like Slynd maintain efficacy with 24h missed window (Curr Obstet Gyn Rep 2022;11); ^Estrogen-progestin methods can be used continuously to avoid withdrawal bleed.

**Oral Contraceptives (OCPs)** (Quick Start Algorithm): start anytime (exclude preg + 7d backup method).

- **OCP selection**: estrogen (ethinyl estradiol) – 30-35mcg: less breakthrough bleeding. 20mcg: less estrogen SE. Progestin – 2gen (levonorgestrel, norgestrel): ↓VTE risk. 3gen (norgestimate, desogestrel): ↓androgenic SE, ↑VTE risk
- **Patient Resources**: Bedsider.org is a great resource for patients to explore options

**Emergency Contraception** (Obstet Gynecol 2015;126:e1; NEJM 2021;384(4); 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/Mirena/Liletta**: place within 120h (Paragard 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**

## Options Counseling (TEACH)

Options counseling is an opportunity for the pregnant person to consider, in conversation with a provider, whether to continue the pregnancy and parent the child, continue the pregnancy with a plan for adoption, or have an abortion. Particular attention to neutralizing language to avoid potential coercion is imperative. For people who desire abortion, see PCOI or abortionfinder.org for list of providers in MA. Avg cost ~$500, 50% pay out of pocket. Counseling: **1-866-4-EXHALE.**

**Medical Abortion (MAB)** (95-98% effective)

- Eligibility: ≤10 wks gestation, no ectopic risk (history alone or U/S if equivocal); **no** (1) IUD in place, (2) mifepristone or misoprostol allergy, (3) chronic adrenal failure/long-term corticosteroid use, (4) hemorrhagic disorders, on AC, symptomatic anemia, (5) porphyria
- Workup: serum or urine hCG test; **no routine pre-MAB lab testing needed if no underlying conditions; LMP can date pregnancy accurately & safely in most cases** (U/S NOT universally required); offer STI testing & immediate post-abortion contraception
- Protocol: PO mifepristone x1 → buccal or vaginal misoprostol in 24-48h → pt passes pregnancy at home over hrs. May experience cramping and bleeding. Tx with NSAIDs. F/u history and home urine pregnancy test OR serial bHCG testing OR U/S in 7-14d

**Surgical Abortion** (<24wks gestation, 99% effective): same-day office procedure → no f/u unless complications

**Parenting:** obstetrics **Adoption:** resources for public and private agencies

## Postpartum Care (ACOG Postpartum Toolkit, 2018)

**Key Screening Items**: proactive questions and anticipatory guidance about nl vs abnl mitigates complications and worry; **Screen for IPV.**

- Vaccines: all vaccines safe while breastfeeding except smallpox (give yellow fever and MenB only if benefits > risks); recommend all w/ baby contact receive flu & Tdap
- Contraception: can start progestin-only options (IUD, implant, injection, pills) immediately postpartum & estrogen-containing options 21-28d postpartum (42d if VTE risk factor).
- Breastfeeding: see Lactmed for restarting medications. Challenges: nipple pain (tx lanolin, breast shield), plugged ducts (aspiration if >72h), inadequate milk supply, mastitis (10% breastfeeding parents; 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 parent federal law requires break time & dedicated space at work for lactation
- SUDs/Analgesia: postpartum period high risk for SUD/relapse. Methadone & buprenorphine safe w/ breastfeeding, should be continued (risk of relapse during postpartum). 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)<br>- 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<br>- If T1DM, TFTs x1 (if never done) | - Encourage breastfeeding<br>- 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<br>- ↑risk of CKD in first 5y<br>- ↑risk of ASCVD (JACC 2019;74:1376) | - Close BP monitoring up to 6w PP<br>- BP >140/90 warrants eval<br>- Repeat UACR/UPCR to quantify baseline proteinuria, CBC for plt, CMP for LFTs and creatinine | - Encourage breastfeeding<br>- Early goal BP <160/100, later <120/80<br>- Add pre-eclampsia as ASCVD risk-enhancer<br>- **Consider ASA 81mg qd in future pregnancies to ↓pre-eclampsia risk** |

# Primary Care — Men's Health

## Benign Prostatic Hyperplasia (BPH)/Lower Urinary Tract Sx (LUTS) (J Urol 2021;206:806; PCOI)

- Sx: increased urinary frequency, urge, difficulty initiating or weak stream, small amount of urine w/each void, leaking or dribbling, and/or sensation of incomplete void. Present in >50% of men over 60 y.o. w/increased incidence with older age (~90% >85 y.o.)
- DDx: urethral stricture, bladder neck contracture, prostate ca, bladder ca, bladder calculi, UTI, prostatitis, neurogenic bladder
- Eval: HPI, sexual hx, assess sx burden via International Prostatism Symptom Score (IPSS), perform a PE (DRE), obtain UA (blood, bacteria, glucose, protein), 24-hr voiding diary, and consider PVR and/or urodynamic testing prior to Rx initiation;
- Possible Complications: urinary retention, persistent gross hematuria, bladder stones, recurrent UTI, hydronephrosis, renal failure
- Screening: BPH/LUTS don't appear to be RFs for prostate Ca; important to counsel pts & have shared decision-making re: PSA screening annually vs q2yrs at ages 55-69 given high degree of false positives (~70%) and risks/benefits of side effects vs medical Rx
- Rx: if sx worsening despite initial watchful waiting & behavior changes (avoid alcohol/caffeine, limit PM fluid intake, avoid antihistamines/decongestants/allergy meds which can worsen sxs), may consider medical therapies including:
  - **Alpha-blockers** (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin): **initial** therapy; MOA - relax muscles near the prostate, max efficacy in 1 month; ADEs: headaches, hypotension, dizziness, or feeling lightheaded or tired.
  - **5-alpha reductase inhibitors** (finasteride or dutasteride): MOA - inhibit testosterone to shrink prostate, max efficacy in 6-12 months; ADEs: decreased libido, problems with erection or ejaculation.
  - **PDE-5 inhibitors** (tadalafil): preferred for men with ED, max efficacy by 4 weeks ADEs: headache and back pain.
  - **Combination Rx (alpha blocker + 5-alpha reductase inhibitor):** consider addition of 5ARI if prostate >30cc, Rx combo may be more effective for sx reduction & decreasing risk of overall BPH progression than either agent alone
  - **Saw Palmetto (plant extract)**: limited data to support efficacy over placebo but anecdotally may help improve sxs
- Uro referral: med refractory retention, renal injury, hematuria, recurrent ifxn (i.e. prostatitis), palpable nodule on DRE, PSA >4
- Procedures: **Transurethral resection of prostate (TURP)**: Most common procedural intervention – involves insertion of thin tube into urethra & cutting away pieces of prostate causing blockage (often does not require total prostatectomy). Additional minimally invasive procedures include transurethral needle ablation (**TUNA**) & transurethral microwave thermotherapy (**TUMT**).
  Potential complications: reverse flow of semen (empties into bladder & not out of penis) – does not affect ability to orgasm but can affect fertility; less common side effects: urinary incontinence, inability to initiate or sustain erection.

## Erectile Dysfunction (J UROL2018;200:633; PCOI)

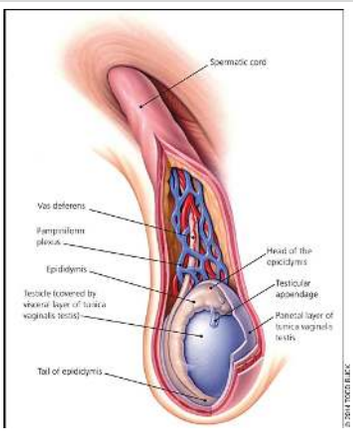
- Sxs: inability to consistently attain or maintain erections rigid enough or of sufficient quality for sexual intercourse. Affects ~22% of men 60-69 and 30% of men >69.
- DDx: distinguish from decreased libido 2/2 testosterone deficiency (see *Endocrine section*), MDD, use of prescription/illicit drugs; ejaculatory dysfunction (ex: premature or retrograde ejaculation); anatomic anomalies (ex: Peyronie's Dz)
- RFs: CVD/PAD, CKD, HLD, HTN, obesity, smoking, sleep disorders (OSA, RLS), hyperglycemia, DM; should additionally perform complete medication review as many commonly prescribed meds can cause ED (PCOI, Table 2)
- Rx: First line - lifestyle modifications for pts with above RFs (ex: tobacco cessation, EtOH reduction), may consider Pharm Rx:
  *All PDE5 inhibitors are contraindicated in pts on nitrates. Co-admin of tamsulosin is less likely to cause hypotension than doxazosin*

| Medication | Dosing | Side Effects |
|---|---|---|
| Sildenafil (Viagra) | • Start: 50 mg, dose range 25-100 mg prn according to side effects.<br>• Take 1 hour prior to sex on empty stomach, effective for 4 hours. | Rarely can cause blue-tinged vision. |
| Vardenafil (Levitra) | • Start: 10 mg, dose range 2.5-20 mg.<br>• Take 1 hour prior to sex, effective for 4 hours. Taking with fatty meals may cause reduced efficacy. | Can cause QTc prolongation (avoid in congenital QT prolongation or with additional QTc prolonging meds) |
| Tadalafil (Cialis) | • Start: 10 mg, dose range 5-20 mg.<br>• Take 30 minutes prior to sex, peaks at 2 hours, effective for 24-36 hours. | More tolerable than other PDE-5 inhibitors with alpha-blocker tamsulosin 0.4 mg. Myalgias in 15% of users. |
| Avanafil (Stendra) | • Start: 100 mg, dose range 50-200 mg.<br>• Take 15-30 minutes prior to sex with or without food. | Fastest onset. Limited side-effect profile. |

Uro referral: adolescents/young adult w/primary ED (never been able to achieve erection); failure of initial first-line oral Rx; contraindications to PDE-5 inhibitor Rx; other specialized testing warranted (ex: penile vascular test, nocturnal penile tumescence)

## Scrotal/Testicular Masses (Am Fam Physician 2014; 89:723)

Scrotal masses = common presentation in primary care – scrotal pain ~1% of all ED visits.




- Normal PE: firm but not hard testes, nearly equal in size, smooth/ovoid, normal testicle length ~4-5 cm after puberty, epididymis is posterolateral to testicle, vas deferens exits via tail of epididymis and joins vascular pedicle of testicle to form spermatic cord.
- DDx: helpful to begin assessment by distinguishing **painful vs painless**:
- Painful: torsion (acute, N/V, abnormal cremasteric reflex, blue dot sign, CRP<24) vs epididymitis/orchitis (most common, +/- fever & dysuria, erythema, CRP>24) vs hematocele/testicular rupture (rare, associated with trauma)
- Mixed pain/painless: testicular cancer (ages: 15-34, firm unilateral nodule, hx of cryptorchidism in childhood or Klinefelter synd.; obtain α-fetoprotein [AFP], ß-HCG, LDH) vs hernia (painful w/strangulation; test via Valsalva maneuver)
- Painless: hydrocele (transillumination w/pen light) vs varicocele ("bag of worms" feel in 15% of males affected, typically occurs in adolescence)

Imaging/labs: Scrotal U/S is best for distinguishing above ddx coupled with inflammatory vs markers as above if there is a high index of suspicion. **If c/f torsion, surg emergency. Consult urology immediately (even prior to US).**

# Primary Care — Transgender Health

## GENERAL CONSIDERATIONS (NEJM 2019;381:2451)

**Gender Terminology**

- Gender identity: a person's sense of one's gender; can be congruent with or differ from sex assigned at birth
- Transgender/trans: a person whose gender identity is different from cultural expectations based on their sex assigned at birth vs cisgender: sex assigned at birth and gender are congruent
- Non-binary, gender non-conforming, genderqueer: a person whose gender identity does not fall within the traditional gender binary. People who are non-binary may see themselves as being both male and female, neither male nor female, or as completely outside of or unrelated to these categories

**History:** use "Sexual Orientation/Gender ID" and "Demographics" activities in EPIC to update patient header w/ chosen name/pronouns

- Gender identity data: name and pronouns, gender identity + sex assigned at birth
- Organ inventory: guides screening and physical exam. Note natal and surgical anatomy. Confirm patient's preferred terms for organs
  - Screening: per usual guidelines based on organs present; Consider past/present HRT use; ex): trans women screen breast CA if >50yo and 5yr HRT
  - Include present organs in ddx: e.g., PID, fibroids, endometriosis in trans M w/ uterus/fallopian tubes; prostatitis in trans F
- Sexual history: "What body parts do your sexual partners have?" "What body parts do you use for sex?" "What terms do you use to refer to your body parts?"
  - Use gender neutral language to use for natal parts (i.e., chest wall instead of breast, monthly bleeding instead of menses)
  - Self-collected rectal, oropharyngeal and vaginal swabs as sensitive as provider-collected swabs for STIs and HPV (Cyto 2019;63); useful for individuals who want to avoid an invasive exam
  - Offer HPV, HBV vaccine series; CDC primary prevention guidelines
  - Consider HIV PrEP for patients who inject drugs or have multiple sexual partners: (AETC prescriber guidelines)

**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: complications from tucking include prostatitis, cystitis, epididymo-orchitis,
- GU: pelvic exam in trans M can be traumatizing and painful 2/2 vaginal atrophy on testosterone. Tips: 1-2w vaginal estrogen before exam; pediatric speculum; trauma-informed care esp physical exam; consider PO benzos 1h before; self-swab if possible.

## GENDER-AFFIRMING CARE (WPATH Standards of Care; Trans Line; MGH Transgender Health)

**Gender dysphoria**: distress a person feels due to a mismatch between their gender identity and their sex assigned at birth

- Affirm gender identity and explore options below for expression of identity and alleviation of gender dysphoria
  - Psychotherapy: safe space to explore gender expression, 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 packing; padding of hips or buttocks; hormone tx; surgery

**Hormone therapy:** initiate w/ informed consent & SDM w/ patient (WPATH standard, Endocrine Reviews Feb 2019,40,97-117)

- 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)
- Masculinization: Testosterone (topical gel/transdermal patch, IM/SQ). Progestins, Aygestin early on may help stop menses
- Fertility: Discuss fertility preservation (egg/embryo freezing, sperm banking) before starting tx
- Testosterone ≠ contraception. If partner makes sperm, discuss birth control: pills, patches, Nexplanon and IUD are all options
- When monitoring treatment, indicate hormonal sex in lab requisition and interpret values using ranges for hormonal, not natal sex.
- Reasonable to provide 1-6 mo of bridge Rx if patient is already on hormones and then refer to another provider who can prescribe.

| | Contraindication | Potential Risks | Irreversible changes | Reversible changes | Monitoring |
|---|---|---|---|---|---|
| **MtF** | Absolute: estrogen-sensitive neoplasm, ESLD | - VTE^ (HR 1.9)<br>- Gallstones<br>- ↑TG, LFTs<br>- HTN<br>- ↑prolactin<br>- Migraines | - Chest growth<br>- ↓ testicular volume | - ↓muscle mass<br>- fat redistribution<br>- hair/skin softens<br>- ↓sex drive<br>- ↓libido, erections | - If spironolactone: BP, BMP baseline and q3 mo, then q1y<br>- total T, E q3-6mo until at goal, then q1y<br>- prolactin PRN if sxs |
| **FtM** | Absolute: ACS, polycythemia (Hct >55%), pregnancy, sex hormone sensitive neoplasm | - Erythrocytosis<br>- HLD, ↑liver enzyme<br>- Sleep apnea | - Deepening of voice<br>- ↑ facial and body hair<br>- Clitoromegaly<br>- Vaginal tissue atrophy<br>- Scalp hair loss** | - menses cessation<br>- ↑ sex drive<br>- ↑ muscle mass<br>- acne | - Before tx: urine HCG<br>- CBC q3mo, then q1y<br>- total T q3mo, then q1y |

^Strongly encourage smoking cessation to attenuate risk. Consult UCSF guide for risk-benefit analysis after VTE. Transdermal route may ↓VTE in age >45 or previous VTE **Treatment with 5-alpha reductase inhibitors may reverse some testosterone effect

**Surgery**: may require 6 mo hormone tx first and support letter from two mental health providers (depends on surgery type). If removing gonads, establish bone mineral density w/ DEXA.

- 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, electrolysis for hair removal
  - Post-op considerations: tissue necrosis, fistulae, urethral stenosis, UTIs, 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 LGBTQIA+ Health

## General Considerations (HRC Glossary of Terms; Providing Inclusive Services and Care for LGBT People)

**Terminology:**

- LGBTQIA+: acronym for "lesbian, gay, bisexual, transgender and queer"; the "+" signs recognizes other sexual orientations and gender identities that are used
- WSW: women who have sex with women
- MSM: men who have sex with men
- Transgender/trans: a person whose gender identity is different from cultural expectations based on their sex assigned at birth vs cisgender: sex assigned at birth and gender are congruent
- Gender-diverse: a person whose gender identity does not fall within the traditional gender binary. People who are non-binary may see themselves as being both male and female, neither male nor female, or as completely outside of or unrelated to these categories

**Documentation Best Practices:** use "Sexual Orientation/Gender ID" and "Demographics" activities in EPIC to update patient header w/ chosen name/pronouns/sexual orientation/gender identity with patients' permission

**Communication Best Practices:** 1) Use inclusive language and try to foster a safe, non-judgmental clinical environment. 2) Use the terms that patients use to describe themselves and their partners. 3) Ask questions that are only necessary for the patient's care. 4) Understand the diversity of sexual and gender identity as well as its fluidity, or ability to change over time. 5) Apologize if you make a mistake while communicating with a patient

**Physical Exam Best Practices for Trauma Informed Care:**

| Timing | Recommendations |
|---|---|
| **Before the Exam** | • Set agenda, explain reasoning for exam<br>• Identify patient concerns, ask about comfort<br>• Reinforce concepts of patient self-autonomy<br>• If needed, offer appropriate alternative options for patients for whom certain aspects of an exam may cause significant harm (eg. self swabs for STI testing) |
| **During the Exam** | • Offer chaperone or allow support person to be present if requested<br>• Attend to draping and modesty<br>• Ask before touching, obtain permission before proceeding<br>• Stay within patient's line of site |
| **After the Exam** | • Discuss results if available and invite questions |

## Mental Health and Substance Use

**General Considerations:**

- Consider screening LGBTQ+ patients with GAD-7 and PHQ-9
- LGBTQ+ youth are more than four times as likely to attempt suicide than their peers
- Significantly increased risk of depression and anxiety among multiple LGBTQ+ patients
- National Survey on Drug Use and Health (NSDUH): increased rates of opioid misuse and alcohol use disorder among LGBTQ+ patients

## Sexual Health (CDC Discussing Sexual Health With Your Patients; CDC STI Screening Recs.; CDC STI Primary Prevention Methods)

**History**: The 5 P's:

- 1. **P**artners: Are you sexually active with one partner or more than one? How would they identify themselves in terms of gender?
- 2. **P**ractices: What types of sex are you having?
- 3. **P**rotection from STIs: Are you currently using barriers or medications for protection during sex?
- 4. **P**ast History of STIs: In the past have you had an STI or been exposed to a partner with an STI?
- 5. **P**regnancy Intention: Is having biological children something you are thinking about?

**STI Screening**

| Population | Recommendations | General Considerations |
|---|---|---|
| **WSW** | - Cervical cancer and STI screening according to guidelines for women based on a discussion of sexual and behavioral risk factors<br>- HIV and HCV screening at least once | Should not be assumed to be at lower risk for STIs on the basis of sexual orientation |
| **MSM** | - HIV at least annually<br>- Syphilis at least annually<br>- Gonorrhea (genital, rectal, pharyngeal) and chlamydia (genital, rectal) at least annually depending on exposure.<br>- Hepatitis A, B, and C at least once<br>- MSM w/ HIV infection should be screened for HCV annually<br>- Consider digital anorectal examination, anal cytology (anal pap), and high-resolution anoscopy to detect early anal cancer in MSM w/ history of receptive anal intercourse and all people with HIV | - Test more frequently (every 3 months) for those at higher risk (e.g. multiple partners or partners with unknown STI history)<br>- Urethral, rectal, and pharyngeal sites based on reported sexual practices as urogenital-only testing can miss a significant proportion of infections |
| **Transgender and Gender-Diverse Individuals** | - STI screening such as HIV, syphilis, gonorrhea, and chlamydia and cancer screening guided by current anatomy and sexual practices<br>- Consider anal cancer screening as described above in transgender women w/ history of receptive anal intercourse | - "Screen what you have" guided by current anatomy<br>- Screen for cervical cancer in all transgender men and gender-diverse individuals with a cervix<br>- Screen at appropriate anatomical sites: urethral, rectal, and pharyngeal sites based on reported sexual practices |

**STI prevention:**

- Barrier methods: condoms, dental dams, diaphragms and cervical caps in conjunction with spermicide
- **Pre-Exposure Prophylaxis for HIV or PrEP**: *Oral PrEP (daily pill)*: Emtricitabine/tenofovir disoproxil fumarate (Truvada) (FTC/TDF) approved for all populations at risk of HIV, emtricitabine/tenofovir alafenamide (Descovy) (FTC/TAF) indicated for MSM and transgender women. *Injectable PrEP (administered intramuscularly every 2 months):* long-acting injectable cabotegravir (Apretude) (CAB-LA) approved for MSM, transgender women, and cisgender women. Lenacapavir: new twice yearly SC injection indicated for all populations at risk of HIV
- Doxycycline Post-Exposure Prophylaxis or Doxy PEP: Single oral dose of 200mg doxycycline taken within 24-72 hours after sex without use of a barrier method to reduce the incidence of STIs such as chlamydia, syphilis, and gonorrhea. Emerging evidence of benefit especially in MSM and transgender women
- Vaccines:
  - HPV: all adolescents at age 11-12; catch up vaccination for through age 21 and for MSM and transgender women through age 26
  - Hepatitis A – all MSM, individuals with HIV, others at risk including individuals with multiple sexual partners
  - Hepatitis B – all MSM, individuals with HIV, others at risk including individuals with multiple sexual partners
  - Meningococcal – all MSM, individuals with HIV, others at risk including individuals with multiple sexual partners

For treatment of STIs, see *STI and Travel Medicine.*

# Primary Care Sleep Medicine

## INSOMNIA (PCOI)

35-50% of population; chronic insomnia **>3mo**. difficulty initiating or maintaining sleep and compromised daytime function (UTD)

- Hx: evaluate chronicity, stressors, effect on fxn/mood, # awakenings and triggers, sleep hygiene; meds, PMH, sleep log for 1w
- Ddx: **Medical:** r/o pain, primary medical condition (e.g., PSYCH: PTSD, mood d/o; PULM: COPD, asthma; CV: CHF; GI: GERD; GU: nocturia), SUDs, medications (e.g., stimulants, steroids, BBs, SSRIs, SNRIs, OCPs, chronic opioids)
  - **Primary sleep d/o**: insufficient sleep syndrome (<7-8h allotted to sleep), psychophysiologic (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)
- Rx: **Sleep hygiene**: regular sleep schedule 7d/wk, exercise (avoid intense exercise just prior to bed), if lying in bed awake get up till sleepy, reduce/eliminate caffeine/EtOH/nicotine, quiet/dark/cool bedroom, eliminate bright lights/screens in pm or use warm light/red tone setting, decrease fluid intake 2 hours prior to sleep, avoid heavy meals prior to sleep; **CBT-I** (**first line** Ann IM;163:191), (J Clin Sleep Med 2021;2,263). **Meds:** mixed evidence low dose melatonin (2-5 mg given one to two hours prior to desired sleep time), trazodone (UTD); **suvorexant (Belsomra):** Dual orexin receptor antagonist (DORA), weak evidence per American Academy of Sleep Medicine (AASM), expensive, drug-drug interactions with CYP-3A inhibitors. **(WEAK evidence)**: sleep maintenance (doxepin), sleep onset (ramelteon, triazolam), eszopiclone, zolpidem, zaleplon, temazepam). Goal is Rx hypnotics (benzos) for <4w only and careful risk/benefit for BZRA agents (J Clin Sleep Med 2017;13:307); treat mental health disorders. Avoid use of antipsychotics for sleep (i.e., quetiapine) or antiepileptic (i.e., gabapentin) unless primary psychiatric or neurologic disorder. Antihistamines (Benadryl, doxylamine, Atarax), not recommended for sleep per the AASM.

## SLEEP APNEA (JAMA 2020;14:389, PCOI)

Obstructive (upper airway occlusion) and/or central (↓resp drive). OSA affects ~10% of adults

- Presentation: daytime somnolence (use Epworth Sleepiness Scale), morning HA, witnessed apnea/gasping, snoring (Sn > Sp), depression, nocturia, pHTN; RF: obesity, anatomy, incr age, ♂, post-menopausal, EtOH, FHx, CHF. Screen for OSA w/ STOP-BANG (≥3 symptoms with Sn 90%) (JAMA 2021; epub)
- Dx: **sleep study in-lab** (polysomnography (PSG); gold standard) vs **at home** (cannot detect other sleep d/o or central apnea, often req by insurance over PSG; home sleep study underestimates the degree of sleep apnea); both quantify apnea-hypopnea index (AHI) = sum of events/h (mild 5-15, mod 16-30, severe >30), minimum $O_2$ saturation, and percent of time below 90%. Apnea/nocturnal $O_2$ requirement often observed inpatients but can confirm diagnosis o/p only.
- Tx: **behavioral**: weight loss, avoid ETOH/sedatives, position (avoid supine sleep, elevate HOB); **Positive Airway Pressure**: CPAP, BiPAP, ASV (for central, risky in CHF), APAP (most common, auto adjusts PAP); **other:** oral appliance (dentist referral), surgery, modafinil (for daytime sleepiness refractory to CPAP). Managed by PCP (HST then APAP), Sleep ENT (PAP, surgery, HGNS), Sleep Neurology (PAP, meds), or Pulmonary (pHTN). Important to identify preoperatively (JAMA 2019;321;18:1788).

## OBESITY HYPOVENTILATION SYNDROME

- Presentation: **awake** alveolar hypoventilation not attributed to other conditions (**dx of exclusion**: r/o alt etiologies of hypercapnia and hypoventilation), in an obese individual (AJRCCM 2019;200;3:e6)
  - RF: obesity (BMI>30) esp severe (BMI≥40, Class III), central obesity, severe OSA
- DDx: COPD, ILD, neuromuscular disorders, chest wall disorders, hypothyroidism, chronic sedative use
- Dx: VBG CO2>27, PaCO2>45, PaO2<70; also BMP (r/o lyte disorder), CBC (polycythemia may be associated, monitor response to rx), TSH, PFTs (to exclude other causes – nml does not exclude OHS), CXR, PSG (identify sleep d/o breathing, gold standard)
- Tx: BiPAP and weight loss/bariatric surgery. Assess for complications (pHTN, HTN, CHF, insulin resistance)

## RESTLESS LEG SYNDROME (RLS) (PCOI)

- Presentation: *URGE*: Urge to move legs, Rest induces symptoms, Getting active brings relief, Evening worsens sxs.
- Common triggers: caffeine, nicotine, ETOH, dopamine antag, most antidepressants, antihistamines
- Assoc conditions: iron deficiency (and work up of etiology), CKD, pregnancy, tremor, Parkinson's, MS, movement disorders, OSA
- Dx: Clinical (PSG if unsure, PLMD), Fe/TIBC/Ferritin/CBC, BMP (CKD); DDx: MS, akathisia, myalgia, PMR/myositis, neuropathy, stasis/edema, PVD, arthritis, nocturnal leg cramps, positional discomfort, habitual foot tapping
- Tx: stop trigger meds, avoid EtOH/nicotine, treat OSA, iron supplement to ferritin >75; DA agonists (take 1-1.5h before trigger or qhs) - pramipexole, ropinirole, carbidopa/levodopa (<3x/w, high risk rebound), rotigotine patch; a-2-d Ca channel ligand: pregabalin, gabapentin; comorbidities may guide Rx; refer to neurology if refractory to monotherapy.

