It is an honor to present the 25th edition of the MGH Department of Medicine Housestaff Manual. “The White Book” is a trusted resource for medical residents and other clinicians at MGH and a great tradition of the Department of Medicine Residency Program. It exemplifies the rigor, autonomy, and pride with which MGH medical residents approach their work and their training.

The White Book is comprised of a collective of clinical experiences on the medical services as well as an annual review of the literature. This book is a product of diligent work of many resident contributors (listed on the bottom of each page) as well as past generations of authors and editors.

We extend our sincere gratitude to those junior and senior residents who contributed significant time and energy in editing entire sections of this manual:

- **Cardiology**: Rachel Frank, Avanthi Raghavan, Samuel Slavin
- **Pulmonology & Critical Care**: Shelsey Johnson, Sneha Kannan
- **Gastroenterology**: Raaj Mehta, Eric Przybyszewski
- **Nephrology**: Dana Larsen, Kate Takvorian
- **Infectious Disease**: Ali Castle, Christian Larsen
- **Hematology**: Jackie Henson, Vinayak Venkataraman
- **Oncology**: Lauren Banks, David Qualls
- **Geriatrics & Palliative Care**: Patrick Malecha, Jay Miller
- **Rheumatology**: Louise Xu
- **Endocrinology**: Alexandra Wick
- **Allergy & Immunology**: Tiara Forsyth
- **Neurology**: Jeffrey Gluckstein, Meabh O’Hare, Pavan Vaswani
- **Psychiatry**: Fiona Gispen, John Weems
- **Primary Care**: Andrew Hoekzema, Margaret Threadgill
- **Consultants**: Melissa Lumish
- **Radiology**: Craig Audin, Reece Golffon
- **Procedures**: Chris Keamey, Paige McLean

In addition, we would like to thank the many faculty who assisted with this book.

Multiple sections have had significant updates and there are many new articles including: Cardiology – Mechanical Support & Transplant, Peripheral Artery Disease, Cardio-Oncology; Infectious Disease – Head & Neck Infections, Sexually Transmitted Infections, Travel Medicine; Geriatrics & Palliative Care – Non Pain Symptom Management, Advanced Care Planning; Endocrinology – Osteoporosis; Allergy & Immunology – Common Allergic Disorders; Psychiatry – Agitation, Psychosis; Primary Care – Decision Aids.

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

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

And of course, none of this would be possible without the guidance and support of so many amazing people that make up the Department of Medicine. In particular, we extend special thanks to Gabby Mills, Libby Cunningham, and Paula Prout for supporting this project. In addition, we would like to thank our Chief Residents – Emily Walsh, Daniel Restrepo, Nino Mihatov, and Nancy Haff for their undying support and sage wisdom. Finally, we are very grateful to Jay Vyas, Hasan Bazari, and Katrina Armstrong for their endless devotion to housestaff education.

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

Melissa Lumish, MD & Shilpa Sharma, MD
Department of Medicine, Massachusetts General Hospital
June 2019

As with any other medical reference, this manual is NOT intended to provide specific clinical care decisions in an individual case, and should NOT substitute for clinical judgment. Every clinical care decision must be made by the exercise of professional judgment by the individual responsible for the care of a patient based on the facts of that individual case, which may differ from the facts upon which entries in this manual are based. You should consult other references and your fellow residents, fellows, and attendings whenever possible. We have carefully inspected every page, but errors may exist. If you find any errors, we would appreciate it if you would inform next year’s editors to make sure these errors are corrected.
**Cardiology**

**ACLS: Arrest & Cooling**

**Non-Senior On Tasks:**
- Confirm code status
- Confirm/stop IV infusions
- Run tele/print strips
- Check labs, med list
- Notify attending, family

**Defibrillators:**
- Biphasic (MGH) 120J-200J
- Monophasic 360J
  - If unknown, use max setting
  - Repeat shocks at same or higher dose

**AIRWAY**
- Obtain advanced airway
- Avoid excessive ventilation
  (10 breaths/min with continuous CPR)

**ACCESS**
- Establish IV/IO access; consider femoral central line if volume resuscitation needed

**LABS TO ORDER**
- Stat ABG with K & Hgb, CBC, BMP, LFTs, lactate, T&S, coags, fibrinogen, cardiac enzymes

**Medication Notes**
- **Epinephrine**: If no IV/IO access, epinephrine can be given via endotracheal tube at 2.5x the IV dose diluted in 10cc water or saline. **For non-shockable rhythms, epinephrine can be administered as soon as available rather than waiting 3-5 minutes (Class IIb recommendation)**
- **VSE protocol**: Can consider vasopressin 20U with first 5 doses of epi + hydrocortisone 200mg x1; class IIb evidence for in hospital cardiac arrest; not currently used at MGH
- **Lidocaine**: 1-1.5mg/kg IV/IO (often 100mg); may follow with 0.5-0.75mg/kg (usually 50mg) every 5-10min x3; maximum dose of 3 mg/kg; consider infusion at 1-4mg/min

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

**ECMO in Cardiac Arrest**

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**ECMO**

- Assess for responsiveness, pulse, and spontaneous respirations (C-A-B)
- Definitive pulse within 10 seconds = start chest compressions (CPR)

1. **Call Code Blue** (x6-3333, blue button on the wall)
2. Call for defibrillator pads, backboard & Ambu bag for mask ventilation
3. Establish monitoring: tele, defibrillator, O2 sat probe, place BP cuff
4. In both **witnessed AND unwitnessed** arrest, rhythm check ± defibrillate as soon as pads are on (Class IIa recommendation)

**2015 AHA Guidelines Update, 2018 AHA Focused Update**

**High Quality CPR**
- Minimize interruptions
- Fast: 100-120/min
- Compress 2-2.4 in deep
- Allow complete recoil
- Change compressors every 2mins
- 30:2 CPR:vent (mask)
- PETCO₂ >10, DBP>20

**Reversible Causes (H & Ts)**
- Hypovolemia, hemorrhage
- Hypoxia
- Hyperion (acidosis)
- Hypo/hyperkalemia
- Hypothermia
- Thrombosis, coronary (ACS) & pulmonary (PE)
- Tension pneumothorax
- Tamponade (cardiac)
- Toxins (drugs, accidents)

**TREAT REVERSIBLE CAUSES (H&Ts)**
- Hyperkalemia Treatment:
  - Ca gluconate 1-2g IV (or CaCl₂), Bicarb 1-2amp IV, D50W 1-2 amp (give first) + insulin 10 units IV

**PROGNOSTICATION**
- In intubated pts, failure to achieve ETCO₂ >10 mmHg by waveform capnography after 20 min CPR →90% sensitive for inability to achieve ROSC

**ROSC CRITERIA**
1. Pulse + blood pressure
2. Sustained increase ETCO₂ >40
3. Spontaneous arterial pressure waves on monitor
Cardiology

2015 ACLS Algorithms

Return of Spontaneous Circulation (ROSC) / Post-Arrest Care

Pulse and blood pressure measurable or spontaneous arterial pressure waves on A-line tracing
1. Ventilation and Oxygenation: maintain SpO2 > 94%. Do not hyperventilate (can induce cerebral vasodilatation). Start at 10-12 breaths/minute. Consider advanced airway waveform capnography. Target ETCO2 of 35-40 mm Hg.
2. Hypotension: cycle blood pressure and continuously monitor pulses. Goal MAP > 65mmHg.
   - IV/IO fluid boluses as needed (LR may be > than NS at larger volumes for treatment of shock)
   - Start vasopressor infusion (bolus code meds will wear off)
     ▪ Epinephrine IV infusion 0.1-0.5 mcg/kg/minute
     ▪ Norepinephrine IV infusion 0.1-0.5 mcg/kg/minute
     ▪ Dopamine IV infusion 2-10 mcg/kg/minute
3. Revascularization: obtain 12-lead EKG
   ▫ Hypothermia does not contraindicate PCI and is not associated with worse outcomes (Resuscitation 2010;81:398)
4. Therapeutic Hypothermia: consider if patient not able to follow commands
   ▫ If patient does not follow commands, call neurology fellow for full evaluation prior to starting cooling protocol

Targeted Temperature Management after Cardiac Arrest (Circulation 2015;132:2448)

Rationale: therapeutic hypothermia decreases cerebral oxygen demand and ischemia-related inflammation
- Class I recommendation for comatose cardiac arrest patients following ROSC for in- and out-of-hospital arrest (Circulation 2015;132:S465)
- Improves neurologic outcomes (NT 6) and survival to discharge (OR 5.25) following out-of-hospital cardiac arrest from VF, pulseless VT, or PEA/asystole of presumed cardiac cause, although the benefit may be from avoidance of hyperthermia rather than from hypothermia (NEJM 2002;346:549; NEJM 2002;346:557; NEJM 2013;369:2197; Circulation 2015;132:2146)

Cooling Criteria
- Comatose (GCS<8, not following commands, no purposeful movements to noxious stimuli) within 6 hours of cardiac arrest
- Able to maintain a blood pressure +/- vasopressors +/- IABP following ROSC

Relative Exclusion Criteria
- Major head trauma: rule out intracranial hemorrhage with non-contrast head CT
- Recent major surgery within 14 days: hypothermia increases risk of infection and bleeding
- Bleeding diathesis/active bleeding: hypothermia can lead to coagulopathy (check PT/PTT, fibrinogen, D-dimer), though patient may still receive thrombolytics, antplatelets, or anticoagulants if indicated for primary cardiac condition
- Systemic infection/sepsis: hypothermia inhibits immune function
- Coma from drug intoxication or pre-existing coma prior to arrest

Abbreviated Therapeutic Hypothermia Protocol

Preparation:
- Consult neurology Stroke/ICU consult (p20202) prior to initiation of hypothermia
- Non-contrast head CT, baseline labs including electrolytes, PT/PTT/INR, fibrinogen, D-dimer
- Access: A-line, central line +/- PA catheter, temperature probe (esophageal/bladder/rectal); access is challenging once patient is hypothermic

Temperature Targets: Reach hypothermia target of 32-34ºC ASAP
   - Maintain at hypothermia target for 24h (starting at the time from initiation of therapy)
   - Rewarm at hr 24 @ 0.5ºC/hr to goal temp 37ºC
   - Maintain sedation and paralysis at normothermia target (37ºC) for 24h
   - Maintain sedation and paralysis to prevent shivering.

Monitoring: maintain normal sodium, potassium, CO2 (35-45 mmHg), MAP (>70), glucose (140-180)
- If water temp <70ºF, pursue fever workup and consider starting antibiotics
- Maintain sedation and paralysis to prevent pain and shivering

Neuro-prognostication (Lancet Neurol 2016;15:597)
- AHA 2015 Guidelines: Recommended Markers of Poor Neurologic Outcomes (Circulation 2015;132:S465)
  ▪ Exam: Absence of pupillary light reflexes (>72 hrs post arrest), status myoclonus (72-120 hrs post arrest)
  ▪ Blood Markers (should not be used alone, no cutoff established): High neuron specific enolase (NSE, 48-72 hrs)
  ▪ Imaging: Brain MRI (extensive restriction/diffusion, 2-8 days post arrest), head CT (reduced gray-white ratio, <2 hrs post arrest if no TTM)
  ▪ Neuro Testing: Bilateral N20 SSEP absence (24-72 hrs post arrest), EEG 1) absence of reactivity 2) persistent burst suppression 3) intractable status epilepticus (72 hrs post arrest)
- In-hospital mortality at 72h post-rewarming (100% if ≥2 criteria present) (Ann Neurol 2010;67:301)
  1. unreactive EEG (most helpful)
  2. bilaterally absent SSEP
  3. early myoclonus
  4. incomplete recovery of brainstem reflexes

Brad Petek
Bradycardia with Pulse
HR<60 bpm and symptomatic

Assess patient, treat underlying causes:
- Monitor / Place defibrillator (pacing) pads
- Maintain airway, give supplemental O2 to maintain > 94%
- IV access
- 12-lead ECG, telemetry, BP monitoring
- Review recent medications, hospital events
- Obtain labs: chem 10, lactate & troponin if concern for ischemia/ACS

Unstable or inadequate perfusion?
- Hypotension / shock
- Altered mental status
- Ischemic chest discomfort
- Acute heart failure / pulmonary edema

If pulseless arrest develops, go to PEA/Asystole algorithm

Prepare for pacing
(see Defibrillation/Cardioversion/Pacing Section)

Atropine 0.5 mg bolus, repeat q3-5min up to 3g (6 doses)
- Caution if 2nd degree AV block Mobitz II (will accelerate sinus rate, leading to worsening of block)
- May not be effective in heart transplant (lack of vagal stimulation)

(if atropine ineffective)

Dopamine IV infusion 2-20 mcg/kg/min
OR
Epinephrine IV infusion 2-10 mcg/min
OR
Isoproterenol 2-10 mcg/min
OR
Transcutaneous/transvenous pacing
AND/OR
Antidotes by cause

Specific antidotes by cause:
- Beta blocker: Glucagon 5 mg IV q10 min (up to 3 doses), insulin 1U/kg bolus (FYI glucagon causes severe nausea)
- Calcium channel blocker: Calcium gluconate 3 g, insulin 1U/kg bolus
- Digoxin: Dig immune FAB 10-20 vials
- Opioids: Naloxone 0.4-0.8 mg IV, consider gtt
- Organophosphate: Atropine 2mg IV (double dose q5-30 mins), pralidoxine 1-2g IV over 15-30 mins

Ijeoma Eleazu
Cardiology

ACLS: Tachycardia

Stable Ventricular Tachycardia
Monomorphic and Polymorphic

If patient becomes unstable:
Proceed to synchronized DCCV for monomorphic VT
OR unsynchronized defibrillation for PMVT or VF

Monomorphic VT
Is cardiac function impaired?

Preserved LVEF (>40%)

- Amiodarone
- Lidocaine

Other medications:
- Metoprolol (not first line; expert consultation advised)
- Sotalol (not first line; expert consultation advised)

Impaired LVEF (<40%)

Normal baseline QTc:
- ischemia (active>scar), idiopathic VT, congenital PMVT

Prolonged baseline QTc:
- TdP, long QT syndrome

Polymorphic VT
Evaluate baseline QTc

IV magnesium
- ↑HR: dopamine, isoproterenol, overdrive pacing
- ↓QTc: lidocaine
- Avoid bradycardia: hold nodal agents and amiodarone

Causes:
- Ischemia (scar>active)
- Electrolytes (low K, Ca, or Mg)
- Structural heart dz
- Drug toxicity (TCA, digoxin, anti-arrhythmics, inotropes)
- Infiltrative dz or scar
- Channelopathies (acquired or inherited)

First line medications:
- Amiodarone
- Procainamide
- Lidocaine
- Adenosine*

Other medications:
- Metoprolol (not first line; expert consultation advised)
- Sotalol (not first line; expert consultation advised)

*Adenosine should be considered per 2015 ACLS update for stable, regular narrow- and monomorphic wide-complex tachycardia while preparing for DCCV to differentiate SVT w aberrancy from WCT

**PMVT is inherently unstable and requires immediate treatment because it is likely to deteriorate to pulseless arrest. Prepare for defibrillation.

Anti-arrhythmic drug dosing (for stable WCT)
- Amiodarone: 150 mg IV over 10 min (may repeat x1); then infusion at 1 mg/min x6hrs followed by 0.5 mg/min x18h (max 2.2 g/24 hours). May complete 10g load with up to 400mg PO TID.
- Lidocaine: 1-1.5 mg/kg IV bolus—usually 100 mg (may repeat 0.5-0.75 mg/kg q5-10min, max 3mg/kg); then maintenance infusion at 1-4 mg/min; agent of choice when prolonged QT
- Procainamide: 20 mg/min until either VT ceases or hypotension or QRS duration prolongs by 50% from baseline or total 17 mg/kg given (~1.2 g for 70kg person); then maintenance infusion at 1-4 mg/min (adjusted for CrCl); avoid in prolonged QT
- Sotalol: 1-1.5 mg/kg IV over 5 min; then maintenance infusion at 10 mg/min; avoid in prolonged QT
- (Adenosine: 6mg rapid IV push (followed by NS flush) →12 mg if required)

Circulation 2010;122:S729
**External Defibrillation/Cardioversion/Transcutaneous Pacing:**

- **About the device:** The Zoll R Series is on all code carts and ICUs at MGH. This device allows for external defibrillation, cardioversion, and pacing with additional benefits (e.g., displaying ET-CO₂, CPR quality feedback, and saving rhythm strips for upload into Epic).
- **Additional supplies needed at bedside:** Ambu bag, intubation equipment, RICU staff, backboard, suction
- **Use procedural sedation (typically fentanyl and midazolam) when possible and call Cardiac Anesthesia early**

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**Display/Operation of Zoll R Series:**

![Zoll R Series Display](image)

### Defibrillation

**Indications:** pulseless VT or VF

1. Turn the Selector Switch to ON. Then press Manual (bottom left softkey) to change to ALS.
2. The default energy selection is 120 J. You can use Energy Select (UP) and (DOWN) arrow keys to increase the energy.
3. If there is a shockable rhythm on the pulse/rhythm check, press Charge. Continue CPR while charging.
4. Once charged, the red shock button illuminates. Shout "Clear!" then press and hold the illuminated Shock button at the top right of the console.
5. Resume CPR for 2 minutes before the next pulse/rhythm check.

### Cardioversion

**Indications:** Unstable SVT or VT

1. Turn the Selector Switch to ON. Then press Manual (bottom left softkey) to change to ALS.
2. Select the desired energy using the up and down arrow keys on the front panel.
   - Narrow, regular: 50-100 J (atrial flutter often converts with 50 J)
   - Narrow, irregular: 120-200 J (atrial fibrillation typically requires 150 J)
   - Wide, regular: 100 J
   - Wide, irregular: 150-200 J (defibrillation dose)
3. Press the Sync On/Off button
   - Confirm that a Sync marker () appears on the monitor above each detected R-wave to indicate where discharge will occur
   - If necessary, use the LEAD and SIZE buttons to establish settings that yield the best display
4. Press the CHARGE button on the front panel.
5. **Press and hold** the illuminated SHOCK button on the front panel. The defibrillator will discharge with the next detected R wave.
6. If additional shocks are necessary, increase the energy level as needed.

### Pacing

**Indications:** Unstable bradycardia

1. Turn the Selector Switch ON. Then press Manual (bottom left softkey) to change to ALS. Then PACER will appear as an option on the Selector Switch. Turn to PACER.
2. Set the PACER RATE to a value 10-20 bpm higher than the patient's intrinsic heart rate. If unknown or absent intrinsic rate, use 100 bpm.
   - Observe the pacing stimulus marker on the display and verify that it is well-positioned in diastole
3. Increase PACER OUTPUT until the paced beats demonstrate capture ("threshold"); the output mA value is displayed on the screen.
   - Capture = widened QRS complex + loss of underlying intrinsic rhythm
4. Set the PACER OUTPUT to the lowest setting that maintains consistent capture
   - Usually ~10% above threshold (typical threshold: ~40 to 80 mA)
   - Pressing and holding the 4:1 button temporarily withholds pacing stimuli, thereby allowing you to observe pt's underlying EKG rhythm & morphology

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**Shilpa Sharma**

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Cardiology

EKG Interpretation

Approach all EKGs systematically. Always note: rate, rhythm, QRS axis, complexes and intervals, chamber enlargement, ischemia/infarction, compare with prior EKG

Rate (atrial, ventricular)
- If the rhythm is regular, use the counting method (300 / # large boxes). See image at right.
- If the rhythm is irregular, count R waves in the rhythm strip and multiply by 6 (EKG printouts record 10 seconds)
- Normal 60-100bpm; <60bpm is bradycardia, >100bpm is tachycardia

Rhythm (regular or irregular; sinus vs. non-sinus)
- Sinus rhythm defined as: P before every QRS, regular w/ rate 60-100, P wave upright I, II, aVF, V5-V6
- P waves/morphology: Determine (1) if a P wave is present (best leads to visualize P wave are II and V1) (2) The atrial rate (100-180: sinus tachycardia; 140-220: atrial tachycardia, AVNRT, AVRT; 260-320: atrial flutter) and (3) Axis (P wave upright in II and biphasic in V1)
- QRS morphology: Narrow (<120ms) → supraventricular rhythm. Wide (>120ms) → aberrant supraventricular conduction or ventricular origin
- P wave/QRS complex association: If not 1:1 association, determine if number of P>QRS (AV block) or P<QRS (accelerated junctional or ventricular rhythm). If P precedes QRS, evaluate the PR interval. If P after QRS, evaluate the RP interval and determine if PR or RP interval is fixed or variable

QRS Axis
- Normal axis (-30 to 90º): QRS complex is positive (upright) in leads I and II
- Leftward axis (-30 to -90º): QRS complex is positive in lead I but negative in lead II
  - Ddx: normal variant, mechanical shifts, LVH, LBBB, LAFB, congenital heart disease, emphysema, hyperK, ventricular ectopic rhythms, WPW, inferior MI
- Rightward axis (90 to 180º): QRS complex is negative in lead I and positive in leads II, aVF
  - Ddx: normal variant, mechanical shifts, RVH, LPFB, dextrocardia, ventricular ectopic rhythms, WPW, lateral MI
  - (NB: RBBB rarely causes RAD)
- Extreme axis deviation/northwest axis (180 to -90º): QRS complexes negative in both I and II
  - Ddx: Lead transposition, ventricular ectopic rhythms, hyperkalemia, artificial pacing, severe RVH
- Clockwise/counterclockwise rotation (i.e. “R wave progression”): R wave amplitude typically increases from V1 to V5, with transition of R>S in amplitude at V3 or V4. CCW: transition occurs prior to V3 due to RVH, WPW, LAFB, posterior MI. CW: transition occurs after V4 due to cardiomyopathy, LVH, LBBB, anterior MI. Both CW and CCW rotation are nonspecific and can be normal (Am Heart J 2004;148:80)

Low voltage: Average QRS amplitude <5 mm in I, II, III and <10 mm in precordial leads
- Ddx: obesity, pericardial effusion, pneumothorax, COPD, restrictive or infiltrative CM (particularly amyloidosis), severe hypothyroidism, or anasarca

Complexes and Intervals (Circ 2009;119:e241)
- P wave: Right and left atrial depolarization; normal duration <120ms
- PR interval: Atrial depolarization, AV node and His-Purkinje conduction. Normally 140-200ms, changes with rate (shortened at faster rates, longer at lower rates due to autonomic effects on AV nodal conduction)
- QRS: Ventricular depolarization. Normal duration 60-100ms, not influenced by HR. QRS 100-120ms is seen with incomplete BBB or interventricular conduction delay (IVCD); >120ms represents BBB, ventricular activation (PVC, VT, fusion beats, WPW, paced beats), hyperK, Na channel poisoning, aberrancy, hypothermia

LAFB: Left axis deviation (-45 to -90º) w/ QRS<120, r in I, aVL; rS in II, III, aVF. Common, nonspecific.
LPFB: Right axis deviation (0 to +90º) w/ QRS<120. No alternate reason (e.g., RVH, emphysema, lateral MI, PE). Rare to see in isolation, usually occurs with RBBB.

Bifascicular block: RBBB with either LAFB or LPFB

ST-segment: Represents a time of electrical silence. See “Ischemia/Infarction” on next page

T-wave: Ventricular repolarization, with a slow upstroke and a rapid return to the isoelectric line after peaking. Usually asymmetric and in the same direction as the QRS. Should have smooth contours (bumps in T are usually buried P waves)

U wave: occurs in the same direction as T wave, rate-dependent (shorter at faster rates); ddx: bradycardia, hypok/Mg/Ca, hypothermia

QT interval: Ventricular depolarization and repolarization. Excludes U-wave unless fused with the T wave. Rate-dependent (shortened at faster rates). Normal <440ms in men, <460ms in women

Chamber Enlargement (Circ 2009;119:e251) (NB: 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 (men) or 20mm (women)
- RVH: R or S ≥7mm in V1, S ≥7mm in V5 or V6
- LAE: negative p wave in V1 >1mm wide and deep, total p wave duration >110ms in II
- RAE: p wave >2.5mm in lead II
Cardiology

EKG Interpretation

Ischemic Infarction (JACC 2009;53:1003)
- Analyze abnormalities along the vectors of ventricular depolarization and repolarization (QRS-ST-T)
- T-wave abnormalities: Hyperacute, symmetric T-waves can be found within minutes; followed by T wave inversions (≥0.1 mV in 2 contiguous leads)
- ST depression: Suggests subendocardial injury; ≥0.05 mV below the baseline (PR segment), measured at the J point, in two contiguous leads, downsloping or horizontal = more ominous. ST depressions do not localize to territories (Circ Res 1998;62:957). NB: always look for ST elevations to rule out reciprocal ST depression. Digoxin toxicity: scooping ST depressions.
- ST elevation: Suggests transmural ischemia; ≥0.1 mV, except for leads V2 to V3 (≥0.2 mV in men ≥40yo and ≥0.15 mV in women), measured at the J point. PR segment is the isoelectric interval on the ECG and can be used to assess ST segment elevation/depression.
- Q-wave: Usually a marker of scar; must be deep (>1 mm) and broad (>0.04 seconds), more likely 2/2 prior MI if inverted T wave in same lead. Pathologic Q wave defined by 40ms duration (1 box wide), 25% height of QRS. “Isolated Q in III is free” (non-pathologic).
- Sgarbossa Criteria: Used to diagnose acute MI in presence of LBBB. Score of 3 = 90% Sp
- Concordant STE > 1mm in any lead = 5 points; Discordant STE > 5 mm in any lead = 2 points; ST depression > 1 mm in V1-V3 = 3 points.
- Ample STE of normal variant

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<tr>
<td>Early repolarization</td>
<td>J point elevation ≥0.1 mV in 2 adjacent leads, slurred/notched, look at V4, reciprocal STD in aVR</td>
</tr>
<tr>
<td>Brugada Syndrome</td>
<td>rSR’ and downsloping STE in V1-V2 (see below)</td>
</tr>
<tr>
<td>LVH</td>
<td>Concave, often with TWI, look in leads I, aVL, V4-6. Cornell criteria: sum of R wave in aVL and S wave in V3 exceeds 20mm for females or 28mm for males. Stand alone criteria: R wave in aVL &gt; 11mm</td>
</tr>
<tr>
<td>LBBB</td>
<td>Concave, ST depressions discordant from QRS</td>
</tr>
<tr>
<td>Acute pericarditis</td>
<td>Diffuse STE (usually &lt; 3mm), PR depression, STE amplitude:Twave amp (in mm) &gt;0.26 specific</td>
</tr>
<tr>
<td>Stress-Induced (Takotsubo’s) Cardiomyopathy</td>
<td>Usually limited to precordial leads w/out reciprocal inferior ST depressions, STE followed by deep TWI</td>
</tr>
<tr>
<td>Prinzmetal’s Angina/Vasospasm</td>
<td>ECG mimics MI but STE are transient</td>
</tr>
<tr>
<td>Ventricular aneurysm</td>
<td>Persistent STE in any leads</td>
</tr>
<tr>
<td>PE</td>
<td>Mimics MI, look in inferior and anteroseptal leads</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Look for other ECG findings c/w hyperkalemia</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>Marked (often &gt; 10mm) following DCCV</td>
</tr>
</tbody>
</table>

Electrolyte Abnormalities

<table>
<thead>
<tr>
<th>Electrolyte derangement</th>
<th>Characteristic ECG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>Prolonged QT, ST depression, flattened T wave, prominent U wave</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Peaked, symmetric T wave, prolonged PR, flattened P and widened QRS (severe hyperkalemia)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Prolonged QT, unchanged T wave</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Shortened QT</td>
</tr>
</tbody>
</table>

J-point elevation syndromes
Early repolarization:
- ERP: ST segment elevation in absence of chest pain, terminal QRS slur, or terminal QRS notch
- Features suspicious for malignant forms of ER: 1) Fh/o sudden cardiac arrest or early unexplained death. 2) evalution and workup suggestive of a channelopathy. 3) h/o unheralded syncope suggestive of an arrhythmogenic pathogenesis (Circ 2016; 133:1520)

Brugada Syndrome (Circ Arrhythm Electrophys 2012;5:606)
- Autosomal dominant, SCNSA
- loss of fxn mutation in 10-30%
- M>F, more common to have nocturnal cardiac arrest
- pw VT/VF or sudden cardiac death

Osbourn Wave
- Hyperthermia, T<93ºF
- Elevation of J point height roughly proportional to degree of hyperthermia (n.b. neg in V1 & aVR)

Epsilon Wave
- Found in ARVC
- Most specific in V1 (30% w/ ARVC)
- Low frequency, positive terminal deflection in V1-V3

Shawn Li, Nora Abo-Sido
Narrow Complex Tachycardia (QRS < 120 ms)  
(NEJM 2012;367:1438)

- **Diagnostic approach & general principles:**
  - if unstable → synchronized cardioversion
  - vagal maneuvers/carotid massage/adenosine can resolve diagnostic dilemmas and treat AVNRT and AVRT
  - acute treatment for all others is BB, CCB or amiodarone (but consider risk of pharmacologic cardioversion if pt is not anticoagulated)

- **Sinus Tachycardia**
  - Gradual in onset (if not consider SANRT, which is similar to AVRT and terminates with adenoside or vagal maneuvers)
  - Consider: hypovolaemia, haemorrhage, withdrawal (EtOH, BZD, opiate, BB), intoxication, fever/infection, pain, hypoxaemia, PE, anaemia, tamponade, dissection, hormonal (hyperthyroidism, adrenal insufficiency, pheochromocytoma)

- **Atrial Tachycardia (AT)**
  - Long RP, single P morphology, non-sinus P wave axis
  - Arises from increased automaticity at single atrial focus
  - Classic digoxin toxicity is AT w/ variable AV block

- **Multifocal Atrial Tachycardia (MAT)**
  - Long RP, 3 or more P wave morphologies
  - Irregular due to varying PP, PR and RR intervals
  - COPD, pHTN, CAD, electrolytes, theophylline

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

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

- **Atrioventricular Nodal Re-entrant Tachycardia (AVNRT)**
  - Usually no RP (slow-fast), uncommon short RP (fast-slow), rarely long RP (slow-slow)
  - Arises from functional re-entry w/in AV node
  - Trigger PAC (slow-fast) > PVC (fast-slow)
  - Young adults, F > M

- **Atrioventricular Re-entrant Tachycardia (AVRT)**
  - Usually short RP, uncommon long RP, rarely no RP
  - Arises from true re-entry via bypass tract
  - Ventricular activation via AV node (orthodromic, NCT) more common than via accessory tract (antidromic, WCT)
  - Rates usually 150-250

- **AVNRT vs AVRT**
  - Both are regular, paroxysmal, re-entrant NCTs w/ variable RPs that terminate w/ adenosine/vagal/AV block
  - Use baseline ECG, trigger, terminal activity to distinguish
  - AVNRT: look for terminal pseudo-r' in V1-2 during tachycardia that is absent on baseline ECG
  - AVRT: look for pre-excitation (short PR) on baseline ECG (delta wave → WPW; no delta wave → Lown-Ganong-Levine syndrome) that is absent during tachycardia

- **Junctional Tachycardia**
  - Usually short RP (retrograde P waves), can be no RP
  - If P waves present, must be negative in aVF
  - Arises from increased automaticity in AV junction

Usama Abbasi and Raymond Parrish
Narrow & Wide Complex Tachycardia

**Wide Complex Tachycardia (QRS ≥ 120 ms)**

- **Goal:** determine VT or SVT with aberrant conduction
- **SVT w/ aberrant conduction includes:** functional/rate-dependent BBB iso encroachment on bundle refractory period; RBBB > LBBB, SVT w/ pre-existing BBB, antidromic AVRT, antidysrhythmic drugs (digoxin, class IA or IC, amiodarone), hyperkalemia, TCA overdose, pacemaker/ endless loop tachycardia (retrograde VA conduction of V-paced beat misidentified as native A-beat leading to additional V-pacing)
- **As majority of VT is due to re-entry (true about scar vs functional iso heterogeneous conduction), history is crucial. MI, cardiomyopathy, reduced LVEF and infiltrative disease all increase pre-test probability of VT
- **QRS w/ sharp initial deflection (some His-Purkinje conduction present) followed by broad terminal deflection favours SVT w/ aberrancy**
- **ECG factors that favor VT:**
  - Very broad QRS (ie > 160 ms), superior axis (II, III and aVF completely negative), indeterminate axis (I and aVF negative)
  - AV dissociation (often V rate > A rate) → diagnostic of VT
  - Concordance – all QRS across precordial completely positive or completely negative
  - Partial (fusion beat) or complete (capture beat) depolarisation of ventricle by underlying supraventricular rhythm

**Brugada criteria (Circulation 1991;83:1649):**
- Highly sensitive and specific in initial paper, but subsequent studies have unanimously demonstrated lower sensitivity and specificity
- Only applicable if rhythm is regular

<table>
<thead>
<tr>
<th>Absence of RS in all precordial leads</th>
<th>Start of R to S nadir &gt; 100 ms in at least one precordial lead</th>
<th>AV Dissociation</th>
<th>Morphology criteria in V1-2 and V6</th>
<th>SVT (96.5 % sen, 96.7 % sp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>VT (21 % sen, 100 % sp)</td>
<td>VT (66 % sen, 98 % sp)</td>
<td>VT (82 % sen, 98 % sp)</td>
<td>VT (96.7 % sen, 96.5 % sp)</td>
<td></td>
</tr>
</tbody>
</table>

**Management of VT**

- **Monomorphic VT:**
  - NSVT: BB if symptomatic, electrolytes (K > 4, Mg > 2)
  - Sustained but stable: chemical cardioversion w/ amiodarone (150 mg), lidocaine (if c/f ischaemia: 1-1.5 mg/kg) or procainamide (only if no structure heart disease, preserved LVEF; 20-50 mg/min for 5-10 mins while monitoring for hypotenison, shall slow rate even if fails to convert),
  - Unstable: synchronized cardioversion (if pulse) vs defibrillation (pulseless)
- **Polymorphic VT w/ normal QT:**
  - Ischaemia → BB, revascularisation, mechanical support
  - If unstable → defibrillation
- **Torsades de Pointes – special case of pmVT iso prolonged QT, often triggered by R on T**
  - Mg
  - Increase HR (dopa, epi, iso, overdrive pacing)
  - Avoid bradycardia (amio, CCB, BB)
  - Decrease QTc (lido)
- **Incessant VT (VT Storm) – refractory VT (defined differently if ICD vs no ICD)**
  - Amiodarone 150 mg IV plus propranolol 60 mg PO Q6H superior to amiodarone plus metoprolol (JACC 2018;71:1897)
  - Anti-tachycardia pacing (unsafe to attempt unless prepared for emergent DCCV/defibrillation as can precipitate unstable VT)
  - Intubation and sedation to suppress adrenergic tone
  - VANISH trial: in patients with ischaemic cardiomyopathy and ICD w/ persistent VT, ablation superior to escalation of antidysrhythmic drugs (composite of death, VT storm and ICD shocks)
Atrial Fibrillation Epidemiology and Classification *(Heart Rhythm 2012;9:632)*
- Prevalence increases with age; <0.1% for age<55 vs 9% for age>80.
- Recurs in majority of cases due to secondary precipitant (surgery, infection, MI, thyrotoxicosis, acute alcohol, PE)

**Classification:**
- First diagnosed: not previously diagnosed irrespective of duration
- Paroxysmal: self-termination within 7 days (includes those cardioverted within 7 days)
- Persistent: continuous afib lasting >7 days
- Long-standing persistent: continuous afib lasting >12 months
- Permanent: term used when decision is made to stop further attempts to restore and/or maintain sinus rhythm

Clinical Evaluation of New-Onset Atrial Fibrillation
- History/Exam: presence and timing of symptoms, HTN, DM, valvular disease, CHF, angina, congenital heart disease, OSA, family hx of AF, acute precipitants (e.g., EtOH, thyrotoxicosis, sympathomimetic drugs, surgery, myocardial ischemia, myocarditis, PE, acute pulmonary disease, infection)
- ECG: absence of discernible p waves, irregularly irregular R-R intervals
- TTE: LV function, LA/RA size, valve function, pulmonary HTN, LA thrombus *(low sensitivity, better with TEE)*
- CXR: evaluate for pulmonary parenchymal processes and pulmonary vasculature/edema
- Labs: TFTs, LFTs, BUN/Cr, CBC, NT-proBNP
- Additional testing: Zio patch, Holter monitor, implantable loop recorder, exercise testing *(to assess rate control with activity or as part of ischemic evaluation)*
- Five “domains” of initial assessment: hemodynamic stability, precipitating factors, stroke risk and need for AC, HR and need for rate control, symptom assessment and need for rhythm control

Cardioversion (ALWAYS consider high risk of embolic stroke if any breaks in AC for one month prior)
- Indications
  - Urgent situations: ischemia, end-organ hypoperfusion, symptomatic hypotension, severe pulmonary edema
  - Elective: new-onset AF or unacceptable symptoms from persistent AF
- Electrical Cardioversion (DCCV)
  - Synchronized DCCV at 150J *(biphasic)*; increase energy in stepwise fashion if SR not achieved
  - Use procedural sedation if possible *(consult cardiac anesthesia)*. If elective, should be performed in ICU or EP lab.
  - Consider anti-arrhythmic drugs as adjunct (e.g., amiodarone)
- Chemical Cardioversion
  - Success rate significantly higher for acute (<7d) compared with longer-duration AF
  - Agents: pill-in-pocket (flecainide, propafenone), dofetilide, ibutilide, amiodarone
    - Amiodarone: IV infusion weakly effective for conversion; PO load over 3-4 wk has 27% rate of conversion
- AC in Patients Undergoing Cardioversion *(applies to BOTH chemical and electrical)*
  - Pre-procedure:
    - Definitive new onset <48 hours: may proceed without anticoagulation
    - Onset >48 hours: must anticoagulate for 3 weeks prior to DCCV or obtain TEE immediately prior to DCCV *(NEJM 2001;344:1411)*
  - Post-procedure: anticoagulate for at least 4 weeks after DCCV (due to myocardial stunning)
  - NB: if obtaining TEE and pt is not anticoagulated, start UFH/LMWH on day of DCCV (or apixaban 2d before DCCV)

Acute Management of Atrial Fibrillation with Rapid Ventricular Response
**Step 1:** Confirm atrial fibrillation or flutter with ECG
**Step 2:** Determine hemodynamic stability:
- Stable: SBP>90
  - Usually if HR > 130 or symptomatic prefer IV, otherwise can consider starting PO / increasing current PO dose
  - Beta-blocker: metoprolol (others: labetalol, propranolol, esmolol)
    - IV: bolus 2.5-10 mg over 2 minutes; repeat as required q10-15 min
    - PO: up to 400mg total daily dose (although doses >200mg usually not effective)
    - Contraindicated: acute decompensated heart failure, history of severe bronchospasm
  - Calcium channel blocker: diltiazem (others: verapamil)
    - IV: bolus of 0.25 mg/kg (average adult dose 10-25 mg) over 2 minutes; repeat as required q10-15 min
    - PO: up to 360 mg total daily dose
Atrial Fibrillation & Flutter

• Contraindicated: LV failure with pulmonary congestion, LVEF <40%
• Reduce dose with hepatic impairment and renal impairment

Once rates are controlled with IV medication, ALWAYS chase with PO for sustained effect

Peri-stable: SBP 80-90

- If borderline BP, carefully attempt low-dose BB / CCA (attempt concomitant IVF if pulmonary edema not a concern)
- Consider BB-sparing agents:
  • Digoxin load (0.5mg IV/PO followed by 0.25mg IV/PO q6hrs x2, total load 1mg), can lead to toxicity with renal impairment, contraindicated if accessory pathways
  • Amiodarone (150mg IV over 10 min followed by gtt; requires transfer to ICU or SDU) [NB: bolus x1 can be done on floor w/ nursing supervisor]
    - Consider risk of pharmacologic cardioversion and consequent embolization of LA thrombus

Unstable: SBP<80 (usually with HR >150); signs of shock (AMS, cool extremities); refractory pulmonary edema or angina.

- Call for early back-up / Senior On for medication administration, cardioversion, and uptriage.
- Synchronized cardioversion (DCCV); usually start with 150J.
- If pressors are required, phenylephrine (neosynephrine) is first-line given reflex bradycardia
  - NB: higher HRs (>140) more likely to cause HoTN alone; lower HRs (<140) may cause HoTN if systolic/diastolic dysfxn or decreased preload (i.e., “loss of atrial kick”).

Step 3: correct underlying causes or precipitants whenever possible (e.g. IVF).

Long-Term Rate vs. Rhythm Control

- Overall, rate control noninferior to rhythm control for AF symptoms, CV mortality, and stroke risk. (AFFIRM, RACE, PIAF, STAF, HOT CAFE, AF-CHF).
- Exceptions: consider rhythm control if persistent AF sx impairing QoL, also if age <65 or comorbid HF (esp if systolic dysfxn). Restoration of NSR may also lead to increased QoL and exercise performance (NEJM 2005;352:1861, JACC 2004;43:241).

- BB more successful than CCA in achieving rate control (70% vs. 54%), either alone or in combination with digoxin.
- Digoxin alone is moderately effective in controlling V-rate at rest, ineffective during exertion or high adrenergic tone.
- Long-term digoxin independently associated with increased mortality in AF patients (JACC 2018;71:1063).

- Rate Targets: Lenient rate control (resting HR <110) non-inferior to strict rate control (HR <80); similar outcomes in CV death, stroke, bleeding, arrhythmia and hospitalization for HF (RACE II). Stricter HR (or rhythm control) may be beneficial in younger pts or pts w/ HF.

- Contraindications/Warnings: Evidence of pre-excitation on ECG (in these patients, IV procainamide is 1st line), cautious use in high-degree AVB. CCA should not be used in pts with EF<40% given negative inotropy.
- “Pill-in-Pocket”: For pts w recent pAFib w infrequent and well-tolerated episodes, ppx may have risk>benefit, and thus pm flecainide or propafenone at sx onset is safe and effective (NEJM 2004;351:2384).

Long-Term Rhythm Control: Overview (Circulation 2012;125:381)

- Choice of Agents:
  - No structural heart disease: pill-in-pocket (flecainide/propafenone), dofetilide, dronedarone, sotalol, amiodarone
  - Structural: CAD: dofetilide, dronedarone, sotalol, amiodarone | HF: amio, dofetilide | LVH: amio, dofetilide
- Catheter ablation (pulmonary vein isolation): associated with a lower long-term AF recurrence rate vs. antiarrhythmic agents in both paroxysmal (MANTRA-PAF, RAAFT-2) and persistent AF (Eur Heart J 2014;35:501). CASTLE-AF trial showed catheter ablation in pts w AFib and HF lowered morbidity/mortality 2/2 HF compared to medical therapy.
- AV nodal ablation with PPM: indicated when pharm rate/rhythm control not achievable (JACC 2014;64:2246); consider CRT for EF<40%.

Antithrombotic Therapy (Stroke 2010;41:2731)

- Treatment recommended for all pts except those with CHADS2-VASc 0, lone AF episode, or contraindications to therapy.
- LA appendage is the source of at least 90% of thrombi in pts with CVA and AF.
- Subclinical AF still associated with increased stroke/systemic embolism (ASSERT).
- Patients at relatively low risk for thromboembolism may be maintained on ASA alone (see below), but no reliable data exist to guide decision between 81mg vs. 325mg ASA dose

Risk assessment


David Olshan
Atrial Fibrillation & Flutter

- Score 0 = no AC or ASA; Score 1 = no AC vs. ASA vs. oral AC based on clinical judgment
- how high is risk from specified risk factor? ex: HTN, DM, age bring greater risk compared to female sex, vascular dz; Score ≥2 = oral AC

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted stroke rate (%/yr)</td>
<td>0</td>
<td>1.3</td>
<td>2.2</td>
<td>3.2</td>
<td>4</td>
<td>6.7</td>
<td>9.8</td>
<td>9.6</td>
<td>6.7</td>
<td>15.2</td>
</tr>
</tbody>
</table>

- HAS-BLED: [HTN (SBP>160); Abnl renal function (CrCl<50); Liver disease (Cirrhosis or Bilis 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/wk) or other drug use]. Risk stratification of bleeding risk w/ oral AC. Score ≥3 suggests caution and regular follow-up.

- http://www.sparctool.com/ can aid in risk assessment and choice of anticoagulation

Choice of Antithrombotic Agent

<table>
<thead>
<tr>
<th>Medication</th>
<th>Action</th>
<th>Dosing</th>
<th>Avoid</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K antagonist</td>
<td>Variable</td>
<td>Pregnancy (X)</td>
<td>Annual RR of 68% for stroke ([Arch Intern Med 1994;154:1449]).</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>150mg BID</td>
<td>CrCl &lt;15</td>
<td>35% reduction in stroke compared to warfarin with no increase in major bleeding (RE-LY).</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibitor</td>
<td>20mg QD (15mg if CrCl 15-50)</td>
<td>Severe hepatic impairment, CrCl &lt;15</td>
<td>Non-inferior to warfarin for prevention of stroke in non-valvular AF; no difference in major bleeding, ↓ICH, and fatal bleeding (ROCKET-AF). For cryptogenic stroke prevention, both non superior and associated w increased bleeding when compared to ASA (NEJM 2018;378:2191). Can be completely and quickly reversed w Idarucizumab. (NEJM 2015;373:511)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5mg BID (2.5mg if Cr &gt;1.5 AND age ≥ 80 OR wt &lt;60kg)</td>
<td>Severe hepatic impairment</td>
<td>Superior to warfarin or aspirin alone in preventing stroke and systemic embolism w/o increasing the risk of major bleeding or ICH (ARISTOTLE).</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60mg QD</td>
<td>CrCl &lt;30</td>
<td>Noninferior to warfarin for prevention of stroke with lower rates of major bleeding and death (ENGAGE AF).</td>
<td></td>
</tr>
</tbody>
</table>

- NOACs vs Warfarin: In meta-analysis, NOACs shown to have lower risk of stroke or systemic embolic events (RR 0.81), all-cause mortality (RR 0.9), and ICH (RR 0.48) but higher risk of GI bleeding (RR 1.25) compared to warfarin (Lancet 2014;383:955). In new AF, start a NOAC unless valvular afib (see below) (Eur Heart J 2016;37:2893).

- Bridging AC: Consider bridging with heparin or LMWH for CHADS2 scores ≥5 (Blood 2011;117:5044, NEJM 2015;373:823).

- Valvular Afib: AF in the setting of rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, mitral valve repair (Circulation 2014;130:2071).

- LAA closure (Watchman device): In non-valvular AFib, device placement provides comparable stroke prevention to warfarin with reduced bleeding risk and improved mortality (JACC 2017;70:2964).

NB: After cryptogenic embolic stroke, ambulatory ECG monitoring for 30 days significantly increased AFib detection when compared to shorter duration of monitoring (NEJM 2014;370:2467). If AF not detected, ASA non-inferior to NOAC.

Atrial Flutter Overview

- Less prevalent but often coexists or precedes AF.
- Type 1 (typical): Reentrant loop in RA via cavo-tricuspid isthmus (CTI). Divided based on direction of circuit:
  - Counterclockwise (more common, inverted flutter waves in II, III, aVF + upright flutter waves in V1)
  - Clockwise (less common, upright flutter waves in II, III, aVF + inverted flutter waves in V1)
- Type 2 (atypical): does not meet criteria for Type 1; is typically faster and often refractory to ablation

Anticoagulation: Risk of thromboembolism lower than AF ([Stroke Cerebrovasc 2018;27:839]) but these are small studies – management should be similar to AF ([Chest 2012;141:e531S]).

- Rate control: Similar strategies (BB,CCA) to AF, but more difficult to successfully rate-control.
- Rhythm control: CTI ablation for typical flutter > 90% effective at 1yr ([Circ Arrhythmia EP 2009;2:393]).
**Cardiology**

**QTc Prolongation**

- **Definition**
  - QT interval correlates with repolarization time of ventricles (prolonged QTc >450 ms in men; >470 ms in women)
  - Measure from beginning of QRS to end of T wave in a lead with T-wave > 2mm; define end point using tangent from peak of steepest slope to isoelectric line
  - QTc – Corrected for HR
    - Bazett’s formula = QT/√RR; overcorrects at high HR and undercorrects at low HR
    - Fridericia’s formula = QT/√(RR); more accurate at high or low HR (Am J Cardiol 1993 26;72:17B).

- **Assessment of QT with underlying BBB** (Heart Rhythm 2014;11:2273)
  - Bundle branch blocks will lengthen QT interval – can use modified QT (QTm) or JT interval (JTI) as surrogate index for repolarization
    - JTI = JT(HR + 100)/518, with a JTI > 112 identifying repolarization prolongation in all ventricular conduction defects
    - QTm = QTb - 48.5% * (QRSb)

- **Congenital Long-QT Syndromes** (Br J Clin Pharmacol 2010;70:16)
  - LQT1: KCNQ1 – (IKs) Romano Ward, autosomal dom. – triggered by exercise, stress
  - LQT2: hERG – (IKr) Jervell Lange-Nielsen, autosomal rec. – assoc. w/ deafness, triggered by emotional stress (acoustic)
  - LQT3: SCN5A – (INa) triggered by rest, sleep
  - Sx include pre-syncpe/syncope, sudden cardiac death, general population screening not indicated
  - Treatment: beta blockers, ICD if previous cardiac arrest and expected survival > 1 year (Circulation 2006;114:e385)

- **Drug-Induced Prolonged QT Interval** (Heart. 2003;89:1363; https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf)
  - Drugs inhibit IKr causing prolonged ventricular repolarization and exaggerate heterogeneity in repolarization times in different layers of myocardium leading to reentry and tachyarrhythmia
  - Torsades de Pointes: Polymorphic VT in setting of prolonged QT; unstable rhythm that can lead to vfib

- **Monitoring for QT/QTc Prolongation**
  - Check QTc before and 12 hours after initiation/increased dose of QT-prolonging drug. Continued monitoring if prolongation is seen.
  - Class I indications for QTc monitoring with ECG (Circulation 2004;110:2721)
    - Initiation of QT-prolonging medication and dose changes Q8-12H
    - Overdose of proarrhythmic drug
    - New bradyarrhythmia
    - Severe hypokalemia or hypomagnesemia

- **Management of Acquired LQTS**
  - Offending drug should be stopped if QTc > 500 ms or increase in QTc of > 60 ms; ECG should be checked for bradyarrhythmias and signs of impending TdP (P on T); electrolytes checked and repleted
  - Supratherapeutic repletion of K+ to 4.5 to 5.0 can be used in pts on QT-prolonging drugs who have had TdP
### Cardiology

**Chest Pain**

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stable Anginal/ACS</strong></td>
<td></td>
</tr>
<tr>
<td>Abrupt onset of tearing/sharp/ripping thoracic or abdominal pain, known aneurysm, Marfan syndrome, HTN. Men 2x &gt; women, age 60s-80s, cocaine use, high-intensity exercise (weight lifting).</td>
<td></td>
</tr>
<tr>
<td><strong>Acute Pericarditis</strong></td>
<td></td>
</tr>
<tr>
<td>Pleuritic, sharp, improves upon leaning forward. May have URI prodrome, though consider bacterial pericarditis if high fevers.</td>
<td>Friction rub (breath hold to distinguish from pleural rub); tachycardia, tachypnea, hypoxemia</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td></td>
</tr>
<tr>
<td>Sudden onset, dyspnea/hypoxemia, pleuritic, hx of cancer/recent surgery/immobility, +/- Tnt.</td>
<td>Ipsilateral absence of breath sounds/deviation of trachea (if tension, contralateral deviation)</td>
</tr>
<tr>
<td><strong>Pneumothorax</strong></td>
<td></td>
</tr>
<tr>
<td>Sudden onset, 20-40 yo (spontaneous and more likely if tall), family or personal history, smoker, known emphysema, men &gt; women, recent chest procedures/lines.</td>
<td>Bronchial breath sounds, rales, dullness</td>
</tr>
<tr>
<td><strong>Pneumonia/pleuritis</strong></td>
<td></td>
</tr>
<tr>
<td>Sharp, pleuritic CP associated with fever/leukocytosis, productive cough, recent radiation, autoimmune (SLE, RA, drug-induced lupus, collagen vascular diseases).</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac: HOCM, AS, vasospasm (Prinzmetal’s angina or drug/toxin), Takotsubo CM, cardiac syndrome X; MSK: Costochondritis, Zoster, Gi: GERD, esophageal spasm (may be relieved by TNG), Boerhaave’s, PUD, biliary colic, pancreatitis; Psych: panic attack</td>
<td></td>
</tr>
</tbody>
</table>

**ECG:** Compare w/prior ECGs & check q10-15m if suspt, but <50% sens for dx of acute MI. Check posterior (if STD in V1-3 or R’S in V1-2) or R-sided leads (if STE in II/III/aVF) to better evaluate LCx/RCA

**Non-diagnostic**

**CXR**

**Widened mediastinum**

**PNA**

**PTX**

**Biomarkers**

**ACS Pathway**

**Non-Invasive Tests**

**Stress Test:** used to rule ACS if pt low-intermediate risk (neg biomarkers).

**Coronary CTA:** 100% NPV in pt w/o CAD. No Δ in LOS or ED if NC rate vs hs-Tn (JACC 2016;67:16). CTA reduces 5yr CHD mortality in pts w/stable angina (NEJM 2016;379:924).

**High-Sensitivity Troponin (hs-cTn)**

MGH ED: Obtain at 0 and 1hr. Rules-in if any cTn ≥52 ng/L or if 1hr Δ >5;

R/o if <10 (©) or <12 (©©) AND 3hr Δ <3. If no r/o or r/o at 1hr, obtain third cTn 3hrs from the first.

MGH Inpatient: Obtain at 0 and 3hrs. Rule if >10 (©) or >15 (©©) AND Δ >7, AND either sx of ischemia, ischemia on ECG, or imaging c/w CAD. **High-STEACS Study:** ≥5 ng/L at presentation, Δ ≥3, or >99% at 3hr showed improved outcomes vs less-strict criteria.

Caveat: intro of hs-cTn, w/ rule-in threshold of cTn ≥99% ULN, may not improve 1-yr mortality vs low-sens cTn (Lancet 2018;392:919).

**CT-PE**

NPV in PE 60%/89%/96% for high/intermediate/low risk (PIOPED II).

Sn 97-100%, Sp 83-100% for aortic dissection (NEJM 1993;328:35).

**Echo**

Useful for assessing valvular disease, RV strain (in PE), and EF. TEE first test if evaluating prosthetic MV, suspected proximal aortic dissection (can eval aortic root and valvular function).

**Biomarkers**

**STEMI**

New ≥1mm STE in any 2 consecutive leads compared to prior ECG (see ACS chapter)

**NSTEMI/UA**

0.5mm STD or TWI in 2 consec leads

**Angiography**

Used to rule ACS in **high risk pts** (NB: all pts with confirmed ACS should undergo angiography). Use GRACE, TIMI, HEART and Mayo Clinic CPC score for risk stratification.
Myocardial infarction: 4th universal definition (Type 1-5): myocardial necrosis (trop >99th percentile + Δ) w/ ischemia [EHJ 2019;40:237]

- Type 1 MI: spontaneous MI (plaque rupture, ulceration, fissure, erosion, dissection ➔ intraluminal thrombus)
- Type 2 MI: supply-demand mismatch – supply may be compromised by dynamic obstruction (e.g., vasospasm), microvascular ischemia (e.g., Takotsubo), non-plaque thromboembolism (e.g., infectious, via PFO), coronary dissection, vasculitis, vascular steal
  - Must be a clear precipitating factor. If there is no identifiable precipitant, treat as a type 1 MI until further evaluation.
  - With widespread introduction of hs-troponin assays in the U.S., type 2 MI may now be more prevalent than type 1 MI.
  - Differs from myocardial injury. T2MI requires evidence of ischemia (EKG changes, symptoms, or new regional wall motion abnormalities on cardiac imaging).
  - Associated with poor outcomes: 1-year mortality rates are 20% and at 5-year 60%, high readmission rate.
  - Currently no proven treatment strategies for type 2 MI and no guidelines for management. 50-70% have obstructive CAD; reasonable to initiate ASA, BB, and high-intensity statin. The utility of PCI uncertain (ongoing ACT-2 trial)

<table>
<thead>
<tr>
<th>Evaluation of CP with hsTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Department – CP onset ≥3h PTA</td>
</tr>
<tr>
<td>Check hsTnT immediately and at 1h</td>
</tr>
<tr>
<td>Rule in: hsTnT ≥52 OR Δ ≥5 from baseline</td>
</tr>
<tr>
<td>Rule out: hsTnT &lt;10(F) or &lt;12(M) AND Δ &lt;3 from baseline</td>
</tr>
<tr>
<td>Intermediate: calculate HEART score, repeat hsTnT in 3h and apply inpatient criteria (right)</td>
</tr>
</tbody>
</table>

MGH Suspected STEMI Protocol

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>Unstable Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mm STE in two contiguous leads (if V2-V3: &gt;2.5mm in men&lt;40, 2mm in men&gt;40, 1.5mm in women) or New LBBB AND (+) biomarkers</td>
<td>+ ECG or hx, (+) biomarkers</td>
<td>+ ECG or hx, (-) biomarkers</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Evaluation and Risk Stratification:
- Consider patient’s baseline CAD risk. Review prior stress test and cath data. (NB: association found between respiratory infections, esp flu, and MI) [NEJM 2018;378:345]
- Treat secondary causes of myocardial demand

Electrocardiography: [NEJM 2003:348:993] obtain serial tracings; q15-30min if initial ECG non-diagnostic in pts with compelling hx and sx
- Non STE ischemic EKG changes: ≥0.5 mm ST depressions (horizontal or downsloping more concerning), new TWI ≥1 mm, or normalization (“pseudonormalization”) of prior TWI in setting of sx

Cardiac Biomarkers:
- hsTnT = ng/L, 4th gen TnT =ng/mL (hsTnT 50 = TnT 0.03)
- hsTnT 99th percentile among normal subjects: Men: 15 ng/L, Women: 10 ng/L
- 75% of healthy individuals will have a measurable hsTnT

EKG Territory | Supplied by (coronary artery) | Notes |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>V2-V4</td>
<td>Septal-Anterior</td>
<td>Proximal-mid LAD</td>
</tr>
<tr>
<td>V5-V6</td>
<td>Apical</td>
<td>Distal LAD, Distal LCx, RCA</td>
</tr>
<tr>
<td>I, aVL</td>
<td>Lateral</td>
<td>LCx (proximal)</td>
</tr>
<tr>
<td>II, III, aVF</td>
<td>Inferior</td>
<td>RCA (85%), LCx</td>
</tr>
<tr>
<td>V7-9</td>
<td>Posterior</td>
<td>LCx &gt; RCA</td>
</tr>
<tr>
<td>V3-4R</td>
<td>RV</td>
<td>RCA, LCx</td>
</tr>
<tr>
<td>aVR, V1</td>
<td>L main or 3v disease</td>
<td>aVR&gt;V1 STE with diffuse ST depressions = LMCA, 3VD or diffuse ischemia</td>
</tr>
</tbody>
</table>

- Posterior leads (V7-V9, “inverse” of V1-V3 on back below scapula); LCx (less commonly RCA) can be electrically silent on conventional ECG⇒check posterior leads in setting of cTn elevation and compelling hx with non-diagnostic ECG (Class IIa)
- R-sided leads (V3R-V6R mirrors L-chest leads): check with inferior STEs to eval for RVMI; STE in V1 + STD in V2 very specific for anterior STE
- Pre-existing LBBB: [NEJM 1996;334:481, Ann Emerg Med 2008;52:329] Sgarbossa criteria: ≥1mm concordant STE in any lead (5 pts); ≥1mm ST depression in V1, V2 or V3 (3 pts); ≥5mm discordant STE in any lead (2 pts). Score ≥3 is 90% Sp for acute MI. Variable Sn of 20-79%. Doesn’t apply to pacers.
- Pre-existing RBBB: Interpret ECG as if there were no BBB. If deep discordant ST depressions in V1-V3, check posterior leads
- deWinter’s T-waves: 2% of STEMs w/tall symmetric T-waves + >1mm STD at J-point in precordial leads +0.5-1mm STE in aVR, may evolve to STEs, consistent w/ acute LAD occlusion [NEJM 2008:359:2071]
- Wellen’s pattern: Symmetric, deeply inverted T waves in V2, V3 (75%) > biphasic T waves (25%)
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- **Wellen’s syndrome**: (Am Heart J 1982;103:730) Wellen’s pattern in pts presenting w/ CP w/ resolution indicates reperfusion of myocardium indicative of LM or proximal LAD stenosis. 75% of pts will have ant MI in days-weeks if not treated. Proceed to cath lab w/o stress testing. **DDx**: apical HCM, elevated ICP (w/ long QTc & brady), MI, PE, post-tachy/pacing, BBB, WPW, idiopathic

**Risk Stratification for PCI Timing in NSTEMI/UA:**

- **Multiple risk models: GRACE, TIMI, PURSUIT, AMIS**
  - GRACE score, based on predictors of 6 mo mortality in pts w/ ACS – age, HR, SBP, Cr, cardiac arrest ?, ST deviation, elevated troponin (BNJ 2006;333:1091)
  - 4 subgroups for urgency to get to the cath lab (JACC 2014;64:a139)
  - **Very high risk** ("immediate invasive," within 2 hrs): Refractory/recurrent angina, hemodynamic or electrical instability
  - **High risk** ("early invasive," within 24 hrs): temporal change in troponin, EKG changes (STD, TWI), high risk pt (GRACE>140)
  - **Conflictng results between TIMAC (NEJM 2009;360:2165) and VERDICT (Circ 2018;138:2741)** trials about outcome benefit of early cath. However both showed improved outcomes with early cath in patients with GRACE >140.
  - **Intermediate risk** ("delayed invasive," within 72 hrs): none of above but risk factors at baseline (ie EF <40%, GFR <60)
  - **Low risk** ("ischemia guided," no cath): no risk factors, GRAACE <109, TIMI 0-1

**Thrombolytic indications**: STEMI only (worse outcomes in NSTEMI), w/ angina >30min and <12h (no benefit after 12h), when projected time to PCI>120min. Rescue PCI indicated for failed lysis of STEMI (persistent symptoms, STE <50% resolved at 60min post-lysis) (NEJM 2005;353:2759).

- **PCI Indications: Recommended over fibrinolysis when at a PCI-capable center (1A).** PCI w/ 20% lower rate of combined cardiac endpoint, 65% ↓ rate CVA vs. lysis when performed at high-volume (>400/yr) center (JAMA 1997;278:2093, Lancet 2003;361:13)
  - STEMI: PCI if <12h sx onset, goal to PCI ideally <60min at PCI centers. PCI regardless of time from onset for cardiogenic shock, malignant arythmia, persistent STE and/or CP. Late PCI (>48h post-event) generally not indicated in stable pts. (NEJM 2006;355:2395)
  - **NSTEMI/UA**: See Risk Stratification in NSTEMI/UA above above

**PCI Strategies:**

- Primary stenting (culprit lesion): current standard of care: radial > fem access, DES > BMS (NEJM 2016;375:1242).
  - Non-culprit lesions: Pts w/ MI + cardiogenic shock had decreased risk of death/RRT with culprit-lesion-only PCI than immediate multi-vessel PCI (NEJM 2018;379:1699).
- **Chronic Total Occlusions (CTO):** PCI only if severe ischemia despite OMT w/ non-3VD equivalent and viable tissue (Eur Heart J 2018;39:2484).
  - No difference in LVEF at 4 months in STEMI non-culprit CTO intervention (JACC 2016;68:1622).

- 2VD with proximal LAD stenosis or EF<50%; large area of viable myocardium or high risk (all class I). Consider if DM + 2VD (NEJM 2012;367:2375)

**Adjuncts to Reperfusion Therapy:**

- **ASA**: Established mortality benefit, give to all patients in an immediate load/maintenance (325mg/81mg) strategy (Lancet 1998;2;8607).

- **P2Y12 Inhibitors**: (AB) Controversial if pre-cath load is beneficial, may delay CABG by 5-7 days. Consult with fellow before loading.
  - Ticagrelor: Decreased mortality compared to clopidogrel w/o increasing major bleeding. Not a prodrug, reversible with platelet bxfn. Common side effect is mild dyspnea on initiation. Avoid in liver disease, previous stroke, oral AC (NEJM 2009;361:1045).
  - Prasugrel: Prodrug, lower rates of MI and stent thrombosis but ↑ bleeding compared to clopidogrel in PCI (NEJM 2007; 357:20) if medical mgmnt. only for UA/NSTEMI, no difference in outcome compared to clopidogrel (NEJM 2012; 367:1297).
  - Cangrelor: IV reversible inhibitor w/ immediate onset and return of nl plt function in 1h. Improved outcomes compared to clopidogrel (NEJM2013;69:1115).

- **TNG**: SL x 3, transition to gtt if refractory CP. Nitropaste and gtt have shorter half-life than SL if c/f hypotension. No mortality benefit; caution in IMI/RMI, SBP<100 or PDE inhibitor use in last 48h. If continued CP despite ↑ dose of TNG, indication for earlier cath.

**Anticoagulation:**

- **UFH**: trend towards mortality benefit in meta-analyses, optimal duration undefined. Usually stopped after 48h if ECG changes improving and concern for ongoing ischemia resolved (BMJ 1996;313:652).
- **LWMH**: possible reduction in death w/ min evidence for ↑ major bleeding, trials vs. UFH largely null (BMA 2012; 344:e653).
- **Fondaparinux**: preferred to UFH/LMWH if medically managed. Contraindicated in PCI 2/2 ↑ catheter thrombosis/complications (JAMA 2006; 295:1519).
- **Iblllia Inhibitors**: Epifibatide (Integrilin) used at MGH. Consider at PCI if high-risk (extensive thrombus). Usually initiated in cath lab as upstream tx provides no mortality benefit and ↓ bleeding risk. Can consider in place of P2Y12 inhibitor if possible CABG (NEJM 2009;360:2176)
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- **Bivalirudin**: direct thrombin inhibitor, bivalirudin + IIb/IIa showed 30-day mortality/complication benefit over heparin+IIb/IIa in invasively managed pts, but ↑ risk of in-stent thrombosis (NEJM 2013; 369:2207). Preferred for HiT+ patients, otherwise cost does not outweigh benefit.

- **Beta-blockers**: start within 24h (1b); mortality benefit; caution in decompensated HF, ↑ risk for cardiogenic shock (age >70, SBP<120, HR>110 or <60); other contraindications to BB include: cocaine-induced MI, PR>240ms, 2° or 3°AVB, severe bronchospasm (Lancet 2005;366:1622).

- **ACE-I or ARB**: start within 24h if BP/renal function normal (2b), but mortality benefit maximal if EF<40%, pulm. edema, or anterior MI (1a) (Lancet 1995; 345: 669).


- **Morphine**: Consider only if unacceptable level of pain refractory to NTG, careful if suspicious for IMI/RVMI. May reduce antplatelet action, risk of higher mortality (retrospective data) (Am Heart J 2005;149:1043, Eur Heart J 2016;37:245).

- **Discontinue NSAIDs**: NSAIDs ↑ risk of mortality, re-infarction, CHF, and myocardial rupture after ACS.


**VEST trial**: no ↓ in arrhythmic death to wearable cardioverter-defibrillator in pts w/ recent MI and reduced EF (NEJM 2018; 379:1205).

**Secondary Prevention:**

- **Aspirin**: aspirin 81mg w/out enteric coating indefinitely (NEJM 2010; 363:930). ASA 81mg prevents vascular events in pts weighing <70kg; higher doses only effective in pts >70kg (Lancet 2018; 392: 387).

- **Dual antiplatelet therapy (DAPT)**: Guidelines recommend 6-12 mo DAPT after DES (JACC 2016; 68:1082-1115, JACC 2011;58:24). DAPT duration ultimately based on individual patient risks – high ischemic/low bleeding risk may benefit from DAPT x 30 mo, high bleeding/low ischemic risk may benefit from DAPT x 3-6mo (use DAPT score to help stratify) (NEJM 2014;371:2155, NEJM 2015;372:1791). In pts treated w medical mgmt. alone (DAPT) following NSTEMI, Ticagrelor>Plavix.

- **Beta-blockers**: start in all pts w/out contrain (1b); no trials assessing appropriate length, usually continued indefinitely.

- **ACE-I/ARBs**: start in all pts (2b), but stronger recommendation (1a) in anterior STEMI, EF≤40%, stable CKD, HTN, or DM; no trials assessing appropriate length, usually continued indefinitely in pts with stronger (1a) indications (NEJM 2000;342:145, Lancet 2003; 362:782, Arch Intern Med 2006;166:787).

- **Aldosterone antagonists**: indicated post-MI w/LVEF≤40% plus symptomatic HF or DM if already on ACE-I/ARB (1a).

- **Lipids**: High intensity statin (atorvastatin 40-80mg or rosuvastatin 20-40mg daily) indefinitely for patients ≤75y post-MI and moderate intensity in >75y (JAMA 2001;285:1711). Updated lipid guidelines recommend in very high risk clinical ASCVD pts w/ LDL>70 mg/dL adding first ezetimibe and then considering PCSK9 inhibitor (JACC 2018;epub, NEJM 2015;372:2387; NEJM 2018;epub).

- **Triple oral antiocoagulant therapy (TOAT)**: grade 2c. For patients w_AFib, 1-12mo triple therapy is recommended depending on bleeding risk. If high bleed risk, triple therapy for 1 month, then consider clopidogrel+Vanicog w/o ASA x 11 months (Lancet 2013;381:1107). RE-DUAL PCI found that dual therapy with dabigatran + P2Y12 inhibitor led to lower risk of bleeding and was non-inferior to TOAT for risk of thromboembolic events (NEJM 2017; 377:1513).

- **CAD**: In pts w/ stable CAD, Rivaroxaban (2.5mg BID) + ASA v ASA alone has improved cardiovascular outcomes but increased risk of bleeding. Rivaroxaban alone (5mg BID) v ASA alone had no cardiovascular benefit and ↑ bleed. (NEJM 2017; 373:1319-1330).

- **Additional**: smoking cessation, BP <130/80 (start treatment if >140/90), cardiac rehab (1c), depression screening (1b).

**MGH P2Y12 Switching Guideline**

**Peri-operative P2Y12 Bridging**

**NOTE**: This guideline does NOT necessarily apply to triple antithrombotic therapy patients

**CONTINUE aspirin 81mg throughout**

**STOP clopidogrel**

**STOP prasugrel**

**START cangrelor**

**SURGERY**

**LOAD clopidogrel**

**LOAD prasugrel**

**NOTE**: **PATIENT SHOULD TAKE LAST DOSE ON THIS DAY, THEN STOP**

**start cangrelor**: initiate at a dose of 0.75 mcg/kg/min (NO bolus) for a minimum of 48 hours and a maximum of 7 days.

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

**only resume cangrelor** if oral administration is NOT possible (patient NPO, patient not absorbing oral medications).

**consider concomitant PPI therapy** if patient is high-risk for GI bleeding.

Anna O’Kelly, Leslie Chang, Cian McCarthy, Jonathon Salik
# Acute Coronary Syndrome

## Acute Setting – within 30 days of index event

**NOTE:** This guideline does NOT necessarily apply to triple antithrombotic therapy patients

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

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

$^2$IF there is concern for lack of absorption of initial LOADING DOSE of oral P2y12 at time of cangrelor initiation and patient is not at high bleeding risk, could consider bolusing with 30 mcg/kg before starting infusion

$^3$Please note that the dose of cangrelor recommended for use in the cardiac catheterization lab is different than the recommended bridging dose. The doses listed here are for **bridging**. The cardiac catheterization PCI dosing is 30 mcg/kg followed by a 4 mcg/kg/min infusion until cardiac catheterization is complete, or 2-4 hours, whichever is longer. Then, the drip rate is dropped to 0.75 mcg/kg/min OR a loading dose of an oral agent is given.