## OTHER SLEEP DISORDER

**Narcolepsy**: chronic daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis (1/3 pts have all three symptoms so consider narcolepsy even if only chronic daytime sleepiness) (NEJM 2015;373:2654); Dx: PSG (exclude alternative causes) and Multiple Sleep Latency Test (MSLT). Tx: Requires specialty management. Basics of treatment include good sleep hygiene and trigger avoidance ( BZD, Opiates, Antipsychotics, EtOH, Caffeine, Alpha1Antag).

**Parasomnias**: complex movements and behaviors during sleep. Associated with NREM (sleepwalking, confusional arousal, sleep terrors, sleep related eating disorder) and associated with REM (nightmare disorder, REM sleep behavior disorder) (AJM 2019; 132:292).Dx: Mayo Sleep Behavior Questionnaire can help dx, obtain video PSG if uncertain and consider MRI. Tx: is to improve sleep hygiene (EtOH, stress, sleep deprivation, Rx OSAS) and assess safety. Melatonin 3-18mg is first line rx.

## CHRONIC COUGH (AFP 2017;96:575; NEJM 2016;375:1544)

- Time course: acute (≤3w) vs. subacute (3-8w) vs. chronic (>8w)
- Common causes: upper airway cough syndrome (UACS), asthma, GERD; these three account for 90% (18-62% pts have combo)
- General approach:
  1) History (smoking, URI, ACEi use, GERD sx, environmental/allergic triggers); remove possible offending agent
  2) Consider CXR if cough >8 weeks, especially if ↓suspicion for UACS/asthma/GERD
  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 *post-nasal drip syndrome*. Most common cause of subacute/chronic cough. Cough may be only sx. Exam: throat/nose may reveal cobblestoning. Common causes: allergic/non-allergic rhinitis, sinusitis | Avoid environmental triggers of allergic rhinitis. Steroid or antihistamine nasal spray, oral antihistamine/ decongestants, and saline nasal rinse for symptom relief. Improve in wks- 2 mos |
| **Asthma** | Typically p/w episodic wheezing & dyspnea. Cough variant asthma p/w only cough. Pt may have h/o atopy. Exam: ± nasal polyps. Need spirometry w/ bronchodilator response & bronchoprovocation (methacholine challenge) for dx | PRN bronchodilators + inhaled corticosteroids. Some pts may use only seasonally. See *Asthma* 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 *H. pylori* 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. 2nd gen (cetirizine) or 3rd 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) |

**Other causes**: post-infxn (self-limited; can last 3+ months, treat sx), COPD, OSA, non-asthmatic eosinophilic bronchitis, chemical irritant (e.g., cigarette smoke), laryngopharyngeal bronchitis, psychogenic/habitual cough, bronchiectasis, CA, TB, sarcoid

## RHINOSINUSITIS (Otolaryngol Head Neck Surg 2015;152:598; NEJM 2016;375:962; Clin Infect Dis. 2012; 54(8):e72)

- Time course: acute (<1mo) vs. subacute (1-3mo) vs. chronic (>3mo); 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 | |
|---|---|---|---|
| Viral: most common cause | 7-10d | Symptom control, oral decongestant | • NSAIDs/Tylenol for pain<br>• Saline irrigation/ Netipot<br>• Topical nasal steroids, decongestant, expectorants |
| Bacterial: only 0.5-2% of acute rhinosinusitis. *S. pneumo* (41%), *H.flu* (35%) | >10d, severe sx for 3-4 days, or worse after initial 5-6d ("double sick") | Watchful waiting in pts w/ follow-up vs. amox-clav 875mg BID** or doxy 100mg BID x5-7d | |
| 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
  - No polyps → trial saline irrigation/intranasal steroid
  - ⊕ polyps → add short course of PO steroid ± ASA desensitization 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)

- **Usually 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, ∅ 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 500mg BID x10d; amoxicillin 500mg BID x10d; IM benzathine penicillin G 1.2milliU x1
    - PCN-allergic: cephalexin 500mg BID x10d
    - β-lactam sensitivity: clindamycin 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*

- Initial eye exam: visual acuity (Snellen chart, w/ glasses if worn), pupils (reactivity, APD), confrontational 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, double vision, new onset flashes or floaters

**Vision Loss**

- Acute, Painless (ED): GCA (temp. HA, +PMR); 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, pain worse w/ eye mvmt); acute closed-angle glaucoma (deep brow ache, ± n/v, halos around lights, sluggish/fixed mid-dilated pupil, conjunctival injxn)
- Gradual, Painless (routine referral): refractive error, cataracts (glare, halos, trouble night driving), open-angle glaucoma (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 VitA, tetracyclines), mild amblyopia

**Red Eye** (AFP 2010;81:137) for tx see *Ophthalmology*

- Painless: subconjunctival hemorrhage (unilateral, no vision Δ), episcleritis (unilateral focal erythema, no vision Δ or discharge, self-limited), dry eye syndrome (b/l itching, burning, photophobia, foreign body sensation, diffuse hyperemia), blepharitis/Meibomian gland dysfunction (b/l lid margin burning, itching, AM crusting, styes)
- 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*), xanthelasma (HLD, yellow plaque)

**Conjunctivitis** (JAMA 2013;310:1721, NEJM 2023;389:2363-2375):

- Viral > bacterial. Very contagious: strict hand hygiene, avoid contacts until sx resolves
- Dx: PCR, GS, or Cx rarely needed – consider if severe purulence, refractory to tx, recurrent, immunocompromised, or c/f GC/CT
- Avoid contact lenses, topical corticosteroids, OTC vasoconstrictors (rebound hyperemia)

| Etiology | Presentation | Dx | Tx |
|---|---|---|---|
| **Viral** (most common) | History: sick contact, URI sx, watery d/c, gritty sensation, itching. Exam: intense hyperemia, ± periocular swelling, preauricular LAD | Typically adenovirus | Cool compresses, artificial tears. If c/f HSV/VZV: topical/PO tx + ophtho |
| **Bacterial** | History: mucopurulent d/c, pain/stinging. Exam: crusting, intense hyperemia, LAD rare | Typically *S. pneumo, S. aureus,* or *H. flu;* 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** | History: intense itching, painless tearing, hx atopy, allergic rhinitis. Exam: **bilateral**, mild hyperemia | Chronic or seasonal | Avoid allergens. Cool compresses, artificial tears. OTC anti-histamine/mast-cell stabilizer drops (e.g., 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** | History: otalgia, itching. DM, water exposure, cerumen. Exam: tragus/pinna pain, ear canal edema/erythema, ± otorrhea/LAD/TM perf | Typically *PsA* or *S. aureus*. Assess for other skin conditions | Depends on if TM is intact and severity. Topical: acetic acid, steroid, abx (FQ) oto-drops (UTD algorithm) |
| **Otitis Media** | History: recent URI, smoking, hx Eustachian tube dysfunction. Exam: TM bulging ± immobile w/ erythema, conductive hearing loss | Viral > bacterial (*S. pneumo, H. flu, M. catarrhalis)* | 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

Patients who have a radiographic/physical exam finding concerning for malignancy that has not yet been diagnosed, strong family history of CA, or have a genetic predisposition to CA should be referred to the MGH Early Detection and Diagnostics Clinic (referral in Epic).

## Adrenal Nodules (>1cm) (NEJM 2021;384:1542-1551; Endocr Rev 2020;41:775; PCOI)

- Q: Is it malignant? (<5% 1° carcinoma, <2.5% mets): high-risk imaging findings: diameter >4 cm (93% Sn for adrenocortical CA), >10 HU on CT, heterogeneous, hypervascularity, irregular shape, calcification, ↑T2 signal on MRI, CT delayed contrast washout
- Q: Is it functionally active? (10-15%): exam & lab testing for all nodules >1cm (unless obvious myelolipoma) to r/o pheo & Cushing's syndrome (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** (~10%) | • HTN, metabolic syndrome, CVD, central obesity, proximal muscle weakness, facial plethora, weight gain, easy bruising, acne<br>• Glucose intolerance, DM<br>• Decreased, normal, or increased bone formation | Baseline DHEAS. 1mg o/n dex suppression test (DST): if ⊕ send 24h urine free cortisol, DHEAS, midnight serum cortisol, then confirmatory 8mg o/n DST |
| **Pheochromocytoma** (7%) | • HTN (5-15% don't have), palpitations, HA, diaphoresis, tremors<br>• ≥10 HU on unenhanced CT, vascularity, cystic/hemorrhagic changes<br>• Cardiomyopathy<br>• "Pheo crisis": HTN/HoTN, psych d/o, multiorgan failure, hyperthermia | Plasma free (after 30m supine) or 24h urine fractionated metanephrines & catecholamines (Sn 98%, Sp 98%)<br>**Do not perform DST (above) if concerned for pheo** |
| **Hyperaldosteronism** (~1.5-3%) | • HTN, hypokalemia<br>• ↑risk stroke, CAD, a fib, HF<br>• ↑mortality (compared to matched population with essential HTN) | Plasma aldo & renin activity (correct hypoK and d/c aldo antagonists before testing). May need 24hr urinary aldosterone excretion test, adrenal venous sampling |
| **Hyperandrogenism** | • ♀: virilization, hirsutism, acne, irregular periods<br>• ♂: 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: cannot distinguish between benign cortical mass & 1° adrenal CA. Useful if c/f adrenal met from another primary without known metastatic disease (**only** after excluding pheo)
- Follow up: repeat CT in 6mo-12mo. Consider annual DHEAS/1mg DST x4-5y (unknown effectiveness, guidelines do not recommend). Adrenalectomy if nodule grows >1 cm in 1 year, reaches 4cm, or becomes functional

## Thyroid Nodules (Thyroid 2016;26:1; Endocr Pract 2016;22:622; PCOI)

- Q: 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 → r/o hypothyroid (FT4/TPO Ab) → U/S-guided FNA if criteria met
- TSH low → FT4/T3, Thyroid radionuclide ($^{123}$I) scan
  - "Cold nodule" → U/S-guided FNA if criteria met
  - "Hot nodule" → 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 >1-1.5cm + 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 6-12mo. If low-moderate suspicious U/S findings, repeat U/S 12-24mo, consider FNA if >1-2cm change. If very low risk, repeat 2-3 yrs. Stop f/u after 2 neg FNAs

## Incidental Pulmonary Nodules (<3cm) (Radiology 2017;284:228; Chest 2013;143:e93S; Thorax 2015;70 Suppl 2:ii1)

*Note: these guidelines are for **incidental findings** (see Fleischner Society Guidelines); 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 (>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
- At MGH, 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 |

## SHOULDER PAIN (PCOI)

- 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<br>- Chronic = age, acromial spurring, overuse<br>- Tendinopathy, partial or full thickness tears<br>- Pain & weakness, often with overhead arm use<br>- Ortho referral often needed | - ↓ROM. Painful arc, impingement<br>- **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. ⊕ if not maintained<br>- **External lag test**: externally rotate shoulder 90°, flex elbow 90°. Ask pt to maintain position. ⊕ if not maintained<br>- **Drop arm**: abduct arm to 90°. ⊕ if cannot smoothly adduct shoulder to waist-level<br>- **Neer**: pronate forearm (thumbs point backwards), bring shoulder to full forward flexion. ⊕ if pain<br>- **Hawkins**: flex shoulder to 90°, flex elbow to 90°, and internally rotate the shoulder. ⊕ if pain<br>- **Ext rotation** (teres minor, infraspin): flex elbow 90°, externally rotate shoulder against resistance. ⊕ if pain<br>- **Empty can** (supraspin): flex shoulder to 90°, internally rotate forearm. ⊕ if pain w/ resistance of downward push |
| **Subacromial Bursitis** | - Referred pain to deltoid<br>- Overuse, heavy lifting | - Pain w/ arc 60°-120° abduction ± impingement<br>- ⊕ Neer & Hawkins |
| **Glenohumeral OA/ Adhesive Capsulitis** | - OA: aching, stiff; age >60<br>- Capsulitis: ↑risk w/ DM, thyroid disease, immobilization; age 40-60 | - OA: crepitus<br>- Capsulitis: loss of active/passive ROM in all planes |
| **AC Joint Pain** | - Young: traumatic sprain, fall with separation<br>- Older: AC evolves into OA & impingement | - Pain, tenderness, swelling over AC joint<br>- ⊕ 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/ ⊕ internal/external lag tests, r/o full thickness RTC tear, previous abnl XR, persistent pain despite 2-3mo of conservative tx
- Rx: **conservative tx** w/ activity avoidance, NSAIDs (Topical/PO), PT/home exercises ± short-term steroid injections (steroid injections can be done by PMNR – place PMR referral); **surgery** for refractory instability, labral/full RC tear, AC joint separation

## LOW BACK PAIN (Acute LBP PCOI)

- Incidence/Prognosis: 84% lifetime acute back pain, 50% sciatica (Mayo Clin Proc 2015;90:1699); 75-90% improve over 4 weeks. RFs for progression to chronic back pain include stress, anxiety, depression, smoking, obesity, and early exposure to non-guideline tx
- PE: 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 | *Muscle spasm:* paraspinal muscle tenderness w/ acute onset, usually unilateral. *Disc*: young, ↑ w/ spine loading (i.e. sitting). *Facet*: >40 yo, ↑ w/ extension, ↓ w/ sitting |
| **Radicular/ Spinal stenosis (7%)** | Disc herniation w/ nerve compression (90% L4-S1), spinal stenosis | *Sciatica* 95% Sn, 88% Sp for herniation: leg > back pain w/ dermatomal distribution of lancinating/burning pain, SLR ⊕. *Spinal stenosis* 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 | *Compression fx*: older, trauma, osteopenia, chronic etoh/tobacco use, steroids. *SI pain*: MVA/falls, rheum. *Inflammatory*: AM stiffness, night pain. *Cancer*: PMH, weight loss, night pain. *Infection*: 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 limited supply 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

## KNEE PAIN (PCOI)

- History: trauma, acute vs chronic, association with activity, constitutional sx, swelling, stiffness, instability, popping, locking 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 anterior pressure. If tibia feels less restrained, ⊕ test | **ACL** injury |
| Posterior Drawer | Pt supine with knee flexed, can stabilize foot by sitting on it. Place hands around tibia, apply posterior pressure parallel to femur. If less restrained motion, ⊕ 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 or pain at around medial joint line, ⊕ 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: 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)
- Rx: all benefit from rest, ice/heat, NSAIDs (topical/PO) ± 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

## FOOT AND ANKLE PAIN (PCOI)

| Etiology | History and Physical | Dx and Tx |
|---|---|---|
| **Ankle sprain** | - Trauma history<br>- Pain/instability/swelling, bruising, focal tenderness over ligament (ATFL most common); squeeze test to r/o syndesmotic sprain | - Imaging: use **Ottawa Ankle Rule** (Sn 96%)<br>- Ice, elevation, rest followed by exercise (consider PT)<br>- 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<br>- Pain & thickening at insertion or 2-6cm proximally; calf squeeze to r/o complete rupture | - MRI only if uncertain<br>- Rest, ice, tendon support, PT<br>- Surgical c/s for complete tear |
| **Stress fracture** | - Overuse; more common in ♀ esp if amenorrheic, underwt (rel caloric deficiency/overtraining syndrome)<br>- Insidious onset of pain after exercising, ± focal tenderness on exam (tibia > tarsal > metatarsal) | - XR insensitive esp early in course; if ⊖ MRI may be req<br>- Rest/non-wt-bearing 2-6w<br>- Consider ortho c/s if high risk for nonunion (anterior tibia, navicular, talus, 1st or 5th metatarsal) |
| **Plantar fasciitis** | - Assoc w/ overuse, pes planus, overweight<br>- Sharp anteromedial heel pain with activity after rest | - If uncertain, US may show thickening<br>- 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**: (note limited evidence; high risks of hyperalgesia, tolerance, dependence, addiction)
  - Exhaust non-opioid options. *Avoid BZD, hypnotics*. Screen for OSA, SUD, mental health. Stress **complete pain relief is unlikely**. Set functional goals. Perform **risk assessment** (SOAPP-R). **Check PDMP**. Obtain prior records, speak to prior prescribers.
  - Can consider suboxone and/or chronic pain consult for some etiologies such as non-healing compression fractures
  - **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**: See at least q1-3mo to review pain/function, side effects, adherence
  - **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**)*
  - Early refill requests should trigger appointment to assess reason, obtain tox screen, discuss use

# Primary Care — Immigrant & Refugee Health

## MEDICAL EXAMINATION (CDC)

***Please Note:*** *This guide is primarily for establishing new care; it is not recommended to obtain extensive migration history unless it is relevant to medical care or social determinants of health. It is important to use sensitivity, communication, discretion, and trust in gathering immigration history and explain the relevance to the patient's care, as some questions may feel intrusive, stigmatizing or cause concerns about discrimination or legal repercussions.*

**Resources:** Refer to **the CDC's page on immigrant and refugee health** or **CareRef** for required/recommended assessments

**Interpreter Services**: In person - x66966, p27403 (M-F 7a-8p; S/Su 8a-6:30p) or via phone service [617-643-3344 Pin #1050]. Speak in **short** sentences & make sure to address the patient (not interpreter) when speaking.

**History**: obtain prior medical records if possible

- SHx: country of origin, travel hx, transit countries, residence in refugee camps/detention centers, time living in US, family structure/hx of separation, food security, housing stability, home/neighborhood safety, education/**literacy**, occupational hx
- PMHx: chronic diseases (incl. pain), surgeries, cancer screens, ♀ OBGYN hx, sexual hx, meds (incl traditional/herbal remedies), smoke/toxin/lead exposures, tobacco/substance use (incl. those legal in country of origin; inform of legality differences in US)
- Mental health: screen for PTSD, anxiety, MDD (on 2nd visit to ↓re-traumatizing). RHS-15 is a consolidated screening tool.
- 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 & not regulatory purposes

- Vision, dental, hearing, BMI, BP. Eval for murmurs, hepatosplenomegaly, LAD, skin lesions (rashes, trauma, nutrient 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 MMR/VZV/HAV. Incomplete HBV vaccination may result in transiently elevated titers. Assess need for polio.

**Screening and Labs**:

- Gen: CBC/diff (eos, anemia), UA (hematuria), BMP (glucose, renal dz), ♀ hCG, lead screen if preg/lactating/taking medications, HBV/HCV screen; age-appropriate screens (lipids, HIV, etc.)
- STIs (see *STI*): syphilis, HIV, GC/CT if ♀≤24+sexually active or ♀>24+RF
- TB: ask yearly about sx, recent travel, sick contacts; retest PRN (see *Tuberculosis*)
- Malaria: Rx if from Sub-Saharan Africa w/o pre-departure Rx or from endemic country w/sx (Rx resistance info here). If preg/breastfeeding, Dx first (do not Rx empirically). Obtain thick/thin 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 & 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, MGH Chelsea LINC referral if pt @ MGH Chelsea CHC )

- **Do NOT** document immigration status in EMR
- MassHealth eligibility is NOT contingent on immigration status. Refer all uninsured 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
- 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 & 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
- Resources on conducting asylum evaluations and working with asylum seekers
- Resources within Boston area: Refugeography (Google map of various food pantries, job training, ESL, social support services, etc.)

| Immigration Statuses | Details |
|---|---|
| **Lawful Permanent Resident (LPR)** | **Green card** recipient; pathway to citizenship. Family can get green card through "family based" immigration |
| **U-Visa, T-Visa<br>VAWA** | Eligible if victim of human trafficking (T) or victim of certain types of crime (U).<br>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 & 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 |

Additional tips: **Travel**: undocumented pts can now apply for driver's license (DL) in MA (H4805); however, DL will likely not meet REAL ID requirements for air travel (to start: 5/7/25) – risk being detained by CBP agents at any US airport if trying to fly **Legal**: can support pt's petition for legal status by documenting pt's medical need for legal status **Advocacy**: Join Asylum clinic and/or IHC groups

# Primary Care — Health Equity & Insurance

## Social Determinants of Health (AAFP EveryONE Project)

Accounts for 30-55% of health outcomes with up to 20-year gap in life expectancy between counties with lowest and highest life expectancy in the US. SDH primarily influence health outcomes through limiting opportunities to live a healthy lifestyle or chronic stress (JAMA 2017; 117:1003). Structural racism limits opportunities through discriminatory practices in labor, housing and educational systems with racism and stress being shown to affect both mental and physical health outcomes (Lancet 2017; 389:1453).

| Economic | Environmental | Education | Food | Community | Health Systems |
|---|---|---|---|---|---|
| Employment<br>Income<br>Expenses<br>Debt<br>Medical bills | Housing<br>Transportation<br>Safety<br>Parks<br>Playgrounds | Literacy<br>Language<br>Early ed.<br>Higher ed.<br>Vocational | Hunger<br>Food deserts<br>Availability of healthy options | Social integration<br>Support<br>Discrimination<br>Racism<br>Stress | Insurance coverage<br>Provider availability<br>Linguistic/cultural competency<br>Quality of care |

↓

| Health Outcomes |
|---|
| mortality, morbidity, life expectancy, health expenditures, functional limitations, health status |

## Strategies to Addressing Health Inequity

1) Understand patient's community (County Health Rankings and Roadmaps); screen for SDOH (useful dot phrase: .SDOHSCREEN, if positive refer to MGH SDoH Services aka "Ambulatory Referral to MGH SDH" or "Navigation" referral @ health center clinics).

- Actionable items: PT-1 for transportation, Goodrx/coupons for meds, SNAP funds/cards, applications for MassHealth
- Check if they are eligible for iCMP ("Risk Contracts" flag in chart) for care coordination (adds case manager + resources)

2) Consciously address implicit bias (Harvard Project Implicit); reflect on gut reactions, ask if they are rooted in implicit bias
3) Address patient health literacy; utilize in-person interpreter services when available, schedule longer visits, employ teach back method, utilize dot phrase .MEDSS for a framework to optimize medication adherence, Patient Gateway setup/assistance
4) Identify and utilize local resources to address SDOH ( eg AAFP Neighborhood Navigator, 211, and FindHelp)

## Insurance Coverage

- Open enrollment: limited time when one can buy a new insurance plan, varies by employer and insurance system; MassHealth ~Nov-Jan.
- Patient Financial Services can assist patients, both inpatient and outpatient, with applying for state-funded programs such as MassHealth and Health Safety Net: 617-726-2191.
- Mass Health: federal and state funded healthcare coverage, MA's interpretation of Medicaid and CHIP; can apply online (if age <65), by mail or fax, will take 45-90d for approval; must renew households annually
  - Basic eligibility requirements: MA resident, eligible citizenship/immigration status, valid SSN
    - MassHealth Limited is an option for patients who have an immigration status that keeps them from getting more services – covers care for emergencies (in & outpatient)
  - Several coverage options available with eligibility for age <65y determined by comorbidities and income, ranging from ≤133-300% federal poverty limit (FPL); age ≥65y eligible if income ≤100% FPL, more lenient for disabled seniors
  - Use .INSURANCE in a patient's chart to find their current coverage

# Primary Care Disability Competent Care

*Authors Comments: Please note that this is an incredibly important and evolving field, which lacks substantial data, publications, and amplification of voices of individuals with disabilities. We write this page with humility and awareness that we are constantly learning how best to support and care for our patients with disabilities. We would welcome any feedback. This White Book page is largely adapted from: Kripke C. Adults with Developmental Disabilities: A Comprehensive Approach to Medical Care. AAFP. 2018;97(10):649-656.*

## DEFINITIONS, MODELS, LANGUAGE

Disability: Differences in cognitive and/or physical function in which individuals benefit from support in areas of major life activity; i.e. self-care, language, mobility, self-direction, ability to live independently and economic self-sufficiency. AAFP. 2018;97(10):649-656

- Disabilities are diverse and can be congenital (e.g., developmental or genetic conditions), acquired (e.g., injuries, stroke, chronic physical, neurologic or psychiatric disorders) or temporary.
- Individuals with disabilities face tremendous amount of discrimination in society, including the healthcare system.
- There are several models of disability which influence how individuals with disability are treated and receive care. AAFP. 2018;97(10):649-656
  - **Medical model**: Disability is a problem of the person, directly caused by disease, trauma, or other health conditions; rehabilitation and is aimed at "fixing" the condition. This model often reinforces stigma and frames the person as flawed or abnormal.
  - **Neurodiversity Model**: Posits that neurocognitive differences are valued components of human neurologic diversity.
  - **Social Model**: Emphasizes that disability is a socially created problem due to lack of appropriate accommodation in physical and social environments and emphasizes inclusion
  - **Biopsychosocial Model:** Views disability as an interaction between health conditions, environmental (e.g., societal attitudes, geography) and personal factors (e.g., socioeconomics, age) (WHO ICF. 2022).
- Disability Competent Care: A model that focuses on caring for the individual beyond the disability, rooted in 3 core values: "1) the individual needs of the participant, 2) respect for the participant's choices, and 3) the elimination of medical and institutional bias." (RIC DCC Model)

## APPROACH TO HEALTHCARE MAINTENANCE, SEXUAL AND MENTAL HEALTH

- **Healthcare Maintenance**: See section on **Age-Appropriate Screenings**.
- Adults with disabilities face profound healthcare inequities. They are at higher risk for heart disease, diabetes, obesity & smoking compared to adults without disabilities (CDC Disability & Health 2023)
- Clinicians have conscious/unconscious biases and make assumptions about adults with disabilities' GOC and QoL that contribute to disparities in health outcomes. (HealthAff. 2021;40(2):297-306)
- Conduct annual physicals, as medical conditions tend to be underrecognized and undertreated, particularly among nonverbal patients. (see Table from AAFP. 2018;97(10):649-656)
- At **initial encounter**, conduct baseline assessment of function, with a focus on: a) cognition b) communication c) sensory function (eg vision, hearing) d) neuromuscular function e) seizure threshold (if applicable) f) mental health. Acute illness among individuals with disabilities often presents as a change from baseline function. (AAFP. 2018;97(10):649-656)
- **Sexual Health**: Offer comprehensive sexual and reproductive health services. Do not assume that adults with disabilities are not sexually active, do not wish to become pregnant, or are not at risk for STIs. (OBGYN. 2024; 143 (4): 475-483)
- **Mental Health**: Adults with disabilities report mental health distress 4.6x more frequently than adults without disabilities. Prioritize mental health screenings, treatment, and lifestyle modifications to promote wellness (eg sleep, healthy weight, physical activity as able) (MMWR 2020:69(36))

## LANGUAGE AND COMMUNICATION

- Commitment to person-centered communication and patient autonomy
- Speak directly to pt regardless of their ability to respond. Use of aides to enhance communication: pictural language, voice amplifiers, demonstrations, alternative formats (large print, braille). View UCSF Toolkit for more resources.
- **Language matters**: Avoid terminology such as "handicap," "mental retardation," and "wheelchair bound" or "confined to a wheelchair." Preferred terms are "disabled," "intellectual disability," and "wheelchair user"

Examples of patient and family centered language (adapted from: *Am Fam Physician*. 2018;97(10):649-656, please view for more examples)

| Common Pitfall | Respectful Alternative |
|---|---|
| Speaking to supporter: Since she is non-verbal, can you share what brings her in today? | Speaking to patient: Can you show me how you say yes and no? Are you in pain?<br>Thank you for sharing. I would like to gather more information. Is it ok if I ask your __ (supporter)? |
| To supporter: Your son is so lucky to have you—you are a super dad! | Patients and their families both deserve support. What types of support do you (supporter) need? |

## ACCOMMODATIONS AND SERVICES

- FMLA: Family and Medical Leave Act provides 12 weeks of unpaid leave per year. Can be used for personal illness, carrying for a family member an illness, parental leave after birth/foster/adoption.
- Short-Term Disability: Replaces a portion of income for 3-6months for patients who develop illnesses, disabilities, or injuries not related to jobs
- Long-Term Disability: Replaces a portion of income if patient cannot work for >90 days
- Social Security Disability Insurance: provides monthly payments to individuals who cannot work due to their disability

*Ethiopia Getachew | Amanda Jowell*

# Primary Care — Outpatient CV Health

## Epidemiology of Cardiovascular Disease

**Cardiovascular disease** includes CAD, CVA, PAD, and aortic disease

- Non-modifiable RF: Age, Sex (F with ~25% ↓ risk than M, though risk ↑ 3x in F post-menopause), FHx premature ASCVD, elevated lipoprotein(a), premature menopause, pregnancy-associated conditions (e.g. pregnancy-induced HTN, gestational DM)
- Modifiable RF: HTN, HLD (↑ Total, LDL-C, ApoB, Non-HDL, or TG; ↓ HDL), DM, CKD, obesity, smoking (esp. current), exercise, alcohol, diet, psychosocial stress (chronic + acute), chronic inflammation (CRP best biomarker), mediastinal radiation, HIV

## Aspirin for CVD primary and secondary Prevention

**Primary prevention:**

- 2019 ACC/AHA 1° prevention: **Not routine;** might consider low-dose ASA for 1° prevention in select pts 40-70y at ↑ ASCVD risk & not at ↑ bleeding risk; avoid ASA for 1° prevention in pts >70y (Circ 2019;140:e596)
- CAC >100 or >75th percentile per MESA calculator (Circ. 2020;141:1541–1553): Consider low-dose ASA in CAC >1000, which requires aggressive management (Circulation. 2021;143:1571–1583).

**Secondary prevention:** In pts w/ stable CVD, low-dose ASA ↓ incidence of CV events and all-cause mortality (AmJMed 2008;121;43)

## Outpatient Blood Pressure Screening and Management

**2017 ACC/AHA guidelines** (HTN 2018;71:1261):

- Definition: HTN = SBP >129 or DBP >79 independent of kidney function or age; US prevalence 46%
- Method: 2 checks >1w apart, sitting 5min with arm at heart level, cuff bladder 80% length & 40% width of arm circumference
- Categories: *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, malb/Cr ratio, CBC, fasting glucose, TSH, lipids, baseline ECG, 10-yr ASCVD risk, consider TTE (eval for LVH)

**2° HTN**: *targeted approach to workup,* consider the following indications (HTN 2018;72:e53):

- Resistant HTN (not controlled on 3+ agents [at least one diuretic]) OR Severe HTN (controlled on 4+ agents [at least one diuretic])
- Acute rise in blood pressure in a previously well-controlled patient, esp. DBP
- Age <30y w/o risk factors (e.g. obesity, OSA, FHx, etc)
- HTN with suggestive electrolyte disorders (hypoK, metabolic acidosis)
- Malignant OR Accelerated HTN (severe HTN presenting with clinical or laboratory signs of end-organ damage)

| Secondary Causes of HTN | | |
|---|---|---|
| **Cause** | **Clinical Clues** | **Work-up** |
| **Medications/Drugs (use or withdrawal)** | NSAIDs, OTC decongestants, OCPs, anti-depressants, corticosteroids, sudden d/c of anti-HTN meds | Thorough history |
| **OSA** | Obesity, snoring, smoking, sleepiness (STOP BANG score) | Sleep study |
| **Renal disease** | Elevated Cr, protein/blood on UA | See *AKI* and *CKD* |
| **Primary aldosteronism** | **HypoK**, hyperNa, adrenal incidentaloma, FHx. **High rates of underdiagnosis and undertreatment:** 20% prevalence in patients with resistant HTN (HTN 2018;72:e53) | Plasma aldo:renin; measure together in morning (~8AM), after pt awake for >2h, seated for >5 min. Ideally off HTN drugs that interact with RAAS axis. |
| **Renal artery stenosis/FMD** | >50% rise in Cr after ACE/ARB initiation; lateralizing abdominal bruit; severe HTN with atrophic/asymmetric kidneys, or diffuse atherosclerosis/FMD | If intervention likely to be pursued, begin with Duplex Doppler US (Sn 85%, Sp 92%) → if stenosis (ARAS>50%) consider angio |
| **Rare**: pheochromocytoma, Cushing's disease, hyper/hypothyroidism, hyperparathyroidism, aortic coarctation, ADPKD | | |

| Lifestyle Counseling (HTN 2018;71:1261) | | |
|---|---|---|
| **Intervention** | **Approach** | **SBP impact in pts w/ HTN** |
| Exercise | Aerobic: 90–150 min/wk at 65-75% HR reserve | ↓5-8mmHg |
| Exercise | Dynamic resistance (see guidelines for program specs) | ↓4mmHg |
| Exercise | Isometric resistance (see guidelines for program specs) | ↓5mmHg |
| Weight loss | Weight reduction in overweight/obese adults | ↓1mmHg for every 1kg of weight lost |
| Diet (DASH) | ↑veg, fruit, whole grain, lean meat; ↓sweets, red meat | ↓11mmHg |
| Sodium | Consume <1.5g/day | ↓5-6mmHg |
| Potassium | Consume 3.5-5g/day | ↓4-5mmHg |
| Alcohol | Limit consumption to <1/2 standard drink/d in F/M | ↓4mmHg |

| Medical Management (HTN 2018;71:1261) | |
|---|---|
| **When to Treat** | **Stage II HTN** (start 2 agents) or **Stage I *if*:** clinical CVD, DM2, CKD, ASCVD ≥10, fails 3-6 mo non-pharm |
| **Target BP** | <130/80 |
| **Choice of Agent** | First-line: thiazides [chlorthalidone may not be > HCTZ, ↑SEs (JAMA IM 2020;180:542)], ACEi/ARB, CCB<br>Other: βB, spironolactone, hydralazine, isosorbide, clonidine, α-blockers (e.g. doxazosin), minoxidil (rare) |
| **Compelling Indications** | DM2: ACEi/ARB (if proteinuria) HF: ACEi/ARB, βB, spiro, diuretic CKD: ACEi/ARB<br>CAD: ACEi/ARB, βB Pregnancy: labetalol, CCB Hyperaldo: spironolactone |
| **Monitoring** | Follow-up eval for BP response/adherence at monthly intervals until BP controlled<br>Labs: check BMP/Mg if starting ACEi/ARB or diuretic, 2-4w after initiation, then yearly or w/ ∆dose |
| **Important Trials Re: BP goals** | SPRINT (NEJM 2015;373:2103): SBP <120 vs 135-139 ↓CVD events & all-cause mortality in high-risk pts, but ↑non-orthostatic HoTN, syncope, & AKI. ACCORD BP (NEJM 2010;362:1575): in pts w/ DM, no CV mortality benefit a/w SBP goal <120 vs <140 |

*Christopher Salazar-Thomson and Spencer Flynn*



Suggest an Edit

## Outpatient Cholesterol Screening and Management

**2018-9 ACC/AHA guidelines** (Circ 2018;139:e1082, Circ 2019;140e596)

- Screening:
  - Check a lipid panel in adults ≥20y to establish baseline LDL-C and estimate ASCVD risk
  - Measurement of apoB (if very high TGs) and Lp(a) may confer nuance to risk estimation; approaches are evolving
- Methods:
  - Fasting: *not necessary*; consider if non-fasting TG >400 or pt has FHx premature ASCVD or genetic hyperlipidemia
  - Low LDL-C: If LDL-C <70 *and precise measurement warranted*, measure direct/modified LDL-C
- **Familial hypercholesterolemia (FH)**: Heterogeneous diagnostic criteria, typically combo of suggestive clinical (premature CVD, tendon xanthomas), lab (LDL-C ↑↑), and FHx (strong FHx premature CVD) findings, and then genetics (LDLR, APOB, PCSK9),
- Common 2° causes: **Diet** (weight gain, anorexia, alcohol, trans/sat fats or refined carbs), **drugs** (orals estrogens, glucocorticoids, diuretics, anabolic steroids, amio, tamoxifen, raloxifene), **diseases** (nephrotic syndrome, CKD), **disordered metabolism** (eg DM2)
- See approach to tx below; *statin therapy is the cornerstone of med rx*, increase to max tolerated before using secondary meds
- Lipid monitoring: Yearly if pt at goal & compliant. Assess LFTs and lipids before statin, at 4-12 weeks, then q3-12 months as needed

| Lifestyle Counseling | |
|---|---|
| **Intervention** | **Approach** |
| Diet | Emphasize: veg, fruit, whole grain, legume, protein sources (low-fat dairy/poultry, fish, nuts), non-tropical veg oils, unsat fats Limit: sweets, refined carbs, processed/red meats, trans/sat fats, sweetened beverages |
| Weight control | Weight loss in overweight/obese pts; reasonable to track risk with BMI, waist circumference measurement |
| Exercise | Target: aerobic, 3-4 sessions/wk, ~ 40min/session, moderate-to-vigorous intensity. At least total/week of 150min of moderate-intensity or 75min of vigorous-intensity physical activity. Decrease sedentary behavior |
| Tobacco | Screen for use at every visit and assist with quitting/reduction when possible |

| Indications for Statin Therapy | | |
|---|---|---|
| | ASCVD Risk Estimator<br>Established pooled cohort 10yr risk calculator for 1° prevention<br>Ages 40-79y<br>Currently in guidelines, likely to be replaced by PREVENT | PREVENT Score<br>New 10yr and 30yr risk calculator for 1° prevention<br>Ages 30-79y<br>Race free. Includes eGFR/UACR, BMI, A1c, and zip code (proxy for SDH) |
| **Clinical ASCVD, <75y** | (e.g. CHD, TIA/stroke/CAS, PAD, TAA/AAA) Maximally-tolerated statin to reduce LDL-C by ≥50% or LDL<70 | |
| **LDL-C ≥190, 20-75y** | Maximally-tolerated statin to reduce LDL-C by ≥50% | |
| **Diabetes (age 40-75)** | Moderate-intensity statin; consider high-intensity statin for ASCVD risk >20%, multiple ASCVD RFs to reduce LDL-C by ≥50% and achieve LDL < 70-100 mg/dL | |
| **Age 40-75 w/o above** | (10 yr ASCVD) Low risk <5%: lifestyle changes<br>Borderline risk 5-7.5%: consider mod-intensity statin based on risk-enhancers*<br>Intermediate risk 7.5-20%: statin to ↓LDL-C ≥30-49% and LDL<100, CAC may help decision<br>High risk >20%: statin to ↓LDL-C ≥50% and LDL <70<br>Extreme risk: progressive CAD despite optimal therapy - LDL goal <55 (Endocr Pract 2017;23:479) | |

*ASCVD risk enhancers: FHx premature ASCVD, LDL-C ≥160, CKD, premature menopause (age <40), HTN or pregnancy d/o, metabolic syndrome, inflammatory dz (RA, HIV, SLE, psoriasis), hs-CRP ≥2, ethnicity (South Asian), TG ≥175, Lp(a) ≥50, apoB ≥130, ABI <0.9

*Coronary artery calcium (CAC) score: 0 no statin in intermed. risk w/o DM, smoking, or early FHx; 1-99 favors statin; CAC 100+, statin

| Common Medications | | | | | |
|---|---|---|---|---|---|
| **Medication** | **Mechanism** | **Indication** | **% ↓ in LDL-C** | **Effect on CV outcomes** | **Adverse effects** |
| **Statins*** | HMG-CoA reductase inhibitors | 1st-line therapy for 1° & 2°prevention | 20-60% LDL-C reduction | 1° & 2°prevention, **↓CV events** (ARR 1.28%, NNT 78, USPSTF) | Myopathy (↓↓prevalent in RCTs vs "practice"), ↑LFTs, memory loss & confusion |
| **Ezetimibe** (10mg qd) | ↓intestinal cholesterol absorption | - Statin-intolerant<br>- LDL-C >70 w/ CVD or <50% ↓LDL-C w/o CVD on max-tolerated statin | Ezetimibe + statin therapy ↓ LDL-C by ~23% | Ezetimibe + statin **↓CV events** (ARR 2%, NNT 50, IMPROVE-IT) | Mild ↑LFTs (usually w/ statin) |
| **PCSK9 inhibitors** (alirocumab, evolocumab) | Block degradation of LDL-R on hepatocyte surface | High risk pts w/ CVD & LDL-C >70 on statin + ezetimibe; approved for use in familial hypercholesterolemia | 38-72% reduction; ~60% in pts on statin therapy | Evolocumab + statin **↓CV events** (ARR 1.5%, NNT 67 at 48w, FOURIER); alirocumab + statin **↓CV events** (ARR 1.6%, ODYSSEY) | Uncommon; mainly injection site reactions |
| **Bempedoic acid** (nexletol) | Blocks ATP-citrate lyase, reduces chol. synthesis | -Statin-intolerant<br>- LDL-C >70 w/ CVD or <50% ↓LDL-C w/o CVD on max-tolerated statin | 20% LDL-C reduction at 6 months | **↓CV events**, ARR 1.6%, NNT 62.5 (CLEAR Outcomes) | ↑LFTs, Cr increases, hyperuricemia/gout, cholelithiasis |
| **O3FAs** (e.g. Vascepa [EPA]) | Incorporate into phospholipids | Severe hyperTG, hyper TG despite statin, CVD prevention | ↓TG ≥30% with no Δ in LDL | EPA + statin **↓CV events** (ARR 4.8%, NNT 21, REDUCE-IT) | Drug-drug interaction (e.g. warfarin), GI sx |
| **Note**: if patient has concomitant **severe hypertriglyceridemia (TG >886 mg/dL)**, then also start **fenofibrate** (many formulations) | | | | | |

| Statin Potency | |
|---|---|
| **High-intensity** (≥50% ↓LDL-C) | atorvastatin 40-80mg<br>rosuvastatin 20-40mg |
| **Mod-intensity** (30-49% ↓LDL-C) | atorvastatin 10-20mg, rosuvastatin 5-10mg, simvastatin 20-40mg, pravastatin 40-80mg, lovastatin 40-80mg, pitavastatin 2-4mg |
| **Low-intensity** (<30% ↓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
HIV patients: pitavastatin (REPRIEVE)
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

## MANAGEMENT OF CHRONIC CORONARY DISEASE (CCD)

**2023 ACC/AHA guidelines** (Circulation. 2023;148:e9–e119)

- Definition: a) prior ACS event or revasc b) impaired LV systolic function from ischemic CM c) medically managed stable angina +/- positive stress test d) angina from microvascular disease and coronary vasospasm, or e) ASCVD based on screening test (eg CCTA)
- Evaluation: Yearly evaluation by cardiologist is recommended to assess for worsening of symptoms. Anatomic or ischemic evaluation in the absence of symptoms is not recommended.
- Medication:
  - **Lipid Lowering**: Goal ≥50% LDL reduction and/or LDL ≤ 55-70mg/dL (for very high risk clinical ASCVD)
    - No evidence for use of fish oil and omega-3 fatty acids/vitamins in reducing cardiovascular events.
  - **Anti-platelet**: ASA 81mg in all patients
  - **Beta-blocker**: Long term beta-blocker is indicated among individuals with prior MI <1 year, LVEF ≤40% regardless of prior MI; in patients with LVEF ≤50%, use of metoprolol succinate, carvedilol or bisoprolol is preferred.
    - Among CCD individuals with prior MI > 1 year and no history of LVEF≤50%, angina, arrhythmias or uncontrolled HTN, can consider discontinuation of long-term use (>1 year) of beta-blocker
    - No known benefit for beta-blockade among individuals with CCD without prior MI
  - **Anti-Hypertension**: Goal BP <130/<80; See Outpatient Blood Pressure Screening and Maintenance above
  - **Special populations**:
    - Patients with diabetes: SGLT2i or GLP-1 receptor agonist reduces risk of major cardiac events
    - Patients with EF ≤40%: SGLT2i reduces risk of cardiovascular death and HF hospitalization.
    - Patients overweight or obese (BMI ≥27): GLP-1 receptor agonist, semaglutide (SELECT trial)

  **Anti-anginal**: Beta blocker or calcium channel blocker as first line agents for symptom management, followed by long-acting nitrates. Ranolazine as 3rd line

## OUTPATIENT HEART FAILURE (JACC 2021;77:772, Circ 2022;145:895)

Helpful to have co-management by cardiology and/or heart failure specialist.

- Each visit: assess med/dietary/lifestyle compliance, document weight, detailed volume exam, classify ACC Stage/NYHA Class, review current GDMT and diuretic dosing, titrate meds according to BP / HR tolerance
- Goal: toleration of target doses of GDMT without symptomatic hypotension or metabolic disarray. For β blockade, target resting HR < 70 without postural hypotension or unacceptable side effects
- Lab monitoring: BMP/Mg 1-2 weeks following up-titration of ACE-i/ARB/ARNi; spironolactone requires close monitoring
- Principles: start GDMT immediately. Starting each class of GDMT at lower-than-target dosing is preferred over maxing out a single agent. Up-titrate to target dosing after starting each class. Even if EF improves (HFimpEF), continue HFrEF quadruple GDMT. If symptomatic hypotension on GDMT, consider over-diuresis or other offending agent prior to reducing GDMT.
- Diuretic: maintenance dose may change when SGLT2i is added due to mild diuretic effect
- Avoid: NSAIDs, CCBs, flecainide, steroids, OTC decongestants (e.g. Sudafed), TMP-SMX (if hyperK concern)
- Special considerations/scenarios for HFrEF:
  - Ivabradine: add if sinus rhythm & resting HR > 70 on max β blockade. Start at 2.5 mg – 5 mg qd
  - Hydralazine/isosorbide dinitrate: add if SBP persistently > 130 on target GDMT
  - Vericiguat: newer option for HFrEF, benefit on top of GDMT, advantage = minimal BP-lowering effect (NEJM 2020;382:1883)
- Adjuvant care and referrals to consider: cardiology or heart failure specialist referral if patient has difficult-to-control volume status or atypical cardiomyopathy; cardiac rehab referral (often under-prescribed); nutrition referral for assistance with dietary (<2g Na) adherence; patient-centered education is critical to enhance GDMT adherence
- Wearables: consideration of implantation of PA pressure sensor (CardioMEMS) to reduce HF hospitalization risk (class 2B recommendation)

# Primary Care — Obesity & Weight Loss

## Overweight & 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 obesity** (avoid stigmatizing terms such as "morbid" or "extreme"). Waist circumference: >40 inches men, >35 inches women

*Caveat: studies suggest using a lower BMI criterion for people of Asian descent (AADI BMI calculator)

**Epidemiology**: 40.3% (CDC 2024) Americans; Midwest, South > West > NE: non-Hispanic Black > Hispanic > non-Hispanic American Indian or Alaska Native > White > Asian; associated with lower SES, income, education (CDC 2023; NEJM 2019;381:2440).

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

**Goal:** set individual goals w/ patient. Benefits at 5% weight loss → ↓BP; >5-10%% →, ↓A1C, improve lipids; >10-15% decreases fibrosis in MASLD, improve OSA; >15% ↓ all cause mortality after bariatric surgery (Curr Obes Rep 2017;6:187)

**Treatment**:

- Diet: 1200-1500 kcal/d for women; 1500-1800 kcal/d for men; 500-750 kcal/day less than usual. Variety of diets can achieve calorie deficit (Circ 2014;129:S102). Patient choice based on highest likelihood to adhere, comorbidities.
- Lifestyle: comprehensive program – dieting, exercise (150min mod-intensity or 75 min vigorous-intensity aerobic activity & resistance training 2-3x/week → effective for weight maintenance > loss), behavioral techniques (Weight Watchers, DM Prevention Programs)
- Meds: *see table.* Indication: wt loss & mgmt. + diet for adults w/ initial BMI ≥30 or BMI ≥27 + wt-related comorbidities (DM, HTN, HLD,etc.) Surgery: *see below.*

## Medications for Weight Loss (JAMA 2023;330:2000)

| Agent | Mechanism of Action | Dose | Mean Wt Loss[1] | Side effects | Notes |
|---|---|---|---|---|---|
| **Semaglutide (wkly, sq)**<br>**Liraglutide (daily, sq)**<br>**Tirzepatide (wkly, sq)** | GLP-1 receptor agonist (Tirz GLP-1/GIP )<br>(NEJM 2021;384:989)<br>(JAMA 2021;325:1414)<br>(JAMA 2022; 327:138)<br>(NEJM 2022; 387:205) | **Sem**: 0.2 -2.4mg<br>**Lira**: 0.6 - 3mg<br>**Tirz**: 2.5 -15mg | **Sem**:12.5%<br>**Lira**: 5.4<br>**Tirz**:17.8% | N/V/D/C, delayed GE, pancreatitis, cholecystitis. Incr. risk of thyroid CA in animals. CI if PMH/FHx of med thyroid CA/MEN2. | **1st line.** Benefit in DM, CAD, MASLD; Potential benefit in HFpEF (NEJM2023;389:1069) |
| **Orlistat (Xenical, Alli OTC)** | Inhibit GI lipases that hydrolyze TGs into FFA; increases fecal excretion of TG | 60-120mg TID AC | 4.1% | Steatorrhea (>10%); fecal incontinence, reduced ADEK absorption; drug interactions; rare liver/ kidney injury. | Reduced BG, lipids, BP; not first-line |
| **Phentermine/topiramate (Qsymia)[2]** | Phentermine: stimulant, anorectic, inc satiety thru hypothalamus<br>Topiramate: modulates GABA CNS receptors | 3.75/23mg x14d → 7.5/46mg x12w;<br>can increase to max 15/92mg | 7.5% | **Teratogenic**. Interacts w/ metformin. Activating/ insomnia. Paresthesia, constipation, dry mouth, HA, URI, dysgeusia | Avoid in HTN, CAD, un-tx hyperthyroid, 14 d of MOAI, caution in anxiety |
| **Naltrexone/bupropion (Contrave)** | Works at hypothalamus by inc satiety + inhibit mesolimbic dopamine (reward) circuit | 8/90mg daily - 16/180mg BID | 4.4% | Nausea, constipation, diarrhea, HA, vomiting; lower seizure threshold; insomnia, dry mouth, HTN, can't take w/ opioids | Not first line due to SE, helpful if AUD; can't use w/in 14d of MAOi |

*[1] Mean wt loss difference compared to placebo at max doses*

*[2] Phentermine (Adipex-P, Lomaira) can be used alone short term but less effective than phentermine/topiramate (Qsymia) (4.4% at 29 wk vs 7.5% at 29 wks at max doses)*

**Choice of agent**: GLP1/GIP most effective. Tirzepatide (GLP-1/GIP) > semaglutide (GLP-1) (JAMA 2024; 184:1056) though no RCTs. Current data: tirze> sema > lira. If <5% weight loss within 3 months on full dose can try another agent/ med class. Metformin can produce modest weight loss in overweight patients (<5% weight loss) but not FDA approved for weight loss.

## Weight Loss Surgery/Procedures (NEJM 2007;356:2176)

**Indications**: BMI ≥35 (Asian BMI ≥27.5) or BMI >30 (Asian BMI ≥25) with T2DM or failed non-surgical methods (Surg Obes Relat Dis: 2022;12:1345). MGH Weight Center referral.