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

## Chronic/Maintenance Setting – more than 30 days after index event

**NOTE:** This guideline does NOT necessarily apply to triple antithrombotic therapy patients, please discuss switching strategies for these individuals on a case-by-case basis

<table>
<thead>
<tr>
<th>Agent switching FROM/STOPPING</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
<th>Cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td></td>
<td>90 mg BID 24 hours after last dose of clopidogrel</td>
<td>10 mg daily 24 hours after last dose of clopidogrel</td>
<td>Start 0.75 mcg/kg/min 48 hours after discontinuation</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>600 mg 24 hours after last dose of ticagrelor$^4$, then 75 mg daily</td>
<td>60 mg 24 hours after last dose of ticagrelor, then 10 mg daily</td>
<td>Start 0.75 mcg/kg/min 48 hours after discontinuation</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>75 mg daily 24 hours after last dose of prasugrel$^4$</td>
<td>90 mg BID 24 hours after last dose of prasugrel</td>
<td>Start 0.75 mcg/kg/min 96 hours after discontinuation</td>
<td></td>
</tr>
<tr>
<td>Cangrelor</td>
<td>600 mg at time of drip discontinuation, then 75 mg daily</td>
<td>180 mg at the time of drip discontinuation, then 90 mg BID</td>
<td>60 mg at time of drip discontinuation, then 10 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

$^4$If switch is for high risk of bleeding/active bleeding, could consider starting clopidogrel 75 mg 24 hours after last dose of ticagrelor or prasugrel. *Consider concomitant PPI therapy if patient on triple therapy or high-risk for GI bleeding
### Cardiology

#### MI Complications (JACC 2013;61:e78)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevalence / Risk Factors</th>
<th>Timing / Clinical Signs</th>
<th>Evaluation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Complications (Hours – Days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Cardiogenic Shock (see CHF chapter) | STEMI ~6%  
NSTEMI ~3%  
Anterior MI, LBBB, prior MI, 3vDz, age, HTN, DM, mechanical complications (see below)  
Accounts for 50% post-MI death | STEMI: 50% develop shock w/in 6 h of MI, 75% w/in 24 h  
NSTEMI: 72-96 h after MI  
New onset CP, cold/wet physiology, hypotension, tachycardia, dyspnea, JVD, rales (66%), new murmur | TTE  
PA catheter | Inotropes/pressors  
Emergent PCI, CAGB (>75y + STEMI + shock w/in 36h of MI). (NEJM 1999;341:62)  
IABP and other MCS |
| Myocardial Free Wall Rupture (Pseudoaneurysm: LV defect contained by only pericardium/scar, more prone to rupture than aneurysm) | 0.5% in modern era  
Transmural MI, 1-vessel MI, 1st MI (poor collaterals), anterior and lateral MI, HTN, late thrombolysis (>14 h), fibrinolysis>>PCI, NSAIIds, female, >70 y  
Accounts for 10% post-MI death | 40% w/in 24h, 85% w/in 1 week  
Tamponade in 85%  
Olivia’s triad: pericarditis, repetitive emesis, restlessness/agitation (PPV 95% w/ 2/3). (JACC 1993;22:720)  
Electromechanical dissociation, aberrant T wave evolution, abrupt episodes of J-HRBP | TTE  
STAT cardiac surgery consult | Emergent surgery |
| Interventricular Septal Rupture → VSD | 0.2-3%  
1st MI, 1-vessel MI (esp. LAD), anterior infarct w/ inferior STE  
2/2 wrap-around LAD, older age, female  
Accounts for 5% post-MI death | Bimodal: 24 h and 3-5 days (can occur up to 2 weeks out)  
New, harsh holosystolic murmur (50% w/ thrill), S3, loud P2, hypotension, BIV failure (R>L) | TTE w/ Doppler  
RHC: O2 sat step-up between RA and PA >5 suggestive | IABP  
Vasodilators (use cautiously to decrease L to R shunt (nitropresside preferred) |
| Papillary Muscle Rupture → acute MR | 1%  
Posterior (supplied by PDA, a/w inf. or post. MI) >> Anterolateral (dual blood supply by LAD and LCx)  
Accounts for 5% post-MI death | No reperfusion: 2-7 d  
With reperfusion: median 13 h  
Abrupt dyspnea, pulmonary edema, hypotension  
Hyperdynamic LV, holosystolic murmur at apex, (radiates to LSB w/ posterior pap muscle rupture) possible thrill, murmur may be absent in severe HF | TTE  
CXR: edema (can be asymmetric to RUL if MR jet directed at right pulm veins)  
Large v wave | Aggressive afterload reduction (nitropresside)  
IABP  
Emergent surgery |
| **Late Complications (Weeks-Months)** |
| LV Aneurysm (can be acute or chronic) | No reperfusion: 10-30%  
Apical transmural > posterior-basal Mls, steroids, NSAIIds | Days to weeks  
Acute: diffuse, displaced PMI, S3 and/or S4, MR murmur, CHF  
Chronic: HF, VT/VF, systemic embolization, may be asymptomatic | ECG w/ persistent STE  
TTE | Acute: management of CHF, ACEI, avoid NSAIIds/steroids, heparin (if EF<35%)  
Chronic: ACEI, digoxin, diuretics, warfarin (if EF<35%) |
| LV Thrombus | Occurs in 15% of AMI pts post-PCI  
Usually in LV apex  
Large infarct size, severe apical akinesis or dyskinesis, LV aneurysm, anterior MI | Can occur within 24 h  
90% of thrombi are formed at a maximum of 2 weeks  
Embolization risk persists for chronic LV thrombus for 6 mo, occurs in 3%, but most at <4 mo. | Sens TTE, TEE, CMR 23%, 40%, 88% respectively (Am Heart J 2006;152:75)  
Anticoag (INR 2-3)  
When to stop anticoag unclear, check for resolution of thrombus on TTE at 3-6 mos. |  |
| Pericarditis | See Pericardial Disease Section | 10% at 2-4d post-transmural MI  
May be focal or diffuse  
Dressler’s syndrome: late autoimmune carditis, rare | See Pericardial Disease Section | ASA + colchicine  
Caution with NSAIIds ( ASA anti-plt effects) and steroids (thins scars with risk of rupture) |

#### Electrical Complications
**Overview:**
- Bradycardia/conduction block: may be due to coronary artery occlusion (see below) or Bezold-Jarisch reflex (Anes 2003;98:1250)
- Tachyarrhythmia: related to creation of re-entrant circuit from scar formation and/or ↑ automaticity from adrenergic surge

<table>
<thead>
<tr>
<th>Circuit</th>
<th>Artery Supplied By</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus Node</td>
<td>RCA in 60% of pts, LCx in 40% of pts</td>
</tr>
<tr>
<td>AV Node</td>
<td>Distal RCA in 90% of pts, distal LCx in 10% of pts</td>
</tr>
<tr>
<td>Bundle of His</td>
<td>AV nodal artery (RCA), LAD septal perforators</td>
</tr>
<tr>
<td>RBB</td>
<td>LAD septal perforators, collaterals from RCA/LCx</td>
</tr>
<tr>
<td>LBB</td>
<td>LAD</td>
</tr>
<tr>
<td>LAFB</td>
<td>LAD septal perforators, 50% w/ AV nodal collaterals</td>
</tr>
<tr>
<td>LPFB</td>
<td>Prox AV nodal arteries, distally dual supply from LAD/PDA septal perforators</td>
</tr>
</tbody>
</table>

Maeve Jones-O’Connor  
19
<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Location/Mechanism</th>
<th>Incidence/Timing</th>
<th>Treatment/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus bradycardia</td>
<td>Anterior or inferior MI</td>
<td>Up to 40% of acute MI</td>
<td>Atropine, atrial pacing if Sx/ unstable, dopamine if also hypotensive.</td>
</tr>
<tr>
<td>First degree AV block</td>
<td>Inferior: ↑ vagal tone or AV node ischemia (RCA) → narrow QRS</td>
<td>More common in inferior MI</td>
<td>If 2/2 inferior MI, transient (vagal). Usually continue CCB or B-blockers unless PR interval is longer than 240ms.</td>
</tr>
<tr>
<td>Second degree AV block (Mobitz Type I)</td>
<td>Usually inferoposterior MI (↑ vagal tone → narrow QRS)</td>
<td>Usually within first 24h of MI</td>
<td>Usually transient; observe. Atropine if symptoms or HR &lt; 45.</td>
</tr>
<tr>
<td>Second degree AV block (Mobitz Type II)</td>
<td>Usually anterior MI with infranodal conduction injury, wide QRS, HR often &lt; 30, 33% progress to CHB</td>
<td>Usually within first 24h of MI</td>
<td>Consider temporary pacing. In infranodal block, atropine may paradoxically worsen AV block.</td>
</tr>
<tr>
<td>Third degree AV block</td>
<td>If inferior MI: intra-nodal lesion; narrower QRS escape</td>
<td>3-7% acute MI</td>
<td>Recovery 3-7 days; temp pacing required.</td>
</tr>
<tr>
<td></td>
<td>If anterior MI: intra-nodal lesion; wide, unstable escape rhythm</td>
<td>Inferior: gradual, stable, more common</td>
<td>- Inferior: more benign, resolves on own. - Anterior: carries high mortality rate (80%) b/c indicates extensive necrosis.</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>Persistent sinus tach, may be compensatory for LV dysfun, common in anterior MI</td>
<td>25% of acute MI</td>
<td>Undesirable b/c decreases coronary perfusion time, increases O2 demand, and may worsen ischemia. Treat underlying cause.</td>
</tr>
<tr>
<td>Atrial premature beats</td>
<td>May reflect ↑ LA pressure</td>
<td>6-8%, may be &gt;30% of acute MI</td>
<td>Associated with mortality, particularly if late (&gt;30d) afib (Circ 2011;123:2094).</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Early: due to atrial ischemia</td>
<td>Variable</td>
<td>Correct electrolyte deficits. Do NOT treat with class I anti-arrhythmics → aw increased mortality in CAST Trial (NEJM 1991;324:781).</td>
</tr>
<tr>
<td>Premature Ventricular Contractions</td>
<td>Due to electrical instability and increased sympathetic tone</td>
<td>Up to 20% of STEMI</td>
<td>Do not treat unless symptomatic or hemodynamically unstable, usually short duration and does not affect prognosis.</td>
</tr>
<tr>
<td>Accelerated Idioventricular Rhythm (AIVR)</td>
<td>50-110bpm, higher V- vs. A-rate; in 40%, considered a reperfusion rhythm</td>
<td>Up to 20% of STEMI</td>
<td>Antiarrhythmic agents; cardioversion/defibrillation to prophylax against VF and restore hemodynamic instability, correct underlying abnormalities (pH, K).</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>Monomorphic VT&lt;170bpm is unusual early after STEMI; suggests pre-existing arrhythmogenic scar (mono VT) vs recurrent ischemia (poly VT)</td>
<td>NSVT 1-7%, sustained VT (2-3% of STEMI, &lt;1% NSTEMI)</td>
<td>Antiarrhythmic agents; cardioversion/defibrillation to prophylax against VF and restore hemodynamic instability, correct underlying abnormalities (pH, K).</td>
</tr>
<tr>
<td>Ventricular Fibrillation</td>
<td>Risk Factors: ↑ age, prior MI (scar), anterior MI, cardiogenic shock, ↓ LVEF, CKD</td>
<td>5% of STEMI</td>
<td>ACLSi: defibrillation, anti-arrhythmic infusion (24-48h amiodarone post-defibrillation); maintain K&gt;4, Mg&gt;2.</td>
</tr>
</tbody>
</table>

**MILLIS trial: prediction of complete heart block (Am J Cardiol 1986;57:1245)**

<table>
<thead>
<tr>
<th>Point</th>
<th>Incidence</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.2-6.8%</td>
<td>36%</td>
</tr>
<tr>
<td>1</td>
<td>7.8-10%</td>
<td>25-30%</td>
</tr>
<tr>
<td>2</td>
<td>≥3 points</td>
<td>≥3 points</td>
</tr>
</tbody>
</table>
Anatomy

- LCA and RCA w/ their branches create two rings around the heart: RCA + LCX in AV plane; LAD + PDA in IV plane (see above)
- 80% of PDA arises from RCA (right dominant), thus inferior MI more likely from RCA lesion

Preparation for Catheterization

- NPO pMN; INR<2; monitor Cr and eGFR closely pre-procedure, no ppx ABX. Continue ASA, statin, BB, heparin. Hold metformin (usually 1 day pre-proc, 2 days post-proc). May need to hold or delay initiating ACE-I.
- Document bilateral radial, femoral, popliteal, DP pulses, and Allen's test prior to cath. Note bruit, hx of: HIT, PVD, Ao aneurysm/dissection
- Pre-hydration w/ crystalloids and NAC/Bicarb have not shown to prevent CIN in most patients with moderate CKD (Lancet 2017; 389:1312; NEJM 2018; 378: 603; CIN risk calculator; Diagnostic cath = 25 cc contrast (CT-PE = 190 cc)
- Contrast allergy: Pre-treatment with steroids, H1, and/or H2 blockers if patient has documented allergy, see MGH 13h protocol. Consult allergy service for expedited protocol if the cath is required emergently.
- Respiratory distress: Patient will need to lie flat; consider intubation if prohibitive hypoxemia/pulmonary edema

Percutaneous Coronary Intervention Considerations

- Access: Fewer bleeding/vascular complications if radial (vs. femoral), possible decreased death in ACS. (JACC 2018;71:1167)
- BMS vs. DES: DES have↓ in -stent thrombosis → subsequent ↓ revascularization; however, ↑ risk of late stent re-stenosis → requires longer duration of DAPT
- Contraindications to stents: predicted DAPT non-adherence, anticipated major surgery within treatment time, elevated bleeding risk
- Antiplatelet Tx: ASA indefinitely (JACC 2016;03.513)
  - No high bleeding risk:
    - BMS: add P2Y12 inhibitor (“DAPT”) for at least 1 month (stable ischemic heart disease), 12 months (ACS)
    - DES: add P2Y12 inhibitor (“DAPT”) for at least 6 months (stable ischemic heart disease), 12 months (ACS)
  - High bleeding risk:
    - BMS: add P2Y12 inhibitor (“DAPT”) for at least 1 month (stable ischemic heart disease), 6 months (ACS)
    - DES: add P2Y12 inhibitor (“DAPT”) for at least 3 months (stable ischemic heart disease), 6 months (ACS)
- Triple therapy is generally tailored based on individual patient risk and de-escalated as soon as possible to dual therapy (NEJM 2016;375:2423, NEJM 2017;377:1513)

Post-Procedure Care

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

Post-Catheterization Complications

- Access site complications: always inform the interventional fellow who performed the procedure, diagnose by U/S and exam
  - Hematoma: Mass w/out bruit. Apply compression. If unable to control, may require Fem-Stop device to apply external pressure.
  - Pseudoaneurysm: presents as pulsatile mass with bruit at access site. Treat with compression if <2 cm, may require thrombin injection or surgery if >2 cm. Urgent U/S and vascular surgery consult.
  - AV fistula: Presents as continuous bruit with no mass. Evaluate w/ U/S. Surgical repair is usually necessary.
  - Limb ischemia: From thrombus, dissection, or malpositioned closure device. Evaluate pulses, limb warmth, and PVRs.
  - Retroperitoneal bleed: presents within hours post-cath, often with hemodynamic instability +/- flank pain +/- ecchymoses, STAT CT A/P if stable. Transfuse, IV fluids, discussion with attending re: stopping/reversing anticoagulation.
- Non-access complications:
  - Inflection: more common in setting of vascular closure devices
  - Atheroembolism: eosinophilia; livedo reticularis; blue toes; mesenteric ischemia; acute, subacute, or chronic renal dysfunction
  - CIN: peak 7Cr 2-5d post contrast load, risk correlated with contrast load and initial GFR
  - Tamponade: post-cath hypotension from coronary or cardiac perforation. Check pulsus paradoxus (SBP Δ >10mmHg w/ inspiration), STAT TTE, alert cath fellow. Give IVF.
  - MI/CVA: due to in-stent thrombosis (MI) or distal embolization post-cath (CVA). Discuss all CP/neuro changes with cath fellow.
Cardiology

Non-Invasive Cardiac Testing

General Considerations

- **Indications:**
  - **Diagnose CAD:** Sx of stable angina in patients w/ intermediate or high risk of CAD. Not indicated for low risk or asympt. pts.
  - **Known CAD:** Stratify prognosis in new or changing sx c/f ischemia or post-MI prior to discharge (i.e., submaximal stress)
  - **Post-revascularization:** Pts w/ angina; asymptomatic pt if incomplete revasc or >2 years post-PCI / >5 years post-CABG
  - **Pre-op risk assessment:** Not routinely indicated; no evidence that revasc ↓ mortality or post-op MI for non-cardiac surgery. (NEJM 2004;351:2795)
  - **Other:** Newly dx HF/cardiomyopathy likely due to ischemia; functional capacity (for exercise prescription); viability testing

- **Contraindications:** untreated ACS, MI within 2d, high-risk or LM CAD, uncontrolled arrhythmia, acute CHF, severe AS or HOCM, recent DVT/PE, acute myo-/peri-/endocarditis, aortic dissection, uncontrolled HTN

- **Patient Preparation:** NPO 3h prior, longer if imaging or adenosine. Must reverse DNR/DNI for the test.
  - If the question is “Does this patient have CAD? → hold BB and nitrates
  - If the question is “How well are meds working in known CAD?” → continue BB and nitrates
  - Hold caffeine >12h for adenosine. Hold BB >24h for dobutamine (>48h for atenolol).

- **Caveats:**
  - Majority of vulnerable plaques are angiographically insignificant (<70% stenosis) → stress testing unable to identify the presence of these plaques (CTA more sensitive)
  - Angiographically significant (>70% stenosis) 3vD may produce false-negative vasodilator stress test → “balanced ischemia”

- **Positive Test Results:**
  - Optimize medical tx. Decision re: angiography/revascularization varies by patient (degree of sx, known stenosis, current meds).

### Schematic Approach to Noninvasive Cardiac Testing (adapted from UpToDate)

<table>
<thead>
<tr>
<th>Stress Modality</th>
<th>Imaging Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise (treadmill)</td>
<td>EKG, TTE, SPECT</td>
</tr>
<tr>
<td>Vasodilator (adenosine, regadenoson)</td>
<td>TTE, SPECT, PET, MRI</td>
</tr>
<tr>
<td>Inotropy (dobutamine)</td>
<td>TTE, SPECT, PET, MRI</td>
</tr>
</tbody>
</table>

**Contraindications**

- **Vasodilators:** Bronchospastic airway disease, hypotension, SSS, high degree AV block, and oral dipyridamole therapy (adenosine and A2A receptor agonists contraindicated). Theophylline and caffeine should be withheld 48 and 12 hrs, respectively.

- **Dobutamine:** Ventricular arrhythmias, recent MI (1-3 days), unstable angina, hemodynamically significant LVOTO, aortic dissection, and severe systemic HTN.
Exercise Tolerance Test (ETT) → EKG or imaging (TTE, SPECT)
- ETT preferred over pharmacologic testing if pt is able to reach goal exertion
- Additional information obtained during ETT: exercise duration, METs, BP/HR response, HR recovery, double product (HR x SBP), Duke Treadmill Score (estimates risk of CHD in patients w/chest pain undergoing treadmill stress testing)
  - Duke Treadmill Score = Exercise time (minutes based on the Bruce protocol) - (5 x maximum ST segment deviation in mm) - (4 x exercise angina [0 = none; 1 = nonlimiting; 2 = exercise limiting]) (NEJM 1991;325:849, Circulation 1998:98:1622)
- Low risk: score ≥ +5; Moderate risk: score from -10 to +4; High risk: score ≤ -11
- Protocols: Bruce (large changes in workload between stages); modified Bruce (for less fit pts adds stages of lower workload)
- Data:
  - Diagnostic if: >85% max-predict HR (220-age); peak double product (HR x BP) >20K; HR recovery (HRpeak – HRmin post-exercise) >12
  - Prognosis worse with: failure to achieve 5 METs, increased degree of STD, degree of symptoms, Duke score ≤ -11, LVEF <35%, transient LV dilatation, radionuclide testing showing lung uptake or 1 large (or 2 moderate) reversible defects
  - Increased probability of ischemia: increased # leads with STD; increased degree of max STD; decreased METs when EKG changes occur; ventricular ectopy during recovery; increased time to recovery of EKG; failure of SBP to rise with exercise

Pharmacologic Stress Test → imaging only (TTE, SPECT, PET, MRI)
a) Adenosine/Regadenoson
- Detects ischemia by coronary steal (vasodilation via cAMP) based on the principle that stenosed coronary arteries are unable to further dilate to adenosine and therefore have limited flow reserve to areas distal to the stenosis, producing a relative perfusion deficit
- May cause wheezing and bradycardia → caution with ACTIVE bronchospasm, high-grade AVB, SSS, bradycardia, severe AS
- Regadenoson: may have decreased respiratory or conduction side-effects, more cost-effective in obese patients. Caution with seizure hx as reversal agent used with Regadenoson (aminophylline) has increased risk of seizure.
- Balanced ischemia: False negative adenosine stress test may occur in 3Vd because no relative perfusion deficit exists since as all three vessels are affected equally
b) Dobutamine
- Workload induced by positive inotropy and chronotropy via beta-1 receptor agonism
- May cause tachyarrhythmias: Caution with MI<48h, hx of malignant arrhythmia, severe AS, HOCE, severe HTN, severe PAH

Cardiac CTA (CCTA)
- 2010 CTA Guidelines (JACC 2010:55:2663)
- Requires cardiac gating (goal HR 60-70, may need to give BB) and respiratory gating (for spatial resolution, breath hold for 5+ seconds)
- General Use/Indications:
  - Screening: CCTA should NOT be used to screen asymptomatic patients
  - Low Risk: CT has a high NPV (99%) in low-risk patients for CAD rule-out (JACC 2008:52:1724)
  - Moderate Risk: CCTA is reasonable for further risk stratification in patients at "intermediate" risk of CAD or patients with equivocal stress test results
    - In large prospective trial, 2-year ACS risk significantly elevated in pts with high-risk plaque (16%) and/or stenotic disease (6%) compared to patients with low-risk plaque/non-stenotic disease (0.6-1.4%) or no plaque (0%) (JACC 2015:28:337)
    - Several RCTs of CCTA vs. standard of care in pts with CAD (or acute chest pain with neg. EKG/troponin) showed similar 90d outcomes, cost of care, and length of stay between groups. Higher mean but decreased median radiation exposure. PROMISE (NEJM 2015:372:1291), ROMICAT-II (NEJM 2012:367:299), BEACON (JACC 2016:67:16)
    - CT less useful in patients with extensive calcifications or stented vessels due to "blooming" artifact (can't evaluate patency)
    - Fractional Flow Reserve (FFR) derived from CCTA closely approximates invasive FFR, providing possible functional data that may be used in decisions to revascularize (Am J Cardiol 2015:116:1469)
    - CTA in stable chest pain reduces non-fatal MIs and deaths from CAD (2.3% vs 3.9%) at 5 years significantly without resulting in a significantly higher rate of coronary angiography or coronary revascularization (NEJM 2018:379:924)
- NB: unlike stress imaging, CCTA (and cMRI) are NOT functional tests (i.e., they cannot discern ischemia) → they can only identify degree of stenosis within coronary vessels

Coronary MRI (cMRI)
- CCTA has higher Sn/Sp (85%/95%) than cMRI (72%/87%) for coronary stenosis (>50%) (Ann Intern Med 2010:152:167)
- cMRI is preferred for post-CABG vessel imaging → Sn/Sp 96%/92% for >70% graft stenosis. (Circulation 2003:107:1502)
- cMRI is also preferred for evaluation of suspected or known congenital or acquired coronary anomalies
- cMRI w/ stress detects significant stenosis (>50%) with Sn/Sp 83%/83% greater than stress echo (Circulation 1999:100:1676)

Viability Testing
- Utility: to determine the viability of ischemic myocardial tissue → “hibernating myocardium”
- Imaging Modalities: SPECT (thallium or sestamibi), PET, TTE, MRI
  - NB: SPECT performed using exercise or pharmacologic stress; PET/TTE/MRI performed using pharmacologic stress only
Reviewing the MGH Report: For questions or clarification of findings, call echo lab (x6-8871) or ask for on-call echo fellow (x6-9292)

- **Valvulopathy**: Look for stenosis/regurgitation (valve area, gradients, trace/mild/moderate/severe), leaflet numbers/motion, vegetations
- **Structure/chamber dimensions**:
  - AOSinus = aortic sinus
  - ASC AO = ascending aorta; → screening for aortic pathology
  - LVId = LV internal diameter in diastole
  - LVIds = LV internal diameter at end-systole → dilated (large) vs. LVH/HOCM (small)
  - PWT = posterior wall thickness → increased thickness seen in LVH, diastolic dysfunction
  - IVS = intraventricular septum
    - if ↑ along with ↑ PWT, consider diastolic dysfxn; if isolated ↑, consider HOCM
- **EF and WMA**:
  - “Preserved” EF≥50%; “Borderline” EF 40-50%; “Reduced” EF<40%. WMA territory correlates w/ coronary vessels (anterior+septal=LAD, inferior=RCA, lateral=LCx). If global WMA, r/o diffuse ischemia vs. non-ischemic insult (sepsis, stress)
- **RVSP**: RVSP=4v^2 + RA pressure (RAP assumed to be 10 mmHg, often not clinically accurate), where v=TR jet velocity. Clinically, often used as surrogate marker for pHTN (present if >35; not gold standard for dx and requires euvoeleva)

Clinical Syndromes and Echo Findings

- **Acute pulmonary embolism**: RV WMA/hypokinesis, McConnell’s sign, D sign, RV dilatation (RV:LV ratio >1), interventricular septal bowing, IVC collapse
  - McConnell’s Sign: RV free-wall akinesia w/ normal RV apex motion (77% Sn, 94% Sp for acute PE)
  - D Sign: septal flattening due to overloaded RV bowing into the LV (ventricular interdependence)
- **Tamponade**: large effusion, swinging heart, R-sided chamber collapse, interventricular septal bowing, dilated IVC (no ↑ w/ inspiration)
- **Stress (Takotsubo) cardiomyopathy**: LV apex ballooning and akinesis/hypokinesis
- **Heart Failure**: depressed EF, RV/LV hypertrophy and/or dilatation, regional WMA
  - E/A Reversal and elevated E/e' > 14; sign of diastolic dysfunction (i.e. elevated LVEDP and lower LV compliance)
  - 
- **E = mitral peak flow velocity during early passive LV filling (v wave on CVP tracing)**
- **A = mitral peak flow velocity during active LV filling from atrial systole (a wave on CVP tracing)**
- **e' = longitudinal velocity of mitral annulus during early passive filling**

### View/Description

<table>
<thead>
<tr>
<th>View/Description</th>
<th>Position</th>
<th>View</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARASTERNAL LONG AXIS</strong></td>
<td>Lying on left side, with left arm under head.</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td>• LV size, function, wall thickness (septum/posterior wall)</td>
<td>Probe: 2-3 inches left of sternum at 3rd-4th intercostal space, probe indicator at 10 o’clock (facing R shoulder).</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td>• MV/AoV function/flow (w/ Doppler)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• LVOT diameter, aortic root size</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PARASTERNAL SHORT AXIS</strong></td>
<td>Same as above.</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td>• Cross-sectional views of the heart from base to apex, at level of AoV, MV and mid-ventricle/papillary muscles</td>
<td>Probe: From long axis view, turn probe clockwise until indicator at 2 o’clock (facing L shoulder).</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td><strong>APICAL 4 CHAMBER</strong></td>
<td>Lying flat on back.</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td>• RV/LV size, function, thrombus</td>
<td>Probe: At PMI w/ probe indicator at 3 o’clock (to the pt’s L side). For 5-chamber view, tilt head of probe upward.</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td>• TV/MV function/flow (w/ Doppler)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Septal size/motion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pericardial effusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In 5-chamber view, can see AoV and proximal ascending aorta</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SUBCOSTAL VIEW</strong></td>
<td>Lying flat on back, consider slightly elevating head or bending legs.</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td>• IVC diameter and respiratory variation gives estimate of volume status and RA pressure</td>
<td>Probe: Below xyphoid process</td>
<td><img src="link" alt="Image" /></td>
</tr>
<tr>
<td>• Pericardial effusion</td>
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</tr>
</tbody>
</table>

*TOC*
Cardiology

Inpatient Heart Failure


Classification and Etiology of Cardiomyopathies

- **Dilated**: ischemic (most common cause, 50-75% pts), HTN/LVH, valvular (e.g., MR), myocarditis, infiltrative (hemochromatosis, sarcoid, amyloid), LVNC, ARVC, peripartum, HIV, CTD, cocaine, ETOH, chemotherapy, nutritional deficiency, stress-induced (Takatsubo's), tachyarrhythmia, cirhotic, septic, idiopathic/genetic
- **Restrictive**: infiltrative (amyloid, hemochromatosis, sarcoid), Löeffler's, radiation, metabolic storage disease, carcinoid
- **Hypertrophic obstructive**: (HCM): genetic

Initial Workup: New Heart Failure Diagnosis

- **Echocardiogram (TTE)**: for all new presentations; obtain thereafter only if concern for clinical/functional change (J Am Soc Echo 2011;24:229)
- **Assess EF/systolic function**: HFrEF (EF ≤40%) vs HFpEF (EF >50%)
  - (NB: EF 41-49% is often called HFrEF for 'borderline EF')
- **Other findings**: Regional WMA (specificity is low for ischemia), dilated chambers (consistent with dCM if LV dilated and ≥ 2 akinetic segments), pHTN, valvular fxn, pericardial disease, restrictive filling, thickened septum, LVOT gradients, shunts, myocardial texture
- **Diagnoses**: Ischemic: EKG, TnT, stress test, cardiac cath; Non-ischemic: CBC, BMP, LFTs, lipid panel, TSH, urine hCG, iron studies, HIV, SPEP w/ UFLC; also consider ANA, A1c, T. cruzi serologies, viral panel, antmyosin Ab, tox screen, thiamine level, genetic testing, endomyocardial bx if serologic testing neg, new onset <6 mo unexplained HF, major arrhythmias (to r/o myocarditis, ARVC, sarcoid), cardiac masses (Cardiovasc Pathol 2012;21:245); HOCM: >50% familial, 70-80% known genetics
- **Further imaging**: Consider MRI (with gadolinium); TEE for better visualization of MV and AV

Clinical Heart Failure Syndromes (JAMA 2002;287:628; JACC 2003;41:1797)

- **Warm vs. Cold**: adequate vs. inadequate tissue perfusion (AKI, decreased UOP, AMS, lactate, cold/clammy)
- **Dry vs. Wet**: presence vs. absence of congestion/edema
  - CXR signs: cardiomegaly, vascular cephalization, peribronchial cuffing, edema, Kerley B lines, alveolar edema
  - Chronic pulmonary congestion may lead to fewer signs of pulm edema on exam and CXR given vascular remodeling (Chester 2004:125-669)

General Inpatient Considerations – ALL HF Patients:

- Admission orders: Tele, Na (2g) and fluid (<2L/d) restricted diet, daily weights, strict I/Os, VTE ppx
- Avoid calcium channel blockers (especially non-dihydropyridines), certain antiarrhythmics (flecainide), NSAIDs
- Optimize pre-discharge outpatient regimen focusing on mortality benefit in HFrEF (but not HFpEF!)
- Natriuretic peptides (NT-proBNP at MGH)
  - ADHF unlikely if NT-proBNP < 300 (NPV 98%, LR -0.1); likely if >450 (>900 if age >50) (LR 2.75 for ≥ 900) (NEJM 2002;347:161; Am J Cardiol 2005;95:948; JACC 2009;54:1515)
  - Studies using BNP to HF management ongoing; TIME-CHF showed NT-proBNP guided bx didn’t improve outcomes, (JAMA 2009;301:383; Am J Cardiol 2006;98:1248; Circulation 2013;127:900)
  - Increased mortality with elevated discharge BNP/NT-proBNP (JACC 2004;43:635; JACC 2008;51:1874) and variations in NT-proBNP related to readmissions and death w/in 6mths (better prognosis with ≥ 30% decr) (Circulation 2004;110:2168)
  - NT-proBNP hard to interpret in CKD/dialysis; may be falsely low in obesity, HFpEF; may be higher in women/older individuals
  - Screen for iron deficiency in all HF pts independent of Hb; replete with IV iron if Tsat <20% to improve functional status (JACC 2008;15:103) no benefit from PO iron in patients without anemia (JAMA 2017;317:1958)
  - If persistent hypoNa despite fluid restriction, consider vasopressin antagonism with tolvaptan (class IIb) for short-term sxs benefit
  - Discharge:
    - Optimize pre-discharge outpatient regimen focusing on mortality benefit in HFrEF (but not HFpEF!): ACEi/ARB, β-blocker, aldo blockade, ivabradine (for pts with HR >70 on maximally tolerated β-blocker) (Lancet 2010; 376:875) isosorbide mononitrate/hydralazine in African-Americans, sacubitril-valsalartan (Entresto) (NEJM 2014; 371:993)
    - Document d/c weight + NT-BNP; consider appt in HF Transitions Clinic (J. Ruckel, NP; 617-724-1400) if pt has MGH cardiologist

Acute Decompensated Heart Failure (ADHF) – Floor/SDU:

- **Etiology**: dietary/med non-compliance (~40%), ischemia/infarction, uncontrolled hypertension, arrhythmia, valvulopathy, tamponade, myocarditis, renal dysfunction/volume retention, PE, comorbid illness (GI, pulmonary), toxins (ETOH, cocaine), endocrinopathy, meds (NSAIDs, steroids, Ca-channel blockers, TZDs, aldosterone), stress-induced cardiomyopathy, nutritional deficiency (i.e. selenium); up to 50% with NO known cause, *high-output HF p/w warm extremities, wide PP, tachycardia and ddx anemia, thyroid, liver failure, Pagets, systemic infection

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Management:

1. Continuation of Optimal Guideline-Directed Medical Therapy (GDMT): For most hospitalized HF patients without cardiogenic shock and no obvious contraindication, recommend continuing BB and ACEi/ARBs B-Convinced (Eur Heart J 2009;30:2186).

2. Diuresis: reduce CVP and PCWP optimize Starling curve mechanics
   - Initial treatment: loop diuretics (furosemide, torsemide, bumetanide); usual initial dose = 2x home dose (IV/PO); No difference between continuous gtt vs bolus dose DOSE (NEJM 2011;364:797)
   - Diuretic conversions (PO): PO furosemide 80 = IV furosemide 40 = PO torsemide 20 = IV/PO bumetanide 1
   - Refractory diuresis: Metolazone 2.5-5mg (use chlorothiazide 500mg IV if cannot take PO) administered 30 minutes before loop diuretic. Consider RRT in truly diuretic-refractory pts (CARRESS-HF (NEJM 2012;367:2296); UNLOAD (JACC 2007;49:675); RAPID-CHF (JACC 2005;46:2043))
   - Low-dose dopamine and/or low-dose nesiritide do not improve diuresis or renal perfusion (ROSE-AHF (JAMA 2013;310:2533); ASCEND-HF (NEJM 2011;365:32))
   - Limited data to support best end-points; potential targets include daily weights, BNP, hemoconcentration, renal function

3. Vasodilation: arterial/venous dilation results in ↓ afterload and ↑ SV. Early administration of vasodilators controversial (NEJM 2017;376:1956); consider especially in severe HTN, acute MR, acute AR
   - Floor: captopril, isosorbide dinitrate, hydralazine, nitropaste; SDU/CCU: TNG, nitropaste

4. Neurohormonal Blockade: spironolactone, eplerenone inhibit aldosterone and decrease myocardial remodeling, vascular fibrosis leading to improved mortality in EF < 35% (Class 1A); hold in AKI. (EMPHASIS-HF; RALES)

Cardiogenic Shock – CCU:

- Definition: MAP<60, Cis 1.8 (w/o inotropes) or ≤2.0-2.2 (w/ inotropes) despite PCWP>18mmHg, evidence of organ hypoperfusion
- Etiology: acute MI ± mechanical complications, end-stage cardiomyopathy, acute myocarditis, acute MR/AR, myocardial contusion
- Evaluation: TTE for LV size, mechanical lesions; consider PAC for inotrope/pressor/volume management (see PA Catheter section)
- Tailored therapy: uses invasive hemodynamic monitoring (i.e., PAC) to guide therapy
  - Goal: augment MAP (CO x SVR) and CO (HR x SV); SV is related to preload, afterload, and contractility
  - CO measured via thermodilution or Fick: CO = VO2/(1.34 x Hgb x [SpO2-MvO2]); CI = CO/BSA; MvO2 is proxy for CO/CI
  - Preload: LVEDV ≈ LVEDP = PCWP; goal PCWP 14-18, PAD 16-20, CVP 8-12
  - Diuresis, TNG, nitroprusside, RRT
  - Afterload: wall stress = MAP (Laplace’s law); SVR = (MAP - CVP)/CO; goal MAP>60, SVR≤800-1200
  - Vasodilators: captopril, hydralazine, nitroprusside, TNG; Vasopressors: vasopressin, phenylephrine (rarely used)
  - Contractility: CO for given preload/afterload; goal CO>4, CI>2.0-2.2, MVO2>65
  - Milrinone (inodilator): PDE-3 inhibitor (↑ breakdown of cAMP); watch for tachycardia, arrhythmias, ischemia, hypotension; longer half-life, greater pulmonary vasodilation, slightly less chronotropy, fewer arrhythmic events than dobutamine. Preferred in patients on beta blockade and w/ RV failure; renally cleared. Often choice for home inotrope for palliative therapy
  - Dobutamine (inodilator): β1-β2 agonist (↑ production of cAMP); watch for tachycardia, increased ventricular response to AF, arrhythmias, ischemia, hypotension, tachyphylaxis in infusions >24-48 hrs
  - Dopamine, Epinephrine, Norepinephrine (inopressors): use if severe hypotension, unable to tolerated inodilators; watch for tachycardia, arrhythmias, end-organ hypoperfusion
  - Limitations: Thermodilution (uses temp gradient between two points on PAC) is less reliable if shunt/valvular insufficiency (e.g., TR); Fick assumes a VO2 (oxygen consumption) that in reality varies depending on physiologic state (e.g., infection)
- Mechanical circulatory support: in critical refractory cases as bridge to transplant or other mechanical intervention
  - Types at MGH: IABP, Impella, VA-ECMO (see MCS & Transplant); if considering, must activate SHOCK team (x6-2241)

Heart Failure with Preserved Ejection Fraction (HFpEF): Overview

Definition: symptoms of HF, “preserved” LVEF (>50%) and normal LVEDV (<97ml/m²). Often, but not always, associated with LV diastolic dysfunction or inability to fill LV except at ↑ LVEDP (see figure)
- Risk factors: aging, F-M, HTN, CAD, AF, obesity, DM, CKD, OSA
- Rarer causes: hypertrophic CM, infiltrative CM (amyloidosis, hemochromatosis), valvular disease, constrictive pericarditis
- Prognosis: Possibly lower mortality compared with HFrEF (Eur Heart J 2012;33:1750)
- Findings: ↑ NT-proBNP, pulm edema; abnml 6MW, CPET w/ ↑ MVO2; E/e' ≥ 15
- Treatment/Options: No evidence-based treatments; most guidelines extrapolated from HFrEF
  1. Pivotal volume overload (fluid/salt restriction; judicious use of diuretics/nitrates)
  2. Treat risk factors associated with HFpEF development and outcomes
  3. Selective use of neurohormonal modulators
    - Consider spironolactone if normal renal function and potassium given improvement in cardiovascular death and HF hospitalizations in US (NEJM 2014;370:1383)
    - Other therapies including digoxin, beta-blockers, ACEi/ARBs, PDE-5 inhibitors have not been proven to have morbidity/mortality benefit in HFpEF. Nitrates may have a deleterious effect (NEJM 2015;373:2314). Phase III trial of sacubitril/valsartan ongoing (Circ Heart Failure 2018;11)

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Specific Causes of Cardiomyopathy

- **Hypertrophic Cardiomyopathy (HCM)** *(Circulation 2011;124:276)*
  - LV and/or RV hypertrophy of various morphologies: + LVOT dynamic obstruction (HOCM), diastolic dysfxn, ischemia, MR
  - Presentation: SOB, arrhythmias/palpitations, CHF, angina, pre-syncpe, SCD (most common in asymptomatic pts <35yo)
  - Physical Exam: LVOT obstruction – medium-pitch SEM at LSBl/apex that augments with Valsalva or on standing (due to ↓ preload); S2 paradox split, S4
  - Routine Diagnostics: EKG (abnl in 90% probands, 75% asymptomatic relatives -- prominent voltages w/ depolarization abnormalities, large normal Q waves in inferior (II, III, avF) or lateral (I, aVL and V4-V6) leads, P wave abnormalities (atrial enlargement), LAD, giant negative T waves in V2-V4 (apical HCM variant → "Yamaguchi's syndrome"), TTE (unexplained LVH >15mm in any pattern, SAM of MV, outflow tract gradient), 2MR (late gadolinium enhancement LGE = fibrosis, possibly early detection not seen on TTE, controversial role in decision making since no strong association with outcomes)
  - Risk Stratification: (1) Ambulatory EKG monitoring 24-48hrs (2) ETT (failure to augment BP to exercise due to dynamic LVOT obstruction, symptoms, arrhythmias, ST depressions) + stress echo (increasing outflow tract gradient, worsening MR)
  - Genetics: Clinical genetic testing (mutation in ~70% of cases) helpful for family screening; not useful for dx or risk stratification
  - Treatment: Avoid volume depletion or high dose vasodilators (may worsen obstruction), activity restriction, medical Rx (BB > verapamil). Use phenylephrine to treat hypotension in patients with HOCM who do not respond to fluid boluses (↑ afterload, stents open LVOT), septal ablation or surgical myectomy for medically refractory sx, ICD (for high SCD risk, risk factors below)
  - Risk factors for SCD/VT in order of decreasing risk: (1) Prior VT/SCD/unexplained syncope; (2) FHx of SCD in 1° relative; (3) alcohol-induced

- **Non-ischemic Dilated Cardiomyopathy (DCM)** *(JACC 2016;67:2996)*
  - Takotsubo (stress-induced) *(NEJM 2015;373:929)*
    - Potential mechanisms: catecholamine surge from physical/emotional stress, coronary artery spasm, microvascular ACS involvement. Regional WMA extend beyond a single coronary distribution (2) Rule out ACS/obstructive coronary disease (via cath) (3) New EKG abnormalities (STE [44%] and/or TWII OR ↑ troponin). (4) absence of pheo, myocarditis. WMA can be apical (82%) mid-ventricle (15%), basal (2%), focal (2%)
    - Treatment: Remove stressor. ACEI (may improve survival), BB, diuretic. If non-obstructive CAD, add ASA+statin.
    - Prognosis: 4% inhospital mortality, 19% severe complications; most recover LV fn in 1-4 wks
  - Alcohol-induced:
    - Acquired DCM a/w >80g/day of EtOH over >5 years (toxic to myocytes via O2 free radicals + defects in protein synthesis)
    - Treatment: Abstinence + HF therapy
    - Prognosis: Better/equivalent to idiopathic CM if able to abstain/consume <20g/day, worse w/ continued EtOH abuse
  - Toxins: Chemotherapy (anthracyclines, cyclophosphamide, trastuzumab, 5-FU), antiretroviral drugs, phenothiazines, chloroquine, clozapine, amphetamine, cocaine, carbon monoxide, cobalt, lead, mercury, lithium
  - Infection: Viral (HIV, lyme, adenovirus, coxsackie A/B, CMV/EBV, HHV6, parvovirus B19, varicella), bacterial (brucellosis, diphtheria, psittacosis, typhoid fever), protozoal/helminthic (chagas, malaria, toxo, schistosomiasis, strongyloidiasis)
  - Other causes of DCM: Pregnancy, nutritional deficiency (carotene, thiamine, selenium, niacin), tachyarrhythmia, electrolyte abnormality (hypocalcemia, hypoxia, uraemia), endocrine (Cushing's disease, acromegaly, DM, hypothryroidism, pheochromocytoma), cirrhotic, septic, CTD (SLE, RA, Scl, dermatomyositis), vasculitis (GPA, EGPA, Kawasaki, PAN), deposition (hemochromatosis, amyloid), hypersensitivity myocarditis, NM disease, genetic (~50% of "idiopathic" DCM)

- **Restrictive Cardiomyopathy** *(JACC 2010;55:1769)*: *(NB: these conditions may also manifest as DCM)*
  - Amyloidosis (AL, TTR)
    - HF with other findings of amyloid (renal, neurologic, hepatic disease)
    - Decreased voltage, pseudo-infarct pattern in inferolateral leads
    - Symmetric LV/RV wall thickness, speckled myocardium on TTE, LGE in subendocardium on cMR

  - Hemochromatosis
    - If hereditary: M>30 yo; F> 40 yo
    - If 2nd: can present at any age
    - LV and/or RV hypertrophy of various morphologies: ± LVOT dynamic obstruction (HOCM), diastolic dysfxn, ischemia, MR
    - Decreased voltage, pseudo-infarct pattern in inferolateral leads
    - Symmetric LV/RV wall thickness, speckled myocardium on TTE, LGE in subendocardium on cMR

  - sarcoidosis
    - If 2nd: can present at any age
    - LV and/or RV hypertrophy of various morphologies: ± LVOT dynamic obstruction (HOCM), diastolic dysfxn, ischemia, MR
    - Decreased voltage, pseudo-infarct pattern in inferolateral leads
    - Symmetric LV/RV wall thickness, speckled myocardium on TTE, LGE in subendocardium on cMR

  - Treatment
    - Treat underlying disease + HF guidelines based on underlying EF (HFpEF vs. HFpEF) as above
    - Amyloidosis: tafamidis (↓ TTR deposition) shown ↓ mortality, admissions, functional/QoL decline (NYHA III-IV) [NEJM 2018;379:1007]: liver transplant in familial disease

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Mechanical Circulatory Support (MCS) – If inotrope-refractory cardiogenic shock, call SHOCK team (x6-2241)

<table>
<thead>
<tr>
<th>Device</th>
<th>Indications</th>
<th>Support Provided</th>
<th>Considerations</th>
<th>Management</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>IABP (intra-aortic balloon bump)</td>
<td>Refractory heart failure (bridge to durable MCS)</td>
<td>Minimal hemodynamic support</td>
<td>Bedside insertion</td>
<td>Pt cannot sit up/bend legs</td>
<td>Limb ischemia</td>
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<tr>
<td></td>
<td>Cardiogenic shock/massive PE</td>
<td></td>
<td>Does not require AC (when at 1:1)</td>
<td>✓ CXR daily (tip 1-4cm below Ao notch)</td>
<td>Vascular injury</td>
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<td></td>
<td>Refractory malignant arrhythmias</td>
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<td>No ↓ mortality in cardiogenic shock</td>
<td>✓ Waveform daily</td>
<td>Thromboembolism</td>
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<td></td>
<td>Support during high-risk procedures</td>
<td></td>
<td>(IABP-SHOCK II, NEJM 2012;367:1287)</td>
<td>✓ Waveform daily</td>
<td>Thrombocytopenia</td>
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<td></td>
<td>o Complex PCI</td>
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<td>Least costly</td>
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<td>Vascular injury</td>
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<td></td>
<td>o Ablation of ventricular arrhythmias</td>
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<td>Position alarm</td>
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<td>o Perc valve repair</td>
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<td></td>
<td>Partial LV support: Cath lab placement: Impella 2.5 (2.5 L/min), Impella CP</td>
<td>Ventricular decompression</td>
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<td>3.5 (L/min), OR placement: Impella 5.0 (5 L/min)</td>
<td>Requires AC</td>
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<td>Partial RV support: Impella RP (4 L/min)</td>
<td>Allows pt mobilization (if axillary placement)</td>
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<td>Longer-term support (weeks)</td>
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<td></td>
<td></td>
<td>Ventricular arrhythmias (device migration)</td>
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<tr>
<td>Impella</td>
<td>Acute allograft failure</td>
<td>HD support (4-10 L/min), oxygenation &amp; CO2 clearance</td>
<td>Bedside insertion possible</td>
<td>P1 (lowest) to P9 (highest support)</td>
<td>Infection</td>
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<td>(Often requires additional device for LV unloading, i.e. Impella)</td>
<td>Short-term support (days/weeks)</td>
<td></td>
<td>Bleeding</td>
</tr>
<tr>
<td>VA-ECMO</td>
<td>Bridge to transplant</td>
<td>Full LV support (10 L/min)</td>
<td></td>
<td></td>
<td>Limb ischemia</td>
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<tr>
<td></td>
<td>Destination therapy (DT)</td>
<td>HeartMate II (150-300 L/min)</td>
<td>Mobility</td>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td></td>
<td>&quot;Bridge to decision&quot; (on transplant or DT)</td>
<td>HeartMate 3 (70-150 L/min)</td>
<td>Long-term support (years)</td>
<td></td>
<td>Vascular injury</td>
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<tr>
<td></td>
<td>Bridge to recovery (LV unloading can be therapeutic)</td>
<td>HeartWare HVAD (10 L/min)</td>
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<td>Position alarm</td>
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<tr>
<td>Heart Transplant</td>
<td>2018 UNOS Adult Heart Allocation Criteria: Status 1: VA-ECMO, MCS with life-threatening vent. arrhythmia; Status 2: non-dischargeable LVAD, MCS + device malfunction, IABP; Status 3: ≥2 inotropes or single high-dose + continuous hemodynamic monitoring, dischargeable LVAD for discretionary 30 days, VA-ECMO after 7d, IABP after 14d; Status 4: re-transplant, inotropes without hemodynamic monitoring, dischargeable LVAD without discretionary 30 days; Status 5: awaiting dual organ Tx; Status 6: all others; Status 7: inactive listing</td>
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<td>Transplant evaluation at MGH:</td>
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<td>Labs: blood typing (2 samples on separate days), second sample for PRA (check with tissue typing x63722), BMP, LFT, amylase, CBC+diff, PT-INR/PTT, TTFs, lipids, PTH, 25-Vit-D, 1,25-Vit-D, HIV, CMV, Toxo lgs, EBV, VZV serology, MMR, RPR, hepatitis serologies, IGRA, UA, 24h urine CrCl (and 24h urine protein if diabetic)</td>
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<td>Vaccines: HBV, PPSV23, Tdap</td>
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<td>Consults: Psychiatry (Dr John Purcell), SW (Kathryn Tsgaronis), Tx coordinators (Sally Keck, Coral Haggan, Kerry Gaj, Karen Turvey – they can all consent patient for Tx), Dental (panorex, inpatient consult), Nutrition, Endocrine, Pall Care</td>
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<td>Diagnostics: RHC (eval for presence &amp; reversibility of pHTN with vasodilator challenge; if unsuccessful vasodilator challenge, note that PVR often declines after 24-48h of treatment [e.g. diuretics, inotropes, vasoactive agents], +/- LHC, level 1 CPET (Paul Pappas, x47825) (complementary ISHLT criteria for Tx: VO2 max ≤14ml/kg/min or ≤12 if on βb), abdominal US, carotid US, TTE, ECG, CXR, DXA, AbIs +/- angiography, cancer screening up-to-date</td>
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<tr>
<td>Post-transplant immunosuppression:</td>
<td>steroids (typically tapered off over 6 months, 1st line for acute rejection), calcineurin inhibitors (cyclosporine/tacrolimus), anti-proliferatives (azathioprine/mycophenolate), mTOR inhibitors (sirolimus/everolimus – most effective for coronary allograft vasculopathy [CAV]; avoid in immediate post-tx phase as inhibit wound healing)</td>
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<td>Monitoring: protocolized schedule of RV biopsies to r/o cellular/humoral rejection, R/LHC and TTE to assess graft function and for CAV</td>
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</table>
**Right Ventricular Failure**

**Right Ventricular Physiology** *(Circulation 2018;137.e578)*
- RV has thinner myocardium compared to LV → ↑ compliance compared to LV, so it does not adapt well to acute increases in pressure
- RV and LV are interdependent → failure of RV leads to failure of LV through several mechanisms: (a) decreased LV preload (because RV output = LV preload); (b) septal bowing into LV, causing diastolic impairment (“Bernheim effect”)

**Acute Changes in RV Hemodynamics**
- ↑ RV afterload (e.g., PE), ↑ RV preload (e.g., L→R shunting through ASD/VSD), or ↓ RV contractility (e.g., MI) all lead to increased RV wall stress and resultant ischemia
- RV CO subsequently ↓ and RV dilates, precipitating RV “death spiral”
- ↓ RV CO leads to ↓ MAP (and ↑ RVP), resulting in ↓ coronary perfusion pressure (CPPRV = MAP – RVP)
- ↓ CPPRV leads to more RV ischemia, propagating “death spiral” further

**Clinical Features and Workup**
- **Exam:** Elevated JVP, peripheral edema, RV heave, pulsatile liver. Less common: Split S2, new tricuspid regurgitation (loudest: RLSB)
- **Imaging:** CXR → hard to evaluate RV 2/2 position, lateral film can help; CT → best for RV size/septum position
- **Echocardiography:** measure RV size/function to elucidate underlying etiology. RVEF based on displacement of base towards apex (tricuspid annular plane systolic excursion [TAPSE]; nl 2.4-2.7cm).
- **RHC:** gold standard for measurement of ventricular filling pressures, CO, PA pressures
  - RVSP: correlates w/ RHC but can vary up to 10mmHg (esp w/ chronic lung dz, pos pressure vent).
- **Labs:** NT-proBNP and troponin are not specific but can indicate RV failure if no L-sided disease.

**Management** *(Am J Respir Crit Care Med 2011;184:1114)*
- Identify and treat triggers: infection, anemia, arrhythmia, PE, MI, hypoxia
- **Preload:** Clinical assessment of optimal preload is challenging. Both hypo- and hypervolemia may ↓ CO.
  - Acute: consider volume loading in pts with acute RVMI or PE in absence of marked CVP elevation (“preload-dependent”)
  - Subacute/chronic: consider diuresis to reduce RV filling pressures and improve RV CO
- **Afterload:**
  - Systemic: if pt hypotensive, start systemic pressors; no clinical data regarding pressor of choice, but often choose or vasopressor or norepinephrine because it affects SVR>>PVR
  - Pulmonary: remove factors that ↑ pulm vasc tone (e.g., hypoxia). Consider pulm vasodilators (inhaled>oral in acute setting).
    - Types: prostacyclin agonists (e.g., epoprostenol), endothelin antagonists (e.g., bosentan, ambrisentan), nitric oxide enhancers (e.g., PDE-5 inhibitors: sildenafil, tadalafil; inhaled NO)
- **Contractility:** often use **milrinone** to enhance pulmonary vasodilation (vasodilates arteries in both systemic and pulmonary circulation)

**Intubation and Mechanical Ventilation** *(Curr Heart Fail Rep 2012;9:228)*
- Intubation/NIPPV in RV failure precipitate risk for HD collapse and arrest
- Drugs commonly used: BZDs, propofol, muscle relaxants → tendency towards vasodilation and negative inotropy → decreases venous return → decreased LV preload
  - Consider RSI (etomidate >> propofol for induction) and push dose epinephrine (10-20mcg)/vasopressin (1-2U) if emergent intubation anticipating hypotension
- Positive pressure ventilation → increased pulmonary pressures and ↓ RV afterload → increased RV dilation → “death spiral”
- Vent Management: cannot allow hypoxia and hypercarbia as drive up PVR, consider moderate TV (~8cc/kg) with low PEEP (<12 cm H2O) with moderate plateau pressure goal (<30 mmHg)

**Right Ventricular Myocardial Infarction** *(Circulation 2012;127.e362)*
- **EKG:** Check R-sided EKG leads in pts with inferior STEMI (10-15% of pts with inf. STEMI have RV involvement)
  - 1mm STE in V4R → 88% Sn, 78% Sp in inferior STEMI; STE III>II suggests RVMI
  - High-grade AV block seen in ~50% of pts with RVMI
- **Management:** pts with RVMI are initially “preload-dependent” and often benefit from **fluid bolus**; caution w/ TNG (↓ preload) and BB (↓HR)
  - If CVP >15mmHg and BP not improving w/ IVF, additional fluids may worsen RV failure/overload *(Eur Heart J Acute Cardiovasc Care 2013;2:226)*
Overview:
- Indications—7 primary indications for the placement of PA lines:
  - (1) diagnose etiology of shock (e.g., cardiogenic vs. distributive)
  - (2) diagnose cardiogenic vs. non-cardiogenic pulm. edema
  - (3) diagnose PH (4) diagnose L→R shunting
  - (5) diagnose valve disease
  - (6) diagnose pericardial disease
  - (7) tailored therapy
- Efficacy: No benefit in the ICU setting or peri-op for mortality, LOS, cost.
- Line course: central vein (Ultrasound/femoral) → SVC/JV → RA → RV → PA → distal pulmonary arteriole

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

Obtaining PA Line Numbers on AM Rounds:
1. Position patient supine with head-of-bed 0-60° elevation
2. Check level of transducer with phlebostatic axis (4th intercostal space and mid-axillary line)
3. Zero transducer to air and assess waveform for dampness
4. Record PA systolic, PA diastolic, PA mean, CVP, and line position
5. Open the PA catheter balloon port and remove 1cc air
6. Inject 1cc air until PCWP waveform observed (use minimum air required to reduce risk of PA infarction/rupture) and record PCWP (limit balloon inflation to no more than 8-10 seconds)
7. Release safety syringe and allow balloon to deflate passively. Verify balloon deflated by confirmation of PA waveform.
8. Troubleshooting:
   a. Arrhythmia: Catheter may be in RVOT. Talk to fellow/attending and consider repositioning catheter.
   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 coiled in the RV.

Calculating Hemodynamic Parameters:
- Normal: “rule of 5s” → RA 5, RV 25/5, PA 25/10, PCWP 10, LV 125/10
- Cardiac Output:
  - Fick = VO₂ / [(13.4 * Hgb * [SpO₂ – MvO₂]) / l/min]
  - VO₂ ≈ 250 ml/min QR 3”wtkg) QR 125*BSA
- Thermodilution: Temperature change (measured by thermistor in PA) is proportional to LV CO (inaccurate w/ TR, intracardiac shunt)
- Cardiac index = CO/BSA [normal: 2.6-4.2 L/min/m²]
- SVR = (MAP-CVP) / CO x 80 [normal: 700-1200 dynes*s*cm⁻⁵]
- PVR = (mPAP-PCWP) / CO x 80 [normal: 20-130 dynes*s*cm⁻⁵]

Hemodynamic Considerations:
- All quantitative pressure measurements (especially PCWP) should be made at end-expiration (when intrathoracic pressure is zero)
  - Spontaneous respiration: RA and PCWP ↑ with expiration → measure from the higher a waves (“patient = peak”)
  - Positive pressure ventilation: RA and PCWP ↓ with expiration → measure from the the lower a waves (“vent = valley”)
- Measure RA and 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
  - If no PA line in place, MvO₂ may be used as a proxy for CO/CI [normal: >65-75%]

Clinical Considerations:
- Placement: Usually through RU 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.
- Contraindications: RA/RV mass/thrombosis, mechanical TV/PV, endocarditis (TV/PV)
- Markings on PA catheter: Each thin line=10cm; each thick line=50cm.
- Position: On CXR: middle 1/3 of the chest bilaterally. Ability to wedge more important than CXR position.
- Complications: infection, bleeding, PTX, VT, RBBB, CHB, PA rupture (place patient on side with the catheter “[bleeding side down”). order STAT CXR, CBC, coags, CT surgery consult), pulm infarct, PE
- Duration: No data defining maximum length of time; at MGH, standard is 7d; others suggest 4-5d

Maeve James-O’Connor, Leslie Chang
Permanent Pacemakers (PPM), Implantable Cardioverter-Defibrillators (ICD), & Cardiac Resynchronization Therapy (CRT):

- **Types**: Single chamber (RA or RV lead) vs. dual chamber (RA + RV leads) vs. biventricular (+/- RA + RV + LV leads)
- **PPM**: sense/pace the RA and RV to treat bradyarrhythmias
- **ICD**: device with an RV lead capable of terminating re-entrant ventricular tachyarrhythmias via pacing, cardioversion or defibrillation
- **CRT**: provides simultaneous RV+LV pacing in HFrEF pts with wide QRS to ↓ reverse remodeling and ↑ LVEF
  - CRT-P = BIV +/- RA pacing; CRT-D = CRT-P w/ ICD functions

### NASPE/BPEG Codes for Pacing Operating Modes:

<table>
<thead>
<tr>
<th>Position I (Chamber Paced)</th>
<th>Common Mode Guide:</th>
</tr>
</thead>
<tbody>
<tr>
<td>O – none, A – atrium, V – ventricle, D – dual (A+V)</td>
<td>Asynchronous pacing; Avoid sensing electrocautery, magnetic resonance or electromagnetic interference</td>
</tr>
<tr>
<td>Position II (Chamber Sensed)</td>
<td>AAI/AI-R</td>
</tr>
<tr>
<td>O, A, V, D (A+V)</td>
<td>Isolated sinus node dysfunction, intact AV nodal conduction; isolated sinus node dysfunction, do not have to cross TV for placement +/- rate response</td>
</tr>
<tr>
<td>Position III (Response to Sensing)</td>
<td>VVIR/VVI-R</td>
</tr>
<tr>
<td>O, T – triggered, I – inhibited, D – dual (T+I)</td>
<td>Atrial arrhythmias (chronic AF) bypasses AV node in high grade blocks/pauses; does not track atrial arrhythmias +/- rate response</td>
</tr>
<tr>
<td>Position IV (Rate Modulation)</td>
<td>DDD/DDD-R</td>
</tr>
<tr>
<td>O, R – rate modulation</td>
<td>Sinus node is intact but AV conduction issue; Allows synchronous pacing with coordination of A and V pacing +/- rate response for chronotropic incompetence</td>
</tr>
<tr>
<td>Position V (Multisite Pacing)</td>
<td>AOO/DOO</td>
</tr>
<tr>
<td>O, A, V, Dual (A+V)</td>
<td>Asynchronous pacing; Avoid sensing electrocautery, magnetic resonance or electromagnetic interference</td>
</tr>
</tbody>
</table>

### Hardware Overview:

- **Types**: Traditional (SQ pulse generator + IV leads in ventricle) vs. leadless (pulse generator directly implanted into RV; no pocket complications but unclear what to do when battery dies) vs. SQ ICD (no IV hardware; low risk for infection but NO pacing capabilities)
- **Placement**: RA lead → RA appendage; RV lead → RV apex; LV lead → coronary sinus → branches of great cardiac vein
- **Interrogation**: Page EP Technician (PPM, p1633) during normal business hours; EP fellow on call if after-hours/weekend.
- **MRI Compatibility**: Not all devices are MRI compatible, however even non-MRI compatible devices may be safe to scan after re-programming (NEJM 2017; 376: 755). Determined on case-by-case basis by radiology. Need to know device model.

### Class I PPM Indications:

- Symptomatic sinus bradycardia (± sinus pauses) or chronotropic incompetence
- Symptomatic medication-induced bradycardia if medication (i.e., BB) is required for underlying medical condition

### AV Block (AVB)/Conduction Disease:

- Symptomatic 2° AVB or 3° AVB
- Asymptomatic Mobitz II 2° AVB or 3° AVB with: asystole ≥ 3 sec (>5 seconds if in AF), escape rate ≤ 40 BPM (or >40 BPM if cardiomegaly also present), or wide-complex escape rhythm
- Permanent Mobitz II 2° AVB or intermittent 3° AVB (regardless of symptoms)
- Alternating bundle branch block

### Neurocardiogenic:

- Recurrent syncope AND inducible asystole ≥ 3 sec with carotid massage

### Class I ICD Indications:

- mortality vs. optimal medical therapy (OMT); guidelines apply only to pts who meet eligibility while on OMT (JACC 2013; 61: e6)

### Cardiac Devices: PPM&ICD

#### Common Mode Guide:

<table>
<thead>
<tr>
<th>Type</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAO</td>
<td>Asynchronous pacing; Avoid sensing electrocautery, magnetic resonance or electromagnetic interference</td>
</tr>
<tr>
<td>AAI</td>
<td>Isolated sinus node dysfunction, intact AV nodal conduction; isolated sinus node dysfunction, do not have to cross TV for placement +/- rate response</td>
</tr>
<tr>
<td>VVI</td>
<td>Atrial arrhythmias (chronic AF) bypasses AV node in high grade blocks/pauses; does not track atrial arrhythmias +/- rate response</td>
</tr>
<tr>
<td>DDD</td>
<td>Sinus node is intact but AV conduction issue; Allows synchronous pacing with coordination of A and V pacing +/- rate response for chronotropic incompetence</td>
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</tbody>
</table>

#### NYHA I / NYHA II

<table>
<thead>
<tr>
<th>Class I</th>
<th>NYHA I</th>
<th>NYHA II</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>- LVEF ≤ 35%, QRS ≥ 150ms, LBBB, &amp; sinus rhythm</td>
<td>- LVEF ≤ 35%, QRS ≥ 150ms, LBBB, &amp; sinus rhythm</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Class IIa</th>
<th>NYHA I</th>
<th>NYHA II</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- LVEF ≤ 35%, QRS 120-149ms, LBBB, &amp; sinus rhythm</td>
<td>- LVEF ≤ 35%, QRS 120-149ms, LBBB, &amp; sinus rhythm</td>
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</table>

<table>
<thead>
<tr>
<th>Class IIb</th>
<th>NYHA I</th>
<th>NYHA II</th>
</tr>
</thead>
<tbody>
<tr>
<td>- LVEF ≤ 30%, QRS ≥ 150ms, LBBB, &amp; ICM</td>
<td>- LVEF ≤ 35%, QRS ≥ 150ms, non-LBBB pattern, &amp; sinus rhythm</td>
<td>- LVEF ≤ 35%, QRS 120-149ms, non-LBBB pattern, &amp; sinus rhythm</td>
</tr>
</tbody>
</table>

Chitra Mosarla, Usama Abbasi
Aortic Stenosis

**Etiology**: senile calcific (most common cause >70yoc; associated with metabolic syndrome, CAD, CKD), bicuspid valve (most common cause <70yoc), rheumatic heart disease (leaflet fusion, often with concurrent MV disease)

**Clinical Manifestations**: most important determinant of prognosis → 50% mortality at 5y for angina, 3y for syncope, 2y for HF

- **Angina**: ↑ afterload/outflow obstruction → ↑ LV pressures → LVH → ↑ O2 demand and compression of coronary arteries
- **Syncope**: exercise-induced vasodilation→ inability to augment CO due to obstruction → hypotension
- **Heart failure (dyspnea)**: LVH → diastolic dysfunction (NB: systolic dysfunction is a rare and late finding)
- **Acquired vWF def.**: 20% of severe AS, can expose bleeding from GI AVMs (Heyde’s syndrome) (NEJM 2012;367:1954)

**Diagnosis**:

- **Physical exam**: harsh, mid-systolic crescendo-decrescendo murmur at RUSB radiating to carotids. If more severe: murmur late-peaking, delayed carotid upstroke (pulsus parvus et tardus), soft S2 (Am Heart J 1999;137:238)
- **TTE**: measure mean (not peak) gradient, valve area, and jet velocity; also important to assess EF (gradient can be underestimated with reduced EF → low flow, low gradient AS)
  - **Severe AS**: peak aortic valve velocity >4m/s, mean aortic valve pressure gradient >40 mmHg, aortic valve area <1cm², for full staging reference (J Am Coll Cardiol 2014;63:2438)
- **EKG**: LVH, LAEF, LBBB
- **Exercise stress testing**: recommended in asymptomatic severe AS to assess for symptoms; do not perform in pts w/ sx

**Natural History**: variable, but on average, AVA ↓ ~ 0.1 cm²/yr and mean gradient ↑ 8 mmHg/yr (J Am Coll Cardiol 1988;13:545)

**Aortic Valve Replacement (AVR)** (AUC Severe Aortic Stenosis 2017): Determining indication for valve replacement is based on evaluating: 1) presence of symptoms 2) severity by TTE criteria 3) LV function (EF)

- **Symptomatic, severe AS**: AVR is indicated
- **Asymptomatic, severe**: intervention appropriate if abnormal stress test or EF < 50%
- **If low-flow (<50%) and low-gradient (<40mmHg) w/ AVA < 1cm²**: dobutamine stress TTE to distinguish between low-flow, low-gradient AS versus “pseudosevere AS” (Circ 2011;124:e739)
  - **Low-flow, low-gradient severe AS**: if dobutamine stress echo results in V max > 4 m/s or pressure gradient > 40mmHg while AVA remains < 1cm², then AVR is warranted
  - **Pseudosevere AS**: if dobutamine stress echo results in AVA > 1cm², then AVR not warranted

**SAVR vs TAVR**: depends on surgical risk (STS-PROM score) and/or concomitant heart/vascular disease that is amenable to surgery. TAVR is recommended for those at extreme surgical risk (compared to medical therapy; PARTNER). TAVR is noninferior to SAVR in those at high (NEJM 2011;364:2187) or intermediate (PARTNER 2 SURTAVI) surgical risk with interim data (NOTION) suggesting that TAVR may be noninferior to SAVR in low-risk patients but longer-term follow-up is required. Valve-in-valve TAVR may additionally be beneficial in pts with surgical bioprosthetic AV failure (JACC 2017;69:2283). If CABG is indicated based on cath, SAVR w/ CABG appropriate. If other valve/aortic disease can be simultaneously fixed by cardiac surgery, SAVR is indicated.

**TAVR Evaluation**: Consult General Cardiology → Direct to Structural/CT-surgery, Pre-TAVR ECHO, TAVR Protocoled CT

**FDA Approved Valves**: Sapien XT (balloon-expandable), Sapien 3 (balloon-expandable), CoreValve (self-expandable)

**TAVR Complications**: Valve embolization, valvular regurgitation (central or paravalvular), shock, coronary occlusion, annular rupture, ventricular perforation, CHB requiring PPM, stroke (ischemic/hemorrhagic), bleeding/hemorrhage, access site complication

**Medical Management**:

- **Treat hypertension**: reduces the “double load” on the ventricle; however, no optimal regimen exists because many anti-hypertensives can lead to hemodynamic issues (diuretics reduce preload which lead to decrease CO, vasodilators can reduce coronary artery perfusion, BB can reduce needed contractility). Bottom line: start low and go slow.
- **Control volume status**: these patients operate within a narrow preload range, prone to both underfilling (“preload-dependent” and overfilling (volume overload)

### Additional Valvular Disorders

<table>
<thead>
<tr>
<th><strong>Aortic Regurgitation</strong></th>
<th><strong>Mitral Stenosis</strong></th>
<th><strong>Mitral Regurgitation</strong></th>
<th><strong>Tricuspid Regurgitation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td><strong>Medical Management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute</strong>: aortic dissection, valve perforation (usually due to MI or endocarditis), traumatic valve leaflet rupture</td>
<td>Elevated LAP → pulmonary HTN, AFib (47%); demand for ↑ CO precipitates symptoms; valve narrows 0.1 cm²/yr</td>
<td>Dilated annulus (&quot;functional MR&quot;), MVP, ischemic papillary muscle dysfunction, ruptured chordae, endocarditis, RHD, CTD</td>
<td>Dilated annulus, pulmonary hypertension (&quot;functional TR&quot;), Direct valve injury, endocarditis, RHD, carcinoid, ischemic papillary muscle dysfunction, CTD, drug-induced</td>
</tr>
<tr>
<td><strong>Chronic</strong>: leaflet abnormalities (bicuspid valve, endocarditis, RHD) or root dilation (HTN, CTD, dissection, syphilis)</td>
<td></td>
<td>Dilated annulus (&quot;functional MR&quot;), MVP, ischemic papillary muscle dysfunction, ruptured chordae, endocarditis, RHD, CTD</td>
<td></td>
</tr>
</tbody>
</table>

**Pathophys**

- **Acute**: diastolic regurgitant flow → sudden TLVDp (w/o remodeling time) → dec. CO → pulm. edema
- **Chronic**: diastolic regurgitant flow → TLVDV → initial maintenance of SV/CO → progressive dilatation, eventual failure

**Chitra Mosaria, Nicky Singh**

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Cardiology

Valvular Heart Disease

Anticoagulation after Valve Replacement

- NOACs are not approved for valve replacement and may cause harm (RE-ALIGN).
- Bridging UFH or SC LMWH if AC interrupted only in mechanical MV or mechanical AV with RFs* (Class I recommendation)
- Mechanical valve bleeding risk > bioprosthetic valve (likely AC related), however bioprosthetic need for reoperation > mechanical

<table>
<thead>
<tr>
<th>Prosthesis</th>
<th>Location</th>
<th>Timing and Risk Factors*</th>
<th>INR</th>
<th>Class</th>
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<tr>
<td>Mechanical</td>
<td>Mitral</td>
<td>Indefinitely</td>
<td>2.5-3.5 (+ ASA 81)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Aortic</td>
<td>Indefinitely, (+) risk factors</td>
<td>2.5-3.5 (+ ASA 81)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indefinitely, (-) risk factors§</td>
<td>2.0-3.0 (+ ASA 81)</td>
<td>I</td>
</tr>
<tr>
<td>Bioprosthetic</td>
<td>Mitral</td>
<td>First 3 months after placement, regardless of RFs</td>
<td>2.0-3.0 (+ ASA 81)</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 months after placement</td>
<td>ASA 81</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Aortic</td>
<td>First 3 months after placement, regardless of RFs</td>
<td>2.0-3.0 (+ ASA 81)</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 months after placement</td>
<td>ASA 81</td>
<td>IIb</td>
</tr>
<tr>
<td>TAVR</td>
<td>Aortic</td>
<td>First 3 months after placement, low risk of bleeding</td>
<td>2.5-3.5 (+ ASA 81)</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First 6 months after placement</td>
<td>Plavix 75 + ASA 81</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;6 months after placement</td>
<td>ASA 81</td>
<td>IIb</td>
</tr>
</tbody>
</table>

*RFs: AFib, LV dysfunction, prev. VTE, hypercoagulable state, older-generation mech AVR (Star-Edwards valve or disc valve other than Medtronic Hall) (Circ 2014;129:2440).

†A lower target (INR 1.5-2.0) may be reasonable in pts with mechanical On-X AVR and no thromboembolic RFs (IIb) (Circ 2017;135:e1159).

§Recent data shows subclinical leaflet thrombosis may occur in patients receiving TAVR with aspirin alone but not with VKA (NEJM 2015;373:2014, Heart 2017;103:1942).

Chitra Mosarla, Nicky Singh
Cardiology

Pericardial Disease

Tamponade:
- **Definition**: hemodynamic insufficiency caused by impaired cardiac filling due to compression by pericardial effusion, leading to ↑ intracardiac pressures & eventual equalization of diastolic pressure in all 4 heart chambers.
- **Pericardial effusion**: common etiologies: idiopathic (20%), iatrogenic (16%), malignant (13%), uremic (6%), HF (5%), autoimmune (5%) (Am J Med 2000;108:95). Tamponade more likely in malignant, post-viral, uremic, idiopathic (i.e. post-cath) etiologies. Also seen with prox. aortic dissection & myocardial wall rupture.