**Mechanism:** restriction (↓stomach capacity), malabsorption (↓nutrient absorption by shortening length of the small intestine), hormonal changes (Annu Rev Physiol 2017;79:313)

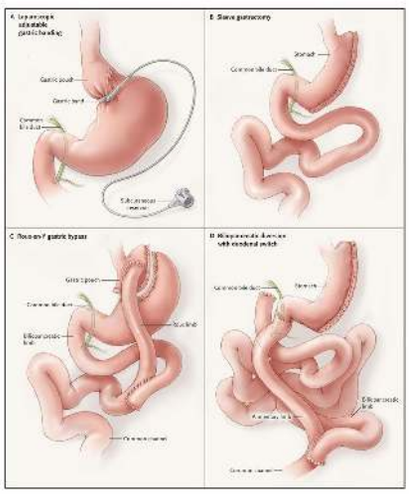
**Types**: Restrictive: sleeve gastrectomy, sleeve gastroplasty, gastric banding, intragastric balloon; Malabsorptive: jejunoileal bypass, biliopancreatic diversion ± duodenal switch; Restrictive + malabsorptive: RYGB, single-anastomosis duodenoileal bypass w/ sleeve gastrectomy. **Most common:** Sleeve gastrectomy & RYGB

**Benefits**: 1 yr wt loss: RYGB 31%, sleeve gastrectomy 25% (Ann Intern Med 2018; 169:741), endo sleeve 49% (Lancet 2022;400:441). Endo balloon ↓13 lb at 9 mos (GI 2021;160:1799); remission of DM, HTN, HLD, OSA; ↓CV & cancer mortality (30-50%), inc life expectancy by 3 yrs (NEJM 2020;383:1535; Annals 2020;173:694), improve MASH (JAMA 2021;326:2031)

**Complications**:

<30d: anastomotic leak, MI, and PE (total 0-1.55%) (Obes Rev 2018;19:529)

Long term: food aversions/intolerances, **vitamin deficiencies** (**ADEK, Vit C, thiamine, B12, folate, iron, zinc, selenium, copper, Ca**), psychosocial impairment, **dumping syndrome** (rapid transit of hyperosmolar carbs cause fluid shifts, hypotension, sympathetic surge), **osteoporosis**, weight re-gain, increased sensitivity to EtOH



# Consultants

Calling Consults

## Tips for Calling Consults

**BEFORE you call**:

- Place **order** in Epic for consult
- **Know your question** – Bigelow JAR should specify consult question in task list. *If not there, ASK. It is always OK to clarify*
- **Know your patient**: review H&P/chart, *see/examine the pt*; review last clinic & operative notes if applicable (Notes → Filters → Specialty); for all below, mention any outpatient providers
  - **GI**: melena/hematochezia, current/prior H/H, plts, coags, transfusions, past EGD/colo, vitals, IV access, NSAID/ASA use, rectal exam findings; for cirrhosis: any prior work-up, social history, complications, decompensation
  - **Cards**: recent and old ECG, telemetry, prior stress/echo/cath (know anatomy), dry weight, biomarkers, current cardiac meds
  - **Renal**: baseline Cr, CKD stage, on/off HD, dialysis access, electrolyte mgmt, current UOP, nephrotoxins
  - **Onc**: known cancers w/ stage/tx history, clinical trial history, biopsy results (for new dx), current anticoagulants, special slide; if on immunotherapy, usually on SIC (Severe Immunotherapy Complications) service list at MGH
  - **ID**: current/past micro data, possible sources, current/prior abx (incl # of days), fever curve, hardware, travel, exposures
  - **Pulm:** imaging results, social hx, prior work-up (e.g., autoimmune), prior/current O2 requirements, PFTs

**DURING the page/call**:

- Call as early in the day as possible (ideally before noon), find out how to page using the paging directory. At MGH: paging directory → find "On Call Directory"
- In your **page** to consulting team, include: **pt name, MRN, location, call back #, brief consult question +/- level of urgency**
- Avoid "curbside" questions unless official curbside consult service. If specific question about management, call a formal consult.
- Tell the consultant the **One-Word reason for your call** (i.e. hematochezia, hemoptysis, hyponatremia etc.) followed by a **brief HPI,** a clear **explanation of the team's thinking,** and a **clear and specific question**

**AFTER the call**:

- Invite the consultant to find you to relay their recommendations or tell them who will be covering for you
- Consultant will often provide prelim recommendations on phone, follow-up recommendations in documentation/note later

## 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 *"Churchill Senior on call"* under **Emergency General Surgery (Churchill)**
  - **Psychiatry:** pt actively leaving AMA w/ unclear capacity; security concerns, major behavioral issues; 8am-6pm: p33061 (Emergency Consult Resident). Wknd/Holiday: p17911 (rounding psychiatrist); 6pm-8am: Call APS (4-7688) or page APS resident at 27792
- **Toxicology (ingestions/overdoses/exposures/interactions)**: call Poison Control Massachusetts (617-355-6607 or 800-222-1222).
- **Cardiac Surgery**: page the Attending On Call. **Thoracic Surgery**: page the Fellow on Call. **Vascular Surgery:** pg 21469.

## Calling Surgical Consults at MGH

- **In the ED**: ED surgery "pit team." They typically sit in North/South bay across from room #5 & listed in Amion as ED Surgery Team
  - For patients in the North/South bay: pit senior (x44169; p13115). Other pts in 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 service. Churchill teams are MGH's EGS/Acute Care Surgery. Baker teams encompass subspecialties (e.g. surgical oncology, colorectal).
  - If patient known to an MGH surgeon, consult senior resident on that team to discuss.
  - If patient not known to a surgeon, consult appropriate team based on disease state. When in doubt, contact the senior resident of the most appropriate team to further triage.
- **Follow up on GENERAL surgery consults:** page PGY1 covering the consult service
- **Cardiac Surgery consult** → if non-emergent (8:30am-5pm) place order. Page NP at 30010 after hours, weekends, and holidays.
- **Ortho consult** → page *"Floor resident"* at 20296 under "Orthopedics" or if ED consult, page 22566
- **Transplant Surgery consult** → page *"Resident"* under "Transplant Surgery"

| Surgical Problem: | MGH Consulting Team |
|---|---|
| Acute abdomen | Churchill on call |
| Perforated viscus | Churchill on call |
| Bowel obstruction | Surgical problem → prior surgical team<br>OSH/adhesions → Churchill<br>CA → approp. Baker team |
| Compartment syndrome | Ortho, Churchill (Abdominal, spont hematoma), Vascular (acute limb ischemia) |
| Hepatobiliary | Baker 4 or Baker 8 |
| Liver | Baker 8 |

## Calling Other Subspecialty Consults

- **ACT (Addiction Consult Team)**: place consult in Epic (no need to call), page 29967 if need help overnight.
- **Acute pain service** for epidurals, periop pain. | **Chronic pain service** for refractory or cancer pain; for interventions (e.g., injections/ ketamine/high dose PCA)
- **AMS (Anticoagulation Management Service)**: for established pts: p30104 or click AMS icon in Epic to see AMS RN. For discharge – place Epic consult; if urgent or questions, page Discharge Pathway Service: p30104
- **Cardiology**: login to Amion under "mghcardiology" to identify appropriate fellow (link also in paging directory)
- **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
- **Medicine Services**: in PPD under "Medical Teams." AMPS: p22229, Sr On: p22337, ED Triage: p28786, HMU lead: p21607, OI: p26955, MOD: p28482, Capacity MD: p23556
- **Optimum Care Committee ("OCC," Ethics)**: page ethics support pager: p32097 (Mon-Fri, 8am-4pm, except holidays)
- **Ophtho**: p21004. Backup # 617-573-4063 (MEEI ED). Before calling *know if OK to **travel to MEEI** for exam & if **ok to dilate**.*
- **Psychiatry**: for non-emergent floor consult: order psych consult. *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

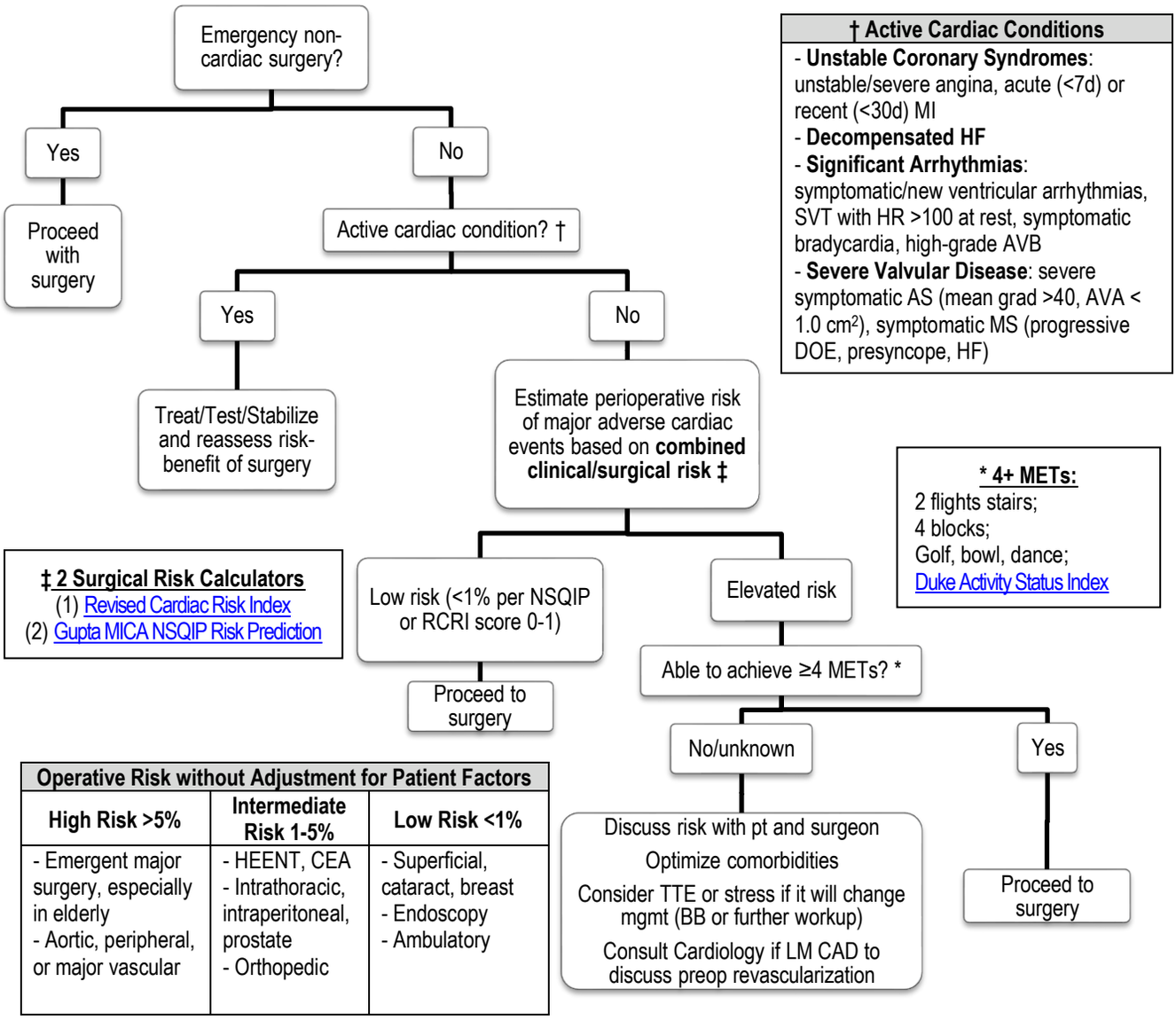
# Consultants — Perioperative Medicine

## PERI-OPERATIVE CARDIAC RISK STRATIFICATION AND RISK REDUCTION

**GOAL**: to **estimate risk** of peri-operative cardiac events, optimize, and pause for cardiac testing if necessary, ***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) preceding condition of patient (2) risk of procedure (3) functional capacity of patient
- Emphasis on risk stratification. **Very few patients need non-invasive/invasive testing,** only if testing would change cardiac optimization management (initiating medical management, PCI, Cardiac Surgery) even *in the absence of surgery*

## PERI-OPERATIVE CARDIOVASCULAR EVALUATION FOR NON-CARDIAC SURGERY (adapted JACC 2014;64:e77)




| Operative Risk without Adjustment for Patient Factors | | |
|---|---|---|
| **High Risk >5%** | **Intermediate Risk 1-5%** | **Low Risk <1%** |
| - Emergent major surgery, especially in elderly<br>- Aortic, peripheral, or major vascular | - HEENT, CEA<br>- Intrathoracic, intraperitoneal, prostate<br>- Orthopedic | - Superficial, cataract, breast<br>- Endoscopy<br>- Ambulatory |

## 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, ECG 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% |

## 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 ⊕ 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). At MGH hold prior to cardiac surgery
  - Failure to restart ARB within 48h ↑30d 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*
- **SLGT-2i**: MGH policy requires that SGLT2is be held for 72h prior to surgery to ↓ risk of euglycemic DKA

## 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 NSQIP Surgical Risk Calculator** can help estimate other post-operative complications including LOS, need for rehab, risk of non-cardiac post-operative complications (Am J Cardiol. 2018; 121:125)
- **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)
  - Myocardial injury after noncardiac surgery (MINS) commonly asymptomatic; variable recommendations for screening with ongoing studies → MINS is an independent predictor of 30-day mortality (Anesthesiology 2014;120:564)
- **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, and low albumin. Multiple risk calculators for different outcomes, including ARISCAT (Anesthes 2010;113:1338), Gupta (for resp failure), and Gupta (for PNA). Mitigation of risk 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 ≥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)
- **GLP-1 antagonist use**: If pt has used GLP-1a in the last month, MGH policy recommends clear liquid diet for 24h prior to procedure to decrease risk of aspiration.

# Consultants Dermatology

**Before Consulting Dermatology: *Upload photos of rash*** *(ideally pre-treatment) to media tab of EPIC using Haiku*

- If c/s for drug rash, note exact timing of rash and suspect meds as well as dates of admin. See chart below for drug culprit timing.
- Note: Erythema in patients with darker skin tones can present with a more violaceous or dark brown hue; textural changes are important to note. Applying gentle pressure to blanch involved skin or use of a bright light may accentuate subtle erythema.

**Quick Steroid Guide**

- Face/intertriginous areas: hydrocort. 2.5% cream, hydrocort. valerate 0.2% cream
- Body: fluocinolone 0.025% cream if symptoms or BSA involvement are mild, clobetasol 0.05% ointment if symptoms or BSA are severe Scalp: 0.01% fluocinolone scalp solution or oil (dermasmoothe); oil better for dry scalp

***Counsel patients:*** Use BID x2 wks then 1 wk "off", avoid mid-high potency on face/skin folds as able (risk = skin atrophy). Prefer non-steroidal (tacrolimus 0.1% cream) on face.

| MGH topical steroid formulary by level of potency | |
|---|---|
| Super-potent | clobetasol ointment 0.05%, betamethasone dipropionate ointment0.05% |
| 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 oil 0.01% |
| Least potent | hydrocortisone 2.5%, hydrocortisone ointment 1.0% |
| Over the counter | hydrocortisone cream 0.5%, 1.0% |

Choice of vehicle: ointments ↑ potent, ↑ stickiness, ↓ irritation
Always confirm vehicle and full name (for example, betamethasone diproprionate is NOT the same as betamethasone valerate)

## Common Dermatologic Conditions

- **Allergic contact dermatitis (ACD)**: often appears in a geometric shape with well-demarcated borders (i.e. square tape, EKG leads, BP cuffs, surgical prep). Usually localized but may be generalized when secondary to chlorhexidine cleaning wipes or may generalize 2/2 autoeczematization (a.k.a. "id reaction", most commonly seen 2/2 tinea anywhere on the body but can occur 2/2 ACD). Identify and remove suspected trigger. Tx w/ high potency topical steroid for limited BSA (low to mid potency for face, if mid potency for face, shorten duration to BID 3-5 days). Pred taper (>1wk) for more extensive BSA involvement. Rebound possible if pred taper too short
- **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 if concerned for superinfection. Bleach baths or swimming pool thought to decrease infections.
- **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 Derm 2018;154:529). **Bilateral LE cellulitis is EXTREMELY rare.** Biopsy not routine
- **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. clinitron, bariatric). **Wound Service consult** (Plastics/Vascular) for: acute wound issues such as limb ischemia, wet gangrene, any wound requiring OR debridement. Consider derm c/s to confirm etiology.
- **Intertrigo:** chronic inflammation in skin folds 2/2 friction/humidity +/- superinfection with yeast or bacteria. Candidal intertrigo →outlying red papules or pustules. Eliminate friction, moisture, heat with wicking fabric (Interdry), barrier cream (Zn oxide paste), avoid powders when active (can erode skin). Topical azole antifungal BID to reduce yeast burden, caution with topical steroids in thin/occluded areas. Immunocomp. patients with severe intertriginous lesions – consider deep fungal infections JAAD 2021;17:92.

## Other Dermatologic Conditions

- **Calciphylaxis**: extreme pain (may precede lesion), violaceous retiform patch/plaque +/- "woody" induration → necrosis, ulcer, eschar. Can appear at sites of trauma (injection sites, surgical debridement) JAAD;13:57.
  - Risk Factors: ESRD on dialysis (most common), warfarin, 1° hyperPTH, malignancy, prior bariatric surgery
  - Dx: skin biopsy (gold standard, not sensitive); $Ca^{2+}$ x phos product, PTH; bone scan w/ increased uptake
  - Tx: normalize serum $Ca^{2+}$/phos/PTH via phos binders (i.e. sevelamer) and cinacalcet; Intralesional/IV sodium thiosulfate; treat 2° infections (death from sepsis), consider hyperbaric $O_2$ (consult MEEI Hyperbaric Med), pain ctrl, wound care (Medihoney), nutrition c/s. D/c warfarin if able; consider AC (often apix). Derm may consider pentoxifylline. Calciphylaxis = indication for HD
- **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 (sclerodermoid), 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: close discussion with oncology team. Immunosuppression with corticosteroids +/- cyclosporine or tacrolimus, supportive care
- **Immunotherapy toxicity:** result of t-cell activation; most common on PDL-1 inhibitors, highest incidence of immune related effects are mucocutaneous (~50% of immunotherapy patients, ~2% severe (>grade 2)); usually managed outpatient; variable timeline

- Wide range of severity (CTCAE grade 0->4), presentations, and treatments. Rx depends on type and severity
- Low threshold to consult Derm +/- SIC to characterize rash and guide therapy especially if bulla or skin sloughing/necrosis/pain
    - 1st line treatments: topical steroid grades 1–2, systemic steroid grade 3, dc of immunotherapy with grade 4

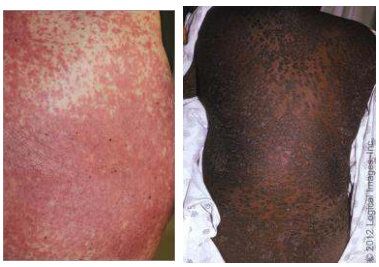
- **Herpes simplex virus 1/2**: always confirm w/ DFA or PCR from vesicle base; cx possible but takes long to result
  - Uncomplicated orolabial: usually gingivostomatitis → acyclovir 400mg TID x7-10d; if recurrent → valacyclovir 2000 mg PO q12h x 1d or famiciclovir 1500mg PO x1 at sx onset; periocular skin involvement warrants ophtho c/s to r/o herpetic keratitis
  - Uncomplicated genital (immunocompetent): 1º ep (<72hr onset)→valacyclovir 1000mg PO BID x10d, acyclovir 400mg PO TID x10d, or famciclovir 250mg TID; recurrent eps (<24hr onset)→valacyclovir 500mg PO BID x3-5d or acyclovir 400mg PO TID x5d.
  - Ppx for immunosuppressed patients: e.g. SOT patients or heme malignancy on induction chemo, 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.
- **Herpes zoster (shingles)**
  - Uncomplicated, <72 hr (immunocompetent): valacyclovir 1000mg PO Q8H x7d or acyclovir 800 mg PO 5x/d x7-10d
  - Disseminated: >20 vesicles and two 1º (non-adjacent) dermatomes; acyclovir 10mg/kg IV q8h; airborne 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 antivirals; if higher risk (≥50yo w/ mod-to-severe acute pain) consider gabapentin 300mg
- **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; caution: can progress to skin sloughing
  - Causes: psoriasis, atopic derm, cutaneous T-cell lymphoma (incl. Sezary), pityriasis rubra pilaris (islands of sparing), drugs
  - W/u: med rec +/- HIV. Tx: derm c/s; emollients, mid-potency topical steroids, antihistamines; fluids/lytes; 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**: usually bilateral; Tx: LE compression with elevation; mid- to super potent steroid ointment BID x 1-2wks +/- occlusion with plastic wrap; mupirocin ointment BID x1-2wks to erosions; intensive moisturization); for hyperkeratosis, NH3 lactate
- **Psoriasis**: depends on severity; avoid PO steroids d/t post-tx flare. Short-term tx: topical steroids, calcipotriene, tacrolimus, moisturizing +/- occlusion w/ plastic wrap; Long-term tx incl phototherapy, acitretin, MTX, biologics w/ outpt derm f/u
- **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" fine scale; tx: topical imidazole (econazole 1% cream QD or clotrimazole 1% cream BID) or allylamine (terbinafine 1% cream BID)x2-6 wks to entire foot and webbed spaces between toes. PO: terbinafine 250 mg QD x 2 wks.

## 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 (cetirizine+ 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 **same location** each time drug ingested. Can evolve to bullae/become disseminated. Oral/anogenital mucosa commonly, can be anywhere. Usually asx. | 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/intertriginous areas → widespread. Usually w/in 2-14 days of med exposure. Sx: Burning, pruritus, fever, marked neutrophilia +/- oral mucosal erosions, facial edema. Severe form can lead to septic shock | Abx (PCN, macrolides), CCB, NSAIDs, rarely due to viral infxn | Anti-pyretics, Topical steroids, 1mg/kg/day prednisone if severe/widespread |
| **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), AED, NSAIDs, allopurinol, phenobarb. | Cyclosporine (preferred at MGH) Steroids possible mortality benefit (JAMA Derm 2017;153:514) but controversial, IVIG, etanercept (Ann Allergy Asthma Immunol 2022;129:360) **Burn level care if >30% BSA** **Ophtho consult, +/- uro/gyn consult** (if vaginal/urethral involvement) |
| **DRESS** | 2-6 wks |  | Morbilliform; spreads down symmetric. from face & mucosal involv. Facial edema (can help diff. from morbilliform drug) Fever, arthralgias, elev abs eos, internal organ involv. (liver, kidney; rarely lung, heart), LAD | Abx, AEDs, carbamazepine, ARTs (nevirapine, abacavir), allopurinol, NSAIDs | Dx: obtain CMP, CBC w/ diff, TSH, consider TTE - Supportive care - IV Solumedrol, SLOW taper (3-6 wks), recheck TSH at 4-6 wks |

# Consultants Surgery

## 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, n/v, obstipation and/or constipation. Labs normal or hypoK/metabolic alkalosis from repeated emesis. Examine for evidence of hernia and abdominal scars. If severe pain or peritoneal signs, consider ischemia from strangulation (lactate, WBC)
- Imaging: KUB – initial, air-fluid levels; **CT A/P w/ IV +/ PO + contrast– best**, dilated bowel proximal to & decompressed bowel distal to obstruction. *Caution*: sending pt with SBO to CT w/o NGT = aspiration risk, empirically place prior to CT
  - SBO vs ileus: SBO - **transition point** between dilated & decompressed bowel; ileus - diffusely dilated loops w/o transition point
- Tx: **strict NPO (no meds via NGT)**, large bore **NGT** (18Fr always) to continuous low suction; consider Gastrografin challenge [90 cc undiluted GG PO or via NGT; clamp NGT x 2 hr (unclamp if vomits); KUB 6 hrs post]. **Consider OR** if signs of bowel ischemia, s/p RYGB (internal hernia), closed loop, or no improvement in 72 hrs. **All pts need strict I/O & IVF, accounting for NGT output.**

## BENIGN BILIARY DISEASE (Prim Care 2017:44(4):575-597), see *Biliary Disease*

- Indications for cholecystectomy (CCY): symptomatic cholelithiasis; cholecystitis; choledocholithiasis; cholangitis; gallstone pancreatitis; gallbladder polyps (>1cm, concerning features, or rapidly growing)
  - Post-cholecystectomy syndrome (PCS): abd pain, dyspepsia recurring after CCY; *early* (biliary injury, retained stones, retained cystic duct), *late* (CBD stones, stricture, stenosis, bil dyskinesia), consider alternate non-bili etiology (Int J Surg 2010;8:15)
- Acute calculous cholecystitis: persistent RUQ pain + tenderness, cholelithiasis caused by cystic duct obstruction. Dx: RUQUS – distended GB, GB wall >3mm, pericholecystic fluid, stones; **HIDA scan** – confirmatory test, non-visualization of gallbladder = positive.
  - Tx: IV abx (CTX/Flagyl or Zosyn), early CCY during hospitalization assoc. with ↓ morbidity (Br J Surg 2015;102:1302). If critically ill, perc chole → delayed CCY (at least 6 wks later).
- Gallstone pancreatitis: See *Pancreatitis*; findings include ↑lipase, ↑LFTs (↑ALT > 3.5x ULN, 95% PPV)
  - Consider Urgent ERCP (24 hrs) if cholangitis or CBD obstruction; same-admission CCY +/- IOC in mild cases associated with ↓ readmission for gallstone-related complications compared to delayed CCY (Br J Surg 2016; 103:1695)
- Acalculous cholecystitis: seen in critically ill ICU pts usually with prolonged NPO + biliary stasis, high mortality rate
  - Tx: perc chole + IV antibiotics
- Choledocholithiasis: CBD obstruction, jaundice. ↑AST,ALT (<1000), ↑ALP, ↑direct bili. RUQUS w/ CBD dilation, **MRCP if indicated**.
  - Tx: GI c/s for ERCP + surgery c/s for same-admission CCY. Can consider immediate CCY+IOC or CCY + choledochoscope
  - If concern for cholangitis (Charcot's triad – fever, RUQ pain, jaundice, Reynolds' pentad – + AMS, shock) → IV abx (Zosyn or CTX/Flagyl), IVF, and **urgent ERCP/IR drainage**, same admission CCY. *Can cause rapid clinical decompensation.*

## NECROTIZING SOFT TISSUE INFECTION (CID 2007;44:705; Front Surg 2014;1:36)

- Definition: progressive, rapidly spreading infection with secondary necrosis of skin and subcutaneous tissues, +/- fascia & muscle
- Microbiology: majority polymicrobial (anaerobes, GAS, *S. Aureus, Clostridium*, *Peptostreptococcus*, *Enterobacterales,* PsA)
- Clinical signs: **rapidly spreading erythema** (hrs to days) → pain disproportionate to exam or beyond borders of erythema, dusky skin, turbid ("dishwater") discharge, crepitus, bullae, fever, hypotension; Fournier's gangrene (perineum) & Ludwig angina (jaw/neck)
- Dx: **clinical dx**, **CT w/ IV contrast** has a ~95-100% NPV. Labs for **LRINEC** score (CRP, WBC, Hg, Na, Cr, Gluc) → score ≥6 has a 92% PPV & 96% NPV (Crit Care Med 2004; 32:1535-41). Bedside I&D if equivocal (dishwater fluid, loss of tissue integrity, malodor)
- Tx: **IV abx** (Vanc+ [Pip/Tazo or meropenem or cefe/flagyl] + [Clinda or LZD] (to inhibit toxin production) + **EMERGENT surgical debridement (consult Churchill service immediately)**

## ACUTE LIMB ISCHEMIA (NEJM 2012; 366:2198)

- Clinical signs: **6 P's: P**ain, **P**oikilothermia (cool to touch), **P**aresthesia, **P**allor, **P**ulselessness, **P**aralysis
- Dx: check pulses & Doppler signals in both affected & unaffected extremities for comparison. Obtain ankle-brachial indices. CTA
  - **Acute limb ischemia** → acute decrease in limb perfusion 2/2 thrombosis or embolism (can be iatrogenic, e.g., s/p vascular access procedure), needs *urgent vascular surgical evaluation*
  - **Chronic limb ischemia** → chronic vascular disease from atherosclerotic changes. Exam with cool, hairless extremities, limited/no pulse/absent Doppler signals that is not acutely painful (perfusion maintained by collaterals). *Non-urgent* surgical eval
- Tx: if unsure, or acute limb ischemia, 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; 2/2 crush injury, edema, bleed, ischemia, etc.
- Clinical signs: tight, tender skin; pain out of proportion to exam; **pain with passive ROM**; ↑lactate or CPK
- Dx: **clinical dx,** measurement of compartment pressures w/ Stryker transducer needle if equivocal (call Ortho or Churchill Service)
- 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 end organ dysfunction (e.g.,↑airway pressures, ↓UOP/AKI, ↑lactate, acidemia). IAP measured via bladder pressure (most reliable if paralyzed, done in ICU)
- Typically occurs after massive resuscitation in ICU patients with trauma, burns, s/p liver txp, severe ascites, pancreatitis, bowel ischemia, sepsis
- Tx: if true Abdominal Compartment Syndrome → **decompressive laparotomy with temporary abdominal closure**
  - If IAP 12-20 w/o clinical instability, temporize w/NGT, rectal tube, paralysis, LVP, ↓tidal volume, diuresis, HOB elevation

## WOUND CARE

- Inpatient Wound Service: Staffed by APPs and MDs. Consult for pts with complex wounds including unstageable pressure wounds, ***non-urgent*** debridement of sharp objects and infected wounds, & all diabetic foot ulcers, venous stasis ulcers, arterial ulcers, dry/wet gangrene.
  - After hours, consult Vascular (foot/ankle), Churchill (pressure ulcers/wounds), or Burn (all others)
- Wound Nurse Service: Unit based CNS or NP who provides local wound care, staging of pressure injuries, and product selection.
- Post I&D Care: For abscess cavities >5cm. Change dressing/packing daily. 1) Irrigate wound with saline 2) loosely pack the cavity with packing (sterile gauze, Iodoform strip gauze, or silver-containing hydrofiber) 3) Leave ≥1cm tail of packing as a wick for exudate & facilitate removal of the packing 4) Cover with pad/gauze.

# Consultants Urology

**Who to call**: page 11300 for Emergencies, Foleys, SPTs, & gross hematuria; page 10300 for other non-urgent inpatient consults
**Consults**: note urine color **in tube** (bag urine appears darker due to volume) before consulting Urology, place urine samples at bedside – use food/drink comparisons like "pink lemonade," "fruit punch," "cranberry juice," and "merlot" to help characterize

## Ureteral Obstruction (commonly due to kidney stones or malignancy)

- **Evaluation/management**: Pain usually present only in **obstructing** stones. +hydronephrosis implies obstruction.
  - Imaging: stone-protocol CT scan **(I⁻, O⁻)**: evaluates position, density/composition & presence of hydronephrosis
    - Alternative: MRI vs combined KUB+US; however, less diagnostic than stone-protocol CT. US helpful to r/o hydronephrosis
  - Vitals, CBC, UA/UCx: if concomitant UTI, decompress urgently with stent by urology or percutaneous nephrostomy (PCN) by IR
  - Rehydration: patients often hypovolemic, bolus as tolerated and increase maintenance IVF → ↑ureteral clearance
  - Alpha-Blockers: **tamsulosin** 0.4mg PO qd (hold for SBP <90) → ureteral relaxation, +evidence for better **distal** stone passage
  - Analgesia: Tylenol, NSAIDs if Cr OK, add IV opioids if inadequate pain control; can also use diazepam (2mg Q8 PRN)
  - Preop considerations: NPO, BMP/CBC, continue AC if plan for Urology stent; hold AC & obtain coags if plan for IR PCN
- **Urgent urology consults**: solitary or transplanted kidney with worsening AKI, UTI, urosepsis in setting of obstruction
- **Obstruction + sepsis**: Non-con CT A/P ASAP, BCx/UCx, urgent Urology consult; broad IV abx to cover GNRs + enterococcus
- **Non-stone hydronephrosis**: often stricture or malignancy, may 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
- *Relevant History:* renal colic is unilateral pain from CVA wrapping around flank radiating towards ipsilateral scrotum/labium
- **Indwelling ureteral stents:** Need exchange every 3-6 months; if +UCx, need abx treatment prior to exchange; can be done as outpt

## Hematuria

- **DDx**: BPH, UTI, INR>3, traumatic catheter placement, bladder CA (5th most common neoplasm), upper urinary tract CA, prostate CA
- **Acute Management**: Obtain post-void residual bladder scan before consulting Urology. If +foley, can manually irrigate & aspirate
  - **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, while CBI *prevents* new clots from forming by diluting active bleeding
- **Diagnostic Workup** (4 C's): 1) in-house **CT hematuria protocol**; 2) urine **Culture**, 3) urine **Cytology**, 4) 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 aspirate and then flush 50cc saline 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; consider **tolterodine** (fewer side effects than oxybutynin), Oxytrol patch
- *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 (if present), **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
  - **All RNs are allowed to place Coudés – the tip (and balloon port) point "up" towards sky**;
    - BPH, men >50yo → 16-20 Fr Coudé (gentle curve directs catheter tip through curve of prostate)
    - Stricture or bladder neck contracture → 12-14 Fr
    - *Pro-tip:* use 8-10cc lubricant **instilled into the urethra** via syringe (urojet) for easier catheter placement in men
  - Urethral trauma: To avoid, fully hub foley on placement prior to balloon inflation; leave foley in 3-5d to allow for urethral healing
- **Suprapubic tubes (SPT)**: externally placed tube travels percutaneously through anterior abdominal 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/anticoag
  - Urine collects in external bag. If low UOP into bags, passage of blood or concern for malposition – flush>obtain US/CT>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 or MAC, requires change every 3-6mo.
  - May cause bladder spasms, urinary frequency or urgency – tx w/ flomax, oxybutynin/vesicare, tylenol, diclofenac, valium PRN
  - NOT changed in setting of infection unless stent has failed (which becomes ureteral obstruction c/b UTI, tx usually = PCN w/ IR)
  - Okay to continue anticoagulation
- *Note:* if stents/PCNs/chronic catheter or SPT/ileal conduit or neobladder – UTIs diagnosed on symptoms over UCx/UA (colonized)
- *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

## EPISTAXIS (NOSEBLEED)

**Acute management**: (UpToDate Epistaxis)

1. Have patient **lean forward**, **pinch nostrils**, and hold firm **pressure for 20 min and order Afrin ASAP (as below)**
   - Guidance: pinch over the soft portion of the nose (NOT hard nasal bones); do NOT lean head back (risks aspiration) and **do NOT "peek"** – hold continuous pressure for 20 min; patient may be unable to hold pinch, best for RN/MD to do
2. **Afrin (oxymetazoline 0.025%**) nasal spray (after gently clearing clots)
   - Guidance: **GENEROUSLY SPRAY (3-4 sprays each side) on both sides then hold pressure again for 20 min as above**
3. Control SBP (goal < 140) if much greater than baseline; correct coagulopathy if present
4. **Consult ENT (Otolaryngology) if continued bleed after above steps**
   - Treatment: bedside cauterization (if appropriate given location/volume), resorbable vs. non-resorbable packing, embolization
   - Non-resorbable nasal packing: risk of Toxic Shock very low but present, so patient needs gram + coverage (keflex, clinda) while packing in; packing typically removed after 5-7d inpt or outpt. Posterior nasal packing is a special form of non-resorbable packing ("Epistat") and requires inpatient admission for cardiac monitoring given potential vagal stimulation.

Location: most are anterior bleeds from Kiesselbach's plexus (90%); posterior bleeds are more rare/serious/difficult to manage

Hx: duration, laterality of, and frequency of bleeding; EBL; prior episodes (and txs); trauma (fingers, fists, foreign body, NGT placement attempts, etc.); prior nasal surgery; PMHx or FHx of coagulopathy; medications (e.g. **anticoagulation**); cocaine or intranasal drug use

Exam: Laterality/rapidity of bleeding ("dripping" vs. "gushing"); **suction clots from OP to protect airway if rapid bleed**

Tests: CBC, PT, PTT, T&S (consider crossmatch pRBC if brisk bleed), consider CTA or CT Face if high-volume after airway protection

Epistaxis prevention: after resolution x 2 weeks: petroleum ointment; avoid nose blowing / digital manipulation / vigorous exercise; keep head above heart; sneeze w/ mouth open; humidification (saline nasal spray TID-QID); Afrin / hold pressure PRN re-bleeding

## STRIDOR

**Acute management**:

1. Administer oxygen (low flow = NC, simple face mask, non-rebreather; high flow = venturi mask, HFNC); ensure IV access
2. Racemic epinephrine neb x 1 STAT (lasts ~2h); 10mg dexamethasone IV x 1 STAT (re-dose q8h)
3. Consider Heliox, abx, and humidification; IM / IV epinephrine and Benadryl if anaphylaxis suspected
4. **If unstable → RICU & trauma surgery (x6-3333) for possible surgical airway; if stable or unstable → ENT for airway evaluation with flexible laryngoscopy**

Hx: timing/evolution; inspiratory / expiratory / biphasic; inciting events, prior episodes; recent intubations (duration, intubation difficulty) 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 or praxis of the recurrent laryngeal nerve from ET tube); infectious (epiglottitis, laryngitis, laryngotracheitis [croup], bacterial tracheitis, Ludwig's angina); allergic / angioedema; mass of larynx or trachea; neurological (vocal cord spasm / immobility); foreign body; trauma

Imaging: if stable, CT with contrast of head / neck / chest to localize source

## DEEP NECK SPACE INFECTION (see *Head & Neck Infections*)

**Acute management**: (UpToDate Deep Neck Infection):

1. **Ensure protected airway**: intubation or surgical airway if threatened airway → consider glucocorticoids (dexamethasone 10mgx1)
2. **Empiric antibiotics**: typically need **polymicrobial** coverage (ensure appropriate anaerobic coverage)
   - E.g., amp/sulbactam vs 3rd gen cephalosporin + flagyl; consider vancomycin in pt with risk of MRSA or if sinogenic source
   - Vancomycin/cefepime/flagyl if healthcare-associated, severe, or immunocompromised
3. **ENT consult for consideration of drainage** (localized infection) and airway monitoring

Symptoms: sore throat; dysphagia / odynophagia; dysphonia/muffled voice; dyspnea / stridor; fevers

Exam: neck tenderness; lymphadenopathy; trismus, fullness / asymmetry of OP; crepitus; pooled saliva; stridor

Tests: CBC, PT, PTT, T&S; blood cultures; CT neck with contrast; MRI neck with contrast if c/f osteomyelitis

Complications: based on location: *parapharyngeal*: involvement of carotid sheath (CCA, IJV, CN X), carotid blowout (life-threatening), jugular thrombophlebitis (Lemierre's); *retropharyngeal*: extension along deep neck spaces/mediastinum (mediastinitis / empyema); *prevertebral*: spine osteomyelitis; *submandibular/sublingual:* Ludwig's angina (floor of mouth swelling, rapid resp compromise)

## ACUTE SINUSITIS (Otolaryngol Head Neck Surgy 2015;152:S2)

Definition: **up to 4 weeks of purulent nasal drainage + nasal obstruction or facial pain / pressure / fullness (or both**); can be viral or bacterial (typically bacterial if symptoms > 10 days)

Symptoms: *uncomplicated* (confined to sinuses): facial pressure / pain, purulent nasal discharge, nasal obstruction, fever, 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**

Workup: *uncomplicated*: no imaging required; *complicated*: CT w/ contrast ± nasal endoscopy to look for evidence of purulence and culture

- If concern for invasive fungal sinusitis, consult ENT for consideration of nasal biopsy with STAT pathology

Treatment:

- Uncomplicated: amoxicillin ± clavulanate 5-10 days; nasal steroid spray / nasal saline irrigations for symptomatic relief; if no improvement after 7 days change antibiotic. Consider Afrin BID x 3 days only as well.
- Invasive fungal sinusitis: **liposomal amphotericin**, urgent surgical debridement, ID consultation

## SUDDEN HEARING LOSS (Otolaryngol Head Neck Surg 2019;161:S1)

1. Use otoscope to examine ears and **ensure no cerumen impaction**
2. Determine conductive hearing loss vs sensorineural hearing loss – obtain **audiogram**, call 617-573-3266 at MEE to schedule urgently
3. If sensorineural hearing loss, consult ENT for initiation of either high dose oral corticosteroids or intra-tympanic steroids if contraindication to systemic steroids; ideally start steroids within 2 weeks of symptom onset

# Consultants — Ophthalmology

**Ask PMH abnl vision, eye sx, meds, cataract, glaucoma, macular degen, DM retinopathy, and do basic eye exam *prior* to consult!**
General inpatient consult: **check paging directory and page/call listed number;** can also call MEEI ED desk **617-573-4063**

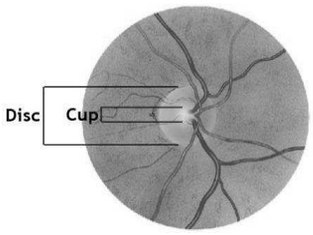
**Basic Eye Exam: "Ocular Vital Signs"**
- Visual Acuity (e.g. 20/200, CF)
- Pupils (4mm → 2mm OD, No rAPD)
- Confrontational visual fields
- Extra-ocular movements
- Intraocular pressure (nl 10-20mmHg)
- Color vision testing (Ishihara cards)

**Common Abbreviations:**

| | | | |
|---|---|---|---|
| AT | Artificial tears | NLP | No light perception (VA) |
| cc/sc | With/without correction (glasses) | NPDR | Non-prolif. diabetic retinopathy |
| CE | Cataract extraction | NS | Nuclear sclerosis (i.e. cataract) |
| CF | Count fingers (VA) | OD/OS | Right eye, left eye |
| CWS | Cotton wool spot | OU | Both eyes |
| DES | Dry eye syndrome | PDR | Proliferative diabetic retinopathy |
| DFE | Dilated Fundal Exam | PF | Pred Forte gtt (prednisolone) |
| EOM | Extraocular movement | PFAT | Preservative-free artificial tears |
| HM | Hand motion (VA) | PH | Pinhole acuity |
| IOL | Intraocular lens | PVD | Posterior vitreous detachment |
| IOP | Intraocular pressure | rAPD | Relative afferent pupillary defect |
| LP | Light perception (VA) | RD | Retinal detachment |
| MGD | Meibomian gland dysfunction | SLE | Slit lamp exam |
| | | SPK | Superficial punctate keratitis/dry eye |
| | | VA, VF | Visual acuity, visual fields |

## High-Yield Pearls

- **Vision loss**: acute (requires urgent evaluation) vs chronic (outpt referral) – assess patient with 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 20 min before exam; light-sensitive 4-6 hours
- **Finding the retina:** dilate the eye and use the ophthalmoscope

## Common Eye Pathology

- **Red Eye**: 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**: b/l itchy+watery. Tx: olopatadine 0.1% gtt bid x 5d, artificial tears. Clear Eyes not rec'd (rebound sx)
  - **Anterior uveitis**: pain and photophobia ± eye injection. Hx autoimmune disease common. **Refer to MEEI ED**
  - **Contact lens keratitis**: pts remove contacts on admit! P/w red/painful eye; infection until proven otherwise. **Refer to MEEI ED**
  - **Acute angle closure glaucoma**: sx include nausea, aching pain, vision loss. Palpation of the eye will be "rock hard" or elevated pressure with tonopen. Exam: red eye, hazy cornea, mid-dilated pupil. Avoid dilation if suspected. **Urgent consult to MEEI.**
  - **Subconjunctival hemorrhage**: blood between conjunctiva and sclera from ruptured vessel. No vision changes or pain. Can be 2/2 blood dyscrasia, Valsalva (cough, vomit), trauma, AC, spont. Resolves spont. No need to consult if no significant trauma.
- **Blepharitis:** erythema of lids, crusting of lashes, red eyes, gritty feeling. Tx: baby shampoo lid cleaning+warm compresses BID, artificial tears QID, emycin ung qHS. Tx for **hordeolum ("stye")** is same. **Dry Eye Syndrome (DES)**: eye pain, sandy/gritty feeling, paradoxical tearing ± "blurriness" comes/goes (esp with blinking). Tx: preservative-free artificial tears QID , Refer to ophtho if no improvement. Approach to blurry vision.
- **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, 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) Consult if no improvement after 24h
- **Anisocoria (unequal pupils)**: old (20% 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 → sympathetic chain → internal carotid → orbit. **Head and neck CTA/MRA to r/o carotid dissection.**
- **Retinal detachment**: painless flashes/floaters/curtain coming over vision. Risk factors: myopia (near-sighted), trauma, diabetic retinopathy, prior eye surgery. Tx: **Refer to MEEI ED** for likely surgery. Approach to flashes, floaters, spots
- **Orbital Cellulitis**: most common from sinus disease; periocular edema/erythema + orbital signs (rAPD, color vision loss, motility disturbance, proptosis). CT face/ orbits w/con for stranding/abscess. **Consult MEEI**, likely needs admission for IV abx. **Preseptal** negative orbital signs, negative scan, can treat with oral abx and reassess symptoms.
- **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 surgery
- **Optic neuritis**: painful EOM, subacute blurry vision (typically monocular), central scotoma. Causes: demyelinating ds (MS), infection, autoimmune (sarcoid, lupus). Dx MRI brain/orbits w/+w/out contrast. Tx: HD steroids; c/s ophtho/neuro.
- **Double vision:** Monocular (present even when one eye is covered, often benign) vs binocular (present only w/both eyes open). **Consult MEEI**. Approach to double vision.

# Consultants OB/GYN

## How to Consult

- **Obstetrics/MFM**: For inpatient consults for patients with a known intrauterine pregnancy, page the MFM team (p17977)
  - If no response, call L&D 617-724-9410
- **GYN Onc**: If pt has biopsy confirmed GYN malignancy or established GYN onc provider (p31037)
- **GYN**: Everyone else (e.g., hCG⊕ without confirmed intrauterine pregnancy, undifferentiated ovarian mass, heavy vaginal bleeding) Obtain pelvic (transvaginal) **U/S**. If hCG⊕ but no confirmed intrauterine pregnancy on imaging, should be on **ectopic list** (p22346)

## Abnormal Uterine Bleeding

- **History**: Verify source of bleeding is uterine (as opposed to vaginal [e.g. laceration, trauma, atrophy], GI, or GU), duration and quantity (#soaked pads, tampons), associated sx, triggers (e.g., postcoital), trauma hx. Other hx: estrogen C.I. (smoking, BMI, HTN, migraines w/ aura, h/o coagulopathy), 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.
  - Postmenopausal bleeding never normal and need w/u to r/o malignancy. If premenopausal, r/o pregnancy and its complications
- **Exam**: External vulvar exam, speculum exam (note how many scopettes required to clear bleeding, volume of blood in vault, cervical lacerations, blood actively coming from cervix), bimanual exam (CMT, uterine size/orientation, adnexal fullness) - do NOT do digital exam if pregnant! GYN is happy to help with these exams.

| Differential Diagnosis for Abnormal Uterine Bleeding | |
|---|---|
| **Pregnant** | **Ectopic pregnancy**, miscarriage (including incomplete and septic abortion), subchorionic hematoma, placental abruption, placenta previa/accreta, vasa previa, trophoblastic disease, cervical/vaginal/uterine pathology (e.g. polyp) |
| **Not pregnant** | PALM-COEIN: Endometrial/cervical polyp, adenomyosis, leiomyoma/fibroids, **malignancy** (e.g., endometrial, cervical), coagulopathy, ovulatory dysfunction, endometrial dysfunction, iatrogenic, not otherwise classified (thyroid disease, hyperprolactinemia, A-V malformations). |

- **Workup**: urine hCG, CBC, T&S, coags (including fibrinogen), pad count (Epic order, monitors bleeding quantity)
  - If premenopausal, first step is **urine hCG:**
    - If ⊕, obtain **serum quant hCG** 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 for at least 3 values** (should increase 35-50% q48h).. Ectopic risk factors: IVF pregnancy, h/o STIs, prior ectopic, h/o tubal surgery, IUD, smoking. If abnormal trend, may need endometrial/Karman biopsy and CMP (to offer MTX vs surgery). If normal, usually repeat pelvic U/S in 2 weeks
  - If postmenopausal, **pelvic U/S**, consider endometrial biopsy if endometrial lining >4mm (difficult to do inpatient) *Regardless of U/S result, postmenopausal bleeding warrants at least outpatient GYN follow up*

## Pelvic Pain

- **History**: Timeline, severity, LMP, associated sx (N/V, GI, GU, fevers/chills, vag bleeding/discharge, wt loss), pain med requirement
- **Exam**: Abdominal, CVA tenderness, bimanual exam, consider speculum exam if bleeding or discharge
- **Differential Diagnosis**: Non-exhaustive list of most common causes of pelvic pain:
  - **Ectopic**: see above; if peritoneal signs on exam or hemodynamically unstable, consider ruptured ectopic **(surgical emergency)**
  - **Adnexal lesions**: benign (simple, hemorrhagic, dermoid, etc) vs malignant. If high c/f malignancy, obtain CA-125, CA19-9, CEA
  - **Ovarian torsion**: clinical dx, most predicted by acute unilateral pain (<8hr), vomiting, mass (>5cm) (HuRepro 2010;25:2276)
  - **PID**: ascending (e.g., GC/CT; usually polymicrobial) vs descending (e.g., diverticulitis); fevers/chills, vaginal discharge, CMT; complications include TOA, infertility
  - **Endometriosis:** chronic dysmenorrhea, dyspareunia, dyschezia w/ menses; r/o acute causes, consider outpatient follow up
  - **Non-GYN**: nephrolithiasis, UTI/pyelo, appendicitis, diverticulitis, constipation
- **Workup**: hCG, pelvic U/S, GC/CT, CBC with diff, UA/UCx; consider alternative abdominal imaging pending H&P (e.g., CTAP)

## Pregnancy and Its Complications

Gravida/para (G/P), G= #pregnancies, P= #births; TPAL (T=term births, P=preterm births, A=abortions, L=living children).

- Dating: By LMP vs US (the earlier, the more accurate). Urine pregnancy tests first positive ~10-12 days post-ovulation/~1 week prior to missed period; serum HCG will be positive earlier. Pregnancy should be confirmed by ultrasound with presence of intrauterine gestational sac (~5 wks gestation) and yolk sac (~5.5 wks gestation). Failed pregnancy dx by Doubilet criteria (NEJM 2013;369:1443)
- General considerations:
  - Cardiovascular: Goal MAP at least 60-65, BP <160/110 (hypertensive disorders of pregnancy work-up initiated w/ BP >140/90). Physiologic state is ↑CO (by 30-50%) at first due to ↑SV (overall ↑intravascular volume), then due to ↑HR (about 15%) later in pregnancy. ↓SVR due to progesterone-induced smooth muscle relaxation, leading to 5-10 mm Hg ↓ in systolic and 10-15 mm Hg ↓ in diastolic BP (but normalizes to pre-pregnancy BP around the end of the 2nd trimester). ↑DCO2 due to ↑RBC mass.

- Acid/Base: General goals of pH ~7.3, pCO2 ~40, PO2 >75. Healthy pregnant patients have a gradually worsening compensated respiratory alkalosis with 3rd trimester usual pH ~7.4, PaO2 100-105, pCO2 25-30, bicarb 17 (not expected to normalize in the setting of critical illness).
- Positioning: Left lateral displacement to be maintained to optimize perfusion and venous return.
- Coagulation: Physiologic hypercoagulable state achieved through ↑ in clotting factors, ↓ in inhibition of clot formation, and venous stasis in the setting of the growing gravid uterus. D-dimer is also ↑ in pregnancy (less useful for PE diagnosis). Decreases in fibrinogen in pregnancy are associated with acute fatty liver disease of pregnancy or disseminated intravascular coagulation. Goal fibrinogen >300. Heparin and lovenox are safe in pregnancy; warfarin contraindicated.
- Hematologic: RBC volume ↑ by 20% while plasma volume ↑ by 50% causing dilutional anemia of pregnancy (RBC concentration will measure as ↓). This, in addition to peripheral destruction, also contributes to a slight ↓ in platelet concentration [moderate to severe decreases (<100 million/mL) and acute loss of platelets should be investigated as abnormal]. WBC are ↑ (6-16 million/mL during pregnancy and >20 million/mL during labor).
- Pulmonary: Though the FRC is ↓ due to the growing uterus elevating the diaphragm (TLC also ↓ by 5%), the lungs compensate by ↑ TV 30-40%, thus minute ventilation (MV) is ↑ which means there will be ↑ alveolar and arterial O2 (PAO2 and PaO2, respectively) and ↓ PACO2 and PaCO2. This creates a greater CO2 gradient between the gravid patient and the fetus, facilitating the removal of CO2 from the fetus and the delivery of O2. FEV1 is not affected.
- Imaging: Ultrasound is preferred. MRI has no known fetal risk, though gadolinium contrast is contraindicated in pregnancy. CT is acceptable if absolutely indicated (teratogenesis requires >200 mGy during early first trimester, risk of childhood cancer increases from 1:3000 to 1:1500 after exposure to 10-20 mGy in 2nd-3rd trimesters). IV nonionic contrast without known risk to fetus; iodinated contrast has risk of fetal hypothyroid, benefits usually outweigh risks. See ACOG Committee Opinion #723.
- Lab References: Normal lab values by trimester (Perinatology.com)
- Medications: See AFP 2014;90:548 for OTC medication guide or LactMed.
- Surgery: Generally, surgery is preferred in 2nd trimester but can be performed at any time if necessary for maternal well-being.

- Hypertensive complications: BP ≥140/90 is abnormal, any BP ≥160/110 is an OB emergency
  - Differential: chronic HTN (HTN <20w), gestational HTN (HTN >20w), pre-eclampsia (new HTN + proteinuria or new HTN ≥160/110), pre-eclampsia with severe features (unrelenting HA, vision changes, RUQ/epigastric pain, lab abnormalities), eclampsia (seizure), HELLP
  - Workup: CBC, BMP, LFTs, LDH, uric acid, urine protein/Cr ratio +/- coags and hemolysis workup
- Hyperemesis: standing meds most effective, see tx algorithm on UTD
- OUD/SUD: can refer to HOPE Clinic.
- Postpartum: Provide with breast pump if breastfeeding (call L&D or Materials Mgmt)

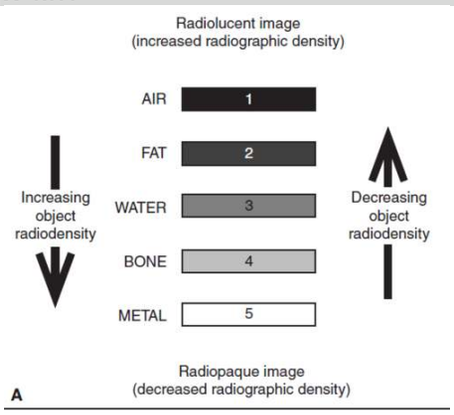
# Radiology

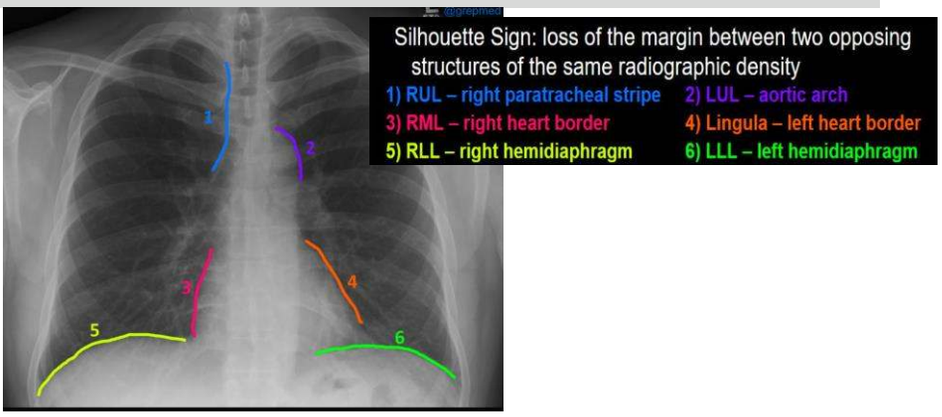


## Imaging Orders

Always include *brief* clinically relevant information to inform the radiologist of your clinical question.
Think of the radiologist as a **consultant** with the goal of adding valuable diagnostic information to patient care via imaging.