Clinical Presentation and Diagnosis:
- **Beck’s Triad**: ↓ BP, ↑ JVP, muffled heart sounds.
- **Pulsus paradoxus (PP)**: exaggeration of normal decrease in SBP during inspiration. (If >10mmHg, L/E=3.3, if ≤10 mmHg, +L/E=0.03).
  - How to measure PP (https://www.youtube.com/watch?v=TsijC90oxW8)
    1. Slowly deflate cuff→note pressure when systolic Korotkoff sounds only heard w/ heart sounds during exp. (a) → cont. deflating cuff until Korotkoff sounds heard during exp & ins (b). PP = a – b
    2. Via A-line tracing (PP = height of Exp. – Insp systolic waveform)
  - False-negative PP conditions: pre-existing disease w/ ↑LVEDP (e.g. chronic HTN), regional tamponade, pericardial adhesion, acute MI, arrhythmia, ASD/VSD, severe AI, hypotension/shock, RVH.
  - Dx PP: severe COPD/asthma, massive PE, hypovol shock, RVMI, const physiology, tense ascites.
- **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 (monitor closely as overfilling can worsen tamponade), starting w/ 250-500cc bolus.
- **Inotropes**: administer if IVF insufficient. Unclear benefit b/c endogenous catecholamines already at max level. Avoid BB.
- **PPV**: Avoid if possible as ↑ positive intrathoracic pressure will further impede ventricular filling.
- **Pericardial effusion removal**: via catheter pericardiocentesis, surgical pericardiectomy (if aortic/myocardial rupture), or HD (if uremic)
  - Analysis of pericardial fluid: cell count, Tprotein, LDH, gram stain/cx, viral markers/cx (coxsackie, HSV, CMV, EBV, HIV), AFB smear/cx, ADA/IFN-gamma/lysozyme (if concerned for TB pericarditis), cytology/tumor markers.
  - Removal of drain: when output <50 cc/day, otherwise may need pericardial window (pleural>abdominal).
- **Pericarditis**:
  - **Classification**: acute (<6 wks), subacute (6 wks to 6 mo), chronic (>6 mo).
  - **Epidemiology**: 5% of pts in ED w/ CP and no MI, male predominance.
  - **Etiology**: 85-90% idiopathic (usually viral/post-viral), bacterial, fungal, post-MI, uremic, mycobact.(TB), autoimmune (CTD, vasculitis), malignancy (e.g. lung, breast), XRT, drugs (proacainamide, hydral, INH)

Clinical Manifestations and Diagnosis:
- **Symptoms**: sudden onset, pleuritic, retrosternal CP relieved w/ sitting up & leaning forward (may radiate to trapezius muscles), +/-pulmonary involvement if effusion is present. If uremic or CTD pericarditis: CP may be absent.
- **Exam**: pericardial friction rub (~30% cases), best heard at LLSB w/ diaphragm of stethoscope at endexpiration w/ pt leaning forward
- **ECG**: 4 stages: (1) ↑ ST & ↓ PR [NB: ↑ 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. In uremic pericarditis: ECG often normal b/c epicardium not inflamed.
- **Diagnosis**: ≥ 2 of the following: (1) characteristic CP, (2) friction rub, (3) suggestive ECG changes, (4) pericardial effusion
  - Workup: infectious w/u, BUN/Cr, ANA/RF/CCP, HIV, IGRA, ESR/CRP, troponin (elevated in ~30%, indicative of myopericarditis)
  - TTE: assess for presence/size/location of co-existing effusion and/or tamponade physiology
  - Pericardiocentesis/Surgical Drainage: if (1) suspect malignancy or bacterial etiology (2) large effusion (> 2cm) (3) tamponade

Treatment: self-limited (days-weeks) in 70-90% of cases
- **Hospitalization**: fever, ↑WBC, large effusion (> 2cm), immunocompromised, anticoagulated, trauma, ↑troponin, unstable/signs of tamponade, failure to respond to NSAIDs after 7d (NB: also consider hospitalization if subacute presentation)
- **First-line treatment: NSAIDs** (e.g. ibuprofen 600-800mg TID; ASA 650-1000mg TID) + colchicine 0.6mg BID (QD if pt <70kg)
  - Colchicine: sig ↓ sxs at 72hrs (15% vs. 40%), improves 1-wk remission (85% vs 55%), and 18-mo recurrence (10% vs. 32%) in acute idiopathic pericarditis (Circ 2005;112:2012, NEJM 2013;369:1522, Heart 2012;98:1078). No benefit w/ malign/uremic cases
  - ASA: preferred over NSAIDs if: (1) post-MI, (2) CAD, (3) concomitant anti-PLT/anticoagulant therapy
- **Glucocorticoids** (prednisone 0.2-0.5mg/kg/d): preferred over NSAIDs if: (1) symptoms refractory to 7d of NSAID trx; (2) recurrent (>2 episodes); (3) uremic pericarditis (4) CTD pericarditis; (5) contra-indications to NSAIDs
- **Duration**: NSAIDs: 1-2 wks until symptoms resolve, then taper (total time of therapy: 3-4 weeks); Colchicine: 3 mo; Glucocorticoids: 2 wks, then taper (total time of therapy: 3 months). If prednisone ineffective: azathioprine, anakinra, surgical pericardiectomy.
Aortic Disease

Sumeet Khetarpal

Aortic Aneurysms (JACC 2016;68:1054)

<table>
<thead>
<tr>
<th>AAA</th>
<th>TAA</th>
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<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>- 4-8% if age &gt;65</td>
<td>- Structural/genetic: Mostly in root and ascending aorta. Causes: CTD disease (Marfan, Ehlers-Danlos, Loeys-Dietz), Turner, bicuspid AoV, trauma</td>
</tr>
<tr>
<td>- Most infrarenal</td>
<td>- Infectious: 3° syphilis, mycotic aneurysm (most common org: Staph spp., Salmonella spp.)</td>
</tr>
<tr>
<td></td>
<td>- Inflammatory: GCA (~10% have TAA), Takayasu, RA, psoriasis, Behcet’s, Wegener’s, IgG4</td>
</tr>
<tr>
<td>**Screening/</td>
<td><strong>Surveillance</strong></td>
</tr>
<tr>
<td>Surveillance</td>
<td>- General population: Not recommended</td>
</tr>
<tr>
<td>- ACC/AHA: One-time abd. ultrasound in all men &gt;60 w/ Fxh of AAA (IC) and all men &gt;65 that have ever smoked (IA)</td>
<td>- Indications: At time of dx of Marfan (IC), Turner (IC), Loeys-Dietz, Takayasu or GCA. 1st deg relatives of pt w/ TAA, dissection, bicuspid valve (IB/IC).</td>
</tr>
<tr>
<td>- USPSTF: One-time abd. ultrasound for men age 65-75 who have ever smoked (Grade B) and selective screening for male never smokers 65-75 (Grade C). Screening women not recommended.</td>
<td>- Surveillance: If aneurysm only, then same as AAA. If also with dissection, image at 1, 3, 6, &amp; 12 months then annually. Image entire aorta (CT/MRI) if multiple aneurysms (~25% TAA will have AAA; ~25% AAA will have TAA).</td>
</tr>
<tr>
<td>- <strong>Surveillance:</strong></td>
<td></td>
</tr>
<tr>
<td>3-3.4 cm: U/S q3y</td>
<td></td>
</tr>
<tr>
<td>3.5-4.4 cm: U/S or CT q12mo</td>
<td></td>
</tr>
<tr>
<td>4.5-5.4 cm: U/S or CT q6mo</td>
<td></td>
</tr>
<tr>
<td><strong>Imaging Modalities</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>- Abdominal U/S: screening and surveillance of infrarenal AAAs. High Se/Sp (&gt;90%), operator-dependent</td>
<td><strong>Medical:</strong></td>
</tr>
<tr>
<td>- CT w/ contrast: high Se/Sp, better than U/S for suprarenal AAAs</td>
<td>- Smoking cessation (slows AAA growth by up to 25%)</td>
</tr>
<tr>
<td>- MRI/MRA: good Se/Sp, preferred for aortic root imaging and for imaging tortuous aortas</td>
<td>- Reduce BP in accordance with ACC/AHA standards</td>
</tr>
<tr>
<td>- CXR: ‘enlarged aorta’ nonspecific (tortuous aorta vs. aneurysm)</td>
<td>- Meds: Statins (reduce all-cause mortality in pts s/p surgery); BBs (may slow expansion; IA for perioperative use); ACEi (controversial; may prevent rupture but may speed growth); low dose ASA (may slow growth); antibiotics (e.g., roxithromycin may reduce expansion rate, not mortality)</td>
</tr>
<tr>
<td>- TTE: useful for root and proximal thoracic aorta; TEE will visualize entire thoracic aorta but rarely used.</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical:</strong></td>
<td><strong>Medical:</strong></td>
</tr>
<tr>
<td>- Men: &gt;5.5cm OR growing at &gt;0.5cm/yr OR symptomatic Women: &gt;4.5-5cm (controversial)</td>
<td>- Reduce BP (&lt;140/90 or &lt;130/80 if DM or CKD; little actual evidence, IB)</td>
</tr>
<tr>
<td>- Open repair (~4-6% 30 day mortality) vs. EVAR (only ~50% suitable, c/b endoleaks [continued blood flow into aneurysmal cavity, ~1% 30 day mortality]).</td>
<td>- BBs proven to decrease TAA growth in Marfan</td>
</tr>
<tr>
<td>- Dissection: pain (chest/abdomen/back), occlusion of aortic vessels, thromboembolism</td>
<td>- ARBs slow aortic root aneurysm expansion in Marfan patients, likely via TGF-B inhibition (NEJM 2008; 358:2787)</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td><strong>Surgical:</strong></td>
</tr>
<tr>
<td>- Rupture: Devastating mortality. AAA annual rupture rates are 4%, 7%, 20% at 5, 6, and 7cm, respectively. Risk factors: size, rate of expansion, female gender</td>
<td>- Root/ascending TAAs: usually concomitant aortic valve replacement</td>
</tr>
<tr>
<td>- Symptoms: Triad of abd/back pain + pulsatile abd mass + hypotension → immediate OR (don’t image)</td>
<td>- Arch/descending TAAs: mostly open graft, (EVAR). Ischemic brain/spine injury most worrisome complication.</td>
</tr>
<tr>
<td>- Dissection: pain (chest/abdomen/back), occlusion of aortic vessels, thromboembolism</td>
<td></td>
</tr>
<tr>
<td>- Post-repair: EVAR: endoleak, graft failure, thrombosis. Open: MI, embolization, AKI, ischemic colitis</td>
<td></td>
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</tbody>
</table>
Acute Aortic Syndromes (AAS) (Nat Rev Cardiol 2015;12:103)

Definitions:
- Acute Aortic Syndrome (AAS): three distinct processes within the aortic wall, all which have inherent risk of aortic rupture
  - Aortic Dissection (AD): intimal tear resulting in development of false lumen
  - Intramural Hematoma (IMH): rupture of vasa vasorum causing hemorrhage within aortic wall resulting in hematoma w/o tear
  - Penetrating Aortic Ulcer (PAU): Ulceration of atherosclerotic plaque that penetrates into intima of aortic wall

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

Epidemiology:
- Prevalence: Among the AAS, AD most common (62-88%), followed by IMH (10-30%) and PAU (2-8%)
- Risk Factors:
  - Male sex (65%), HTN (72%)
  - Age (avg 60-70 yo). If < 40 yo, think Marfan Syndrome or other CTD.
  - Additional risk factors: atherosclerosis, prior cardiac surgery, aortic aneurysm, family history of AAS, aortitis, trauma, pregnancy
- Prognosis:
  - Aortic Dissection:
    - Type A: Medical: 50% 2-week mortality, 90% 1-year mortality. Surgical: 10-35% mortality.
    - Type B: Medical: 9% in-hospital mortality, 16% 1-year mortality, 20% 5-year mortality.
  - IMH: Will progress to complete dissection in 28-47% of pts
  - PAU: Will progress to aortic rupture in 42% of pts (highest among all AAS)

Diagnosis:
- Clinical Features: AD, IMH, and PAU cannot be distinguished by presentation alone
  - Signs: AI murmur, pulse deficit, upper extremity BP differential (>20mmHg), CHF
  - Symptoms: Chest or back pain most commonly reported sx in 61-84% of patients with AAS (radiates to neck/jaw if ascending; back/abdomen if descending)
- Complications: Syncope, shock, tamponade, branch artery occlusion (MI, CVA, paraplegia, cold extremity, renal failure)
- Labs:
  - D-dimer: < 500ng/mL has 96% NPV for absence of aortic dissection (can still be positive in other AAS)
  - Troponin: High Sn and Sp for diagnosis of ACS; however, AAS may still be present even if + (extension into coronaries)
- Imaging:
  - CXR: 50% of patients with AAS have normal CXR; only 1/3 will have widened mediastinum
  - CT: Sn: 95%, Sp: 87-100% First-line imaging modality in patients with high clinical probability of AAS.
    - Combined I+I- (assess for IMH, mediastinum hemorrhage, or hemopericardium)
  - TEE: Sn: 73-100% Sp: 71-91%, least accurate of diagnostic imaging modalities
  - MRI: Also highly accurate for detecting AAS: Sn: 95-100%, Sp: 94-98%
  - TTE: Sn: 99%, Sp: 90-100% for AAS. Often used intra-op to confirm dx prior to surgery.
  - MRI: Also highly accurate for detecting AAS: Sn: 95-100%, Sp: 94-98%
  - Rarely used in the initial evaluation of AAS due to long acquisition time in the MRI suite

Management:
- Goal: "impulse control" → minimize aortic wall stress by decreasing LV ejection force (dP/dT): HR < 60bpm, SBP < 100-120mmHg
- Agents: First-line is IV beta blockade (esmolol, labetalol). If additional BP control required, consider IV nitroprusside, TNG, nicardipine
  - NEVER use vasodilators without concomitant beta blockade → will increase wall stress, thereby increasing dP/dT
- Aortic Dissection:
  - Type A: Immediate open surgical repair 10-35% intra-operative mortality vs. 90% at 1 year with medical management
  - Type B: Uncomplicated: Medical therapy (80% survival at 5 years); Complicated (compromise of renal/mesenteric vessels): TEVAR preferred to open surgery (which has 25-50% in hospital mortality)
- IMH and PAU:
  - Type A: Urgent (i.e., within days) open surgical repair
  - Type B: Medical management or TEVAR (endovascular repair generally reserved for those with higher risk features such as persistent pain, growth over time, aortic expansion or rupture, compromise of renal/mesenteric vessels)
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 (hypoglycemia, hypoxia, intoxication, etc.)
- **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, EKG features of ischemia/arrhythmia, FHx of SCD, preexcitation syndromes, high-risk occupation (e.g., airline pilot)
  - San Francisco Syncope Rule (SFSR)—admit pt if >1 of: EKG changes or non-sinus rhythm, dyspnea, Hct<30, SBP<90, HF
- **Ddx:** seizure, metabolic causes (hypoglycemia, hypoxia), intoxication, vertebrobasilar TIA, fall, psychiatric

Etiology and Diagnosis:

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Historical Features</th>
<th>Diagnosis</th>
</tr>
</thead>
</table>
| Reflex (60%)      | **Vasovagal (VV)**
  - Situational: cough, sneeze, laugh, micturition, defecation
  - CSS: neck turning/surgery/irradiation | **Vasovagal:** Can dx w/ **tilt table test** *(Class IIa)* (Sn 32-85%, Sp 90%) *(JACC 1996;28:263)* |
| Orthostasis (15%) | Prodrome of dizziness, nausea, warmth, diaphoresis, pallor. Risk factors for autonomic failure:
  - 1°: PD, Lewy body, Shy-Drager
  - 2°: DM, amyloid, spinal cord injury, chronic EtOH, Lyme, syphilis, B12
deficiency, meds (vasodilators, diuretics, BB, TCAs, PD meds, opiates) | **Orthostatic vital signs:** (systolic ↓ 20mmHg or diastolic ↓10mmHg within 3 min of standing)
  - **NB:** ↑ HR **NOT** part of definition
  - **Consider:** Guaiac, Hct, A1C, SPEP if c/f amyloid, RPR, B12 |
| Cardiogenic (15%) | **Arhythmia**
  - Structural
  - Obstruction (e.g., PE, tamponade)
  - Dissection
  - No prodrome, syncope while in sitting or supine position, palpitations, family or personal history of heart disease | **Causes of Cardiac Syncope in Young People (+ EKG signs):**
  1. WPW (delta wave)
  2. HOCM (LVH, apical TWI)
  3. Brugada (pseudo-RBBB with coving/saddleback pattern in V1-V2)
  4. Long QTc syndrome (QTc >500ms)
  5. ARVC (Epsilon wave)
  - **Consider cardiac monitoring** on basis of frequency and nature of syncope events (inpatient telemetry, Holter, Zio patch, implantable cardiac monitor).
  - **ONLY consider TTE if hx suggestive of cardiac cause <1% yield if no underlying heart disease and normal ECG**
  - **Consider PE if no other apparent cause Identified in 17.3% of pts hospitalized with 1st episode of syncope (and 25.4% of pts with no other apparent cause for syncope) *(PESIT NEJM 2016;375:1524)* |
| Neurologic (<10%) | **Seizure:** Tongue biting, urinary/fecal incontinence, aura, postictal confusion.
  - Focal deficits: stroke, TIA
  - **Steal:** syncope after arm exercise | **Seizure:** EEG
  **Stroke:** CT, MRI/MRA
  **Steal: UENI w/ Dopplers (specify for subclavian steal)**
  **NB:** carotid dopplers of **low clinical utility** *(changes management in <2% of patients)* *(JAH 2014;3:e001063)* |

Treatment:
- **Reflex:**
  - (a) Avoid provocative stimuli; (b) isometric counterpressure maneuvers of the limbs (e.g., leg crossing, hand grip, Valsalva, squatting); (c) medications used in select cases only (i.e. midodrine, fludrocortisone, βB). *(NEJM 2005;352:1004)*
- **Orthostasis:**
  - Secondary: treat underlying etiology, replete volume (NS, consider salt tablets), d/c contributing meds
  - Primary: **midodrine** (5-20mg TID), **fludrocortisone** (0.1-0.2mg QD), pyridostigmine, droxidopa (for PD-associated orthostasis)
- **Cardiogenic:** Based on etiology, follow guideline directed management and therapy.

Recommendations from **2017 AHA/ACC/HRS Syncope Guidelines**

*Usama Abassi, Sean Mendez*
Hypertensive Urgency & Emergency

Definitions, Triage, and Management:
- Hypertensive urgency: BP >180/120 without evidence of end-organ damage (may have mild headache)
- Hypertensive emergency: BP >180/120 with evidence of end-organ damage
  - End organ damage = Neuro: HTN encephalopathy (severe HA, seizure, AMS), PRES, TIA, CVA (SAH, ICH);
    Retinopathy: papilledema, hemorrhage; Resp/CV: pulm edema, MI, +cTN, angina, Ao dissection; Hem: MAHA; Renal: AKI, hematuria
- NE: no standardized def'n of HTN crises; absolute values not as important as rate of rise and Δ from baseline Chest 2007;131:194

<table>
<thead>
<tr>
<th>Triage location</th>
<th>Hypertensive Urgency</th>
<th>Hypertensive Emergency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floor vs. outpatient management (can be managed in ambulatory setting with close follow up)</td>
<td>JAMA IM 2016;176:381</td>
<td>Floor vs. ICU (ICU → if need for arterial line, continuous infusion of anti-HTN medications, or severe end-organ damage)</td>
</tr>
</tbody>
</table>

| Correction time course | Reduce BP to <160/100 over the course of several hours; then reduce to normal range (<130/90) over 1-2 days | Reduce MAP 10-20% within the first hour, and no more than 25% over first 24 hours. Then reduce to normal range (<130/90) over 1-2 days |

| Route of medication administration | Initial PO short-acting medications; convert to long-acting prior to d/c | Initial short-acting titratable IV agents; transition to PO agents for floor/discharge |

| Suggested medications (see below for dosing table) | PO: captopril, labetalol > hydralazine, (unpredictable effect, reflex tachycardia), isosorbide dinitrate | IV: labetalol, hydralazine
Topical: nitropaste (may be used on the floor)
Gtt: labetalol, nitroglycerin, nitroprusside, esmolol, nicardipine, clevidipine, fenoldopam (rarely used) |

Comments: Assess compliance with prior medication regimen before aggressively uptitrating in order to avoid overcorrection of BP leading to hypotension

*Specific management situations:
- Ischemic CVA: permissive hypertension (goal: <185/110 if tPA, <220/120 if no tPA)
- Aortic dissection: BP should immediately be reduced to SBP<120mmHg and MAP<80mmHg within 20 minutes to avoid shearing forces (dP/dt)

### Antihypertensive Medication Dosing – ICU – choice of agent depends on indication

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Onset</th>
<th>Duration</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol (IV)</td>
<td>500µg/kg load + 25-50µg/kg/min; then adjust by 25µg/kg/min q10-20min up to 300 µg/kg/min</td>
<td>&lt;1min</td>
<td>10-20min</td>
<td>Ao diss., CAD</td>
</tr>
<tr>
<td>Labetalol (IV)</td>
<td>0.5-2mg/min, adjust to goal, max dose 10mg/min</td>
<td>&lt;5min</td>
<td>3-6 hrs</td>
<td>Ao diss.</td>
</tr>
<tr>
<td>Nitroprusside (IV)</td>
<td>0.25-2mcg/kg/min (dose limit to avoid cyanide toxicity), temporarily (&lt;10min) can use up to 10mcg/kg/min.</td>
<td>&lt;1min</td>
<td>&lt;2min</td>
<td>AS/LVSD and HF; not CAD (cф coronary steal), CVA, high ICP</td>
</tr>
<tr>
<td>Nitroglycerin (IV)</td>
<td>Start 5µg/min, titrate by 5µg/min q5-10minutes, Max= 400µg/min (if no response by 200 µg/min= non-responder)</td>
<td>2-5 min</td>
<td>5-10 mins</td>
<td>ACS, flash pulmonary edema.</td>
</tr>
<tr>
<td>Nicardipine (IV)</td>
<td>Start at 5mg/h, 1 by 2.5mg/h q5-15 min to max 15mg/h</td>
<td>&lt;10min</td>
<td>30 min</td>
<td>SAH, Ao diss. (w/ BB)</td>
</tr>
<tr>
<td>Clevidipine (IV)</td>
<td>Start a 1 mg/h, max 21mg/h.</td>
<td>2-4 min</td>
<td>5-15 min</td>
<td>HTN post-card surg</td>
</tr>
</tbody>
</table>

### Antihypertensive Medication Dosing – Floor

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Onset</th>
<th>Duration</th>
<th>Specific Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>IV 20-80mg q10min until effect seen, then use PO</td>
<td>5-10 min</td>
<td>3-6 hrs</td>
<td>Ao dissection, CVA; avoid if ADHF</td>
</tr>
<tr>
<td>PO</td>
<td>Start 100mg q8-q12h (max: 2400mg/day)</td>
<td>20 min</td>
<td>8-12 hrs</td>
<td>Eclampsia</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>IV 5-20mg q30min until see effect, then use PO</td>
<td>10-20 min</td>
<td>1-4 hrs</td>
<td>Eclampsia</td>
</tr>
<tr>
<td>PO</td>
<td>Start 10 mg Q6H, inc by 10-25mg/dose q2-5d.</td>
<td>20-30 min</td>
<td>~8 hrs</td>
<td>Routine mgmt</td>
</tr>
<tr>
<td>Captopril (PO)</td>
<td>12.5-25mg q8h (do NOT dose TID)</td>
<td>30-90 min</td>
<td>6-8 hrs</td>
<td>Routine mgmt</td>
</tr>
<tr>
<td>Lisinopril (PO)</td>
<td>Initial 2.5-5 mg QD. Inc 10 mg q2 weeks to max of 40 mg QD. (Can use ARB if ACEI intolerance).</td>
<td>1 hr</td>
<td>24 hrs</td>
<td>Routine mgmt</td>
</tr>
<tr>
<td>Amlodipine (PO)</td>
<td>Initial 5 mg QD. Inc 2.5 mg q7 days to max 10 mg QD. Requires few days to take effect.</td>
<td>24-48 hrs</td>
<td>24 hrs</td>
<td>Routine mgmt</td>
</tr>
<tr>
<td>Nifedipine (PO)</td>
<td>10-30mg TID. Use with caution (may cause pronounced vasodilatation, orthostasis)</td>
<td>20 min</td>
<td>6-8 hrs</td>
<td>Routine mgmt</td>
</tr>
<tr>
<td>Hydrochlorothiazide (PO)</td>
<td>Initial 12.5 mg QD (max: 50 QD, doses &gt;25mg associated with ↑ electrolyte abnabnormalities)</td>
<td>2 hrs</td>
<td>6-12 hrs</td>
<td>Routine mgmt</td>
</tr>
<tr>
<td>Isosorbide dinitrate (PO)</td>
<td>Initial 5-20mg 2-3 times/day (dose TID not q8h for nitrate holiday). Mononitrate = long-acting</td>
<td>1 hr</td>
<td>~8 hrs</td>
<td>Anti-anginal, CHF</td>
</tr>
<tr>
<td>Nitropaste (Topical)</td>
<td>0.5-1.5 inches. Apply to chest. Need 10-12hr nitrate holiday to avoid tachyphylaxis.</td>
<td>15-30 mins</td>
<td>~12 hrs</td>
<td>If lacking IV/PO access</td>
</tr>
</tbody>
</table>
PERIPHERAL ARTERY DISEASE

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

Clinical Presentation and Diagnosis:
- **Symptoms:** classic claudication (10-35%); reproducible exertional pain in muscles distal to occlusion; *atypical leg pain (40-50%); asymptomatic (20-50%)* (Circulation 2006;113:e463). Critical Limb Ischemia (CLI) (1-2%): rest pain (improved w/ hanging feet off bed or walking), ulcers at pressure points, dry gangrene, > 2-wks duration (vs. ALI).
- **Exam:** arterial bruit, diminished peripheral pulses, ↓ cap refill, pallor on elevation, ulcers, atrophic changes, ↓ hair growth
- **ABI:** Doppler US. Ratio of pressure (higher of the two) to brachial SBP. Nl: 1.0-1.40; Borderline: 0.91-0.99; Abnl ≤0.9. o Resting(R)/Post-exercise(PE): Mild: Rs ≤0.90; Mod: R ≤0.70, PE ≤0.50; Sev: R ≤0.50, PE ≤0.15. CLI: R ≤0.40, rest pain.
  - If ABI abn, obtain segmental ABI w/ pulse volume recording (PVR) to localize the disease
  - ABI ≥1.30 suggests ↓ compressibility usually due to ↓ calcifications (e.g., elderly, DM, ESRD). Further evaluate w/ PVR.
- **Exercise testing:** if high suspicion for PAD and normal resting ABIs.
- **CTA (with distal run off), MRA, or Angiography:** if considering revascularization.

Treatment:
- Optimize cardiac risk factors (e.g., HTN, DM, HLD, weight loss), **formal exercise program,** high-intensity statin, **smoking cessation**.
- **Anti-platelet therapy:** for symptomatic pts, ↓ MI, CVA, vascular death. ASA 75-325mg QD or clopidogrel 75mg QD or ticagrelor 90mg BID (NEJM. 2017;376:32); vorapaxar 2.08mg QD: thrombin-receptor antagonist, ↓ revascularization and hospitalizations (JACC 2016;9:2157). Avoid DAPT unless clinically indicated.
- **Rivaroxaban** 2.5mg BID plus ASA decreased major adverse cardiac and limb events compared to ASA alone, but increased major bleeding w/o inc in fatal bleeding in pts w/ stable PAD (Lancet 2016;381:219)
- **Clopidogrel** 100mg BID. Adjunct agent, ↑ exercise capacity (Am J Cardiol 2002;90:1314). Contraindicated in HF.
- **Endovascular repair** (angioplasty vs. stent) if: (1) CLI, (2) severe symptoms refractory to medical management.

Acute Limb Ischemia (ALI):
- **Sudden decrease in limb perfusion threatening viability.** (BMJ 2000;320:764).
  - **Viable:** no immediate threat of tissue loss; audible arterial Doppler signal, intact motor/sensory.
  - **Threatened:** salvage requires prompt intervention; no audible arterial Doppler signal, motor or sensory.
- **Etiologies:** embolic (e.g., AF, endocarditis) > acute thrombosis (e.g., atherosclerosis, APS, HITT), trauma.
- **Precipitating factors:** Dehydration, hypotension, abnormal posture (i.e. kneeling), malignancy, hyperviscosity, hypercoagulability
- **Presentation:** (6Ps) pain, paresthesia (unable to sense light touch), paralysis
- **Diagnosis:** Pulse (w/ Doppler) + neuro checks; Angiography (CT w/ b/l run-offs or arteriography).
  - **Precipitating factors:** Dehydration, hypotension, abnormal posture (i.e. kneeling), malignancy, hyperviscosity, hypercoagulability

Common Cardiotoxicities (Circ Res 2016;118:1008):
- Anthracyclines (doxorubicin): HF, LV dysfunction (5-23% pts), based on cumulative dosage
- HER2 agents (trastuzumab): 2.1% risk in reducing LV function, resolves once stopped, TTE q3mo
- TKI (esp with sunitinib): HF, cardiac dysfunction
- Angiogenesis inhibitors (bevacizumab, lenalidomide): HTN, 3-fold ↑ in arterial TE events
- Platinum-based (cisplatin): HTN, HL, CAD, thromboembolic, in advanced testicular disease
- Microtubule inhibitors (paclitaxel): arrhythmias
- Anti-metabolites (5-FU, cytarabine): MI, angina, CP, EKG changes, 1-8% pts, early onset
- Immune checkpoint inhibitor (ICI): fulminant lymphocytic myocarditis, HF, cardiac arrest; onset variable, risk factor = combo therapy
- Radiation: CAD (up to 85%), periperalzd (6-30%), CM (up to 10%), valvular abn, PVD, arrhythmias, autonomic dysfunction, can occur 10-15 yrs later, many risk factors incl dosage, metabolic RF

CARDIO-ONCOLOGY

**JACC 2017:70:2552**
- **Definition:** Toxicities include HF, ischemia, HTN, myocarditis, pericardial dz, thromboembolism, QTc prolongation, arrhythmia; chemo-induced CM = EF drop ≥10% to < 55% w/o sx or decline ≥5% to < 55% w/sx (Eur Cardiol. 2016;13:64)
- **Risk factors:** Heart disease, DM, HLD, Young or Old, Female, High-dose chemo
  - **Dx:** Baseline TTE, EKG, TnT elevation correlates to adverse cardiac events post-chemo; MRI/PET/bx if suspect immune checkpoint inhibitor myocarditis (Lancet Oncology 2018;19:e447)

**Prevention:**
- Anthracycline: use liposomal-encapsulated form, continuous infusion, dexrazoxane; avoid if EF ≤ 45%
- Consider BB/ACE-I if EF < 50%, EF drop > 10% or abnl TnT, unclear but potential beneficial role for ppx ACE-I and/or BB in better LVEF preservation in anthracyline-based therapies (Am J Clin Oncol 2018;41:909). ARB > BB protection against LVEF decline in early breast Ca with adjuvant tx (Eur Heart J. 2016;37:1671)
- Consider pre-emptive vasodilators/serial EKGs in 5-FU + capcitabine

**Monitoring:**
- **TTE surveillance schedule depends on therapy and baseline cardiac risk; ranges from Q3 Q6 months with long-term risk > 10yrs**
- Monitor weekly BP in 1st cycle, then Q2-3wks on therapy, initiate therapy when DBP > 20mmHg
- **Cessation of chemotherapy is a last resort**
  - **Appropriate risk factor modification, standard HF therapy, ischemia w/u and tx (stress/cath, ASA if PLT > 10k, DAPT if PLT > 30k)**
  - Stress testing w/5-10 yrs after chest radiation
  - **ICI myocarditis:** stop therapy, glucocorticoids/other immunosuppressives; re-challenging will depend on type of cardiotoxicity

Erika Parisi, Charlotte Lee

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Cardiology

Outpatient CV Health

Epidemiology of Cardiovascular Disease

Overview: Leading cause of death in developed countries; CVD includes (1) CAD, (2) CVA, (3) PAD, (4) Aortic disease

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

Aspirin for CVD Prevention
- Aspirin traditionally used for 1st prevention in healthy pts with ASCVD risk ≥10%; however, ASCEND (pts >40 with diabetes), ARRIVE (moderate CVD risk pts), and ASPREE (elderly pts >70) showed variable CV benefit at expense of increased bleeding events

Outpatient Blood Pressure Screening and Management

2017 NEW ACC/AHA guidelines: HTN = SBP > 130 and/or DBP > 80 independent of kidney function or age; US prevalence = 46%
- Method: 2 checks > 1wk apart, sitting 5min with arm at heart level, cuff bladder 80% length & 40% width of arm circumference
- 24h ambulatory SBPs show greater association w/ all-cause mortality than clinic BPs. Masked HTN (normal BP in clinic, ↑ outside) more strongly associated than sustained HTN (↑ in both) or white coat HTN (↑ in clinic, normal outside).

Definition: Normal BP: <120/(and)<80; elevated BP: 120-129/(and)<80; stage 1 HTN: 130-139/(or)80-89; stage 2 HTN: >140/(or)>90

Initial Workup: BMP, UA (with protein/Cr ratio), CBC, TSH, lipids, baseline EKG (consider TTE to assess for LVH)

2° HTN: Indications for workup include:
- Severe HTN (control w/ 4+ agents) or resistant HTN (not controlled on 3+ agents)
- Acute rise in blood pressure in a previously well-controlled patient, esp. diastolic BP
- Age less than 30 years without risk factors (e.g., obesity, fam hx)

### Secondary Causes of HTN

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical Clues</th>
<th>Work-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications (use or withdrawal)</td>
<td>NSAIDS, OTC decongestants, OCPs,</td>
<td>Thorough history</td>
</tr>
<tr>
<td></td>
<td>sudden d/c of anti-HTN meds (i.e., clonidine)</td>
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</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>Obesity, snoring, smoking</td>
<td>Sleep study</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Elevated Cr, protein/blood on UA</td>
<td>See AKI and CKD sections</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>Hypokalemia, hypernatremia, adrenal</td>
<td>Plasma ald:renin activity; ratio&gt;30. MUST measure in the morning (~ 8AM), after being upright/ambulatory for &gt;3 hrs, with both drawn at same time</td>
</tr>
<tr>
<td></td>
<td>incidentaloma, family history</td>
<td></td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>&gt;50% rise in Cr after ACEi initiation</td>
<td>If intervention likely to be pursued, begin with Doppler US (Se: 85%, Sp: 92%) → if stenosis (ARAS&gt;50%) or ambiguous results, then angiography</td>
</tr>
<tr>
<td></td>
<td>Lateralizing abdominal bruit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atrophic or asymmetric kidneys</td>
<td></td>
</tr>
</tbody>
</table>

Rare: Pheochromocytoma (screen w/ 24h urine fractionated metanephrines/catecholamines [Se 98%, Sp 98%], plasma frac metanephrines if high suspicion), Cushing's disease, hyper/hypothyroidism, hyperparathyroidism, aortic coarctation, ADPKD

Lifestyle counseling (J Am Coll Cardiol. 2014;63:2960)

<table>
<thead>
<tr>
<th>Exercise</th>
<th>40 min per day, 3-4x week, moderate to vigorous intensity</th>
<th>↓ 5mmHg for aerobic exercise, unclear for resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Dash diet (salt intake &lt; 2g per day); dec sweets &amp; red meat</td>
<td>↓ 8-14 mmHg (DASH); dec by 2-8 mmHg (low Na)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Limit to &lt; 2cup per day</td>
<td>↓ 5/2.5 mmHg</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Limit consumption (&lt; 2-3 standard drinks per day)</td>
<td>↓ 2-4 mmHg</td>
</tr>
</tbody>
</table>

Medical Management – 2017 ACC/AHA Guidelines

When to Treat | Stage II HTN or Stage I if: (a) clinical CVD; (b) DM2; (c) CKD; or (d) ASCVD>10% |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Target BP</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Choice of Agent</td>
<td>First line: thiazides (NB: chlorthalidone &gt; HCTZ), ACEi, ARB, CCB. Other: ββ, hydralazine, isosorbide, clonidine, α-blockers (ex: doxazosin), minoxidil (rare)</td>
</tr>
<tr>
<td>Compelling Indications</td>
<td>African-American: CCB, thiazide DM2: ACEi, ARB (if albuminuria)</td>
</tr>
<tr>
<td></td>
<td>CAD: ACEi, ARB, BB CKD: ACEi, ARB</td>
</tr>
</tbody>
</table>

Monitoring:
- BP check 2-4 weeks after change in medication (home readings vs. office)
- Labs: yearly BMP/Mg if on ACEi/ARB or diuretic

Important Trials for considering goal SBP
- SPRINT: High risk for CVD: SBP goal <120 vs 135-139 ↓ CVD events and all-cause mortality but ↑ non-orthostatic hypotension, syncope, electrolyte abnormalities, and AKI.
- ACCORD BP: Showed no benefit for CV mortality in pts w/ DM for SBP goal of <120 vs <140.

Outpatient Cholesterol Screening and Management

Screening: 2018 ACC/AHA guidelines refine ASCVD risk categories with focus on “risk-enhancing” factors to further adjudicate CV risk
- Screen adults ≥ 20 years
- Fasting not routinely needed unless evaluating for hyperTG; if non-fasting TG >400, then obtain fasting panel
- AHA criteria for FH: LDL-C >190 and either: 1° relative w/ LDL-C >190 or premature CAD or genetic testing for LDLR, APOB, PCSK9

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Outpatient CV Health

- Assess lipids 4-12 wks after initiation of med or dose change, repeat 3-12 mo as needed
  
  Lifestyle modification: weight loss, exercise, smoking cessation, diet low in sat. fat a/w 15-20 mg/dL ↓ in LDL-C, ~50% ↓ risk of CAD

### Indications for Lipid-Lowering Therapy

- Clinical ASCVD
- LDL-C ≥ 190
- Diabetes (age 40-75)
- Age 40-75 w/o above

ASCVD risk enhancers: FHx premature ASCVD, LDL-C ≥ 160, CKD, metabolic syndrome, inflammatory dz (RA, HIV, psoriasis), ethnicity (South Asian), TG ≥ 175, hs-CRP ≥ 2, apoB ≥ 30, apoA < 0.9. Coronary artery calcium (CAC) score 1-99 favors statin therapy.

### Common Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Indication</th>
<th>% ↓ in LDL-C</th>
<th>Effect on CV outcomes</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins*</td>
<td>HMG-CoA reductase inhibitor</td>
<td>- 1st-line therapy for 1° &amp; 2° prevention</td>
<td>20-60% LDL-C reduction</td>
<td>For 1° &amp; 2° prevention, ↓ CV events (ARR 1.1%, NNT 91, HOPE-3)</td>
<td>Myopathy, ↑ LFTs, memory loss and confusion</td>
</tr>
<tr>
<td>Ezetimibe (10mg QD)</td>
<td>↓ intestinal cholesterol absorption</td>
<td>- Statin-intolerant - LDL-C &gt; 70 w/ CVD or &lt;50% ↓ LDL-C w/o CV on max-tolerated statin</td>
<td>Ezetimibe + statin therapy ↓ LDL-C by ~23%</td>
<td>Ezetimibe + statin ↓ CV events (ARR 2%, NNT 50, IMPROVE-IT)</td>
<td>Mild ↑ LFTs (usually w/ statin)</td>
</tr>
<tr>
<td>PCSK9 inhibitors (alirocumab, evolocumab)</td>
<td>Enzyme that binds and degrades LDL-R on hepatocyte surface</td>
<td>High risk pts w/ CVD and LDL-C &gt; 70 on statin+ezetimibe; approved for use in FH</td>
<td>38-72% reduction; ~60% in pts on statin therapy</td>
<td>Evolocumab + statin ↓ CV events (ARR 1.5%, NNT 67 at 48 wks, FOURIER)</td>
<td>Uncommon; mainly injection site reactions. Cost: 150k/QALY</td>
</tr>
</tbody>
</table>

Note: if patient has concomitant severe hypertriglyceridemia (TG > 886 mg/dL), then also start fenofibrate (many formulations)

### Properties of Different Statins

- High-intensity: atorvastatin 40-80mg, rosuvastatin 20-40mg
- Moderate-intensity: atorvastatin 10-20mg, rosuvastatin 5-10mg, simvastatin 20-40mg, pravastatin 40-80mg, lovastatin 40mg
- Low-intensity: simvastatin 10mg, pravastatin 10-20mg, lovastatin 20mg

### Statin Potency

#### Benefits of Weight Loss on Comorbidities

- **To lose 1-2 pounds per week:**
  - Daily caloric intake should = Daily caloric requirement – 500
  - Daily caloric requirement = basal metabolic rate (BMR) + daily activity level + thermic effect of food [theoretically]

#### Benefits of Different Dyslipidemias

- **At risk for DM / DM**
  - 2.5-6kg weight loss over ≥2 yrs: ↓ risk T2DM 30-60%
  - 2-5% weight loss: ↓ HbA1c by 0.2-0.3% in 1-4 years

- **HDL**
  - 5-8kg weight loss: ↓ LDL 5 mg/dL, ↑ HDL 2-3 mg/dL

- **HTN**
  - 5% weight loss: ↓ SBP 3 mmHg & ↓ DBP 2 mmHg

- **CVD**
  - MI: HR 1.26 for overweight and HR 1.88 for obese

### Outpatient Obesity Screening and Management

**Definition:** Overweight BMI 25.0-29.9 kg/m²; Obesity BMI ≥ 30 kg/m²; Severe Obesity BMI ≥ 40 kg/m²

**Management:**

- **Set goals:** Target initial weight loss of 5-7% body weight
- **Diet:** Diet compliance (↓ # calories) more important than macronutrient composition. No data to guide specific diet choice. JAMA 2014;312:923
  - Mediterranean: High in monounsaturated fats, fruits, vegetables, legumes, grains; moderate dairy & EIOH; low meat (↓ overall mortality, CV mortality; may ↓ DM incidence independent of weight loss) PREDIMED NEJM. 2018 21:378
  - DASH: High in fruits/vegetables, moderate dairy, <25% caloric intake from fat (↓ SBP/DBP) Br J Nutr. 2015 14:113
- **Exercise:**
  - >30 min, 5-7 days/wk; combine aerobic + resistance training for optimal health gains Arch Intern Med 2009;169:122
  - Not sufficient for wt loss; improves glycemic control, BP, and physical functioning; ↓ CV risk, predicts long-term weight mgmt

#### Medications

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

#### Bariatric surgery

- Recommended for: BMI ≥ 40 OR BMI ≥ 35 with comorbid conditions; BMI ≥ 35 with insufficient evidence

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<tr>
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<th>Mechanism</th>
<th>Usage</th>
<th>Dosing</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Procaïnamide (IV)</td>
<td>Pronestyl</td>
<td>Na+ channel blockade; slows conduction; lengthens action potential</td>
<td>VT; atrial fibrillation, especially in accessory bypass tracts (WPW)</td>
<td>Load 20mg/min until total 17 mg/kg reached (e.g., ~1h, BP q8 min); then 1-4 mg/min in urgent situations, up to 50 mg/min may be given for a total max dose 17 mg/kg</td>
<td>HoTN, PVCG, VT, 1QT, drug-induced lupus, agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>Disopyramide (PO)</td>
<td>Norpace</td>
<td>Na+ channel blockade; also has anticholinergic effects</td>
<td>Used in HOCM (efficacy relates to negative inotropic effect), VT, AF, A-flutter</td>
<td>VT: If &lt;50kg ➔ load 200mg x1, then 100mg q6h If &gt;50kg ➔ load 200mg x1, then 150mg q6h AF conversion: 200mg q4-6h AF prevention: 400-750mg QD divided q6h</td>
<td>Anticholinergic side effects, negative inotropy, hypotension, ↑ QTc</td>
</tr>
<tr>
<td>IB</td>
<td>Lidocaine (IV)</td>
<td>Xylocaine</td>
<td>Na+ channel blockade; no effect on conduction; may shorten action potential</td>
<td>VT, pulseless VT/VF</td>
<td>Load: 1.0-1.5 mg/kg bolus IV. May give additional 0.5-0.75 mg/kg IV push PRN q5-10 min; max total: 3 mg/kg</td>
<td>Bradycardia, junctional arrhythmia, HoTN, angina, AMS, tremor, seizure, dysarthria, paresthesias, nausea, dizziness</td>
</tr>
<tr>
<td></td>
<td>Mexiletine (PO)</td>
<td>Mexitil</td>
<td>Na+ channel blockade; analog of lidocaine (PO form)</td>
<td>VT</td>
<td>Load: 400mg x1 Maintenance: 200mg q8hrs</td>
<td>Tremor, nausea</td>
</tr>
<tr>
<td>IC</td>
<td>Flecainide (PO)</td>
<td>Tambocor</td>
<td>Na+ channel blockade; Some β1 blockade</td>
<td>pAF (“pill in the pocket”), rarely ventricular arrhythmia</td>
<td>Pill in the pocket: 200mg(&lt; 70kg) or 300mg (&gt;70kg) max. once/24hrs</td>
<td>Ventricular arrhythmia (high risk if any structural heart disease)</td>
</tr>
<tr>
<td></td>
<td>Propafenone (PO)</td>
<td>Rythmol</td>
<td>Na+ channel blockade; Some β1 blockade</td>
<td>Same as above</td>
<td>Pill in the pocket: 450mg(&lt; 70kg) or 600mg (&gt;70kg) max. once/24hrs</td>
<td>GI sx, dizziness, pro-arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Esmolol (IV) [Br]</td>
<td>Brevibloc</td>
<td>β1 antagonist. 1/2 = 0.9 min</td>
<td>Acute HR/BP control in Ao dissection, SVT</td>
<td>Load: 20-30 mg IV (500 mcg/kg) x1 min Maintenance: 2-21 mg/min IV (25-300 mcg/kg/min)</td>
<td>As with other β-blockers (n.b. atenolol is renally cleared)</td>
</tr>
<tr>
<td></td>
<td>Atenolol (PO)</td>
<td>Tenormin</td>
<td>β1 antagonist, atenolol 2x more potent than metoprolol</td>
<td>SVT, ACS, post-MI, CAD, HTN, chronic HF</td>
<td>25-50mg QD (max: 100mg QD)</td>
<td>Crosses blood-brain barrier and may cause AMS. Less hypotension than β1 antagonists.</td>
</tr>
<tr>
<td></td>
<td>Propranolol (IV, PO)</td>
<td>Inderal</td>
<td>Non-selective β-blocker</td>
<td>Thyroid storm, Ao dissection, tremor, variceal bleed ppx, pheo, anxiety</td>
<td>IV: 0.5-1mg load, followed by 1-3mg every several hours PO: 120-320 mg/day (based on indication)</td>
<td>Changes in mental status. Less hypotension</td>
</tr>
<tr>
<td></td>
<td>Nadolol (PO)</td>
<td>Corgard</td>
<td></td>
<td>Variceal hemorrhage prophylaxis</td>
<td>20-80mg QD (max: 240mg)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Amiodarone (IV/PO)</td>
<td>Cordarone</td>
<td>Blocks K+ channels, slowing repol. Multiple effects including class la, II, and IV properties. Class II property (i.e., BB) is fastest effect.</td>
<td>SVT, VT, pulseless VT/VF</td>
<td>Pulseless VT/VF: 300 mg IV push, may repeat 150 mg IV push every 3-5 min as needed WQT: IV load with 150 mg IV x1 (may repeat q10 min as needed), then 1 mg/min IV x 6h (360 mg), then 0.5 mg/min IV x 18h (540 mg) PO: total 8-10 grams over days (200-400mg, BID-TID) Maintenance: 100-200 mg PO QD-BID</td>
<td>Hypotension (IV), bradycardia, ↑QT. Long half-life (56 days), Multiple systemic side effects with long-term use (lung, hepatotoxic, thyrotoxic – check baseline PFTs, LFTs, TFTs). Do NOT use for torsades, pre-excitation.</td>
</tr>
<tr>
<td></td>
<td>Ibutilide (IV)</td>
<td>Corvert</td>
<td>Blocks K+ channels; slows repol PR Hodgkin-Huxley (HH) model</td>
<td>AF/AFL</td>
<td>&gt;60kg: 1 mg over 10min; can repeat x1 in 10min &lt;60kg: 0.01mg/kg over 10min; can repeat x1 in 10min</td>
<td>Dose-related QT prolongation; 1.7% TdP, HA (3.6%)</td>
</tr>
<tr>
<td></td>
<td>Sotalol (IV, PO)</td>
<td>Betapace</td>
<td>Nonselective β1/β2 antagonist, K+ channel blocker</td>
<td>AF, VT</td>
<td>IV: Start 75mg IV q12h, may increase dose by 37.5mg/dose q3d (max: 600mg/day) PO: Start 80mg PO q12h, may increase dose by 40mg/dose q3d (max: 640mg/day)</td>
<td>QT prolongation, typical effects of β-blockade</td>
</tr>
</tbody>
</table>
# Cardiology

## Less Common Cardiac Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade</th>
<th>Mechanism</th>
<th>Usage</th>
<th>Dosing</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diltiazem (IV, PO)</strong></td>
<td>Cardizem</td>
<td>CCB→slows AV node conduction and phase II of the cardiac action potential</td>
<td>AF, AFib, SVT, MAt, angina&lt;br&gt;IV: 0.25 mg/kg (max 25 mg, usual 15-20 mg) IV&lt;br&gt;over 2 min; may repeat q15min as needed; gtt @ 5-15 mg/hr&lt;br&gt;PO: 120-320mg QD (max: 480/day) IV infusion: 5-10mg IV bolus over 2 min, repeat q15-30min PRN (max: 20-30mg); start gtt at 0.3mg/kg/hr if needed&lt;br&gt;PO: 80-120mg TID (max: 480/day)</td>
<td>Contraindicated in SSS, bradycardia, 2°AVB, 3°AVB, VT, AF + WPW, hypotension, pulmonary edema, HF/EF</td>
<td></td>
</tr>
<tr>
<td><strong>Verapamil (IV, PO)</strong></td>
<td>Calan, Verelan</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>Trade</td>
<td>Mechanism</td>
<td>Duration of Action</td>
<td>Initial</td>
<td>IV bolus max</td>
</tr>
<tr>
<td>----------</td>
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</tr>
<tr>
<td>Ethacrynic Acid (IV, PO)</td>
<td>Edecrin</td>
<td>Loop diuretic</td>
<td>6h</td>
<td>50 mg PO QD-BID</td>
<td>100 mg</td>
</tr>
<tr>
<td>Metolazone (PO)</td>
<td>Zaroxyl</td>
<td>Thiazide diuretic, inhibits NaCl channel in DCT. Used to augment loops.</td>
<td>24h</td>
<td>2.5-10 mg PO QD or 5 mg BID</td>
<td>No IV form</td>
</tr>
<tr>
<td>Chlorothiazide (IV, PO)</td>
<td>Dioril</td>
<td></td>
<td>6-12h</td>
<td>500-1000mg PO/IV QD-BID</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Spironolactone (PO)</td>
<td>Aldactone</td>
<td>Aldosterone antagonist (also tx acne, hirsutism)</td>
<td>48-72h</td>
<td>12.5-50mg QD-BID</td>
<td>No IV form</td>
</tr>
<tr>
<td>Eplerenone (PO)</td>
<td>Inspira</td>
<td>Unknown</td>
<td></td>
<td>25-50mg QD-BID</td>
<td></td>
</tr>
<tr>
<td>Acetazolamide (IV, PO)</td>
<td>Diamox</td>
<td>Carbonic anhydrase inhibitor</td>
<td>4-5h</td>
<td>PO/IV: 250-500mg QD-TID (max: 1,000mg daily)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Mannitol (IV)</td>
<td>Osmotrol</td>
<td>Osmotic diuretic</td>
<td>1.5-6h</td>
<td>12.5-25g IV push</td>
<td>~100 g</td>
</tr>
</tbody>
</table>

## Miscellaneous Cardiac Arrest, Chronotropic, and Emergency Medications

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Mechanism</th>
<th>Usage</th>
<th>Dosing</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Atropen</td>
<td>Anticholinergic (muscarinic)</td>
<td>Bradyarrhythmia, anticholinesterase overdose</td>
<td>Bradyarrhythmia: 0.5mg IV q3-5 min as needed, max 3mg Tracheal: 1-1.5mg in 3-5cc NS, follow w/ 5 breaths.</td>
<td>Tachyarrhythmia (but paradoxical bradycardia for dose &lt; 0.5 mg), worsening of infra-AVN block, ↓PO, anticholinergic effects</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Glucagen</td>
<td>↑cAMP in myocardium</td>
<td>β-blocker toxicity, CCB toxicity</td>
<td>3-10mg IV bolus (0.05-0.15mg/kg), gtt @ then 3-5mg/h</td>
<td>Nausea, vomiting, GI hypotonicity</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Adrenalin</td>
<td>Agonizes β1 (low dose), α1 (high dose), β2</td>
<td>ACLS, anaphylaxis, bronchospasm</td>
<td>ACLS: 1mg q3-5 mins OR 1-10 mcg/min gtt Anaphylaxis: 0.3-0.5 mg IM/SQ (1:1,000 solution) OR 0.1-0.3 mg IV (1:10,000 solution) q5-15 mins</td>
<td>Tachyarrhythmia, cardiac ischemia</td>
</tr>
<tr>
<td>Magnesium Sulfate</td>
<td></td>
<td>Cofactor for Na⁺/K⁺ ATPase, ↓Mg a/w ↓K, ↑PR, ↑Qt, PAC, AT, Pvc.</td>
<td>Torsades de pointes, bronchospasm, eclampsia</td>
<td>2g over 10-15 minutes; may repeat as needed (NB: max dose in eclampsia: 40gd/day!)</td>
<td>Hypotension, PR prolongation, AVB, negative inotropy, hypocalcemia, flushing, vasodilation, respiratory and CNS depression</td>
</tr>
</tbody>
</table>

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Respiratory Distress is a constellation of symptoms that portends impending respiratory collapse. It is different from dyspnea, which is the subjective sensation of shortness of breath. Key symptoms of respiratory distress are:
- Tachypnea (go look at the patient and measure yourself. RR ≥ 20)
- Cyanosis (typically SpO2 < 80%)
- Increased WOB (nose flaring, retractions, grunting, tripod-ing, diaphoresis)
- Obstruction (wheezing, stridor)

**APPROACH:**
1) Confirm Code Status
2) Low Threshold to Call Rapid Response for Assistance
3) Assess Respiratory Status
   - Red Flags (CALL RICU STAT for intubation, 6-3333): GCS < 8 (hard criteria for intubation), pooling airway secretions, hemoptysis, life-threatening hypoxemia despite treatment with supplemental O2 (SpO2 < 80%, PaO2 < 55 mmHg), severe hypercarbia despite BiPAP treatment, tiring out, RR > 35
   - Temporize: succioning, jaw-thrust or chin lift to open airway, AMBU bag ventilation
4) Initial Workup (think PNA>Chf>COPD>Sepsis>ARDS) (J Hosp Med 2013;8:76)
   - ABG: Worrisome if PaCO2 > 45 mmHg (poor ventilation), PaO2 < 60 mmHg (poor oxygenation), pH < 7.25
   - EKG: ST depressions/elevations (ischemic changes), sinus tach or e/o RV strain (PE), arrhythmia (AF+RVR, SVT, VT)
   - CXR (order STAT and must call 6-3305): look for new infiltrate (aspiration, PNA), pulmonary edema, lobar collapse (consider mucus plug), PTX. If normal, think about cardiac etiologies such as ischemia or PE.
   - Labs: VBG (and ABG if possible, helpful to correlate to VBG), hs-Trop, NT-proBNP, lactate, BMP, CBC
5) Additional Studies Based on Clinical Suspicion: CT-PE (if stable to travel), TTE (acute valvular disease, RH strain)

**TREATMENT:**
- Supplemental Oxygen Therapy (see Oxygen Delivery Therapies section for more detail):
  - NC: for every liter increase in O2, ↑ F O2 0.03/L (max: 6L = 0.40 FiO2)
  - Venturi masks: pre-set F O2 0.24, 0.28, 0.31, 0.35, 0.40 (flow rate decreases with increasing F O2)
  - NRB: can give F O2 ~0.90, but in tachypneic patient, F O2 ~0.60 (due to entrainment of room air)
  - HFNC: F O2 0.6 to 1.0 at 10-60 L/min (humidified air); 90-day mortality vs. NIPPV for pts with hypoxic respiratory failure not due to 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, PPAO2 >45mmHg
  - Intubation: See Red Flags above

**DISEASE SPECIFIC TREATMENT RECOMMENDATIONS:**
- CHF: CPAP, IV diuresis, nitrates (paste or drip, if BP room), low dose morphine (1-2mg) but do not mask chest pain
- COPD: BiPAP, nebulizers (stacked DuoNebs x3), steroids (oral pred 40mg qd is equivalent to 32mg IV methylpred); if severe exacerbation, consider methylpred 60-125mg q6h; abx if 2 of 3: ↑ sputum volume, purulence, or dyspnea
- PE: If high suspicion and no contraindication, start empiric anticoagulation
- PTX: Consider needle thoracostomy (14G angiocath, 5th ICS at mid-axillary line); STAT page Thoracics/IP for chest tube
- Pleural effusion: Consider thoracentesis (see Procedures; must be performed by IP or supervised by pulm attending)
- Opioid overdose: Narcan 0.4-2mg IV/IM Q2 minutes, observe response; given short half-life, consider gt if response
- Anaphylaxis: Epi (1:1000) 0.3 mL = 0.3 mg IM, methylprednisolone 125mg IV, diphenhydramine, ranitidine
- Cardiac Ischemia: per ACS treatment guidelines (see Cardiology section)

**SENIOR ON PAGER: p22337 | Rapid Response: x6-3333** (Senior On, nursing supervisor, RT, pharmacy)
- RICU communication guide: have information ready for RICU prior to intubation; greet RICU in patients’ room
- Code status
- Hemodynamics – LV, RV, valves, volume status, access
- Aspiration risk – NPO status, last meal, risk factors
- Have Ready: Sedation (fentanyl/versed/propofol), Pressor (Neo >> Levo), IV fluids w/ push line; RICU brings paralytic
- MICU/CCU: Resource RN will call for RICU, make sure attending/OI, fellow, RT and RN are aware of plan
- INTUBATION IS NOT AN ACT OF WEAKNESS: do not delay intubation in patients with impending respiratory failure

Sam Wainwright
Respiratory Failure: Inability to oxygenate (deliver O₂) or ventilate (blow off CO₂). Can be hypoxemic (PₐO₂ < 60 mmHg), hypercarbic (PₐCO₂ > 45 mmHg), or both. A quick algorithm can be used to determine the etiology based upon ABG results:

Hypoxemic? (PₐO₂ < 60 mmHg)
[~O₂ sat ≤ 95%, see Hgb dissociation curve]
Elevated A-a gradient? (Normal = Age+4)
A=Alveolar | PₐO₂=FiO₂ x (760-47) - PAₐCO₂/0.8
a=arterial | PₐO₂ via blood gas

Does your PaO₂ correct with supplemental O₂?
No
Yes
V/Q Mismatch
Focal alveolar disease
PNA, mucous plugging, atelectasis, ILD, pulmonary edema
Airway disease
2. Asthma, COPD, bronchiectasis
3. Vascular: pHTN, PE
4. Iatrogenic: too much PEEP

Shunt: Flow of blood through lung without encountering oxygenated air, “perfusion without ventilation” (severe V/Q mismatch)
1. Diffuse alveolar disease: cardiogenic pulmonary edema, ARDS
2. Alveolar collapse: PTX, atelectasis
3. Intra-cardiac/intra-pulmonary shunt: PFO, AVM (e.g. hepatoportal)

Impaired diffusion (decreased D,CO): hypoxemia worse with exertion
○ ILD (correlates with severity on CT), pHTN, advanced COPD

Hyperventilation
↓VT ↑RR ↑Alveolar dead space
↓Alveolar perfusion
Deadspace
↑VT ↓RR ↓Alveolar perfusion
Deadspace

Acid-Base Interpretation:
Hypercarbia → Respiratory acidosis (↑pCO₂)
• Acute: HCO₃ ↑ by 1 (per pCO₂ ↑ 10)
• Chronic: HCO₃ ↑ by 3–4 (per pCO₂ ↑ 10)

Hypocarbia → Respiratory alkalosis (↓pCO₂)
• Acute: HCO₃ ↓ by 2 (per pCO₂ ↓ 10)
• Chronic: HCO₃ ↓ by 5 (per pCO₂ ↓ 10)

“Won’t breathe” (↓RR): sedatives, central sleep apnea, obesity hypoventilation, brainstem stroke, tumor or infection (pons & medulla), hypothyroidism (myxedema coma), compensation for metabolic alkalosis (chemoreceptors).

“Can’t breathe” (↓Tidal volume (Vₕ)): factors affecting nerves/muscles/heart wall/airways
1. OSA (upper airway obstruction)
2. Airway: asthma or COPD exacerbations, tumor, foreign body
3. ↑Alveolar dead space (Vₕ): Anatomic (~150cc upper airspace without perfusion) + Alveolar (capillaries get destroyed as in COPD, fibrotic lung disease, etc.) or compressed (i.e. too much PEEP)

V: ↑CO₂ production (VCO₂): ↑ WOB, fever, seizure
**OXYGEN DELIVERY DEVICES**

**Low Flow Devices**
- **Nasal cannula:** $F_O_2$ 24-40%. Easy to administer but highly variable flow/$F_O_2$ relationship. Keep flow <6. Humidify if >4L.
- **Oxymizer:** $F_O_2$ 24-45%. Primary function is to conserve oxygen, but can deliver slightly higher $F_O_2$ than NC.
- **Simple facemask:** $F_O_2$ 35-50%. Keep flow >5L to avoid rebreathing trapped CO2 in mask, only short-term.
- **Shovel mask:** $F_O_2$ 24-50%. Difficult to control $F_O_2$ - consider in patients with stable need for O2 who do not tolerate NC.
- **Non-rebreather:** easily accessible – consider starting with this for the acutely hypoxemic patient.
  - Theoretically delivers 100% $F_O_2$, but true delivery 60-90% $F_O_2$ due to entrainment of room air.
  - Air entrainment is increased (true $F_O_2$ lower) when patient is tachypneic or drawing large tidal volumes.
  - Flow should be set >10L to adequately fill the reservoir.

**High Flow Devices**
- **Venturi mask:** $F_O_2$ 24-50%. Delivers a fixed $F_O_2$ independent of RR, tidal volume. Flow rate decreases with increasing $F_O_2$. Consider for patients who need more careful titration of oxygen, as in COPD patient with specific SpO2 goals. **NOT** for use in acute respiratory distress.
- **High-Flow Nasal Cannula (HFNC):** Delivers up to 100% $F_O_2$ (when mouth is closed) at flow rates 10-60 L / min and provides small amount of PEEP (approximately 0.7 cmH2O / L) when patient’s mouth is closed.
  - Some evidence for ↓90-day mortality vs. NIPPV for pts with hypoxemic respiratory failure not due to pulmonary edema or obstructive lung disease (NEJM 2015;372:2185).
  - Decreases intubation rate but no change in mortality in immunocompromised pts (Intensive Care Med 2017;43:1808).
  - Extubation to HFNC equivalent to extubation to NIPPV in terms of reintubation rate (JAMA 2016;316:1565).
  - Consider use in pure hypoxemic respiratory failure.

**Caution:** Liberal supplemental oxygen to improve SpO2 above 94-96% in acutely ill adults is associated with increased mortality (Lancet 2018;391:1693).

**NONINVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)**
- **CPAP** (continuous positive airway pressure): provides PEEP, which prevents upper airway collapse (e.g. OSA) and lower airway collapse (e.g. atelectasis) while raising intrathoracic pressure and decreasing venous return (e.g. helpful in cardiogenic pulmonary edema). In CHF, ↓ intubation, ↓ mortality (Eur Respir J 2017:50:1602426).
- **BiPAP** (bi-level positive airway pressures): Provides both inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP = PEEP). In COPD, ↓ mortality, ↓ intubation, ↓ length of stay (Ann Intern Med 2003;138:861; Cochrane 2017;7:CD004104). IPAP decreases respiratory fatigue, especially in obstructive lung disease and neuromuscular disease.

**Strong Indications for NIPPV**
- Cardiogenic pulmonary edema (CPAP)
- COPD exacerbation with acute resp acidosis (BiPAP)
- Ppx against extubation failure in high risk pts (“Extubate to CPAP or BPAP”)

**Weak Indications for NIPPV**
- Hypoxemic respiratory failure (other than CHF/COPD)
- Patient is DNI with indication for intubation
- Palliation for increased WOB, dyspnea
- Asthma exacerbation with acute resp acidosis (poor data in adults)

**Contraindications for NIPPV**
- **Risk of Delay:** Emergent indication for intubation, acute life-threatening non-respiratory organ failure.
- **Risk of Aspiration:** Cannot clear secretions, AMS if pt cannot remove mask (exception: AMS due to hypercarbia).
- **Risk of Injury:** Pneumothorax (can induce tension physiology), recent esophageal anastomosis or tear, patient cannot tolerate decreased preload (↓ venous return), facial trauma or recent facial surgery.
- **Will Not Work:** Patient cannot initiate breath, anatomic deformity or facial hair interrupting seal.

**BiPAP/HFNC Trial on the Floor:** huddle with nursing and RT (consider including Senior On), then trial BiPAP or HFNC ~2-3 hours and trend response; consider ABG/VBG pre- and post- huddle to assess change in oxygenation or ventilation. If no improvement, discuss escalation of care to ICU.

**REMEMBER:** BiPAP/HFNC should NOT be used to delay intubation!
Indications for Intubation:
- Failure of NIPPV: No clinical improvement
- Cannot ventilate: PaCO2 >60 with severe acidemia
- Cannot oxygenate
- Airway protection/instability: Unconsciousness, AMS, shock, facial/head trauma
- Nausea/vomiting/GIB, severe secretions, severe bronchospasm/anaphylaxis
- Hemodynamic instability: unstable arrhythmia, HoTN
- Ventilator-Induced Lung Injury (VILI)
- Dynamic Hyperinflation (Auto-PEEP)

Ventilator Complications: Problems and Troubleshooting
- Ventilation: delivers a breath until set tidal volume is reached
- Control: delivers a breath until set tidal volume is reached
- Pressure Support Control
- Pressure Support Ventilation: delivers a breath triggered by patient's spontaneous breathing

Ventilator Modes (Respir Care 2007;52:301)

<table>
<thead>
<tr>
<th>MODE</th>
<th>SET VALUES</th>
<th>MEASURED VALUES</th>
<th>PROS/CONS</th>
<th>HOW TO READ</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC/VC Assist Control/Volume Control: delivers a breath until set tidal volume is reached</td>
<td>Tidal volume (Vt) RR PEEP FiO2 I:E or flow</td>
<td>PIP &amp; Pplat</td>
<td>↑ control over ventilation (fixed Vt prevents barotrauma or atelectrauma, e.g., ARDSNet) ↓ LV afterload and preload (may help pts with heart failure)</td>
<td>&quot;Pt is on Volume Control, Vt of 400 (4 mg/kg), set rate 16 breaths/min, breathing at 16 breaths/min, PEEP of 8, FiO2 60%.&quot;</td>
</tr>
<tr>
<td>AC/PC Assist Control/Pressure Control: delivers a breath until set pressure is reached</td>
<td>PEEP Pplat RR FiO2 I:E</td>
<td>Flow Vt</td>
<td>variable flow (and variable Vt) during inspiration to satisfy patient demand, ↓dyssynchrony ↓ volutrauma as compliance or pt effort changes</td>
<td>&quot;Pt is on Pressure Control of 16/5, Vt in the 400’s, set rate 16 breaths/min, FiO2 30%.&quot;</td>
</tr>
<tr>
<td>PSV Pressure Support Ventilation: delivers a breath set pressure triggered by patient's spontaneous breathing</td>
<td>PEEP (= PEEP) FiO2 (NB: may set backup rate to ensure pt never stops breathing!)</td>
<td>I:E Flow Vt RR</td>
<td>better tolerated, less sedation required, used as trial setting prior to extubation (i.e. SBT of 0/0) less control over respiratory parameters, volutrauma possible, no fixed RR (only backup rate)</td>
<td>&quot;Pt is on Pressure Support of 10/5, breathing Vt of ~500, at 20 breaths/min, FiO2 30%.&quot;</td>
</tr>
</tbody>
</table>

Ventilator Dynamic Hyperinflation (Auto-PEEP): 2/3 incomplete alveolar emptying during expiration; measured during expiratory hold
- Diagnosis: end-expiratory flow >0 (residual pressure); see graphic
- Risk factors: high RR, I:E ratio or obstructive disease (asthma, COPD, CF)
- Consequences: adverse hemodynamic effects (hypotension), alveolar over-distention (resulting in worsening lung injury)
- Treatment: allow longer exhalation (↑I:E ratio), set exogenous PEEP to 2/3 auto-PEEP, bronchodilators for obstruction
- If severe hemodynamic or respiratory compromise, transiently disconnect patient from ventilator and manually bag ventilate to allow deflation

Ventilator-Induced Lung Injury (VILI): includes barotrauma (injury from high Pplat→ pneumothorax), volutrauma (over-distention of alveoli due to high Vt), atelectrauma (injury from cyclic alveolar recruitment and derecruitment), biotrauma (cytokine release from lung epithelium → organ dysfxn), oxytrauma (elevated FiO2→free radical production and lung injury)
- To avoid, set Vt to 6 mL/kg IBW, keep PEEP <30 cm H2O, utilize best PEEP strategy to find best "tidal compliance" = Vt / (Pplat – PEEP) (i.e. driving pressure) with goal driving pressure ≤ 15 (NEJM 2015;372:747)
- Other forms of VILI: ventilator-associated pneumonia, laryngeal edema, tracheal stenosis

Ventilation: delivers a breath until set tidal volume is reached
- Control: delivers a breath until set tidal volume is reached
- Pressure Support
- Pressure Support Ventilation: delivers a breath triggered by patient's spontaneous breathing

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, last K (succ may cause hyperK)
E = events (prompting intubation)
During intubation, have at bedside:
(1) Good access (2) IVF (3) sedative agent (e.g., propofol) (4) pressure (neo >> levo)
Mechanical Ventilation

- High Peak-Inspiratory Pressure (PIP = airway resistance + Pplat): due to increased airway resistance (normal PIP <35cm H2O) or increased airway compliance (Pplat). See flowchart for differential.
  - Management: Consider steroids, nebulizers, or bronchoscopy to clear secretions/mucus plugs

  ![Flowchart for differential diagnosis of high PIP](Adapted from Marino FL. The ICU Book, 3rd ed. Philadelphia: Lippincott Williams & Wilkins. 2007:447)

### Monitoring Mechanics

- **Equation of Motion for the Lung:**
  \[ \Delta P = PIP - PEEP = \dot{V} \times R_{\text{airway}} \text{ (resistive pressure)} + \frac{VT}{C_{\text{resp system}}} \text{ (elastic pressure)} \]
  - **Resistive Pressure:** \( \dot{V} \times R_{\text{airway}} = PIP - P_{\text{plat}} \)
  - **Elastic Pressure:** \( \frac{VT}{C_{\text{resp system}}} = P_{\text{plat}} - PEEP \) ("driving pressure")
  - **NB:** To calculate Pplat, perform inspiratory hold; at end-inspiration, resistive pressure is 0 and PIP = Pplat
  - **Target Values:** Pplat < 30; driving pressure < 15; CRS > 50; resistance (resistive pressure) < 10
  - **Ventilator maneuvers for monitoring mechanics:**
    - Expiratory hold: end expiratory pause; measures auto-PEEP
    - Inspiratory hold: end inspiratory pause; measures Pplat and compliance

### Algorithm for Respiratory Plan on MICU Rounds (REMIX)

<table>
<thead>
<tr>
<th>R</th>
<th>Reason for intubation</th>
<th>ARDS, PNA, COPD, aspiration, hypoventilation, altered mental status, CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Exchange (gas exchange)</td>
<td>Most recent ABG value; how can we improve PaO2 (i.e. diuresis) and/or PCO2 (i.e. ↑RR)?</td>
</tr>
<tr>
<td>M</td>
<td>Mechanics</td>
<td>Lung resistance (PIP) &amp; compliance (Pplat), chest wall, resp. muscle strength, cuff leak</td>
</tr>
<tr>
<td>I</td>
<td>ID/infection (abx)</td>
<td>Sputum cx data, abx day #, source control, need for bronch</td>
</tr>
<tr>
<td>X</td>
<td>eXtubation barriers</td>
<td>Daily SAT/SBT, secretion clearance, mental status, planned procedures</td>
</tr>
</tbody>
</table>

### Liberation and Extubation

- **Liberation Protocol:**
  - **SAT:** ↓ ventilator time, ICU LOS, and mortality if paired with SBT (Lancet 2008;371:126; NEJM 2000;342:147)
  - **SBT:** ~30 min daily trials with little/no vent support (≤ 5 of PEEP on PSV, generally 0 PEEP unless COPD) = ↓ vent time (NEJM 1996;335:1864; NEJM 1995;332:345)
    - Ways to fail SBT: Hypoxemia (SaO2 <90%, PaO2<60), hypercarbia (PaCO2 ↑ by >10), respiratory distress (THR/RR, accessory muscle, diaphoresis, dyspnea, anxiety), arrhythmia, hemodynamic instability, AMS

- **Extubation Strategies:**
  - Exubation to NIPPV or HFNC in patients with hypercarbia / risk factors for reintubation → ↓ post-extubation respiratory failure (NEJM 2004;350:2454; JAMA 2016;316:1565) (NB: worse outcomes if NIPPV used as rescue therapy during post-extubation respiratory failure vs. re-intubation) (Lancet 2009;374:1082)
  - Early tracheostomy if expect intubation >14 days → ↑ comfort, allows ↓ sedation, ↓ risk of tracheal stenosis (CCM 2007;35:802)
  - Check for absence of cuff leak / laryngeal edema before extubation → consider methylpred 20mg IV QH during 12hr prior to extubation if concerned for laryngeal edema (JAMA 2010;303:1483; Eur J Anaesthesiol 2010;27:534)
  - If agitation is limiting ability to extubate, consider dexmedetomidine → may improve odds of extubation (JAMA 2009;301:489)
Sedation

GOAL OF ICU SEDATION: addressing the ICU triad of pain, agitation, and delirium (NEJM 2014;370:444)
1. Pain: Common, ↑ energy expenditure; analgesia alone adequate in some (Lancet 2010;375:475)
2. Agitation: target RASS -1 to -2 in intubated pts (AJRCCM 2002;166:1338)

Go through the ABCDE Bundle daily on rounds; evidence-based measure for ICU pts a/w ↑ vent free days (21 vs. 24d over a 28-day study period), ↓ delirium (OR 0.55), ↓ mortality (OR 0.56) (CCM 2014;42:1024).

A – Spontaneous Awakening Trial (SAT): Daily interruptions of sedation ↓ ICU LOS, vent days (NEJM 2000;342:1471; CCM 2018;46:e829); PTSD sx (AJRCCM 2003;168:1457)
C – Choice of sedation: see below
D – Delirium: Assess CAM-ICU daily
E – Early mobility: ↓ pressure sores, ↓ functional status at discharge, ↓ vent days, ↓ delirium (NEJM 2014;370:1626; CCM 2008;36:2281)

SEDATION AGENTS: (CCM 2013;41:263)

Opioids: Primarily analgesia. Side effects (SE): resp depression, tolerance, constipation (prescribe w/ bowel reg), ileus, ↑ delirium w/ ↑ use

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine bolus 2-4mg, gtt 2-30mg/hr</td>
<td>Inexpensive, generally well-tolerated but can cause pruritus, bradycardia, HoTN</td>
<td>Accumulates in renal failure</td>
</tr>
<tr>
<td>Hydromorphone bolus 0.25-1mg, gtt 0.5-5mg/hr</td>
<td>↑ potency (compared to morphine)</td>
<td>Accumulates in hepatic/renal failure</td>
</tr>
<tr>
<td>Fentanyl bolus 25-50 mcg, gtt 50-200 mcg/hr</td>
<td>↑1/2 30-60m w/ bolus; ↑1/2 with gtt (9-16h); can cause chest wall rigidity</td>
<td>Accumulates in adipose</td>
</tr>
</tbody>
</table>

Non-BZD sedatives: primarily anesthesia, amnesia; do NOT provide pain control (analgesia) (* = consider in intubated patients)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol* 25-300mg/hr or 1-3 mg/kg/hr</td>
<td>1st line sedative (MGH) (rapid onset/awakening); used in status epilepticus, EIOH w/d; ↑ mortality vs benzos (RR 0.76), earlier extubation (AJRCCM 2014;189:1383)</td>
<td>Metabolism unaltered by renal/liver failure</td>
</tr>
<tr>
<td>Dexmedetomidine* 0.2-1.5mcg/kg/hr</td>
<td>No respiratory depression, no amnestic effects, or analgesia</td>
<td>Dose-reduce in renal, liver failure</td>
</tr>
<tr>
<td>Ketamine* 5-30mcg/kg/min</td>
<td>Causes “dissociated amnesia” and analgesia w/o resp depression</td>
<td>Metabolites accumulate in renal, liver failure</td>
</tr>
</tbody>
</table>

BZD: primarily amnesia, anxiolysis. SEs: resp depression, agitation, withdrawal/tolerance, ↑ duration of action w/ gtt vs. IV

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam bolus 1-2mg</td>
<td>Propylene glycol (solvent) tox @ ↑1/2 dose (lactic acid, HoTN, arrhythmia); ↑ sedation, cost-effectiveness vs. midazolam (CCM 1999;27:2454); especially useful in seizures</td>
<td>Preferred in renal, liver failure over midazolam but caution in severe liver disease</td>
</tr>
<tr>
<td>Midazolam* bolus 0.5-4mg, gtt 2-8mg/hr</td>
<td>CYP3A4 metabolites med interactions (fluconazole, azithro, flagyl, amio) Shorter t1/2 vs. lorazepam (~2-6h vs 14h), both w/ fast onset (2-5min)</td>
<td>Accumulates in adipose Metabolites accumulate in hepatic/renal failure</td>
</tr>
</tbody>
</table>

Anti-Psychotics: useful in treating delirium + helping to liberate agitated pts from ventilator; SEs: ↑ QTc, EPS, anti-cholinergic, NMS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>May ↓ time to resolution of delirium w/ hal-dol (CCM 2010;38:419) ↓ NMS, EPS; also treats insomnia</td>
<td>No dosing adjustment in renal or hepatic failure</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Does not reduce mortality, delirium incidence, duration of ICU stay or hospitalization, vent time (JAMA 2018;319:880; NEJM 2018;379:2506)</td>
<td>No dosing adjustment in renal or hepatic failure</td>
</tr>
</tbody>
</table>
Pulmonary & Critical Care

ARDs

Berlin Definition for ARDS & Management Summary
(JAMA 2012;307:2526)
1) Onset within 1 week of insult (usually 72 hours)
2) Not primarily due to hydrostatic edema
3) Imaging showing bilateral opacities on CXR

Mild ARDS
- PaO₂/FIO₂ (P:F) 200-300 mmHg w/ PEEP > 5 cmH₂O
- Mortality: 27%

Moderate ARDS
- P:F 100-200 mmHg w/ PEEP > 5 cmH₂O
- Mortality: 32%

Severe ARDS
- P:F ≤ 100 mmHg w/ PEEP ≥ 5 cmH₂O
- Mortality: 45%

Controlled Mechanical Ventilation
- Target tidal volume 6cc/kg predicted body weight (PBW) and Pplat ≤ 30 cmH₂O
- Consider higher PEEP in moderate and severe ARDS
- Keep PaO₂ 55-80 mmHg or SpO₂ 88-95% with pH ≥ 7.25

Detailed Management Principles

Treat Underlying Etiology: Direct lung injury: Pneumonia, aspiration, inhalational injury, near drowning, pulmonary contusion;
Indirect lung injury: Sepsis, trauma, pancreatitis, drugs, burns, cardiopulm bypass/pump, transfusion-related acute lung injury (TRALI)
⇒ Common 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)

Strategy

Low Tidal Volume Ventilation
- Maintain oxygenation while preventing ventilator-induced lung injury (VILI)
- V₉ < 6 mL/kg IBW, Pplat - PEEP (driving pressure) ≤ 15 cmH₂O for goal PaO₂ 55-80 (~ SpO₂ 88-95%) (NEJM 2007;357:1113)
- Can allow higher Pplat if ascites, obesity, etc. as Pplat may not accurately predict transpulmonary pressure (see next page on esophageal balloon catheter)
- Permissive hypercapnia with pH goal > 7.25 allows for lower V₉ to minimize VILI
- Non-ARDS: V₉ 10 mL/kg vs 4mL/kg no difference in mortality (PreVENT trial)

Positive End-Expiratory Pressure (PEEP)
(NEJM 2004;351:327; AJRCCM 2010;181:578)
- Best PEEP: Maximize recruitment, minimize trauma from cyclic atelectasis
- Higher PEEP → distributes V₉ over more alveoli → less over-distension → improves oxygenation (via ↓ V/Q mismatch and ↓ shunt fraction) & compliance
- CV effects of PEEP: ↓ preload, ↑ RV afterload, ↓ LV afterload, ↓ CO but variable
- Harms of PEEP: barotrauma, ↑ dead space, ↑ mortality w/ lung recruitment and PEEP titration in moderate/severe ARDS (JAMA 2017:318:1335)

Conservative Fluid Management
- Minimize pulmonary edema: “Dry lungs are happy lungs”
- Conservative fluid management strategy preferred (FACTT Trial: CVP<4 [conservative] vs. CVP<10-14 [liberal]) (NEJM 2006;354:2564)
- No clearly established mortality benefit, possible subgroup benefit if P:F ≤200 (JAMA 2010;303:865)

Neuromuscular Blockade
- Maximize oxygenation by ↓vent dyssynchrony and metabolic demand
- Early paralysis (cisatracurium) within 48 hours of onset of severe ARDS (P:F <150), continue infusion x48 hours (NEJM 2010:363:1107, CCM 2013:17.R43)
- Post-paralysis myopathy is a potential risk but no difference in cisatracurium trial

Improved 90d mortality (HR 0.68) and vent-free days vs. non-paralyzed

Is the patient stable, tolerating noninvasive ventilation, P:F > 200mmHg?
YES
Continue noninvasive: NIPPV = HFNC (Chest 2017:151:764)

NO

Is P:F ≤ 150 mmHg?
YES
1) Sedate and prone
2) Consider paralysis
3) Lung recruitment maneuvers

Is P:F < 80 mmHg?
Consider alternative therapies, i.e. VV ECMO

Is P:F < 150 mmHg?
Mild ARDS
- PaO₂/FI O₂ (P:F) 200-300 mmHg w/ PEEP > 5 cmH₂O
- Mortality: 27%

Moderate ARDS
- P:F 100-200 mmHg w/ PEEP > 5 cmH₂O
- Mortality: 32%

Severe ARDS
- P:F ≤ 100 mmHg w/ PEEP ≥ 5 cmH₂O
- Mortality: 45%

FACTT: ↓ ICU LOS, ↓ vent-free days, no Δ in 60d mortality, no Δ in renal failure

Viral Shah
Summary of Rescue Therapies for Hypoxemia (6 P’s of refractory hypoxemia)

- **Pees**: Consider diuresis to reduce pulmonary edema (see “conservative fluid management”)
- **PEEP**: Optimize PEEP (see “PEEP” above)
- **Paralysis**: Early paralysis within 48 hours of ARDS onset (see “neuromuscular blockade” above)
- **Pulmonary Vasodilators**: Start with iNO trial and if effective, use inhaled Epoprostenol.
  - Should see at least 15% ↑ in PaO2 with iNO, otherwise do not initiate 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 but may improve oxygenation in first 24hrs (Cochrane 2010;7:CD002787) and decreased mortality (Cochrane 2016;11:CD006667) seen; avoid massive PIPs (>50 cmH2O)

- **Esophageal balloon catheter**: Estimates intrapleural pressure; used to calculate transpulmonary pressure ($P_{p} = \text{alveolar pressure} - P_{EEP}$ - intrapleural pressure). PEEP then titrated to maintain optimal $P_{p} (<25 \text{ cmH}_2\text{O end-inspiration to prevent VILI, 1-2 cmH}_2\text{O end-expiration atelectrauma})$ (NEJM 2008;359:2095)
  - No effect on mortality, ventilator free days, or ICU days, despite improved oxygen and lung compliance
  - Consider in cases of high intra-abdominal pressure (e.g., obesity, ascites, abdominal compartment syndrome)

**Lung Protective Strategies: ARDSNet Ventilation**

- **Initial Ventilator Set-Up Calculations**: discuss initial ventilation strategy and titration with respiratory therapist
  1. Calculate predicted body weight (PBW): Men: $50 + 2.3 \times \text{[height (inches) – 60]}$; Women: $45.5 + 2.3 \times \text{[height (inches) – 60]}$
  2. Set ventilator settings to achieve initial $V_t$ by 1 ml/kg PBW
  3. Reduce VT with lowest risk for over-distention based upon 1-2 cmH2O end-expiration atelectrauma (NEJM 2008;359:2095)
  4. Set ventilator settings to achieve initial VT = 8 ml/kg PBW
  5. Calculate predicted body weight (PBW): Men: $50 + 2.3 \times \text{[height (inches) – 60]}$; Women: $45.5 + 2.3 \times \text{[height (inches) – 60]}$
  6. Set initial rate to approximate baseline minute ventilation (RR <35)

- **Goals of Therapy**
  - Oxygenation: $\text{PaO}_2 >55-80 \text{ mmHg or SaO}_2 >88-94%$
    - If $\text{PaO}_2/\text{FiO}_2 <150$ on PEEP 5 cm H2O, assess ability to recruit lung by increasing PEEP from 5 to 15 cm H2O
    - If improvement, use high PEEP/lower FiO2 scale; if no improvement, low PEEP/high FiO2 scale (see below)
  - Plateau pressure (obtain with 1 sec inspiratory pause): $P_{\text{plat}} \leq 30 \text{ cm H}_2\text{O}$ to minimize VILI, driving pressure ($P_{\text{plat}} - \text{PEEP}$) <15 cm H2O and $P_{\text{Peak}} <45 \text{ cm H}_2\text{O}$
    - $P_{\text{plat}} >30 \text{ cm H}_2\text{O}$; ↓ $V_t$ by 1 ml/kg PBW (minimum $V_t$ 4 ml/kg PBW).
    - $P_{\text{plat}} <25 \text{ cm H}_2\text{O}$ and $V_t <6 \text{ ml/kg PBW}$; ↑ $V_t$ by 1 ml/kg until PEEP >25 or $V_t$ 6 ml/kg PBW
  - pH: 7.25-7.45 (can tolerate lower pH depending on clinical scenario, “permissive hypercapnea”)
    - pH >7.55: ↓ RR if possible
    - pH <7.25: ↑ RR (to 35/min max) until pH >7.25 or $\text{PaCO}_2 <25$
    - pH <7.15: set RR = 35/min; ↑ $V_t$ by 1 ml/kg until pH >7.15 (may exceed Pplat goal)

**Optimal PEEP for ARDS**

- **Best PEEP trial**: Typically performed on all ARDS cases. Goal is to select the PEEP corresponding to best global recruitment with lowest risk for over-distention based upon respiratory system compliance ($CRS = V_t / (P_{\text{plat}} - \text{PEEP})$)
  - Keep $V_t$ constant and use decremental titration of PEEP; choose best PEEP based on balance of compliance, driving pressure, oxygenation, and hemodynamics
  - Driving pressure: $\Delta P = P_{\text{plat}} - \text{PEEP}$ (goal: <15)
    - Represents the relationship between tidal volume and lung compliance ($\Delta P = V_t/C_{RS}$)
    - Lower $\Delta P$ associated with ↑ survival independent of other variables ($V_t$, PEEP, Pplat) (NEJM 2015;372:747)

- **Recruitment maneuvers**:
  - Used to open collapsed alveoli to ↓ tidal opening and closing (atelectrauma) and ↑ participation in gas exchange
  - Begin with high PEEP to open up alveoli, then decremental PEEP titration to optimize mechanics (JAMA 2008;299:637)
  - Outcomes are mixed w/ both increased (JAMA 2017;318:1335) and decreased mortality (Cochrane 2016;11:CD006667) seen; avoid massive PIPs (>50 cmH2O)

- **Esophageal balloon catheter**: Estimates intrapleural pressure; used to calculate transpulmonary pressure ($P_{p} = \text{alveolar pressure} - P_{\text{EEP}}$ - intrapleural pressure). PEEP then titrated to maintain optimal $P_{p} (<25 \text{ cmH}_2\text{O end-inspiration to prevent VILI, 1-2 cmH}_2\text{O end-expiration atelectrauma})$ (NEJM 2008;359:2095)
  - No effect on mortality, ventilator free days, or ICU days, despite improved oxygen and lung compliance
  - Consider in cases of high intra-abdominal pressure (e.g., obesity, ascites, abdominal compartment syndrome)
Two Types of ECMO: (JACC 2014;63:2769)

1. Venoadarterial (VA, replaces heart and lungs): treats cardiogenic shock and hypoxemic respiratory failure
   - Venous blood is removed, oxygenated, CO2 extracted, and returned to arterial system
   - Venous cannula is placed in common femoral vein (drainage from IVC or RA); arterial cannula is placed in R femoral artery

2. Venovenous (VV, replaces lungs): treats hypoxemic respiratory failure; relies on native hemodynamic (cardiac) support
   - Venous blood is removed, oxygenated, CO2 extracted, and returned to venous system
   - Either two venous cannulae (common fem. vein and SVC) or a single bicaval device via R IJ (Avalon) that allows for early mobility

Indications: (all must be met; criteria suggested by ELSO but no consensus)
- Resp failure (VV): Consider when PaO2/FIO2 <150. Indicated when P/F<100 or Pplat>30 despite recruitment maneuvers, or if unable to ventilate due to poor compliance with pH<7.2.
- Cardiogenic shock (VA): refractory low cardiac output (CI<2L/min/m2) and hypotension (SBP<90mmHg) despite adequate volume, inotropes, and intra-aortic balloon pump
- Reversible etiology (ARDS, Massive PE, Cardiac Arrest)
- Bridge to definitive therapy (transplantation, VAD, recovery)
- Less invasive strategies have failed:
  - VV: FiO2 1.0, paralysis, iNO/Veletri, proning, PEEP, diuresis
  - VA: pressors, inotropes, IABP, mechanical support

Contraindications
- Absolute: irreversible etiology without an exit strategy; active comorbidities precluding survival; contraindication to anticoagulation
- Relative: ventilated >7d (ECMO most effective if started within 7d), DIC, age>75, GVHD, brain injury, prolonged unwitnessed arrest, metastatic disease, aortic dissection, aortic insufficiency, obesity, sepsis/distributive shock (for VA-ECMO)

ECMO Variables
- **Sweep**: increasing sweep lowers PxCO2 in blood returning to pt; titration of sweep affects CO2 elimination >> oxygenation
- **FiO2**: (circuit oxygen) usually set at 1.0
  - Note: VV circuit oxygenates fraction of native CO; if native CO increases, more blood naturally flows via lungs → may allow FiO2 settings to be decreased if the lungs are functioning
- **RPM**: RPM is predominant determinant of blood flow (2-5 L/min; also affected by cannula size and native CO)
- **Hgb goal**: normally 9g/dL; if concern for ischemia, use 10g/dL
- **Clotting**: PTT 60-80 (monitor q2h); Plt >50K; Fibrinogen >100 (may change if bleeding).
  - UFH for anticoagulation and check AT-III and anti-Xa levels.