## X-ray



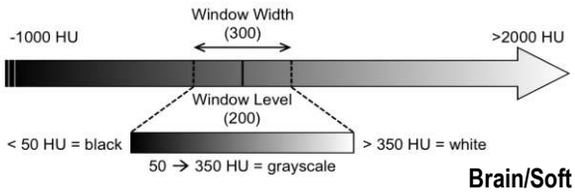




## Computed Tomography (CT)

Hounsfield Units (HU): measurement of CT attenuation (see table for reference range)
Windowing: adjusting contrast (width) and brightness (level) to better visualize specific structures.

- Window width ("contrast" - *range* of grayscale): range of Hounsfield units. HU < window = black, HU > window = white, within window = gray. Wide windows for large diff in density (e.g. air/vessel in lung), narrow for similar density (grey vs white matter)
- Window Level ("brightness" - *center* of grayscale): HU at center of window, corresponds to attenuation of structure of interest (e.g. high lvl for bone window, low lvl for lung window)

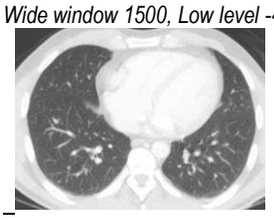
| Phase | Time Post-Injection | Structures Evaluated |
|---|---|---|
| CT-PE | 5-15 s | Pulmonary arteries |
| Arterial (CTA) | 15-20 s | Systemic arteries, no organs |
| Late arterial | 35-40 s | Arteries, renal corticomedullary differentiation |
| Late Portal | 70-80 s | Organs (Routine abdomen) |
| Nephrographic | 100 s | Renal parenchyma |
| Delayed (Vascular) | 120 s | Active contrast extravasation (bleeding), peripheral veins |
| Delayed (Urogram) | 10-15 min | Ureters, bladder |




| Substance | HU |
|---|---|
| Air | -1000 |
| Fat | -100 |
| Water | 0 |
| Blood | 50 |
| Soft tissue | 100 |
| Bone | 1000 |
| Metal | >2000 |

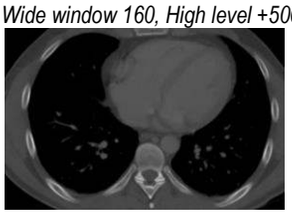
**Lung Window**

*Wide window 1500, Low level -40*



**Bone Window**

*Wide window 160, High level +500;*

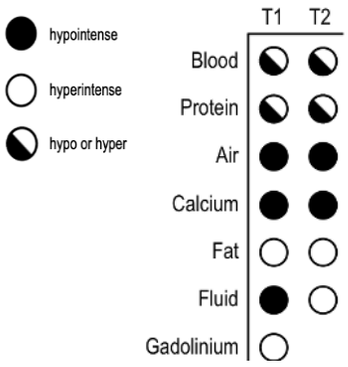


**Brain/Soft Tissue Window**

*Narrow window 80, Medium level +40*

## Magnetic Resonance Imaging (MRI)

MRI safety: search device compatibility at mrisafety.com




| Basics of Common MRI Sequences | |
|---|---|
| **Sequence** | **Purpose** |
| T2 weighted +/- fat-sat | Identify fluid/edema (e.g. most pathology, malignancy). Fat sat refers to technique to make fat appear hypointense. |
| T1 weighted +/- contrast | Evaluate anatomy; identify T1 hyperintense products, including hemorrhage, fat, protein & contrast (gadolinium) enhancement. |
| STIR | T2W (fluid/edema) with technique to make fat appear hypointense (more consistent than fat-sat). Common in MSK MRIs. |
| MRCP | Heavily T2W sequence to eval gallbladder + intrahepatic, extrahepatic, and pancreatic ducts. |
| HASTE/SSFSE | T2W sequence that is rapidly acquired (fast sequence). |
| GRE | ID hypointense susc (blooming) artifact a/w blood & calcium. |
| SPACE | High resolution 3-D sequence (cor, sag, axial). |
| DWI | Identify restricted motion of intra-/extracellular water molecules (e.g. acute stroke, abscess, highly cellular tumors like lymphoma). |

*Monica Cheng, Nelson Gil*



Suggest an Edit

# Radiology — Contrast

## Indications for CT Contrast Administration

- IV positive (**I+**): vast majority of studies more sensitive when given, particularly for **infection, tumors, and vessel imaging**
- IV negative (**I-**): urinary tract stones, retroperitoneal hematoma, pulmonary nodule follow-up, intracranial bleed
- PO positive (**O+**): bowel obstruction, bowel leak/perforation/fistula, differentiate bowel from other abdominal structures
- PO negative (**O-**): inflammatory bowel disease, GI bleed, mesenteric ischemia, retroperitoneal hematoma

## Pregnancy and Breastfeeding (ACR 2024 Manual)

- Contrast Use in Pregnancy:
  - *Iodinated contrast for CT studies*: no need to withhold (no data to suggest potential harm to fetus, although limited data)
  - *Gadolinium contrast for MRI studies*: do not use unless essential + no suitable alternative (radiology consultation). Req consent.
  - Written consent required if predicted fetal dose >0.05mGy. 1 CT = ~25mGy to fetus. No consent for CXR, C/T-spine, mammo
- Breastfeeding: Current rec: I & G* safe for mother & infant, may choose to "pump and dump" for 24h after scan.
  - ***Exception – EOVIST**: unknown if Eovist excreted in milk. Consider "pump & dump", but likely safe to nurse after 10h

## Renal Function (ACR 2024 Manual; MGPO 2020 (CIN); MGPO 2020 (NSF); JAMA IM 2020;2:223)

| | Contrast Induced Nephropathy / Post Contrast Acute Kidney Injury (PC-AKI) | Nephrogenic Systemic Fibrosis (NSF) |
|---|---|---|
| **Definition** | • Association between intravenous / intra-arterial (cath) contrast and development of renal impairment<br>• Occurs 48-72 hours after contrast admin | • Association b/w gad-based contrast (MRI) in pts with renal impairment & development of systemic fibrosis<br>• Occurs weeks to months after contrast admin |
| **Risk factors** | • **CKD (consensus most important)**<br>• Diuretic use<br>• > 2x contrast doses in <24 hrs<br>• Diabetes mellitus<br>• Dehydration<br>• Cardiovascular disease<br>• Age >60 years<br>• Hyperuricemia | • 3 classes of contrast based on risk: I (highest risk), II (minimal risk), III (likely very low risk but limited data)<br>• Some risk with Group I and III (e.g., **Eovist**) in patients with **kidney disease** (acute or chronic) and/or **DM**.<br>• Risk "sufficiently low or possibly non-existent" w/ default Group II GBCAs (e.g. **Dotarem, Multihance**) |
| **Screening** | **Screen if h/o kidney dz or diabetes mellitus**<br>Outpatient: eGFR within 30d, ED: eGFR within 30d, Inpatient: eGFR within 24h | Outpatient: not necessary for most scans<br>Inpatient/ED: eGFR within 24hr for class III agent (e.g. Eovist). None needed for class II agent |
| **Prevention** | **eGFR ≥30: contrast per protocol (NO prehydration)**<br>**eGFR <30 or AKI** → I- or alternative study. Consult radiology if I+ is medically urgent. Consider prehydration. Dose reduction not considered effective prevention | **Group II GBCA:** given regardless of eGFR<br>**Group I GBCA:** consult radiology if eGFR <30<br>**Group III GBCA**: do *not* give if eGFR <30 |
| **On Dialysis** | If maintenance dialysis **w/o possible renal recovery**: administer contrast. If **possible renal function recovery,** (e.g temporary dialysis catheter): consult radiology | **Consult radiology. Typically Gadolinium withheld.**<br>Prompt post-scan HD suggested (PD inadequate) |
| **<24h repeat studies** | Decision is clinical and subjective<br>Insufficient evidence to hold contrast for 24h | No risk factors: proceed<br>At risk patients: consult radiology |
| **Metformin** | eGFR ≥30: continue metformin<br>eGFR <30 or AKI: hold for 48h after scan | Continue metformin |
| **Renal txplt** | Consult Radiology | Consult Radiology |

***Post contrast peak effect on creatinine occurs 48-72 hours after administration**

**Pre-hydration protocol**: (ACR 2024) ***If you want an I+ CT scan in a patient w/ eGFR <30, speak to radiology**
- Prophylaxis indications: **eGFR <30** (not on long-term HD), **AKI**
- PO hydration: Not well-studied. Historical MGH regimen: 1-2L PO non-caffeinated beverage 12-24h prior to scan
- IV hydration: *Start 1 hr prior & cont 3-12 hrs after. Fixed volume (250-500 mL NS) before & after **vs.** weight-based (1-3 mL/kg/hr)*
- N-acetylcysteine is **NOT** recommended for IV contrast prophylaxis

## Contrast Reactions (ACR 2024)

| | Mild | Moderate | Severe |
|---|---|---|---|
| **Allergic** | Limited urticaria<br>Itchy throat, congestion<br>URI symptoms | Diffuse urticaria<br>Facial/laryngeal edema w/o dyspnea or hoarseness<br>Bronchospasm w/o hypoxia | Anaphylaxis<br>Facial/laryngeal edema w/ dyspnea or hoarseness<br>Bronchospasm w/ hypoxia |
| **Physiologic** | N/V, flushing/warmth<br>HA/dizziness<br>Mild HTN<br>Transient vasovagal rxn | Protracted N/V<br>HTN urgency<br>Isolated Chest Pain<br>Vasovagal rxn requiring tx | HTN emergency<br>Arrhythmia<br>Seizure<br>Protracted vasovagal rxn |

**Indications for Premedication**
- Prior mild-moderate allergic reaction
- Prior unknown contrast reaction
- None for prior physiologic reactions
- None for shellfish allergies
- **No** cross-reactivity b/w iodinated contrast and gadolinium

Standard contrast allergy pre-medication regimen: **13h**
- You *must* indicate standard premedication regimen in the imaging order
- Epic order set – "Contrast Allergy Prophylaxis: Regular Protocol Order Panel"

- Urgent contrast allergy pre-medication regimen: **4h**
  - Requires discussion with a radiologist before starting regimen
  - Epic order set – "Contrast Allergy Prophylaxis: Urgent Protocol Order Panel"
- See *Drugs and Contrast* section on pre-medication prior to scan

*Monica Cheng, Nelson Gil*



Suggest an Edit

# Radiology Protocols

## ORDERING STUDIES

- **All cross-sectional studies are protocoled by radiology** – simply provide the necessary information:
  - Body part: Head, abdomen only, abdomen and pelvis, etc.
  - Modality: Ultrasound, Radiograph, CT, MRI, Fluoroscopy, PET whole body, PET Brain, HIDA Scan, etc.
  - Indication: clinical history relevant to the study
  - Contrast: "per radiology discretion" unless *specific* reason otherwise **(I+ IV; O+ oral; R+ rectal)**
  - Contraindications for contrast: renal transplant, kidney injury or prior allergic reaction
  - Questions? - call the appropriate division or page the appropriate on-call radiologist (see *MGH Directory*)
    - Inpatient study questions? - call ED reading room **after 7PM weekdays/5PM on weekends** (unless STAT study). Otherwise, call divisions during work hours (8am-7pm weekdays/8am-5pm on weekends; vascular 8am-noon weekend).
- **Level of Urgency**:
  - Routine: order of interpretation depends on acquisition time
  - Urgent: takes priority over routine studies (performed within 6 hours)
  - STAT: **means NOW, high acuity/life threatening emergencies (i.e., trauma patient may be removed from the scanner for your patient);** these studies are typically (not always) performed in White 1 (ED scanners)
    - Must call the body or neuro ED radiologist for approval
    - Patient must be ready for immediate transport. Responding team must transport patient (no transport provided)
    - Patient must be accompanied by a responding clinician (≥PGY-2) 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 BODY EXT.4-1533 | NEURO EXT.6-8188

- Full interpretation reads overnight: All ED studies
- Preliminary interpretation reads overnight:
  - All acute CT-PE studies (inpatient and ICU)
  - **By verbal request**: inpatient and ICU studies
    - **Routine/Urgent ICU & inpt studies** only reviewed overnight if **urgent clinical question**. Consider face-to-face c/s in ED.
    - **STAT ICU and inpatient studies will receive a prelim interpretation.**
  - After communication with the primary team, all verbalized prelim reads for ultrasound and cross-sectional studies (CT/MRI) will be documented in the chart. Verbalized prelim reads for radiographs (XR) will be documented as needed.
  - All inpatient and ICU full interpretations will be generated the following morning by appropriate division

## ED PROTOCOLS BODY X4-1533 | NEURO X6-8188

- Trauma: I+ (IV contrast), single phase (combo of arterial/portal venous – images checked at scanner by rads to decide if need delays)
  - Blunt trauma: includes bone kernel reformats for better visualization of bones; +/- Delays for parenchymal bleed
  - Penetrating trauma: O+R+ (Oral contrast, rectal contrast) for increased sensitivity of bowel injury
  - CT Cystogram: retrograde filling of bladder with contrast via Foley catheter to evaluate for bladder rupture
- Cervical spine: I-, need for follow-up CTA head/neck 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+, possibly O+ or R+ (if GI contrast requested, please specify PO or PR), image kidneys through pelvis only
- Retroperitoneal Bleed: I-,O-
- Indications for MRI in the ED: Pediatric appendicitis after equivocal ultrasound || Appendicitis suspected in pregnancy || Rule out occult fracture || Osteomyelitis || Choledocholithiasis (MRCP)
- OB Ultrasound Studies: Covered up until 14 weeks

## ABDOMINAL PROTOCOLS X6-5162

- Stone protocol: I-O-, low dose, prone
  - Order contrast-enhanced (I+) CT if there is c/f ANYTHING else (e.g. pyelonephritis) as stones likely still visualized
- Retroperitoneal hemorrhage: Routine abdomen/pelvis I-O-
- 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 via excretion of IV contrast (delayed phase)
  - Cystogram: retrograde filling of bladder with contrast via Foley catheter to evaluate for bladder rupture
- Arterially-enhancing tumors: add arterial phase along to usual CT protocol
  - MR CHIT: **M**elanoma, **R**CC, **C**horiocarcinoma, **H**CC, **I**slet cell (neuroendocrine) tumors, **T**hyroid
- Time 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: eval esophagus, GE junction, proximal stomach → dysphagia, GERD
    - Modified barium swallow: eval mouth, pharynx, upper esophagus → dysphagia, **aspiration**

- UGI series: barium swallow plus stomach, pylorus, and duodenal bulb → bariatric surgery pre-op eval
- SB follow-through: small bowel, terminal ileum, and proximal LB ± UGI series beforehand

## CARDIOVASCULAR PROTOCOLS VASC X4-7115 | CARD CT X4-7132 | CARD MR X3-4457

- DVT imaging:
  - Compression ultrasound is the best initial test of choice; Epic order "LENI" (**L**ower **E**xtremity **N**on-**I**nvasive)
  - CTV/MRV: primarily used for central venous thrombosis when initial US is equivocal or non-diagnostic
- Arterial imaging:
  - CTA: three phases (noncontrast, arterial, venous delays) → stenosis, dissection, aneurysm, active bleeding, systemic embolism/thrombosis (**not pulmonary embolism)**
  - Requisition: specify vessel of interest, field of view, and indication
- Coronary CTA:
  - ECG-gated study of the coronary vessels → only performed by cardiovascular CT
    - Requires beta blocker and vasodilator administration
    - **Not performed after 7pm on weeknights or noontime on weekends**, as cardiac techs are typically not in house
    - On call Cardiac CT Fellow is available for urgent questions after hours: p22122
  - Specify if body parts other than the heart should be imaged (thoracic aorta, CABG grafts, etc.)
- Other ECG-gated CTAs:
  - Indications: any eval of the heart or ascending aorta. ECG-gating unnecessary for descending thoracic/abd aorta & pulm arteries
- Noncontrast vascular studies:
  - Indications: Retroperitoneal hematoma, pre-op aortic calcifications, coronary calcium score, follow-up aortic size

## THORACIC PROTOCOLS X3-3899

- All chest CTs are high resolution
- Routine chest vs CT-PE vs CTA chest:
  - Routine chest: single phase (late arterial) → workhorse protocol (read by Thoracic)
  - CT PE: single phase (pulmonary arterial) → **pulmonary** arteries (read by **Thoracic**), prelim by ED during off-hours
  - CTA chest: three phases (non-contrast, arterial, delays) → **systemic** arteries (e.g. aorta) (read by **Vascular**)
- 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, bronchiectasis
  - Phases: Inspiratory and expiratory images, plus prone images to differentiate between atelectasis and fibrosis
- Nodule follow-up: (Radiology 2017;284:228; Please refer to Fleischner guidelines)
  - Indications: incidental nodule on prior CT, age >35y, **AND** no hx immune compromise, malignancy or recent infection
- Dual energy esophageal leak (I+/I-): Esophageal perf, postop leak; Tracheal Protocol: Tracheal stenosis, mass, stent

## NEURORADIOLOGY PROTOCOLS

- Inpatients: page Neuro IP on-call radiologist at p32535
- Inpatients/ICU Acute Stroke: call x6-3333 & page p21723 acute stroke consult fellow (ED: activated ED2CT 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

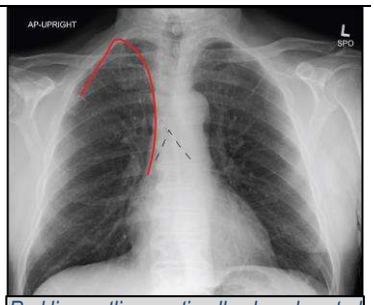
## NUCLEAR MEDICINE PROTOCOLS NON-PET X6-1404 | PET X6-6737

- Tagged RBC study: BRBPR (**NOT** guaiac positive stools, melena, or massive bleeding)
  - Requirements: consult **IR BEFORE STUDY** to confirm angiogram will be performed if study is positive
- VQ scan: acute PE (NOT chronic PE), can happen overnight if results will immediately alter management (i.e., AC tonight) and patient cannot undergo CT PE.
  - Requirements: CXR or I- CT chest within 24h, patient stable and can tolerate laying supine for duration of scan (~4h)
- HIDA scan: acute cholecystitis
  - Requirements: NPO 4h prior to study, no opiates 12-24h prior to study, bilirubin <10, pt will need to tolerate lying supine
- PET: must be fasting, hold everything but meds and water (NO glucose containing fluids either ex: D5W)
  - Overnight is ideal for NPO, 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
- Gastric emptying study:
  - Patient must tolerate PO (consume a standardized meal in 10 minutes), best performed as outpatient study

## MUSCULOSKELETAL PROTOCOLS: if questions: page MSK IR on-call radiologist at p36321

# Radiology — Interpretation of Common Studies

## CHEST X-RAY



*Red line outlines optimally placed central line. Dotted line denotes carina.*

1. **Line placement**
   - ETT positioning: tip 3 - 7 cm above the carina in an adult
   - SVC: between the R tracheobronchial angle and R heart border (Chest 1998;114:820)
   - Superior cavoatrial jxn: ~2 vertebral bodies below the carina (JVIR 2008;19:359)
   - Line positioning:
     - PICC or Central line: tip in the lower SVC or at the superior cavoatrial jxn
     - HD catheter: tip in the right atrium
   - Post placement: check for pneumothorax, except with PICC/midline (see below)
2. **Pneumothorax**
   - Sensitivities:

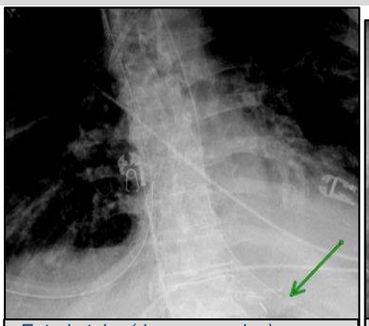
| Imaging Position | Detectable PTX Size | Imaging Findings |
|---|---|---|
| Supine/Portable | 500 cc (LEAST Sensitive) | Deep sulcus sign, lucency along mediastinal border |
| Upright | 50 cc | Sharp pleural edge, absence of distal lung vessels |
| Lateral decubitus | 5 cc (MOST sensitive) | Nondependent collection of air |

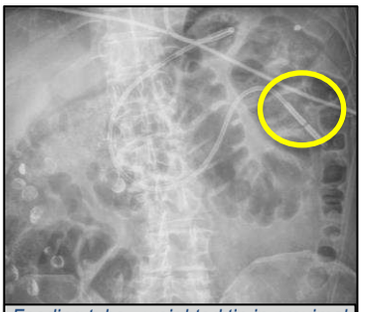
   - Tension: contralateral mediastinal and tracheal shift, collapse of ipsilateral lung, flattening of ipsilateral hemidiaphragm, widening of ipsilateral rib spaces
   - Artifacts that mimic visceral pleural lines: (BMJ 2005;330:1493)
     - Skin folds: form an interface (not a line), extension beyond rib cage, presence of distal lung vessels
     - Medial border of scapula: extension beyond rib cage w/ rest of scapula

*Bilateral pleural effusions*

3. **Pulmonary edema (example images)**
   - Vascular redistribution (first sign): increased caliber of pulmonary vessels in upper lobes ("cephalization")
   - Interstitial edema: incr. interstitial opacities, indistinct pulmonary vasculature, **Kerley B lines** (peripheral subpleural linear opacities), peribronchial cuffing
   - Alveolar edema: perihilar/central opacities, pleural effusions, cardiomegaly
   - Pearls: typically bilateral and symmetric, rapid appearance/resolution of findings
   - Pitfalls: low lung volumes mimic increased interstitial opacities via crowding of normal vasculature

## ABDOMINAL X-RAY (KUB)


*Enteric tube (decompression) – arrow shows side port*


*Feeding tube - weighted tip in proximal jejunum*

1. **Line placement**
   - For Decompression: gastric fundus or dependent portion of stomach. Side-port AND tip should be 4-6 cm below the GE junction to reduce risk of aspiration.
   - For Feeding: distal duodenum or proximal jejunum; C-loop of duodenum is only reliable indicator of post-pyloric placement
   - Post placement Assessment: check for endobronchial placement. Should descend vertically in midline, pass diaphragm, tip should be visualized
2. **Small bowel obstruction** (RadioGraphics 2009;29:423)
   - **KUB**: preferred initial examination
     - Assess for: small bowel dilatation >3 cm, decompressed distal small/large bowel, air-fluid levels, stacked loops of bowel, free air as a complication
     - Main differential: post operative ileus → often large bowel is also dilated
   - **CT**: equivocal cases / further evaluation
     - Findings: SB dilatation with collapse of distal bowel loops and transition point
     - Severity:
       - Partial: passage of air or contrast beyond the obstruction
       - 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 just proximal to transition point)
     - Common causes: adhesions, Crohn's, malignancy, hernias; colon cancer most common cause in LBO
     - Closed loop obstruction: radially oriented bowel loops, engorged mesentery, whirl sign
     - Strangulated/incarcerated hernia (ischemia): bowel wall thickening, lack of bowel wall enhancement, pneumatosis intestinalis, portal venous gas

*Small bowel dilation in case of small bowel obstruction (SBO)*

3. **Pneumoperitoneum** (AJEM 2009;27:320)
   - Upright: air beneath the diaphragm
   - Left lateral decubitus: air overlying the liver
   - Supine: **insensitive** exam

*Pneumoperitoneum*

## ULTRASOUND

1. **Cholecystitis** (AJR 2011;196:W367)
   - US is preferred initial examination
   - Common findings: gallstones, gallbladder wall thickening >3 mm, gallbladder distension (>4cm transverse, >8cm longitudinal), peri-cholecystic fluid
   - Sonographic Murphy's sign: 92% sensitivity (unreliable if recent analgesics)
   - Gallstones and gallbladder wall thickening: 95% positive predictive value for acute cholecystitis
   - Key Differential - Gallbladder wall thickening without stones and without distension is more likely to be from third spacing (CHF/renal failure/cirrhosis) or underlying liver disease (hepatitis); much less likely cholecystitis
2. **Deep venous thrombosis** (Cardiovascular Diagnosis and Therapy 2016;6:493)
   - Compression U/S: noncompressibility of vein (*key finding*), echogenic thrombus within vein, venous expansion
   - Venous duplex U/S: absence of color Doppler signal, flow phasicity, & response to augmentation maneuvers
   - Non-obstructive vs. Obstructive thrombus: both are non-compressible, obstructive lacks color Doppler flow
   - 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 US
     - Cons: invasive, requires contrast, radiation, possible streak or mixing artifacts

## CROSS SECTIONAL IMAGING

Excellent resources for anatomy, image interpretation, and sample cases:
https://radiopaedia.org/; https://radiologyassistant.nl/; https://introductiontoradiology.net/; https://www.learnabdominal.com/ (GI/GU); http://xrayhead.com/ (MSK)

**CT Head Example Search Pattern**

1. **Brain parenchyma**
   a. Mass lesion: brain window
   b. Intraparenchymal hemorrhage: brain window
   c. Infarction: stroke window
2. **Epidural / Subdural Hematoma**
3. **Vessels**
4. **CSF spaces**: ventricles, sulci, basal cisterns
5. **Midline shift or herniation**: coronals helpful
6. **Soft tissues** (great to start with for trauma head CTs)
7. **Bones/sinuses**

**MRI Brain Example Search pattern**

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 non-contrast MRA
3. **CSF spaces**: T2
4. **Midline shift or herniation**: coronals helpful
5. **Soft tissues**
6. **Bones/sinuses**

**CT Chest Example Search Pattern**

1. **Lines and tubes** (scout can be very helpful)
2. **Upper Abdomen**
3. **Soft tissues**
4. **Bones**
5. **Heart and mediastinum**: thyroid, lymph node stations, heart and pericardium, asc/desc aorta, great vessels, esophagus
6. **Pleura**: pleural effusion, pneumothorax
7. **Airways**: trachea, bronchi, bronchioles
8. **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 Example Search Pattern**

1. **Lung bases and partially visualized heart**
2. **Liver/gallbladder**: focal lesions, biliary dilatation
3. **Spleen**
4. **Pancreas**: focal lesions, pancreatic ductal dilatation
5. **Adrenals**
6. **Kidneys/ureters**: hydronephrosis, stones, focal lesion
7. **Bladder/Prostate/Uterus/Adnexae**
8. **Peritoneum**: free air or fluid
9. **Lymph Node Stations**
10. **Vessels:** AAA
11. **GI tract**: bowel distension, bowel wall thickening, appendix, terminal ileum
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.*