Complications: (Heart Lung Circ 2014:23:10)
- **Clots** (oxygenator, pump, tubing, hemofilter), 0.13-22% pts; **bleeding** (cannulation site, GI, intracranial, hemolysis, DIC), 5.3-79% pts; **neurologic & MSK** (intracranial bleed, stroke, seizure, encephalopathy), 10–33% pts; **limb ischemia**, 13–25% pts; **infection**, 17-49% pts; **AKI**, 30-58% pts; **multi-organ failure**, 10% pts; **cannulation problems**, 0.8-8% pts; **hyperbilirubinemia**, 27% pts

Troubleshooting the Circuit:
- **Chatter**: “shaking” sound caused by high (-) pressure in the tubing; usually due to hypovolemia, treat w/ volume (5% albumin)
- **Poor Oxygenation** (as measured on patient ABG):
  - a) Recirculation: blood recirculates from the outflow (return) catheter back into the inflow (drainage) catheter, bypassing body; usually due to catheter malposition → discordant circuit O2 and patient O2 content (treatment: reposition cannula, ↓ RPM)
  - b) Machine malfunction: hypoxemia on post-membrane ABG (treatment: replace membrane)
  - c) Shunt: occurs if native CO > ECMO CO (large fraction of blood travels through diseased lungs rather than ECMO circuit and is poorly oxygenated) → hypoxemia on patient ABG only (treatment: ↑ RPM, reduce fever, reduce inotropes, beta blockade may be helpful (dw/ECMO team))

Harlequin Syndrome (VA only); **Hypoxia of upper extremities, heart, brain** – can occur only when femoral artery is cannulated.
Cardiac recovery, but poor lung fx → native cardiac output (de-oxygenated) pushes against oxygenated ECMO blood in aortic arch leading to hypoxia of UE, brain, heart; treated by relocation of arterial cannula to R subclav or aorta (Heart Lung Ves 2015;7:320).

Outcomes:
- **Acute Respiratory Failure**: major studies show ↓ mortality, though unclear if benefit from referral to ECMO center or ECMO itself
  - a) 75 matched pairs ARDS d/t H1N1; transfer to ECMO center ↓ mort. (23% vs. 52%); 85% bx w/ ECMO (JAMA 2011;306:1659)
  - b) CESAR: RCT of 180 pts w/ severe ARDS randomized to referral to single ECMO center vs. conventional management. ECMO-referred group had ↑ survival without disability in 6 months (83% vs. 47%) (Lancet 2009;374:1355)
  - c) EOLIA: RCT of 249 with severe ARDS (P:F <80) to ECMO w/in 7d vs. conventional therapy; early ECMO showed more days free of renal failure (46 vs 21 days), fewer ischemic strokes (0% vs 5%), and no significant difference in 60-d mortality (35% vs 46%) (NEJM 2018;378:1965) though stopped early d/t prelim results in favor of ECMO (NEJM 2018;378:2031)
- **Refractory Cardiogenic Shock**: 40-41% survive to discharge (all comers); ECMO implantation while under CPR was strongest predictor of death (CCM 2008;36:1404, ASAIO 2017:63:80)
- **ECPR**: ECMO as extension of CPR in pts with cardiac arrest – in-hospital cardiac arrest: improved survival (OR: 0.17) compared to conventional CPR (CCM 2011;39:11), out-of-hospital arrest: 22% with meaningful neurologic recovery (Resuscitation 2016:101:12); overall: 29% survive to discharge (ASAIO 2017:63:80)
PULMONARY FUNCTION TESTING

ASTHMA - OUTPATIENT CARE

DEFINITION: Chronic dz with variable airway narrowing + intermittent dyspnea, wheeze, and/or cough (JAMA 2017;318:279)

DIAGNOSIS: (NAEPP Guidelines 2007; VA/DoD Guidelines 2009)

- Spirometry
  - Obstructive (FEV1/FVC<0.7), reverses with bronchodilator, worsens with methacholine
  - Low amena, early ILD, pulm vascular dz

- Peak Expiratory Flow (PEF)
  - Can estimate degree of control, <80% personal best c/w poor control.
  - ♀: 350 - 550 L/min, ♂: 450 - 750 L/min

- Sputum
  - Eos >3% eosinophilic asthma; allergic component suspected: IgE, CBC + diff, refer to Allergy/Immunology

In new onset/adult cases, consider w/u for systemic disease: allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic esophagitis, systemic mastocytosis

MANAGEMENT: (NAEPP Guidelines 2007) improve symptoms, reduce impairment, and prevent hospitalizations.

- **Trigger avoidance is key!** Common triggers: exercise, cold air, irritants (smoke, perfume), allergens, infxn (URI, bronchitis, sinusitis), drugs (ASA, NSAIDs, beta-blockers, opioids)

- **Exacerbations:** consider short course prednisone (40mg x5d) plus SABA q4-6h standing x24 hrs; lower rates of severe exacerbations with temporary quadrupling of inhaled steroids at onset of symptoms (NEJM 2018;378:902)

- F/u visits q1-6 months; assess control and re-educate on trigger avoidance/med technique

- Treatment is stepwise based on asthma severity (see below)

- Contraindicated to use LABA without ICS (NEJM 2010;362:1169)

- **Vaccines:** Flu, PCV13, PPSV23

Severe Persistent

<table>
<thead>
<tr>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose ICS + LABA</td>
</tr>
<tr>
<td>AND consider biologics</td>
</tr>
</tbody>
</table>

| Severe Persistent |
| Step 3 |
| Med-dose ICS + LABA |
| OR: Med-dose ICS + either LTA or theophylline |

| Moderate Persistent |
| Step 3 |
| Low-dose ICS + LABA (Chest 2006;129:15) |
| OR: Med-dose ICS |

| Intermittent |
| Step 1 |
| SABA PRN (ALWAYS prescribe for ALL STEPS) |

| Mild Persistent |
| Step 2 |
| Low-dose ICS OR: leukotriene antagonists (LTA), cromolyn, theophylline |

**Step Up:** reassess q2-4 weeks for improvement. **Step Down:** if well-controlled for ≥3 months

**Biologics:** Anti-IL4: Dupilumab (NEJM 2018;328:2486); Anti-IgE: Omalizumab (J Allergy Clin Immunol 2001;108:184)


**Asthma - Inpatient Care**

- Obtain PEF (page RT to get baseline and trend), SpO2, ABG if severe, CXR, viral panel if suspect infection

- Expect respiratory alkalosis; normalization of pH can be harbinger of impending respiratory failure

- **Impending respiratory failure:** DuoNebs, methylpred IV 125mg, Mg IV 2g over 20 min, transfer to ICU, RICU consult

**ICU PATIENT** (Thorax 2003;58:81)

- **Floor Patient:** Mild-moderate → PEF ≥40% predicted

  - Albuterol+ipratropium (DuonNeb) x3 doses in first hour ("stacked") (AJRCCM 2000;161:1862)

- **O2 supplement** for goal SpO2 >90%

- Pred 40-60mg (x3-14 days) (Am J Med 1983;74:845)

- **Floor Patient:** Severe → PEF <40% predicted

  - Albuterol+ipratropium nebs ± continuous albuterol neb

  - Pred 40-60mg or methylpred 40-60mg IV

- **Mg 2g IV over 20 min** (JAMA 1989;262:1210)

  - Methylpred 125mg IV q6h (Archives 1983;143:1324)

  - Mg 2g IV over 20 min

  - BiPAP: Limited data, generally avoided in adults

  - Rescue therapies: continuous albuterol nebs, Heliox (lower density gas, data controversial)

  - **Mechanical ventilation:** large ET tube, high insp flow rate (80-100 L/min), low Vt (6-8 cc/kg), low RR (10-14), paralysis

  - **Goal:** maximize expiratory phase, permissive hypercapnia

- **Referral to Asthma Specialist**

- **Trigger avoidance is key!** Common triggers: exercise, cold air, irritants (smoke, perfume), allergens, infxn (URI, bronchitis, sinusitis), drugs (ASA, NSAIDs, beta-blockers, opioids)

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  - AND consider biologics

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# Pulmonary & Critical Care

## COPD - IN PATIENT CARE

### DEFINITION: Expiratory airflow limitation due to small airway inflammation/parenchymal destruction

**Symptoms:**
- Dyspnea, chronic cough, chronic sputum production

**Risk Factors:**
- Smoking (incl. second-hand), biomass fuel (indoor air pollution), occupational exposures, A1AT deficit

### Diagnosis:

<table>
<thead>
<tr>
<th>Obstructive spirometry (FEV1/FVC&lt;0.7), Required to establish diagnosis. Post-bronchodilator FEV1/FVC ratio &lt; 0.7 (actual, not predicted)</th>
<th>Management: (goal is to improve symptoms and QOL, reduce exacerbation frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity: defined by 4 variables</td>
<td></td>
</tr>
<tr>
<td>1. mMRC breathlessness grade</td>
<td></td>
</tr>
<tr>
<td>2. CAT health status impairment test</td>
<td></td>
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<tr>
<td>3. Gold Staging of Spirometry: (FEV1: &gt;80% = mild, 50-80% = moderate, 30-50% = severe, &lt; 30% = very severe)</td>
<td></td>
</tr>
<tr>
<td>4. Frequency of exacerbations</td>
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</tr>
</tbody>
</table>

### Treatment

#### Short-acting beta agonist (SABA)
- Albuterol, Levalbuterol
- Rapid onset, good side relief, ↑ bronchodilation; typically used PRN to limit side effects, but can be used standing if needed

#### Short-acting muscarinic antagonist (SAMA)
- Ipratropium (Atrovent)
- LABA and LAMA both improve QOL but tiotropium ↓ exacerbations in COPD (NEJM 2011;364:1093)

#### Long-acting beta agonist (LABA)
- Salmeterol, Formoterol
- AVOID w/ LABA alone in asthma (NEJM 2010;362:1169) Caution w/ LABA in pts with arrhythmia/CHF

#### Long-acting muscarinic antagonist (LAMA)
- Tiotropium (Spiriva), Umeclidinium (Incuret Elipta)
- ICS+LABA preferred over LABA alone in asthma Flutic+salm ↓ exacerbations, ↓ mortality trend, but ↑ risk of PNA (NEJM 2007;356:775)

#### Inhaled corticosteroid (ICS) + LABA
- Fluticasone-salmeterol (Advair), Budesonide-formoterol (Symbicort), Mometasone-formoterol (Dulera)

See Asthma section or COPD section (below) for appropriate use guidelines.

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**Nora Abo-Sido and Michael Kelly**

54
### Bronchiectasis & Hemoptysis

#### Bronchiectasis

**Definition:** Permanent airway dilatation from recurrent infection/inflammation (AJRCCM 2013:188-647)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>(1) Idiopathic (50%), (2) Post-Infectious (20%), (3) Chronic Infectious (15%): ABPA, Mycoplasma, mycobacteria, MAC, HIV/AIDS, (4) Systemic (10%): CF, Primary Ciliary Dyskinesia (PCD), Immunodef, Autoimmune (RA, SLE, IB), (5) Anatomic (5%): Aspiration/GERD, RML Syndrome, Foreign Body</td>
<td>Sx: ↑ cough/sputum/dyspnea - generally no fevers</td>
</tr>
</tbody>
</table>

**Symptoms:** Chronic productive cough, dyspnea, recurrent pneumonia, hemoptysis

**Natural Hx:** Exacerbations (avg 1.5/yr), progressive ↓ in FEV1, PsA colonization→worsening disease

**Diagnosis/Work-up:** CT diameter of bronchus >1.5x adj artery: bronchi fail to taper, bronchial thickening (Thorax 2010;65:1)

1) Exclude CF with gene/sweat Cl- testing
2) Bacterial and mycobacterial sputum cultures, immunoglobulins (IgG, IgA, IgM), pneumococcal vaccine titers, ANA, RF, anti-CCP, SSA, SSB, alpha1-antitrypsin
3) Consider bronch, nasal nitric oxide (PCD), Endoscopy

**Chronic Management** (AJRCCM 2014:88-647, Eur Resp J 2017:50)

- Treat underlying cause if identified
- **Airway Clearance:** inhaled tx (hypertonic saline, bronchodilators, ICS) + chest physiotherapy (Acapella + PT)
- **Antibiotics in bronchiectasis:**
  - Long-term azithro for >3 exacerbations/yr: controversial; ↓ exacerbations but c/f abx resistance
  - PsA eradication: 500mg cipro BID (IV → PO cipro, then neb colistin) → ↓ exacerbations (Resp Med 2012;106:356)
  - Chronic colonization: consider inhaled abx (i.e., TOBI)
- **Evaluation:** Consider c/s thoracic adj artery
  - PsA colonization
  - Requires IV antipseudomonal
  - For all exacerbations, treatment is 14d

**Chronic Exacerbation**

- Sx: ↑ cough/sputum/dyspnea - generally no fevers
- Obtain resp cx prior to abx:
  - Use previous cx data; if no data, start Levaquin;
  - If sensitive, amox (500mg TID) or clarithromycin (500mg BID)
  - If PsA, cipro (500-750mg BID); if resistant PsA (or history of), requires IV antipseudomonal
  - For all exacerbations, treatment is 14d

**PsA eradication:**

- 500mg cipro BID (IV → PO cipro, then neb colistin) → ↓ exacerbations (Resp Med 2012;106:356)

**Cystic Fibrosis**

**Definition:** CFTR mutation → Defective Cl-/HCO3- transport onto airway surface → mucus accumulation, recurrent infection

**Chronic Management** (AJRCCM 2013:187-680)

- **Airway clearance:** 1) albuterol 2) hypertonic saline 3) Chest PT/exercise + DNase
- Prophy abx/anti-inflamm tx = azithro+inhaled abx (tobra)
- Colonization with resistant pathogens common
- Potentiators open CFTR channel: Ivacaftor (for 4% w/G551D or similar class mutations)
- Corrector (brings CFTR to surface): Lumacaftor, Tezacaftor
- Pancreatic supplementation: vit ADEK + lipase + insulin

**Acute Exacerbation** (AJRCCM 2009;180:802)

- Rule out spontaneous PTX (0.7% annual) and hemoptysis (1% annual) (AJRCCM 2010;182:298)
- IV abx per micro data (surveillance sputum cx q3mo), PsA + S. aureus >> Stenotroph., Achromobact., H. flu, others (10-21+ day course)
  - Tips: Dose aminoglycosides daily rather than TID; unclear evidence for double coverage for PsA, though standard of care; no steroids
  - Continue chronic tx (airway clearance, etc) + nebs +/- prednisone (short course steroids may be helpful)

**Hemoptysis**

**Definition:** Expectoration of blood from lower respiratory tract

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Work-up</th>
</tr>
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<tbody>
<tr>
<td><strong>Airway:</strong> bronchitis, bronchiectasis, malignancy (usually primary lung CA), trauma (incl. foreign body)</td>
<td>1) Consider other sources (GI or nasopharyngeal)</td>
</tr>
<tr>
<td><strong>Pulmonary parenchyma:</strong> infection (PNA, abscess, TB, aspergillosia), ANCA-associated vasculitis (GPA), immune-complex mediated vasculitis (SLE, cryo, HSP), Goodpasture syndrome (anti-GBM), drug-induced vasculitis (cocaine, PTU, TNFi), coagulopathy, endometriosis, inhalation injury, sarcoid</td>
<td>2) CXR (most important), CBC/coags, UA (screen for vasculitis), sputum Cx, CT chest (if stable)</td>
</tr>
<tr>
<td><strong>Pulmonary vascular:</strong> PE, CHF, mitral regurgitation, bronchovascular fistula, aneurysm, AVM</td>
<td>3) In select pts: NT-proBNP (if CHF on ddx), ESR/CRP, C3/C4, ANA, ANCA, anti-GBM, APLA (anti-cardiolipin, beta-2 GP1, LA), IGRA/AFB to r/o TB, D-dimer (if PE on ddx)</td>
</tr>
</tbody>
</table>

**Massive Hemoptysis** (>500mL/day or >100mL/hr) is a life-threatening emergency with mortality rate 50-80%

Source is often arterial. Asphyxiation NOT exsanguination is mechanism of death. (Crit Care Med 2000;28:1684)

1) Control airway: STAT RICU consult (x63333); consider bronchoscopic intubation; use largest ET-tube (>8mm) possible
2) Lie patient on side where bleeding is suspected (preserve gas exchange in unaffected lung)
   - Call IP→bronch to localize bleeding source to lobe/segment and treat (topical vasoconstriction, coagulant, electrocautery, laser, balloon tamponade);
   - Call IR→CTA (embolization of bleeding site); correct coagulopathy
   - Consider c/t thoracic surgery. Consider pulse dose methylprednisolone if vasculitis is suspected cause.
Overview: Diverse group of disorders that cause scarring/fibrosis in the lungs, often leading to structural changes in the parenchyma (alveoli, interstitium, alveolar-capillary interface) → loss of lung volume/compliance

Clinical Presentation: Progressive dyspnea, non-productive cough, hypoxemia (esp. w/ exercise), acute and chronic presentations

Physical Exam: “Velcro-like” crackles, wheezing, tachypnea, clubbing, signs of connective tissue disease (e.g. heliotrope eruption, photosensitive rash, Gottron’s papules, mechanic’s hands, joint disease, muscle weakness, skin fibrosis, sicca)

Etiologies: Known and unknown causes broken down by subcategories (as well as some rare etiologies) (NEJM 2018;378:1811)

Unknown Causes (i.e. Idiopathic)

<table>
<thead>
<tr>
<th>Chronic</th>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic Pulmonary Fibrosis (IPF), Cryptogenic Organizing Pneumonia (COP)</td>
<td>Acute Interstitial Pneumonia (AIP) AKA idiopathic ARDS</td>
</tr>
</tbody>
</table>

Known Causes

<table>
<thead>
<tr>
<th>Systemic Diseases</th>
<th>Connective Tissue Disease</th>
<th>Inhalation Exposures</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Interstitial Pneumonia (AIP)</td>
<td>Sarcoid, Amyloid, ANCA-vasculitis</td>
<td>Organic inhalation (ask about exposure to molds, birds)</td>
<td>Amiodarone, Nitrofurantoin, Methotrexate, Nivolumab, Pembrolizumab, Iplimumab, Radiation</td>
</tr>
<tr>
<td>Chronic Interstitial Pneumonia (CIP)</td>
<td>Scleroderma, Polymyositis, Dermatomyositis, RA, SLE</td>
<td>Inorganic inhalation (ask about exposures to silica, asbestos)</td>
<td></td>
</tr>
</tbody>
</table>

Other (rare): Lymphangioleiomyomatosis (LAM), seen in young women with reticular opacities on CXR and thin walled cysts on CT chest; Pulmonary Langerhans cell histiocytosis, seen in young adults with upper zone predominant cysts (can be bizarrely shaped) and nodules; Eosinophilic Pneumonia, acute form (AEP) suspected with < 1 mo of sx, BAL with > 25% eos vs. chronic form (CEP) with > 1 mo of sx and peripheral eos (>6%) with bilateral peripheral consolidations that are “photographic negative” (i.e. opposite pattern from pulm edema)

Diagnostic Work-up of ILD:
- Labs: CBC+diff, CMP, ESR/CRP, CPK/aldolase, C3/C4, auto-antibodies (ANA, anti-RNP, anti-Ro/La, Scl-70; RF/anti-CCP, ANCA, hypersensitivity panel, myositis panel 3, anti-Jo1 (included in myositis panel but comes back faster)
- Radiology: CXR, HRCT ILD-protocol (see below)
- PFTs: Restrictive defect (↓ TLC, ↓ FRC, ↓ RV and ↓ DLCO = early sign; FEV1/FVC normal to increased)
- BAL: Not diagnostic for most ILDs (except eosinophilic PNA) but helpful to rule out infection which can have role in acute ILD exacerbations
- Lung biopsy: Pursue when radiology not definitive; gold standard for diagnosis

Radiographic features → High Res CT chest is key for diagnosis
- Usual Interstitial Pneumonia (UIP) is the radiographic corollary of IPF
  - UIP (left): basilar predominant, honeycombing, traction bronchiectasis
  - Non-IPF pathologies will have a Non-Specific Interstitial Pneumonia (NSIP) pattern
  - NSIP (right): subpleural sparing, increased reticular markings, ground glass, mosaic attenuation due to air trapping (requires inspiratory/expiratory high-res CT), hypersensitivity pneumonitis will be upper lobe predominant

Treatment:
- IPF:
  - Chronic therapy: consideration for pirfenidone (antifibrotic), nintedanib (tyrosine kinase inhibitor) (reduces FVC decline but no ↑ survival) (NEJM 2014;370:2083 and NEJM 2014;370:2071), aggressive GERD treatment and aspiration precautions may be beneficial (Lancet Respir Med 2013;1:369), ↑ mortality with azathioprine/prednisone/NAC (NEJM 2012;366:1968) and NAC monotherapy with minimal side effects but no clear benefit (NEJM 2014;370:2093), steroids are not indicated, lung transplant evaluation
  - Acute exacerbations: steroids and broad spectrum abx recommended (AMJRCCM 2011;183:788)
- NSIP: remove inciting exposures, treat underlying condition, can be steroid-responsive; consider biologic agents such as rituximab or cyclophosphamide in myositis-associated ILD (rheum consult) (Chest 2016;150:1118)
- COP: monitor but if symptomatic/disease progression with respiratory impairment → prednisone
- AIP: supportive; usually not steroid-responsive but consider high dose methylpred as in-hospital mortality >50%
**CLINICAL MANIFESTATIONS**

**Signs/Symptoms**
- **DVT:** calf pain, edema (esp. asymmetric), palpable cord, venous distention. Homan’s sign (pain with dorsiflexion) has little value given low sensitivity (sn) and specificity (sp)
- **PE:** dyspnea (77-79%), tachypnea (57%), pleuritic chest pain (39-47%), orthopnea (36%), tachycardia (26%), hemoptysis (7.6%), calf or thigh swelling (23-39%), dizziness (12.2%), JVD (13%), syncope (5.5%), angina (3.9%), accentuated P2 (15%), rales/crackles (8.4-21%). *(Am J Med 2007;120:871; JACC 2011;57:700)*

**Risk Factors** *(JAMA 2003;290:2849)*
- Major Risk Factors (OR 10-20): Hip, pelvis, femur fracture; major trauma; abdominal/pelvic surgery; recent spinal cord injury
- Moderate Risk Factors (OR 6-8): Arthroscopic knee surgery; immobility > 48 hours; malignancy; central line; CHF/COPD exacerbation; OCPs/hormone replacement tx; hypercoagulability (protein C/S or AT deficiency > FVL)
- Weak Risk Factors (OR 2-4): Bed rest > 3 days; plane flight > 6 hrs; age; obesity; postpartum period
- Other risk factors: previous VTE (RR 7.9), IBD, nephrotic syndrome; *acute medical illness likely most common cause* → incidence may be 15% without prophylaxis *(NEJM 1999;341:793)*; Virchow’s triad (classical model of pathogenesis): venous stasis, vascular injury, hypercoagulability

**Prophylaxis**
- LMWH preferred *(Chest 2008;133:381)*. TID heparin more effective in preventing clinically relevant VTE however with ↑ bleeding compared to BID dosing *(Chest 2007;131:507)*. LMWH favored over apixaban, as apixaban is associated with ↑ bleeding *(NEJM 2011;365:216)*. Intermittent compression stockings as non-pharmacologic therapy.


<table>
<thead>
<tr>
<th>Wells’ Criteria for PE</th>
<th>Pre-test Probability</th>
<th>PERC: PE Rule-out Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical S/Sx of DVT (3 points)</td>
<td>Low (0-1 points, 1.3% risk): D-Dimer or use PERC</td>
<td><em>(J Emerg Medicine 2009;36:317)</em></td>
</tr>
<tr>
<td>PE is # dx OR equally likely (3 points)</td>
<td>Intermediate (2-6 points, 16.2% risk): D-Dimer</td>
<td>Can help r/o PE if none of the following criteria are present in patient with low pretest probability:</td>
</tr>
<tr>
<td>Heart rate &gt; 100 (1.5 points)</td>
<td>High (&gt;6 points, 37.5% risk): PE-CT</td>
<td>(1) Age &gt; 50 (2) HR &gt; 100 (3) SpO2 ≤ 95%</td>
</tr>
<tr>
<td>Immobilization at least 3 days OR surgery in last 4 wks (1.5 points)</td>
<td></td>
<td>(4) Hemoptysis (5) Estrogen use (6) Surgery/ trauma/recent hosp in preceding 4 weeks</td>
</tr>
<tr>
<td>Previous PE/DVT (1.5 points)</td>
<td></td>
<td>(7) Prior VTE (8) Unilateral leg swelling</td>
</tr>
<tr>
<td>Hemoptysis (1 point)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy with bx w/in last 6 months (1 point)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INTERPRETING D-DIMER** *(nml < 500 ng/mL)*
- **DVT:** nml + low pre-test prob, excludes DVT *(NEJM 2003;345:1227, JAMA 2006;295:199)*
- **PE:** if nml excludes PE in low/intermediate protest probability *(Thromb Haemost 2009;101:886)*
- **If age > 50, use age x 10 as cut off** *(JAMA 2014;311:1117)*
- **In patients with prior VTE, nml D-dimer excludes recurrent thrombus formation** *(Ann Intern Med 2004;141:839)*
- **DDx for T D-dimer:** arterial thrombi (MI, stroke, afib, intracardiac thrombus), DIC, inflammation/infection, ESLD (↓ clearance), renal disease, pregnancy, advancing age, neoplasm, aortic dissection.

**DIAGNOSTICS**

**Deep Venous Thrombosis:** Venous ultrasound (“LENIs” = Lower Extremity Non-Invasive; “UENI” = Upper Extremity); Se and Sp 89-100%

- **PE-CT:** Study of choice: Se 83%, Sp 95%, PPV 86%, NPV 95% *(PIOPED II, JAMA 2006;354:2317)*; even better with modern scanners.
- **LENIs:** (+) in ~20% of patients with documented PE, but *does not exclude PE* (false negatives, embolization of clot, alternative source of emboli)
- Echocardiogram: non-specific findings include RV hypokinesis, dilation, and TR. McConnell’s sign = diffuse RV wall hypokinesis with apical sparing, Se 77% and Sp 94% *(Am J Cardiol 1996;78:469)*
- **V/Q Scan:** Validated in PIOPED *(JAMA 1990;263:2753)*. At MGH, reserved for pts with c/i to contrast and nml CXR (minimize other causes of V/Q mismatch); *study of choice for chronic thromboembolic PH/T (CTEPH)*
- **ABG:** Hypoxemia (+ A-a gradient, normal in ~20%), respiratory alkalosis
- **EGK and Cardiac Biomarkers (hsTnT, NT-proBNP): Must send for all patients to guide risk stratification. EGK findings in acute PE *(J Emerg Med 2001;21:263, Am J Med 2009;122:257):* normal (up to 24%), sinus tachycardia (up to 69%), T WI in V1-V4 (up to 77%), complete/Incomplete RBBB (up to 67%), S1Q3T3 (seen in up to 50%). Rare: Qr in V1, new RA abnormality, RV strain.

<table>
<thead>
<tr>
<th>High Risk PE (Massive)</th>
<th>Intermediate Risk PE (Submassive)</th>
<th>Low Risk PE (Non-Massive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe cases; mortality ≥15%; defined by right heart strain with hypotension</td>
<td>35% of cases; mortality <em>RH strain without hypotension:</em></td>
<td>Low risk of mortality; defined by absence of right heart strain and hypotension</td>
</tr>
<tr>
<td>EKG, Echo: as above</td>
<td><strong>EKG, Echo: as above</strong></td>
<td></td>
</tr>
<tr>
<td>Biomarkers: <strong>NT-proBNP &gt; 500; hsTnT &gt; 52</strong></td>
<td><strong>CT-PE: RV enlargement (RV-to-LV diameter ratio &gt;0.9)</strong></td>
<td></td>
</tr>
<tr>
<td>↑ TnT + ↑ CK-MB + RV-dilatation indicate highest mortality <em>(Am J Cardiol 2011;107:774)</em></td>
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</tbody>
</table>

Louise Xu
Pulmonary & Critical Care

VTE Management

MANAGEMENT (Eur Heart J 2014;35:3033, CHEST 2016;149:315)

<table>
<thead>
<tr>
<th>Pulmonary Embolism</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pulmonary Embolism Response Team (PERT): consult for all high risk pts and intermediate risk pts with risk factors below (x47378)</td>
<td>• Iliofemoral DVT: AC only. CDT if limb-threatening circulatory compromise, progression on AC</td>
</tr>
<tr>
<td>• High Risk: thrombolysis + AC; if strong contraindication, consider surgical embolectomy vs. catheter-directed thrombolysis (CDT, see below)</td>
<td>• Isolated Distal/Calf DVT: 15% may extend to popliteal vein w/ ↑PE risk if untreated. Antiocoagulate if severe sx or high risk, otherwise repeat LENI in 1-2wkss → if still present or clot extends, then AC</td>
</tr>
<tr>
<td>• Intermediate Risk: AC +/- thrombolysis/CDT if patient has either:</td>
<td>• UE DVT involving axillary or more proximal veins: AC alone over thrombolysis. AC also indicated for catheter-induced UE DVT.</td>
</tr>
<tr>
<td>(a) Moderate/severe RV strain AND any hypotension/AMS/desaturation/acute distress (AHA criteria)</td>
<td></td>
</tr>
<tr>
<td>(b) Both biomarker AND imaging evidence of RV Strain. Can also include sPESI score (predicts 30-day mortality, AJRCCM 2005; 172:1041)</td>
<td></td>
</tr>
<tr>
<td>• Low Risk: AC alone. If subsegmental PE with no proximal LE DVT and low risk for recurrent VTE, consider surveillance over AC (Thromb Res 2016;138:55).</td>
<td></td>
</tr>
</tbody>
</table>

Testing in Unprovoked VTE: Age-appropriate cancer screening and symptom-directed studies only (Ann Intern Med 2017;167:410). Hypercoag panel is NOT part of routine workup (see “Coag. Disorders” in Heme/Onc section for more)

Anticoagulation (see Heme/Onc section for more information)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trials</th>
<th>Dosing</th>
<th>Dose Reductions</th>
<th>Bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (Xa)</td>
<td>EINSTEIN-DVT/PE (NEJM 2010;363:2499, NEJM 2012;366:1287)</td>
<td>15mg BID x3wk then 20mg QD</td>
<td>Contraindicated if CrCl&lt;30, ESLD: 15mg for AF with CrCl 15-30</td>
<td>Apixaban trends towards less GIB compared to warfarin.</td>
</tr>
<tr>
<td>Apixaban (Xa)</td>
<td>AMPLIFY/EXT (NEJM 2013;368:699)</td>
<td>10mg BID x7d then 5mg BID</td>
<td>2.5mg BID if: Cr ≥ 1.5, ≥80yo, or ≤ 60kg (afib data)</td>
<td>Edoxaban and Dabigatran showed significantly less bleeding compared to warfarin.</td>
</tr>
<tr>
<td>Edoxaban (Xa)</td>
<td>HOKUSAL-VTE (NEJM 2013;369:1406)</td>
<td>60mg QD w/ IV AC overlap for 5-10d</td>
<td>30mg if CrCl 15-50 or ≤ 60kg</td>
<td>All DOAC trend towards less intracranial bleeding risk compared to warfarin.</td>
</tr>
<tr>
<td>Dabigatran (Ila)</td>
<td>RE-COVER I &amp; II (Thomb Haemost 2016;116:714)</td>
<td>150mg BID w/ IV AC overlap for 5-10d</td>
<td>No data for CrCl ≤ 30</td>
<td></td>
</tr>
</tbody>
</table>

• Choice of AC: (NEJM 2003;349:146, NEJM 2018;378:615)
  o Pt w/ cancer: LMWH preferred due to ↓ recurrent VTE in cancer, new data suggests edoxaban equally effective
  o Pt w/ APLAS: warfarin preferred
  o Pt undergoing thrombolysis or need for rapid reversal: UFH
  o All others: DOAC > warfarin (Grade 2B) > LMWH (Grade 2C)

• Length of Tx: 3 months if provoked. Indefinite if cancer-associated. If unprovoked, duration depends on risk/benefit assessment as follows:
  o 1st or 2nd VTE w/ low or moderate bleeding risk → indefinite treatment; high bleeding risk → 3 months treatment
  o Normalization of D-dimer may help determine duration of anticoagulation (PROLONG, NEJM 2006;355:1780)
  o In unprovoked proximal DVT or PE, aspirin should be started if patient decides to stop AC at 3 months and there is no c/f to aspirin, given 33% reduction in major vascular events (NEJM 2012;367:1979)

Systemic Thrombolytics

• Dosing: Hold AC while administering. Prefer 2hr infusion vs 12-24h infusion. Usually 1st choice is alteplase IV 100mg over 2h.
• High Risk PE: Thrombolysis generally indicated if no contraindications. If contraindications, consider surgery vs CDT, and likely IVC filter.
• Intermediate Risk PE: No consensus, consider for intermediate-high risk pts w/ severe distress, impending shock, or sPESI >1 (COR IIb, LOE B)
  o Overall mortality only ~3%, so difficult to see benefit, but there is significant ↓RVSP and ↓sOB
  o PEITHO (NEJM 2014;370:1402): hemodynamic decomposition (1.6% vs. 5%, p=0.002) but no significant difference in mortality, ↑major bleeding (11.5% vs. 2.4%), ↑hemorrhagic stroke (2.0% vs. 0.2%)
  o MOPPET (Am J Cardiol 2013;111:273): ↓HTN after low-dose thrombolysis at 28mo
  o Meta-analysis found thrombolysis was associated with ↓mortality (NNT 59) but ↑bleeding (NNH 18); however, bleeding risk w/ thrombolysis decreases for age <65 y/o (NNH 176) (JAMA 2014; 311:2414)

Catheter-Directed Thrombolitics (CDT):
Growing body of data for CDT in high-risk submassive/massive PEs, esp in those with concern for bleeding or contraindication to thrombolitics
• SEATTLE II (JACC Card Interv 2015;8:1382): ↓RVSP and ↓major bleeding
• ULTIMA (Circ 2014;129:479): 1st RCT, improved short term outcomes (RVSP), no mortality data collected
• PERFECT (Chest 2015;148:567): ↓RVSP and a/w survival to discharge, no major bleeds
**Presentation** (nonspecific/insidious sxn; ~2 year delay to diagnosis, *Chest* 2011;140:19):
- **Early:** dyspnea on exertion, lethargy, fatigue
- **Late:** exertional chest pain, syncope, edema, hepatic congestion
- **Rare:** cough, hemoptysis, hoarseness (Ortner’s syndrome)
- **Exam:** JVP, edema, ascites, loud P2, prominent a wave, TR, PR, L parasternal heave

**WHO Classification:** *(JACC 2013;62:D34)*

<table>
<thead>
<tr>
<th>Group 1: Pulmonary arterial hypertension</th>
<th>Group 3: Lung disease/hypoxia</th>
<th>Group 4: CTEPH</th>
<th>Group 2: L heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (F&gt;M); Genetic <em>(BMPR2, ALK1, ENG, SMAD9, CAV1, KCNK3)</em>; Drug/toxin <em>(e.g., anorexigens, rapeseed oil, dasatinib, cocaine, amphelamines, SSRIs)</em>; CTD (MCTD, scleroderma, SLE); HIV; portopulmonary HTN; congenital heart disease; schistosomiasis</td>
<td>COPD; ILD; OSA; Alveolar hypoventilation disorders; Developmental lung disease, among others</td>
<td>Chronic thromboembolic (occurs after ~ 4% of PEs)* <em>(NEJM 2004;350:2257)</em></td>
<td>HFEF; HfPEF; Valvular disease; Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
</tr>
</tbody>
</table>

**Diagnosis:** chest pain, dyspnea, exercise intolerance, orthopnea, PA hypertension, decreased RV & PA capacity

**Differential:** intractable CHF, CHF exacerbation

**PH Failure** (to refer to “RV Failure” in Cardiology section)
- Assess for reversible causes: PE, arrhythmia, ischemia, etc
- **Acute:** ↑ preload to ↑ CO; avoid intubation and PPV if possible
- **Chronic:** ↓ preload (improves RCA perfusion, reduces ventricular interdependence, improves LV diastolic filling)
- Maintenance of sinus rhythm and atrioventricular synchrony is especially important given preload-dependent state.
- **↑ RV contractility:** ↓ RV afterload: reverse hypoxia, hypercapnia, and acidemia; IV/inhaled pulm vasodilators; milrinone or dobutamine for inotropic support with pulm vasodilation (use norepi/phenylephrine/vaso if hypotensive)
- **ECMO** for reversible causes, pre-lung tx *(Circ 2008;117:1717)*

**Management:** Close monitoring and specialist involvement recommended before starting these medications

1. Primary therapy to treat underlying etiology: CTD, CHF, hypoxemia (O2 therapy), VTE, etc.
3. Surgery: lung transplant (group 1), pulmonary thromboendarterectomy (group 4), atrial septostomy *(NEJM 2002;346:896)*, remains investigational; used primarily for sickest patients *(NEJM 2013;369:809)*

**Table:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ET-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine, diltiazem</td>
<td>Positive vasoreactivity test</td>
<td>↓ BP, palpitations, LE edema, flushing, nausea, dizziness, headache, MI, CHF, hepatotoxicity</td>
</tr>
<tr>
<td>Inhaled NO (INO)</td>
<td>Group 1: remains investigational; used primarily for vasoreactivity testing</td>
<td>Hypotension, methemoglobinemia, rebound pHTN if discontinued</td>
</tr>
<tr>
<td>PDE5 inhibitors: sildenafil, tadalafil</td>
<td>Group 1: ↑ exercise capacity, hemodynamics <em>(NEJM 2005;353:2148)</em></td>
<td>Erythema, flushing, indigestion, HA, insomnia, epistaxis, rhinitis, retinal hemorrhage</td>
</tr>
<tr>
<td>sGC stimulator: riociguat</td>
<td>Group 1, Group 4 <em>(NEJM 2013;369:330)</em></td>
<td>↓ BP, constipation, diarrhea, GERD, vomiting, anemia, dizziness, headache, hemorrhage</td>
</tr>
<tr>
<td>Analogues: epoprostenol, treprostinil, iloprost</td>
<td>Groups 1, 3-5: reserved for sickest patients <em>(NEJM 1996;334:296)</em></td>
<td>CP, ↓ BP, THR, flushing, ab pain, anoxemia, n/v/d, jaw pain, MSK pain, dizziness, HA, hemorrhage</td>
</tr>
<tr>
<td>R Agonist: selexipag</td>
<td>Group 1: 40% ↓ hospitalization; no Δ mortality <em>(NEJM 2015;373:2522)</em></td>
<td>Diarrhea, nausea, jaw pain, headache, anemia</td>
</tr>
</tbody>
</table>

**Mean PA pressure (mPAP) = (PVR x CO) + PCWP**

**Definition of PH:** mPAP ≥ 25 mm Hg at rest

**Measure:** mPAP from RHC

**Calculate:** PVR = (mPAP – PCWP) / CO (Fick’s or TD)

**Pre-Cap PH:** PCWP ≤ 15, DPG > 7, PVR > 3

**Post-Cap PH:** PCWP > 15, DPG < 7, PVR ≤ 3

**Mixed PH:** PCWP > 15, DPG > 7, PVR > 3

**Diastolic pulm. gradient (DPG) = PAd - PCWP (NE): may also use transluminal gradient [TPG] > 12)**

Louise Xu
Overview: (NEJM 2013;369:1726)
- **Definition:** state of tissue hypoxia due to decreased or 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/hr), altered mental status, metabolic acidosis (+/- anion gap, ↑lactate); cool & clammy vs. warm & flushed extremities (N.B. any of the above can be normal in a patient who is in shock, so a high index of suspicion is often needed)
- **Initial Workup:** focused H&P, ensure access, review meds, order EKG/CXR, labs (ABG/VBG, CBC+diff, CMP, TnT, lactate, CVO2)
- **MAP:** determined by CO (cardiac output) and SVR (systemic vascular resistance)

MAP = RAP + CO x SVR

Determined by vessel diameter/length and blood viscosity

(2/3) DBP + (1/3) SBP

HR x SV

Determined by preload, afterload, and contractility

**Etiologies of Shock:**

**Signs of ↑CO:**
- Increased pulse pressure
- Low diastolic BP
- Warm extremities
- Normal cap refill (early)

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

**Etiologies of Shock:**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Distributive (66%)</th>
<th>Hypovolemic (16%)</th>
<th>Cardiogenic (16%)</th>
<th>Obstructive (2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophys.</td>
<td>Decreased systemic vascular resistance and altered oxygen extraction</td>
<td>Low cardiac output and therefore inadequate oxygen delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>Sepsis/SIRS, anaphylaxis, adrenal insufficiency, liver failure, toxins/meds, spinal/neurogenic</td>
<td>Bleed (GI, RP, abdominal, thigh), GI losses (diarrhea/vomiting), third spacing (pancreatitis),</td>
<td>MI, HF, severe valve disease, myocarditis, arrhythmias</td>
<td>Extra-cardiac causes (PE, tension PTX, tamponade)</td>
</tr>
<tr>
<td>Extremities</td>
<td>Warm and dry</td>
<td>Cold and dry</td>
<td>Cold and wet</td>
<td>Cold and dry</td>
</tr>
<tr>
<td>CVP/PCWP</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CO or CVO2</td>
<td>↑ or normal</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>SVR</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Echo Findings</td>
<td>Normal chamber size, preserved contractility</td>
<td>Small chambers, normal/high contractility</td>
<td>Large ventricles, poor contractility</td>
<td>Tamponade: pericardial effusion, small ventricles PE/PTX: dilated RV</td>
</tr>
<tr>
<td>Basic Management</td>
<td>All causes: fluids, pressors&lt;br&gt;Sepsis: source control, abx&lt;br&gt;Adrenal: steroids (hydrocort +/- fludicort)&lt;br&gt;Anaphylaxis: epi 0.3mg IM</td>
<td>Ensure adequate access!&lt;br&gt;Most cases: fluids&lt;br&gt;HRS/SBP: albumin&lt;br&gt;Hemorrhage: pRBCs, surgery/IR/GI hemostasis</td>
<td>Diuresis, pressors, inotrope, +/- PA line</td>
<td>Tamponade: pericardiocentesis&lt;br&gt;PE: heparin/lysis&lt;br&gt;PTX: chest tube vs. needle decompress</td>
</tr>
</tbody>
</table>

**If the etiology of shock is unclear, the most useful ways to quickly distinguish include:**
- **First step:** Vitals: wide vs. narrow pulse pressure; Exam: warm vs. cold, dry vs. wet, rashes or mottling
- **Quick data points:** CVO2, and TTE (consider POCUS and/or STAT TTE)
- **Consider:** PA catheterization for shock differentiation. See PA Catheterization for full discussion, but no benefit in terms of mortality, LOS, or cost (Cochrane 2013;2:CD003408, ESCAPE—JAMA 2005;294:1625, PAC-Man—Lancet 2005;366:472)

**Management Considerations**
- **Ventilatory Support:** intubate if necessary, but have pressors available as intubation often worsens hypotension; be aware that SpO2 is often unreliable due to peripheral vasocostriction (even on earlobe), may require frequent ABG Plus (includes SaO2)
- **Antibiotics:** If septic shock is on the differential, get early cultures and start broad spectrum antibiotics without delay
- **Fluid Resuscitation:** Crystalloid or albumin given as bolus (not infusion) for quick response. Assess fluid responsiveness by: pulse pressure variation, passive straight leg raise, IVC diameter (see Sepsis: Resuscitation). Good approximation = improvement in BP, UOP, lactate after fluid challenge. If cardiogenic shock is possible, be careful with fluid resuscitation as it will worsen shock.
- **Vasoactive Agents:** (see Vasopressors); typically titrate to MAP >65 mmHg (if cardiogenic, MAP >60 mmHg)
- **Steroids:** if known adrenal insufficiency or patient chronically on steroids, administer stress-dose steroids; unclear role and highly debated for septic shock
- **Specialized Teams:** STEMI team (x6-8282), PERT team (x4-7378), Shock team (p29151 → if considering IABP, Impella, VA-ECMO)
Pulmonary & Critical Care

Sepsis

**OVERVIEW**
- **Definitions:** Recently updated in 2016 by Sepsis Definitions Task Force (Sepsis-3): (JAMA 2016;315:801)
  - Sepsis: *Life-threatening* organ dysfunction caused by a dysregulated host response to infection
  - Septic Shock: Pt meets sepsis criteria + (1) requires pressors to sustain MAP >65 AND (2) has lactate >2 mmol/L without hypovolemia
- **Diagnosis:** Former SIRS + infectious source definition failed to identify 1 in 8 patients with sepsis and organ failure (NEJM 2015;372:1629).
  - More recently, organ dysfunction has been quantified using the Sequential Organ Failure Assessment (SOFA) score. In patients w/ infection, quick SOFA (qSOFA) is an easy-to-use score that identifies pts at ↑ risk of prolonged ICU stay or in-hospital mortality

**PATHOPHYSIOLOGY**
- Low SVR due to cytokine dysregulation, acidemia, and increased NO with blood flow redistribution
- Impaired tissue oxygen extraction (“cytopathic hypoxia,” Crit Care 2002;6:491) and mitochondrial dysfunction
- Cardiac: altered cardiac function – may be either hyperdynamic or depressed
- Renal: AKI of multifactorial etiology, including microvascular dysfunction, oxidative stress, global hypoperfusion
- Pulmonary: endothelial damage, ARDS/ALI
- Hepatic: sepsis frequently causes cholestasis and jaundice (“sepsis-induced cholestasis”) due to hepatocyte injury
- Hematologic: early inflammation followed by late immunosuppression, procoagulant and anticoagulant disequilibrium: DIC, ↓ platelets

**INITIAL MANAGEMENT**

**Keys:**
- Sepsis/septic shock are medical emergencies, so early recognition is critical. Components of initial management include:
  1) administering broad spectrum empiric antibiotics within 1 hour of diagnosis
  2) initial fluid resuscitation with a 30 mL/kg fluid challenge over 3 hours (+ more as needed if patient is volume-responsive)
  3) vasopressor support if needed
  4) source identification and control

1) **Antibiotics:** ***Antibiotics should be administered, not just ordered, within one hour of recognition. Order STAT.***
- Broad, empiric intravenous antibiotics must be started within one hour (CCM 2010;38:1045).
- Rapid administration of antibiotics is associated with lower in-hospital mortality (NEJM 2017;376:2235); increase in mortality of 7.6% per hour delay in adequate antimicrobial administration (CCM 2006:34:1589).
- Antibiotic selection should be guided by old micro data and exposures (SNF, lines, recent antibiotic use, MDROs, etc)
- **Consider double coverage of GNRs if:** (1) immunocompromised (2) healthcare exposures in prior 3-6mo (3) pseudomonal infection in prior 3-6mo (4) institutional prevalence of resistant GNRs >20% (Antimicrob Agents Chemother 2005:49:760). Data for this practice is mixed but recent cohort studies showed benefit with anti-pseudomonal beta-lactam + aminoglycoside or FLQ (Crit Care Med 2010;38:1773, Antimicrob Agents Chemother 2010:54:3590).
- If there is suspicion of toxic shock syndrome, add clindamycin for anti-toxin effects and staph/strep coverage

2) **Resuscitation:**
- Initial fluid challenge is minimum of 30 mL/kg of crystalloid administered over 3 hours
- Balanced crystalloids (e.g., LR), compared to NS associated with lower mortality and less renal impairment (NEJM 2018;378:829)
- After the initial resuscitation effort, further fluid administration should be guided by dynamic measures of fluid responsiveness:

<table>
<thead>
<tr>
<th>Assessing for Fluid Responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Techniques and Monitors</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Clinical/Lab Assessments: BP, mental status, UOP, lactate</td>
</tr>
<tr>
<td><strong>Pulse Pressure Variation:</strong> Measure PPV (PPmax-PPmin/PPmean) in patients mechanically ventilated with tidal volumes of 8 mL/kg or higher (Crit Care 2014;18:650)</td>
</tr>
<tr>
<td><strong>Passive Leg Raise:</strong> Raise legs to 45° w/ supine torso x 1 min. in a mechanically ventilated patient (less accurate if spontaneous respirations)</td>
</tr>
<tr>
<td><strong>Ultrasound evaluation of IVC collapsibility:</strong> Measure 1cm proximal to hepatic vein junction in M-mode; cIVC= Dmax-Dmin/Dmax.</td>
</tr>
<tr>
<td><strong>Dynamic CVP Assessment:</strong> Measure CVP before administration of IVF bolus and then immediately after. Note that static CVP measurement alone is poor predictor of volume responsiveness (Curr Opin Crit Care 2005;11:264)</td>
</tr>
</tbody>
</table>

- No response to volume challenge suggests patient is on the flat part of the Frank-Starling curve; consider vaspressors instead
- **Consider albumin** when patients require ↑↑↑ crystalloid; meta-analysis showed trend toward decreased mortality in septic shock (CCM 2014;18:702)

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3) Vasopressors: (see Vasopressors page for full details):
- Target a mean arterial pressure (MAP) of >65 mm Hg (SEPSIS-PAM trial, NEJM 2014;370:1583)
- Per MGH MICU guidelines, arterial lines are needed for BP monitoring only in pts on moderate doses of pressors (e.g., 10 -15 of NE)
  - Norepinephrine (NE, Levoephed): Often first choice vasopressor
  - Vasopressin: Can be added to NE with intent of either raising MAP or decreasing NE dosage (Circulation 1997;95:1122)
  - Epinephrine: Recommended when additional agent is needed to maintain adequate blood pressure; can be used instead of vasopressin
  - Phenylephrine (Neo): Recommended primarily when: (a) NE is associated with serious arrhythmias, (b) CO is high and BP persistently low, (c) as salvage therapy when norepinephrine + vasopressin have failed to achieve MAP target (d) hypotension a/w AFRVR
  - Dopamine: reserved for highly selective patient population with bradycardia and low risk of tachyarrhythmia, associated w/ increased risk of arrhythmias/mortality in all-comers (Cochrane 2011;5:CD003709)
  - Methylene blue: Uncommonly used, pressor of last resort when NO-mediated vasoplegia is suspected
  - Angiotensin II: not currently available in MGH MICU; anticipate eventual availability given ATHOS-3 trial (NEJM 2019;377:419)

4) Source Control:
- Cultures: Obtain cultures prior to antimicrobials (unless this will significantly delay administration). Get at least 2 sets of BCx (both aerobic and anaerobic bottles), with at least one drawn percutaneously.
- Evaluate early for conditions that would require emergent source control (e.g., necrotizing soft tissue infections, peritonitis, cholangitis, intestinal infarctions, abscess, obstructive renal stone w/ hydro)
- Routine blood cultures will grow Candida, Trichosporon, Fusarium and Cryptococcus. Consider 1,3 beta-D-glucan assay and/or cryptococcal Ag if concerned for fungemia.
- Imaging studies: Failure to improve on broad spectrum antibiotics should prompt evaluation for an occult source

CONTINUING MANAGEMENT

Antibiotics:
- Attempt to narrow within 48 hours, ideally guided by culture data + sensitivities and clinical improvement
- Duration of therapy should typically be 7-10 days; longer courses in patients w/ slow clinical response, undrainable foci, bacteremia, S. aureus, some fungal or viral infections, peritonitis, or immunologic deficiencies (e.g., neutropenia)
- Procalcitonin levels can inform decision to discontinue antibiotics or shorten course (Lancet Inf Dis 2016;16:819; PRORATA trial, Lancet 2010;375:463)

Resuscitation: Overall conservative fluid management results in faster recovery in ARDS (FACTT trial, NEJM 2006;354:2564)

Transfusion: No evidence to support transfusion goal higher than hgb 7 g/dl unless cardiac ischemia, hemorrhage, or severe hypoxemia is present (TRISS trial, NEJM 2014;371:1381)

Ventilation: see ARDS page

Renal Dysfunction:
- CVVH and HD are largely equivalent for treating AKI, but CVVH can help minimize fluid shifts in hemodynamically unstable patients.
- Can consider early renal consult for RRT in patients with refractory acidosis, though recent data suggests no mortality benefit to early (<12h) versus delayed (>48h) initiation of RRT in patients with septic shock and severe AKI (NEJM 2018;379:1431)
- Caution: amylase of bicarbonate cause intracellular acidosis and pH- and calcium-dependent reductions in cardiac contractility (NEJM 2014;371:2309)
- Traditionally, bicarbonate is not recommended for treatment of lactic acidosis (CHEST 2000;117:260)
- In patients with AKI and severe metabolic academia (pH<7.20, PaCO2 <45mmHg, bicarb <20mmol/L), recent BICAR-ICU trial showed mortality benefit with infusion of 125-250ml 2% IV bicarb over 30 min with max of 1000ml in 24h (Lancet 2018;392:31), goal pH >7.30

CONTROVERSIAL MANAGEMENT STRATEGIES

Corticosteroids: An initial study suggested a mortality benefit for corticosteroids in patients with septic shock (“Annane” or French trial, JAMA 2002;288:862). Patients were randomized to placebo or hydrocortisone + fludrocortisone x 7d. ICU mortality, 28-day mortality, and in-hospital mortality were significantly improved compared to placebo. The same author showed similar results in a recent study (NEJM 2018;378:809). Controversy: Findings were not replicated in recent trials by other groups (CORTICUS, HYPRESS, and ADRENAL).
- Key points: Consider IV hydrocortisone for patients in whom fluids and pressors do not restore hemodynamic stability. Note that cortisol measurements are not appropriate predictors of response to steroids in ICU patients, and that etomidate (used by RICU for rapid sequence intubation) directly inhibits adrenal steroid biosynthesis.

Esmolol: RCT demonstrated significant mortality difference in pts w/ septic shock treated w/ esmolol (49.4% v. 80.5% in control group, JAMA 2013;310:1683). Controversy: Single-center trial performed in Italy; control group had a significantly higher mortality rate (80.5%) than that expected for septic patients. No subsequent studies have confirmed these findings.
- Key points: Esmolol not routinely used for pts in septic shock

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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.
### INOTROPES

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Usage</th>
<th>Side effects</th>
<th>Dosing: initial/max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milrinone</td>
<td>PDE inhibitor</td>
<td>Cardiogenic Shock</td>
<td>Hypotension, Ischemia</td>
<td>50 mcg/kg over 10 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tachyphylaxis, Cardiogenic Shock</td>
<td>75 mcg/kg/min</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>β1 agonist</td>
<td>Symptomatic Brady</td>
<td>False positive O2, arrhythmias, PVR, rash, hemolysis, serotonin syndrome; contraindicated in G6PD</td>
<td>2-6 mcg bolus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anemia, Angina, Arrhythmias Tachyphylaxis</td>
<td>30 mcg/min</td>
</tr>
</tbody>
</table>

### PRESSOR CHEAT SHEET

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Usage</th>
<th>Side effects</th>
<th>Dosing: initial/max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>α &gt; β1 agonist</td>
<td>Septic shock</td>
<td>Arrhythmia, Digital Ischemia (+FSBG)</td>
<td>8-12 mcg/min</td>
</tr>
<tr>
<td>Levophed “Levo”</td>
<td></td>
<td></td>
<td></td>
<td>(0.1-0.15 mcg/kg/min)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Low: β1&gt;β2&gt;α2: CO, neutral</td>
<td>Septic shock</td>
<td>Reflex Brady, Digital Ischemia</td>
<td>100-180 mcg/min</td>
</tr>
<tr>
<td>Adrenaline “Epi”</td>
<td>High: α1: β&lt;β2: CO, SVR</td>
<td></td>
<td></td>
<td>(0.5-2 mcg/kg/min)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Low: D1&gt;β1: CO, UOP</td>
<td>Symptomatic Brady w/ Brady (No benefit in low “renal” dosing)</td>
<td>Tachyarrhythmia (NEJM 2010:362:779), BP (low dose)</td>
<td>1-2 mcg/kg/min</td>
</tr>
<tr>
<td>Intropin “Dopa”</td>
<td>Med: β&gt;β-D1: CO, SVR</td>
<td></td>
<td></td>
<td>5-20 mcg/kg/min</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>↓NO and cGMP</td>
<td>Septic shock + anaphylaxis (J Med Toxicol 2013:3:242)</td>
<td>Falsely ↓SpO2, arrhythmias, PVR, rash, hemolysis, serotonin syndrome; contraindicated in G6PD</td>
<td>1-2 mg/kg</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>β1 agonist: CO, LSVR</td>
<td>Cardiogenic Shock</td>
<td>↓BP, ↑HR, Angina, Arrhythmias Tachyphylaxis</td>
<td>0-5-1 mcg/kg/min</td>
</tr>
<tr>
<td>Dobutrex “Dobuta”</td>
<td></td>
<td></td>
<td></td>
<td>20-40 mcg/kg/min</td>
</tr>
<tr>
<td>Milrinone Primacor</td>
<td>PDE inhibitor: CO, PVR/SVR</td>
<td>Cardiogenic Shock</td>
<td>Hypotension, Ischemia</td>
<td>50 mcg/kg over 10 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75 mcg/kg/min</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>β1 agonist: H, LSVR</td>
<td>Symptomatic Brady</td>
<td>↓BP, ↑HR, flushing, anxiety, angina</td>
<td>2-6 mcg bolus</td>
</tr>
<tr>
<td>Isuprel</td>
<td></td>
<td></td>
<td></td>
<td>30 mcg/min</td>
</tr>
<tr>
<td>Drug/Toxin</td>
<td>Presenting Symptoms</td>
<td>Diagnostic Workup</td>
<td>Management</td>
<td></td>
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<tr>
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<tr>
<td>Acetaminophen</td>
<td>Tinnitus, fever, vertigo, N/V/D, tachypnea, pulmonary edema, AMS (can have neuropsychopoenia w/ normal serum glucose), respiratory alkalosis (early), metabolic acidosis (late)</td>
<td>ABG (mixed respiratory alkalosis / metabolic acidosis), BMP, CXR, salicylate level (&gt;30-50 mg/dL toxic, though a clinical dx). Repeat levels and ABG Q2H until improving.</td>
<td>Avoid intubation (if required, hyperventilate to avoid acidemia), IVF, charcoal (1 g/kg), glucose (100 ml D50), bicarb, alkalize urine to pH 7.5-8, avoid acetazolamide. Consider HD.</td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td>RR and tidal volume, CNS depression, ↓ bowel sounds, miosis</td>
<td>EKG, core temp, glucose, CPK</td>
<td>IV or intranasal naloxone (0.4-2 mg). Repeat PRN. Naloxone 1/2-life shorter than most opioids → repeated dosing or gtt, esp if long-acting opioids (2/3 effective bolus dose per hr).</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>Depressed MS, ataxia, slurred speech, hyporeflexia, IRR, coma</td>
<td>Hx, urine tox can give qualitative result</td>
<td>Supportive; avoid fumazenil as it precipitates withdrawal + seizures.</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Mydriasis, hyperthermia, decreased sweating, flushing agitated delirium, urinary retention, ileus, tachycardia, HTN</td>
<td>Hx, EKG, CPK</td>
<td>Supportive, cooling for hyperthermia; charcoal (1 g/kg) if &lt;1hr, benzos for agitation &amp; seizure, physostigmine if severe (ICU, atropine at bedside; not for TCA ODs).</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Mydriasis, hyperthermia, decreased sweating, flushing agitated delirium, urinary retention, ileus, tachycardia, HTN</td>
<td>Hx, EKG (brady, long PR), blood levels slow &amp; correlate poorly. Extended release preps dangerous.</td>
<td>Calcium (2-3 g), pressors, glucagon, HIGH DOSE-insulin (1 U/kg bolus, then 0.5-1U/kg/hr gtt, adjust to cardiac response), IVF; consider pacing, atropine, ECMO.</td>
<td></td>
</tr>
<tr>
<td>Atropine, Benztropine, Scopolamine, Diphenhydramine</td>
<td>NV, HoTN, CHF, brady, AV block, stupor, cardiac arrest, hyperglycemia</td>
<td>Hx, EKG, blood levels slow and correlate poorly; propranolol highest mortality.</td>
<td>Digoxin-specific Fab fragments (if K&gt;5.5, severe end-organ dysfxn, or life-threatening arrhythmia), magnesium, AVOID hypokalemia.</td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td>HoTN, bradycardia, AV block, long QTc (sotalol), CHF, bronchospasm, hypoglycemia, stupor, hyperkalemia, seizure (propranolol), miosis</td>
<td>EKG, digoxin level (nl 0.9-2.0 ng/mL; may not be accurate if drawn within 6h of last dose, also tests for bound Fab fragments, may need send out &quot;free&quot; dig level after treatment), lysates, BUN/Cr, UOP.</td>
<td>Pressors, calcium, glucagon (0.05-0.15mg/kg bolus q3-5min or gtt), high-dose insulin (see above), IVF; atropine, pacing, ECMO.</td>
<td></td>
</tr>
<tr>
<td>B-Blockers</td>
<td>Bradycardia, AV block, N/V/abd pain, hyperkalemia, AMS, xanthopsia (yellow-green halo), bidirectional VT, &quot;regularization of AF&quot;</td>
<td>EKG, digoxin level (nl 0.9-2.0 ng/mL; may not be accurate if drawn within 6h of last dose, also tests for bound Fab fragments, may need send out &quot;free&quot; dig level after treatment), lysates, BUN/Cr, UOP.</td>
<td>EKG toxicity common with AKI from high glucose = poor prognosis.</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Prolonged QRS, arrhythmia, hypotension, anticholinergic toxicity, myoclonus, hyperthermia, AMS, coma, seizure</td>
<td>Tox screen, EKG (↑ QRS duration, terminal R wave &gt;3mm in aVR, QRS &gt;100ms correlates w/ 26% seizure risk; &gt;160ms correlates w/ 50% risk. Monitor for ventricular arrhythmia, CPK.</td>
<td>Frequent neuro checks; IVF (NS preferred), maintain UOP, HD if encephalopathy, renal dysfunction.</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>N/V/D, tremor, hyperreflexia, clonus, ataxia, AMS, seizure, hyperpyrexialdemia, AV block, sinus brady, long QT, nephrogenic diabetes insipidus if chronic</td>
<td>BUN/Cr, serial Li levels (nl 0.5-1.5 mmol/L), EKG</td>
<td>IV bicarbonate (for the Na not the alkalization) if QRS &gt;100ms or hypertensive. Benzos for seizure. Salvage Rx: hypertonic (3%) saline, lipid emulsion.</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>AMS, hyperreflexia (LE predominant), hyperthermia, mydriasis, ↑HR, HTN, diarrhea, diaphoresis, clonus, rigidity</td>
<td>Toxicity search for causative agent. CBC, CPK, BMP, coags, LFTs, UA, CXR.</td>
<td>Serotonin Syndrome</td>
<td></td>
</tr>
<tr>
<td>Antidepressants, Linezolid, Tramadol</td>
<td>AMS, hyperreflexia (LE predominant), hyperthermia, mydriasis, ↑HR, HTN, diarrhea, diaphoresis, clonus, rigidity</td>
<td>Search for causative agent. CBC, CPK, BMP, coags, LFTs, UA, CXR.</td>
<td>Benzos for agitation (avoid antipsychotics); supportive care for altered VS (esmolol, nitropresside for ↑HR and HTN and cooling). If all else fails, consider cyproheptadine.</td>
<td></td>
</tr>
<tr>
<td>Neuroneptic Malignant Syndrome (NMS)</td>
<td>N/V/D, tremor, hyperreflexia, clonus, ataxia, AMS, seizure, hyperpyrexialdemia, AV block, sinus brady, long QT, nephrogenic diabetes insipidus if chronic</td>
<td>Search for causative agent. CPK (often very high). CBC (leukocytosis), LDH, LFTs, BMP, serum iron (often low); consider brain imaging, LP, EEG.</td>
<td>Metabolism (before glucose), folate, MVI, IVF w/ dextrose. Calculate discriminant fnx if EtOH hepatolysis.</td>
<td></td>
</tr>
<tr>
<td>EtOH</td>
<td>Disinhibition, stupor, nystagmus, memory loss, discoordination, ↓ RR, coma</td>
<td>ETOH level, methanol and ethylene glycol if + osmol gap . BMP, LFTs.</td>
<td>Methanol</td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Inebriation, AMS; flank pain, hematuria, reversible kidney injury, calcium oxalate crystals in urine</td>
<td>AG metabolic acidosis (severe), osmol gap, oxalate crystalluria, renal failure, hypocalcemia, lactate elevation</td>
<td>Fomepizole (15 mg/kg bolus over 30min then 10mg/kg G12H), bicarb if pH&lt;7.3, leucovorin 50mg IV, consider HD</td>
<td></td>
</tr>
<tr>
<td>Antifreeze</td>
<td>Inebriation, retinal injury (visual blurring, papilledema, blindness)</td>
<td>AG metabolic acidosis (severe), osmol gap, visual acuity testing</td>
<td>Agitation, psychosis, seizure, HTN, ↑</td>
<td>Serum, urine tox (metabolites)</td>
</tr>
</tbody>
</table>
Dialyzable Toxins and Acid/Alkaline Diuresis

Decontamination Therapies

- **Anion and Osmol Gaps**

<table>
<thead>
<tr>
<th>Anion Gap</th>
<th>Osmolal Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td><em>With normal AG:</em> ETOH, isopropyl-OH, Ether, glycine/sorbitol/mannitol, hyperproteinemia, hyperlipidemia</td>
</tr>
<tr>
<td>Uremia (CKD)</td>
<td><em>With elevated AG:</em> Ethylene/propylene glycol, Methanol, Ketocidosis, Lactic Acidosis</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td></td>
</tr>
<tr>
<td>Ethylene/proplene glycol</td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td></td>
</tr>
<tr>
<td>Cyanide</td>
<td></td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td></td>
</tr>
</tbody>
</table>

Anion Gap = (Na⁺) – (Cl⁻ + HCO₃⁻)

*Normal: 8-16 (avg: 12)

Osmolal Gap = Osmplasma - Osmcalc

*Normal ≤10, but wide variability, so interpret with caution

Osmcalc = 2×[Na⁺] + [BUN]/2.8 + [gluc]/ 18 + [EtOH (mg/dL)]/4.6

**Decontamination Therapies:**
- **Activated Charcoal**
  - Most effective if given when substance is still in stomach (usually considered to be within 1hr of ingestion, but data is lacking)
  - Not useful for: Cyanide, Lithium, Ethanol/methanol, Glycols, Mineral acids (e.g., sulfuric acid, nitric acid), Alkali metals (potassium, magnesium, sodium, including sodium hydroxide [Drano]); Iron; Ammonia
- Other therapies not routinely used: whole bowel irrigation (with polyethylene glycol), gastric lavage, ipecac

**Dialyzable Toxins and Acid/Alkaline Diuresis:**

<table>
<thead>
<tr>
<th>Dialyzable Toxins</th>
<th>Acid Diuresis (give Vitamin C)</th>
<th>Alkaline Diuresis (give NaHCO₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETOH, methanol, isopropyl alcohol, Glycols, Acetone, Lithium, Salicylates, Barbiturates, INH, Atenolol, sotalol</td>
<td>Quinine, PCP</td>
<td>Phenobarbital, Salicylates, Methotrexate, TCAs</td>
</tr>
</tbody>
</table>
Urgent Assessment & Management of GI Bleeding:

- **Assess & reassess V/S for hemodynamic stability**
- **Attempt to quantify amount & rate** of blood loss; nasogastric tubes likely do not add clinical benefit
- **≥2 PIV** (18 gauge) – NB this is rarely done by IV nurse; look at their arms (green 18; pink 20; blue 22)
- **Type & screen** (type & cross if plan to transfuse), IVF (and blood if indicated): liberal transfusion if ongoing bleed or unstable VS. Hct drop lags 24-72h from onset of bleeding.
- **Correct coagulopathy:** IV vit K, FFP, Plt, PCC; if uremic, consider ddAVP (0.3 mcg/kg), if ESLD, consider amicar (may ↑ risk of thrombosis). DOAC reversal agents as available.
- **Transfusion goals:** Hb>7, Plt>50k, INR<2, PT+5s<50, Plt>100
  - See Transfusion Medicine - Massive Transfusion Protocol
- **GI consult** for EGD and/or colonoscopy → better outcomes if resuscitated well prior to endoscopic intervention
- **Surgery or IR consult** if hemodynamic instability or difficult endoscopic correction
- **Intubation:** if high volume UGIB/AMS/variceal bleeding requiring balloon tamponade

### Acute Upper GI Bleeding (NEJM 2016;374:2367):

- **Definition:** proximal to ligament of Treitz
- **Symptoms:** hematemesis, melena, orthostasis, brisk UGIB can p/w hematochezia, BUN/Cr > 20-30 without CKD
- **Risk Stratification** (30d mortality): AIMS65 (Sn71%;Sp96%) and Glasgow-Blatchford Score (GBS) (Sn88%;Sp76%); combine for best prediction (Am J EM 2018;36:27)

### Management:

- **Transfusion:** restrictive goal (Hb 7) ↓ mortality vs. liberal (Hb 9); caution w/ restrictive goals if HD unstable given lag time in Hct drop. Avoid overtransfusion in variceal bleed.
  - **Management of anticoagulation** (data are limited):
    - **Aspirin:** Hold during active bleed; for ulcer-related bleeds, resume ASA w/ PPI in pts w/ CV dz (2° prevention) after bleeding stops, best if w/in 1-7d; adding PPI or H2RA may ↓ risk of bleeding (Gastro 2017;152:105)
    - **Coumadin:** Hold during active bleed; resume after ~7 days, ↓ risk of thrombosis, death in afib (Am J Cardiol 2014;113:662)
    - **DoAC:** can resume post-EGD if low risk bleed, and strong indication vs 48-72hr if high risk bleed & prophylactic a/c.
    - **DAPT** (for coronary stents): continue aspirin, resume P2Y12 inhib immediately for low-risk ulcers, for high-risk ulcers consider holding P2Y12 inhib temporarily, based on type/duration of stent, discussion with Cardiology.
  - **Prior to EGD:**
    - **IV erythromycin:** 250mg 30min prior to EGD to ↑ gut motility & visualization (Am J Gastroent 2006;101:1211)
    - **IV PPI:** high-risk lesions requiring endoscopic therapy, but unclear clinical impact pre-EGD (Cochrane Syst Rev. 2010;7:7)
    - **If cirrhosis:** IV octreotide: 50 mcg x 1 → 50 mcg/hr + IV CTX 1g q24hr x 7 days for ppx against bacterial infections (Gastro 2006;131:1048; Aliment Pharmacol Ther 2011;34:509).
      - If continues to bleed, consider amicar (5g bolus followed by 1gr/hr, max ~24g in 24h), ddAVP (if uremia)
    - **After EGD:**
      - If high risk PUD → Intensive PPI x 72 hr reduces re-bleeds & need for repeat endoscopy. Pantoprazole 40mg IV BID, as intermittent dosing is non-inferior to bolus+gtt (80mg, 8mg/hr) (JAMA Intern Med. 2014;174:1755).
        - Oral PPI may replace IV PPI if good PO intake given similar intragastric pH
        - Treat H. pylori if positive test
      - If variceal bleed → continue octreotide x 3-5d
      - If angiodysplasia → consider long-term octreotide (Am J Gastroent 2007;102:254)
      - If re-bleed: repeat EGD, consider angiography, surgical/IR consult. If variceal consider balloon tamponade, TIPS as well.