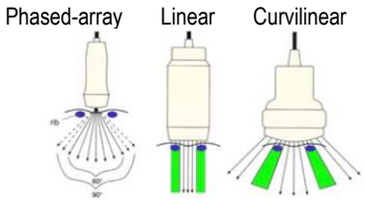
## EQUIPMENT (NEJM 2011;364:749)

**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/stones have high attenuation)

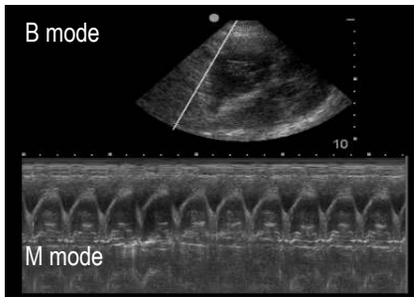
**Transducer** (**probe**): converts electricity into sound waves → transmits sound wave into tissue → receives sound waves echoed back from tissue. Indicator (denoted by dot or notch on probe) displays on **left of the screen**. *Exception*: echocardiography → indicator displays on **right side**. For most indications, position probe with indicator to patient's 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 phased-array 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

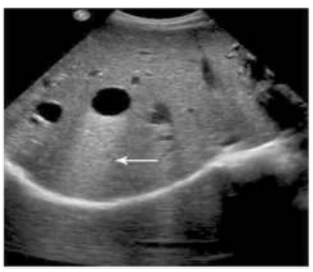
**Typical Appearance of Normal Tissue**:

- 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, ascites) is black on US (**anechoic**), though thick fluids (e.g. pus) can be brighter than typical fluid. Fluid can have a layered appearance based on density.
- Tendons and nerves are bright (**hyperechoic**) if perpendicular to probe, dark (hypoechoic) when angle is changed (anisotropy)
- Bone has a hyperechoic rim (due to reflection) with dark shadow beyond it

Acoustic Shadowing (gallstone)

**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


Acoustic Enhancement (liver cyst)

# Procedures

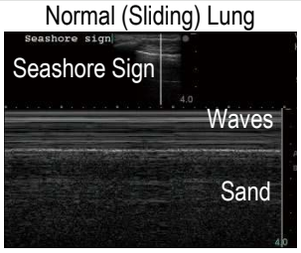


## IMAGING AND TIPS (see The POCUS Atlas for reference)

**Diagnostic Use**:

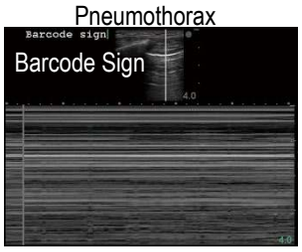
- **Pneumothorax**: use LINEAR (vascular) or CURVILINEAR probe. In supine patient, look in 3rd intercostal space on anterior chest, pointing indicator cranially. Identify hyperechoic rims of the ribs with posterior shadowing. The pleura is the hyperechoic stripe that is within the intercostal space. 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)

Normal (Sliding) Lung



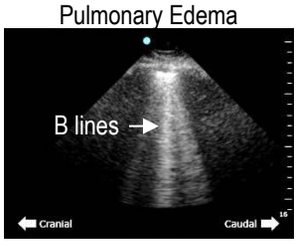

- **Pulmonary embolism**: use PHASED-ARRAY (cardiac) probe. Bedside US can be used to identify right heart strain. Look for RV size ≥ LV size, septal bowing (D-sign in parasternal short), note Sn 53%, Sp 83% for PE. RV/LV ratio most easily visualized in apical 4 chamber view, can be misleading based 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)

Pneumothorax



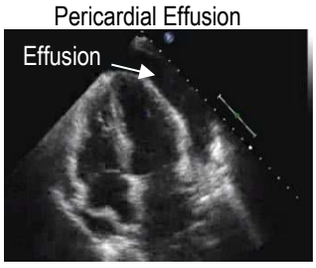

- **Pulmonary edema**: use PHASED-ARRAY (cardiac) or CURVED (abdominal) probe. Evaluate the lung between rib spaces and across multiple lung fields similar to auscultation. Look for B-lines: comet like artifacts that shine perpendicular from the pleural line and obliterate A-lines. ≥3 in one interspace is consistent with interstitial fluid, and bilaterally suggests pulmonary edema. Ddx of B-lines is broad. Operator dependent but can outperform CXR (Intensive Care Med 2012;38:577; Acad Emerg Med;23:223)

Pulmonary Edema



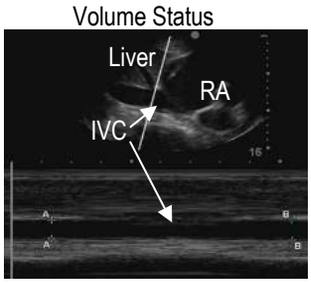

- **Pericardial effusion**: use PHASED-ARRAY (cardiac) probe. Look for an anechoic collection between the heart and the hyperechoic pericardium. Hemorrhagic or purulent effusions may appear more complex. On parasternal long axis, pericardial effusion will be anterior to the descending aorta while a pleural 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)

Pericardial Effusion



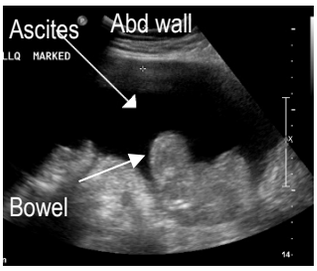

- **Volume status**: use the PHASED-ARRAY (cardiac) probe. IVC collapsibility has been proposed as a proxy for CVP and fluid responsiveness, though data is mixed. There are no consensus guidelines. Start with subcostal view of RA/RV, then rotate probe to the sagittal plane to find the IVC draining into RA and abutting the liver. Look at IVC 2cm from RA: fluid responsiveness or an underfilled IVC is suggested by 1) IVC diameter ≤1.5cm and 2) IVC collapses ≥½ its diameter with inspiration. Can use M mode to assess collapsibility. IVC diameter ≥2.1cm with ≤50% inspiratory collapse can indicate elevated CVP. Pair IVC POCUS w/ lung US for volume status evaluation. (Crit Care 2012;16:R188; CCM 2013;41:833; Shock 2017;47:550)

Volume Status

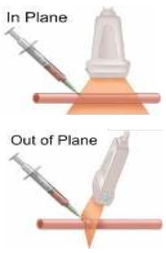



**Procedural Use**: *refer to pages on specific procedures for more details*

- **Paracentesis**: use CURVILINEAR (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, ensure prior to procedure scanning in multiple locations and fanning to assess for bowel (to avoid perforation). 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

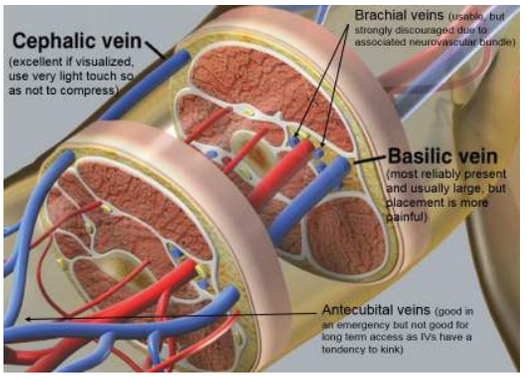
## General Considerations

**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, overlying infection/cellulitis
**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/cultures + labels (if labs needed)

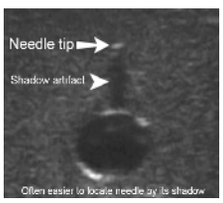
- Angiocath selection: standard length (30mm) good for vein <0.8cm deep; long needle (48mm) preferred for ≥0.8cm deep (48mm 18G [green] stocked in most supply rooms, but 48mm 20G [pink] more difficult to find.

## Transverse Technique

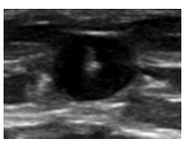
NEJM 2012;366:e38: *choosing a vein (8:45), transverse (10:05), longitudinal (12:28)*




1) **Setup**: positioning is crucial. 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
3) **Confirm anatomy**: use vascular probe at minimum depth to locate adequate superficial veins, M-mode line can be helpful to stay centered
   - 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 – 1.2cm) (J Emerg Med 2010;39:70). Common veins: basilic, cephalic > deep brachial (see figure)
   - Confirm venous: gentle pressure differentiates non-thrombosed veins (fully compressible, non-pulsatile) and arteries (poorly compressible, pulsatile); color doppler can confirm; scan both arms if able
   - Trace vessel course: follow the vessel course proximally and distally; recognize and avoid branch points, diving veins, and irregularly coursing veins → identify the trajectory along which the ultrasound probe travels to maintain center of 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 5th finger/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 skin insertion, eyes should be on the *site of venipuncture*, not on the US screen, though after puncture, should be watching screen at all times and not hand

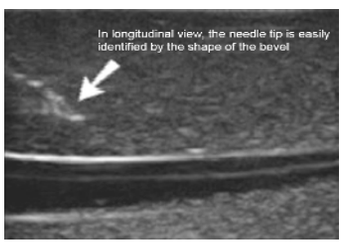



7) **Find tip and advance**: needle tip (and shadow) should appear on screen → advance PROBE until you lose needle tip → advance NEEDLE tip until it reappears on US screen; continue to advance until tip is "tenting" the roof of the vein
8) **Enter vein**: a quick short jab will allow you to enter vein; visualize needle tip as "target sign" (see image)
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, pull back on saline flush (ensure drawback), REMOVE TOURNIQUET, flush with saline → can also confirm lack of extravasation of saline under US visualization
12) **Secure**: secure catheter and tubing with Tegaderm, +/- additional tape; nurses may redress IV

## 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 to go through the back wall. Advance the catheter under direct visualization

| Technique | Pros | Cons |
|---|---|---|
| Transverse (short axis) | - Faster, requires less finesse with US probe<br>- Allows visualization of adjacent structures | - Harder to visualize the needle tip<br>- Risk of "through and through" |
| Longitudinal (long axis) | - Improved visualization of the needle tip (depth)<br>- Can advance catheter under direct visualization | - Challenging to maintain probe/vein/needle in plane<br>- 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 or slight fanning of the ultrasound probe until the tip is in view
- *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, $CVO_2$); admin. of noxious meds (pressors, chemo, hypertonic solution, TPN); rapid large volume resuscitation (Cordis/MAC); 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). Additionally, it is helpful to predict if RIJ may be needed for dialysis catheter, in which case LIJ placement is preferred.
**Catheter selection**: select based on number of lumens and speed of infusion; if rapid infusion required → large bore, short length (Cordis/MAC). *Right IJ* catheter length: 16cm. *Left IJ* catheter length: 20cm
**Alternatives**: PICC (if no concern for bacteremia, often requires negative BCx >48hr) 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)

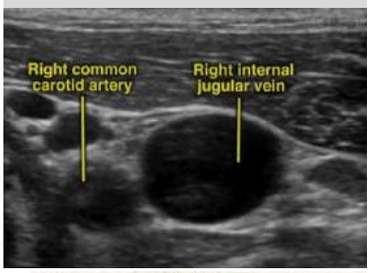
## Internal Jugular Vein (Video: NEJM 2010;362:e57)

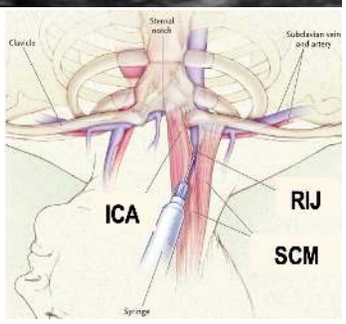
| Advantages | Disadvantages |
|---|---|
| Compressible vein | Carotid artery puncture 2-10% |
| Lower risk of pneumothorax (< 1%) than subclavian | Less patient comfort |
| Ability to use real-time ultrasound | Anatomy not as consistent as subclavian |

**All IJ CVCs placed with real-time US guidance at 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. Site selection (typically R > L, unless preserving right side for HD line).

- Locate triangle formed by medial and lateral portions of SCM with the clavicle as base
- Find IJ, typically superficial and lateral to carotid, compressible; can also use color Doppler
- RIJ generally preferred due to direct course to SVC, LIJ ↑risk of PTX and thoracic duct injury

Transverse ultrasound view showing RIJ anterior & lateral to carotid artery




**Target:** aim at ipsilateral nipple, 45 degrees (map out trajectory of vessel using ultrasound)

1) Preparation and positioning are ESSENTIAL; ensure someone is always available to help
2) Obtain consent; perform TIME-OUT with RN; complete checklist with RN assistance
3) Use US to ensure your target anatomy is in good position. Assess LIJ & RIJ
4) Use 2% chlorhexidine solution to prep (in the kit); drape the entire patient in sterile field
5) Place caps on CVC, flush all lines with sterile saline, remove cap from brown port **(where wire will emerge)**; ensure guide wire advances easily and syringe comes off needle easily
6) Locate IJ vein & carotid artery using ultrasound
7) Anesthetize with lidocaine; can make wheal & inject along tract (aspirate before injecting!)
8) 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% $FiO_2$, decompress if tension
9) Once flow obtained, drop US probe and stabilize needle with your non-dominant hand, flatten needle angle while drawing back to ensure continued flow, remove syringe from locator (occlude hub with thumb to minimize risk of air embolism in non-ventilated patients)
10) Feed the curved end of the loaded 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)
11) Remove needle over guidewire
12) Confirm wire is in vein using US in transverse and longitudinal planes
13) 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 and cover angiocath opening → replace wire through angiocath → remove angiocath
14) Extend puncture site with scalpel (face cutting edge away from wire to prevent cutting wire)
15) Thread dilator over wire (using twisting motion, grip near the skin) 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)
16) Advance catheter over wire (wire comes out brown port); remove wire
17) Draw back vertically off all ports through caps using saline flush (only small amount of flash needed), flush all lines clean, clamp ports
18) Secure with sutures; place Biopatch prior to securing with dressing
19) Order CXR (ASAP) to assess position, rule out PTX/hemothorax; MUST **look at the CXR yourself to confirm placement**; 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"
20) Write procedure note (create note in notewriter, then select "Central Line")

***For subclavian or femoral vein access, please discuss with attending and ensure appropriate oversight prior to procedure!***

*Natalia Sutherland and Chris Radcliffe*



Suggest an Edit

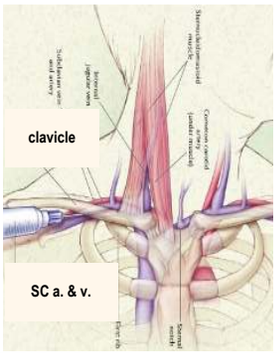
# Procedures Central Line

## 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**: at 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)



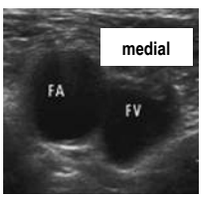

## Femoral Vein (Video: NEJM 2008;358:e30)

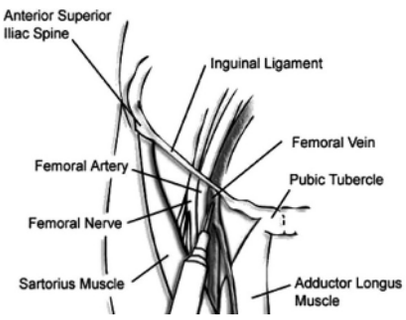
| Advantages | Disadvantages |
|---|---|
| Compressible | Femoral artery puncture 5-10% |
| No risk of PTX | Risk of development of DVT |
| Can be cannulated more easily during CPR | Less patient comfort in hip flexion, requires immobility |
| Large caliber vein technically easier to cannulate | May 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, generally use 20 cm line
**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, best to use US to visualize
- "**NAVEL toward the NAVEL**" → 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 → increased risk for RP bleed & peritoneal perforation

**Target**: directly superior at 30-45° **No confirmatory imaging needed




## Hemodialysis Lines

**Sites**: IJ (R preferred), subclavian vein, femoral vein
**Placement technique**: Same steps as CVC placement, additional dilation step is key difference (double dilation). For manometry, can use catheter from Arrow arterial kit. Note, the wire will come out of the blue colored port.

## Cordis (AKA Venous Introducer Sheath)

Combined dilator and sheath w/ side port for IV access
**Indications**: rapid resuscitation, introducer sheath for PA catheter, 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 1 inch inferior (IJ) or 2 inches superior (femoral) to puncture mark
**Methods for ensuring venous placement include manometry/waveform measurement, ABG sampling*
**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 at 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**: remove needle, 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

## CVC Removal (MGH Policy)

**Materials**: suture removal kit (for the scissors), gauze x2, alcohol wipes, sterile gloves, Tegaderm, Chloraprep, sterile Vaseline or lube
- Put pt supine/Tberg and remove dressing → clean the field with Chloraprep (with attention to NOT moving the central line position) → Cut the sutures and ensure the string removed → using gauze with Vaseline on it, place the Vaseline side over the central line → hold central line with your dominant hand → ask pt to take in a deep breath and hum → while pt hums, pull the line in a single confident motion (STOP if you meet resistance) → Inspect the tip
- Hold pressure for 10 m using gauze + sterile Vaseline (if jugular and femoral); similar procedure for HD line but hold 30min
- Place a Tegaderm overtop a piece of gauze at prior insertion site and avoid getting hair in dressing
- Keep the patient flat for 30m-1h afterwards

# Procedures Arterial Line

## General Considerations

**Indications**: real-time BP monitoring (pressors, HTN emergency, CVA); frequent ABGs, softer indication for 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 sufficient 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). Pre-assembled kits available.

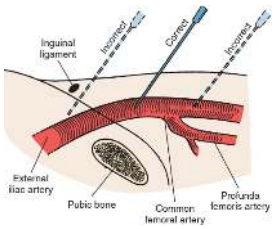
- If pt awake → consider lidocaine w/o epi (small syringe and 25G needle)
- **Use PINK SOLID STRIPE angiocath**; do NOT use pink interrupted stripes, which has a one-way valve so can't pass wire
- Alt: use Arrow arterial line / Micropuncture kit; the kit's longer catheter is preferable for femoral site

## 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. *Note: Avoid catheterizing very distal (near angle of extension) as A-line more likely to displace later when pt moved*
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 steadying the catheter (should be no blood flow)
10) Hold guide wire close to head of angiocath w/ dominant hand
11) Level and pull back : lower angiocath as parallel to skin as possible and SLOWLY pull it back until pulsatile blood flow is obtained, then hold angiocath very still to avoid pulling out of vessel
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) Clean the area with gauze and dress 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 advancing needle under US guidance and once firmly in vessel, advance catheter over needle (no guide wire; similar to PIV)
- After multiple attempts, the artery may spasm or hematomas may form. Pursue alternative site (or more distal site).
- If unable to thread guide wire after attempting spinning during insertion, consider micropuncture wire (with supervision). May help with atherosclerotic arteries at ↑risk of perforation. Kit includes introducer needle, microwire, and microcatheter w/inner stylet.
  - Use micropuncture needle to puncture vessel under US guidance until flash, can walk forward in vessel, then drop probe
  - Thread microwire (more pliable end first) through needle, then remove needle
  - Thread microcatheter over the wire
  - Once hubbed, unscrew to remove inner stylet and microwire
- 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, or aiming to insert immediately proximal to femoral bifurcation (*see graphic*)



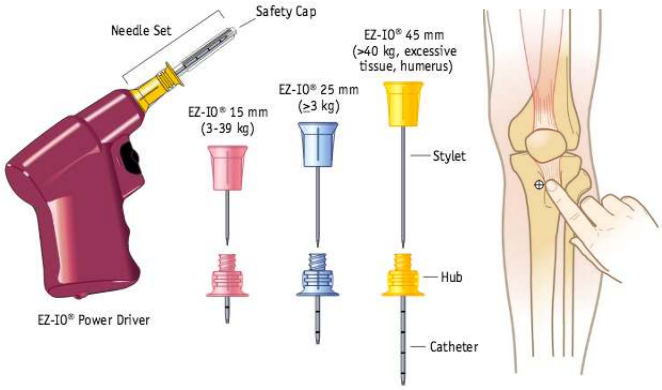
# Procedures Intraosseous Line

## 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

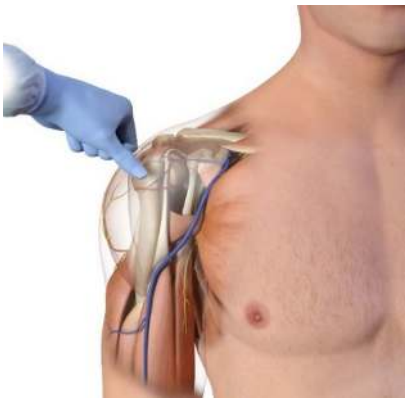
## Set-Up

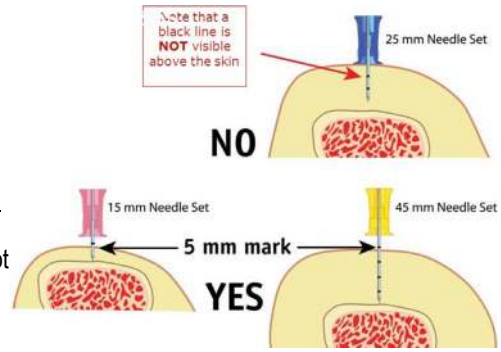
- **Materials**: ALL IN KIT → EZ-IO Power Driver, IO needle-set, connector tubing, 10cc syringe with saline flush, chlorhexidine/povidone iodine, sterile gloves. If awake, 3cc syringe with 1% lidocaine via 25G needle
- **Replace**: Blake 7 MICU, Materials Management (Lunder LL019)
- **Location**:
  - 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 (see illustration)
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/pressor 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 (not good for long term access), or if signs of erythema, swelling or extravasation. To remove: don procedure mask, goggles, non-sterile gloves. Remove IV extension tubing from needle hub. Then, place sterile syringe on needle hub (acts as handle for removal). Grasp at needle hub and rotate clockwise while pulling gently at 90-degree angle from the bone. Do not rock the syringe. Once the needle hub is out, place needle hub in sharps container. Apply pressure over IO site until bleeding has stopped and dress with gauze and tegaderm.

# Procedures — Paracentesis

## INDICATIONS (Video: NEJM 2006;355:e21)

- **Diagnostic**: new-onset ascites, unknown etiology of ascites, rule out SBP. Low threshold for patients with cirrhosis, consider concurrent RUQUS with Doppler to rule out venous thrombosis. Para w/in 24hr = better outcomes (Liver Transpl 2023;29;919).
- **Therapeutic**: Performed for abdominal pain/discomfort, diuretic-refractory ascites, respiratory compromise, abdominal compartment syndrome, adjunctive treatment of esophageal variceal bleeding (can lower portal pressures). Larve volume para ≥ 5L removed.

## CONTRAINDICATIONS

- Overlying cellulitis, inability to demonstrate ascites on US, bowel obstruction/distention, acute abdomen, 2nd or 3rd trimester pregnancy
- ↑INR, ↓plt are **NOT** contraindications in cirrhosis (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 2021;74:1014).

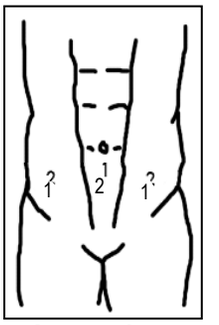
## MATERIALS

- 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 2021;74:1014)

## 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**. Simulate planned angle of needle insertion with probe. Measure subcutaneous tissue and fluid pocket.
- 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** (in practice, rarely used)



**Approaches**

## INSTRUCTIONS

1. Identify best site with abdominal/curvilinear US probe and mark site with pen or round base of needle; avoid applying excess pressure to ensure accurate pocket size is visualized. Use vascular/linear US probe with doppler to ensure no blood vessels in identified site.
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 by using skin as barrier. 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/slows: 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, apply pressure, & insert new catheter at different site
- BRB return: injury to mesentery or inferior epigastrics → 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 bacterascites/sepsis → surgery consult for potential laparotomy
- Fluid leak: prevent with Z-line technique or up-front dermabond → apply pressure dressing, seal w/ Dermabond or single stitch

# Procedures Lumbar Puncture

## INDICATIONS

**Diagnostic**: suspicion for CNS infection (most common), CNS malignancy/mets, SAH, CNS demyelinating/inflammatory process, or ↑ICP
**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) of any etiology
**Preparation**:

- **Time frame needed to hold AC prior to LP**: IV heparin (4-6h, 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 ago, immunocompromised, AMS, aphasia, cranial nerve deficit. If none of these, then 97% NPV for no mass lesion risking herniation (NEJM 2001;345:1727)

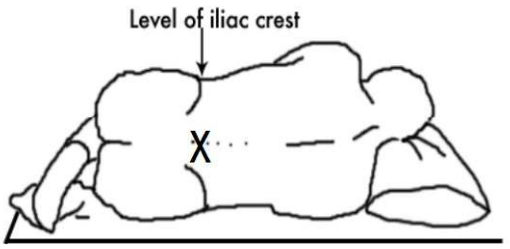
## TECHNIQUE (Video: NEJM 2006;355:e12)

**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 crests. Confirm location by palpating spinous processes above/below. Ensure needle midline before inserting
- 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 with palpation (betadine will make this easier). 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 for 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 or withdrawing**
3) Troubleshoot: if hitting bone, partially withdraw (needle shouldn't leave skin), adjust angle, re-advance. Try 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 patient's 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 save extra CSF. **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 fluids, caffeine, and pain meds. No evidence for bed rest. If persistent, c/s anesthesia for epidural blood patch (65-98% success, often quick relief) |
| **Spinal hematoma** | Suspect if on AC w/ persistent back pain or neuro sx → STAT MRI → IV dex + NSGY c/s |

# Procedures Thoracentesis

## INDICATIONS

**Diagnostic**: to establish etiology of ≥1cm pleural effusion visualized by US (not necessary for small effusions w/ probable alternative dx)
- pleural effusions are visible on CXR when >200mL of fluid is present (i.e. lower sensitivity)

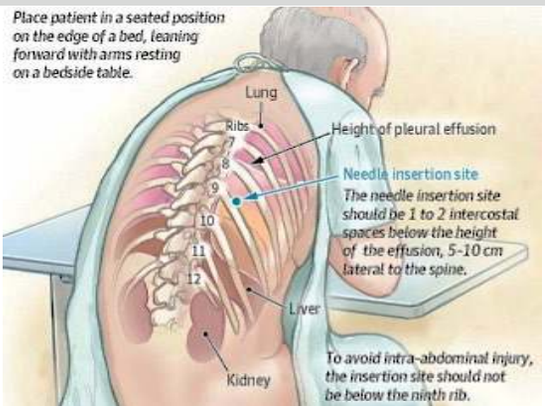
**Therapeutic**: large effusions → resp compromise or sx (e.g., dyspnea), hemothorax, empyema, complicated parapneumonic effusion

**Relative Contraindications**: *no absolute* (Chest 2013;144:456)
- Consider reversing coagulopathy (INR >1.5, recent LMWH) or thrombocytopenia (plt <50k), 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). US guidance associated with lower risk.

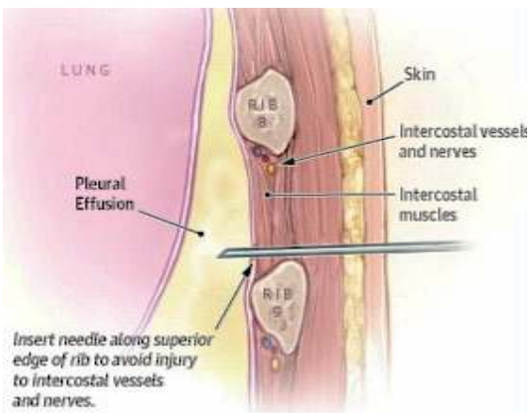
## PREPARATION

- 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), Pulmonary, 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 meniscus. Lowest level recommended is 8th ICS (above diaphragm)
  - In patients who cannot sit upright → 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 plunger 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 (urinothorax), 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 → 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 → 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 <1.5L. 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 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 / hemodynamic collapse (Pulm Circ 2013;3:467)

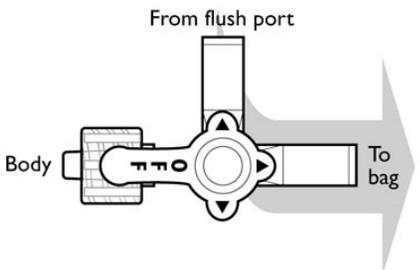
## MANAGEMENT OVERVIEW: *if in doubt about management, page the Cardiology team that placed the drain*

- 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 repeat pericardiocentesis
- 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. Typically space out as output decreases.
- **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.
- **Pericardial drains at MGH are now managed by nursing policy. If your patient comes from an OSH without a pericardial drainage bag, please see the protocol and technique listed below for periodic drainage.**
- 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. Limited TTE. Remove with cardiology fellow/attending present

## MATERIALS

- Sterile technique: sterile gloves, mask, hat
- Identify assistant (must be MD, NP, or PA)
- Sterile towels
- Chlorhexidine swabs (at least 3)
- 60cc Leur 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 (holding end of port). Place sterile OR towels around and underneath pericardial drain. Sterilize distal exposed catheter and stopcock with chlorhexidine swab. Once finished, hold the recently sterilized area and take catheter from assistant to sterilize remaining distal portion. Once fully sterilized, lay the catheter down on the sterile field of blue OR towels.
3. **Ensure the stopcock is turned towards the patient**. This means the catheter line is closed.
4. Remove and throw away one blue cap (does not matter which). There will be one capped tip and one open tip
5. Sterilize open stopcock tip with iodine or chlorhexidine 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 towards the patient**, 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. Gently pull back on syringe but may require significant neg pressure. Consider different patient positions (Trendelenburg, lateral decubitus, etc.) to mobilize fluid. Patient may experience chest discomfort. Monitor hemodynamics and telemetry
9. Can stop draining once fluid flow diminishes/ceases/severe pain. **Turn stopcock towards patient** then remove syringe
10. Save/transfer pericardial fluid if needed for analysis. Otherwise discard
11. Repeat step 6 (flush port with another 2cc heparin). **Turn stopcock to the patient** (to close catheter)
12. Remove heparin syringe and attach new sterile blue cap to open flush port
13. Consider re-sterilizing distal exposed catheter and stopcock with chlorhexidine 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: typically not needed routine, serial drainage

- 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 (Clin Infect Dis. 2018;67(6):e1–e94) | | | | | | |
|---|---|---|---|---|---|---|
| **Condition** | **Pressure (cm H2O)** | **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 | <220 | 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 |
| **TB meningitis** | 18–30 | 50-300 | Lymph | <50 | 50-300 >2000 if subarach 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/μL*** | **S**pontaneous **B**acterial **P**eritonitis (SBP) (Secondary Peritonitis → polymicrobial) | **C**ulture **N**egative **N**eutrocytic **A**scites (CNNA) |
| **PMN <250/μL** | **N**on-**n**eutrocytic **B**acter**a**scites (NNBA) | Normal |
| **Culture Negative Neutrocytic Ascites (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)<br>*Does not apply to PD pts. Effluent fluid WBC >100 w/ >50%PMNs (after >1-2 hr dwell) is concerning (see ellucid for sampling protocol) | | |
| **Calculations**: # of PMNs = Total nucleated cells x % of PMNs<br>Correction for RBCs (RBC count >50,000/mm$^3$, seen in "traumatic tap") = measured PMN – (measured RBC / 250) | | |
| **Clues for SBP vs. Secondary Peritonitis**:<br>- Runyon's Criteria: if ≥2 present, ↑suspicion for secondary peritonitis: 1) ascitic total protein >1; 2) ascitic glucose <50; 3) ascitic LDH > ULN<br>- Fluid CEA >5 or Alk Phos >240 (92% Sn, 88% Sp for secondary peritonitis) (J Hepatol 2001;34;215)<br>- Consider **repeat para. 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<br>Budd-Chiari syndrome | Pancreatitis<br>Peritoneal carcinomatosis<br>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 \| JAMA. 2014;311(23):2422-2431) | |
| **Light's Criteria**: exudate if ≥1 criteria present (98% Sn, 83% Sp)*<br>1. **Pleural fluid protein / serum protein >0.5**<br>2. **Pleural fluid LDH / serum LDH >0.6**<br>3. **Pleural fluid LDH >2/3 ULN of serum LDH (i.e. >140)**<br>*Diuretics cause ~25% of transudates to be misclassified as exudates<br>**Three-Test Rule**: exudate if ≥1 criteria present<br>1. Pleural fluid protein >2.9<br>2. Pleural cholesterol >45<br>3. Pleural LDH >0.45 upper limit | **If ≥ 1 of these, fluid is exudate with 98% Sn, 70% Sp**:<br>▪ Pleural fluid protein >2.9, LDH >95, cholesterol >45<br>**More specific criteria for confirming exudate**:<br>▪ Pleural fluid cholesterol >60 (54% Sn, 92% Sp)<br>▪ Serum albumin – pleural albumin ≤1.2 (87% Sn, 92% Sp)<br>▪ Pleural NT-proBNP <2,300pg/mL (>80% Sn, >70% Sp)<br><br>Three-test rule is preferred by MGH Pulmonary Department. |
| • Other tests: adenosine deaminase, amylase, triglyceride, cholesterol, Gram stain/Cx, cell count, IFN-γ, NT-proBNP, pH, tumor markers<br>• 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 (if can't take PO)
- Lactulose (hepatic encephalopathy) (if can't take PO)

**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. Frequently takes troubleshooting.
- 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 ideally shows 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 S-s: decompression |

**Dobhoff tube/Enteroflex**: thinner, more flexible; more comfortable but **↑risk of placement into lung**
- Requires 2-step 2-CXR placement method. Placement at MGH must be supervised by an attending
  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
  - Caution: *never* administer tube feeds or medications prior to confirmation. Dobhoff can pass into mainstem bronchus.

**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"
- Consider bridling tube if patient is frequently pulling out tube or if experiencing skin breakdown from security sticker. Plan ahead, as easier to place bridle prior to NG placement. Beware, very uncomfortable for the patient.

**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: insertion into 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

## 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 $H_2O$ to female Leur adaptor. Pulse plunger to force through debris. Flush w/ 30cc warm $H_2O$ to ensure not clogged
  - Can also try Seltzer, ginger ale, Coca-Cola. If persistent, can try pancrealipase (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 infection: try topical abx ± antifungal before systemic (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 coudés
- 3-way Foleys (drainage, balloon, irrigation ports): 20F/22F used for **continuous bladder irrigation (CBI) in gross hematuria to minimize intra-vesicular clots**

**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 $H_2O$ 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 inner thigh 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**)

**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

**Bladder Pressure**: *only done in the ICU*
*Indications*: concern for intra-abdominal hypertension (≥12mmHg) or frank abdominal compartment syndrome (>20mmHg)
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

**Special Circumstances**:
**Required urology catheter consults at MGH**: 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 for full details.*

**Troubleshooting**:
- **Difficulty in female patient**: likely poor positioning. Place sheets under hips & place pt in Trendelenburg
- **Urethral trauma**: blood at meatus. Leave catheter in for ~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)

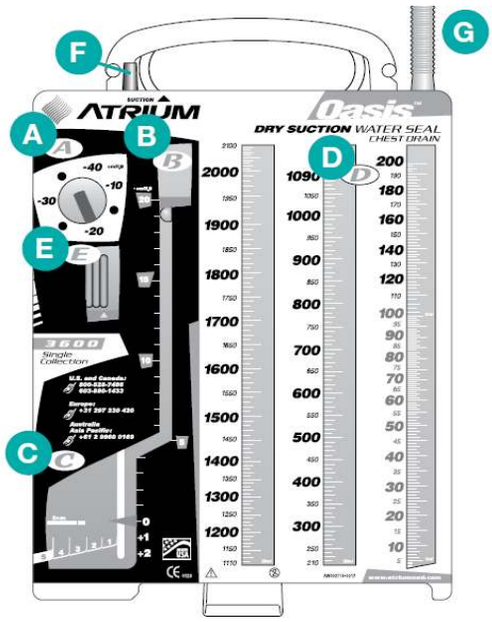
**Suprapubic Tubes**:
- Many different types although usually a standard Foley catheter
- Know type & size catheter, who exchanges, how exchanged, how frequently
- First exchange performed by IR. Subsequent exchanges should be performed by RNs. Urology available to assist PRN
- If need to reinsert, decompress 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
- See hospital policy

## 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
- Daily CXR while hospitalized until removal
- 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/thoracic surgery (whoever placed tube)

**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; 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/kit, device manufacturer, safety design type
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: |
|---|---|
| 1. Obtain a special HIV occupational exposure consent form/lab requisition from the OA<br>2. Write STAT result in the comment section<br>3. Have the patient sign, then sign it yourself<br>4. Ensure form is marked with BILLING NUMBER CL00009 so patient is not charged | 1. A valid and invoked health care proxy (you need paperwork!) can sign the occupational exposure consent form **OR**<br>2. Facility legal staff can assume temporary guardianship<br><br>If the exposure occurs to a member of the *primary team*, 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 |

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%<br>Mucocutaneous (blood): 0.09%<br><br>*There has only been 1 confirmed case of occupational transmission since 1999* (CDC) | PEP can vary but usually includes 3 anti-retroviral drugs:<br>• 2 NRTI **tenofovir PLUS emtricitabine AND** INSTI **raltegravir**<br>• 28 days of treatment recommended but optimal length unknown<br>• Regimen usually well-tolerated, side effects include:<br>  ○ Common but mild: n/v/d, fatigue, HA<br>  ○ Rare: hepatitis, hyperglycemia, fevers, rash, pancytopenia<br>• 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<br>Vaccine non-responders should be seen in occupational health |

6. **Always file a safety report**

# Logistics

# Monitoring, Prophylaxis, & Peri-Procedural Anticoagulation

## CARDIAC MONITORING (MGH Clinical Guidelines for Cardiac Monitoring)

| | Low Risk | Moderate Risk | High Risk |
|---|---|---|---|
| **Monitoring** | • Cardiac monitoring for diagnostic purposes only | • Continuous cardiac monitoring<br>• 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<br>• Unaccompanied | • With cardiac monitor<br>• Accompanied by MD, PA, NP, or RN | • With cardiac monitor<br>• Accompanied by MD, PA, NP, or RN |
| **Example indications*** | • Make dx or guide treatment<br>• Post-op or post-CVA AF<br>• Routine syncope evaluation<br>• Low risk chest pain syndrome | • Typical chest pain syndrome<br>• ADHF until precipitant treated<br>• Uncontrolled AF<br>• 24 hr s/p PPM/ICD placement<br>• Suspected cardiogenic syncope<br>• Actual or risk for QTc prolongation | • Early ACS or ROSC after arrest<br>• Temporary pacing wire<br>• Advanced 2nd deg. AVB or CHB<br>• Unstable arrhythmias<br>• Consider in ICU to floor transfer with potential for decompensation |

*See 2017 AHA guidelines on ECG monitoring for more detailed indications/monitoring duration (Circ 2017;136:e273). See *Telemetry.*

## $O_2$ SATURATION MONITORING (MGH Clinical Guidelines for O2 Saturation Monitoring)

| | Low Risk | Moderate Risk | High Risk |
|---|---|---|---|
| **Monitoring** | • Spot check $O_2$ sats as clinically indicated | • Continuous $O_2$ sat monitor<br>• Off monitor ONLY in presence of licensed clinical personnel | • Continuous $O_2$ sat monitor |
| **Pt Location** | General care unit | General care unit | Step-down or ICU |
| **Travel** | • No $O_2$ sat monitor<br>• Unaccompanied | • With $O_2$ sat monitor<br>• Accompanied by MD, PA, NP, RN, or RT | • With $O_2$ sat monitor<br>• Accompanied by MD, PA, NP, RN, or RT |
| **Example Indications** | • Stable chronic respiratory disease<br>• Post-procedure<br>• Opioid naïve patients receiving PO opioids | • COPD exacerbation<br>• OSA not on CPAP<br>• PCA use | • Acute respiratory distress<br>• High-risk airway<br>• NIPPV or intubation<br>• Continuous opioid infusion |

## DVT PROPHYLAXIS FOR MEDICAL PATIENTS (BLOOD ADV 2018;2:3198)

- Risk stratify patient using Padua VTE or IMPROVE VTE score; consider DVT ppx contraindications (e.g. GIB, plt <50 in ESLD, etc.)
- Pharmacologic prophylaxis options:
  - Enoxaparin (LWMH): 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
  - 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)

## GI PROPHYLAXIS (MGH Stress Ulcer Prophylaxis Guidelines, HCICU)

- Indications (Crit Care Med 2016;44:1395):
  - Admitted to ICU AND one of the following: 1) mechanically ventilated >48h or 2) coagulopathy (plt <50, INR >1.5, PTT >2x ULN)
  - Consider if ICU and ≥1 of the following: 1) GI bleed in the last year, 2) TBI with GCS ≤10, 3) burns >35% BSA, 4) AKI on RRT, 5) steroids >60mg prednisone daily (or equivalent), 6) spinal cord injury not tolerating enteral feeding
  - HCICU Additions: mechanical circulatory support, DAPT/triple therapy, scheduled NSAIDs, all lung and/or heart transplants
- Prophylaxis options (PO unless contraindicated): **PPI** (omeprazole, pantoprazole) or **H2 blocker** (famotidine)

## GENERAL ANTIPLATELET & ANTICOAGULATION GUIDANCE

- Before resuming anti-platelet and/or anticoagulation agents, conduct a basic bedside evaluation of the patient with specific attention to vital signs, mental status, vascular access sites, specific procedural site(s), and neurological exam (if relevant)
- For cardiology-related procedures, patient-specific recommendations are common. It is prudent to refer to MGH Cardiac Cath Lab Anticoagulation Guidelines and confirm with the procedural team prior to altering or resuming anti-platelet or anticoagulation
- See MGH Interventional Radiology Periprocedural Management for guidance on resuming AC after low-risk and high-risk IR procedures
- For anesthesia-related neuraxial interventions, see MGH Guidelines for AC and Neuraxial Interventions

# Logistics Post-Acute Care

## Post-Acute Care

- High cost growth (NEJM 2014;370:689) & risk of readmission (Health Aff 2010;29:57)
- For a minority of patients, the cycle of post-acute care then re-admission presages the end of life in our contemporary medical system (NEJM 2019;380:408)
- Vast majority of facilities do not have the capacity for rapid diagnostics (e.g. CT scan), procedures, and/or medical staff needed for treatment of acute issues (e.g. new hypoxemia or hypotension)
- Accurate and **succinct** discharge documentation is essential for transitions of care
- Case manager, PT, OT, +/- caregivers help determine who qualifies for the following post-discharge destinations

| Setting (most to least intensive) | Description | Patients / Diagnoses | Avg LOS | MD | Therapy / Ancillary Services |
|---|---|---|---|---|---|
| **Long Term Acute Care Hospital (LTACH)** | High intensity hospital-level care | - Tracheostomy<br>- Chemotherapy<br>- **≥3d ICU stay required** | 20+ days | Daily MD visits | - RT<br>- PT/OT PRN<br>- HD |
| **Inpatient Rehabilitation Facility ("acute rehab")** | Intensive therapy for recovery of function | - Post-stroke<br>- Spinal cord injury<br>- Specific ICD dx codes required | 7-21 days | 2-4x/week MD visits; PM&R presence | - 3h+ of daily therapy (pt must be able to participate) |
| **Skilled Nursing Facility (SNF)** | "Sub-acute" rehabilitation; must have 3-night hospital stay to qualify under Medicare | - CHF, PNA, UTI<br>- 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 daily therapy (pt must be able to progress) |
| **Home Health** | Home-based services post-hospitalization or via PCP referral | - Wound care<br>- IV antibiotics<br>- Post-hospital functional decline<br>- Home safety evaluation | N/A | Managed by PCP or prescribing outpatient clinician; assume no MD visit at home | - 4-8 PT/OT visits<br>- RN visits PRN |

## Home Hospital

- The service should be viewed as a **continuation of the hospitalization.** Referral process begins by contacting p29694
- Consider referral for patients with (1) safe home within MGH Home Hospital radius and (2) stable to improving medical diagnoses needing additional days of IV therapy or lab checks. Updated info linked here
- Example diagnoses: simple ADHF needing IV diuresis, cellulitis needing short course IV abx, COPD flare, etc.
- Service includes daily visits from hospitalist team, NP/PA daily, RN twice daily, and lab checks PRN

## Special Cases

- **Hospice**: see *End of Life & Hospice*
  - Criteria: terminal illness with prognosis of ≤6mo as certified by a physician. Depending on the hospice agency, pt may need to forego curative treatments (e.g., chemotherapy, 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 discharge. Caregivers generally administer medications and 24/7hr support phone line is available
  - Inpatient hospice (SNF or dedicated inpatient hospice facility): room & board (~$400 per day) only covered by MassHealth, but not always guaranteed coverage by other insurers
  - GIP (in-hospital hospice): fully funded by Medicare, patient must qualify (e.g. IV meds needed for symptom relief)
- **Long-term care (LTC)**:
  - Patients residing in "nursing home"/SNF with stable poor functional status who require assistance with ADLs/IADLs who do not require post-acute level care (e.g. due to stable function or inability to participate with rehab)
  - An assisted living facility ≠ SNF and will most often require high level of functional independence
  - If return to home rather than LTC facility is pursued, ensuring 24/7hr 1:1 support for select patients almost uniformly requires high-cost private pay
  - LTC covered by private pay or MassHealth, but not funded by Medicare. Finding a payer can be challenging
- **Alternative programs**: if patient is in Partners ACO, discuss additional home-based care options with case manager

# Logistics Inpatient Care of Incarcerated Patients

**Jail:** short-term facilities for people serving shorter sentences or are awaiting trial, supervised by city or county law enforcement
**Prison:** Longer-term state or federal facilities where people serve sentences for at least a year
**Concept of "dual loyalty":** Providers who care for incarcerated patients may encounter the ethical dilemma of "dual loyalty," where the provider feels caught between their professional duties to the patient and the interests of a third-party, such as the state or prison administration (AJPH 2012;102:475-480)
**Approach to the care of a hospitalized patient who is incarcerated (JGIM 2024;39:1905-1909):**

1) Do not ask the patient why they have been incarcerated as it rarely clinically relevant and can hinder therapeutic alliance
2) To maintain patient's health privacy, ask the correctional officers to step out of the room while examining the patient or updating the patient on the daily plan (correctional officers can leave the room and still maintain line of sight on the patient)
3) Incarcerated patients present to the ED in metal shackles and may remain in shackled restraint for the entirety of their hospitalization unless their clinical team explicitly advocates for their removal. Ask that shackles be removed for medical necessity (e.g., shackles promote delirium, VTE) or undergo continuous reassessment if unable to be removed due to behavioral or safety concerns. The shackling of pregnant women in the peripartum period is illegal according to Massachusetts state law
4) Though correctional officers are present in the room, a patient's medical decision-making capacity is not impacted by their incarcerated status
5) When the patient is ready for discharge, attempt to provide a warm hand-off to the jail or prison to which the patient is returning. Discharge the patients with medications in hand; some facilities have pharmacies with limited hours or inventory

# Logistics

# MGH Directory

| 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) | 4-3417, p28786 |
| Med Consult Pager (Code Backup) | p13480 |
| RICU Team (intubation), Code Stroke | 6-3333 |
| ECMO Consult | 857-310-0335, p29151 |
| SHOCK Consult | p29151 |
| STEMI Team (CCL activation) | 6-8282 |
| PERT (massive PE) | 4-7378 |
| Critical Care Consult | pg 26955 |
| IV Nurse | p26571 |
| ED Rad (STAT imaging scheduling) | 6-3050 |
| RT (pager # for RT if floor RT unknown) | p24225 |
| ICU Nursing Supervisor | 6-6718, p25213 |
| Poison Control (ingestion) | 617-232-2120 |
| **Pharmacy** | |
| Outpatient pharmacy (fax: 6-3789) | 4-3100, p38121 |
| **Laboratories** | |
| General lab info | 4-LABS |
| Chemistry/Heme (Core Lab)/Toxicology | 6-2345 |
| STAT Chemistry | 4-7617 |
| Serology | 4-7645 |
| Special coagulation | 4-2969 |
| Blood gas (STAT or routine) | 6-3856 |
| Blood bank (call for cooler or MTP) | 6-3623 |
| Microbiology – Bigelow 5 | 6-3613 |
| Micro desk after hours (available 24/7) | 6-7919 |
| Parasitology | 6-3861 |
| Virology | 6-3820 |
| Surgical/Procedural Pathology | 4-1449 |
| Flow cytometry | 6-8487 |
| Cytology / Cytopathology – Warren 1 | 6-3980 |
| **Cardiology Studies** | |
| Cath Lab | 6-7400 |
| Echo Lab | 6-8871 |
| Stress Lab (in/outpatient) & PYP scan | 4-3600 |
| Stress Lab (outpatient) | 3-1552 |
| Holter Lab (Yawkey 5B 8:30-16:00 M-F) | 6-7737 |
| EP Lab | 6-5036 |
| **Pulmonary Studies** | |
| PFTs – Cox 2 | 6-1200/3-9680 |
| Sleep Study (inpatient/outpatient) | 4-7426 |
| **GI Studies** | |
| Endoscopy Suite – RN station | 6-3732 |
| **Neurology Studies** | |
| EEG – Blake 12 | 6-3640 |
| EMG/NCS – Blake 12 | 6-3644 |
| **Subspecialties** | |
| Anticoagulation (AMS) 8:00-15:45 M-F | 6-2768 |
| Boston Healthcare for the Homeless | 781-221-6565 |
| Ortho inpatient casting & braces | 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

- **Powershare/Powerfoil** available at certain OSH. (1) call OSH and ask rads (or medical records) to send studies of interest to MGH via Powershare. (2) Search Powerfoil on MGH desktop, enter your and patient info (MRN/DOB) then import selected studies. Alternatively, call Dodd for assistance after confirmed with OSH that images shared via Powershare
- **Life Images**
  - Upload images to LifeImage and Epic: Partners Applications → Utilities → MGH Upload Image to Radiology (LifeImage) → Access LifeImage → find exam on CD/DVD → Upload images (Contact x44270 for troubleshooting)
  - 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 LifeImages of the same body part: upload all images → request a read only on the most recent

| Radiology Reading Rooms | |
|---|---|
| Dodd Reception | 44212 |
| Cardiac CT | 47132 |
| Cardiac MRI | 34457 |
| Chest CT | 33899 |
| CXR Inpatient | 42051 |
| CXR Outpatient | 62197 |
| ED | 41533 |
| GI CT | 65162 |
| GI Fluoro/KUB | 32605 |
| GI MR | 42162 |
| IR (GI & VIR) | 34723 |
| Mammography | 40228 |
| MSK | 65339 |
| Neuroradiology | 41931 |
| Neuro ED | 68188 |
| Nuclear Cardiology | 43600 |
| Nuclear Medicine Clinic | 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 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** (MedEdPortal 2024;20:11424. JGME 2019;11:371):
**1) Prepare before the encounter**:
Within your team, discuss how leadership should respond when this arises. E.g., team leader: *"During our block, we may encounter a patient who demonstrates bias towards one of our team members. Some prefer to respond directly in these scenarios, whereas others hope upstanders will address the language/behavior. How do you think you'll want us to support each of you? It's ok not to know!"*
**2) During the encounter**:
1) Ensure patient stability, assess if patient is altered: if unstable, call for help to stabilize. If patient is altered (see *Consent & Capacity*), consider redirection, support colleagues (encourage they step out if desired), frequent debriefing. If stable and has capacity, proceed
2) Check your emotions: if you're not in a good headspace to respond, it is OK to step out of the situation, process, ask for support
3) If you respond, address the bias explicitly: "*That's frustrating to hear." It's hard to hear you say that" "I'm disappointed you'd say that."* If you are the target of bias, consider curiosity: *"What do you mean by that?"* (Don't employ curiosity when upstanding).
4) Align with your team: Present a unified front. *"Our team is doing our best to respect you. We ask that you respect Dr. ___/me as well." Consider adding a microaffirmation: "Dr. ___ is an excellent physician & a strong team member."*
5) Set boundaries: varies by context. *"I'd ask that you refrain from commenting on ___." "Please call them/me Dr.___." "We do not accommodate staff changes based on [race/ethnicity/religion/etc], Dr. __/I will be in charge of your care today." "Our [code of conduct/institution] does not permit that behavior/language/etc."*
6) Recenter on patient care: Estabilsh a mutual goal. *"Our team is here to focus on your health." "Our goal, like yours is to ___."*
7) Give space: If tensions need diffusing, step out & say when to expect your return. This is also an opportunity to acknowledge patient frustration if present. *"We are going to give you space for 15 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 bias, seek support, debrief however feels right to you. If you were a bystander, explicitly acknowledge what you witnessed, offer to support your colleague and ask permission to debrief further. 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

**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. 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. Using 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 declined, 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 __*benefits here*___. 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 subpoenaed by law enforcement/immigration officials and used as evidence. It can also bias care the patient receives
**What to do if ICE/DHS inquires about a patient**? (see here for recent federal actions)
If an Immigration and Customs Enforcement (ICE) or Department of Homeland Security (DHS) Agent asks for a patient or patient info, **do not provide any info about the patient**. Instead say, "We are here to work with you, but please allow me a moment to contact my supervisor for the best response to your request." Immediately contact your attending or manager and **the Partners Office of General Counsel** (during business hours, call 857-282-2020. During off hours, call MGH Page Operator at 617-726-2241 to contact the attorney on call). ICE, DHS, or any governmental entity must have warrant or court order signed by a judge. See current MGB guidance here

*Gabrielle Bromberg (Microaggressions/Bias) & Christopher Radcliffe*



Suggest an Edit