### Prognosis:

- **PUD rebleeding w/o med management:** 90% if active bleed, 50% if visible vessel, 30% if clot, 20% if oozing, else < 10%
- **Esoph variceal bleed:** 50% resolve spontaneously; 30% mortality → 70% if continued bleeding; 60% risk re-bleeding overall
Acute Lower GI Bleeding *(NEJM 2017;376:1054)*

- **Definition:** bleeding distal to ligament of Treitz resulting in vital sign instability, anemia and/or need for blood transfusion
- **Symptoms:** hematochezia (maroon colored stools, bright red blood, or blood clots) or less commonly melena (generally requires that blood spends 14 hr in the GI tract)
  - *Stool appearance is a poor indicator of GI bleeding source* - hematochezia can also be seen with brisk UGIB (suspect if pt is hemodynamically unstable)
  - Anorectal/L colon: Bright red blood
  - R colon: Maroon colored stools, melena possible if slow colonic transit
  - Bleeding will stop spontaneously in 80-85%
- **History:**
  - Painless hematochezia: diverticular bleed, angioectasia, hemorrhoid
  - Abdominal pain: IBD, ischemic colitis, perforation
  - Weight loss: malignancy, IBD
  - Fever/Diarrhea: IBD, ischemic colitis, perforation
  - History of AAA: aortoenteric fistula
  - AS, vWF, LVAD, ESRD: angioectasia
  - Atrial Fibrillation: acute mesenteric ischemia
  - Medications: NSAIDs (could precipitate diverticular bleed), anticoagulants, antiplatelets
- **Diagnosis:**
  - Exonerate UGIB source first (signs include orthostatic HoTN, hemodynamic instability, BUN:Cr >20-30 without CKD)
  - Consider NGT placement if there is moderate suspicion for UGIB (~15% of hematochezia is UGIB)
    - Coffee-ground material, bright red blood → EGD
    - No blood or bile seen: Indicates indeterminate source → consider EGD before Colonoscopy
    - Bilious fluid: No active UGIB source → Colonoscopy
- **Risk Stratification:**
  - Several risk-factor models have been developed, but they are less well studied than models of upper GI bleeding. Overall only limited ability to predict which patients will have poor outcomes.
    - NOBLADS score: NSAID use, no diarrhea, no abdominal tenderness, SBP <100 mmHg, antiplatelet agent, albumin <3.0 g/dL, ≥2 comorbidities, syncope *(Clin Gastroenterol Hepatol 2016;14:1562)*
    - HR >100 bpm, SBP <115 mmHg, syncope, non tender abdomen, bleeding in <4 hr of eval, ASA use, >2 comorbidities *(Am J Gastroenterol 2005;100:1821)*
- **Management** *(Am J Gastroenterol 2016;111:459):*
  - Transfusion goals: Hgb >7 (consider >8 in active CAD), Plt >50k, INR <1.5 (INR 1.5-2.5 ok to perform endoscopic hemostasis before reversing; INR >2.5 consider using reversal agent)
  - Diverticular hemorrhage, angioectasia, post-polypectomy bleeding, and hemorrhoids amenable to endoscopic treatment
  - **IF HEMODYNAMICALLY STABLE:** Prep for colonoscopy (after discussion with GI)
    - If ongoing bleeding or high risk perform within 24hr
    - Use order set in EPIC
    - OK to place NG tube for high-risk patients with ongoing bleeding who are intolerant of prep (if no known h/o varices)
    - Urgent colonoscopy (within 12hr) improves localization but not mortality *(Am J Gastroenterol 2010;105:2636)*
    - No data to suggest bowel prep increases or reactivates bleeding
  - **IF HEMODYNAMICALLY UNSTABLE:** EGD to r/o UGIB, IR and surgical consult (“blind” surgery mortality ~29%), massive transfusion protocol
- **Unknown Source of GI Bleeding after Colonoscopy/EGD (“Occult GIB”):**
  - Tagged RBC scan: (bleeding rate needs to be >0.5 mL/min): more sensitive for slow bleed, but poor localization
  - Video capsule study: allows visualization of full length of small bowel
  - Push enteroscopy: allows visualization of approximately the proximal 60cm of the jejunum
  - CT Angiography: (bleeding rate >1 mL/min) *(ACR Radiologic Management of Lower Gastrointestinal Tract Bleeding)*
  - IR Angiography: (bleeding rate needs to be >0.5 mL/min): success rate 25-70% in identifying cause, allows for intervention (e.g. embolization, intra-arterial vasopressin) but incurs risk of arrhythmias, bowel ischemia, and vascular injury.
GERD & Peptic Ulcer Disease

Gastroenterology

Gastroesophageal Reflux Disease (GERD)

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

Alarm symptoms: dysphagia/odynophagia, wt loss, GIB, Fe def, anemia, vomiting, persistent sx despite appropriate medical rx

Complications:

- Barrett’s Esophagus (BE): Squamous epithelium → columnar intestinal epithelium. AdenoCa risk is 0.1-2%/year. Combined high dose PPIs and aspirin may ↓ mortality, cancer risk and dysplasia (Lancet 2018;392:400)
  - Screen w/ EGD only in: men w/ chronic GERD sx + 2 RFs (age≥50, Caucasian, obesity, tobacco hx, FH of BE or adenoca)

- Esophageal stricture: pH/progressive solid food dysphagia. Endoscopy w/ biopsy can differentiate stricture from cancer.


- If sx’s suggestive of uncomplicated GERD, trial of empiric PPI QD for 4-8 wks is diagnostic test of choice.
- If alarm symptoms → EGD w/ biopsy: detects tissue damage and/or complications, alternative DDx (i.e. EoE, malignancy)

Ambulatory pH monitoring/impedence testing: indicated if endoscopy negative but persistent symptoms

Management:

- Mild/Intermittent symptoms -> see algorithm figure 1 in Gastro 2018;154:302
  - Lifestyle rx: weight loss, head of bed elevation, tobacco cessation, reduce food triggers, no bedtime snacks
  - PPIs: superior to antacids/H2RAs for sx relief in empiric treatment, and optimal for erosive esophagitis (Coch 2013)
  - Omeprazole/pantoprazole (initiate 20mg QD). 30min before meals. Reassess 2-4 weeks, uptitrate to 40mg QD then BID if no relief. Maintain patients on lowest PPI dose that controls symptoms
  - Tapering off PPI: Recommended if ax=3 months, no Barrett’s or severe EoE. Decrease dose by 50% per wk until d/c.
  - PPI risks (controversial): Probable association: Mg wasting (↑TQtc), AIN. Possible association: ↑risk of osteoporosis, dementia, CKD, C diff/other enteric infx (Gastro 2017;152:706)
  - H2RAs (ranitidine, famotidine): can be given for nighttime sx prn w/ PPI, tachyphylaxis common after wks

Severe/Persistent symptoms: (Am J Gastro 2013:108:308)

- If there is no symptom relief after 2-4 weeks on high-dose twice daily PPI, refer for EGD and consider alternative dx
- Consider gastric fundoplication (in general thought to be equivalent to PPI, reserved for severe & refractory cases).

Peptic Ulcer Disease (PUD)

Signs & Sx: intermittent gnawing, dull, aching, or “hunger-like” epigastric pain relieved w/ antacids; duodenal ulcers p/w classic pain 2-5 hrs after meal (persistent acid secretion w/o buffer). Other sx: early satiety, nausea, vomiting, reflux.

Etiology: 90% caused by H. pylori infxn or NSAIDs. Other: EtOH, smoking, meds (bisphosphonates, steroids, clopidogrel), ZES,

Complications:

- Gastric outlet obstruction:
  -screening: ↑ fasting serum gastrin, ↓ serum Ca
  -screen: ↓ enzyme (ALT, AST) in portal hypertensive gastropathy

- Perforation: Graham patch

H. pylori testing:

- Serum Ab: Sn >90%, Sp 76-96%. For all other tests, must hold PPIs 7-14 days, abx/bismuth for 4 weeks, then Urea breath test.
- Stool Ab: Sn > 90%, Sp 86-92%; useful for testing for active infection (Ab can be + even after tx) and for confirming eradication.

ZES: check fasting serum gastrin (↑ if on PPI, recheck 1 week s/p cessation), secretin stimulation test if non-diagnostic

Management: anti-secretory therapy. H. pylori eradication if positive, removal of offending agents, optimization of comorbidities

- Anti-secretory therapy: PPIs > H2RAs
  - H2RAs: Healing rates 70-80% at 4 wks, 87-94% at 8 wks (Gastro 1990;99:345)
  - PPIs: Healing rates 63-93% at 2wks, 80-100% at 4wks (Eur J Gastro Hepatol 1995;7:661)

- Sucralfate: use w/ anti-secretory therapy for duodenal ulcers 2/2 excess acid (i.e. not NSAID-induced or gastric ulcers). Improves mucosal barrier defense (forms complex by binding to protein exudates).

H. pylori eradication therapy: (Gastro 2016;151:51)

- First line = Quadruple Therapy: PPI BID, amoxicillin 1g BID, clarithromycin 500mg BID, metronidazole 500 BID x 14d.
- If PCN allergic: PPI BID + metronidazole 500 BID + doxy 500 QID + bismuth QID x 14d. Combo pill: pylera (no PPI)
- Complicated ulcers (see below): continue PPI for additional 2-4 wks if duodenal ulcer, or 4-6wks if gastric ulcer
- Confirmation of eradication: breath test, stool Ag test, or upper endoscopy >4 wks after completion of abx and PPI

- For patients with PUD 2/2 NSAIDs (other than low-dose aspirin): stop NSAIDs, consider starting a COX-2 inhibitor plus a PPI

Refractory symptoms

- Maintenance rx in recurrent/refractory ulcers: Can trial high dose PPI.
- Surgical rx include sectioning of vagus nerve, antrectomy, partial gastrectomy.

Complications and Management: Ulcer considered complicated if any of the following are present:

- Bleeding: IVF, transfusion, IV PPI, endoscopy (see GI Bleed management). If refractory, consider surgery.
- Perforation: Graham patch (omentumal piece covering ulcer)
- Gastric outlet obstruction: commonly due to pyloric channel/duodenal ulceration. Antrectomy/distal gastrectomy +/- vagotomy
Gastroenterology

Nausea & Vomiting

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

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Etiologies (VOMITING mnemonic)</th>
<th>Receptor</th>
<th>Targeted treatment (tx underlying etiology)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Vestibular &amp; Vertigo</td>
<td>Labyrinthitis, BPPV, vestibular neuritis, Menière’s disease</td>
<td>ACh</td>
</tr>
<tr>
<td></td>
<td>Obstruction</td>
<td>Adhesions, hernia, volvulus, constipation, gastric outlet obstruction</td>
<td>Multiple</td>
</tr>
<tr>
<td>Labs to consider</td>
<td>Operative</td>
<td>Post-op nausea/vomiting (PONV; risk factors: female, nonsmoker, post-op opioids, hx of PONV, type of surgery)</td>
<td>Multiple</td>
</tr>
<tr>
<td>Studies to consider</td>
<td>Motility</td>
<td>Gastroparesis, autonomic dysfunction, cyclic vomiting syndrome, chronic idiopathic nausea (See Motility Disorders)</td>
<td>D₂ (periph)</td>
</tr>
<tr>
<td>Don’t-miss diagnoses</td>
<td>Meds (drugs &amp; withdrawal)</td>
<td>Antibiotics, anti-epileptics, chemo, opioids, illicits (cannabis hyperemesis), anti-arrhythmics</td>
<td>D₂ (central)</td>
</tr>
<tr>
<td></td>
<td>Inflammation/Ifection/Ischemia</td>
<td>Chemo, XRT, bowel ischemia, gastroenteritis, PUD, hepatitis, pancreatitis, cholecystitis, pyelonephritis</td>
<td>5-HT₃ NK1</td>
</tr>
<tr>
<td></td>
<td>Toxins</td>
<td>Uremia, ketoacidosis, hypercalcemia, food poisoning, hypo/hyperglycemia</td>
<td>D₂ (central)</td>
</tr>
<tr>
<td></td>
<td>Intracranial</td>
<td>Elevated ICP, migraine, meningeal irritation, acute glaucoma</td>
<td>ACh</td>
</tr>
<tr>
<td></td>
<td>Nerves</td>
<td>Anxiety, depression, anticipatory nausea, pain</td>
<td>Multiple</td>
</tr>
<tr>
<td></td>
<td>Gums/mouth</td>
<td>Mucositis thrush, oral HSV</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

Management

Address underlying cause of nausea/vomiting while treating symptoms with targeted agents
- Non-pharm options:
  - Acupuncture/acupressure to anterior wrist (P6) meditation, ginger root
  - Chemo PNX: dex ± lorazepam ± ondansetron ± apreanit ± olanzapine (NEJM 2016; 375:134)
  - Adhesive SBO (prior GI surg): cons mgm x 48h (NGT, NPO) → undiluted therapeutic gastrografin (100 cc) per NGT ↓ surg by 74% (BJJ 2010; 97:473)

<table>
<thead>
<tr>
<th>Med</th>
<th>Receptor</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron (Zofran)</td>
<td>5HT₃</td>
<td>4-8 mg PO/IV q8h</td>
<td>↑QTc, constipation, headache</td>
</tr>
<tr>
<td>Palonosetron (Aloxi)</td>
<td>5HT₂</td>
<td>0.075-0.25mg IV x1</td>
<td>No ↑ in QTc, more potent</td>
</tr>
<tr>
<td>Metoclopride (Reglan)</td>
<td>D₂</td>
<td>10-20 mg PO/IV q6-8h</td>
<td>EPS, dystonia (peripheral)</td>
</tr>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>D₂</td>
<td>5-10 mg PO/IV q8h</td>
<td>↑QTc, EPS, sedation</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>5-HT₂</td>
<td>0.5-4 mg PO/IV q8h</td>
<td>↑QTc, EPS, sedation</td>
</tr>
<tr>
<td>Dexamethasone (Decadron)</td>
<td>Cortical</td>
<td>4-8mg PO q4-6h</td>
<td>Psychosis, CHF, ↑Tachpetite</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td></td>
<td>0.5-2 mg PO/IV q4-6h</td>
<td>Delirium, sedation</td>
</tr>
<tr>
<td>Apreanit (Emend)</td>
<td>NK₁</td>
<td>125mg day 1, 80mg days 2-3</td>
<td>CYP3A4 inhibit, GI upset</td>
</tr>
<tr>
<td>Dronabinol (Marinol)</td>
<td>CB₁</td>
<td>2.5-10 mg q4-6h</td>
<td>Dysphoria, asthenia, ↑appetite</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>5HT₂,D₂</td>
<td>5-10mg PO QD</td>
<td>Metabolic (wt gain, ↑lipids)</td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>H₁,ACh,D₂</td>
<td>12.5-25 mg PO/IV q4-6h</td>
<td>EPS, sedation</td>
</tr>
<tr>
<td>Scopolamine</td>
<td></td>
<td>0.3-0.6 mg q24h</td>
<td>Delirium, sedation, dry mouth, urinary retention, ileus, blurry vision</td>
</tr>
<tr>
<td>Hyoscine</td>
<td>ACh,D₂</td>
<td>0.125-0.25 mg SL/PO/IV q4h</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl)</td>
<td></td>
<td>25-50 mg PO/IV q6h</td>
<td></td>
</tr>
</tbody>
</table>

Sally Knooihuizen

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**Gastroenterology**

### Diarrhea


- **Evaluation:** character of s (small bowel=watery, large vol., <cramping/bloating; large bowel=freq., small vol., painful, +/- fever, blood, mucus), exposure hx (travel, abx/hospitalization, food, sick contacts, daycare), immunocompromised, s/sx volume depletion
- **Workup:** BMP if vol. depletion; BX if fever/ill, immunocompromised; stool CX if severe (>6M/s/d, severe pain), inflammatory, high-risk host (age >70, immunocompromised, IBD), or persistent >2w; QP if persistent, immunocompromised, MSM; C. diff if risk fx
- **Common pathogens:** Viral (most cases); norovirus (outbreaks during winter, N/V prominent), rotavirus (often daycare-associated), adenovirus. **Bacterial (most severe cases):** E. coli (toxigenic = traveler’s diarrhea; hemorrhagic, O157:H7 = undercooked meats, a/w Shiga toxin, HUS), Campylobacter (undercooked/unpasteurized foods, can be a/w reactive arthritis or GBS), Salmonella (eggs, poultry, milk, often bacteremic), Shigella (low inoculum, often hematochezia), Vibrio cholerae (shellfish; toxin-mediated), Yersinia (undercooked pork, “pseudoappendicitis”), C. diff (see Clostridium difficile). **Parasitic:** Giardia (outdoor streams; watery stool progressing to malabsorptive/greasy), Cryptosporidium (water-related outbreaks), Cyclospora (contaminated produce); E. histolytica (contain food/water outside US, a/w liver abscesses). Immunocompromised: CMV, C. diff, Cryptosporidium, Isospora, Microsporidium, MAC, TB, Histoplasma, Cryptococcus.
- **Treatment:** Volume & lyte repletion critical (PO if able). **Empiric abx: controversial; if febrile, septic, inflammatory diarrhea: FQ or azithro. Consider in age >70, hospitalized, serious comorbidities. Avoid abx if suspect EHEC as can ↑ risk of HUS. Caution w/ loperamide (OK if no fever or bloody stool). Probiotics controversial: not recommended by ACG except for post-abx diarrhea.

**Chronic Diarrhea:** ≥3 loose stools/d for >4wk. 5 types: secretory, osmotic, functional, malabsorptive, and inflammatory. **See table below.**


- **Hx:** freq., stool vol., tenesmus, adb pain, fever, bloating, wt loss, nocturnal sx, postprandial sx, steatorrhea, surg hx (CCY, resection, obstruction), travel, immunocompromised, meds, radiation
- **Labs:** CBC, BMP, ESR/CRP, LFTs, TSH; stool lysates (Na, K, pH), fecal WBC/calcprotectin, fecal fat (24-48h coll), FOBT
- **Stool osmotic gap for watery diarrhea:** 290 – 2*(stool [Na] + [K]); Normal 50-100 mOsm/kg

<table>
<thead>
<tr>
<th>Physical Exam Findings</th>
<th>Disease Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostasis, hypoTN</td>
<td>Dehydration, neuropathy</td>
</tr>
<tr>
<td>Tremor, lid lag</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Flushing, wheezing</td>
<td>Carcinoid</td>
</tr>
<tr>
<td>Hepatomegaly, macrogliosis</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>HIV, lymphoma, CA</td>
</tr>
<tr>
<td>Migratory nec. erythema</td>
<td>Glucagonoma</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Celiac disease</td>
</tr>
</tbody>
</table>

### Table: Diarrhea

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Watery</th>
<th>Osmotic</th>
<th>Functional</th>
<th>Fatty</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
</tr>
<tr>
<td>Osmotic substance</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
</tr>
<tr>
<td>Multi-factorial</td>
<td>Multi-factorial</td>
<td>Multi-factorial</td>
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</tr>
<tr>
<td>Structural problem, mucosal dz, panc. or bile acid insufficiency</td>
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<tr>
<td>Inflammation interferes w/ mnl function/absorption</td>
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</tbody>
</table>

**Chronic Diarrhea:** ≥3 loose stools/d for >4wk. 5 types: secretory, osmotic, functional, malabsorptive, and inflammatory. **See table below.**


- **Hx:** freq., stool vol., tenesmus, adb pain, fever, bloating, wt loss, nocturnal sx, postprandial sx, steatorrhea, surg hx (CCY, resection, obstruction), travel, immunocompromised, meds, radiation
- **Labs:** CBC, BMP, ESR/CRP, LFTs, TSH; stool lysates (Na, K, pH), fecal WBC/calcprotectin, fecal fat (24-48h coll), FOBT
- **Stool osmotic gap for watery diarrhea:** 290 – 2*(stool [Na] + [K]); Normal 50-100 mOsm/kg

<table>
<thead>
<tr>
<th>Physical Exam Findings</th>
<th>Disease Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostasis, hypoTN</td>
<td>Dehydration, neuropathy</td>
</tr>
<tr>
<td>Tremor, lid lag</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Flushing, wheezing</td>
<td>Carcinoid</td>
</tr>
<tr>
<td>Hepatomegaly, macrogliosis</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>HIV, lymphoma, CA</td>
</tr>
<tr>
<td>Migratory nec. erythema</td>
<td>Glucagonoma</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Celiac disease</td>
</tr>
</tbody>
</table>

### Table: Diarrhea

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Watery</th>
<th>Osmotic</th>
<th>Functional</th>
<th>Fatty</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
<td>Secretagogue, rapid transit, ↓ surface area</td>
</tr>
<tr>
<td>Osmotic substance</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
<td>Lactose intolerance, mannitol, sorbitol, magnesium, laxative use/abuse</td>
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</tr>
</tbody>
</table>

### Celiac Disease

**NEJM 2012;367:2419:** abnormal immune response to gluten → diarrhea, wt loss, adb pain, Fe def anemia, vit D def

- **Diagnosis:** Total IgA, IgA anti-TG (Sn >95%, Sp >95%), HLA-DQ2 (~100% NPV); IgA endomysial Ab (Sn >90%, Sp 98%, useful if dx uncertain), IgG GGP (Sn >90%, Sp >90%, ? IgA def), IgG anti-TG (Sn/Sp widely variable, useful in IgA def). Dx should be confirmed w/ EGD and duodenal biopsy → intraepithelial lymphocytes, elongation of crypts, and partial or total villous atrophy.

- **Treatment:** Strict adherence to gluten-free diet, IgA anti-TG titer should decrease and return to normal over time
Gastroenterology

Constipation & Colonic Disorders

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


- 1° constipation:
  - Slow-transit constipation (STC): sitz-marker study shows delay in colonic transit; associated with bloating & pain
  - Normal-transit constipation (NTC): normal testing, doesn’t meet criteria for IBS-C, but has constipation sx
  - Defecatory disorders: impaired rectal evacuation w/ normal or delayed colonic transit; inadequate rectal propulsive forces or increased resistance to evacuation (e.g. failure to relax or inappropriate contraction); “dyssynergic defecation”
  - IBS-C: see *Mobility Disorders*, recurrent abd. pain or discomfort a/w hard or infrequent stools or relieved by defecation

- 2° constipation:
  - Lifestyle: low fiber, sedentary, dehydration
  - Medications: analgesics, opioids, anticholinergics (antihistamines, antidepressants, antipsychotics), iron, aluminum (antacids, sucralfate), diuretics, clonidine, amidodarone, CCB, ondanestron
  - CTD: amyloidosis, sarcoidosis
  - Metabolic: hyperCa, hypothyroid, hypoMg, hypoK, uremia, heavy metal poisoning, pregnancy
  - Neuro: autonomic neuropathy, DM, Hirschsprung’s, multiple sclerosis, spinal cord injury, Parkinson’s, stroke
  - Obstruction: anal stenosis, colon cancer, stricture, rectocele, compression


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

**Hospital Prophylaxis and Bowel Regimens:**

- Risk factors: >60 yo, prolonged immobility, decreased fluid intake, preexisting constipation, meds (see above)
- General pxr for at-risk patients: senna 2 tabs QHS or BID standing + Miralax 17 gm daily prn
- High-risk pxr for patients on opioids: senna 2 tabs BID standing + Miralax 17 gm daily standing
- Step-wise approach: senna → miralax → lactulose → mag citrate/MOM → bisacodyl PR → enemas → disimpaction (NB: disimpaction can cause vasovagal syncope; contraindicated in neutropenic pts as are other PR meds)
- Avoid Mg and Phos containing products in renal insufficiency (MOM, Mg citrate, Fleets enema) → can cause nephrocalcinosis

**Colonoscopy Prep:** Adequate preparation is essential for successful colonoscopy. General instructions: Place pt on clears at noon the day prior to colonoscopy; the prep should start no later than 6PM the day prior to colonoscopy. Sample prep:

- 4L Nulytely (can be split day before and morning of) + 10mg Dulcolax (*preferred prep at MGH*)
- Alternatively, could Rx 238g Miralax mixed in 2 quarts Gatorade + 10mg Dulcolax
- Tricks to make more tolerable: chill in the fridge; drink through straw; also Rx gas tabs (e.g. simethicone, Mylanta)

Contact GI team if not clear (completely see-through) in the AM, as the procedure will need to be rescheduled. Rx additional Nulytely the day prior to colonoscopy; the prep should start no later than 6PM the day prior to colonoscopy. Sample prep:

**DIVERTICULOSIS:** herniation of colonic mucosa into muscularis propria, where vasa recta penetrate

- Risk factors: Low fiber diet ± chronic constipation, obesity, ↑ age (present in 50% of patients >60yo); common incidental finding on imaging, smoking, NSAIDs, red meat consumption, ♀ = ♂
- Location: 90% L-sided (primarily sigmoid) in “Western” populations; 75-85% R-sided in Asia
- Complications:
  - Bleeding: Painless bleeding of vasa recta within the diverticuli. 75% are self-limited & resolve with bowel rest. Recurrence is common. Tx if bleeding does not stop: 1) endoscopic, 2) angio (IR embolization), 3) surgery
  - Diverticulitis (20% of pts with diverticulitis develop, see below)
- Prevention: Limited data for increasing fiber or for avoidance of seeds.

Jacqueline Henson

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DIVERTICULITIS: infection of the diverticuli: micro-perforation 2/2 erosion of the diverticular wall by increased intraluminal pressure

- Uncomplicated (75%): Abdominal pain (LLQ), fever, leukocytosis, anorexia/obstipation/diarrhea
  - Segmental colitis associated with diverticulosis (SCAD): an infectious/inflammatory condition manifesting as chronic diarrhea and/or abdominal pain and/or hematochezia.
- Complicated (25%): Abscess/stricture/fistula, potentially with bladder, vagina, skin or peritoneum
- Diagnosis: CT scan (93-97% sens/99-100% spec) shows sigmoid diverticula, thickened colon wall >4mm, evidence of inflammation within pericolic fat + characteristic signs/symptoms (+ abscess/fistula in complicated dz)
- Management:
  - Uncomplicated (medical): antibiotics (Cipro/Flagyl, Bactrim/Flagyl, or Augmentin), bowel rest, narcotics
  - Complicated (surgical): antibiotics (IV GNR + anaerobe coverage), bowel rest, narcotics, AND surgical evaluation (peritonitis typically present; evaluation of potential for abscess drainage or colonic resection). Typically 6-8 weeks following an acute episode, colonoscopy may be indicated to exclude IBD/malignancy.


<table>
<thead>
<tr>
<th>Type</th>
<th>Agent</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk agents</td>
<td>Psyllium (Metamucil), methylcellulose (Citrucel)</td>
<td>1tsp up to TID (for psyllium: up to 30g/d)</td>
<td>In some (esp. STC), can increase bloating &amp; distention in large amounts. Should start low &amp; ↑.</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Docusate (Colace)</td>
<td>50-360mg QD</td>
<td>Less effective than other laxatives; may be inferior to psyllium.</td>
</tr>
<tr>
<td>Non-absorbed substances (osmotic)</td>
<td>Polyethylene glycol Miralax (PEG alone) GoLyteyl, NuLytey (PEG + salts)</td>
<td>17 g QD; max 34g/d</td>
<td>Modestly more effective and better tolerated (less bloating) than lactulose (Cochrane Reviews 2010;7). Dose PEG daily.</td>
</tr>
<tr>
<td></td>
<td>Lactulose, sorbitol</td>
<td>15-30 ml QD or BID</td>
<td>↑ flatulence/bloating. Less effective than PEG.</td>
</tr>
<tr>
<td></td>
<td>Milk of magnesia (MOM)</td>
<td>15-30 mL QD or BID</td>
<td>Benefit of simultaneous neutralization of gastric acidity and water retention in stool. Avoid if renal failure (Mg).</td>
</tr>
<tr>
<td></td>
<td>Magnesium citrate</td>
<td>150-300 mL QD</td>
<td>Exact mechanism unknown: Can be used as a lower-volume alternative to PEG bowel prep (2+ bottles + Dulcolax PR). Avoid if renal failure (Mg).</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Senna</td>
<td>1-4 tabs QD or BID</td>
<td>↑ colonic secretions and stimulates motility. Can cause cramping.</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl (Dulcolax)</td>
<td>5-15 mg up to 3x/w</td>
<td>↑ colonic motility. Can cause cramping. Can be given PO (best QHS) or PR (AM).</td>
</tr>
<tr>
<td>Enemas</td>
<td>Tap water Soapsuds Mineral oil Milk &amp; molasses Fleets (sodium phos.)</td>
<td>Varies</td>
<td>All work via lubrication. Soapsuds also stimulates peristalsis. Fleets is hypertonic and also has osmotic effect. Avoid Fleets in elderly or renal failure (phos).</td>
</tr>
<tr>
<td>Secretory drugs</td>
<td>Lubiprostone (Amitiza)</td>
<td>24μg BID for STC/NTC; 8μg BID for IBS-C</td>
<td>Binds Cl- channel &amp; increases secretion, ↑ SB and colonic transit. Most common side-effect is nausea.</td>
</tr>
<tr>
<td></td>
<td>Linacotide, plecanitide (Linzess/Trulance)</td>
<td>Linacotide: 145μg QD for STC/NTC; 290μg QD for IBS-C Plecanitide: 3g daily</td>
<td>Agonists of guanylate cyclase-C; ↑ Cl, HCO3 secretion &amp; colonic transit.</td>
</tr>
</tbody>
</table>
| Peripheral opioid receptor antagonists | Methylnaltrexone, naloxegol (pegylated naloxone), alvimopan | Methylnaltrexone: 1 dose SQ QOD PRN - 38-62kg: 8mg - 62-114kg: 12 mg - <38 kg or >114 kg: 0.15mg/kg - CrCl <30: 1/2 dose | At MGH, methylnaltrexone approved only if on stable dose of opioids ≥ 2 weeks x 3d w/o BM AND failed multiple other laxatives. Contraindicated in obstruction, small risk of perforation. See AGA Guidelines for opioid-induced constipation: Gastro 2019;156:218 & Gastro 2019;156:229.
## Gastroenterology

### Motility Disorders

<table>
<thead>
<tr>
<th>Oropharyngeal Dysphagia</th>
<th>Esophageal Dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Difficulty initiating swallowing, coughing, choking</td>
<td>Difficulty seconds after initiation, food stuck in esophagus</td>
</tr>
<tr>
<td><strong>Neuromuscular (solids &amp; liquid)</strong></td>
<td><strong>Neuromuscular (solids &amp; liquid)</strong></td>
</tr>
<tr>
<td>Central: tumor, stroke, PD, ALS, MS, polio</td>
<td>Primary: achalasia, esophageal motility disorders (e.g. distal esophageal spasm, Jackhammer esophagus)</td>
</tr>
<tr>
<td>Peripheral: neuropathy, myasthenia gravis</td>
<td>Secondary: diabetes, scleroderma, Chagas (JAMA 2015;313:18)</td>
</tr>
<tr>
<td>Muscular: polymyositis, muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td><strong>Structural (solids at onset)</strong></td>
<td><strong>Structural (solids at onset)</strong></td>
</tr>
<tr>
<td>Intrinsic: tumor, XRT, trauma/surgical resection, Zenker’s</td>
<td>Intrinsic: tumor, stricture, inxn (Cand., HSV, CMV), rings, EoE, webs, foreign body, pills (NSAIDs, tetracyclines, bisphosphonate)</td>
</tr>
<tr>
<td>Extrinsic: anterior mediastinal mass, goiter, cervical spondylisis</td>
<td>Extrinsic: vascular rings, aortic enlargement, LA compression, mediastinal, substernal thyroid, LAD (Gastro 2014;147:1238)</td>
</tr>
<tr>
<td><strong>Work-up</strong></td>
<td><strong>Work-up</strong></td>
</tr>
<tr>
<td>History: sx onset &amp; duration, solids v. liquid dysphagia, underlying med conditions (e.g. CNS, malignancy, thyroid, DM, scleroderma), use of <strong>offending meds</strong> (pill esophagitis), immunocompromise (?HIV, chemotherapy → infectious esophagitis), radiation, etc. Dysphagia in older adults is an alarm sx, should not be attributed to normal aging. PE: gen appearance (?Systemic disease or CNS issue), HEENT exam (?evidence of LAD, tumor, asymmetry), FOBT labs (consider): CBC, TFTs, ANA, α-Scl-70, α-centromere, α-RNP, α-Jo, HgbA1C, iron studies, HIV, ACI-R-Ab</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnostics</strong></td>
<td><strong>Diagnostics</strong></td>
</tr>
<tr>
<td>1) Modified barium swallow, ENT eval, +/- EGD to identify obstructive structural problem</td>
<td>1) EGD +/- barium swallow (mucosal pathology or structural abnormality)</td>
</tr>
<tr>
<td>2) Consider chest/en CT to diagnose extrinsic compression</td>
<td>2) If normal → esoph. manometry to diagnose motility disorder</td>
</tr>
<tr>
<td>3) Consider chest/en CT to diagnose extrinsic compression</td>
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</tr>
<tr>
<td><strong>Selected conditions</strong></td>
<td><strong>Selected conditions</strong></td>
</tr>
<tr>
<td>Zenker’s diverticulum: p/w halitosis, regurgitation of food, cough. Tx w/ endoscopic surgery (rigid vs. flexible). Peptic strictures &amp; rings: if lumen &lt;13mm, dysphagia common. Tx PPI, dilation, intraloesion steroid inj, stent Dilat esophageal spasm: uncoordinated peristalsis a/w intermittent chest pain and regurgitation. Versus Jackhammer (hypercontractile) esophagus. Tx both w/ PPI, nitrates/CBB/PDEI, TCA/SSRI trial</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic esophagitis (EoE): dysphagia + hx allergies or atopy. EGD w/ stacked rings, strictures, Bx &gt; 15 eos/hpf. Tx PPI, diet modulation (culpits: dairy, wheat &gt; soy, eggs, nuts, fish), use swallowed inhaler steroids; consider dilation. Achalasia: Progressive dysphagia solids/liquids, + regurgitation; barium swallow with bird’s beak appearance of distal esophagus; Manometry: absent distal peristalsis, incomplete LES relaxation; tx w/ pneumatic dilation, Heller myotomy, POEM, botox injections, CCBs (least effective) (World J Gastroenterol 2013;19:5806)</td>
<td></td>
</tr>
</tbody>
</table>

### Gastroparesis

**Description**: decreased gastric motility w/o obstruction. Sx: N/V, early satiety, postprandial fullness; rarely abdominal pain **Causes**: diabetes (vagus nerve damage 2/2 hyperglycemia), post-surgical (e.g. vagus nerve injury post-bariatric surgery), post-viral, systemic disease (thyroid disease, crinal illness, Parkinson’s, connective tissue d/o), meds (opiates, CCB, anti-cholinergics) **Exam**: succussion splash (sloshing on abd ausc). Labs: TSH, ATc, tol protein, alb, CBC-diff. **Studies**: exclude mech obstruction w/ EGD; → gastric emptying scintigraphy (gold std, hold motility meds 48 hrs prior); motility capsule, CO2 breath test. **Treatment**: Small meals, prokinetic agents (metoclopramide or erythromycin, consider domperidone), antiemetics, feeding tube if needed; pyloric botox is not recommended (Gastro Clinics of NA 2015;44:3; World J Gastro 2015;21:6842; ANZ J Surg 2015;85:709; Am J Gastroenterol 2013;108:18)

### Ileus

**Description**: slow motility of the gut w/o obstruction, often post-op, p/w nausea/vomiting, ‡ BMs and ‡flatus, abd distention **Post-operative paralytic ileus**: Often post intra-abdominal surgery, KUB with dilated loops of small bowel w/o transition point. Treat with bowel rest, IVF, decompression (via NGT), avoid opioids. **Acute colonic pseudo-obstruction (Ogilvie’s)**: typically in elderly, hospitalized, ill patients. A/w severe illness (e.g. sepsis, pancreatitis, peritonitis), systemic disease (thyroid dis., DM, renal or liver failure), neuro problems (spinal cord compression or trauma, Parkinson’s, MS), meds (opiates, CCB, anti-cholinergics). **Studies**: KUB or CTAP with colonic dilatation **Treatment**: bowel rest, avoid opiates, repley lites. PRN: rectal decompression, IV neostigmine (requires monitoring for bradycardia), methylprednisolone.

### FUNCTIONAL GI DISORDERS: GI disorders caused by aberrant neuronal signaling (dysfunction of the gut-brain axis) rather than structural or known molecular abnormality. Classification of >20 disorders per the Rome IV Criteria. (Gastroenterology 2016;150:1393)

<table>
<thead>
<tr>
<th>Functional Dyspepsia</th>
<th>Globus Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early satiety, epigast pain/burning. Must r/o structural/organic cause. Tx: TCAs, metoclopramide</td>
<td>Sensation of obstruction in the throat when there is none</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cyclical Vomiting Syndrome</th>
<th>Cannabis Hyperemesis Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oscillation of intense N/V and no symptoms. More common in kids. Often trigger and prodrome. Tx: avoid triggers, use benzos acutely to sedate, limited evidence for other tx (TCAs, Zofran)</td>
<td>Frequent cannabis use, N/V w/o normal periodic, frequent hot bath/shower. Tx: M2 cessation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sphincter of Oddi Dysf Knox</th>
<th>Irritable Bowel Syndrome (IBS):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary pain, +/- pancreatitis 2/2 sphincter inability to relax, often post-CCY. Dx/Tx: ERCPC</td>
<td>Definition (per Rome IV Criteria): recurrent abd discomfort ≥ 1x/wk on average for 3 months a/w 2+ of the following: (1) related to defecation, (2) change in stool frequency, (3) change in stool form. No nocturnal pain, weight loss, bleeding, elevated ESR/CRP. Epidemiology: ↑ risk w/ younger age, ♀ &gt; ♂, psychosocial stressors, low QoL, hypochondriasis; bacterial gastroenteritis may be trigger. Types: IBS-C (constipation-predominant), IBS-D (diarrhea-predominant), IBS-M (mixed), IBS-U (unclassified), by Bristol Stool Score. Treatment: exercise, diet modification, cognitive-behavioral therapy: laxatives (lubiprostone, linacotide, PEG) for IBS-C; rifaximin, lubadoline, loperamide for IBS-U (limited data) (World J of Gastro 2014;20:12144)</td>
</tr>
</tbody>
</table>
**Gastroenterology**

**Inflammatory Bowel Disease**

### When to Suspect IBD? (Cohn’s disease = CD, Ulcerative Colitis = UC)

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

**GI manifestations:** ABD pain, diarrhea, bloody stools (UC>CD), incontinence/sooling, tenesmus, N/V, oral ulcers, perianal dz (CD)

**Extra-intestinal manifestations:** Rheum (seronegative arthritis, sacroilitis), cutaneous (erythema nodosum, pyoderma gangrenosum), ophthalmic (uveitis, iritis, episcleritis), heme (DVT, AIHA), GU (Ca-Ox or UA stones), pulm (bronchiectasis, ILD)

**CD:** Skip lesions, fibrosis/strictures, fistulae, transmural inflammation, noncaseating granulomas, cobblestoning

**UC:** Continuous colonic mucosal inflammation spreading proximally from rectum, crypt abscesses, pseudopolyps

### Inpatient Work-up and Management:

**H&P:** baseline pain, BRBPR, BMI/consistency, #BM at night, surgical hx, date of onset, presenting sx, dz extent (fistulizing, strictureing, for CD), new meds (OTCs, NSAIDs, abx), smoking, nutrition/TPN, travel, extra-intest. sxss, current/past IBD meds ➔ compliance/efficacy

**Labs:** CBC, Chem 10, LFTs (↑ALP:↑TNF), ESR/CRP, Mg, fecal calprotectin/lectoferrin, Stool Cx, O&P. C. diff, Fe/TIBC/B12 (if anemic)

**Imaging:** if physical exam suggests peritonitis/obstruction/mass (abscess) ➔ KUB upright or CT A/P. Consider MRE to eval sm intestine.

#### Severity of IBD

**Mild**
- <4 stools (bloody or not), febrile, nl ESR
  - Ambulatory, tolerates PO/no dehydration, no pain/toxicity

**Moderate**
- 4-6 BM, bloody BM, low fever, ↑pain, mild anemia
  - 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
  - Failed advanced b, toxic, abscess, obstruction, peritonitis, cachexia

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug*</th>
<th>Use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Prednisone (PO)</td>
<td>Induction</td>
<td>AEs: Osteoporosis, AVN, infection, AI, weight gain, mood lability, delirium</td>
</tr>
<tr>
<td>Aminosalicylates (UC/CD)</td>
<td>Sulfasalazine</td>
<td>Induction and maintenance</td>
<td>Sulfasalazine: -pro drug with more AEs, also systemic effects Mesalamine forms differ in gut penetration: Pentasa (ileum, R&gt;L colon), Ascol (R&gt;L colon), Lialda &amp; Apriso (pancolon), Canasa &amp; Rowasa (distal).</td>
</tr>
<tr>
<td>Thiopurines (UC/CD)</td>
<td>Azathioprine (pro-drug) 6-MP</td>
<td>Induction and maintenance</td>
<td>Labs: Need TPMT testing prior; CBC, LFTs</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Infliximab (Remicade)</td>
<td>Induction and maintenance (Inflix and adal)</td>
<td>Anti-TNFs are c/i if toxic megacolon, pyogenic infections, Labs: Need T-spot, hepatitis panel prior. Albumin (low albumin predictor of poor response in UC), CBC, LFTs.</td>
</tr>
<tr>
<td>Anti-integrin</td>
<td>Vedolizumab (Entyvio)</td>
<td>Induction and maintenance</td>
<td>2nd line, after Anti-TNF</td>
</tr>
<tr>
<td>IL-12, -23 inhibitor</td>
<td>Ustekinumab (Stelara)</td>
<td>Induction and maintenance</td>
<td>2nd line, after Anti-TNF, or for those &gt;60, hx malignancy or infectious AEs</td>
</tr>
<tr>
<td>JAK inhibitor</td>
<td>Tofacitinib (Xeljanz)</td>
<td>Induction and maintenance</td>
<td>AEs: Infection, herpes zoster, HA, nasopharyngitis, arthritis</td>
</tr>
<tr>
<td>Calcineurin inhibit (IV)</td>
<td>Cyclosporine</td>
<td>Induction only</td>
<td>C/i in s/o toxic megacolon. Labs: troughs (q2-q3d) Cr, Mg, lipids, LFTs</td>
</tr>
</tbody>
</table>

*For UC and CD unless otherwise noted

### Maintenance Treatment:

**Step-up** therapy (least to most toxic drug) preferred, but starting w/TNFαa may be beneficial in severe dz

**Malignancy screening:** colonoscopy after 8 years of active disease, repeat every 1-3 years w/ random 4-quadrant bx q10cm of colon


Amanda PeBenito, Sam Miller 74
### Intestinal Ischemia

**Background:**
- Acute or chronic insufficiency of blood flow to GI tract; due to systemic hypoperfusion, arterial/venous occlusion, or arterial vasospasm
- Can present in a variety of ways (see below); often in elderly pts or young pts with vascular disease, vasoconstrictive meds (digoxin, α-adrenergic agonists – e.g. phenylephrine, cocaine), or vasculitis
- Useful clinical guideline: pt with acute abdominal pain AND metabolic acidosis has intestinal ischemia until proven otherwise
- Risk factors: CAD, AF, Valvular disease, CHF, PAD/PVD, vasculitis (SLE/PAN), CKD, HD, hypercoagulable states, prior embolism/DVT, intraabdominal pathology (adhesions, hernias, intussusception, volvulus), intraabdominal infxn/sepsis, aortic surgery

<table>
<thead>
<tr>
<th>Ischemic Colitis (favorable prognosis)</th>
<th>Acute Mesenteric Ischemia (~60-70%, associated with high mortality)</th>
<th>Chronic Mesenteric Ischemia (aka “intestinal angina”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs/Symptoms</td>
<td>Sudden severe abd pain out of proportion to exam; hx ASCVD (CHF, MI, AFib)</td>
<td>- Recurrent, post-prandial, dull, crampy abd pain (starts 10-30 min, lasts 1-3 hr) - WT loss, fear of eating</td>
</tr>
<tr>
<td>- Cramping pain (mostly LLQ)</td>
<td>- Often insidious onset in mesenteric vein thrombosis (younger patients) - Abdominal distention, NV, diarrhea</td>
<td>Blood supply: SMA (prox duodenum supplied by GDA) - Atherosclerotic narrowing of vessels mostly due to underlying ASCVD - “Abdominal angina” similar to ischemic cardiovascular disease - If pain becomes constant, could mean acute thrombosis (see Acute Mesenteric Ischemia)</td>
</tr>
<tr>
<td>→ mild/mod hematochezia</td>
<td>- SMA occlusion (~75%): Embolic (~50%): SMA has narrow take-off angle; AF/ endocarditis/ aortic plaque ↑ risk of total occlusion - Thrombotic (15-25%): acute-on-chronic is/o underlying ASCVD</td>
<td>Blood supply: SMA (prox duodenum supplied by GDA) - Atherosclerotic narrowing of vessels mostly due to underlying ASCVD - “Abdominal angina” similar to ischemic cardiovascular disease - If pain becomes constant, could mean acute thrombosis (see Acute Mesenteric Ischemia)</td>
</tr>
<tr>
<td>- Often not critically ill, but can present w/ gangrenous bowel or fulminant colitis</td>
<td>- Non-occlusive mesenteric ischemia (~20-30%): - Splanchnic arterial vasospasm or hypoperfusion, typically after CV event, cocaine, vasopressin, vasculitis (SLE, PAN)</td>
<td>Blood supply: SMA (prox duodenum supplied by GDA) - Atherosclerotic narrowing of vessels mostly due to underlying ASCVD - “Abdominal angina” similar to ischemic cardiovascular disease - If pain becomes constant, could mean acute thrombosis (see Acute Mesenteric Ischemia)</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Mesenteric vein thrombosis (~5%): - Hypercoagulability (50% have h/o DVT, heritable [JAK2], cirrhosis/portal HTN); malignancy; post-operative; local inflammation Mayo Clin Proc 2013;88:285</td>
<td>Blood supply: SMA (prox duodenum supplied by GDA) - Atherosclerotic narrowing of vessels mostly due to underlying ASCVD - “Abdominal angina” similar to ischemic cardiovascular disease - If pain becomes constant, could mean acute thrombosis (see Acute Mesenteric Ischemia)</td>
</tr>
<tr>
<td>Blood supply: SMA and IMA Non-occlusive state (95%); watershed areas (splenic flexure, rectosigmoid) most susceptible; 25% R-sided - Predisposing factors: CHF, MI, HD, vasculitis, hypercoag state, long-distance running, meds (OCPs, pressors, anti-HTN, diuretics, PCNs, NSAIDs, laxatives), cocaine, infections, colonic lesions (i.e. volvulus, strangulated hernia), s/p abdominal aortic surgery</td>
<td>Non-occlusive: - SMA occlusion (~75%): Embolic (~50%): SMA has narrow take-off angle; AF/ endocarditis/ aortic plaque ↑ risk of total occlusion - Thrombotic (15-25%): acute-on-chronic is/o underlying ASCVD</td>
<td>Blood supply: SMA (prox duodenum supplied by GDA) - Atherosclerotic narrowing of vessels mostly due to underlying ASCVD - “Abdominal angina” similar to ischemic cardiovascular disease - If pain becomes constant, could mean acute thrombosis (see Acute Mesenteric Ischemia)</td>
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### Diagnosis

| Labs: Tlactate, LDH, CK, & amylase if advanced - Stool guaiac ⊕ in ~50% - Stool cx, O+P, C. diff | Labs: nonspecific, most abnormalities arise after ischemia progressed to necrosis: ↓ pH, ↑ lactate, AGMA (in 50%), WBC >15K (75%), stool guaiac ⊕ in +50%; normal D-dimer may help exclude | Imaging: - Angiography (gold standard): stent/TPA - CT-A: ≥ 2/3 vessels (91% with 2 vessels, 55% with all 3 vessels) suggestive - MRA (alternative) - Doppler US to measure mesenteric blood flow - Gastric tonometry exercise testing |
| Abd CT (+/O+): wall thickening, edema, thumbprinting, pneumatosus (late). no vessel occlusion | Imaging: - Angiography (gold standard): stent/TPA - CT-A: ≥ 2/3 vessels (91% with 2 vessels, 55% with all 3 vessels) suggestive - MRA (alternative) - Doppler US to measure mesenteric blood flow - Gastric tonometry exercise testing |
| Colonoscopy can confirm: petechial blood, pale mucosa, segmental edema/ulceration | | |

### Treatment

| - Bowel rest - IVF resuscitation - D/C vasoconstrictive meds - GNR/anaerobic abx (no RCTs) - If suspicion for bowel necrosis, gangrene, or perforation, call surgery | For all occlusive disease: - Infarction/peritonitis/perforation -> surgery - NGT/NPO, IVF/blood product resuscitation - Broad-spectrum abx - Anti-coagulation if not bleeding (heparin +/- tPA) - SMA occlusion: Thrombectomy/embolectomy vs intra-arterial vasodilators vs thrombolysis Non Occlusive: treat underlying cause Mesenteric vein thrombosis: anticoag x3-6 mo | - Surgical revascularization: open (aortomesenteric grafting) vs. endovascular (percutaneous angioplasty) - Nutrition/TPN support |

### Prognosis

| 85% spontaneous resolution in 2 wk (rarely life-threatening) - 5% have recurrence | - Mortality 50%, but can be 70-90% if delay in diagnosis leading to intestinal gangrene | - Variable - Restenosis is common (7% for open revasc; 34% for endovascular) |
Gastroenterology

Nutrition & Feeding

GENERAL APPROACH
1) Assess nutritional status (Clin Nutr ESPEN 2018;26:13-20)
   - History/PE: Dietary intake/tolerance, N/V/D, muscle and fat wasting, myalgias, dermatitis, loose skin/clothes
   - Weight loss as an indicator of malnutrition:
     - >2% in 1 week, >5% in 1 month, >7.5% in 3 months, >10% in 6 months,
     - >20% in 1 year
   - Labs: Albumin, pre-albumin, transferrin, retinol binding protein (RBP) to assess synthetic function. Note that all are negative acute phase reactants and will decrease during inflammation. INR prolongation may be indicator of malnutrition
   - 24-hr calorie count; nutrition c/s if c/f malnutrition
2) Determine dietary route:
   - Oral: Aspiration risk, dysphagia, odynophagia? Consider SLP c/s for dietary modifications (e.g. pureed, thick liquids etc.)
   - Enteral: If patient unable to tolerate oral diet safely, or if unable meet caloric needs through oral diet alone may need NGT. Place tube post-pyloric if gastroparesis, obstruction or intractable nausea/vomiting.
   - Parenteral: TPN or PPN. Used when GI tract non-functional (e.g. short gut, mechanical obstruction). Start if no enteral feeding for >7 d or e/o malnutrition on admission.
3) Determine nutritional needs: healthy: ~25 kcal/kg/d; increased needs: (e.g. lung dz, IBD, burn): increase by 1.2-2x
4) Initiate Diet: Nutrition and TPN consultants will help with specific recs, may include testing pre-albumin, CRP at 2-3 d
5) 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 and gallstones
   - Bloodstream infection: increased risk of infection (fungal and bacterial)

SPECIAL CONSIDERATIONS
- IBD flares, pancreatitis: Early enteral feeding may be beneficial (ideally within 24-72 hrs of admission)
- Critical care: Enteral feeding should start within 24-48 hrs of ICU stay (superior to TPN if GI tract functional); contraindications include significant GI pathology (e.g GI bleed or obstruction) for which patient should be NPO.
- Bariatric surgery (e.g. RYGB, Gastric Sleeve): High risk of micronutrient deficiency from poor intake + malabsorption → Vit A, D, E, K, Iron, Folate, B12, Ca, Cu, Zn, lipids.
- Management: ensure patient taking chewable/liquid MVI with minerals/iron (2 pills if RYGB), Ca2+/Vit D, B12.
- Dumping syndrome: nutrients rapidly enter duodenum leading to pain, diarrhea, flushing, tachycardia, syncope (<30min after meal), hypoglycemia (1-3hr later). Tx w/ low carb, high protein/fat diet and frequent small meals.

REFEEDING SYNDROME
- Electrolyte/fluid shifts caused by initiation of nutrition in severely malnourished patient, can be fatal
  - Risk Factors: poor/minimal intake for >7 days, significant weight loss, history of excessive alcohol intake, malnutrition due to chronic disease/malabsorptive conditions, anorexia nervosa, persistent N/V/D
  - Characterized by:
    - Early: hypo-Phos, hypo-K, hypo-Mg²⁺, vitamin deficiency (thiamine)
    - Late: cardiac damage (CHF), respiratory failure (volume overload)
  - Other symptoms: N/V, diarrhea, tremors, paresthesias
  - Prevention and management: Treat electrolyte abnormalities before refeeding, slow initial feeding, close monitoring of labs (Phos, K, Mg²⁺), Q8-Q12h and tele over first 24 hrs. Aggressive repletion of electrolytes (IV preferred). Replete thiamine prior to initiating feeding; stop feeding if electrolyte abnormalities persist.

ARTIFICIAL NUTRITION
- Supplements: Ensure Plus (standard), Ensure Clear (low fat), Mighty Shake (standard, has lactose), Magic Cup (pudding for dysphagia), Glucerna Shake (DM), Nepro (CKD), Beneprotein (protein powder), Prosource Protein (liquid)
- Tube Feed Formulas:

<table>
<thead>
<tr>
<th>ISOTONIC FORMULAS</th>
<th>HYPERTONIC FORMULAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolite 1.0</td>
<td>Normal absorptive capacity</td>
</tr>
<tr>
<td>Jevity 1.5</td>
<td>Long-term TF Preconstipation (high fiber)</td>
</tr>
<tr>
<td>Promote</td>
<td>Wound healing (high protein) ICU patients (on propofol)</td>
</tr>
<tr>
<td>Vital (semi-elemental)</td>
<td>IBD, pancreatitis Post-abdominal surgery</td>
</tr>
<tr>
<td>Osmolite 1.5</td>
<td>Respiratory failure/ARDS Volume overload (high protein)</td>
</tr>
<tr>
<td>Nepro</td>
<td>Renal or liver failure (low Na/K/phos)</td>
</tr>
<tr>
<td>Beneprotein/ProSource Hi Protein (modular protein)</td>
<td>Wound healing</td>
</tr>
<tr>
<td>TwoCal HN (normal protein, no fiber)</td>
<td>Max fluid restriction</td>
</tr>
</tbody>
</table>

- TPN (page “TPN (Nutritional Support Unit” in paging directory)): Consider if NPO ≥7d. Need central access w/new/clean dedicated TPN lumen. Order by 1 PM to start same day.

Sally Knooihuizen
**Gastroenterology**

**ETIOLOGY** *(Clin Gastro Hepatol 2007;5:648)*

Gallstones/sludge: 40-75% of cases, #1 in women

Alcohol: 30% of cases, #1 in men

**Hypertriglyceridemia:** Typically pre-existing lipid abnormality with TG now >1000-2000 (risk starts when >500 mg/dL), lower amylase values, a/w genetic dio, (+) FHx, #3 overall

**Idiopathic:** 10-25% of cases

**Anatomic:** ampullary diverticular/stenosis, duodenal stricture, tumor, divisum, parastis, foreign body

**Autoimmune:** TgG4, +ANA (rare)

**Genetic:** cationic trypsinogen (PRSS1), SPINK1, CFTR, chymotrypsin C, calcium-sensing receptor, cacnu-2

**Post-ERCP:** 3-5%. In high-risk pts, post-ERCP rectal NSAIDs reduce rate of pancreatitis *(NEJM 2012;366:1414)*


- 2/3: 1) Consistent clinical presentation, 2) Lipase or amylase > 3x ULN, 3) Suggestive cross-sectional abdominal imaging

- Clinical: abd pain (90%) → band-like pain to back is specific (50%), N/V (90%), ileus, jaundice, flank/umbilical ecchymoses

- Mild: absence of organ failure and local or systemic complications; 80% of cases w/ interstitial edema, focal fat necrosis

- Mod-Severe: defined by local complications (pancreatic necrosis, peripancreatic fluid collections, gastric outlet obstruction, splenic and PVT, colonic necrosis) or persistent organ failure (AKI, respiratory failure, shock, GIB) and SIRS. High rates of mortality.

**WORKUP**

- CBC, BMP, LFTs, albumin, lipids, lactate. ALT >3x ULN best predictor of gallstone pancreatitis (>95% PPV).

- Lipase: *early peak*, specificity > sensitivity compared to amylase (DO NOT TREND). Higher baseline levels in DM and ESRD

- Amylase: ↑ after 6-12 hr, stays ↑ 3-5 days. >3x ULN has sens 67-83%, spec 85-98%. Normal on admission in 20% pts w/ alcoholic pancreatitis and 50% pts w/ hyperglycemia, hyperlipidemia pancreatitis. No correlation between peak level and severity.

- IgG4, ANA: consider in pt w/ recurrent, idiopathic AP w/ associated biliary stricture, Sjogrens syndrome, thyroiditis, IBD, nephritis

- RUQs: all patients on first attack to r/o gallstones. RUQ may miss distal CBD stone → EUS more sensitive

- CT/MRI w/ contrast useful to establish dx, exclude other dx, or after >48-72 hr + compensation to n/c complication (e.g. necrosis)


- Reverse precipitants: Treat ↓Ca or ↓TG, stop culprit meds, *urgent* (24-72 hr) ERCP for choledocholithiasis, CCY ideally prior to discharge as ↓ biliary complications if CCY is delayed in non-necrotizing pancreatitis but no ↓ mortality *(Surgery 2009:145:260)*

- IVF: Severe hypovolemia from 3rd spacing. LR>NS (↓SIRS, ↓CRP; avoid if ↑Ca). Bolus + gtt (150-250/hr). Goal: Reduce HR, BUN, Hct, UOP >1cc/kg/hr. Stop aggressive resuscitation before 48 hr. Monitor for abdominal compartment syndrome (bladder pressure >20)

- Nutrition: Start PO (low fat) immediately once no n/v or abd pain. At 96 hr if PO not tolerated start TFs. Enteral feeding maintains intestinal barrier, prevents gut flora translocation; NJ = NG in efficacy and safety

- **HyperTG:** Gemfibrozil 600mg BID, Insulin gtt (0.1-0.3U/kg/hr after 6-12 hr, stays ↑ 3-5 days, ↓ 30% of cases, #1 in men

- **Arterial BP:** 18% mortality

- **ARDS:** 1% mortality, ≥3 inflammatory pancreaticosis, → splanchnic venous thrombosis, → varices

- **Infections:** Viral (Coxsackie, EBV, CMV, HIV, Mumps, VZV, HAV, HBV, HSV), Bacterial (Mycoplasm, Legionella, Salmonella), Fungal (Aspergillus), Parasitic (Toxoplasma, Crypto, Ascaris)

- **Ischemia:** vasculitis (SLE, PAN), hypton/shock, cholesterol emboli

- **Toxins:** organophosphates, scorpion venom, methanol, smoking

- **Trauma:** blunt, especially s/p MVA

- **Hypocalcemia:** Ca activates pancreatic enzymes

- **Tropical:** Pt from low SES in SE Asia, first bout as child, central ductal stones, fibrocalfic diabetes

- **Drugs:** <5%, Class Ia: ACEi, dapsone, lasix, flagyl, pentamidine, statins, sulfa, tetracycline, valproate, mesalazine; Class Ib: amiodarone, azathioprine/6-MP, dexamethasone; Class II: didanosine, estrogen, propofol, tamoxifen, hydrochlorothiazide

- **SIRS**


- **SIRS:** Thromboses (spenic, portal, SMV), Metabolic ( ↑ Mg, Cal), ARDS (phospholipase degradation of surfactant)

- <4w: peripancreatic fluid collection, necrotic collection, infected necrosis. 1/3 necrosis → infected; suspect if ↑-10d w/o improv or w/ decom. CXTX/flagflg (community), cefepime/flagyl/zosyn (recent procedure/hospitalized). C/S GI and surg for necrosectomy (if stable, wait 4 wks while tx w/ abx).

- >4w: Pseudocyst: pain, ↑amylace → drain if rapid enlarg. or local compression. Abscess: fever, pain, ↑amylace → usually needs drainage.

- **Walled-Off Pancreatic Necrosis:** pancreatic necrosectomy (endoscopy vs surgery vs IR) *(Gastro Endosc 2011:73:718)*

- **Pseudoaunerysm:** Bleeding into pseudocyst. Suspect if ↓Hgb, expansion of walled off collection, hematochezia /melena/ hematemesis. Dx: arterial phase CT, surgery/GI c/s. Tx: IR embo prior to drainage, if severe may require surgery w/ high morbidity.

- **Long term:** (1) pancreatic exocrine/endocrine dysfunction (20-30%) (2) chronic pancreatitis (33-50%): p/w abd pain → back, wt loss, steatorrhea, bloating. Rad: calcifications, pancreatic ductal dilatation. Chronic pancreatitis → splanchnic venous thromboses → varices. Labs: fecal elastase, vit A,D,E, K, B12. Tx exocrine dysfunction w/ Creon.

**PROGNOSIS** *(Am J Gastro 2009:104:966)*

- **BISAP:** w/ 24 hr 1) BUN >25, 2) ↓MS, 3) SIRS, 4) abd pain >60, 5) pleural effusion; <3 → 1% mortality, ≥3 → 18% mortality

- **SIRS** (practical): never → 0% mortality, admission only → 8% mortality, persistent → 25% mortality. Ranson/APACHE less practical.

**PANCREATIC MASSES** *(Curr Gastro Rep 2013:15:347)*

| Solid | adenoCA (85-90%), autoimmune pan, neuroendocrine (1-5%), 1st lymphoma (<1%), mets (melanoma, RCC, etc) |
| Cystic | inflammatory (pseudocyst, paraduodenal wall cyst), IPMN (mucinous cystic or serous adenoma or adeno Ca) |
| Imaging | CT Abd pancreatic mass protocol; EUS with FNA allows biopsy (87% Se & 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% Se, 92% Sp) |
| Serology | CA 19-9 (+ in 80% of panca ca, 86% Se, 87% Sp), CEA (mucinous lesions), ANA, IgG4 (if autoimmune pan suspected) |
1. Causes of hepatocellular injury (↑AST/ALT; R ratio >5): Always consider relevant history (meds, OTCs, herbalis) and clinical picture

Any degree of AST/ALT elevation:
- Meds/toxins, e.g. acetaminophen. See list below*
- ETOH (typically 2:1 AST:ALT ratio, AST<8x ULN)
- Nonalcoholic fatty liver (often AST & ALT <4x ULN)
- Viral infection (Hep A-E, CMV, EBV, VZV, HSV)
- Cirrhosis (usually nl or mild degree of elevation)
- Other causes:
  - Autoimmune Hepatitis (AIH)
  - Celiac disease: Anti-TTG, total IgA
  - Hemochromatosis: Fe/TIBC > 45% and ferritin > 200 (men) or > 150 (women) → HFE testing
  - A1AT: even without significant lung involvement
  - Wilson’s: Ceruloplasmin, turine Cu, ALKP:TB<4, AST:ALT>2.2
  - Congestive hepatopathy (right sided HF)

Extreme AST/ALT elevation, e.g., >1000 (acute processes):
- Ischemia – e.g. shock, cardiac arrest, Budd-Chiari
  - LDH of little diagnostic value; an ALT:LDH ratio <1.5 favors dx of ischemia/APAP toxicity over viral hepatitis with (sens: 94% | spec: 84%) (J Clin Gastro 1994 19:118)
  - Natural history of shock liver: rise in ALT/AST (often >50xULN), then rise in bilirubin usually peaking 1 week later
- Meds/toxins – e.g. acetaminophen overdose
- Acute viral infection – hepatitis A-E, HSV, VZV, EBV, CMV
- Acute biliary obstruction
- Rarer causes: autoimmune hep, acute Wilson’s, HELLP syndrome, alcoholic hep, malignant infiltration

Stop offending meds/toxins
- Viral hepatitis serologies
- RUQS with dopplers to evaluate both vasculature and obstruction
- See Acute Liver Injury * Failure for tx recommendations

Commonly used drugs that can cause hepatocellular injury: Acetaminophen, Amoxicillin-clavulanate (Augmentin), Amiodarone, Allopurinol, Carbamazepine, Fluconazole/ketoconazole, Fluoxetine, Glyburide, Heparin, INH, Labelatal, Lisinopril, Losartan, Nitrofurantoin, NSAIDs, Phenytion, Protease inhibitors, Statins, Sulfa drugs, Trazodone, Valproic acid

Illicit drugs: Anabolic steroids, Cocaine, Ecstasy, Phencyclidine

Reference Liver Tox, Aliment Pharmacol Ther 2007; 25:1135

2. Causes of cholestatic injury pattern (↑ALK and bilii; R ratio<2):
- Bile duct obstruction, – cholecholestolithiasis, malignancy (cholangio, pancreatic, ampullary), ascending cholangitis, primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), chronic pancreatitis with strictures
- Hepatitis in general – usually also with AST/ALT elevation
- Cirrhosis – e.g. MELD score includes bili
- Meds/toxins – meds: anabolic steroids, allopurinol, amox/clav, cephalosporins, captopril, carbamazepine, diltiazem, erythromycin, estrogen, TPN, TMP-SMX

Workup and Management
- Stop offending meds/toxins
- Viral hepatitis serologies
- RUQS with dopplers to evaluate both vasculature and obstruction
- See Acute Liver Injury * Failure for tx recommendations

3. Causes of infiltrative pattern (primarily ALK-P elevation):
First send GGT, if ↑likely hepatic, can also test fractionated ALK-P (bone, gut, hepatic)
- Sarcoïdosis or other granulomatous disease (e.g. TB, certain fungal infxns)
- Amyloidosis
- Malignancy: lymphoma, metastasis to liver, HCC
- Hepatic extramedullary hematopoiesis

Workup and Management
- Can send SPEP
- Imaging needed likely with liver MR
- If chronic, consider liver biopsy

4. Non-hepatic causes of abnormal LFTs:
- Indirect hyperbilirubinemia – Gilbert’s syndrome (5% of population), hemolysis, resorption of large hematoma
- Alk phos elevation – ALK-P is also expressed in bone (e.g. ↑ in Paget’s, bony mets), intestines (e.g., ↑ in SBO), and placenta (third trimester pregnancy)
- AST elevation – AST is most abundant in liver tissue but also present in muscle (e.g., ↑ rhabdomyolysis, heat stroke, acute MI), kidney, brain, and RBCs

Evaluation based on clinical scenario

Gastro 2002;123:1367
Gastroenterology

Biliary Disease

Gallstone Diseases:
- **Biliary colic**: dull RUQ/epigastric pain, 30 min-6 hrs, caused by GB contracting around sludge/stone often postprandial
- **Cholelithiasis**: presence of stones in the gallbladder (6% of men, 9% of women); labs typically normal
  - **Stone Types**: Cholesterol (most common) → 5 Fs: fat, female, forty, fertile (multiparous), fair (Caucasian); Pigment: Crhon's/ileal disease, extravascular hemolysis, TPN
  - **Imaging**: best test is RUQUS (sens 84%, spec 99%) showing stones in GB; CT has poor sensitivity (55-80%)
  - **Treatment**: Asymptomatic: observe; CCY only if at increased risk for gallbladder carcinoma (stone >3cm, porcelain gallbladder, gallbladder adenoma); Symptomatic ("biliary colic"): elective CCY (67% recurrence rate if no CCY)
- **Cholecystitis**: calculous (gallstone in cystic duct) or acalculous (10% of cases, usually critically ill pts, starts as bile stasis "sludge" or gallbladder ischemia); often caused by sterile inflammation of gallbladder ± secondary infection. WBC↑↑, other labs WNL
  - **Clinical Manifestations**: RUQ pain, fever, Murphy’s sign; jaundice uncommmon
    - **Acalculous cholecystitis**: Unexplained fever, leukocytosis, vague abd pain ± jaundice ± RUQ mass in ICU pt or jaundice in pt post-CCY. **Risk factors**: trauma, burns, TPN, critical illness, fasting, sepsis (Clin Gastro Hep 2010;8:15)
  - **Imaging**: RUQUS (GB wall thickening, pericholecystic fluid, sonographic Murphy’s sign), HIDA scan if RUQUS negative
  - **Treatment**: Antibiotics—may not ↓mortality but often given empirically (Zosyn or ciprofloxacin/CTX AND metronidazole), consider stopping abx 1d after definitive intervention. Early (<7d) CCY during hospitalization ↓morbidity if ↓surgical risk (Br J Surg 2015;102:1302); GB drainage (i.e. perc chole) if ↑risk and unimproved w/ abx+bowel rest
- **Cholecod cholithiasis**: gallstone in CBD; complications: acute pancreatitis, acute cholangitis; WBC - ; AST/ALT-↑; AlkP↑↑; Bilis ↑↑
  - **Clinical Manifestations**: RUQ pain, n/v, jaundice; sx may be intermittent if "ball-valve" effect
  - **Imaging**: RUQUS to look for CBD dilation >6mm (poor sensitivity for visualizing stones themselves), MRCP if equivocal.
  - **Treatment**: Endoscopic or surgical stone removal (ERCP ≥ CCY)
- **Acute Cholangitis**: asc biliary infx 2/2 obstruction (stone/stent/malignancy/post-ERCP/PSC) WBC ↑↑;AST/ALT-↑; AlkP↑↑; Bilis ↑↑
  - **Clinical Manifestations**: Charcot's triad (RUQ pain, fever, jaundice), Reynolds' pentad (Charcot's triad + AMS, shock)
  - **Imaging**: RUQUS (CBD >6mm); may proceed directly to ERCP (i.e., no US) if pt has Charcot's triad + cholestasis
  - **Treatment**: Antibiotics (Zosyn OR ciprofloxacin/cetriaxone AND metronidazole) x7-10d); CBD drainage (ERCP or PCT if ERCP not feasible); CCY during hospitalization
  - **Others**: gallstone pancreatitis (obstrnx at Sphincter of Oddi), gallstone ileus (obstructing gallstone from cholecysto-enteric fistula)

Autoimmune Biliary Diseases:
- **Primary Biliary Cholangitis (PBC)**: autoimmune destruction of intrahepatic bile ducts (Hepatology 2019;69:394)
  - **Clinical Manifestations**: F=M, asymptomatic (50-60%), pruritus and fatigue, sicca syndrome, cirrhosis (late)
  - **Diagnosis**: ≥2 of the following: alk phos >1.5x upper limit of normal; AMA >1:40 titer (95% pts); biopsy findings
  - **Other Labs**: +ANA (70% pts), ↑total 1gs, ↑IgM. NB: <10% of pts with +AMA develop PBC
  - **Complications (some)**: hypothyroidism (20%) pts, anemia, metabolic bone disease, overlap with Sjogren’s syndrome
  - **Rx**: ursodiol: first line, ↓cholestasis + improve LFTs; obeticholic acid: use as adjunctive or replacement for ursodiol, fibrates: off label alternative; cholestyramine: for pruritus; modafinil: for fatigue; liver transplant: definitive treatment
  - **Follow-up**: LFTs q3-6mo, TFTs annually, Vit ADEK levels annually, DXA scan at dx and q2-4yrs

- **Primary Sclerosing Cholangitis (PSC)**: autoimmune destruction of intra + extrahepatic bile ducts (NEJM 2016;375:1161)
  - **Clinical Manifestations**: M=F, asymptomatic (50%), pruritus and fatigue (most common), cirrhosis (late)
  - **Diagnosis**: cholestatic LFTs, MRCP/ERC (segmental strictures), ↑biopsy; order AMA/IgG4 to exclude alternative dx
  - **Other Labs**: +p-ANCA (30-80%), ↑total 1gs (30%), ↑IgM (40-50%)
  - **Complications (some)**: IBD (>75% pts, UC>>Crohn’s), cholangiocarcinoma (10-15%) pts, metabolic bone disease
  - **Treatment**: ursodiol: may ↓cholestasis + improve LFTs; cholestyramine: for pruritus; liver transplant: definitive treatment
  - **Follow-up**: RUQUS q1yr (for gallbladder Ca/cirrhosis), MRCP q6-12mo (cholangiocarcinoma), CA19-9/CEA q1mo (colon cancer); colonoscopy q1yr if pt with IBD, q3-5yrs if no IBD; other: LFTs q3-6mo, Vit ADEK levels annually, DXA q2-4yrs

Rare forms of intrahepatic cholestasis: Vanishing bile duct syndrome (s/p liver tx/BMT), AIDS cholangiopathy (CMV or cryptosporidia)

Malignant Disease of the Biliary Tract:
- **Gallbladder Carcinoma**: risk factors: gallstone disease (34x more likely to develop Ca), porcelain GB, GB polyps
  - **Clinical Manifestations**: usually asymptomatic; sx may include N/V, weight loss, biliary colic, jaundice (if obstruction)
  - **Diagnosis**: LFTs usually normal, ↑CA19-9/CEA; RUQUS best screening test, then EUS + MRI/MRCPC
- **Cholangiocarcinoma**: may be extrahepatic (90%) or intrahepatic (10%); risk factors: PSC, liver flukes, intrahepatic gallstones
  - **Clinical Manifestations**: cholestasis (jaundice, pruritus, acholic stool, dark urine), RUQ pain, N/V, weight loss, fever
  - **Diagnosis**: ↑CA19-9/CEA, cholestatic LFTs; RUQUS best screening test, then ERCP + MRI/MRCPC

Algorithm for radiographic assessment of suspected biliary pathology (Am J Roentgenol 2011;197:551):

```
RUQUS

<table>
<thead>
<tr>
<th>Stone</th>
<th>ERCP with stone removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected stone</td>
<td>MRI/MRCP for dx</td>
</tr>
<tr>
<td>Stricture, PSC or congenital abnl</td>
<td>Dx. MRCP</td>
</tr>
<tr>
<td>DvTx. ERCP</td>
<td></td>
</tr>
<tr>
<td>Mass</td>
<td>CTAP to confirm/characterize</td>
</tr>
<tr>
<td>EUS +/- Bx</td>
<td></td>
</tr>
<tr>
<td>Bile duct neoplasm</td>
<td>MRI/MRCP</td>
</tr>
<tr>
<td>MRI/ERC P FOX Bx +/- Brushings</td>
<td></td>
</tr>
<tr>
<td>Suspected infection</td>
<td>ERCP or PCT for drainage and source control</td>
</tr>
</tbody>
</table>
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Nate Alhalel, Sumeet Khetarpal

79
Gastroenterology

Acute Liver Injury & Failure

**Acute Liver Failure (ALF):** King’s College Criteria: characterized as encephalopathy and coagulopathy (INR >1.5) of duration <26 weeks in patients without cirrhosis or known liver disease. ([Hepatology 2012;55:965])

**Acute Liver Injury (ALI):** liver injury that involves the development of coagulopathy but not encephalopathy.

**Presentation:** Fatigue, anorexia, N/V, RUQ pain, pruritis, +/- jaundice/ascites

**Initial Diagnostics:** CBC, CMP, PT/INR, T&S, Lactate, ABG, NH3, FSBG, hCG, HIV, Full Serum Tox, APAP level, viral hepatitis serologies (see below), ceruloplasmin, autoimmune markers (see below), RUQUS

**Etiologies and Specific Diagnostics**

- **Drug-Induced** (most common cause; see Liver Chemistry Tests for list)
  - Acetaminophen (most common cause of ALF in US): dose-dependent, >4g/d, ask about all APAP-containing meds
  - Idiosyncratic Reactions: (aka DILI, dose-independent, usually within 6 months of initiation) → anticonvulsants, abx (esp. augmentin, nitrofurantoin), NSAIDs, supplements.

- **Viral**
  - Viral hepatitis → HAV IgM/IgG, HBsAg, HBcAb total, HBV DNA (PCR), HCV RNA, HCV Ab, HDV, HEV
  - HSV-1/2, EBV, CMV, adenovirus, VZV (esp. pregnant/↓immune fxn)

- **Autoimmune Hepatitis**
  - Total protein, SPEP(IgG), ASMA, ANA, LKM-1 antibody

- **Vascular/Ischemic**
  - Budd-Chiari (hepatic vein thrombosis) → RUQUS w/ Doppler, MRV
  - Ischemic hepatitis → hx of hypotension, shock, ALT:LDH <1.5 is suggestive. ([J Clin Gastroenterol 1994;19:118])

- **Wilson’s Disease**
  - Ceruloplasmin (can be nl or elevated in ALF), 24-hour urine Cu
  - Coombs-negative hemolytic anemia
  - AST:ALT >2.2 & AlkPhos:TBili <4 (Sn/Sp ~100%), low Alk Phos ([Hepatology 2008;48:1167])

- **Others:** HELLP Syndrome, Fatty Liver of Pregnancy, Malignant infiltration, HLH

**Consider liver biopsy if diagnosis remains elusive after thorough evaluation**

**General Management** ([AASLD Position Paper 2011, NEJM 2013;369:2525])

- **“First step” consult Hepatology for orthotopic liver transplant (OLT) workup and evaluation**
- **Disposition:** ICU level care should be instituted for patients with HE Grade III or higher; consider for earlier grades
- **IV N-Acetylcysteine:** improves survival in APAP and non-APAP induced ALF with Grade I/II HE
- **Hemodynamics:** Support w/ IVFs and/or pressors: norepinephrine +/- vasopressin; MAP >75 ideal for CPP 60-80
- **Encephalopathy:** Consider intubation for HE Grade III or higher. Tx: lactulose (per rectum or per NGT) + rifaximin
- **Sedation:** Avoid BZDs for sedation due to worsening HE and hepatic clearance. Treat seizures with Phenytoin
- **Cerebral Edema:** HOB to 45°, hypertonic Na for goal 145-150, goal PCO2 ~35 (transient benefit), IV mannitol
- **Infection:** high risk → BCx/UCx/SpCx/CXR with fever, worsening HE, SIRS (low threshold for empiric abx +/- antifungal)
- **Labs:** monitor K/Na/glucose/phosphate/Cr
- **Nutrition:** Early enteral feeding (w/2-3 days). Avoid TPN (infxn risk). GI ppx with PPI or H2-receptor antagonist
- **Coagulopathy/Bleeding:** Trial vitamin K for high INR and transfuse Plt goal >10, ulcer ppx; no mortality benefit for FFP
- **Experimental:** Hypothermia induction, plasmapheresis; liver assist devices (i.e. ELAD, MARS) not commonly used

**Etiology-Specific Management**

- **APAP** → NAC w/in 8hrs. ([Rumack-Matthew Algorithm])
- **HBV** → OLT. Possible role for antivirals (i.e. entecavir)
- **HCV** → OLT (fulminant). Consider tx if no improvement in 12 weeks
- **HAV/HEV** → Supportive care, possible OLT
- **AFLP/HELLP** → Delivery and follow up for need of OLT

**Prognosis:** Refer to King’s College Criteria. Poor prognosis a/w HBV, Wilson’s, Budd-Chiari, Autoimmune, Drug Injury

**Hepatic Encephalopathy**

**Extrahepatic Complications of ALI/ALF**

**King’s College Criteria:**

- Characterized as encephalopathy and coagulopathy (INR >1.5) of duration <26 weeks in patients without cirrhosis or known liver disease. ([Hepatology 2012;55:965])

**Extrahepatic Complications of ALI/ALF**

- CNS: encephalopathy, hemianopsia (esp if NH3>200)
- Renal: AKI, renal dysfunction present in >50% ALF cases
- Hematology: Coagulopathy (↑ risk of CNS bleed with INR >10), DIC, thrombocytopenia
- Infectious: Bacterial (Staphylococcus) and fungal sepsis
- Metabolic: Hypo/hypernatremia, hyper/hypokalemia, acidosis

**Acute Liver Injury (ALI):** liver injury that involves the development of coagulopathy but not encephalopathy.
**Hepatitis B**

- **Clinical Pres.**: Fever, malaise, RUQ pain. **Extrahaepatic**: membranous nephropathy/MPGN, polyarteritis nodosa, aplastic anemia.
- **Diagnosis**: **Screening**: HBsAg, anti-HBs, anti-HBc (identifies all infected, even in “window period”). **Other seromarkers below.**
- **Treatment**: First line: tenofovir or entecavir. **Goal**: suppress HBV DNA, lose HBsAg and HBeAg.

<table>
<thead>
<tr>
<th>Seromarkers</th>
<th>Dz State</th>
<th>sAb</th>
<th>sAg</th>
<th>clgM</th>
<th>clgG</th>
<th>eAg</th>
<th>DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Hallmark of active HBV infxn. Recovery→ disappearance f/b appearance of anti-HBs (persists)</td>
<td>Acute</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>HBc</td>
<td>Indicates recovery and immunity</td>
<td>Chronic Active</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>HBe</td>
<td>Indicates HBV replication/infectivity (~↑ HBV DNA), though pre-core mutants (HBeAg-) still replicate</td>
<td>Inactive Carrier</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>anti-HBe</td>
<td>Correlates w/level of HBV DNA, infectivity</td>
<td>Recovery</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>anti-HBc IgM indicates acute infxn, anti-HBc IgG persist in recovery and chronic HBV.</td>
<td>Vaccine</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Whom to treat**

**Criteria**: Measures disease activity, used for monitoring

<table>
<thead>
<tr>
<th>Whom to treat</th>
<th>Criteria</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Liver Failure</td>
<td>Acute hepatitis, chronic w/ flare</td>
<td>Eval for transplant in addition to treating (Nat Rev Gastro Hep 2011:8:275)</td>
</tr>
<tr>
<td>Decomp. Cirrhosis</td>
<td>HBV DNA+</td>
<td>Rx regardless of ALT values</td>
</tr>
<tr>
<td>Comp. Cirrhosis</td>
<td>HBV DNA &gt;2k</td>
<td>Consider Rx if HBV DNA&gt;2k due to risk of HCC</td>
</tr>
<tr>
<td>HBeAg*</td>
<td>HBV DNA &gt;2k, ALT &gt;2x ULN</td>
<td>If new dx, wait 3-6 mos before Rx as pt may spontaneously resolve</td>
</tr>
<tr>
<td>HBeAg*</td>
<td>HBV DNA&gt;2k, ALT &gt;2x ULN</td>
<td>Rx immediately as unlikely to seroconvert; monitor if no Rx</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>HBsAg+ * or anti-HBc+ are at risk for reactivation, even if anti-HBs+</td>
<td>Immunosuppressive therapies are risk stratified*</td>
</tr>
<tr>
<td>Hepatocellular CA</td>
<td>Patients with HCC and HBV</td>
<td>↓ recurrence, better outcomes (Can J Gastro Hep 2016:2016:523)</td>
</tr>
<tr>
<td>Coinfection with HCV</td>
<td>Rx HBV simultaneously with HCV. Causes severe hepatitis.</td>
<td>↑ risk reactivation if HCV is treated, monitor if not meeting HBV Rx criteria. HBV may suppress HCV VL (Hepatology 2009:49:1090)</td>
</tr>
</tbody>
</table>

* Can consider biopsy if HBV DNA >2k and ALT normal or mildly elevated to determine severity of inflammation (Hepatology 2016:60:261) |
† Higher risk therapies include Rituximab, anti-TNF, high dose steroids (>20mg pred/day), HSCT, chemotherapy, anti-rejection therapy

**Hepatitis C**

- **Screening**: Screen high-risk patients (see below) and all patients born 1945-1965 ("Baby Boomers")
- **Risk Factors**: Blood products before 1992 or from infected individual, MSM, HIV, chronic HD, incarceration, immigration from high prevalence area, birth to HCV infected mother, sex with HCV partner
- **Diagnosis and Clinical Course**: **Most common cause of acute viral hepatitis (8% of all cases)** (CDC). Onset is 9 weeks after initial infxn; fatigue, abdominal pain, jaundice. However, more commonly asymptomatic (Dig Liv Dis 2003:35:104). Fulminant hepatic failure rare. 20% resolve acute infection; more likely to resolve spontaneously if female, acute sx, G1 (Alim Pharm Ther 2011:33:559) 80% chronic infxn→ liver disease/periodic ALT elevations in 60-70% of those, 20% progress to cirrhosis, ~5% incidence of HCC, reduced to 1% with SVR (BMC Med 2017:15:52) |
- **Extrahepatic**: Porphyria cutanea tarda, mixed cryo, MPGN, lichen planus, necrolytic acral erythema, Sjogren’s sxs, ITP |
- **Treatment**: Treat with ID and/or Hepatology input. Varies based on genotype (1-type), comorbidities (cirrhosis, CKD, HIV), Rx failures. DAAs x 12 weeks. Requires labs and assessment for fibrosis/cirrhosis. If acute infxn, wait 16 weeks to initiate Rx as pt may clear. Recheck HCV RNA 12 weeks after therapy to ensure SVR. See hcvguidelines.org.

<table>
<thead>
<tr>
<th>Seromarkers</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Ab reactive</td>
<td>Current infxn, past resolved infxn, or false +. Check HCV RNA</td>
</tr>
<tr>
<td>HCV Ab reactive, HCV RNA detected</td>
<td>Check HCV genotype and treat</td>
</tr>
<tr>
<td>HCV Ab reactive, HCV RNA not detected</td>
<td>Past exposure/treatment. No active infxn. (spontaneous clearance)</td>
</tr>
</tbody>
</table>

**Hepatitis D**: Coinf xon/superinf xon with HBV. Consider in pt w/severe HBV; superinf xon is most severe. Causes 50% of ALF in HBV (Semin Liv Dis 2012:32:228)


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81
**Gastroenterology**

**Alcohol Related Liver Disease**

**General Considerations**

- **3 histological stages**
  1. Simple steatosis (usually reversible w/ abstinence in 4-6 wks);
  2. Steatohepatitis (steatosis + neutrophil infiltration + Mallory-Denk bodies);
  3. Steatohepatitis (extreme is cirrhosis)

- **Alcohol related hepatitis**: an acute inflammatory syndrome that develops in setting of chronic liver inflammation w/ alcohol use.
  - Risk factors: amount of alcohol consumption (risk increases when 8-14 drinks/wk for women and 14-27 drinks/wk for men).
  - Duration of alcohol use (>5-10 yrs for cirrhosis), pattern of use (risk w/ binging & non-mealtime), gender (F>M), ethnicity (risk in AA & Hispanics), HCV (>30x risk for cirrhosis), genetic mutations (PNLPA3), obesity

- **Clinical presentation**: hepatomegaly (87%), jaundice (60%), ascites (57%), encephalopathy (44%), fever (23%) (Clin Gastro 1981:10:417). Alcohol consumption has often stopped weeks prior to presentation due to malaise and anorexia.
  - NB: alcohol related hepatitis can lead to portal HTN and its sequelae (i.e. varices, ascites) in the absence of cirrhosis due to hepatic swelling and transient portal venous obstruction.

- **Differential diagnosis**: other causes of acute hepatitis (check acute viral hepatitis serologies; ask about APAP, OTCs, herbs, FH of liver disease or autoimmune disease), decomposition of underlying cirrhosis, whether from alcohol (93% w/ alcohol related hepatitis & MDF≥32 had cirrhosis on biopsy) or another process.

**Diagnoses for Alcohol Related Hepatitis**

- **Labs**: usually cholestatic LFTs ↑ (alk phos) with moderately elevated AST & ALT (usually <300), typically in >2:1 ratio. AST & ALT >500 rare except in foamy degeneration; should consider concurrent injury such as acetaminophen, viral, or ischemia. ALT can be normal with concomitant vitamin B6 deficiency.
  - Other findings: ↑WBC (<20,000; ↑PMNs), ↑Tbili, ↑GGT, ↑INR, ↑ or normal ammonia, ↑iron sat, ↑TG
  - Exclude infection: blood & urine cultures, diagnostic paracentesis if ascites present; CXR, sputum culture if clinically indicated

- **Imaging**: US w/ doppler to exclude thrombosis, HCC, biliary obstruction

- **Liver biopsy**: not essential, but helpful to establish diagnosis if any ambiguity, exclude other etiologies, and establish severity

- **Severity & prognosis in acute alcohol related hepatitis**
  - MELD >20 → 3 mo mortality 20%; some consider this indication for steroids in acute alc liver failure (Hepatology 2005;41:353)
  - MELD + Lille model may be best predictor; MELD, Glasgow Alcoholic Hepatitis Score & ABIC may be better than MDF (Gastroenterology 2015:149:398)

**Treatment for Alcohol Related Hepatitis**

- **Abstinence**: can result in rapid improvement in outcomes w/in 3 mo. Relapse is high at 67-81% at 1 yr. At discharge, patients should receive counseling, medication assisted therapy (acamprosate 666 mg TID, naltrexone 50mg QD (↓dose in cirrhosis), baclofen 5-10mg TID, gabapentin 600mg TID) (JAMA 2014:174:70) and be referred to Bridge Clinic or treatment program for alcohol use disorder

- **Supportive therapy**: monitor closely for infection, consider acid suppression with PPI/H2RA, monitor for signs of HRS and avoid nephrotoxic drugs, hold beta blockers if MDF ≥ 32 as increased incidence of AKI

- **Nutrition therapy**: MVI, thiamine, folate, enteral feeding; nutrition independently decreases mortality; daily protein intake 1.5g/kg and 30-40cal/kg recommended. Consider nutrition consult while inpatient, as insurance may not cover outpatient consult.

- **If MDF ≥ 32 and/or presence of encephalopathy, initiate medical therapy**
  - Steroids: prednisolone 40mg/d for 4 weeks +/- taper x 2-4 weeks; ↓ short term survival w/ MDF ≥ 32 although debated, (NEJM 2015;372:1619)
    - However, at higher MDF (eg >54) risks may outweigh benefits. Prednisolone chosen as no need for hepatic metabolism.
    - Contraindications: active infection, chronic HBV/HCV, GI bleeding, renal failure (exclusion criteria in steroid trials)
    - Lille Score: composite score of age, Cr, alb, PT, Tbili on day 0 and Tbili on day 7 of steroids. Calculate on day 7 to evaluate response to steroids; a score >0.56 indicates lack of response at 7 days → can discontinue steroids (Gut 2011:60:255)
  - NAC + steroids: 150mg/kg over 1hr→50mg/kg over 4hrs→100mg/kg over 16hrs on day 1→100mg/kg on days 2-5; in pts with severe AH (MDF≥32), prednisolone + IV NAC x 5d. prednisolone alone x5 d w/ significantly ↓ mortality at 1 mo. (8% vs. 24%) but not at 3 mo. (22% vs. 34%) or 6 mo. (27% vs. 38%). May also increase transplant-free survival for patients with non-acetaminophen acute liver failure and prevent HRS mortality and infections at 6 mo. (NEJM 2011:365:1781)
  - Pentoxifylline: conflicting data on none vs possible mortality benefit w/ pentoxifylline 400mg TID x 28d (driven by decreased incidence of HRS), but also higher adverse effects (NEJM 2015;372:1619) → consider only if steroids are contraindicated
  - Pentoxifylline + steroids: no survival advantage compared to steroids alone, but trend towards ↓ HRS (JAMA 2013:310:1033)
  - Liver Transplant: European and US studies show that early transplant prior to abstinence from alcohol dramatically increases 6 month survival (77% survival for early transplant vs. 23% survival for medical management alone) (NEJM 2011:365:1790)
  - New MGH pilot offers early liver transplant evaluation prior to abstinence for patients with 1) their first alcohol-related decompensating event (i.e. no prior knowledge of alcohol-related liver disease or alcohol-related legal issues), 2) MDF >32, 3) non-responsiveness to steroids, 3) grade 1 or 2 HE (to allow for psych eval), 4) strong social support, 5) absence of severe psychiatric co-morbidities, and 6) no other substance use disorder → consult hepatology for candidacy.

- **Summary**: Consider steroids if MDF >32 (or MELD>20) and there are no contraindications. Adding NAC may be beneficial. Consider pentoxifylline if steroids are contraindicated. Consult hepatology for consideration of early liver transplant. Long-term, only abstinence from alcohol and liver transplant are effective for treating alcohol related hepatitis.

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Gastroenterology

End Stage Liver Disease

Definitions

- Cirrhosis: advanced state of fibrosis and regenerative nodules that distorts hepatic architecture and vasculature
- Decompensated cirrhosis: development of ascites, hepatic encephalopathy, jaundice, or variceal hemorrhage
- 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, confusion, muscle cramps
- Exam: ↓BP, splenomegaly, caput medusae, ascites, jaundice, spider angioma (>3), gynecomasia, testicular atrophy, palmar erythema, asterixis, nail δς, Dupuytren’s contracture
- Labs: ↑TBili, ↑INR, ↓Alb, ↓Na, ↑platelets, +/- Hgb/Hct, ↓WBC; AST, ALT, Alk phos, and GGT may be elevated or normal
- Diagnostics: viral hepatitis panel, iron studies, ANA, ASMA, AMA, α1AT, ceruloplasmin, SPEP
- Imaging: RUQUS (with doppler) to assess echogenicity/morphology of liver, ascites, vascular patency, biliary tree, HCC
- Biopsy: gold standard (percutaneous vs. tranjugular; tranjugular allows simultaneous measurement)

Etiologies

- Most common: alcohol, viral (HBV/HCV), non-alcoholic fatty liver disease (NAFLD), hemochromatosis
- Genetic disorders: hereditary hemochromatosis, Wilson’s, α1AT deficiency, cystic fibrosis, inherited disorders of glucose metabolism
- Immune-related: autoimmune hepatitis, primary biliary cholangitis (PBC), primary sclerosis cholangitis (PSC), celiac disease
- Vascular: post-hepatic portal HTN (right heart failure, Budd-Chiari syndrome, veno-occlusive disease)
- Other: infection (i.e. schistosomiasis), meds (e.g. MTX, isoniazid, amiodarone; see https://livertox.nlm.nih.gov/), cryptogenic/idiopathic

Complications of Cirrhosis

- Portal hypertension: esophageal varices, portal hypertensive gastropathy, hypersplenism (→cytopenias), ascites, SBP, hepatorenal syndrome, hepatic hydrothorax, hepatopulmonary hypertension, portopulmonary hypertension, cirrhotic cardiomyopathy
- Hepatic encephalopathy: ↑mucosal & luminal NH₃, ↓clearance of NH₃ & endogenous BDZ-like compounds (NEJM 2016;375:17)
- Immune dysfunction: increased risk of infection; bacterial infection is a major cause of morbidity & mortality
- Endocrinopathies: hypoglycemia, thyroid dysfunction, hypergonadism, hyperestrinism (palmar erythema, spider angioma)
- Coagulopathy: ↓ in both pro- (II, V, VII, IX, X, XI) AND anticoagulant factors (protein C/S, ATIII, plasminogen). Coags do not reflect risk of bleeding or thrombosis & patients not auto-anticoagulated (NEJM 2011;365:147)
- Portal vein thrombosis: ↑risk due unbalanced hemostasis & slowing of portal flow. AC started unless CPS C or high risk of bleeding
- Hepatocellular carcinoma: 1-8% risk per year. May be asymptomatic, lead to decompensation, and/or have sx related to mass effect (pain, early satiety, palpable mass). Screen with US +/- AFP (AASLD guidelines: Hepatology 2018;68:723)

VIBES: a systematic approach to the management of cirrhosis

For all patients: etiology of cirrhosis, complications, compensated or decompensated & etiology of decompensation: infection, SBP, GIB, EtOH, HCC, PVT, meds, surgery, etc.), current MELD score

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

- Current diuretics (spironolactone/losax 5:2 ratio) & response; dietary Na+ restriction (<2 g/d), fluid restriction 1.5L (if Na<125)
- Prior history of LVPs, thoras for hepatic hydrothorax, consideration of TIPS if refractory

Infection (SBP)

- Prior history of SBP, whether has indication for 1° or 2° ppx
- Current treatment (if diagnostic paracentesis reveals PMNs >250) or ppx (CTX if active GIB; otherwise cipro or Bactrim)

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

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

Encephalopathy (portosystemic encephalopathy)

- Prior history of encephalopathy, precipitant, and treatment
- Current severity, trend, precipitant, goal #BM on lactulose/rifaximin (eg: goal 4 BM/day or titrate to improvement in mental status)

Screening/Surgery (transplant)

- Vaccinations: HAV, HBV, Influenza, Pneumovax, Prevnar (and up-to-date on all other vaccines), should see Transplant ID
- Maintenance: alcohol abstinence, avoid NSAIDs
- Malignancy: HCC screening with q6m RUQUS + AFP
- Transplant status: listed or not listed, MELD score, Milan criteria if HCC, classically requires ~6 months sobriety
**Gastroenterology**

**End Stage Liver Disease**

**COMPLICATIONS OF CIRRHOSIS**

**Ascites** (AASLD Guidelines: *Hepatology* 2013;57:1651)

- Most common complication of cirrhosis (50% in 10 years); development of ascites → 15% 1-yr mortality, 44% 5-yr mortality
- **Pathophysiology**: portal hypertension → ↑NO, prostaglandins → splanchnic vasodilation → ↓EABV → ↑RAAS, ADH → Na & water retention. Severity of hypoNa (from ADH secretion) correlates with worsening survival.
- **Diagnosis**: dx para indicated for all new-onset or worsening ascites, pts w/ ascites presenting w/ acute decom or hospitalization
  - Studies: cell count, albumin, total protein, GS/Cx +/- glucose, LDH, amylase, cytology (malignancy), AFB Cx/ADA (TB)
  - DDx: portal HTN (usually see w/ HVPG>10-12) vs. non-portal HTN (see table below)
- **Management**:
  - **1st line**: 2g Na restriction, diuretics (oral), alcohol cessation, d/c NSAIDs, consider fluid restrict to 1.5L if Na <120-125
  - **Initiating therapy**: 100mg/day spironolactone + 40mg/day furosemide is usual starting dose (5:2 ratio), Combo maintains normokalemia & mobilizes fluid faster. Consider spironolactone alone for mild first ascites on an outpatient basis.
  - **Ongoing therapy**: ↑diuretics every 3-5 days if inadequate diuresis (5:2 ratio, though can adjust PRN if abnormal K). Max doses: 400mg spironolactone and 160mg furosemide. Amloidone 10-40mg qd if painful gynecomastia w/ spironolactone.
  - **Weight loss goals**: 2g Na restriction, diuretics (oral)
  - **Check Uvw/Uk ratio if pt gaining weight/requiring LVPs on diuretics. Value >1 suggest >2g daily urinary Na excretion (which, if not losing weight, indicates >2g Na dietary intake). Value <1 suggests ineffective diuretic dose or resistance.
  - **Therapeutic LVP**: Indicated for tense or refractory ascites (see below) or inability to use diuretics; if >5L, transfuse 6-8g albumin for every L ascites removed (~30-40g or 2-3 bottles of 25% albumin)
  - **Albumin**: Long term administration may offer survival benefit for cirrhotic patients with ascites (Lancet 2018;391:2417)

**Paracentesis Interpretation**

| PMN ≥250/μL | (+) Ascites culture | (-) Ascites culture |
| PMN <250/μL | (secondary peritonitis ↔ polymicrobial) | Culture negative neutrocytic ascites (CNNA) |
| Non-neutrocytic bacterascites (NNBA) | Normal |

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

**Hepatology 2010;52:1017**, avoid ACEi/ARB (↓renal perfusion), midodrine 7.5 mg TID, serial LVPs, TIPS as bridge to OLT

**Paracentesis Interpretation**

| SAAG ≥1.1 g/dL | SAAG <1.1 g/dL |
| Etiology related to portal hypertension | Etiology not related to portal hypertension |
| Cirrhosis (ascites fluid total protein [AFTP] <2.5 g/dL) | Secondary bacterial peritonitis |
| CHF (AFTP typically >2.5 g/dL) | TB peritonitis |
| Acute hepatitis (including EtOH) | Peritoneal carcinomatosis (+cytology) |
| Massive liver metastases | Chylous ascites (triglycerides >200) |
| Hepatocellular carcinoma | Hypoalbuminemia (malnutrition, nephrotic syndrome) |
| Budd-Chiari syndrome | Serosis (e.g. SLE) |
| Portal vein thrombosis | Pancreaticobiliary |

SAAG (serum-ascites albumin gradient) differentiates portal hypertensive vs. non-portal hypertensive ascites 97% of the time

**Spontaneous Bacterial Peritonitis (SBP)** (AASLD Guidelines: *Hepatology* 2013;57:1651)

- **Must r/o SBP in all inpatients w/ cirrhotic ascites** (can be ax on presentation); 10-30% hospitalized cirrhotics have SBP
- **Diagnosis**: >250 PMN/L regardless of GS/Cx (CNNA = similar mortality to those w/ +Cx)
  - Usually monomicrobial; GNR 70% (E. coli, Klebsiella), GPC 25% (S. pneumoniae), anaerobes 5%
  - If polymicrobial, consider secondary bacterial peritonitis 2/2 perforation vs. loculated abscesses
  - Boup perf. suggested if ≥ 2 of the following: AFTP >1, LDH >ULN, or Glc<50; also CEA>5 & ALP>240 (Runyon's criteria)
- **Treatment**:
  - **CTX 2g q4h x 5d AND 25% Albumin** (1.5 g/kg on day 1 and then 1.0 g/kg on day 3, max 100 g, indicated if Cr >1, BUN >30, or TBill >4); IV cipro (400mg q12) is alternative if unable to take cephalosporin (unless taking it for ppx)
  - **Discontinue BBs indefinitely given increased risk of AKI & HRS once SBP is diagnosed** (Gastro 2014;146:1680)
  - **Repeat para if no improvement in 48 hr** to rule out 2° peritonitis → add anaerobic coverage, CT A/P +/- surgery c/s
- **Prophylaxis**:
  - **IV CTX 1g q24 x 7 days if GIB**: ok to switch to tx dose PO cipro (500mg q12) or PO Bactrim (BID) once bleeding controlled & stable
  - **All patients w/ prior SBP should receive 2° PPX (after full tx above) w/ PO cipro 500 qd (at MGH) or PO Bactrim DS qd**
  - **Consider 1° PPX if ascitic TP<1 or TP <1.5 AND 1 of following**: BUN ≥25, Cr ≥1.2, Na ≤130, or Child-Pugh ≥9 w/ TB ≥3

**Variceal Bleeding** (AASLD Guidelines: *Hepatology* 2017;65:310)

- **Pathophysiology**: usually occurs when hepatic venous pressure gradient (HVPG) >10-12 mmHg in the distal 2-5 cm of the esophagus
- **Screening**: baseline EGD at diagnosis unless liver stiffness <20kPa (by FibroScan) and platelets >150 (very low probability)
### Gastroenterology

**End Stage Liver Disease**

- **Primary PPX** if high risk of bleeding: (1) medium/large size; (2) small w/ red wale signs; (3) decomp. cirrhosis w/ small varices:
  - If medium/large (>5mm): non-selective βB (dosing below), carvedilol (6.25mg QD for 3 days → increase to 6.25mg BID), or serial EVL (endoscopic variceal ligation, q2-8wks until eradication)
  - If small (<5mm): non-select βB
- **Secondary PPX** if prior bleed: combination of non-sel βB + EVL
  - Non-sel βB: nadolol 20-40mg QD or propranolol 20-40mg BID; adjust dose to goal HR 55-60, SBP>90, max dose: propranolol 160mg/320mg QD or nadolol 80mg/160mg QD in patients with/without ascites
  - Serial EVL: repeat q1-4 wk until obliteration, repeat EGD 3-6 mo after obliteration & then q6-12 mo
- **Acute bleeding**: IV access, IVF, pRBC (+/-FFP), PPI, octreotide, CTX, EGD (GI). May need intubation, Blakemore as a bridge (GI), TIPS (IR), surgery, Amicar (if fibrinogen), Conservative transfusion: goal Hgb 7-9 (NEJM 2013;386:11). See Upper GI Bleeding.
- **Indications for TIPS**: early “preemptive” TIPS (<72hrs) in pts with high risk of treatment failure or rebleeding (NEJM 2010;362:2370; Hepatology 2019:69:282); “rescue” TIPS if uncontrolled bleeding or if recr despite max medical & endoscopic therapy
- **Stop βB if**: SBP, refractory ascites, HRS, low BP, sepsis; "window hypothesis" (J Hepatol 2014;60:643; Gastro 2014:146:1597)

### Hepatic Encephalopathy (HE)

**Pathophysiology**: ↑NH₃ → neurotoxic effects, abnl neurotransmission, ↑GABA- & BDZ-like neurotransmitters & altered glutaminergic inputs → excitatory transmission. In ALF, acute ↑NH₃ → cerebral edema.

**Diagnosis**: clinical; serum NH₃ should not be used to screen for HE. ↑NH₃ does not add diagnostic, staging, or prognostic value in chronic liver disease. Best way to trend is by regularly assessing for asterixis and/or concentration.

**Asterixis**: "flapping tremor" is negative myoclonus w/ loss of postural tone; alternative = hand grip: oscillates b/w tight and loose (J Hepatol 2013:31:537)

**Precipitants**: infection, dehydration/overdiuresis, GIB, hypok or alkalosis (↑NH₃), constipation, sedatives/BZD, new HCC, new clot, TIPS

**Treatment**: ↓GI NH₃ absorption, avoid/correct precipitating factors
  - Lactulose: Δs gut microbiome, has laxative effect; 25mL q2h until BM → titrate to 3-4 soft BM/day (PO, PR or NG)
  - Lactulose + rifaximin 550 mg BID + lactulose alone for HE reversal (NNT = 3) & all-cause mortality (NNT = 4) (Am J Gastro 2013:108:1458); prevents recurrence of HE (NEJM 2010;362:1071)
  - Polyethylene glycol (4L dose): Δs gut microbiome, has laxative effect;
  - If refractory, consider non-standard therapies: oral branched-chain AAs (Cochrane Reviews 2017:2), zinc (Cochrane Reviews 2017:2), zinc
  - FMT may have role (Hepatology 2017:66:1727; Gastro 2019:156:1921)

### Hepatorenal Syndrome (HRS)

**Pathophysiology**: portal HTN → ↑NO, prostaglandins → splanchic vasodil. → ↓EABV → ↑RAAS, ADH, SNS → renal vasoconstr.

**Diagnosis**: dx of exclusion: need: (1) chronic or acute hepatic dz w/ portal HTN, (2) ↑Cr >0.3/48hrs or >50%/7d, (3) absence of shock, (4) no parenchymal dz, (5) no current/recent nephrotoxins, (6) no improvement after 2d cessation of diuretics + albumin challenge (1g/kg albumin x2d, max 100g/d; use 25% albumin; goal is ↑ oncolytic pressure, not volume expansion) (Gut 2015:64:531)

**Type I**: ↑Cr 2x baseline and >2.5 mg/dL in <2wk + multorgan dysfunction; **Type II**: slower decline, often have refractory ascites

**Precipitants**: infection (SBP > other), GI bleed, shift after LVP, alcoholic hepatitis

**Management**: see Hepatorenal Syndrome. Use albumin + octreotide + midodrine or levophed to increase MAP & albumin levels. No diuretics, βB, & or other vasodilators or nephrotoxins. RRT if ineffective and a candidate for OLT. OLT is definitive treatment.

### Hepatocellular Carcinoma (HCC)

**Screening indicated in**: Cirrhosis due to any etiology: HCV (including after cure w/ DAA treatment), HBV, NAFLD, ETOH, others

**Screen with**: RUQU5 +/- AFP q6 months (MGH practice to include AFP); if US inadequate, can use multiphase CT or MRI.

- If nodule <1cm, repeat US in 6-8 months
- If nodule ≥1cm or AFP ≥20, obtain multiphase CT or MRI & proceed according to LI-RADS class.

**Staging**: Barcelona stage; incorporates size, # of nodules, LN & portal vein involvement, mets, Child-Pugh score, perform. status

**Management**: surgical resection (1st line if CPS A & T1-T2 nodule), OLT (non-acceptable but within Milan criteria), ablation (RFA), TACE (chemoembolization), TARE (radioembolization), SBRT, systemic chemotherapy (sorafenib)

- Within Milan criteria → local-regional tx (LRT) as bridge to OLT. Outside Milan → LRT to downstage to w/ Milan → OLT.
- Not OLT candidate (and non-acceptable) → LRT and/or systemic chemotherapy (if advanced).

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**Grades of Hepatic Encephalopathy (West Haven Criteria)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Covert</th>
<th>Overt</th>
<th>Over</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inattention, euphoria/ anxiety, altered sleep pattern, ↓ attention span</td>
<td>Lethargy, behavior Δs, time disorientation, asterixis, personality Δs, hypoaactive DTRs</td>
<td>Somnolence to semistupor, responsive to stimuli, time &amp; place disorientation, asterixis, hyperactive DTRs</td>
<td>Coma</td>
<td></td>
</tr>
</tbody>
</table>

**Hepatology 2019;69:282; Gastro 2019:156:1921**

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**Jacqueline Henson, Amy Yu**

85
Hepatic Hydrothorax (AASLD Guidelines: Hepatology 2013:57:1651)
- Transudative effusion due to shift of ascites into pleural space (due to neg. intrathoracic pressure) via small diaphragmatic defects. Usually unilateral, R-sided. Can become infected (spontaneous bacterial empyema) even in the absence of SBP.
- Diagnosis: exclude other causes of transudative effusion; can visualize w/ radioisotope injection into ascites
- Treatment: same as for ascites (diuretics, <2g Na); therapeutic thora for dyspnea. TIPS if refractory. Chest tube and pleurodesis not recommended.

Hepatopulmonary Syndrome (HPS) (NEJM 2008;358:2378; EASL Guidelines: J Hepatol 2018;69:406)
- Syndrome of intrapulmonary shunting through vasoconstriction/AVMs; mechanism unclear, possibly due to circulating NO
- Presentation: shunting tends to occur at lung bases → platypnea (dyspnea when upright, relieved when supine) & orthodeoxia (upright hypoventilation, PaO₂ ↓ by 4 mmHg or ≥5%), clubbing, cyanosis, hypoxemia (↓ PaO₂ <70-80)
- Diagnosis: TTE with late bubbles (3-6 cardiac cycles after RA), ↑A-a gradient ≥15 (or ≥20 if age >64).
- Management: O2; no effective medical therapies; PFTs can be performed to evaluate for intrinsic lung disease; DLCO in HPS
- OLT: increased risk with mPAP ≥35; mPAP ≥45 is a contraindication

- Rare cause of group 1 pulmonary hypertension in setting of portal HTN
- Pathogenesis: unknown; possibly 2/2 humoral substances (ex. serotonin, interleukin-1, endothelin-1, normally cleared by liver) that reach pulmonary circulation through portosystemic collaterals, resulting in PPHTN
- Presentation: DOE, chest pain, fatigue, palpitations, syncope, hemoptyis, orthopnea; often w/ TR mumur, EKG w/ RVH, RAB, RBBB
- Diagnosis: RHC w/ PAH (mPAP >25 mmHg, PCWP <15 mmHg) in pt with established portal hypertension in absence of other etiology of PAH or venous hypertension
- Management: may benefit from advanced therapies (epoprostenol, bosentan, sildenafil, iloprost); OLT can improve/normalize the PAH; BB and TIPS may be harmful and should be avoided
- Transplant: increased risk with mPAP ≥35; mPAP ≥45 is a contraindication

- Definition: chronic cardiac dysfunction in cirrhotic patients with no known cardiac disease; characterized by 1) impaired cardiac contractility in response to stress, 2) altered diastolic relaxation, 3) electrophysiological abnormalities such as prolonged QTc
- Prevalence: up to 50% of patients undergoing liver transplantation have signs of cardiac dysfunction
- Diagnosis: echocardiography with dynamic stress testing w/ pharmacologicals or exercise
- Pathophysiology: myocardial dysfunction 2/2 systemic inflammation; shear stress from portal hypertension → mechanical force on myocardial fibers; other possible mechanisms involve collagen configuration, sodium retention and activation of RAAS
- Treatment: same as HF management in non-cirrhotic patients
- Prognosis: largely subclinical and asymptomatic; however poses risk in the presence of stress such as infection, TIPS, or OLT; thus detailed cardiac assessment required prior to interventions

- Cytopenias: multifactorial; thrombocytopenia (splenomegaly, ↓TPO), leukopenia (splenomegaly), anemia (bleeding, spur cell anemia); also can have BM suppression by EIOH, nutritional deficiencies (e.g. folate), direct effect of HCV/HBV
- Coagulation abnormalities: ↓coagulation factors (except for VIII), ↓ anticoagulant proteins (C, S, ATIII), dysfibrinogenemia, accelerated fibrolysis (↑fPA) → ↑ risk of both clotting and bleeding & patients not auto-anticoagulated; balance tends to favor thrombosis in early stages and bleeding in late stages of cirrhosis
- Labs: ↑PT/INR, ↑PTT, ↑fibrinogen (though does not function normally; ↓ in tubular, ↑/nl D-dimer (vs. ↑↑ in DIC), ↑fVIII (vs. ↓ in DIC); note PT and PT/INR do NOT correlate with risk of bleeding or clotting
- Anticoagulation: VTE ppx should not be withheld unless high risk of bleeding, plts<50. Systemic AC ok unless decom. CPS C or high risk of bleeding. EGD for EVs prior to starting, VKA, LMWH, or DOAC all options. VKA dosing can be c/b baseline PT/INR; LMWH can be c/b ATIII levels; DOACs not easily reversible & some are hepatically-cleared (J Hepatol 2017;66:1313, JACC 2018;71:2162)
- Bleeding: consider role of coagulation factor deficiency, dysfibrinogenemia, hyperfibrinolysis, thrombocytopenia
- If suspect vitamin K deficiency, give vitamin K 10mg x 3 days to correct nutritional component
- Transfuse pRBCs Hgb<7, platelets <50k, cryo for fibrinogen <150 (or if >150 but c/f dysfibrinogenemia)
- Persistent bleeding despite cryo or requiring many pRBCs → can give FFP (though large volume → ↑ portal pressures)
- Delayed bleeding or oozing from mucocutaneous sites → c/f hyperfibrinolysis → Amicar or TXA (topical and/or systemic)
- Procedures:
  - Platelets: >50k for surgery, TIPS, liver biopsy, or other procedure w/ high bleeding risk; TPO agonists can reduce need for peri-procedural plt transfusions (NEJM 2012;367:716; Gastro 2018:155:705)
  - PT/INR: NO benefit to giving FFP pre-procedure to "correct" INR; ↑ volume can ↑ bleeding risk by ↑ portal pressures.
MGH Algorithm for the Diagnosis and Treatment of Hepatorenal Syndrome


**AKI and Cirrhosis**

\[ AKI = \text{serum creatinine (sCr) } \geq 0.3 \text{ mg/dL within 48h or } sCr \geq 1.5 \times \text{baseline (may use admission sCr) or } sCr > 4.0 \text{ mg/dL} \]

**Diagnostics and Early Treatment**
1. Check urine Na, sediment, renal U/S
2. Remove risk factors (nephrotoxic drugs, NSAIDs, withdraw diuretics, treat infections/GI bleed, vasodilators/antihypertensives)
3. Volume expansion with albumin if indicated (suggest 1g/kg/day)

**Inpatient**
- Close monitoring of sCr
- Early flu with liver and renal teams
- RenalAssociates@partners.org

**Outpatient**
- Early flu with liver and renal teams
- RenalAssociates@partners.org

**MAP-Directed Treatment of HRS**

**Baseline MAP**
Calculate average MAP for the 24h prior to midodrine/octreotide

\[ \Delta MAP = \text{Current Average MAP – Baseline MAP} \]

<table>
<thead>
<tr>
<th>If...</th>
<th>Midodrine TID</th>
<th>Octreotide SC TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of therapy</td>
<td>5mg</td>
<td>100ug</td>
</tr>
<tr>
<td>( \Delta MAP = 10-20 \text{ mmHg} )</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>( \Delta MAP &lt; 10 \text{ mmHg, 1st 24 hr} )</td>
<td>10mg</td>
<td>200ug</td>
</tr>
<tr>
<td>( \Delta MAP &lt; 10 \text{ mmHg, 2nd 24 hr} )</td>
<td>15mg</td>
<td>No change</td>
</tr>
<tr>
<td>( \Delta MAP &gt; 20 \text{ mmHg} )</td>
<td>50% of current dose</td>
<td>No change</td>
</tr>
</tbody>
</table>

**After 24 hours of maximum midodrine and octreotide, does MAP increase \( > 10 \text{ mmHg from baseline} \)?

**Resolution**
- Continue treatment for \( \geq 24 \text{ hours after resolution of HRS} \)
- Discuss possible TIPS with liver consult team

**No resolution after 7 days despite desired \( \Delta MAP \)**

**If recurrence, resume MAP directed HRS treatment**

**MAP-Directed Treatment of other AKI**

**Liver Consult**
(Consider transplant evaluation)

**Treatment of other AKI**

**Meets criteria for HRS?**
- Cirrhosis and ascites
- No shock
- No recent nephrotoxic drugs
- No signs of structural kidney injury (< 500 mg/day proteinuria, <50 RBCs/HPF, normal renal US, inactive sediment)

**Administer albumin PRN**
(25-50g/d unless more is clinically indicated). Consider CVP goals or serum albumin goal > 3

**Discuss ICU transfer for vasoressors with patient, Medical Senior, attending and renal/liver consultants**

**Consider only if candidate for liver transplant, RRT, or escalation of care.**

**Multidisciplinary discussion of options:**
1. Continue MAP-directed HRS treatment
2. Renal replacement therapy
3. Palliative care
Gastroenterology

Liver Transplant Evaluation

**Indications for Liver Transplant** *(Hepatology 2014;59:1144)*

- Acute liver failure as defined by King’s College Criteria
- MELD >15 (MA is in region 1, where average MELD at transplant is typically >30)
- Complications of cirrhosis: ascites, refractory variceal bleeding, chronic GI blood loss due to portal hypertensive gastropathy (PHG), encephalopathy, liver cancer, synthetic dysfunction
- Liver-based metabolic conditions with systemic manifestations: A1AT deficiency, amyloidosis, NASH, Wilson’s, hemochromatosis, glycogen storage disease, primary oxaluria
- Systemic complications: hepatopulmonary syndrome, portopulmonary syndrome

**Disease-specific Indications for Liver Transplant**

- Hepatitis B: should receive pre-transplant antiviral tx to suppress HBV replication
- Hepatitis C: consider antiviral treatment pre- or post-transplant
- Autoimmune: consider in pts w/ decomp AIH not responsive to medical therapies
- Primary Biliary Cirrhosis: consider with intractable pruritus and decompensated PBC
- Primary Sclerosing Cholangitis: consider with recurrent bouts of cholangitis or sepsis; annual colonoscopy
- Alcohol: typically 6-mo abstinence, though early transplant in severe alc hep may improve survival *(Ann Surg 2017;265:20, NEJM 2011;365:1790)*
- HCC: must fulfill Milan Criteria- one lesion <5cm OR ≤3 lesions each <3cm without metastatic spread; automatically assigned MELD score of 22; larger tumors may be “down-staged” into Milan with treatment


- Formal Hepatology and Transplant Surgery evaluations
- Laboratory testing: Iron studies, ceruloplasmin, A1AT, immunologic (ANA, ASMA, AMA, IgG and SPEG), hepatitis [HAV Ab (IgM and total), HBsAg, HBsAb, HbcAb (IgG and IgM), HBV DNA, HCV Ab and RNA, HDV Ab, HEV Ab and DNA], EBV, CMV, VZV, HSV, HTLV, syphilis/RPR, toxoplasma, HIV, measles/mumps/rubella titers, TP, lipase, amylase, HgbA1C, total cholesterol, ammonia, lactate, U/A, UCx, T&S
- Cardiopulmonary: TTE and PFTs. Stress testing in all patients age>40 and cardiac cath if appropriate.
- Renal: if CKD with GFR <30 or if AKI with dialysis >8weeks, may warrant combined Liver-Kidney transplant
- Infectious Disease: consider Transplant ID consult; evaluate for latent TB, consider coccidiomycosis, strongyloides, dental assessment for caries/abscesses; HIV+ patients are candidates if immune function is adequate
- Oncology: prior extrahepatic malignancy should be definitively treated with adequate tumor-free survival
- Radiology: RQUOS with doppler, triple-phase CT or gadolinium MRI for tumor diagnosis and staging
- General health assessment: CXR, pap smear, mammography, colonoscopy, bone density, vaccinations
- Psychiatry/Psychology: especially if prior substance use disorder or psychiatric illness
- Social Work: address psychosocial issues, adequacy of support, financial screening, and insurance counseling
- Adult Living Donor Transplant (LDLT): Recipients should fulfill same minimal listing criteria as for deceased donor

**MELD Exceptions:** Certain conditions result in impaired survival but are not directly accounted for in the MELD scoring system. Patients who meet specific dz-related criteria for MELD exceptions may be eligible for upgrade in MELD points with subsequent automatic upgrades every three months. Appeals for MELD exception points may be made to regional boards *(Radiology 2013;266:376. Semin Liver Dis 2006;26:211. Gastroenterology 2008;134:1342).*

- **Exceptions include:** HCC, hepatopulmonary syndrome (PaO2<60mmHg on room air), portopulmonary HTN (but mPAP must be <35mmHg for successful outcomes), familial amyloid polyneuropathy (TTR gene mutation), primary hyperoxaluria, cystic fibrosis (FEV1<40%), hilar cholangiocarcinoma, hepatic artery thrombosis (occurring within 14 days after liver transplantation, catastrophic post-transplant complication)

**Contraindications to Liver Transplant**

- MELD score <15, severe cardiac or pulmonary disease, AIDS, ongoing alcohol or substance use (within 6mo), hepatocellular carcinoma with metastatic spread, uncontrolled sepsis, anatomic abnormality that precludes liver transplantation, intrahepatic cholangiocarcinoma, extrahepatic malignancy, fulminant hepatic failure with sustained ICP >50mm Hg or CPP<40 mm Hg, hemangiosarcoma, persistent noncompliance, lack of adequate social support system

**Kings College Criteria:**

**Acetaminophen-induced ALF:** Arterial pH<7.3 (irrespective of encephalopathy) OR **all 3** of the following: INR>6.5, Cr> 3.4 mg/dL, grade 3 or 4 encephalopathy

**All other causes of ALF:** INR>6.5 (irrespective of encephalopathy) OR **3/5 of the following:** age<10 or >40, etiology indeterminate, time from jaundice to encephalopathy >7 days, INR >3.5, bilirubin >18 mg/dL

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**On the Bigelow:**

While we care for many patients with ESLD and manifestations that warrant transplant listing, if they do not follow regularly with a hepatologist and/or have ongoing substance use, they cannot be listed.

---

Allyson Kaplan, Eric Przybyszewski
Nephrology

Acute Kidney Injury

### MEDS Causing AKI

<table>
<thead>
<tr>
<th>Chronic/acute interstitial nephritis</th>
<th>Acute tubular necrosis</th>
<th>Crystal nephropathy</th>
<th>Rhabdomyolysis</th>
<th>Thrombotic microangiopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>APAP</td>
<td>Aminoglycosides</td>
<td>Acyclovir/ Ganciclovir</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Allopurinol</td>
<td>Amphotericin B</td>
<td>Indinavir</td>
<td>Cyclosporine</td>
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<tr>
<td>Phenoxytoin</td>
<td>NSAID</td>
<td>Cephalosporins</td>
<td>Glomerular hemodynamics</td>
<td>Quinine</td>
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<tr>
<td>Rifampin</td>
<td>Beta lactams</td>
<td>Contrast</td>
<td>Ace-ii/ARB</td>
<td>Methadone</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Cisplatin</td>
<td>Tacrolimus</td>
<td>Vanc (esp w/ Zosyn)</td>
<td>Methadone</td>
</tr>
<tr>
<td>Sulfas</td>
<td>Furosemide</td>
<td>Tetracyclines</td>
<td>Hydrocortisone</td>
<td>Methadone</td>
</tr>
</tbody>
</table>

**Meds**

- APAP
- NSAID
- ACEI/ARBs
- Loop diuretics
- Thiazides
- Metolazone / Diuril
- Sodium bicarbonate
- Metabolic Acidosis: Sodium bicarb tabs
- Bleeding with concern for uremic platelets: DDAVP
- Acyclovir: (Mayo 2009;84:170; Circ 2012;122:2451; NEJM 2006;354:379)
- Thrombotic microangiopathy (TMA): May be a cause of AKI
- Acute tubular necrosis (ATN): Common cause of AKI
- Acute interstitial nephritis (AIN): Rare cause of AKI
- Acute tubular injury (ATI): Result of hypovolemia
- Rhabdomyolysis (RM): Common cause of AKI

**Renal Emergencies**

- Acidosis: Severe metabolic acidosis, unstable patient, usually in the ICU with pH < 7.1. Temporize with HCO3 pushes and isotonic bicarb gtt, intubation and hyperventilation if unable to compensate by breathing off CO2. Likely CVVH.
- Ingestions: Ethylene glycol, methanol (elevated osmolar gap) with end organ damage (i.e. renal failure, vision loss).
- Hyperkalemia: Marked hyperkalemia leading to ECG changes or arrhythmia (K>6.5). Temporize with Ca gluconate, Lasix, Insulin/D50, etc. Note HD much faster at clearing K than CVVH.
- Hyponatremia: Call if severely symptomatic (AMS with low GCS, seizures, etc) requiring bolus hypertonic saline.
- RPGN: When clinically suspected, urgent Nephrology consultation to consider pulse dosen steroids +/- plasmapheresis (as above)

**CONTRAST-INDUCED NEPHROPATHY (CIN):**

**Definition:** ↑Cr ≥ 0.5 or 25% within 48-72h of contrast without other causes.

**Clinical syndrome:** Starts 24-48hr, peaks 3-5d, resolves 10d; FENa usually <1% but can be normal or high. Usually non-oliguric.

**Controversy:** More recent controlled studies and meta-analyses have raised questions regarding the risk of AKI following contrast, which is probably lower than many previous studies indicated.

**Prophylaxis:** For high risk pts receiving arterial or IV contrast, give NS at 1ml/kg/hr for 6-12hr pre, 6-12hr post. No added benefit for Na bicarb.

**CARDIORENAL SYNDROME (TYPE 1):**

- Refers to 5 categories of disease processes which impact the heart and kidneys with various causal relationships, but at MGH we use the term to refer to type 1, in which acute chief causes to AKI.
- Pathophysiology: Decreased renal perfusion from low CO is one factor, but more importantly, RV failure and high CVP lead to a low trans-renal perfusion pressure. More of a problem with “underdraining” (congestion) than with “underfilling” (perfusion), though worsened by neurohumoral activation in setting of low EABV.

**Treatment:** Relief of renal venous congestion. Trend creatinine against TBB to test hypothesis, but expect a lag effect.

- Loop diuretics are first line for type 1 +/- addition of thiazide (metolazone / diuril).
- ROSE trial (JAMA 2013;310:2533): No benefit of low dose dopamine or nesiritide to improve forward flow.
- CARESS-HF (NEJM 2012;367:2296): Ultrafiltration showed similar outcomes in regard to weight loss and decompensated CHF symptoms, but worsened renal function compared to pharmacologic therapy with loop/thiazide diuretics.

**Dana Larsen**

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DEFINING AKI + GENERAL MANAGEMENT: (KIDIGO 2012.2.1)
Prevention: (1) maintain volume status & perfusion pressure, (2) monitor Cr & UOP, (3) avoid hyperglycemia and nephrotoxins, (4) caution w/ contrast.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine</th>
<th>Urine Output</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↑ ≥ 0.3 mg/dl within 48 h, or ↑ 1.5-3x baseline</td>
<td>&lt; 0.5 ml/kg/hr for ≥ 6 hours</td>
<td>Preventive measures + non-invasive diagnostic workup: (1) H&amp;P, (2) obtain Cr and follow UOP, (3) UA and sediment (4) urine electrolytes, (5) renal US and other tests (below)</td>
</tr>
<tr>
<td>2</td>
<td>↑ 2-3x baseline</td>
<td>&lt; 0.5 ml/kg/hr for ≥ 12 hours</td>
<td>Preventive measures +: (1) renally dose meds, (2) consider RRT, (3) consider ICU admission for CVVH, pressors for renal perfusion, (4) avoid subclavian catheters and PICC</td>
</tr>
<tr>
<td>3</td>
<td>↑ 3x baseline, Cr ≥ 4, ↓ eGFR to &lt; 35 (&lt; 18 yo), or RRT</td>
<td>&lt; 0.3 ml/kg/h for ≥ 24 h, or anuria ≥ 12 h</td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic Tips
- ↑ BUN out of proportion to Cr: pre/post-renal, UGIB, steroid
- ↑ Cr out of proportion to BUN: rhabdo, AIN, Bacitracin, ↓ nutrition

Serum Cr approximates GFR at steady-state only (unable to estimate GFR w/ ΔCr):
- must assume GFR < 10 if ΔCr > 1/day

Drugs can impair Cr excretion without ΔGFR (BUN should remain stable): trimethoprim, H2 blockers (cimetidine/famotidine), dronaderone

STEPWISE WORKUP:
1) History/Exam: Vitals (hyper/hypoTN), volume status, exposures (contrast, meds, see below), recent infection (IgA nephropathy in 1-2 days, PSGN in 10-14 days), active infection (sepsis can induce ATN Independent of BP or ↓RBF (JASN 2011;22:999); also see AIN section), trauma/myalgias (rhabdo), rashes (AIN, vasculitis).
2) Urinalysis (UA): See urinalysis section for more details, particularly heme, protein, and specific gravity (SG).
3) Urine chemistries:
   - FENa: (Urine Na * Serum Cr) / (Serum Na * Urine Cr). FENa< 1% is suggestive of pre-renal AKI, >2% with ATN. Note this is ONLY verified in oliguric AKI. Healthy controls with low Na intake can have FENa<1% to keep Na balance even. Diagnostic accuracy is improved if repeated (Clin Nephrol 1980;19:73).
   - FEUrea: If on diuretics, FENA unreliable. Calculate FEUrea as above, <35% consistent with pre-renal (Kid Int 2002;62:2223).
   - Urine Osm: >500 is consistent with a pre-renal etiology. Patients with ATN are only rarely able to concentrate to this degree.
   - Urine protein: if proteinuria identified on UA, send urine protein and albumin to determine if glomerular vs tubular. Urinary albumin/protein ratio <0.4 strongly suggests tubulointerstitial (Sens 88%, spec 99%) (Clin J Am Soc Nephrol 2012;7:541).
4) Urine sediment: Spin urine on Bigelow 10 across from dialysis unit (call security for access if after hours). Important if clinical history/above studies are not strongly suggestive or if AKI fails to respond to initial management. Findings will guide next steps.
   - Muddy brown casts: ATN, the differential for which is ischemic, septic, or toxic
   - Red cell casts, dysmorphic RBCs: Glomerular disease. Note: dysmorphic RBCs can also be seen if urine is left to sit too long.
   - White cell casts: Can be seen in pyelonephritides vs AIN, though for AIN sensitivity <10%
5) Eosinophilia/eosinophiluria: Poor test stats for AIN. Urine eos >1% has sens 31%, spec 68% (Clin J Am Soc Nephrol 2013;8:1857).
6) Imaging: Renal ultrasound to exclude hydronephrosis. However, in absence of a suggestive history, <1% of renal US for AKI indicated
7) Next: If sediment or history suggest glomerular/tubular disease, broaden workup with C3/C4, ANCA, anti-GBM, ANA, anti-dsDNA, Legionella, low complement (normal vs low), active infection (sepsis can induce ATN Independent of BP or ↓RBF)

ACUTE KIDNEY INJURY (Kid Int 1996;50:811)

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PRE-RENAL (21%)</th>
<th>INTRINSIC</th>
<th>VASCULAR</th>
<th>POST-RENAL (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute ↓ volume</td>
<td>Bleeding</td>
<td>GI or skin loss</td>
<td>Diuretics</td>
<td>Cerebral salt wasting</td>
</tr>
<tr>
<td>Effective ↓ volume</td>
<td>CHF / cardiorenal</td>
<td>Cirrhosis / hepatorenal</td>
<td>Nephrotic syndrome</td>
<td>Sepsis / Third-spacing</td>
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<tr>
<td>Δ renal dynamics</td>
<td>NSAIDs / COX-2s</td>
<td>ACE / ARBs</td>
<td>Abd compart. syndr.</td>
<td>Relative hypotension</td>
</tr>
<tr>
<td>GLOMERULAR (&lt;4%)</td>
<td>Anti-GBM</td>
<td>ANCA +</td>
<td>Low complement:</td>
<td>Microvascular (&lt;4%)</td>
</tr>
<tr>
<td>- Microscopic polyangitis</td>
<td>- Granulomatosis with polyangitis (GPA)</td>
<td>- Eosinophilic GPA</td>
<td>- PSGN, SLE, cryo, MPGN,</td>
<td>- TTP/HUS</td>
</tr>
<tr>
<td>- Drug-induced ANCA</td>
<td>Normal complement:</td>
<td>Normal complement:</td>
<td>MGRS</td>
<td>- APLS</td>
</tr>
<tr>
<td>Immune complex</td>
<td>- IgA nephropathy/HSP</td>
<td>- IgA nephropathy/HSP</td>
<td>- T-cells, acetylcholine, ethylene glycol</td>
<td>- HELLP</td>
</tr>
<tr>
<td>Low complement:</td>
<td>- Fibrillary/immunotactoid</td>
<td>- Fibrillary/immunotactoid</td>
<td>Proteins</td>
<td>- Eclampsia</td>
</tr>
<tr>
<td>ΔRenal dynamics</td>
<td>- MM, amyloid, Ig deposition</td>
<td>Thrombosis</td>
<td></td>
<td>- Scleroderma</td>
</tr>
<tr>
<td>NSAIDs / COX-2s</td>
<td>- Atheroembolic</td>
<td></td>
<td></td>
<td>- Malignant HTN</td>
</tr>
<tr>
<td>- APLT</td>
<td>- Retroperitoneal fibrosis</td>
<td></td>
<td></td>
<td>- Meds (calcineurin inhibit/CIN, gemicitabine)</td>
</tr>
</tbody>
</table>

Tips
- Calculate FEUrea (JASN 2011;22:999) to confirm or exclude ATN.
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Dana Larsen

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Nephrology

NEPHROTIC SYNDROME

Etiology: ↓ podocyte integrity w/ podocyte foot process effacement → proteinuria > 3.5g/day, Alb < 3.0g/dl, periorbital edema, HLD

Associated sequelae: foamy urine, hypercoagulability; 10-40% VTE risk 2/2 loss of antithrombin & plasminogen, VIt D deficiency 2/2 loss of VIt D binding protein, infectious risk 2/2 ↓ IgG (esp. Pneumococcal), premature atherosclerosis, protein malnutrition

Workup: Basic: UA/ed, spot urine P/C, HBATc. Most proteinuria is 2/2 DM nephropathy (see below), if no diabetes, then send advanced w/; Advanced: ANA, anti-dsDNA, anti-PLA2R, SPEG, SFLEC, HBV, HCV, HIV, C3/C4, nephrology c/s for possible renal biopsy

Labs: ↑ protein on dip or > 3 g/mg spot urine P/C, urine sediment w/ oval fat bodies = epithelial cells that have engulfed lipid → form Maltese crosses when polarized, Cr normal or elevated, may have mild nephritic features (hematuria, HTN more common in primary dz)

Treatment: depends on cause, generally immunosuppression (steroids 1st line), tx proteinuria w/ ACEI, edema w/ diuretics, HLD w/ statins

GLOMERULONEPHRITIS (GN)

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

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

Workup: UA/ed, spot urine P/C, HBATc. Most proteinuria is 2/2 DM nephropathy (see below), if no diabetes, then send advanced w/; Advanced: ANA, anti-dsDNA, anti-PLA2R, SPEG, SFLEC, HBV, HCV, HIV, C3/C4, nephrology c/s for possible renal biopsy

Labs: ↑ protein on dip or > 3 g/mg spot urine P/C, urine sediment w/ oval fat bodies = epithelial cells that have engulfed lipid → form Maltese crosses when polarized, Cr normal or elevated, may have mild nephritic features (hematuria, HTN more common in primary dz)

Treatment: depends on cause, generally immunosuppression (steroids 1st line), tx proteinuria w/ ACEI, edema w/ diuretics, HLD w/ statins

Nephrogeny

<table>
<thead>
<tr>
<th>Nephrosis</th>
<th>Associations</th>
<th>Biopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>DM &gt; 10 yrs + retinopathy, most common cause of nephropathy</td>
<td>Nodular glomerulosclerosis</td>
</tr>
</tbody>
</table>
| FSGS      | ↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑∪...
Overview

**CKD definition**: GFR <60 OR presence of kidney damage (typically albuminuria ≥ 30mg/d) for ≥ 3 months (JAMA 2015;313:837)
- Cockroft-Gault formula overestimates GFR, MDRD underestimates at high levels (GFR > 60), **CKD-EPI equation preferred**
- Stages of albuminuria: A1 = mild <30mg/d; A2 = moderate 30–300mg/d; A3 = severe >300mg/d
  - Note: UA detects albumin but not other proteins; if UA with +protein → check UProt:Cr to quantify
- Albuminuria is an independent predictor of all-cause mortality, CV mortality, and progression of CKD at all stages

*Etiologies (US)*: DM (44%), HTN/nephrosclerosis (29%), cystic kidney disease (20%), GN, unknown (7%) (USRDS 2014)

*Epidemiology* (15% US adults): White (60%), Black (30%), Hispanic (17%), Asian (5%), Native American (1%) (Natl Kidney Fndn 2016)

**KDIGO GUIDELINES**

<table>
<thead>
<tr>
<th>G Stages</th>
<th>Description</th>
<th>GFR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal-High</td>
<td>&gt;90</td>
<td>Risk factor reduction (including CVD), dx and tx, slow progression</td>
</tr>
<tr>
<td>G2</td>
<td>Mild</td>
<td>60-69</td>
<td>Estimate progression</td>
</tr>
<tr>
<td>G3a</td>
<td>Mild-mod</td>
<td>45-59</td>
<td>Evaluate and treat complications</td>
</tr>
<tr>
<td>G3b</td>
<td>Mod-severe</td>
<td>30-44</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severe</td>
<td>15-29</td>
<td>Nephrology referral, preparation for RRT +/- transplant</td>
</tr>
<tr>
<td>G5 (or G5D)</td>
<td>Renal failure</td>
<td>&lt;15 (G5) or HD (G5D)</td>
<td>RRT (if uremia or other indication present), consider transplant</td>
</tr>
</tbody>
</table>

**MANAGEMENT**

Proteinuria: reduce to goal <500-1000mg/d with RAAS blockade (ACEI or ARB, but not both simultaneously) (NEJM 2013;369:1892)
- **BP control**: reduce to goal <130/80 if proteinuria OR SBP <120 if GFR 20-60 by MDRD (NEJM 2015;373:2103)
- If *proteinuria* → ACEI, then non-dihydropyridine CCB; if *edema* → loop diuretic

- **CVD risk reduction**: risk is 2-4x that of general population → ASA, statin, exercise, smoking cessation

Avoid nephrotoxins: aminoglycosides, acyclovir, contrast (iodinated, gadolinium), lithium, NSAIDs, TMP/SMX, herbals with aristochic acid

*Renally dose meds*: abx/antivirals, atenolol, colchicine, fluconazole, gabapentin, glyburide, levetiracetam, metoclopramide, opioids

*Nutrition*: nephrocaps (B-complex + c), Na <2 gm/d, fluid <2L/d, K/phos restriction; if Ca low/nl, give

- **Acidosis**: check Ca, PO4, 25-OH vitD (not 1,25-OH vitD as level will fluctuate)

*Pathophysiology and Treatment***

<table>
<thead>
<tr>
<th>Complication</th>
<th>Hyperparathyroidism</th>
<th>Anemia</th>
<th>Acidosis</th>
<th>Hyperkalemia</th>
<th>Hyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>50</td>
<td>44</td>
<td>40</td>
<td>39</td>
<td>37</td>
</tr>
</tbody>
</table>

**Bone Disease**: Check Ca, PO4, 25-OH vit D (not 1,25-OH vitD as level will fluctuate)

**Classification and Treatment of Hyperparathyroidism***

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Ca</th>
<th>PO4</th>
<th>PTH</th>
<th>VitD</th>
<th>Pathophysiology and Treatment</th>
</tr>
</thead>
</table>
| 1º HyperPTH | ↑ | ↓ | ↑ | nl | Pathophys: excess PTH gland production
Tx: parathyroidectomy if Ca >1 above ULN, 24h urine Ca >400 mg/d, age <50, CrCl <60, osteoporosis, or nephrolithiasis/calcinosis (J Clin Endocrinol Metab 2014;99:3561) |
| 2º HyperPTH (2/2 ↓ Vit D) | ↓ | ↓ | ↑ | ↓ | Tx: if non-HD: replete with ergocalciferol; if HD: replete with calcitriol or paracalcitriol (Zemplar) if Ca-PO4 product <55 (NEJM 2003;349:446) |
| 2º HyperPTH (2/2 CKD) | nl / | nl↑ | ↑ | nl | Pathophys: ↓ PO4 excretion increases PTH secretion
Tx: dietary PO4 restriction; if Ca low/nl, give Ca acetate (phosito); if Ca high, give sevelamer (renagel) or lanthanum (fosrenol)
Goals: PTH (CKD3: 35-70, CKD4: 70-110, CKD5: 150-300), PO4 (non-HD <3.5, HD 3.5-5.5) |
| 3º HyperPTH | ↑ | ↑ | ↑ | nl | Pathophys: longstanding 2º hyperPTH leads to PTH gland hyperplasia
Tx: phos binders, cinacalcet (calcimimetic), parathyroidectomy |

**Anemia**: Goal Hb 10-11.5; Hb >13 increases risk of HF, CVA, and mortality compared to goal Hb <9 (NEJM 2009;361:2019)
- Iron repletion (PO or IV) for goal transferrin sat >20%, hold if ferritin >500-800
- Erythropoiesis stimulating agents (ESAs): ↓ transfusions, risk of Fe overload and Ab formation; contraindicated in cancer, HTN, HF

*Metabolic acidosis*: NaHCO3 650-1300mg BID for goal HCO3 >22, may slow progression of CKD (JASN 2015;26:515)

Uremic bleeding: no need to treat if no bleeding; DDAPV or cryoprecipitate pre-procedure, or conjugated estrogen for chronic bleeding

**Preparation for HD access**: avoid BP measurements and venipuncture in non-dominant arm, avoid subclavian/PICC lines

Dana Larsen, Kate Takvorian 92
OVERVIEW

Definitions (NEJM 2012;367:2505)
- Diffusion: concentration gradient drives small molecules (e.g., urea, creatinine) across semi-permeable membrane
- Convection: hydrostatic pressure forces medium-weight molecules across membrane pores
- Ultrafiltration (UF): removal of plasma water by hydrostatic pressure; Hemodiafiltration: uses all three of the above

### Important Considerations

- **Timing:** Controversial - ELAIN RCT: early RRT (within 8h) ↑ renal recovery, ↓ RRT duration, ↓ mechanical ventilation duration, ↓ LOS, ↓ 90d mortality; IDEAL-ICU: multi-center RCT showed no significant difference for early RRT in patients w/ septic shock and severe AKI
- **Access:** Dialysis lines can only be accessed by dialysis/ICU RNs (except in codes); contact dialysis unit (6-3700) to request new access
- **PICCs:** HD pts or future HD candidates cannot receive PICCs unless first cleared by Renal (to preserve options for vascular access)
- **Abx:** Be sure to dose abx based on IHD vs. CRRT vs. PD and w/ pharmacy; communicate directly w/ dialysis fellow to give during HD

### INTERMITTENT HEMODIALYSIS (IHD) (NEJM 2010; 363:1833)
- **Mechanism:** Cr, Urea, K+ move from blood to dialysate; Ca++ and HCO3- move from dialysate to blood (down concentration gradients)
- **Volume removal:** occurs via UF; HD can rapidly remove solute and volume; usually three 4h sessions weekly (MWF or TuThSa)
- **Access:** double-lumen central catheter (tunneled or temporary, ↑ infection); AV graft (↓ maturation time but ↑ thrombosis and long-term complications); AV fistula (↓ infection, ↓ overall mortality vs catheters/AVG, but 6+ week maturation time + 50% primary failure rates)
- **Intradialytic medications:** erythropoietin, iron, vitamin D analogues, antibiotics
- **Complications:** HoTN, cramps, dialyzer reaction (SOB, urticaria, diffuse pain), HIT, hemolysis, ETOH w/drawal (rapid clearance of ETOH)

### PERITONEAL DIALYSIS (PD) (Perit Dial Int 2001:21-25) - Call PD RN (617-720-1317) on call 24/7 for any inpatient on PD
- **Mechanism:** peritoneum acts as membrane; infusion of fluid rich in osmotic agent (eg: dextrose) → solute removal via diffusion and osmotic gradients → similar survival to pts on IHD (Arch Int Med 2011;171:110)
- **Benefits:** preserves residual GFR better than IHD, better medium weight molecule clearance, no access complications, independence
- **Modalities:** (1) Continuous ambulatory PD (CAPD): Manual exchanges occurring both day and night. All inpatients receive CAPD (2) Automated PD (APD): Multiple automated exchanges overnight
- **Complications:** peritonitis, encapsulating peritoneal sclerosis, hernia, pleural effusion, hyperglycemia, HLD, hyperNa, catheter leaks

### CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)
- **Principles:** Depends on high UF rate to achieve clearance → replacement fluid must be added back to restore volume, acid base balance + electrolytes. Solute clearance + volume removal are slow and not effective in toxin removal or significant volume overload
- **CVVH:** continuous veno-venous HF, removes solute via convection; AVVH: intermediate CVVH circuit setting w flow rates over 12h
- **CVVHF:** continuous veno-venous HD, removes solute by diffusion; CVVHDF: combines convection and diffusion to remove solute
- **SCUF:** slow continuous ultrafiltration, removes plasma water via hydrostatic pressure applied across hemofilter (NO dialysate)
- **Indications:** Hemodynamic instability; continuous large volume IV fluid in pt who cannot undergo intermittent HD; increased ICP
- **Volume management:** can run patient negative (up to 200-250 ml/hr), even, or slightly positive
- **Anticoagulation:** used to decrease risk of circuit clotting, use heparin + bicarbonate OR citrate, citrate achieves regional A/C by calcium chelation → follow iCa levels (will see ↑ total Ca but ↓ iCa), metabolized in liver → AG = possible citrate toxicity
- **Complications:** HoTN, arrhythmias, hypothermia, ↓ iCa/ KPO4, bleeding, thrombocytopenia (mechanical destruction in circuit), HIT
- **Drug dosing:** drugs can bind to circuit resulting in ↑ Vd → work with pharmacy to re-dose all meds based on flow rate

### RENAL TRANSPLANT
- **Listing:** refer EARLY, pts can be listed when GFR <20; pt and graft survival are improved if transplant occurs PRIOR to starting HD
- **Contraindications:** short life expectancy, active malignancy, SUD, nonadherence; age/HIV/psych comorbidities NOT contraindications
- **Allograft dysfunction:** Delayed Graft Function: <1wk (prerenal, ATN, thrombus, obstruction), Early: 1-12 wks (prerenal, CNI tox, infxn [BK virus, CMV], acute rejection), Late Acute: >3mo (prerenal, CNI tox, noncompliance), Late Chronic: yrs (HTN, CNI toxicity, BK virus, recurrence of original pathology, chronic allograft nephropathy)

### IMMUNOSUPPRESSION

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin inhibitor (can check levels)</td>
<td>Cyclosporine, Tacrolimus (FK506)</td>
<td>Inhibits calcineurin-mediated activation of NFAT → blocks T-cell cytokine production</td>
<td>Nephrotoxicity (long-term fibrosis), HTN, tremor, insomnia, hirsutism (CsA only)</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>Sirolimus (Rapamycin)</td>
<td>Inhibits mTOR → blocks IL-2 production</td>
<td>Pulmonary edema, ↓ wound healing, hyperTG</td>
</tr>
<tr>
<td>Antimetabolite</td>
<td>Mycophenolate (Cellcept, Myfortic), Azathioprine</td>
<td>Inhibits de-novo purine synthesis</td>
<td>N/V/D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Purine analogue</td>
<td>BM suppression, N/V/D, hepatitis</td>
</tr>
</tbody>
</table>

Elizabeth Kurtz

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Nephrology

Advanced Diuresis

GENERAL PRINCIPLES
- Loop diuretics have a sigmoidal dose-response curve so double dose until adequate response is achieved.
- If respiratory distress in patient w/ unknown history, start with furosemide 20-40mg IV and double Q1H until response (may need higher doses if impaired renal function).
- Daily standing weights, Na+ restriction 2g/day; consider fluid restriction (esp. if HypoNa).
- Loop + thiazide → sequential nephron blockade (counteracts natural ↑ in DCT Na reabsorption from loop diuretics); use if refractory edema; monitor for ↓K+, ↓Mg2+, ↓bicarb.

<table>
<thead>
<tr>
<th>Thiazide Diuretics</th>
<th>Loop Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Inhibit NaCl channel in DCT to ↓Na reabsorption and prevent urinary dilution (avoid if SIADH); no effect on medullary concentrating gradient</td>
</tr>
<tr>
<td>PO Bioavailability</td>
<td>Variable</td>
</tr>
<tr>
<td>Duration</td>
<td>Variable</td>
</tr>
<tr>
<td>Dosing considerations</td>
<td>Administer 30 min before loop diuretic to “disable” DCT (use PO metolazone, IV chlorothiazide)</td>
</tr>
<tr>
<td>Side effects</td>
<td>↓Na*, ↓K+, ↓Mg2+, ↑Ca2+, ↑urate, HLD, pancreatitis</td>
</tr>
<tr>
<td>Other</td>
<td>Try metolazone 2.5-10mg PO before chlorothiazide 500-1000mg IV ($$$)</td>
</tr>
</tbody>
</table>

*FYI* chlorthalidone has longer half-life/duration → significantly lower SBP and nominally ↓K+ vs HCTZ ([Am J Hypertens 2010;23:440](https://doi.org/10.1093/ajh/hpq017)).

Other Diuretics
- Carbonic anhydrase inhibitors: acetazolamide 250-1000mg PO QD, can do TID x1d vs QD x3d for metabolic alkalosis (pH > 7.6).
- Aldosterone antagonists: spironolactone 25-200mg QD-BID, eplerenone 25-50mg QD-BID, mortality benefit in class II-IV HFrEF.
  - ↑K+, gynecomastia (10%, only spironolactone).
  - Epleronone has greater aldosterone receptor selectivity but more expensive.

Stepwise Approach
1. IV loop diuretic. Starting dose: 2.5x home dose as IV furosemide (CHF) (e.g. if home 80mg PO, give ~80-100mg IV) vs Cr×30 as IV furosemide (e.g. if Cr=4, use lasix 120mg IV); if unknown, start with furosemide 20-40mg IV
2. Reassess in 1-2 hrs and double dose Q1H until response achieved. An adequate dose should cause brisk diuresis.
3. Consider loop diuretic bolus + gtt (should bolus when initiating gtt and re-bolus every time gtt increased).
4. Add thiazide (metolazone PO or chlorothiazide IV) to achieve sequential nephron blockade.
5. Nephrology consult for consideration of UF/RRT.

MANAGEMENT SPECIFICS BY DISEASE

<table>
<thead>
<tr>
<th>Specific Conditions</th>
<th>Mechanism</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Insufficiency</td>
<td>↓GFR so ↓ delivery of diuretic to nephron</td>
<td>High-dose loop ± thiazide augmentation</td>
</tr>
<tr>
<td>Chronic Diuretic Use</td>
<td>Compensatory DCT hypertrophy</td>
<td>Add metolazone or chlorothiazide</td>
</tr>
<tr>
<td>CHF</td>
<td>↓GFR; edema leads to ↓ absorption of PO furosemide; ↓GFR; effect from renal venous HTN (↑CVP, ↑PCWP) more significant than low perfusion (↓CI) (<a href="https://doi.org/10.1016/j.jacc.2008.11.044">JACC 2009;53(7):589</a>); ↑ high sympathetic tone → ↑RAAS, Na+ reabsorption</td>
<td>DOSE trial: ADHF; symptomatic improvement but transiently worse renal function w/ high dose (2.5x home PO dose as IV) vs low dose (1x home PO dose as IV); no difference bwtw Q12H bolus and gtt; No benefit of RRT over stepwise diuresis; Consider sequential nephron blockade</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Loop diuretic (binds to albumin) leaks out of vasculature (↑V0) resulting in ↓ delivery to nephron</td>
<td>Consider bumetanide (lower albumin-binding); No evidence for benefit of albumin + loop diuretic</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Decreased delivery to nephron in setting of hypoalbuminemia; Splanchnic vasodilatation → ↓EABV → renal hypoperfusion (pre-renal azotemia); SNS and RAAS → ↑Na reabsorption</td>
<td>Avoid IV diuretics unless respiratory distress; Spironolactone alone if hypokalemia; Can do spironolactone/furosemide 5:2 (optimal K balance), uptitrate Q3-5d up to 400mg:160mg; ↓If gaining weight, measure urine Na and K; if K &gt; Na (ineffective diuresis), uptitrate meds; if Na &gt; K (effective diuresis) enforce Na restriction</td>
</tr>
<tr>
<td>Nephrotic Syndrome</td>
<td>Decreased delivery to nephron due to low albumin; Urinary albumin binds drug→ loss of diuretic in urine</td>
<td>Use 2-3x normal dose of diuretic</td>
</tr>
</tbody>
</table>
Nephrology

Acid-Base Disorders

TREATMENT OF ACID-BASE DISORDERS: treat underlying cause

Metabolic acidosis:
- Severity of metabolic acidosis reflects disease severity but does not contribute to mortality (Sci World J 2014;2014:627673)
- On giving bicarb: BICAR-ICU multicenter RCT of patients with metabolic acidosis (pH < 7.2) treated with 4.2% sodium HCO3 for goal pH > 7.3 → general population had no change in overall mortality, but ↓ RRT initiation. A subset of pts with AKIN stages 2-3 had improved mortality at 28-days (63% v. 46%, p=0.017) (Lancet 2018;392:31)
- When HCO3 loss is primary cause: (i.e., RTA, diarrhea), can replace by administration of NaHCO3
  o If pH < 7.2 or HCO3 < 6, administer 1-2 mEq/kg as IV bolus → re-dose pm targeting pH
  o Caveats: HCO3 generates CO2 and provides Na load
- Methanol or ethylene glycol intoxication: oral charcoal, HCO3-, fomepizole, or HD (if level >50 mg/dL, vision Δ, AKI)
- Salicylate poisoning: NaHCO3 to urine pH >6.5 or HD (if level > 80 mg/dL, coma, AKI, hypervolemia)
- Consider HD or CVVH in patients with volume overload, catabolism, ethylene glycol >300 mg/dL, isopropanol >500 mg/dL

Metabolic alkalosis: replete volume, K, and Cl:
- Treat both (1) underlying cause of metabolic alkalosis and (2) cause of renal retention of HCO3:
  - If saline responsive: NS w/ KCl until urine pH >7. For patients w/ CHF/cirrhosis, consider K-sparing diuretic
  - If saline resistant: For mineralocorticoid excess → use K-sparing diuretic (amiloride) and consider surgical removal of adenoma

Respiratory acidosis:
- NaHCO3 unlikely to be helpful, theoretically harmful if unable to blow off CO2 produced by conservation of mass (CO2 + H2O ⇄ H2CO3 ⇄ HCO3 + H+); for every 100mEq HCO3 administered, 2.2 L CO2 must be exhaled (~10 min of normal body production)

Respiratory alkalosis:
- Address underlying cause (correct hypoxemia, treat pain/anxiety/fever); adjust vent settings if intubated

Consider in any patient with non-AG metabolic acidosis or hyperK (Type IV)

Pathophysiology: inappropriate net retention of acid or inadequate excretion of bicarb
- In acidemia, kidney should ↑ NH4+ excretion; urine pH should be < 5.3; this process is defective in RTAs
- Caveat: CKD of any etiology is associated with ↓ NH4+ production and acidosis

ETIOLOGIES:

Distal RTA (Type I): ↓ distal acidification
- Primary: genetic loss of H+ or HCO3 transporters (basolateral Cl/HCO3 exchanger or luminal H+-ATPase in intercalated cells)
- Acquired: Autoimmune dz (RA, SLE, SS); hypercalcuria (any cause); obstructive nephropathy; SCD, MM, amyloid, cryoglobulinemia, tubulointerstitial injury; renal bp rejection, cirrhosis, glue sniffing (toluene)
- Meds: Amphotericin B, Li+, ifosfamide

Proximal RTA (Type II): ↓ proximal reabsorption HCO3:
- Primary (rare): Na-HCO3 cotransporter defect
- Acquired: Amyloidosis, multiple myeloma, post-renal transplant, heavy metals (Pb, Cd, Hg, Cu), ↓ Vit D, Wilson’s disease, PNH
- Meds: acetazolamide, cisplatin, tenofovir, aminoglycosides, topiramate
- Often a/w Fanconi Syndrome: glycosuria (w/ serum gluc <180), hypouricemia, aminoaciduria

Type IV: effective hypoaldosteronism: ↓ aldo secretion OR tubular resistical NH3 synthesis → ↓ NH4+ excretion
- Acidosis to inhibition of ammonia-genesis by hyperkalemia of any cause
- Hyporeninemiac hypoaldosteronism: diabetic nephropathy, chronic interstitial nephritis, NSAIDs, calcineurin inhibitor, HIV
- ↓ Aldo production: adrenal insufficiency, ACEi/ARB, hepatic, severe illness
- Aldosterone resistance: (ENaC inhibition) K-sparing diuretic, trimethoprim, pentamidine

Workup:
- Serum HCO3 and K, urinary pH, fractional excretion of HCO3 (ideally, check urine NH4+ but most labs will not do this)
- Estimates of Urine NH4+: UAG = Na + K - Cl (not useful when ↑ urine anions or UNa < 25); UOG/2 (<150 RTA, >400 GI loss)

<table>
<thead>
<tr>
<th>Defect</th>
<th>DISTAL RTA (TYPE I)</th>
<th>PROXIMAL RTA (TYPE II)</th>
<th>TYPE IV RTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum HCO3</td>
<td>&lt; 10</td>
<td>12 – 20</td>
<td>&gt; 17</td>
</tr>
<tr>
<td>Plasma K</td>
<td>↓ or normal</td>
<td>↓ or normal</td>
<td>↑</td>
</tr>
<tr>
<td>Urine pH during acidemia</td>
<td>&gt; 5.5</td>
<td>Varies, but &gt; 5.5 after HCO3</td>
<td>&lt; 5.5</td>
</tr>
<tr>
<td>FE-HCO3 after loading</td>
<td>&lt; 3%</td>
<td>&gt; 15% (diagnostic)</td>
<td>&lt; 3%</td>
</tr>
<tr>
<td>UAG = Na + K - CL</td>
<td>(+)</td>
<td>Can be (-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Additional dx testing</td>
<td>N/A</td>
<td>N/A</td>
<td>Renin, aldosterone, cortisol</td>
</tr>
<tr>
<td>Complications</td>
<td>Nephrocalcinosis/stones</td>
<td>Rickets or osteomalacia</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Tx (goal HCO3 22-24)</td>
<td>NaHCO3 (1-4 mEq/kg) K or Na citrate if persistent ↓K</td>
<td>NaHCO3 (10-20 mEq/kg)</td>
<td>Treat hyperk: loop, low K diet</td>
</tr>
</tbody>
</table>

Alexander Blair, Sarah Street, Elizabeth Kurtz

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DEFINITIONS
ABG vs VBG: pH (~0.04), HCO₃ (~2 mEq) but NOT pCO₂ (~8 ± 17 mmHg); VBG can screen for hypercarbia w/ pCO₂ cutoff ≥ 45 mmHg (100% Sn), but does NOT accurately assess degree of hypercarbia; when in doubt → check ABG (AJEM 2012;30:896)
• Severe acidemia (pH < 7.2) → vasodilation, ↓ inotropy / SVR / MAP, ↓ response catechol, arrhythmia, TK, insulin resistance, AMS
• Severe alkalemia (pH >7.6) → vasoconstriction, ↓ cor/cerebral perfusion, SVT/VT, ↓ K/Ca/Mg/P, AMS, seizure, hyperventilation

STEP-WISE APPROACH (NEJM 1998;338:26, NEJM 2014;371:1434)
1. Is there acidemia (pH < 7.36) or alkalemia (pH > 7.44)?
2. Is primary d/o metabolic (parallels pH ∆) or respiratory (opposite pH ∆)?
3. Is pt compensating? (respiratory takes min-hrs, renal 3-5 days)
4. Is there an anion gap? Regardless of pH or HCO₃
AG = Na – (Cl + HCO₃) = unmeasured anions – unmeasured cations
Correct AG for albumin: AG = 2.5 x (4 – Albumin)
Negative AG: ↑↑ Na, lipids (interfere w/ chloride), bromide intoxication
5. If there is ↑ AG, calculate “delta-delta” and Osm gap
∆/∆ = ∆ AG /∆ HCO₃ = AG – (albumin x 2.5) / (24 – HCO₃)
6. Consider Osm gap = 2x (Na + K) + Urea/2.8 + glucose/18 – serum Osm

ALGORITHMIC APPROACH
Metabolic acidosis: 2-24 hr
Winter’s formula: pCO₂ = 1.5 x HCO₃ + 8 ± 2
Metabolic alkalosis: start 30 min, complete 24 hrs
PaCO₂ = 0.7 x (HCO₃ -24) + 40 ± 2 = HCO₃ + 15
∆ HCO₃ ↑ 1 → expect ∆ pCO₂ ↑ 0.7
Respiratory acidosis:
Acute: ∆ pCO₂ ↑ 10 → ∆ HCO₃ ↑ 1 or ↓ pH 0.08
Chronic: ∆ pCO₂ ↑ 10 → ∆ HCO₃ ↑ 4 or ↓ pH 0.03
Respiratory alkalosis:
Acute: ∆ pCO₂ ↓ 10 → ∆ HCO₃ ↓ 2 or ↑ pH 0.08
Chronic: ∆ pCO₂ ↓ 10 → ∆ HCO₃ ↓ 4 or ↑ pH 0.03

EXPECTED COMPENSATION (JASN 2010;21:920)

AG
OG
Ingestions
Toxin
Manifestations
↑ ↑
Methanol
Formic acid
∆MS, blurry vision, pupil dilation, papilledema
↑ Ethylene glycol
Oxalic acid
∆MS, ↓Ca, Ca oxalate crystals → AKI
Propylene glycol
Lactic acid
AKI, liver injury
↑ Diethylene glycol
Diglycolic acid
AKI, n/v, pancreatitis, neuropathy, ↑ lactate
↑ n/n
Isopropyl alcohol
Acetone
∆MS, fruity breath, pancreatitis, ↑ lactate
Ethanol
Acetaldehyde
Ketoacidotic acidosis ± met. alk 2/2 emesis
OVERVIEW
Serum Na concentration (mEq/mL): reflects plasma tonicity (Osm/kg) and is inversely related to total body water (TBW)
- Na disorders are generally due to changes in TBW (not sodium), which regulate plasma tonicity and effective arterial blood volume
Plasma tonicity: regulated by thirst and ADH release
- High SOsm (increased tonicity) → thirst (fluid intake) and ↑ ADH (decreased free water excretion, ↑ UOsm) → ↓ SOsm
Effective arterial blood volume (EABV): regulated by RAAS
- Hypovolemia/low EABV → RAAS activated (↑ Na retention) and ↑ ADH → ↑ TBW and ↑ EABV

Symptoms: often asymptomatic; AMS, HA, vertigo, N/V, weakness, falls, seizures
Step-wise approach:
1. Check SOsm to confirm hypotonic hyponatremia
   - If SOsm ≈ 300 → isotonic hyponatremia (“pseudo hyponatremia”)
   - If SOsm > 300 → HYPER Tonic hyponatremia (Na correction for hyperglycemia: ∆ glc ‡ 100 → true Na ‡ 2.4)
2. Determine if ADH is present (UOsm >100)
   - Approximate UOsm from SG on a UA
     - If SOsm < 300
       - UNa < 30 suggests ↓ EABV state: UNa > 30 suggests the kidney is not retaining Na
       - UNa unreliable if on diuretics. Fractional Excretion of Uric Acid can distinguish risk if Na ≤ 105, low K, EtOH, ESLD, malnourished
3. If ADH is present, determine if ↑ ADH is appropriate
   - UNa < 30 suggests ↓ EABV state: UNa > 30 suggests the kidney is not retaining Na
   - UNa unreliable if on diuretics. Fractional Excretion of Uric Acid can distinguish risk if Na ≤ 105, low K, EtOH, ESLD, malnourished
   - UNa < 30: RASS active, Na avid
     - ▼ effective art blood volume (EABV)
     - True Hypovolemia (↓ TBW and ↓ EABV)
     - ↑ TBW but ↓ EABV
     - 3rd spacing (pancreatitis, musc injury)
     - CHF, Cirrhosis, Nephrotic syndrome
   - UNa > 30: RASS inactive, Na wasting
     - Common: Diuretics, Na-wasting nephritis, SIADH
     - Cerebral Na Wasting / Pain / Nausea
     - ↓ Mineralocorticoid / ↓ Glucocorticoid
     - Hypothyroidism (severe)
   - Correct underlying cause: Hold diuretics, fix endocrinopathy
     - SIADH: Restrict free H2O. Consider NaCl tabs (1mg TID ↓ Na delivery thus H2O excretion). If UOsm > 2x SOsm or if UNa + UK > SNa → consider Lasix (10-20mg BID). ↑ cortico-medullary gradient. Consider vaptans (NEJM 2006;355:2099).

- Initial therapy: Goal Na ‡ 4-6 mEq/L in 24h; if severe or symptomatic hypoNa → achieve goal Na in <8 hrs and maintain steady Na level for rest of 24h; consider 3% NaCl (100 ml x 3 pm until sx resolve or Na ‡ 4-6 mEq/L)
- Overcorrection: ADH is suppressed once euvolemic → accelerated rate of correction, risk of overcorrection (JASN 2017:28:1340)
  - Rapid overcorrection ≥ 9 mEq/L in 24h or ≥ 18 mEq/L in 48h can result in osmotic demyelination syndrome (ODS)
    - (↑ risk if Na ≤ 105, low K, EtOH, ESLD, malnourished)
  - To prevent overcorrection, give DDAVP 1-2mcg IV or SC q8-8hr x24-48hrs or until Na > 125 + 3% NaCl infusion ~6mL/kg (“DDAVP clamp” → c/s Renal/Endo to assist w/ dosing; must have reliable fluid restriction (Am J Kidney Dis 2013;61:571)
  - Treat hypokalemia: K and Na are freely exchanged via cell shifts, giving 1 mEq of K → giving 1 mEq of Na; be aware of overcorrection

HYPERNATREMIA: free water loss in excess of NaCl loss, very rarely excess Na ingestion (Crit Care 2013;17:206, NEJM 2015;372:55)
Etiologies: impaired access to free water or impaired thirst; ↓ urinary concentrating ability or DI (↓ production or efficacy of ADH)
- Renal losses: Uosm <700–800 → post ATN diuresis, osmotic diuresis, DI, rarely loop diuretic; elderly ↓ max concentrating ability
- Extrarenal losses: Uosm >700–800 → GI loss from NGT, vomiting, diarrhoea, insensible losses, hypodipsia

Step-wise approach:
Calculate free water deficit = TBW x (Na / 140 – 1); TBW = IBW (kg) x 0.4 x 0.5 in ♀ or 0.5 in ♂; shortcut 70kg: FWD (liters) = (Na-140)/3
1. Calculate rate of free water replacement using http://www.nephromatic.com/sodium_correction.php and provide as PO free water, NGT free water boluses (200-400ml Q6-8h), or IV D5W; may also need DDAVP for DI (in conjunction with Endocrine consult)
2. Monitor: Expected ↓ Na/L fluid = (Na_serum − Na fluid) / (TBW +1), but actual response is variable so check Na frequently
3. Goal: correct no faster than 1-2 mEq/L/h to prevent cerebral edema (risk not as well characterized as for ODS)
**Nephrology**

**Potassium Disorders**

**NORMAL POTASSIUM HANDLING / HOMEOSTASIS** (*NEJM 2015;373:60*)

- K+ ingested and absorbed in intestines → taken up by liver / muscle cells vs insulin & β2 receptors → ↑Na-K ATPase activity
- 98% of K is intracellular; remaining extracellular levels trigger aldosterone secretion → K+ secretion → excretion in urine

**HYPERKALEMIA**

- Signs and symptoms: muscle cramps, paralysis, conduction delays (e.g.: CHB, BBB, sinus arrest) and arrhythmia (VT/VF, asystole, idioventricular rhythms) (Crit Care Med 2008;36:3246)
- Dx: confirm true ↑ K and not hemolyzed sample, PLT > 500K, WBC > 120, or infusion of K-containing IVF; consider ABG plus
- Low utility in checking TTKG:
  - Etiologies:
    - Redistribution: cell lysis (hemolysis, rhabdo, TLS, RBCs, crush injury), acidosis, ↓ insulin (DM, octreotide), meds (digoxin, β-blockers, succ, calcineurin inhib, minoxidil), hyperK periodic paralysis, post-hypothermia → transient unless ↓ excretion
    - Renal K excretion:
      - ↓ Aldo production / action: ACEIs/ARBs, NSAIDs, K-sparing diuretics, CNI, pentamidine, TMP, type IV RTA
      - Impaired Na delivery to distal nephron: CHF, cirrhosis
      - AKI/CKD (esp if oliguric); usually GFR must be < 15
      - Other: ureteroejunostomy
- Management: acute changes are most dangerous → STAT ECG: peaked T waves → flat P → ↑ PR interval ± AVB → wide QRS ± BBB → sine wave pattern → PEA / asystole / VF; ECG does not correlate w/ K level (Clin J Am Soc Nephrol 2008;3:324)
  - Treat if EKG changes, K > 6.5, or rapid rise
  - Key is elimination, other measures are temporizing. Address reversible factors (optimize volume status, low K diet, meds)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Treatment</th>
<th>Onset</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilize</td>
<td>Calcium</td>
<td>1-3 min</td>
<td>30-60 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(calcium gluconate or CaCl2 1-2 g IV, can give q5min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redistribute</td>
<td>Bicarb</td>
<td>5-10 min</td>
<td>1-2 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(sodium bicarbonate 1-2 amps IV vs gtt)*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>10-30 min</td>
<td>4-6 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10 units IV) + Glucose (DS50, if BS&lt;250)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albuterol</td>
<td>15-30 min</td>
<td>15-90 min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10-20mg neb preferred over IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliminate</td>
<td>Furosemide</td>
<td>30 min</td>
<td>Variable</td>
<td>Urinary K excretion</td>
</tr>
<tr>
<td></td>
<td>(240mg IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kayexalate</td>
<td>1-2 hr</td>
<td>4-6 hr</td>
<td>Swap K for Na in gut</td>
</tr>
<tr>
<td></td>
<td>(15-30g PO/PR)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
<td>Immediate</td>
<td>3 hr</td>
<td>Removes K, may rebound d/t shifts</td>
</tr>
<tr>
<td></td>
<td>(definitive Rx)***</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bicarb not effective in patients with CKD on HD w/o residual renal function
** Colonic necrosis reported w/ Kayexalate but very rare; contraindicated post-op, ileus, bowel obstruction (Am J Kidney Dis 2012;60:409)
*** HD lowers K immediately; CVVH lowers K slowly so not ideal in acute setting

**HYPOKALEMIA**

- Signs and symptoms: usually with K < 2.5 → cramps, ileus, weakness (LEs > trunk/UEs > respiratory muscle paralysis) (Ann Intern Med 2009;150:619)
- ECG: flat T waves, ST dep, U waves, prolonged QT, atrial or ventricular ectopy → VT, VF (esp if K <3, susceptible pts, or on digoxin)
- Etiologies:
  - Lab artifact (pseudo-hypokalemia): WBC >100 → WBC absorb K if sample sits out (check arterial potassium)
  - Inadequate intake (unlikely to be primary cause unless very low Ca diet, usually combined with another etiology)
  - Redistribution: ↑ pH, ↑ insulin, hypothyrotic periodic paralysis, ↑ RBC prod (eg s/p G-CSF), hypothyromia, ↑ β-adrenergic activity (e.g. albuterol), refeding syndrome, toxins (cesium, barium, chloroquine)
  - Extrarenal losses: diarrhea (esp if chronic, VIPoma, villous adenoma), laxatives, vomiting/NGT, insensitive losses
  - Renal losses (w/o HTN):
    - ↑ urine flow (psych polydipsia, excess IVF), ↓ Mg, meds (ampho B, lisophage, cisplatin, gent)
    - Acidemia: DKA, RTA (proximal and some distal)
    - Alkalaiemia: diuretics, UGI losses (2° hyperaldo), Bartter’s (~loopt diuretic), Gitelman’s (~thiazide)
  - Renal losses (with HTN):
    - 1° hyperaldo: ↑ ald → renin (e.g. adrenal adenoma)
    - 2° hyperaldo: ↑ ald, ↑ renin (e.g. renin-secreting tumor, renal artery stenosis)
    - Other: ↑ glucocorticoid or ↑ ENaC activity (e.g. Cushing’s, Liddle’s syndome, black licorice)
- Management: 10mEq raises K by 1.0 mmol/L; caution if ↑Cr or if due to transcellular shifts
  - Oral KCI prefers for treatment as SAFER, quick acting, ↑ retention of K, and many patients are CI depleted as well
  - KCI ER = pill; KCI IR = powder
  - IV formulation KCI if unable to take PO or if severe / symptomatic → max 10mEq/hr (floor), 20mEq/hr (ICU)
  - Always replete Mg, otherwise K repletion ineffective (JASN 2007;18:2649)
  - Avoid dextrose-containing solutions → can acutely worsen hypok (dextrose ↑ insulin secretion → K shifts into cell)
Nephrology

Magnesium & Phosphorus Disorders

HYPOMAGNESEMIA

- Signs/symptoms: other electrolyte disturbances (↓ K, ↓ Ca), weakness, anorexia, confusion, hyperreflexia, tetany, ↑ PR, ↑ QRS, ↑ QTc, peaked / inverted T waves, U waves, VT / torsades, accentuation of digitalis toxicity

- Etiologies:
  - ↓ GI absorption: ↓ intake (EtOH, malnutrition), ↑ loss (diabetes, pancreatitis, malabsorption, small bowel resection, PPIs)
  - ↑ renal losses: thiazides, loops, amphotericin B, aminoglycosides, foscarnet, cyclosporine A, cisplatin, pentamidine
  - Can distinguish GI vs renal with 24hr urine Mg or FeMg (>10mg or >2% suggest renal wasting)

- Treatment: oral (very slow) vs. IV repletion (IV typically given inpatient)
  - MgSO4 1-2 gm IV over 15 min, max 1-2gm/h, up to 8gm in 24h
    - Give ½ dose if CrCl <30
  - Mg oxide 800-1600mg PO in divided doses (240mg Mg per 400 mg tab); limited by diarrhea
  - If hypoMg due to thiazide or loop diuretic, add K-sparing diuretic to decrease Mg excretion

HYPERMAGNESEMIA (rarely pathologic)

- Signs/symptoms (typically only if Mg >4): neuromuscular (hyporeflexia [first sign], areflexia, lethargy, weakness/paralysis, resp failure), CV (hypotension, bradycardia, conduction defects [↑ PR, ↑ QRS, ↑ QTc, CHB, cardiac arrest]), hypocalcemia (hyper Mg can suppress PTH)

- Etiologies: Mg intake > renal clearance (only method of excretion)
  - Medication overdose (Epsom salts, laxatives, Maalox, Mg enemas) → avoid these agents in ESRD
  - Increased Mg absorption with gastritis / PUD / colitis
  - Mild hyperMg may be seen in DKA, hypercatabolic states (TLS), lithium, adrenal insufficiency

- Treatment (symptomatic only): Ca gluconate 1 gm IV over 10 min vs gtt to counteract resp depression/hypotension.
  - IVF, loop diuretics to enhance renal excretion. If oliguric/anuric ESRD, requires HD for removal.

HYPOPHOSPHATEMIA

- Signs/symptoms (typically only if phos < 1.0mg/dL, esp if acute):

- Etiologies:
  - Redistribution (into cells): ↑insulin (DKA, HHNK, refeeding), acute respiratory alkalosis (↑ pH →↑ glycolysis), hungry bone syndrome (deposition of Ca and phos in bone immediately following parathyroidectomy)
  - ↓ GI absorption: poor PO, chronic diarrhea, antacid use (aluminum, Mg), ↓ vit D (steatorrhea, chronic diarrhea), overuse of phos binders
  - ↑ renal excretion: ↑ PTH (primary or secondary), Fanconi syndrome (multiple myeloma, meds), ↑ FGF-23 (genetic/paraneoplastic), meds (acetazolamide, tenofovir, metolazone, IV iron) (QJM 2010;103:449), osmotic diuresis (glucosuria), proximally acting diuretics (acetazolamide, metolazone), CVVH (esp at high flow)
  - Can determine if GI/redistribution vs renal with 24hr urine Phos or FePhos (>100mg or >5% → renal wasting)

- Treatment:
  - Severe (<1 mg/dL) or symptomatic: Na or K phos 0.08-0.50 mmol/kg IV over 6-8h (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, hypotension (often due to hypocalcemia), AKI, arrhythmia
  - Asymptomatic (<2 mg/dL): Na or K phos 1mmol/kg/d PO in 3-4 divided doses (total 40-80mmol)
    - NeutraPhos: 1 packet = 250mg Phos (8mmol), 7.1mEq K, & 6.9mEq Na; preferred if also need K or if want lower Na
    - K-Phos Neutral: 1 tablet = 250mg Phos (8mmol), 1.1mEq K, & 13 mEq Na; preferred if do not need K
    - If poorly tolerated (causes diarrhea), can give scheduled skim milk (8oz = 8mmol Phos)

HYPERPHOSPHATEMIA

- Signs/symptoms: acute hyperphosphatemia signs/symptoms result from effects of hypocalcemia (muscle cramps, tetany, tingling, perioral numbness), acute phosphate nephropathy (bowel prep); rarely sx from chronic hyperphosphatemia

- Etiologies:
  - Acute phos load (TLS, rhabdo, exogenous/phosphate-containing laxatives); acute extracellular shift (DKA, lactic acidosis, severe hyperglycemia); acute or chronic kidney disease
  - Increased tubular reabsorption (vit D tox, hypoPTH)
  - Pseudohyperphos (hyperglobulinemia, hyperlipidemia, hyperbili, hemolysis)

- Treatment: acute – normal saline (though can worsen hypoCa), dialysis; chronic – see Chronic Kidney Disease
Nephrology

IV Fluids & Electrolyte Repletion

IV FLUIDS
- Types: crystalloid (e.g., NS or LR), free water (e.g., D5W), and colloid (e.g., albumin, blood products)
  - Crystalloid can be isotonic (NS, LR), hypotonic (1/2 NS, 1/4 NS), or hypertonic (3% saline)
- Bolus fluids = volume expansion in shock, sepsis (30 ml/kg), hemorrhage (initial resuscitation), GI losses, burns
  - Normal saline in large volumes can cause hyperchloremic non-AG metabolic acidosis and ↑ need for RRT
  - Rate: ~500cc-1L over 30 min-2 hr. If concerned about volume overload, start w/ smaller volume (250-500cc).
  - LR or Plasma-lyte associated with better renal outcomes compared with NS (SMART, NEJM 2018;378:829, SALT-ED, NEJM 2018;378:718).
  - Colloid is not superior to crystalloid for volume resuscitation in sepsis (SAFE, NEJM 2004;350:2247)
- Maintenance fluids = replace daily losses (~1.6L per day in adults w/ normal renal function and perspiration). Also used at higher rates in conditions such as pancreatitis and rhabdomyolysis. (NEJM 2015;373:1350)
  - If patient is taking PO, there is no need for maintenance IV fluids
  - D5-1/2 NS is typical main maintenance fluid for NPO patients. Insufficient calories to replace a diet (~170 kcal/L).
  - Maintenance rate: 60 ml/hr + 1 ml/kg/hr for every kg above 20 kg — ex. 60 kg adult = 100 ml/hr

<table>
<thead>
<tr>
<th>Fluid</th>
<th>pH</th>
<th>Osm</th>
<th>[Na+]</th>
<th>[Cl-]</th>
<th>[K+]</th>
<th>[Ca2+]</th>
<th>[Mg2+]</th>
<th>Dextrose</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human plasma</td>
<td>7.35-7.45</td>
<td>275-295 mOsm/L</td>
<td>135-145 mEq/L</td>
<td>94-111 mEq/L</td>
<td>3.5-5.0 mEq/L</td>
<td>2.2-2.6 mg/dL</td>
<td>0.8-1.0 mg/dL</td>
<td>60-100 mg/dL</td>
<td>1-2 mEq/L lactate</td>
</tr>
<tr>
<td>Normal Saline</td>
<td>4.5-7</td>
<td>308</td>
<td>154</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactated Ringer’s</td>
<td>6-7.5</td>
<td>280</td>
<td>130</td>
<td>109</td>
<td>4</td>
<td>1.35</td>
<td></td>
<td></td>
<td>29 mEq/L lactate</td>
</tr>
<tr>
<td>1/2 NS</td>
<td>5</td>
<td>154</td>
<td>77</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D5-1/2 NS</td>
<td>3.5-6.5</td>
<td>406</td>
<td>77</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 g/dL</td>
</tr>
<tr>
<td>Plasma-lyte ($$$)</td>
<td>4-6.5</td>
<td>294</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>1.5</td>
<td></td>
<td></td>
<td>23 mEq/L gluconate 27 mEq/L acetate</td>
</tr>
<tr>
<td>H2O</td>
<td>3.5-6.5</td>
<td>252</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 g/dL Used in hyperNa (see Sodium Disorders)</td>
</tr>
</tbody>
</table>

MGH Albumin Policy (Feb 2019, ellucid): 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

Use to replace serum oncotic pressure. Albumin amt is the same in both formulations. If you need volume, give crystalloid.

- SBP: Improves renal outcomes. Dosing: Albumin 25% at 1.5g/kg IV within 6hrs arrival, decrease to 1g/kg on Day 3.
- Large Volume Paracentesis in Cirrhosis: Only if >5L removed. Dosing: Albumin 25% at 6-9g/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 IV q8hr for 3 doses (Requires attending approval. Stop once alb >2.5. MAX 3 days).
- Hepatorenal Syndrome: Diagnosis and/or Treatment by protocol, see Hepatorenal Syndrome.
- Other: chatter in ECMO/VADs, Burns, Nephrotic Syndrome.

Electrolyte Repletion – see Potassium Disorders, Magnesium and Phosphorus Disorders, and Calcium Disorders (Endocrinology) for more specific guidelines about treating electrolyte disturbances

<table>
<thead>
<tr>
<th>Potassium</th>
<th>Magnesium</th>
<th>Phosphorus</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal</td>
<td>- CAD/arrhythmia: ≥4</td>
<td>- CAD/arrhythmia: ≥2</td>
<td>- Replete if sx or phos &lt;1</td>
</tr>
<tr>
<td></td>
<td>- Everyone else: ≥3.5</td>
<td>- Everyone else ≥1.7</td>
<td>- At risk for refeeding syndrome: &gt;2</td>
</tr>
<tr>
<td>PO or IV?</td>
<td>PO &gt; IV</td>
<td>IV &gt; PO</td>
<td>PO &gt; IV</td>
</tr>
<tr>
<td>PO repletion</td>
<td>- KCl IR (packets): 0.4-6 hr</td>
<td>- Mg oxide 400mg (240 mg elemental Mg) TID x1 day</td>
<td>- K-Phos: 1 packet QID</td>
</tr>
<tr>
<td>PO repletion</td>
<td>- KCl ER (pills): giant pills</td>
<td></td>
<td>- Neutra-Phos: 1 packet QID</td>
</tr>
<tr>
<td>PO repletion</td>
<td>- If K &lt;3.5, ≥20 mEq KCl IR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV repletion</td>
<td>- Peripheral IV: 10 mEq/hr</td>
<td>- Mg sulfate 2g IV</td>
<td>- Give 15-45 mmol phos at a time</td>
</tr>
<tr>
<td>IV repletion</td>
<td>- Central line: 20 mEq/hr w/ telemetry monitoring</td>
<td></td>
<td>- K-Phos (1.5 mEq K/mmol phos)</td>
</tr>
<tr>
<td>IV repletion</td>
<td></td>
<td></td>
<td>- Na-Phos (1.3 mEq Na/mmol phos)</td>
</tr>
<tr>
<td>Comments</td>
<td>- 10 mEq K ↓ serum K by 0.1</td>
<td>- 2g will ↑ serum Mg by 0.5</td>
<td>- IV Phosphate can precipitate Ca → causing hypocalcemia</td>
</tr>
<tr>
<td>Comments</td>
<td>- Max 80 mEq → re-check K</td>
<td>- ↓Mg can cause ↓K and ↓Ca</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>- Correct hypoMg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nephrology

URINE DIPSTICK – urine should be analyzed within 2-4 hr

Specific gravity
- Can help approximate UOs: multiply last 2 decimals of SG x 30 (eg SG 1.020 → 20 x 30 → ~ 600 mosms)
- SG < 1.010: post-ATN (concentrating defect), diuretics, DI, polydipsia, hypovolemic hypoNa after resuscitation
- SG 1.010 – 1.025: normal
- SG > 1.025: prerenal, contrast (esp >1.030), ↓ EABV, glycosuria (DM), proteinuria, SIADH

pH
- Normal 4.5 – 8, but strongly depends on serum pH and dietary intake
- If normal urine pH + metabolic acidosis, suspect distal RTA (kidney not secreting NH₄⁺)
- If pH ≥ 7, suspect urease-producing organisms (Proteus, PsA), strict vegetarians (low protein diet), type I RTA

Leuk esterase
- 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, GC/CT, Ureaplasma, urethritis, TB, foreign body, exercise, steroid use, cyclophos

Blood
- Detects heme (glomerular, renal, or urologic); FP: hemoglobinuria (hemolysis), myoglobinuria (rhabdo), semen, drugs (rifampin, chloroquine, iodine), peroxidase-producing bacteria

Protein
- Detects albumin when excretion >300mg/dl: glomerular, tubular, and overflow causes; does NOT detect light chains
- Semiquantitative categories (trace, 1+, 2+, 3+) are not reliable, vary with SG
- Falsely elevated by high SG, heavy hematuria (heme protein), and iodinated contrast (w/in 24h)

Ketones
- Detects only acetocetate, NOT β-hydroxybutyrate: yield decreases as collected urine sits

Glucose
- Reflects glomerular overflow (serum glucose >180mg/dl or SGLT-inhibitor/mutation) OR PCT failure (glucosuria w/ normal serum glucose → consider Fanconi’s syndrome 2/2 MM, heavy metal, drugs, etc.)

URINE SEDIMENT (MICROSCOPY)
(1) Obtain 10cc of urine
(2) Dipstick
(3) Centrifuge using a balance @ 3000 RPM x 3-5 min.
(4) Pour off supernatant and resuspend sediment with pipette; place one drop of sample on slide, place coverslip, analyze.
(5) Standard or bright field microscopy: keep light source subdued, lower condenser to slide, place coverslip, analyze.
(6) Phase contrast microscopy: review components of phase contrast microscopy. Raise condenser up high and turn light source to maximal brightness. Rotate the condenser annulus (6)
(7) Please use the urine sediment guide adjacent to microscope to guide analysis.

Cells:
RBCs
- Glomerular (dysmorphic RBCs "mickey mouse ears") vs non-glomerular (trauma, exercise, infxn, tumor, stone, SCID)

WBCs
- UTI/cystitis, pyelonephritis, AIN, atheroembolic, glomerular injury, renal/bladder TB, nephrolithiasis

Epithelial Cells
- Tubular (ATN), transitional (proximal urethra to renal pelvis), squamous (contamination by genital secretions)

Casts:
- Viewed best w/ phase contrast: Hyaline, RBC, WBC, Muddy brown, Granular, Waxy, Fatty (see below)

Crystals:
- Viewed best w/ phase contrast: Acylovir ("needles"), Tenofovir, Struvite (↑ urine pH), ethylene glycol (oxalate)

CONDITION | UA | CELLS | CASTS / CRYSTALS | COMMENTS
--- | --- | --- | --- | ---
Pre-renal Azotemia | SG > 1.010 | Hyaline, granular | ↓ FENa, ↓ FEUrea |
CIN | SG >1.010, +Prot | Tubular cells | Granular, muddy brown | ↓ UNa, ↓ FENa, FP: proteinuria |
Nephrotic Synd. | 3+ Prot | | Oval fat bodies, hyaline |
Glomerulonephritis | 3+ heme | Dysmorphic RBCs | RBC casts, WBC, granular |
ATN | SG ~ 1.010 | Tubular cells | Granular, muddy brown |
Rhabdomyolysis, Hemolysis | 3+ heme w/o RBCs | NO cells | Acellular hyaline casts with red or brown pigmentation | ↓ FENa, red/brown urine |
AIN | WBCs; +/- eos | WBC casts, granular | Urine eos NOT Sens or Spec |
Renal Infarct | Sterile pyuria; +Pro | Eos, RBCs, WBCs | ↑ urine LDH (↑ serum LDH) |
Cholesterol emboli | Sterile pyuria | +Eos | Cholesterol |
Myeloma kidney | | Bland | Bland |
Ethylene Glycol | | | Proteinuria NOT detected by UA |
CKD | | | Ca oxalate |

WBC CAST | "MUDDY BROWN" CAST | GRANULAR CAST | RBC CAST

Elizabeth Kurtz 101
For an additional schematic, see the nephron schematic at this Columbia Nephrology link.
**Empiric Antibiotics**

### Principles of Antibiotic Selection
- **Empiric Therapy from MGH, IDSA Guidelines, Sanford Guide, Johns Hopkins Abx Guide**
- **CULTURES BEFORE ANTIBIOTICS**
  - **TIME TO ABX CORRELATES WITH MORTALITY IN SEPSIS**
- **HOST**: Presence of foreign bodies (e.g., drains), structural organ disease (e.g., CF, bronchiectasis, IBD), prior surgeries; when immune clearance is poor (i.e., neutropenia, endocarditis, meningitis, etc.), cidal antibiotics are preferred to static antibiotics
- **PATHOGENS**: Prior micro data; risk factors for MDRO, especially IV antibiotic use within 90d
- **ANTILOGRAM**: Identify local susceptibility and resistance patterns for likely pathogens
- **SOURCE CONTROL**: Remove infected lines/hardware, evaluate for and drain abscesses/effusions

### More nuanced discussions on antibiotic choices can be found on topic-specific pages

### Empiric Antimicrobial Therapy

#### Suspected Process

<table>
<thead>
<tr>
<th>Process</th>
<th>Suspected Pathogens</th>
<th>Additional Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Viral, HSV, S. pneumonia + N. meningitans - If &gt;50yo, immunocompromised, ETOH use - If hardware or nosocomial - Staph, PsA</td>
<td>Vanc AND CTX 2g Q12 - If concern for Listeria: add Amp or TMP/SMX (if severe PCN allergy) - If concern for HSP: add Acyclovir - Dex 10 mg PO/IV q6h x 4 days w/ initial abx dose if S. pneumonia - If HCA / hardware / VP shunt / IVDU: Cefepime or Cefaz or Meropenem in place of CTX</td>
</tr>
<tr>
<td>Community Acquired Pneumonia (CAP)</td>
<td>Viral (most common), S. pneumonia, H. flu, Moraxella, Legionella, Mycoplasma, Chlamydia, Klebsiella (EOH)</td>
<td>CTX + azithro or levofloxacin - IV abx in past 90d: cefep + vanc + razithro - Consider flu testing + Oseltamivir - post-flu/cavitation/empyema: add Vanc for MRSA - If structural lung dx: Levo&gt;Azithro - If Legionella: Levo&gt;Azithro</td>
</tr>
<tr>
<td>Hospital-acquired and Ventilator-Assoc. Pneumonia (HAP/VAP)</td>
<td>CAP organisms + S. aureus + GNRs including PsA</td>
<td>Vanc + Cefepime (NB: double GNR coverage usually not necessary, but consider if ICU + shock) - See HAP / VAP for more nuanced discussion; consider local MDRO and MRSA prevalence</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Native: S. aureus, Strep, Enterococcus, few GNRs, HACEK &lt;5% - Prosthetic: S. aureus, S.epi</td>
<td>Native: Vanc + CTX - Prosthetic: Vanc +/- Gent ID d/o improves mortality! - MSSA: t-lactam &gt;&gt; Vanc - Check Rx list for rif interactions - Consider GNRs if subacute</td>
</tr>
<tr>
<td>Cholecystitis/ Ascending Cholangitis</td>
<td>E. coli, Klebs; less likely Enterococcus, anaeobes. Often polymicrobial; broad abx for 48h even if BCx growing 1 org</td>
<td>[CTX + MNZ] or Pip/Tazo - If nosocomial: consider cefepime - Source control with ERCP vs. PCT</td>
</tr>
<tr>
<td>Other Intra-abdominal</td>
<td>Abscess: GNRs, anaeobes, Enterococ, Candid; S. aureus, Strep rare -Diverticulits: Polymicrobial, enteric GNR, anaeobes, role of Enterococcus unclear</td>
<td>[CTX or Cipro] AND MNZ - If nosocomial/severe: cover PsA, add Vanc if recent instrumentation - Need CT-US-guided drainage - Severe: [Pip/Tazo or Mero or Lmi] Surgical indication: peritonitis, perf, fistula, recurrent diverticulits</td>
</tr>
<tr>
<td>Spontaneous Bacterial Peritonitis (SBP)</td>
<td>Enteric GNR, incl Enterobacter, Strep, Enterococcus; rarely anaeobes</td>
<td>CTX - Cipro reserved for patients w/ beta-lactam allergies and for ppx</td>
</tr>
<tr>
<td>UTI (requiring hospitalization, non-pregnant)</td>
<td>Uncomplicated: E.coli, Klebsiella, S.saprophyticus, Proteus Complicated (i.e. w/ &gt;= 5sx of systemic infxn; includes Pyelonephritis): above + Enterococcus, PsA, Serratia, Providencia</td>
<td>Uncomp: NFT or Fosfomycin or Bactrim Comp: CTX or Cefepime (if c/f PsA), Penem if ESBL, add Vanc if c/f GPC - Comp: If abx x 48h, transition to PO FQ; can consider Bactrim or Cefpodoxime but need longer course</td>
</tr>
<tr>
<td>Catheter Associated UTI (CAUTI)</td>
<td>GNR's, Enterococcus - Prior cx data useful</td>
<td>CTX AND Vanc; consider PsA if risk MDRO, hosp. acquired - Tx only if sx; repeat UA/UCx 48 hrs after removal or replacement (Pyrina = Infection)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Hematogenous source: S aureus - Direct inoculation/vascular (e.g., DM ulcer); S. aureus &gt; Strep, PsA (diabetic, GNR, GNR, Enterococ, Eikenella (human bites), Pasteurella (animal bites))</td>
<td>-No tx until after bone bx+cx unless HD unstable. Usually NOT an emergency - Vanc; ADD CTX or Cefepime if DM/PVD/Ulcer or direct innoculation - Dx: MRI, CRP, bone bx - Debride (Plastics/Ortho/Vasc surj) w/ bone bx+cx - Site: Amp/Sulbact 1.5-3g qIV 48h</td>
</tr>
<tr>
<td>Septic Arthritis (Curr Opin Rheumatol)</td>
<td>Staph, Strep, N. gonorrhoea (sex. active), E. coli, Salmonella (sickle cell); PsA (IVDU); Lyme, viruses (poly-articular)</td>
<td>Blood + joint aspirate cx prior to abx - Vanc AND CTX (consider Cefepime if IVDU, other risk factor for PsA) - GC: CTX AND Azithro - PCN allergy: Vanc + Quinolone - Consult ortho for joint washout</td>
</tr>
<tr>
<td>Septic shock, no source (Sepsis Pathway in EPIC)</td>
<td>GNRs, S. aureus, Strep, PsA, anaeobes. Consider toxic shock syndrome (TSS)</td>
<td>Vanc AND [CTX or Cefepime or Cefaz or Pip/Tazo] + MNZ (if c/f anaeobes and not on Pip/Tazo)</td>
</tr>
</tbody>
</table>

**More nuanced discussions on antibiotic choices can be found on topic-specific pages**

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Nicky Singh, David Olshan

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| Gram Positive | Cocci | Clusters or tetrads (never chains > 4) | Coagulase (+) | Staphylococcus aureus |
|               |       | Long chains > 6 (never in tetrads)   | α-hemolytic   | Viridans group (optochin resistant) |
|               |       | Pairs and short chains < 6          | β-hemolytic   | Streptococcus pneumoniae (GAS) |
|               |       |                                               | α-hemolytic (partial, green hemolysis) | Enterococci (GDS) (also γ-hemolysis) |
|               |       |                                               | β-hemolytic (complete hemolysis) | Streptococcus agalactiae (GBS) |
|               |       | Anaerobic                               | γ-hemolytic   | Peptostreptococcus |
|               |       | Large (and spore forming)              | Aerobe        | Bacillus |
|               |       | Short                                   | Faculative anaerobe | Listeria, Envelophlotrix |
|               |       | Irregular/Pleomorphic                   | Aerobe ("club" shaped) | Corynebacterium |
|               |       | Filamentous                             | Aerobe        | Nocardia, Tropheryma |
|               |       |Anaerobic|Facultative intracellular|Neisseria|
|               |       | Lower respiratory|Aerobe|Moraxella|
|               |       |Cocobacilli and Pleomorphic|Respiratory and Oropharyngeal|Acinetobacter, Bordetella, Haemophilus (H. parainfluenzae = HACEK), Cardiobacterium hominis (HACEK), Kingella kingae (HACEK)|
|               |       |Facultative Anaerobe|Respiratory and Oropharyngeal|Aggregatibacter actinomycetemcomitans (HACEK), Eikenella corrodens (HACEK)|
|               |       |Curved Rods|Microaerophilic|Campylobacter, Helicobacter|
|               |       |          | Halophilic | Vibrio |
|               |       |Obligate Aerobes (all lactose non-fermenters) | Oxidase Negative | Stenotrophomonas |
|               |       |Oxidase Variable | Burkholderia |
|               |       |Oxidase Positive | Pseudomonas, Alcaligenes |
|               |       |Respiratory | Legionella |
|               |       |Enteric Gram Negative Rods: Lactose Fermenting (Coliforms) | Escherichia, Enterobacter, Klebsiella |
|               |       |Enteric Gram Negative Rods: Non-Lactose Fermenting | Proteus |
|               |       |Zoonoses | Pasteurella, Yersinia |
|               |       |Anaerobes|Bacteroides, Fusobacterium, Prevotella |
|               |       |Acid Fast | Mycobacteria |
|               |       |Spirochetes | Borrelia, Leptospora, Treponema |
|               |       |Obligate Intracellular | Cell wall present | Anaplasma, Erlichia, Rickettsia |
|               |       |Obligate Intracellular | Respiratory | Chlamydophila, Coxiella |
|               |       |No cell wall | Mycoplasma, Ureaplasma |
|               |       |Fungi | Yeast (unicellular) | Budding, pseudohyphae |
|               |       |Dimorphic | Lives part of life cycle as yeast and part of cycle as a mold | Blastomyces, Histoplasma, Coccidioides, Sporothrix |
|               |       |Mold (multicellular) | Branching, septate hyphae |
|               |       | |Irregular aseptate hyphae, sporangia | Mucor, Rhizopus (zygomycetes) |
Infectious Disease

Multidrug Resistant Organisms

Extended Spectrum Beta Lactamases (ESBL)

- **Definition**: Plasmid-mediated enzymes exclusively seen in GN organisms conferring resistance to PCNs, most cephalosporins, and aztreonam
  - MGH Laboratory Definition of MDRO that qualify as a potential ESBL: GNRs resistant to Ceftriaxone
- **Pathogens**: Klebsiella (#1), E. coli (#2), Acinetobacter, Burkholderia, Citrobacter, Enterobacter, Morganella, Proteus, Pseudomonas (PSA), Salmonella, Serratia, Shigella, Vibrio cholerae
- **Risk factors**: abx within past 6mo, long inpt hosp., nursing home, >65yo, lines/cath/tubes/vent, TPN, HD, travel to Asia
- **Treatment**: empiric tx w/ Carbapenems IF pt is critically ill (bacteremia) AND has prior +BCx w/ ESBL-producing org.
  - First-line: Meropenem 1g Q8 (for normal renal function). Consider Ertapenem on discharge for QD dosing
  - May consider Cefepime 2g Q8 (for normal renal function) if both the Cefe MIC<2 AND Pip/Tazo MIC<4 for less severe infections (CID 2017;64;972). Do not use Pip/Tazo (JAMA 2018;320:984). Discuss with ID. FQs may retain activity, consider once sepsis has resolved. For UTIs, fosfomycin, TMP/SMX, doxy, or nitrofurantoin may be options, if susceptible.

AmpC Beta-Lactamases (Cephalosporinases) – one type of ESBL

- Neutralize 3rd gen Cephalosporins. Pip/Tazo. AmpC gene expression can be constitutive or inducible
- Inducible AmpC producers include SPICE / SPACE-M organisms: Serratia, Providencia, Indole-positive Proteus (non-mirabilis species), Acinetobacter, Citrobacter, Enterobacter, Morganella.
- **Treatment**: empiric tx w/ Cepofime (2g Q8) if MIC <2 vs. Carbapenem. FQs possible, but not advisable in severe illness.
  - Do not use Ceftriaxone, Ceftazidime, or Pip/Tazo regardless of susceptibilities.

Carbapenem Resistant Enterobacteriaceae – another type of ESBL

- **Mechanisms**: 1) Carbapenemase or 2) AmpC/ESBL (some hydrolyze penems) + Porin loss (limits penem entry)
- **Risk Factors**: Cephalosporin/carbapenem use in past 3mo (*penem exposure not req*), medical care in India/Pakistan
- **Laboratory Detection**: suspicious when MICs >2 mcg/ml for imi, mero, or ertapenem
- **Treatment**: Limited (may include Aminoglycosides, Ceftaz-avibactim, Colistin/polymixin B, Tigecycline, etc.). Consult ID.

Methicillin-Resistant Staphylococcus Aureus (MRSA)

- **Community-associated MRSA**: No healthcare exposure
  - Skin and soft tissue infections in young healthy individuals. Usually sensitive to non-lactam abx (at MGH, Doxy >> Clinda)
  - If shock, consider toxin-producer (PVL MRSA causes necrotizing PNA, severe SSSI). Tx: Add Clinda/Linezolid
- **Hospital-acquired MRSA**
  - Risk: abx use, prolonged hospitalization/ICU, HD, MRSA colonization, tubes/hardware (biofilms→ET tubes, urinary/endovascular catheters)
  - Bacteremia: TTE +/- targeted imaging to eval metastatic infxn
  - Nasal Swab: High NPV for pneumonia (up to 96.5%), not as well studied for other MRSA infections. Therefore more useful if (-) swab-> consider discontinuing MRSA coverage in pneumonia (Clin Infect Dis 2017;64;1867)
- **Treatment**: Always check the Vanc MIC! (see Box above)
  - Serious infections (i.e., bacteremia): Vanc (w/ full loading dose) and ID c/s. If persistent bacteremia or MIC ≥2, consider Dapto (NOT in PNA [inactivated by surfactant] or meningitis [doesn't cross BBB]), or add Ceftaroline
  - Mild infections (e.g., PNA, SSSI): Bactrim, Doxycycline, Clindamycin (less sensitive), Linezolid

Vancomycin-resistant Enterococci (VRE)

- **Pathogenesis**: Low virulence, colonizer. E. faecium: often resistant & generally less virulent. E. Faecalis: less resistance.
- **Risks**: multiple prior abx, urinary catheters & indwelling lines; proximity to other VRE infected/colonized patients; long hosp. or nursing home residence; transplant / HIV / DM / ESRD or HD.
- **Clinical Sites of Infection**: UTI (NB: more commonly asymptomatic bacteriuria and rarely causes UTI in normal host; if pt not critically ill, pull catheter first if possible and retest urine); bacteremia (2nd most common CLABSI); intra-abdominal and pelvic infections; endocarditis (esp. if prosthetic valve); meningitis (rare unless immunocompromised or VP shunt)

**Vancomycin-Intermediate and Resistant Infections (VISA/VRSA):**

- **Vanc-susceptible**: ≤2 mcg/mL (though increasing risk of tx failure and mortality once MIC reaches ≥2)
- **Vanc-intermediate (VISA):** 4 to 8 mcg/mL
- **Vanc-resistant (VRSA):** ≥16 mcg/mL

**VRE Treatment (JH Guide)**

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Treatment</th>
</tr>
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</table>
| Invasive infection (e.g., bacteremia, endocarditis) | -Linezolid 600mg Q12h  
-Dapto 8-12mg/kg IV q 24h |
| UTI | -Fosfomycin 300 mg x 1; consider repeat dose on days 4 and 7  
-Doxy 100mg BID |
# Infectious Disease

## Community Acquired Pneumonia (CAP)

- **Definition:** PNA acquired in the community, including patients from nursing homes, dialysis, or with outpt clinic exposure
- **Diagnosis:** New CXR consolid’n (required) AND signs/sx eg fever, cough, leukocytosis, purulent sputum, hypoxemia
  - Elderly at ↑ risk of blunted s/sx but also ↑ prevalence of atelectasis/aspiration
  - Radiographic consolid’n NOT specific for bacterial vs viral PNA; lobar consolid’n can be viral
  - If CXR (-) but clinical suspicion is high → treat and repeat CXR in 24 hrs (PNA may “blossom” after fluid resuscitation and/or time); if still negative → consider chest CT or other dx
- **Triage:** CURB-65 (Confusion, BUN>20, RR>30, BP<90/60, age>65) → Outpt if Score 0-1; Inpt if 2, consider ICU if 3-5; Pneumonia Severity Index (PSI) more comprehensive
- **Micro:** S. pneumoniae (most common in inpts, ICU), H. influenzae, GNRs, S. aureus, Legionella. In inpt PNA, most common pathogens ID’d viruses – rhinovirus, influenza, others (NEJM 2015;358:415)
- **Work-Up (inpatient):**
  - Sputum culture and gram stain (ET aspirate if intubated): adequate sample if >25 PMN/lpf and <10 SEC/lpf
    - NOTE: “abundant squamous cells” or more squamous cells than poly suggests the sample is saliva
  - Blood cultures controversial benefit, positive <20% of inpt PNA, 2/3 of positive cx are S. pneumoniae. Obtain if severe pneumococcal UAT test, pleural effusion (Clin Infect Dis 2007;44:S27)
  - Procalcitonin (PCT): biomarker upregulated in acute respiratory infections from bacterial but not viral causes. PCT-based tx algorithms (consider antibiotics if PCT>0.25 ng/mL, highly suggested if >0.75 ng/mL) associated with ↓ mortality rates, abx exposure (Lancet Infect Dis 2018:18:95). Not validated in immunocompromised pts.
  - S. pneumoniae urine Ag (sens 70%, spec 96%): only positive test in 44% of S. pneumo PNA
  - Legionella urine Ag detects only serogroup 1 (sens 70%, spec 99%); predicted by prior B-lactam use, lack of prior URI, T > 102, myalgias, EtOH, male, GI sx, lack of purulent sputum, lack of pleuritic chest pain

### IDSA/ATS CAP Empiric Treatment (Clin Infect Dis 2007;44:S27)

<table>
<thead>
<tr>
<th>Outpatient</th>
<th>Preferred</th>
<th>Alternative/Other info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>Azithro OR Doxy</td>
<td>NOT for use in U.S. due to high rates of macrolide- and doxy-resistant S. pneumo</td>
</tr>
</tbody>
</table>
| Complicated** | Levofloxacin (750mg) QD OR [β-lactam (Amox/Clav 2g BiD) AND Azithro 500mg QD on Day 1, then 250mg x4d] | **ALL outpatient PNAS in U.S.**
| Inpatient | Preferred | Alternative/Other info |
| Non-ICU | [β-lactam (CTX 1g QD) AND Azithro OR Levofloxacin (750mg) QD]** | Amp/subl can replace CTX |
| ICU | [β-lactam (CTX 1g QD) AND Azithro OR Levofloxacin (750mg) QD]** | In ICU, azithro >> levofloxacin (anti-inflamm. effect); consider add’t agents for drug-resistance (as below) |

*Antibiotics w/in 3 mos, COPD, CKD, CHF, cirrhosis, cancer, DM, alcoholism, immunosuppressed, resistance rates >25%

** CAP START trial revealed that β-lactam monotherapy noninferior to combo β-lactam/macrolide or fluoroquinolone alone, however trial was conducted in areas with lower rates of atypical pathogens (NEJM 2015;372:1312)

### Risk Factors for Drug-Resistant Pathogens in CAP:

- **General:** Hospitalization w/in past 30d; IV abx w/in past 90d
- **PsA:** GNR on gram stain, h/o PsA, bronchiectasis, COPD w/ freq exacerbations req abx/steroids. **Tx:** For normal renal function Cefepime 2g q8h, Ceftazidine 2g q8h, Pip/tazo 4.5 q6h, Meropenem; double coverage usually not necessary
- **MRSA:** GPC clusters on gram stain, recent flu-like illness, necrotizing/cavitation/empyema, + nasal swab, risk factors for colonization (ESRD, IVDU, prior abx [esp. fluoroquinolones]). **Tx:** Vancomycin or Linezolid.
- **Steroids:** Not standard practice, but meta-analysis show reduced mortality, length of hospitalization, mech vent in severe CAP in pts who received glucocorticoids (Cochrane Database Syst Rev 2017:12). Consider in severe CAP (FiO2 requirement >0.5 + at least one of: pH<7.3; Lactate >4; CRP>150) and AVOID in INFLUENZA as steroids might increase mortality. Several dosing strategies exist (e.g., pred 40mg x/4d; IV methylpred 0.5mg/kg BiD x5d)
- **Duration:** 5-7d (atebrile for 48-72h, no O2 requirement, ≤1 vital sign abnormality before stopping); may be extended for more complicated circumstances (e.g., extrapulmonary infection, necrotizing pneumonia, empyema, abscess/cavitation)
  - Convert IV → PO when clinically improving; no need to observe x24h on PO
  - Can utilize procalcitonin to guide course of therapy: repeat PCT on Day 3 and every other day while still on antibiotics; stop antibiotics when PCT<0.25 ng/mL or decrease by >80% from peak if initial PCT>5 ng/mL
- **Response to Therapy:** Tachycardia resolves by 2-3d; fever resolves by 2-4d; hypoxemia resolves by 3-6d
  - **CXR clears by 1mo in 50% (delayed up to 12wks in older pts, pts with lung disease); do not repeat CXR for f/u if clinical improvement (Clin Infect Dis 2007;45:963)
  - If no response to therapy after 72h: consider chest CT (+/- BAL) to evaluate for empyema, abscess, fungal infxn

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Eftitan Akam

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Hospital-Acquired and Ventilator-Associated Pneumonia

**Definitions:**
- **Hospital-Acquired (HAP):** Pneumonia that develops >48 hrs after admission
- **Ventilator-Associated (VAP):** HAP that develops >48 hrs after endotracheal intubation

**Common Microbiology:** Enteric GNRs (*Klebsiella*, *E. coli*), MRSA/MSSA, PsA, *Acinetobacter*

**MDRO Risk Factors:**
- **For MDR pathogens:** IV abx use within 90 days (most important risk factor); high local prevalence (>10%) of MDR GNRs and MRSA; structural lung disease (CF, bronchiectasis)
- **Additional risk factors for MDR VAP:** septic shock/ICU, ARDS, >5 days hospitalization or Renal Replacement Therapy preceding onset

**Workup:** CXR, sputum/blood cx, MRSA swab (see MDRO section regarding interpretation); consider induced sputum, bronch with BAL

**Antibiotic Choices and Empiric Treatment:**
- **HAP/VAP w/o MDRO risk:** 1 antipseudomonal agent (preference for B-lactam)
- **HAP/VAP w/ MDRO risk:** 1 antipseudomonal agent (preference for B-lactam) AND 1 anti-MRSA agent
  - Consider **empiric double PsA coverage** (e.g., 2 antipseudomonal agents (1 B-lactam and 1 Non-B-lactam))
  - IF: hx of MDR PsA, septic shock w/ suspicion for PsA, CF/bronchiectasis, febrile neutropenia + PsA bacteremia
- **Typical empiric regimen at MGH:** Vancomycin + Cefepime
- **MRSA:** Vancomycin IV (trough 15-20) OR Linezolid 600mg IV q12hrs
- **Antipseudomonal agents (B-lactams):** normal renal func Cefepime OR Ceftazidime 2g IV q8h OR Pip/Tazo 4.5g IV q6h OR Meropenem 1g IV q8h (aztreonam 2g IV q8h only if severe PCN allergy [https://id.partners.org/allergy/])
- **Antipseudomonal agents (Non-beta-lactams):** Tobramycin 5-7mg/kg IV x 1 then dose by level OR Levofloxacin 750mg (PsA susceptibility at MGH is 73%) IV QD OR polymyxin B (Call ID)

**Tailoring Therapy:**
- Improvement after 48h or pathogen identification→ Narrow abx/convert to PO/discontinue MRS + PsA coverage if possible. In VAP, if negative tracheal aspirate, consider d/c antibiotics after 72 hours (NPV 94% for VAP)
- No improvement after 48h→ Broaden to cover MDROs (if not currently covering), consider other sites of infection/abscess
- **Duration:** 7d for both HAP/VAP. Can also utilize serial procalcitonin levels (1-3 day turnaround at MGH)→ discontinue abx when <0.25ng/mL [Eur Respir J 2009; 34:1364]

Aspiration Pneumonia:

**Definition:** Pneumonia caused by the excessive entry of secretions, particulate matter, or fluid into airways (NB: ALL pneumonias are secondary to micro-aspiration events; the term ‘aspiration pneumonia’ refers to macro-aspiration events)

**Predisposing Factors:** ↓ consciousness (seizure/overdose), esophageal dysmotility, post-bronchial obstruction, gum dz

**Microbiology:** Classically caused by polymicrobial infections including oral anaerobes (*Peptostreptococcus, Fusobacterium, Bacteroides*), but most common organisms are GNRs and standard CAP/HAP organisms. [Am J Respir CC Med 2003;167:1650]

**Characteristics:** Indolent, putrid sputum, pulmonary necrosis w/ cavitiation/abscess/empyema

**Workup:** CXR, sputum culture (anaerobic respiratory culture not performed at MGH due to low utility)

**Empiric Treatment:**
- **Anaerobic Coverage:** Per IDSA guidelines, anaerobic coverage only recommended in pts w/ loss of consciousness secondary to alcohol/drug overdose or seizure AND concomitant gingival disease or esophageal dysmotility. [Clin Infect Dis 2007;44:S22]
- **First line:** ampicillin-sulbactam (or amox/clavulanate if not severely ill); **alternative:** [CTX + metro] OR clindamycin
- **Duration:** 7d (unless complicated by cavitiation/abscess/empyema)

Aspiration Pneumonitis:

**Definition:** Aspiration of chemical substances into the airways without bacterial infection

**Clinical Manifestations:** Abrupt onset (2hr), low-grade fever, ↑ WBC, hypoxemia, CXR consolidation (RML/RLL upright, RUL supine) → may be indistinguishable from pneumonia in the acute setting!

**Treatment:** If concern for aspiration pneumonia (i.e., bacterial infection), may cover with abx for 48hrs → d/c if no consolidation develops on CXR OR if signs/sx/consolidation resolve rapidly (less likely to be PNA)
Infectious Disease
Viral Respiratory / Head & Neck Infections

Viral Respiratory Infections

- **Epidemiology:**
  - URI: rhinovirus (30-50%), coronavirus (10-15%), influenza (5-15%), parainfluenza (5%), RSV (5%)
  - LRTI (bronchitis, bronchiolitis, PNA): influenza, RSV, parainfluenza, adenovirus (Lancet 2011;377:1264)

- **Presentation:**
  - Risk factors: immunosuppression (T cell defects: HIV, transplant), extremes of age
  - Symptoms: fever, dry cough, myalgias, dyspnea, sore throat, rhinorrhea, malaise, confusion, anorexia, wheezing
  - Labs: leukocytosis or leukopenia (esp. lymphopenia), high CK (influenza)
  - Complications: viral PNA (continued worsening after onset); secondary bacterial PNA (initial improvement followed by worsening after ~7 days → micro: S. pneumo [1st], S. aureus [2nd]), ARDS

- **Diagnosis:**
  - Rapid influenza 50-70% Se, >90% Spe; influenza A/B and RSV PCR >95% Se & Spe (J Clin Micro 2013;51:2421)
    - Se/Spe depends on high quality nasopharynx swab. Can test multiple days if clinical suspicion high; if LRTI consider BAL vs ET aspiration
  - Viral resp panel (adenovirus, parainfluenza, metapneumovirus) → nasopharyngeal swab > induced sputum

- **Treatment (Influenza):**
  - Indications: Hospitalized, severe disease, or risk for complications (>65, SNF, pregnant, immunosuppressed, DM, CHF/CAD, COPD, asthma, BMI>40, neurological disease)
  - Rx: Oseltamivir 75mg BID x5d (dose reduce for CKD; no data to support double dose if severe/ICU (BMJ 2013;346:3039)); initiate within 48h of sx (note: >48h OK if severe disease or hospitalized pt)
  - Ppx: Oseltamivir 75mg daily recommended for all residents of institutional settings during outbreaks (14d)
  - High dose influenza vaccine in adults >65, solid organ transplant recipients (J Infect Dis 2018;217:1718)

Head and Neck Infections


- Organisms: Streptococci (mainly Viridans), Oral anaerobes (Fusobacterium spp., Bacteroides sp).
- Typically from odontogenic or tonsillar infection with spread to adjacent tissue planes.
- Diagnostics: Panorex, CT Neck. IR or ENT for deep cx.
- Rx: B-lactam+ anaerobic agent or B-lactamase inhb. early involvement of ENT, airway monitoring.

- **Ludwig’s Angina:**
  - Definition: Infection involving the submandibular space.
  - Risk factors: Periodontal infections, especially involving 2nd and 3rd molars (70-85% of cases)
  - Symptoms: Fevers, mouth pain, submandibular swelling/erythema, tongue swelling, stiff neck, drooling.
  - Complications: Mandibular osteo, abscesses.

- **Lateral Pharyngeal Space Infections:**
  - Carotid Sheath (IJ, ICA, CN9)
  - Lemierre’s Syndrome: septic thrombophlebitis of IJ
  - Usually with + blood cx’s; pt’s at risk for septic emboli
  - Add enoxaparin for clot management.

- **Deep Neck Space Infections**
  - Definition: Infection, originating from oropharynx involving retropharyngeal, “danger,” and prevertebral spaces
  - Symptoms: fevers, neck pain, chest pain
  - Complications: Mediastinitis (via danger space), vertebral osteo, paravertebral abscess
**Urinary Tract Infections**

### Asymptomatic Bacteriuria
- **Definition:** Bacteriuria without symptoms (>20% of women age >80; 6-15% of men age >75)
- **Treatment:** Bacteriuria or pyuria should NOT be treated in the absence of sx (exception: pregnant woman, s/p renal transplant in first 3-6 months, prophylaxis for invasive urologic procedures) (*Infect Dis Clin NA 2014;28:1*)

### Cystitis (UTI)

**Clinical Features:** frequency, urgency, dysuria (premenopausal); malaise, incontinence, nocturia, suprapubic tenderness (*Infect Dis Clin NA 2014;28:1*)

- **Fever, other sx of systemic illness e.g., chills/rigors, flank pain, CVA tenderness, pelvic or perineal pain (men)?**
  - No **↓**
  - Yes **↓**

### Uncomplicated UTI (JAMA 2014; 312:1677)
- **Diagnosis:** Clinical; UA can be used to confirm; pyuria (>10wbc) has NPV>PPV
  - Women: If dysuria and ↑ frequency with vaginal discharge/irritation, >90% likelihood of UTI. In outpt, UA unnecessary unless immunocomp. or w/ risk factors for compl UTI
  - In outpt, get UCx only if atypical sx, persist 48-72 hr after abx initiated, or recur w/in 3 mos of tx
  - **Nitrites:** only positive with Enterobacteriaceae (convert urinary nitrate to nitrite)
- **Differential Diagnosis:** vaginitis, urethritis, structural abnormality, PID, nephrolithiasis
- **Microbiology:** *E. coli*, Klebs, Proteus, *S. Saprophyticus*. **Enterococc. rarely causes true infxn**

### Complicated UTI
- **Definition:** UTI + systemic s/sx. Uncomp/complication distinction not strict, some guidelines include structural/fnxl GU tract abnormality, DM2, stones, etc.
  - 30% pts w/ UTI and fever are bacteremic (usually older, flank / suprapubic pain, ↑ CRP, ↓ BP) (*JAMA 2018;378:48*)
- **Pyelonephritis is a complicated UTI,** may itself be complicated by perinephric or renal abscesses
  - WBC casts on UA are suggestive of pyelo
- **Microbiology:** same as UTI plus *Serratia, Morganella, Providencia, Pseudomonas, Citrobacter*. Gram-positives still rare. If *S. aureus*, think bacteremia. Increasingly resistant organisms (especially to FQ, TMP/SMX)

### Catheter-associated UTI (CAUTI) (Clin Infect Dis 2010; 50:625)
- **Definition:** leading HCA-infection; requires: (1) signs/sx of UTI with no other identified source of infection; AND (2) urine midstream voided specimen from patient whose catheter was removed w/in previous 48 hours
  - In pts w/ neurogenic bladder and ↓ sensation, other signs of UTI include new onset incontinence, autonomic hyperreflexia, malaise, lethargy, bladder pain (*Urology 2015;6:321*)
- **Prevention:** restrict catheters to pts w/ appropriate indications; remove catheters ASAP; consider short-term straight cath
- **Dx:** don’t screen asymptomatic patients; pyuria, turbidity, odor cannot differentiate asymptomatic bacteriuria from CAUTI
- **Micro:** same as complicated UTI, with addition of *Candida* (see below); can be polymicrobial

### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Empiric Antibiotics</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Uncomplicated UTI</strong></td>
<td>NFT 100mg BID x5d OR T/S* DS BID x 3d OR Fosfomycin 3g x1; alternatives: Oral β-lactam (e.g. Augmentin, Cefpodox) x7d</td>
<td>• Avoid NFT if CrCl&lt;40 and empiric T/S if resistance is &gt;20% (E. coli 28% at MGH)</td>
</tr>
<tr>
<td><strong>Complicated UTI (includes Pyelo)</strong></td>
<td><strong>Outpt:</strong> CPO 500mg BID x 5-7d OR LVO 750mg x 5-7d OR T/S DS BID x 7-10d. Can give 1x IV CTX prior to oral tx.</td>
<td>• Avoid NFT and fosfomycin (poor soft tissue penetration from oral administration)</td>
</tr>
<tr>
<td></td>
<td><strong>Inpt:</strong> CTX OR CEF; Narrow to oral agent if improving. Add Vanc / Linzolid if c/f GPC infxn (e.g., if GPC on urine G/stain). <em>Duration:</em> 5-14d, depending on clinical course and oral agent chosen (5-7d for FQ; 7-10d for T/S; 10-14d for β-lactam). Alternatives: PIT (if PsA); CBPN if c/f ESBL on micro</td>
<td>• Remove (or replace) coated uro devices</td>
</tr>
<tr>
<td></td>
<td><strong>CAUTI</strong> (CTX OR FQ) AND VANC (risk of MRSA) <em>Duration:</em> 7d if improving; 10-14d otherwise</td>
<td>• Low threshold to image to define anatomy</td>
</tr>
<tr>
<td></td>
<td>Alternatives: PIT OR CEF; if c/f ESBL on micro</td>
<td>• Remove catheter ASAP, obtain repeat UA/UCx from new cath PRIOR to abx</td>
</tr>
<tr>
<td><strong>Funguria</strong></td>
<td>FLUC 200-400mg (pyelo) PO QD 14d OR conventional AmB 0.3-0.6 mg/kg QD x1-7d if c/f FLUC-R</td>
<td>• Common colonizers; ONLY tx if sx or neutropenic, before uro procedure</td>
</tr>
<tr>
<td></td>
<td>• If resistant C. alabrata or kruze: use conventional AmB</td>
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</tbody>
</table>


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**KEY:** NFT – nitrofurantoin; T/S – TMP/SMX; CTX – ceftriaxone; FQ – fluoroquinolone; PIT – piperacillin/tazobactam; CEFE – cefepime; CBPN – carbapenem; AMG – aminoglycoside; CPO – ciprofloxacin; LVO – levofloxacin; FLUC – fluconazole; AmB – amphotericin B; R – resistance
Infectious Disease

Skin & Soft Tissue Infections


- Clinical Features: erythema, warmth, tenderness, edema, induration +/- purulence; smooth, poorly demarcated (vs. erysipelas-well demarcated). May have lymphangitis, LAD, vesicles/bullae, fever (20-77%), leukocytosis (34-50%)
- Risk factors: venous stasis, lymphedema, PVD, DM, obesity, IVDU, linea pedis, ulcer, trauma/bite, eczema, XRT
- Differential Diagnosis: (NB: if “bilateral cellulitis,” strongly consider alternative diagnosis)
  - Non-infectious: stasis/contact dermatitis, drug rxn, DVT, eosinophilic cellulitis, lymphedema, vasculitis, gout
  - Infectious: abscess, nec fascitis/gas gangrene, bursitis, osteo, zoster, erythema migrans
- Diagnosis: Clinical. Can use ALT-70 score (shown to reduce abx use) (J Am Acad Derm 2017;76:618; JAMA Derm 2018;154:529)
  - Blood & wound cultures not recommended for typical cellulitis. Obtain if: evidence of systemic toxicity, extensive skin involvement, immunosuppression, special exposures (bites, water), recurrent/persistent cellulitis.
  - Consider ultrasound to assess for presence of abscess
- Microbiology:
  - Purulent (abscess or fluctuance): MRSA (67%) > MSSA (17%) > Strep (5%)
  - Non-purulent: Strep >> S. aureus > aerobic GNRs
  - Specific associations: gas gangrene (myonecrosis) → C. perfringens; dog/cat bite → Capnocytophaga, Pasteurella; human bite/IVDU → Eikenella; water exposure → Aeromonas (freshwater); saltwater → Vibrio vulnificus
- Treatment: Based on 1) purulence and 2) severity. Erythema may worsen before improves; should improve w/ 72h of appropriate antibiotics.

<table>
<thead>
<tr>
<th>Mild</th>
<th>Purulent</th>
<th>Non-purulent*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I&amp;D only</td>
<td>Oral: cephalexin, dicloxacinill, pen VK, amox/clav</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate</th>
<th>(systemic signs of infx or abscess&gt;2cm or abscess w/overlying infx)</th>
<th>I&amp;D + culture + TMP-SMX OR doxycycline</th>
<th>IV: cefazolin, ceftriaxone, pen G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>(systemic signs of infx AND &gt;1 of: HoTN/immunocomp/rapid evolution)</td>
<td>I&amp;D + culture + IV Vanc/IV or linezolid + clinda (for toxin inhibition in TSS)</td>
<td>Vancomycin + CTX + clindamycin (for toxin inhibition in TSS)</td>
</tr>
</tbody>
</table>

  - If non-purulent w/ MRSA risk factors (IVDU, Prev infx/colonization, Abx in prev 8wks, DM, Hosp. in 1yr, athletes, staff, children at daycare, prisoner, military, LTC facilities, MSM): add empiric PO/IV MRSA coverage (CJEM 2009;11:430)
  - Additional coverage: anaerobes (if necrosis, putrid smell, crepitus, certain diabetic infections [see below]); GNRs (cirrhosis w/severe infection, immunocomp, certain diabetic infections [as below]); PsA (neutropenic, trauma, post-op)
  - Duration: 5 days; up to 14 days if delayed signs of improvement. Take pictures and draw margin lines to track progress.

Necrotizing Fasciitis

- Microbiology: Type I (polymicrobial [mixed aerobes/anaerobes]; risk factors include DM, immunosuppression, PVD); Type II (monomicrobial [usually GAS, less often other Strep or Staph, Vibrio, Aeromonas]; associated with TSS); myonecrosis (i.e., gas gangrene; caused by C. perfringens, presents with gas in tissues, severe pain, toxin-mediated shock)
- 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); ↑ CK, lactate, Cr, WBC
- Diagnosis: Early suspicion and involvement of a surgeon for surgical exploration and ID is critical
  - LRINEC score > or = 6 raises high suspicion for nec fasc; 90% Se 95% Sp (Crit Care Med 2004;32:1535)
  - Treatment: urgent surgical debridement + Abx: (Vanc or linezolid) + (pip/tazo or penem) + Clinda for toxin inhibition


- Severity Classification: Mild (superficial ulcer, no involvement of deeper structures, erythema <2 cm); moderate (ulcer with involvement of deeper structures or erythema >2 cm); severe (moderate + systemic signs of infx)
- Initial Evaluation: Cleanse, debride, probe, culture. Check pulses/sensation, ABIs (40% will have PAD), consider XR/MRI
- Diagnosis: Wound culture. Most polymicrobial w/ GPCs>GNRs, anaerobes. For mod-severe infx: add blood cx + ESR/CRP
  - Osteomyelitis: Increased risk if: grossly visible bone/probe to bone, ulcer > 2 cm², ulcer >1-2 weeks, ESR > 70mm/h
  - If able to probe to bone, sens/spec for diabetic osteo is 87%/83%
  - If suspicious for osteo, obtain plain films ± MR ± surgical consult for bone/tissue biopsy ± ID consult
- Treatment: Definitive tx based on deep cx obtained PRIOR to the initiation of abx. Appropriate wound care is critical.
  - Mild: Oral→target GPCs (diclox, cephalexin, amox/clav, levo); use TMP-SMX or doxy for MRSA; 1-2 weeks tx
  - Moderate/Severe IV→target GPCs (vanc, linez, dapto), GNRs* (CTX, levo, Unasyn), anaerobes (Flagyl/clinda); 2-4 wks
  - *Use anti-PsA GNR (cefezpine, pip/tazo) if: severe, immunocomp, neutropenia, water exposure, burn/puncture, nosocom
  - If improved, may deescalate Mod/Severe treatment to highly bioavailable PO regimen to complete course

Jimmy Lam and Theodora Karagounis

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Infectious Disease

Osteomyelitis

Clinical Manifestations:

- **Acute**: dull pain, local tenderness/warmth/erythema/swelling, systemic sx (fevers, rigors)
  - Hip, vertebra, pelvis: often have fewer symptoms, can present as septic arthritis
  - Vertebral: point tenderness, unremitting, usually febrile, pts > 50 (NEJM 2010;362:1022)
- **Chronic**: pain (absent i/s/o neuropathy), erythema, swelling; poorly healing ulcers (J Internal Med 2008;263:99); draining sinus tract is pathognomonic
- **Etiology**: hematog seeding (most common, usually monomicrobial), contiguous spread (polymicrobial), direct inoculation

Diagnostic approach: (JAMA 2008;299:806)

- **Goal**: obtain culture data of causative org. (to avoid long empiric antibx)
- **Physical exam**: probing to bone sufficient for dx in patients w/ DM (83% Sp, 90% PPV) w/o need for further imaging (Clin Infect Dis 2016; 63:944)
- **Blood cx**: often + with hematogenous infxn involving vertebra, clavicle, pubis (always obtain BCxs before starting antibx)
- **Labs**: ESR/CRP, leukocytosis (acute > chronic), PPD/IGRA in pts at risk for TB, Brucella serology in at-risk pts

    **Imaging**:
    - Obtain plain XR 1st, especially in suspected appendicular osteo (normal early in disease, lytic lesions at 2-6wks)
    - MRI: Sn 90%, Sp 82%(Arch Intern Med 2007;167:125); best in DM or if concern for vertebral osteo (Clin Infect Dis 2015:61:e26)
    - CT: if MRI not available; can demonstrate periosteal reaction and cortical and medullary destruction
      - CT & MRI very sens but non-spec; false + if contiguous focus with periosteal reaction, Charcot changes
      - Radionucleide bone scan: very sens, but non-spec (false+ if soft-tissue inflam), option if hardware prevents above
- **Bone biopsy**: gold standard diagnostic test
  - C/s Ortho vs. IR; Ortho > IR if concern for overlying cellulitis to mitigate risk of seeping. If evidence of osteo on imaging or positive probe to bone, bone biopsy positive up to 86% of cases (Clin Infect Dis 2006:42:57)
  - Bone cx may be + even on abx; req 2 specimens: GS/Cx (aerobic, anaerobic, mycobacterial, fungal) + histopath
  - Open bx preferred to FNA (23% correlation [Clin Infect Dis 2009:48:888]). If FNA (-) and suspicion high, repeat bone biopsy. Deep wound cx if bone bx not tenable (73.5% correlation [Diabet Metab Res Rev 2013:29:546])

Treatment:

- **Antibiotics** (consult ID, tx based on culture data, see table)
  - **“Delay empiric tx until bxx”** if pt HD stable, no neurologic compromise, or epidural abscess
  - Can consider addition of Rifampin if hardware + Staph, (Arch Intern Med 2008:168:805); d/w ID
  - Duration: usually ≥6 wks
  - If debridement required, abx start date = date that debrided bone is covered by new soft tissue
  - Consider rechecking ESR/CRP; if elevated at end of abx course, consider further w/u (NB: routine repeat MRI NOT done b/c MRI findings take weeks to months to resolve)
  - If infected bone fully resected (i.e., amputation), may consider shorter course

- **Surgical Debridement**: Indicated if failure to respond to medical therapies, chronic osteomyelitis, complications of pyogenic vertebral osteo (e.g., early signs of cord compression, spinal instability, epidural abscess), or infected prosthesis
  - **Consults**: Ortho (for debridement or bone bx), Neurosurg (vertebral Osteo w/ c/f CNS extension), Plastics (if need for flap), IR (abcess drainage/bone bx), wound nurse (if no surgical service following)
  - **Adjunctive Rx**: Hyperbaric O2 and neg. pressure may be considered if refractory (Am J Med 1996;101:550)
- **Special Cases**:
  - **Sternal**: Post-CT surg +/- mediastinitis (33% morality [J Thor. Card Surg 2006;132:537]); +stenal crepitus.
  - **Mandibular**: Usually contiguous spread of oral flora/odontogenic infxn; cover anaerobes (e.g.Amp-sulbactam)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Dosing (w/ nl Cr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>Nafcillin</td>
<td>2g IV q4h</td>
</tr>
<tr>
<td></td>
<td>Cefazolin</td>
<td>(not if a/w CNS infxn) 1-2g IV q8h</td>
</tr>
<tr>
<td>MRSA</td>
<td>Vancomycin</td>
<td>dose for trough 15-20</td>
</tr>
<tr>
<td>CoNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCN-S Strep</td>
<td>Penicillin G</td>
<td>4 million U IV q4h</td>
</tr>
<tr>
<td>PCN-R Strep</td>
<td>Ceftriaxone</td>
<td>2g q24h</td>
</tr>
<tr>
<td>GNR</td>
<td>Ciprofloxacin</td>
<td>500 PO BID, 750 if PsA</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>2g IV q12h, q8h if PsA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Dosing (w/ nl Cr)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer area &gt; 2 cm</td>
<td>7.2 (1.1-49)</td>
</tr>
<tr>
<td>+“probe-to-bone” test</td>
<td>6.4 (3.6-11)</td>
</tr>
<tr>
<td>ESR&gt; 70 mm/h</td>
<td>11 (1.6-79)</td>
</tr>
<tr>
<td>Abnormal plain X-ray</td>
<td>2.3 (1.6-3.3)</td>
</tr>
<tr>
<td>MRI c/w osteo</td>
<td>3.8 (2.5-5.8)</td>
</tr>
<tr>
<td>Normal MRI</td>
<td>0.14 (0.08-0.26)</td>
</tr>
</tbody>
</table>
Infectious Disease

Bacteremia & Endocarditis

**Bacteremia:**

Evaluation: (JAMA 2012;308:502)

- **Signs:** Rigors - severity correlates w/ risk of bacteremia (Amer J Med 2005;118:1417.e1); SIRS sensitive but not specific
- **Source:** Lines, procedures, endocarditis, PNA, UTI, osteomyelitis/septic arthritis, soft tissue infection, abscesses, meningitis
- **Blood cx:** Obtain prior to initiation of antibiotics; 2 sets minimum, ideally 3 different peripheral venipunctures over 1 hr (NOT from port or IV cath at time of insertion); draw from central line if cf catheter related infection (criteria: catheter cfu’s 3X peripheral blood OR cath growth 2h before peripheral) (CID 2009;49:1)
- **If known bacteremia, daily surveillance blood cultures until 48h of negative cultures. Not necessary for GNRs 2/2 high FP rate** (CID 2017;65:1776)
- **TTE/TEE for Staph aureus and Staph lugdunensis. Consider TTE for high grade Strep spp. No need for routine echo for GNRs.**

**Empiric Management:**

- **GP cocci/clusters: Vancomycin**
- **GPRs:** Diverse resistance patterns; **Call ID on call.** Empiric regimen will depend on Gram stain and RFs
  - More likely true infection in immunocomp. hosts, multiple bottvles, indwelling catheters or assoc. with other GPR infections [e.g., Erysipelothrix (STTI), Actinomycosis (H+H infxn, neutropenia/GVHD (Clostridia spp.))
- **GN:** CTX (community-acquired) or Cef (if prior MDRO)
- **Other Considerations:** Anaerobes (intra-abdominal, empyema, obstruction, cavitition) → Add Metronidazole or substitute Pip/Tazo;
  - **Candida** → micafungin + ID c/s; Catheter-associated generally remove line except in long-term lines; discuss w/ID (CID 2009;49:1)

**Endocarditis:**

- **Etiology:** Point of entry, cutaneous (40%), oral (29%), GI (23%)
- **Diagnosis:** Duke criteria → 2 maj OR 1 maj + 3 min OR 5 min
  - ECHO (J Am Soc Echo 2017;20:639) TTE Sn 70% (native) & 50% (prosthetic) w/ Sp 90% (both); TEE Sn 96% (native) & 92% (prosthetic) w/ Sp 90%
- **Monitoring:** Repeat BCx q24h until sterile; serial ECGs
- **Microbiology:** Native Valve: Strep, CoNS/GNR/Enterococcus (esp. >60yo)/Cx neg; Prosthetic Valve (>12 mos post-op): CoNS, Staph, GNR/Enterococcus/Fungi; Prosthetic Valve (>12 mos post-op) similar to NVE (w/ more CoNS)
- **Indications for Surgical Consideration:** L-sided: HF cardiac shock (only emergent indication), fungal/MDRO, heart block, abscess; prosthetic valve dehiscence, recurrent emboli, +BCx after 5-7 days of therapy, vegetations>10 mm; R-sided: RH failure, recurrent PEs, TV veg>20 mm, fungi or MDR infection (Circulation 2015; 132:1435).

**Endocarditis Antibiotic Regimens** (Circulation 2015; 132:1435, EHJ 2015;36:3075)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Native Valve (PVE)</th>
<th>Prosthetic Valve (PVE)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptococcus</strong> such as VGS (e.g., mitis, mutans, argininosus, etc.); S. bovis (aw colon cancer); Gemella spp.; Abiotrophia (treat as ↑ M/C)</td>
<td>If PCN MIC&lt;0.12; PCN 2-3 MU q4h OR CTX 2g q4h OR vanc 4 wks</td>
<td>PCN 4 MU q4h OR CTX 2g q24h AND Gent 1 mg/kg q8h 4 wks</td>
<td>-For low/intermed PCN MIC, 2 wks regimens adding gent 3 mg/kg daily single dose to β-lactam available. -For all regimens with q8h gent, target peak 3.3, trough &lt;1</td>
</tr>
<tr>
<td><strong>Staphylococcus</strong> (S. aureus, CoNS – often methicillin-resistant)</td>
<td>MRSA: Vanc (trough 15-20) OR Dapt (8-10 mg/kg q24h) 6 wks</td>
<td>Early surgical consult</td>
<td>-Do not use cefazolin for CNS involvement due to ↓ penetration -S. lugdunensis is virulent and should be treated like S. aureus +BCx after 5-7 days of therapy, vegetations&gt;10 mm</td>
</tr>
<tr>
<td><strong>Enterococcus</strong> (E. faecalis, E. faecium)</td>
<td>Amp 2g q4h OR Vanc AND Gent 3 mg/kg/d 4-6 wks</td>
<td>Early surgical consult</td>
<td>-Same tx as for NVE</td>
</tr>
<tr>
<td><strong>Gram-neg (HACEKs mostly, PsA, other GNRs possible)</strong></td>
<td>HACEK: CTX 2g q24h OR Amp 2g q4h</td>
<td>Early surgical consult</td>
<td>-Same tx as for NVE -Rare etiology, minimal data to firmly direct treatment modalities</td>
</tr>
<tr>
<td><strong>Fungi</strong> (Candida, Aspergillus)</td>
<td>Liposomal Ampho B 3-5 mg/kg/d followed by lifelong suppressive therapy w/ azole</td>
<td>Early surgical consult</td>
<td>-Risk factors: TPN, lines, PPM / ICD, prophylaxis, IVDU -Ophth c/s for candidemia</td>
</tr>
</tbody>
</table>

Justin Belk 112
Infectious Disease

Meningitis & Encephalitis

Bacterial Meningitis

Clinical Features

- **History:** 95% have ≥2 of: fever, ruchal rigidity, AMS, and HA. Lethargy, hypothermia may be common in elderly. Abdominal pain, peritonitis can be seen in those with VP shunts (CID 2017:64:701)
- **Exam:** most findings more specific than sensitive, e.g., neck stiffness (30-48% Se, 68-71% Sp); Kernig's sign (5-11% Se, 95% Sp); Brudzinski's sign (5-9% Se, 95% Sp); Jolt sign [worsening headache with horizontal rotation of the head] (64% Se, 43% Sp) (Am J Emerg Med 2013; 31:1601). Meningococemia associated with petechial rash, palpable purpura.

Diagnosis (CID 2004:39:1267)

- Blood cultures STAT; draw blood cultures **BEFORE** antibiotics, but **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 neurological deficit
  - Obtain opening pressure with simple column manometer (nl 200mm H2O; mean 350mm H2O in bacterial meningitis)
  - For CSF analysis/interpretation, see "Lumbar Puncture" section in "Procedures"
  - Repeat LP if no clinical improvement after 48 hours of appropriate antibiotics


<table>
<thead>
<tr>
<th>Community</th>
<th>Adults 18-34</th>
<th>Adults 35-49</th>
<th>Adults &gt;50</th>
<th>Nosocomial (intracranial procedure, &gt;48 hrs in hospital, head trauma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae (50%)</td>
<td>S. pneumoniae (75%)</td>
<td>S. pneumoniae (76%)</td>
<td>S. pneumoniae (76%)</td>
<td>Gram neg bacilli (40%)</td>
</tr>
</tbody>
</table>
| N. meningitidis (33%) | N. meningitidis (10%) | GBS (5%) | GBS (5%) | S. aureus (10%)
| H. influenzae (7%) | H. influenzae (6%) | Listeria (5%) | Listeria (3%) | Coag neg Staph (10%)
| Listeria (2%) | Listeria (3%) | Listeria (3%) | Listeria (3%) | P. acnes takes 10 days to grow! |

Empiric Treatment (Lancet 2012:380:1693) Vancomycin is added to regimen due to high S. pneumoniae resistance patterns

<table>
<thead>
<tr>
<th>Adults &lt; 50</th>
<th>Adults &gt; 50</th>
<th>Immunocompromised</th>
<th>Nosocomial</th>
<th>SEVERE β-lactam allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanc (tough 15-20) + CTX 2g q12h (consider acyclovir)</td>
<td>Vanc (tough 15-20) + CTX 2g q12h + Ampicillin 2g q4h</td>
<td>Vanc (tough 15-20) + [Cefepime 2g q8h OR Meropenem 2g q8h] + Ampicillin 2g q4h (no Amp if on Mero)</td>
<td>Vanc (tough 15-20) + [Cefepime 2g q8h OR Cefazidime 2g q8h OR Meropenem 2g q8h]</td>
<td>Vanc (tough 15-20) + Meropenem 2g q8h OR Moxifloxacin 400mg QD</td>
</tr>
<tr>
<td>(consider acyclovir)</td>
<td>(consider fungal &amp; viral)</td>
<td>(consider fungal &amp; viral)</td>
<td>(consider fungal &amp; viral)</td>
<td>(If &gt;50 or immune compromise for Listeria: Bactrim 5mg/kg IV QD qv q6-12h) if not on Meropenem</td>
</tr>
</tbody>
</table>

- **Duration:** N meningitidis/H flu (7d); S. pneumo (14d); Listeria (2-4 wks if immunocompetent; 4-8 wks if immunocompromised)
- **Dexamethasone:** greatest benefit in suspected or confirmed pneumococcal meningitis w/ GCS 8-11 (↓ mortality, hearing loss, and short-term neuro sequelae in high-income countries. 0.15 mg/kg q6h x 4d; start prior or w/ 1st dose of abx but do not delay abx.
- **CSF Shunts:** Consult Neurosurgery for assistance with mgmt and/or shunt removal (CID 2017:64:701)

Aseptic Meningitis (meningeal inflammation with negative bacterial cultures)

- **Etiology:** Infectious: partially treated endocarditis (most common cause), enteroviruses, HACEK orgs (NB: usually NOT culture negative!), HSV, VZV, partially tx’d bacterial meningitis (usually days-wks of b), any stage of syphilis, Lyme, leptospirosis, mumps, nocardia, TB, fungal (Cryptococcus), brain abscess; Non-infectious: autoimmune (Behcets, Sarcoid, SLE, SJS), neoplastic (leukemia, lymphoma), drugs (NSAIDs, antimicrobials, IV/G)
- **Clinical Presentation:** Similar to bacterial, usually less toxic, LP: lymphocytic pleocytosis
- **Treatment:** if concern for encephalitis (HSV, VZV) → acyclovir 10 mg/kg IV q8h; otherwise tx is supportive. If suspect TB, call ID consult for consideration of quadruple therapy with INH, RIF, PZA and 4th agent (FQ or Aminoglycoside) (Tuberculosis 2010:90:279)

Fungal Meningitis

- **Causes:** Primary (immunocompetent pts): Cryptococcus, blastomyces, histoplasma, coccidioides, and other dimorphic fungi; Secondary (immunocompromised pts): Candida, aspergillus, other molds
- **Diagnosis:** Submit CSF for acid-fast stain, India ink preparation, and cryptococcal antigen. Attempt to obtain large volumes (up to 40-50 mL) for culture.
- **Cryptococcal Meningitis Treatment:** amphi B IV 3-4 mg/kg qd + fluocytosine PO 25mg/kg q6h (CID 2010:50:291)

Encephalitis (CID 2008:47:303)

- **Etiology:** Infectious: HSV, VZV, arbo (West Nile, WEE/EEE, St Louis, Japanese), enteroviruses, HIV, CMV (extremely rare), JC, echo, adenov, influenza; Non-infectious: Post-infectious demyelination (ADEM), autoimmune, paraneoplastic (anti-Hu [SCLC]), anti-Ma2 [testicular], anti-CRMP5 [SCLC/thymoma], anti-NMDA receptor [ovarian teratoma, idiopathic]
- **Presentation:** AMS with focal neuro deficits or seizures. Differentiating Sx: presence (meningitis) or absence (encephalitis) of normal brain function
- **Diagnosis:** Submit CSF for HSV and VZV PCR; other viruses less common, only send if clinical suspicion high (West Nile IgM, JC, CMV/EBV [extremely rare]); consider MRI (HSV temporal lobe enhancement, W. Nile basal ganglia/thalamic foci); EEG
- **If sx recur after Rx, consider viral relapse vs. autoimmune encephalitis as high rates of autoimmune disease wks later (Lancet Neuro 2018:17:760)***
- **Treatment:** HSV, VZV → acyclovir 10 mg/kg IV q8h; otherwise supportive care
Infectious Disease

C. Difficile Infection

General Information

Risk factors:

Antibiotics within last 3 months. All antibiotics have been associated with CDI, including 3rd/4th gen cephs, fluoroquinolones, carbapenems and clindamycin. Receipt of abx by pt previously in same bed and ward abx prescribing patterns also weakly associated. ↑ age, CKD, IBD, chemo/immunocompro. ± PPI/H2RA.

Pathogenesis: fecal-oral, colonized host; most often infection requires both acquisition of C. diff plus loss of gut microbial abundance/diversity (i.e., due to abx). Symptoms are toxin-mediated: toxin A (enterotoxic) & toxin B (cytotoxic).

Community-acquired CDI: 33% of new cases; p/w diarrhea w/o traditional RFs (abx, ↑ age).

Clinical Manifestations

- Features: loose/watery diarrhea (+/- mucous/occult blood); fever, abd pain, isolated ↑↑ WBC; ileus in severe infection

- Complications: fulminant colitis (65% mortal), ileus (<1% pts), toxic megacolon, perf, protein-losing enteropathy, AKI

Diagnosis

- Glutamate dehydrogenase antigen produced by all c.diff strains (toxigenic &non-toxigenic)

- Toxin A/B EIA: more specific to toxin producing strains (poor sensitivity)

- NAAT/PCR toxin gene: can be + even in the absence of active infection (strain may have toxin gene but not necessarily produce the toxin) Open forum ID 2014

MGH protocol: GDH EIA &toxin A/B assay first. If both positive = positive test. If both negative = negative test. If discordant results but high clinical suspicion for active C. difficile, call micro lab to request PCR testing. (NB: discordant results can be 2/2 asymptomatic (non-toxin producing) colonization)

- DO NOT retest within 1-2 weeks without significant clinical change.

- DO NOT test for “cure”. Studies have shown that toxin A+B EIA may remain positive for a long as 30 days in patients who have resolution of symptoms. Am J Gastroenterol2013; 108:478

- Consider early CT A/P if suspected C. diff w/ ileus or if concern for complications. Flex sig used in rare cases.

Treatment (MGH ID Recs, updated IDSA guidelines)

**Initial Episode:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe</td>
<td>WBC &lt; 15 AND Cr&lt;1.5</td>
<td>-Vanc 125 mg PO q6h or Fidaxomicin’ 200 BID. Di/c cholestyramine if using (binds vanc) -Metronidazole no longer first-line (due to ↑↑ resistance) -Stop antiperistaltics and all non-essential antibiotics</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC&gt;15 OR Cr&gt;1.5</td>
<td>As above</td>
</tr>
<tr>
<td>Fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>-Vanc 500 mg PO q6h and metronidazole 500 mg IV q8h - If ileus: consider adding Vanc PR 500mg in 100cc retention enema Q6H) -Obtain imaging, ID and surgical cs</td>
</tr>
</tbody>
</table>

Duration: 10d for non-fulminant infections; If concurrent abx use, treat CDI through abx course plus 7-14d after abx completion; PO vanc preferred for continuation once colitis resolves


Recurrent: Occurs in 25% of pts after 1st episode w/in 30d

- 1st recurrence: Tapered and pulsed PO Vanc regimen for 6-8 wks OR fidaxomicin 200mg BID x10d if Vanc used for initial episode

- 2nd recurrence (40-60% pts after 1st recur): Tapered and pulsed vanc regimen for 6-8 wks OR 125mg PO Vanc x10d followed by Rifaximin 400mg TID x20d

- 3rd recurrence: Evaluate for fecal microbiota transplant (FMT); improves outcomes compared to 14d PO Vanc. Can also trial regimens used to tx 2nd recurrence (as above). NEJM 2013;368:407 BMC Med 2016;14:134

Other Considerations:

- PPX: PO vanc 125 mg BID lowers risk of recurrence from 27% to 4%; consider for pts needing abx with hx of fulminant/recurrent CDI Clin Infect Dis 2016; 63:651

- Probiotics: Administration around first dose of abx reduces risk of CDI by >50% with no significant adverse effects (based on systemic review, not yet in guidelines) Gastroent 2017;152:1889

- Bezlotoxumab: Promising new option; decreased recurrence compared to placebo when added to standard of care

- FMT: obtain ID consult for initiation of FMT if refractory C. diff despite treatment (>2 recurrences)
Invasive Fungal Infections

Diagnostic Testing Summary:
Risk Factors: heme malignancy, HSCT >> solid organ transplant >> patients on biologic therapies

Fungal Markers:
- 1,3-β-D Glucan (BDG) (Clin Infect Dis 2011;52:750): Cell wall polysaccharide, detects Candida, Aspergillus, Pneumocystis, Fusarium, Trichosporon, Histo, Coccidio; CANNOT detect Mucor, Rhizopus, Blasto; Crypto; Sens 77%, Spec 86% w/ cut-off 80; false- w/ IVIG, albumin, HD
- Galactomannan (GM) (Cochrane Database Syst Rev 2015;CD007384): Aspergillus cell wall component, detect Aspergillus; Sens 65-80% for serum test (BAL 90-95%), Spec 88%. False + w/ some TPN formulations. Can be used serially to monitor tx in pts.
- Histo urine/serum Ag: Sens 90% urine Ag if disseminated (serum Ag Sens 80%); Spec limited by cross-reactivity
- Crypto Ag: serum Ag Sens & Spec > 90% if disseminated, less so for pulmonary dissemination
- Blastomyces: urine > serum Ag, high Sens, but modest Spec due to cross-reactivity

Culture: Candida grows in blood/urine cx but decreased Sens if deep tissue infxn; if high off Coccidio, alert lab (biohazard)

Antibody Detection: Clinically most useful if testing for Coccidio

Treatment Summary: x indicates activity, shading indicates 1st line Tx

<table>
<thead>
<tr>
<th>C. glabrata &amp; kruusei</th>
<th>C. albicans</th>
<th>Crypto</th>
<th>Endemic</th>
<th>Aspergillus</th>
<th>Mucor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
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</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td>x</td>
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<tr>
<td>Posaconazole</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Isavuconazole*</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Micafungin</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td>x***</td>
</tr>
<tr>
<td>Ampho B</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

*Only approved for Invasive Aspergillus/Mucor. **91% of MGH glabrata fluc-S. ***vori + mica not superior to vort alone

Pathogen-Specific Information:

Invasive Opportunistic Fungi: Strongly recommend ID consult for most of these infections

- Candidal/yeast (risk factors: neutropenia, immunocompromised, TPN, IVDU, CVC, prior abdominal surgery)
  - Spectrum of illness: sepsis (25% mortality), macronodular skin lesions (10%), endophthalmitis, endocarditis, osteo
  - Diagnostics: blood cultures (Candidemia never contaminant in blood), obtain optho exam, TTE, & ID consult
  - Treatment: Micafungin 1st line/empiric, transition to fluc/if albicans, high dose fluc/vori if glabrata/krusei (or AmphoB for resistant strains);
    - Duration: 2 weeks after 1st neg cx and no dissemination in candidemia, longer for deep-seated infxn
  - Source: Non-neutropenic: lines most likely source (remove early); neutropenic: GI most likely.
  - Prophylaxis: fluconazole, posaconazole or micafungin (for SOT, SCT, neutropenic)

- Cryptococcus/yeast (RFs: immunocompromised, liver dz, HIV, but can occur in immunocompetent) (Clin Infect Dis 2010;50:291)
  - Spectrum of illness: meningitis, pulmonary, cutaneous nodules, liver abscesses
  - Diagnostics: Serum/CSF CrAg, LP/CSF OP <20, L-glucose, TTP, lymphs, +Hind ink
  - Treatment: amphoB + flucytosine (x2 wks), followed by fluconazole (≥8 wks), serial LPS if OP>25 or symptoms of ↑ICP
  - Prophylaxis: typically not recommended

- Pneumocystis/yeast (risk factors: HIV with CD4 <200, steroids equiv to pred 20 mg x4 wks)
  - Spectrum of illness: Pulm symptom onset over days/weeks, PTX, hypoxia out of proportion to CXR (BL diffuse GGO)
  - Diagnostics: LDH >500 (sens not spec), BAL > induced sputum for silver stain, 1,3-BDG (Eur J Clin Microbiol Infect Dis 2014;33:1173)
  - Treatment: TMP/SMX with steroids (if A-a > 35, PaO2 < 70); Alternatives: atovaquone or pentamidine; Duration: 21 days
  - Prophylaxis: TMP/SMX (1 SS qD or 1 DS MWF), atovaquone or dapsone (see UpToDate for ppx criteria)

- Aspergillus/mold (risk factors: immunocompromised esp neutropenia/stereoids/transplant, COPD with prolonged IUCA stay)
  - Spectrum of illness: invasive pulm w/ hemoptysis, PTX, aspergillosis, sinustis, CNS, endophthalmitis
  - Diagnostics: CT with halo sign, BAL/sputum culture, 1,3-BDG (not spec), GM (spec, can trend in tx, BAL > sputum)
  - Treatment: vori (requires monitoring of drug levels and drug-drug int) or isavuconazole,
    - Duration: Pulm: 6-12 weeks minimum
  - Prophylaxis: consider posaconazole in grade III-IV GVHD (NEJM 2007;356:348), vori in lung transplant w/ IVIG aspergillus.

- Mucor/mold (risk factors: DKA, iron overload, heme malig, prolonged neutropenia, immunocomp.)(Semin Respir Crit Care Med 2015;36:692)
  - Spectrum of illness: rhino/orbital/cerebral invasion, pulmonary, GI, renal, black eschars over ulcers, rapidly progressive
  - Diagnostics: culture, wet prep (non-septating hyphae with wide-angle branches), CT with reverse halo sign
  - Treatment: DEBRIDEMENT, AmphoB, consider posaconazole or isavuconazole (for salvage therapy or if renal disease)

Endemic Fungi:

- Histoplasmosis (Endemic areas: Houston, OH/MS river valleys, Central America, Asia, Africa) (Clin Infect Dis 2007;45:807)
  - Spectrum of illness: PNA, meningitis, mediastinal disease, disseminated disease.
  - Diagnostics: Ag from urine/serum/BAL, CX, note chest imaging may appear similar to sarroid
  - Treatment: Itraconazole (mild-mod) or amphot B (severe), followed by Itraconazole, Duration: 6-12 weeks
  - Prophylaxis: for both Histo and Biasto (below), consider itraconazole ppx for HIV+ with CD4 <150 in hyperendemic areas

- Blastomycosis (Endemic areas: OH/MSM river valleys)
  - Spectrum of illness: fever, PNA, ARDS in severe, ulcerated skin lesions, prostatilis, CNS
  - Diagnostics: wet prep (broad-based, budding yeast), culture, urine > serum Ag, never colonizer
  - Treatment: Itraconazole (mild-mod) or amphot B (severe), followed by Itraconazole, Duration: 6-12 mos

- Cocccidiomycosis (Endemic areas: SW and S US)
  - Spectrum of illness: fever, cough, rash, HA, eosinophilia, meningitis, osteo.
  - Diagnostics: serologies, cx, sphenules on bx/aspirate
  - Treatment: Fluconazole or Itraconazole, consider amphoB if severe; Duration: 3-12 mos
  - Prophylaxis: fluconazole for 1° ppx ONLY for transplant recipients in endemic areas, not in HIV; use fluconazole for 2° ppx
Infectious Disease

Tuberculosis

Epidemiology: 1 in 4 infected worldwide; US incidence 2.8/100,000 persons; 5.6% HIV coinfection; 4% MDR (CDC MMWR TB US 2017)

Risk Factors: Acquisition: travel hx to/from high-prevalence area, homelessness or incarceration, PWID, health care work, racial/ethnic minority; Reactivation: risk is 5% in first 2 years and 5%-10% over lifetime, but higher if pt has >1 of the following: HIV+, immunosuppress, CKD (esp. HD), DM, cancer, transplant, TNFα inhibitors, silicosis, malabsorption malnutrition, tobacco, ET(h) (NEJM 2011;364:1441)

Screening for Latent TB: Decision to test based on likelihood of exposure + likelihood of progression to active disease. IGRA preferred (Quant-GOLD test of choice at MGH); TST acceptable (NB: only 60% spec in pts who received BCG vaccine). Both IGRA and TST are 80-90% sens and >95% spec in immunocompetent hosts. ↓ sens in immunocompromised pts. Neither test rules in/out active TB and they can be discordant ~30% of the time. If + test but no risk factors, repeat either IGRA or TST prior to treatment. (Clin Infect Dis 2017;64:111)

Clinical Manifestations:
- Primary TB: fever, chest pain, cough, arthralgias. CXR often normal or (+) hilar LAD
- Reactivation TB: fever, cough, hemoptysis, night sweats, weight loss; CXR often involves posterior/upper lobe or superior aspect of lower lobe, or cavitation [seen in 1/3 of pts, a/w ↑ org. burden → ↑ infectious, AFB+]: more common than primary TB

Diagnostics for Active Pulmonary and Extrapulmonary TB (J Clin Microbiol 2007;45:4064; Lancet 2007;369:9578)

<table>
<thead>
<tr>
<th>Site of Infxn</th>
<th>Diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td>Send expectorated or induced sputum for AFB smear and culture x3 ≥8hrs apart (get NAAT/PCR on one of the specimens); smear may be - if burden is low. ~20% smear negative (HIV-), ~60% smear negative (HIV+)</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Send brushings, washings, BAL, sputum for AFB smear, NAAT/PCR and culture; +/- transbronchial biopsy. Obtain post-bronch induced sputum to increase yield.</td>
</tr>
<tr>
<td>Ascites or pleural fluid</td>
<td>Adenosine Deaminase (ADA): if &gt;39 units/L → high sens/spec; Free IFN-gamma (if elevated, high sens/spec); AFB smear, NAAT/PCR, and culture (poor sensitivity, helpful if positive)</td>
</tr>
<tr>
<td>CSF</td>
<td>At least 3 large vac (10-15cc) serial LPs if possible (increases dx yield). Cell counts w/ ↓ glucose, ↑ protein, lymphocyte predominance; elev ADA useful adjunct. Send smear, Cx, and NAAT</td>
</tr>
<tr>
<td>Wound/Tissue</td>
<td>AFB-positive staining and caseating granulomas; if cytopenic, consider bone marrow biopsy</td>
</tr>
<tr>
<td>Urine</td>
<td>Classically sterile pyuria; send first AM void (large vol -50cc for culture x 3 days to improve yield</td>
</tr>
<tr>
<td>Blood</td>
<td>Must send mycobacterial cultures for AFB (isolators)</td>
</tr>
</tbody>
</table>

Patient Isolation: clinical decision based on likelihood of active TB
- When: cough, dyspnea, or hemoptysis + >1 risk factor (HIV+, foreign born, substance use disorder, homeless, recent incarceration, prior TB or exposure); first obtain CXR; if CXR normal (and HIV- or CD4>200), TB less likely. If CXR abnormal/equivocal (or HIV+ and CD4<200), maintain isolation and obtain 3 sputum samples for AFB smear and mycobacterial culture as above. Consider ID c/s.
- Discontinue: if alt dx OR AFB smear neg x 3 with very low suspicion OR on TB tx x 2wks + AFB smear neg x 3 + clinical improvement

Approach to Treatment: (Clin Infect Dis 2016;63:e147; NEJM 2015;373:2149)
- Prior to Starting Treatment:
  - General: check baseline LFTs/Cr, visual acuity/color discrimination, screen for HIV, Hep A/B/C, CM, ETOH use, pregnancy
  - Before treating latent TB: need to rule out active TB (obtain relevant history, CXR)
  - Before treating active TB: obtain ID consult, send TB for drug sensitivity testing
- Treatment Regimens:
  - Latent TB: INH 5mg/kg daily (max 300mg) + B6 for 6-9mo, OR Rif 10mg/kg daily (max 600mg) for 4mo, OR INH + Rifapentine weekly for 3mo (requires DOT)
  - Active TB: INH + Rif + pyrazinamide (PZA) + ethambutol (EMB) daily for 2 mo, followed by INH + Rif for 4 mo
  - Quinolones: 1st line tx with MDR-TB, so avoid in bacterial PNA if suspicious of active TB (will ↓ diagnostic yield and ↑ 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 for 12-24 month tx course. 80% mortality
- HIV co-infection: if CD4<50, start ART within 2 weeks after starting TB therapy. If CD4>50 with severe clinical disease, start in 2 weeks, and if CD4>50 and absence of severe clinical disease, may start within 8 weeks to reduce risk of IRIS. In TB meningitis, consider deferring ART initiation to 8 weeks.
- Extrapulmonary TB: highly variable presentations, variable multi-drug regimen, duration depends on site of infection & response. Add glucocorticoids for TB meningitis for 25% RR reduction in mortality (Cochrane Sys Rev 2016;4:1-64) may also consider in TB pericarditis
- 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)

Rebecca Abelman 116
Infectious Disease

HIV/AIDS & Opportunistic Infections

Definition and Clinical Manifestations:
- Acute HIV: mono-like syndrome → rash, LAD, fever, oral ulcers, pharyngitis, myalgias, diarrhea; presents 3-6 wks after infection
- AIDS: HIV+ with: CD4 count <200 or CD4 T-cell <14% of total lymphs or AIDS defining illness

HIV Screening and Diagnostics:
- SCREEN ALL 13-64Y ONCE, every pregnancy; risk-based: at least annually in IVDU, CSW, MSM >1 partner since last test, partners of all high-risk pts, another STI; In MA: opt out verbal consent (“We’ll be conducting a number of tests, including for HIV”)
- 4th gen combined HIV 1/2 Ab/p24 Ag assay: mean detection limit @ ≥15d (5d sooner than 3rd gen) (STD 2017:44:739)
- HIV RNA PCR/viral load (VL): mean detection limit @ ≥12d, high sensitivity but slow; expensive, used for: (1) confirm for acute HIV (Ab/Ag testing are negative early in disease course); (2) confirmation of HIV diagnosis; (3) viral load

PrEP (Pre-Exp Ppx): sero-discordant couples w/ HIV+ partner on ARVs < 6mos, CSW, high-risk IVDU/MSM/ heterosexuals, recent STD.

- Regimen: TDF/FTC (Truvada) QD reduces risk (40-75%, >95% w/excellent adherence), d/c if when risk is no longer present. HIV testing and STI testing while on therapy; test for HBV prior to initiation
- If the partner of the patient is HIV positive but has an undetectable VL, risk of HIV transmission is near 0! (JAMA 2016;316:171)

nPEP (Non-Occupational Post-Exp Ppx): persons presenting at ≤72hrs after non-occupational high-risk exposure from HIV source; case-by-case decision if HIV status of source unknown; test w/ HIV AbAg at baseline & test for STIs, HBV, HCV.

- Regimen: TDF/FTC (Truvada) + [raltegravir or dolutegravir] x28d; if ≥1 course nPEP in last year, consider PrEP

Basic Evaluation for Newly Diagnosed HIV/AIDS Patients:
- CD4 count, VL, genotyping/resistance testing, CBC w/diff, BMP, U/A, LFTs, lipase, A1c/FLP, Hep A/B/C, HCG, cervical and/or anal pap, RPR, GC/CT, PPP or IGRA; CMV, VZV, toxo, mycobacterial BCx if CD4 < 100, dilated eye exam if CD4 < 50
- Initiate ARVs early through referral (p36222) at all CD4 levels to decrease mortality (NEJM 2015;373:795) In many cases, ART can be initiated on site, even prior to genotype return, even in high-risk patients (AIDS 2018:32:17) Make sure ID is involved in this decision.

Treatment for ARV-Naïve Patients:
- 1st line: 2 NRTI “backbone” (typically TAF/FTC or TDF/FTC [Truvada]) + 1 from different class, typically integrase inhibitor
- If patient is on ART: determine regimen & adherence; typically continue ARVs (interruptions can ↑ disease progression)
  - If must hold ARVs because of significant non-adherence or recent severe adverse reaction, hold all ARVs and consult ID
  - Beware of drug-drug interactions, particularly with boosted PIs (e.g. PPIs, check http://arv.ucsf.edu/insite/?page=ar-00-02)
- If patient not yet on ART: prioritize OI tx, ppx, consult ID for help on early inpt vs outpt initiation of ART
- IRIS: worsening sx of underlying infx (TB, MAC, CMV, others) 1-3 mos post-ART initiation, high risk if low CD4 count
  - Nevertheless, early ARV init safe after OI dx, except in crypto meningitis (PLoS ONE 2009;4:e5575)

Opportunistic Infections

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Prophylaxis</th>
<th>Criteria for D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza, HAV, HBV, HPV, VZV, S.pneumo, TB</td>
<td>Vax: Flu; HAV, HBV, HPV, PCV 13, PPSV23 after 8 wks; no live vax w/ CD4&lt;200; latent TB: INH/B6 x 3mo</td>
<td>None</td>
</tr>
<tr>
<td>Pneumocystis jiroveci (or hx of thrush)</td>
<td>TMP-SMX DS QD (preferred) or 1 SS QDdapson 50mg QD or atovaquone 1500mg QD</td>
<td>CD4 &gt;200 x 3mo</td>
</tr>
<tr>
<td>Histoplasmosis (only if endemic; not in MA)</td>
<td>Itreconazole 200 mg PO QD</td>
<td>CD4 &gt; 150 x 6 mo</td>
</tr>
<tr>
<td>Toxoplasma</td>
<td>TMP-SMX DS QD or dapson 50mg QD + pyrimethamine 50mg qwk + leucovorin 25 qwk</td>
<td>CD4 &gt; 200 x 3mo</td>
</tr>
<tr>
<td>Mycobact. avium complex (MAC)</td>
<td>Ppx no longer recommended if ARVs started</td>
<td>CD4+100 x3mo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Diagnosis</th>
<th>1st Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>Cx (blood/sputum/bronch/marrow/tissue), AFB stain</td>
<td>Azithro 600mg qday or clarithro 500mg BID + ethambutol 15mg/kg QD</td>
</tr>
<tr>
<td>Pneumocystis jiroveci</td>
<td>Typically induced sputum (sens 50-90%) or BAL wash (sens ≥90%) for dx; Cx not reliable</td>
<td>TMP-SMX (15-20 mg/kg/day of TMP IV) x 21d, ≥ steroids if PaO2 &gt; 70 or A-a &gt;35</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>CT/ MRI: ring-enhancing, most pts have IgG+ but not IgM+, brain Bx if Rx fails (r/o CNS lymphoma)</td>
<td>Pyrimeth 200mg x1; then by weight + sulfadiazine + leucovorin x6wks</td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV)</td>
<td>Oral/genital: DFA, PCR, viral cx CNS: LP + CSF PCR</td>
<td>Acyc 400 PO q8h or valacy 1g PO q12h x5-10d; CNS: acyc. 10mg/kg IV q8h x3wk</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Reinitis: exam; Colitis/esophagitis: bx; PNA: bronch; Neuro: LP with PCR, brain Bx, Blood: PCR</td>
<td>In general: ganciclovir or foscarnet IV, switch to PO w/improvement</td>
</tr>
<tr>
<td>PML</td>
<td>MRI: non-enhancing lesions, LP with JCV PCR</td>
<td>Only disease-modifying tx is ARVs</td>
</tr>
<tr>
<td>Cryptococcus (rare in US pts)</td>
<td>Serum and CSF CrAg, serum and/or CSF culture, ≥ CSF opening pressure</td>
<td>Ambisome + flucytosine 2 wk x3 then high-dose fluc x 8 wk x then low-dose x 1yr</td>
</tr>
<tr>
<td>Mucocutaneous candidiasis (esophageal/oral)</td>
<td>Clinical dx. White plaque removed w/tongue depressor, +KOH; EGD + Bx</td>
<td>Oral: fluc 100mg PO x7-14d vs nystatin S&amp;S; Eso: fluc 100-400mg PO/IV x14-21d</td>
</tr>
</tbody>
</table>
Infectious Diseases

**General Principles:** (Am J Transplant 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:**
  - **Tests:** Mumps IgG, Measles IgG, Rubella IgG, VZV IgG, HAV IgG, HBV (sAb, sAg, cAb), HCV, HIV, syphilis, CMV IgG, EBV IgG. Consider: T. Spot, Endemic fungi, T. cruzi, Strongy Ab. Goal is to immunize prior to solid organ transplant.

**Infections After Solid Organ Transplant:**

- **<4 weeks:** nosocomial infxns, CLABSI, C. diff, surgical complications, GPC/GNR, Aspergillus, Pseudomonas, Crypto, less commonly donor-transmitted infxns (LCMV, West Nile, HIV, crypto)
- **1-6 mos:** CMV, EBV (incl PTLD), VZV, PJP, toxo, Pseudomonas, GPC
- **>6 mos:** CAP, UTI, GNR bacteremia, viral (CMV), endemic fungi, Aspergillus, mucor

**Infections After Hematopoietic Stem Cell Transplant:**

**HSCT Prophylaxis:** (J NCCN 2016;14:882)

- **Candida:** flucon 400mg PO (d0-365 at MGH)
- **PJP:** TMP/SMX 1 SS tab QD or 1 DS QD TIW; also covers Toxo, Nocardia, Listeria, all atovaquone, dapsone (d0-180 or 365)
- **HSV/VZV:** Famciclovir 250mg PO BID, or Acyclovir (d0-365)
- **High risk for HBV reactivation:** Entecavir, Tenofovir, or Lamivudine (duration varies)
- **CMV:** pre-emptive monitoring and treatment when elevated, letermovir in select cases

**Select Transplant-Associated Infections:**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Clinical Syndrome</th>
<th>Diagnosis/Treatment</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>Pw fever, leukopenia, +/- hepatitis, colitis, pancreatitis, retinitis</td>
<td>Dx: CMV PCR +/- bx involved organ. Serum PCR may be neg in colitis. Tx: PO valganciclovir vs. IV ganciclovir. C/s ID.</td>
<td>Most common infxn s/p solid tx: Highest risk D+/R- in SOT and D-/R+ in HSCT. May ↑ rejection and susceptibility to OIs.</td>
</tr>
<tr>
<td>PJP</td>
<td>Subacute dyspnea, hypoxemia, fevers.</td>
<td>Dx: BAL PJP stain/PCR +/- TBBx, LDH, 1-3-B-D-Glucan. Tx: TMP-SMX (15–20 mg/kg/day of TMP IV in divided doses q6-h) or</td>
<td>In contrast to HIV, there is limited data to support the routine use of glucocorticoids</td>
</tr>
<tr>
<td>BK Virus</td>
<td>Nephritis w/ AKI, ureteral stenosis, hemorrhagic cystitis.</td>
<td>Dx: BKV PCR +/- biopsy. Tx: ↓ immunosuppression</td>
<td>Mainly in Renal tx and HSCTx pts</td>
</tr>
<tr>
<td>Strongyloides</td>
<td>Hyperinfection syndrome: fever, N/V/D, cough/wheeze/hemoptysis, no eos with hyperinfection; 2° polymicrobial bacteremia (e.g., GNRs)</td>
<td>Ivermectin 200 ug/kg/day until stool neg x2 weeks</td>
<td>Should identify at-risk individuals and treat pre-transplant</td>
</tr>
</tbody>
</table>

**Symptom-Driven Diagnostics:**

- **SOB:** CXR (PA/lateral), CT chest w/ contrast, induced sputum (GS/Cx, consider AFB stain, MB Cx, PJP stain), Legionella urine Ag (Sn 70-90%,Sp 100%), viral resp panel. If cavitating or nodular lesions: beta-D-glucan/galactomannan, Crypto Ag, urine/serum Histo Ag, early bronch w/BAL (NB: engraftment syndrome, cryptogenic organizing PNA also on DDx)
- **Diarrhea:** stool cx, O&P (consider Micro Add-on for: Cryptosporidium, Isopora, Cyclospora, Microsporidia.), C. diff, CMV PCR. DDx: If high suspicion for viral colitis (e.g., CMV, adenovirus), c/s GI re colo w/ bx. In HSCT, consider typhlitis and GVHD.
- **AMS/H/A:** CT head, LP (OP, GS/Cx, glucose, TP, HSV PCR, Crypto Ag, ask to save extra tube for additional tests). (NB: Fludarabine, cytarabine and calcineurin inhibitors (via PRESS) can also lead to encephalopathy)
- **Rash:** GVHD, medication allergy, HSV, cellulitis, fungal infection
- **Leukopenia:** CMV PCR, EBV PCR, consider tick borne illnesses during the correct season or if frequent blood transfusions
- **Hepatitis:** if post-HCT, consider viral (HAV, HBV, HCV, EBV, CMV, adenovirus + more rarely enterovirus and HHV6), Candida, and non-infectious (GVHD, iron tox, meds, hepatic sinusoidal occlusion syndrome)
- **AKI:** UA/UcX, renal US, BKV PCR if renal transplant. Consider med toxicity and check levels (tacro, cyclosporine)
STIs & Travel Medicine

**STIs**

<table>
<thead>
<tr>
<th>LESIONS</th>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Syphilis (T pallidum)          | 1°: painless, firm, round ulcer  
|                                | 2°: fever, condyloma lata of skin/mucus  
|                                | membranes, LAD, myalgia, uveitis, meningitis  
|                                | 3°: aortitis/aneurysm, disseminated  
|                                | gummata, CN palsyies, tabes dorsalis  
|                                | (impaired gait, sensation, reflexes)         | VDRL, RPR (nontreponemal):  
|                                | titers are used to track infection.  
|                                | Detects cardiolipin Ab; Nonspec TPPA, TP-EIA  
|                                | (treponemal); detects Ab. specific to T. palidum, but positive for life once syphilis acquired | 1°/2°: PCN G benzathine 2.4 million units IM x1  
|                                | 3°: PCN G benzathine 2.4 million units IM week x3 | Neuro: IV/IM PCN G x10-14d (CID 2011;53:S110) |
| Genital herpes (HSV2>HSV1)     | Prodrome → painful vesicles → ulcers  
|                                | 1° infection may include systemic sx          | Confirm clinical dx with PCR or viral culture | Chronic suppressive (if 6 outbreaks/yr) vs episodic therapy  
|                                |                                               |                                               | (acyclovir, valacyclovir, famcyclovir) |
| Lymphogranuloma venereum (C trachomatis) | 1°: transient, painless anogenital lesion  
|                                | 2°: 2-6w later, painful inguinal LAD, back pain, systemic sx  
|                                | 3°: ‘Genitoanorectal syndrome’ from pelvic and abd LAD with inflam diarrhea, fistulas, strictures, abscesses, necrosis | Positive IgG/complement fixation + clinical diagnosis; NAAT in pipeline | Doxy 100mg bid x21d + aspiration of buboes |

**DISCHARGES**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Gonorrhea (N gonorrhoeae), Chlamydia (C trachomatis) | Purulent malodorous vaginal discharge, pruritus, dysuria, frequency, dyspareunia  
|                                               | Usually asymptomatic in ⊛                     | Wet mount → vaginal swab NAAT                                               |
|                                               |                                               | Metronidazole 2g po or tinidazole 2g po (better tolerated than MTZ) + GC/CT tx; treat partner |

**Travel Medicine**

**Pre-travel evaluation**
- **Patient**: Medical conditions (immunosuppressed ?), allergies (particularly to vaccines), pregnant/planning to get pregnant, immunization hx, prior travel history (experience with malaria prophylaxis/prior travel related illnesses), med list
- **Trip**: Place, duration, season, purpose of a trip (medical / visiting family), itinerary (urban vs. rural areas, cruise ship, exposure to animals, cave exploration, water exposure)
- **USE MGH Developed tool** (Heading Home Healthy) to enter your patient’s details for specific recommendations

**Immunizations**
1. Ensure routine vaccinations are uptodate
2. Use CDC site to get country-specific recommendation on vaccination (clinician view & select country).

**Malaria Prophylaxis**
Search by country in CDC tool to know what and when to prescribe (based on resistance patterns).
Start ~ 1 week before travel and up to 4 weeks after.

**Traveler’s diarrhea**
- Bacteria most common pathogens: ETEC, C. Jejuni, Shigella & Salmonella spp. Tx : Loperamide/Bismuth. Antibiotics (fluoroquinolones/azithromycin) if moderate/ severe cases (interfere with activity or dysentery).
- Assess if life threatening illness or if transmissible via respiratory, contact, etc (isolate pts)
- Broad ddx which depends on exposure risk, host/patient vulnerability and incubation periods.
- Common culprits : Malaria, TB, STIs, Tick-Borne disease, Mosquito-Borne illnesses, Enteric fever (NEJM 2017;376:548)
Infectious Disease

Tick-Borne Diseases


<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Presentation</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early localized (within 1 month)</td>
<td>-Erythema migrans (spreading red patch +/- central clearing) -Fatigue, myalgia, arthralgia, HA</td>
<td>Clinical dx only (serologic conversion &gt;1wk after EM appears)</td>
<td>If EM: doxycycline 100mg PO BID x 14d (amoxicillin 500mg TID x 14d if pregnant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If no EM: consider serology in 2 weeks</td>
</tr>
<tr>
<td>Early disseminated (days to months)</td>
<td>-Multiple EM lesions -Neuro (CN palsies, meningitis, mononeuritis, radiculopathy) -Cardiac (heart block, myopericarditis)</td>
<td>2-Tier Testing: 1. Screening ELISA IgM/IgG 2. Western blot if serology positive or equivocal</td>
<td>AxB: CTX 2g IV QD OR doxycycline 100mg PO BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IgG becomes positive after 6-8wks; if only IgM positive on ELISA/Western blot after 6-8wks = false positive</td>
<td>Duration: 14-28 days depending on indication and severity (IV abx for encephalitis or severe cardiac involvement)</td>
</tr>
<tr>
<td>Late disseminated (months to yrs)</td>
<td>-Arthritis (mono- or polyarthritis of large joints, esp. knee) -Neuro (mild encephalopathy, peripheral neuropathy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Western blot interpretation: IgM considered positive if 3 particular bands present; IgG positive if any 5 of 10 total bands present

Chronic Lyme disease: not a scientific entity, while post-infectious syndromes (e.g., fatigue) are reported in up to 20% of pts after treatment for Lyme disease, these are NOT due to persistent Lyme infection → abx NOT indicated (NEJM 2007;357:1422)

Prophylaxis: Doxy 200mg PO x1 if Ixodes tick attached & engorged ≥36h in endemic area AND pt presents <72h after tick removed

Pears:
- Always consider possible coinfection w/ other tick-borne illnesses (see below)
- Recurrent symptoms after completion of treatment course are likely re-infection, NOT relapse (NEJM 2012;367:1883)

Other Tick-Borne Illnesses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vector / Geography</th>
<th>Presentation</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplasmosis (HGA)</td>
<td><em>I. scapularis</em> tick NE, MW, Atlantic</td>
<td>Common: fever, myalgias, HA Uncommon: rash rare in HGA, 36% in HME</td>
<td>-PCR -Morulae seen in 20-80% of neutrophils on smear</td>
<td>Doxycycline 100mg BID x 10d</td>
</tr>
<tr>
<td>Ehrlichiosis (HME)</td>
<td><em>A. americanum</em> (Lone-star tick) South, MW, Atlantic</td>
<td>Labs: leukopenia, thrombocytopenia, ↑ALT/AST</td>
<td>-PCR -Morulae seen in 0-20% of monocytes on smear</td>
<td></td>
</tr>
<tr>
<td>Babesiosis (NEJM2012;36 6:2397 CID2003:5:53)</td>
<td><em>I. scapularis</em> tick Endemic to the regions surrounding Cape Cod, Southern NE, NY, north central MW</td>
<td>Mild-to-moderate: viral-like sx (fever, fatigue, chills, sweats), less commonly arthralgia, myalgia, HA, NV, cough Severe: immunosup/HIV+, (functionally) asplenic, tituximab, &gt;50 yo; can p/w severe hemolysis, DIC, ARDS, multiorgan failure</td>
<td>-Blood smear (ring forms within RBC: Maltese cross rare; malaria appears similar) NB: parasitemia determined by % infected RBCs on smear -PCR (sens &amp; spec but $$$) not routine at MGH.</td>
<td>-Atovaquone + azithromycin (dose varies with severity) -Alt.: clinda + quinine -Exchange transfuse if severe hemolysis, parasitemia ≥ 10%, or end-organ failure</td>
</tr>
<tr>
<td>Borrelia miyamotoi (NEJM2013;36 8:2910)</td>
<td><em>I. scapularis</em> Same regions as Lyme disease</td>
<td>Fever, HA, chills, leukopenia, thrombocytopenia, ↑ALT/AST (mimics anaplasmosis); rash usually absent</td>
<td>PCR &gt; serology NB: EIA cross-reacts w/ B. burgdorferi</td>
<td>Doxycycline 100mg BID x 14d</td>
</tr>
<tr>
<td>Powassan virus (CID2016;62:707)</td>
<td><em>I. scapularis</em> Summer in NE, MN, WI, NY</td>
<td>Fever, encephalopathy, MRI T2/FLAIR hyperintensities (esp. basal ganglia enhancement), lymphocytic pleocytosis in CSF (can also be neutrophilic)</td>
<td>Serum/CSF serology (send-out test to state lab); consider WNV Serum/CSF</td>
<td>Supportive; consider steroids, IVIG</td>
</tr>
<tr>
<td>Rocky Mountain Spotted Fever (Rickettsia rickettsii)</td>
<td>Dermacentor tick Canada, Mexico, Central/South America, OK, TN, AR, MD, VA, NC, SC; peaks spring &amp; summer</td>
<td>-Early (3d): non-specific (fever, myalgia, HA, conjunctivitis, N/V/abdominal pain) -Late (2 wks): fever/HA/rash triad in ~60%; rash (90%) progresses from wrist/ankle (palms/soles) → trunk; rash macular (3d) → petechial (6d) -Severe: shock, DIC, organ failure; 20% mortality if untreated; 5% if treated -Labs: leukocytosis or leukopenia, thrombocytopenia, hypoNa, AKI, ↑LFTs</td>
<td>-Initially clinical dx (start empiric abx) -Serology (undetectable until 7-10d after sx onset), need to repeat at convalescence (14-21d after sx onset) to confirm diagnosis -Skin biopsy (100% spec, 70-90% sens)</td>
<td>Doxycycline 100 mg BID x 5-7d and at least 3 days after afebrile (still give doxy even to kids and pregnant women) Chloramphenicol is the only alternative, if available</td>
</tr>
</tbody>
</table>
**Infectious Disease**

**Fever of Unknown Origin**

**Definition** ([Crit Care Med 2008;36:1330], [Medicine 1961; 60:1])

Originally defined as: temp >38.3°C, assessed on multiple occasions, for >3 weeks without an obvious cause or etiology. FUO is far more often caused by an atypical presentation of a rather common disease than by a very rare disease.

**Workup:**

- **Ddx:** most commonly ID vs. cancer vs. rheumatologic vs. meds (see box)
  - In 25-50% of cases, no source is identified ([Medicine 2007;86:26])
- **Patient History:** verify fever trend/pattern, past medical history including dental history and history of immunocompromise, travel, animal/tick/mosquito/environmental/food exposures, h/0 blood product transfusions, sick contacts, sexual history, illicit, occupation, TB history, meds, vaccines, family history, valve disorders, recent procedure/hospitalization, changes in weight/anorexia
- **Physical Exam:** Assess for dental caries/thrush, sinus tenderness, temporal arteries, thyromegaly, abd tenderness, HSM, CV murmur; inspect eyes, fundi; perform complete lymph node, skin/nails, rectal, and joint exam

**Diagnostic Testing:**

- **Initial:** CBC w/ diff, CMP, ESR/CRP, UA/Ucx, BCx x3 (diff. sites), CXR (AJM 2015:128:1138e1)
- **Inflammatory Markers:**
  - ESR: Measure of chronic inflammation. Falsely elevated in ESRD (can be very high), paraproteinemias, anemia, obesity, and advanced age. **Must correct for age** → (Age / 2) for males and (Age / 2) + 10 for females.
  - CRP: rises more acutely than ESR; may be falsely low in cirrhosis
  - Procalcitonin: Acute rise in bacterial inixmns (also seen with sterile serositis). See CAP/Viral Infections for appropriate use
- **Other Labs to Consider:** PPD/IGRA, HIV Ab/Ag/PCR, RPR, LDH, TFTs, SPEP/SFL/UFL, ANA, ANCA, RF/CCP, cryo, CK/aldolase, EBV serologies, CMV PCR, ferritin, blood smear, HBV/HCV
- **Imaging** ([Arch Intern Med 2003;163:545]): CT abd/pelvis (19% Se, 71% Sp), LENIs, TTE, FDG-PET/CT (Sens 50-100%, Spec 46-88% - 35%, Malignancy 3-10%), maxillofacial CT
- **Tissue diagnosis:** biopsies of LN, liver biopsy (14-17% yield), BM (low yield at 0-2%), b/l temporal artery biopsy (GCA), kidney (RPGN), consider LP in patients with CNS findings.

**Treatment:**

- **Try to avoid empiric antibiotics** and observe (unless hemodynamic instability or immunocompromised)
- Discontinue possible offending medications
- If high suspicion for GCA/vasculitis, strongly consider empiric steroids (prior to biopsy) to prevent vision loss / end-organ damage
- If extensive workup is negative, prognosis is usually good and most cases defervesce (AJM 2015:128:1138e1)

**Etiologies by Patient Population:**

<table>
<thead>
<tr>
<th>Population</th>
<th>Study</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly patients ([Am Geriatr Soc 1993:41:1187])</td>
<td>Infection 35% (Abscess 12%), Malignancy 19% (Heme 10%, Solid 9%), Rheum 28% (most common GCA/PMR)</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled HIV* ([Clin Infect Dis 1999:28:341])</td>
<td>Infection 88% (dMAC 21%, PJP 13%, CMV 11%, Histo 7%, other Viral 7%), Malignancy 8% (Lymphoma 7%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenic (refractory to abx) ([NEJM 2002:346:222])</td>
<td>Fungal infections 45%, bacterial infections 10% (resistant, biofilms), GVHD 10%, Viral 5%, Misc 25%</td>
<td></td>
</tr>
</tbody>
</table>

*Based on analysis of studies after 2000 in Europe or North America ([Am J Med Sci 2012;344:307]), **Mean CD4 count 53/mm³

**Select Causes of FUO:**

- **Central Fever.** Most common causes include SAH, intraventricular bleed, brain tumors ([JAMA Neurol 2013:70:1499])
- **Drug Fever:** Diagnosis of exclusion that broadly refers to any febrile response to medication. Can occur at anytime while taking drug, with resolution ~2-3 days post-cessation (can take up to 1 week)
  - FEVER: Can be in excess of >102°F. Rarely, pts have accompanying signs (e.g., morbilliform rash, LFT elevations, eosinophilia)
  - Mechanisms of drug fever include: Hypersensitivity reaction (including SJS/TEN), dysfunctional thermoregulation, aseptic meningitis, Jarisch-Herxheimer reaction, NMS/serotonin Syndrome, G6PD deficiency
  - Medications commonly assoc. with drug fever: Antimicrobials (β-lactams, sulfia, macrolides), AEDs, dexamethasone, chemo
- **VTE:** DVT, PE, and thrombopilebite may cause fever. Likely low grade (6% w/ fever >101° and 1.4% >102°) ([Chest 2000:117:39])

Theodora Karagounis

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### Infectious Disease

**Rare Diseases**

<table>
<thead>
<tr>
<th>Organism/Syndrome</th>
<th>Epi &amp; Transmission</th>
<th>Symptoms</th>
<th>Abi Labs</th>
<th>Diagnostic Tests</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malaria</strong> (Plasmodium spp.)</td>
<td>Africa, Latin Am, Asia, MidEast, Eastern Europe</td>
<td>12-55d incubation; fever, HSM, AMS, jaundice, petechiae</td>
<td>Anemia, ↑Plt, AKI, ↑LFTs, ↓Glucose, acidemia</td>
<td>BinaxNOW (RDT)</td>
<td>Treatment: Variable, call ID; ppx doxy, Malarone, mafenique</td>
</tr>
<tr>
<td><strong>Mosquito-borne viruses:</strong> Dengue, chikungunya, and Zika are often indistinguishable clinically/epidemiologically; considering testing for all 3 if concerned.</td>
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<td></td>
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</tr>
<tr>
<td>Dengue fever (DENV serotypes 1-4; <em>Flavivirus</em>)</td>
<td>India, Asia/Pac, Africa, Lat Am</td>
<td>Fever, retro-orbital HA, arthralgia, petechiae, shock</td>
<td>Lymphopenia, thrombocytopenia, increasing Hct</td>
<td>Serum RNA early → IgG/IgM (cross-nxn w/ Zika); tourniquet test</td>
<td>Rest, fluid; avoid NSAIDs due to ↑ hemorrhagic sx</td>
</tr>
<tr>
<td>Chikungunya fever (Alphavirus)</td>
<td>Africa, Asia/Pac, Caribbean, Lat Am, S USA</td>
<td>1-14d incubation; fever (&gt;102 in chik), HA, polyarthralgia, rash, conjunctivitis, GBS &amp; (fetal microcephaly (zika))</td>
<td>Chik: lymphopenia, thrombocytopenia, ↑LFTs, AKI</td>
<td>Chik: RT-PCR if &lt;7d sx; serology if ≥7d. Zika: serum/urine PCR if &lt;14d sx; serology/plate red if negative; serology if ≥14d of sx</td>
<td>Rest, fluid; avoid NSAIDs unless definitely not dengue</td>
</tr>
<tr>
<td><strong>West Nile virus</strong> (Flavivirus)</td>
<td>Africa/MEast, Europe, Americas</td>
<td>Asympt; fever, HA, myal, 1% meningitis</td>
<td>CSF pleocytosis (lymphs)</td>
<td>Serum + CSF Abs &gt; PCR</td>
<td>Rest, fluid</td>
</tr>
<tr>
<td><strong>Leishmaniasis,</strong> cutaneous/visceral (Leishmania spp.)</td>
<td>C/S America, S Europe, Mid East, E Africa, S Asia</td>
<td>CL: painless ulcer(s), regional lymphaden.</td>
<td>VL: cytopenias, ↑LFTs</td>
<td>Clinical dx, tissue smear/cx; rarely Ab if superinfected lesions</td>
<td>Variable, call ID; abx if superinfected lesions</td>
</tr>
<tr>
<td><strong>Bacterial Zoonoses:</strong> Coxielia, Bartonella quintana, and Brucella are important causes of culture-negative endocarditis.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cat scratch disease (Bartonella henselae)</td>
<td>Worldwide</td>
<td>Fever, LAD 1-3 wks, neuro, ocular</td>
<td>↑ESR/CRP, ↑AST/ALT</td>
<td>PCR 1-3d; Ab 1-2wks; histology</td>
<td>Regimens vary</td>
</tr>
<tr>
<td>Leptospirosis (Leptospira spp.)</td>
<td>Worldwide; tropics &gt; temperate</td>
<td>Fever, HA, myalgia, jaundice, rash, conjunctival suffusion</td>
<td>↑Bill, ↑AST/ALT, anemia, AKI, hypoN, ↑CK</td>
<td>Serology if 3-5d sx</td>
<td>Outpt doxy 100 bid x7d; impr PCN G, doxy, or CTX</td>
</tr>
<tr>
<td>Q fever (Coxiella burnetti)</td>
<td>Worldwide (not New Zealand)</td>
<td>Fever, HA, myalgia, PNA, endocarditis</td>
<td>↑AST/ALT, ↑Bill, ↑Plt, ↑CK</td>
<td>PCR if &lt;7d sx, serology if ≥7d</td>
<td>Doxy 100 bid x14d</td>
</tr>
<tr>
<td>Brucellosis (Brucella spp)</td>
<td>Worldwide</td>
<td>Undulant fever, arthritis (SI joint, spine), endocarditis</td>
<td>↑AST/ALT, ↓WBC with relative ↑lymp</td>
<td>Serology if 7-1d sx</td>
<td>Doxy 100 bid x6 wks + gentamycin or rifampin</td>
</tr>
<tr>
<td><strong>Tularemia</strong> (Francisella tularensis)</td>
<td>N America, Europe &gt; Asia</td>
<td>Regional LAD; 6 syndromes: PNA, glandular, etc.</td>
<td>Non-specific ↑ESR/CRP; normal WBC, LFTs, Cr, ↓Plt</td>
<td>Serology if sx &gt;2wks; cx cytostasis + media; gram stain</td>
<td>Streptomycin 7-10d; cipro or doxy 10-21d if mild dz</td>
</tr>
<tr>
<td><strong>Rickettsia</strong></td>
<td>In general, rickettsial diseases with eschars are scrub typhus, African tick-bite fever, RMSF, Mediterranean spotted fever, and rickettsialpox.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Murine typhus (Rickettsia typhi)</td>
<td>SE Asia, N Africa, N America</td>
<td>Fever, centrifugal rash, HA, myalgia</td>
<td>↑Plt, ↓AST/ALT</td>
<td>Serology performed 2wks apart</td>
<td>Doxy 100 bid x7d</td>
</tr>
<tr>
<td>Scrub typhus (Orientia tsutsugamushi)</td>
<td>India → E Asia, Pacific, Chile</td>
<td>Bites from infected mite larvae (AKA chiggers)</td>
<td>↑Plt, ↓AST/ALT, ↑Bill, AKI, WBC usually wnl</td>
<td>Serology performed 2wks apart; consider eschar bx</td>
<td>Doxy 100 bid x7d; azithromycin if tetracycline-resist.</td>
</tr>
<tr>
<td><strong>Schistosomiasis</strong> (Schistosoma spp.)</td>
<td>Africa, Brazil, MidEast, Asia</td>
<td>Fresh water with free cercariae from infected snails</td>
<td>↑Teos (30-60%) in acute, ↑Plt, LFTs usually wnl</td>
<td>Serology at 6-12wks; stool/urine microscopy for speciation</td>
<td>Acute: pred 20-40 x5d + praziquantel Chronic: 40-60 x1 of praziquantel</td>
</tr>
<tr>
<td><strong>Trichinellosis</strong> (Trichinella spp)</td>
<td>Worldwide, esp. Europe</td>
<td>Undercooked meat, esp. pork</td>
<td>↑Teos, ↑WBC, ↑TCK, ↑LDH</td>
<td>Serology 2-6d; muscle biopsy</td>
<td>Albendazole 400 bid + pred 30-60 qd x8-14d</td>
</tr>
<tr>
<td><strong>Strongyloidiasis</strong> (Strongyloides stercoralis)</td>
<td>Rural tropics/subtropics; Appalachia, SE USA</td>
<td>Skin nem, epigastric pain, diarrhea, resp. sx; fever, N/V, sepsis or shock if hyperinfection</td>
<td>↑Teos, ↑WBC; in immunosupp pts → hyperinfection and disseminated dz (normal eos.)</td>
<td>Serology more sens (83%+) than stool but less spec (95%+)</td>
<td>Ivermectin 200 mcg/kg/day x2d; treat for x5-7d if disseminated dz</td>
</tr>
</tbody>
</table>
| **Other Infections**

| Typhoid fever (Salmonella enterica serotype Typhi) | India, SE Asia, Africa | Fever, abd pain, "roses spots", diarrhea (>50%), constipation (30%), HSM, AMS | ↓HR, ↓LFTs, ↓WBC (WBC sign of intest. perf.), anemia, abd coags | Stool/blood cx (BMBx 90% sens.); serology effective in non-endemic regions | S Asia: azithro Other: ciprofloxacin Severe: CTX (mero- penem if Pakistan) |
| Melioidosis (Burkholderia pseudomallei) | India → SE Asia, N Australia | Fever, PNA, skin abscess, community-acquired sepsis, GU | ↑WBC, other nonspecific values ↓c/organ failure | Blood cx on Ashdown’s agar, gram stain | Abscess xid + IV mero/celtaz x2wks → TMP-SMX x3mo |
| Hantavirus (Sin nombre, Andes) | SW USA, Lat Am, Europe, Asia | Hemorrhagic fever, renal failure, ARDS | TPTT, ↓Plt, AKI, proteinuria | Serology via state department of health | Supportive care |
| Toxoplasmosis (Toxoplasma gondii) | Worldwide | Cervical LAD, fever for wks/mos, myalgia | Atypical lymphs, ↑AST/ALT | Serology 1-7d; CSF 2-5d | Tx if CNS, preg, or chorioretinitis |

**Note:** Brady Page 122
### Standard Precautions apply to all patients
- **“Hand hygiene”:** Disinfect with an alcohol-based hand rub before AND after gloving, contact in room or with patient. If hands are visibly soiled, wash hands with soap and dry hands, and apply an alcohol-based hand rub.
  - Gloves/gowns for contact w/blood, bodily fluids (e.g., wound), secretions, excretions, mucous membranes, broken skin
  - Mask/goggles/face shield for procedures that can splash blood, bodily fluids, or secretions (e.g., ABGs)
  - Dispose of materials heavily soiled with blood or bodily fluids into biohazardous waste (red bag)
  - Disinfect reusable equipment (e.g., personal stethoscope, U/S) using correct wipes after patient use
- **Cough etiquette:** Cover mouth/nose, mask coughing person, prompt disposal of used tissues, hand hygiene, spatial separation (>3ft)
- **Safe injection practices:** Use sterile, single-use, disposable needle/syringe and single-dose vials whenever possible

### Transmission-Based Precautions (in addition to standard precautions above):

<table>
<thead>
<tr>
<th>Isolation</th>
<th>Pt Population &amp; Transmission</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact <a href="#">Link to Policy</a></td>
<td>Transmitted by direct or indirect contact with patient or his/her environment.</td>
<td>- Clean, nonsterile gloves + isolation gowns must be worn upon entering patient’s room. Change PPE if seeing subsequent patient. - Do not touch phones or beepers while in room - <strong>Doffing gowns and gloves:</strong> Remove together with only touching inside of PPE. Dispose of in the patient’s room. - Dedicate the use of equipment (stethoscope, BP cuff) to avoid sharing with other patients. All equipment residing within the Contact Isolation room is presumed contaminated. -Disinfect using correct wipes for pathogen of concern</td>
<td>MRSA†, VRE†, MDROs†, CRE, Uncontained drainage</td>
</tr>
<tr>
<td>Contact PLUS <a href="#">Link to Policy</a></td>
<td>Patients with known/suspected spore forming or alcohol-resistant organisms transmitted by indirect/direct contact.</td>
<td>- Contact instructions as above. - After doffing; wash hands with soap and water for 15-20 seconds, dry, then use CalStat; Bleach wipes for equipment - <strong>Isolate patient empirically while awaiting results of tests for C. diff and Noro</strong></td>
<td>C. diff, Norovirus, C. aurois, Cutaneous anthrax</td>
</tr>
<tr>
<td>Droplet <a href="#">Link to Policy</a></td>
<td>Patients with organisms transmitted by large respiratory droplets.</td>
<td>- Disposable surgical mask must be worn when entering the room. Discard upon exit. - Patient travel: surgical mask -<strong>Isolate patient empirically while awaiting results for bacterial meningitis, influenza, pertussis</strong></td>
<td>N. meningitidis (1st 24 hrs of effective antimicrobial therapy), Influenza, Pertussis</td>
</tr>
<tr>
<td>Airborne <a href="#">Link to Policy</a></td>
<td>Transmitted by droplet nuclei that can remain suspended in the air and be dispersed widely</td>
<td>- Airborne Isolation room (i.e. “negative pressure”) - <strong>PAPR for facial hair or if not fit-tested- Patient travel:</strong> surgical mask</td>
<td>Pulmonary TB, Measles, Varicella</td>
</tr>
<tr>
<td>Enhanced Isolation <a href="#">Link to Policy</a></td>
<td>Required for patients with Cystic Fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strict Isolation <a href="#">Link to Policy</a></td>
<td>Patients w/ highly pathogenic organisms transmitted by airborne + direct/indirect contact.</td>
<td>- Airborne + Contact + Eye Protection If suspected, mask patient, isolate patient, page Biothreats - Patient travel: surgical mask</td>
<td>SARS, MERS, Avian Influenza</td>
</tr>
</tbody>
</table>

† Pts w/ prior history of MRSA/VRE/MDRO will be identified in the Infection Status banner in EPIC; can click to see detail on when they were initially identified; ANY questions or to ask if patient’s infection status can be discontinued, contact Infection Control (x62036)

* Full listing from within Epic: Resources → Handbook → Manuals → MGH Infection Control Manual & Policies → Isolation Precautions

### Immunocompromised Hosts: see specific policies at [https://hospitalpolicies.ellucid.com/documents/view/956/20303/](https://hospitalpolicies.ellucid.com/documents/view/956/20303/)

### When to Remove Precautions:
For questions regarding screening for resolution of infection status for patients with histories of MRSA, VRE, and MDROs call the Infection Control Unit (x6-2036). Details are provided here. Discontinuation of isolation should be discussed with Infection Control directly.
- **TB:** 3 negative sputum specimens (via cough or induction at least 8h apart or 24h if known) is not sufficient for rule out; TB must be excluded entirely from the differential. Please consult Infection Control to discuss discontinuation of isolation.
- **Influenza:** 7d after onset or until 24h after resolution of fever and non-cough symptoms (whichever is longer); although in some patients shedding may be prolonged; discuss with Infection Control

For MGH resources: see [http://infectioncontrol.massgeneral.org/icu/](http://infectioncontrol.massgeneral.org/icu/) (MGH Infection Control Manual and Guidelines)

**Link to Current MGH Infectious Disease Outbreaks of Concern List.**
Vancomycin Dosing and Monitoring: (MGH:ID intranet=>antimicrobial stewardship=>Practice Guidelines=>Drug specific=> Vanc)
OR: http://handbook.partners.org/content/pdf/MGHInfDisVancomycinDosingGuidelines.pdf (copy into browser)

- **Loading dose**: depends on body weight (20mg/kg; max 2g)
  - **NB**: if meningitis/septic shock/endocarditis, consider load with 25mg/kg, max 2g
- **Maintenance dose**: dose depends on body weight (15mg/kg), frequency depends on CrCl and Age (see online guidelines)
  - **NB**: if meningitis/septic shock/endocarditis, consider load with 25mg/kg, max 2g
  - **NB**: if meningitis/septic shock/endocarditis, consider load with 25mg/kg, max 2g
- **Serum concentration monitoring**: Use trough as surrogate for area under curve
  - **NB**: if meningitis/septic shock/endocarditis, consider load with 25mg/kg, max 2g
    - **NB**: if meningitis/septic shock/endocarditis, consider load with 25mg/kg, max 2g
- **Hemodialysis Dosing** (Loading dose as per body weight = 20-25mg/kg; max 2g)
  - **For Maintenance Dose**: Obtain Vanc Trough Pre-HD with goal of 20-25mcg/mL
    - **Protocol**: calculate Post-HD level = Pre-HD trough x (0.7) **Note**: 0.7 for 3hr-HD session, use 0.6 for 4hr
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- **Important Dosing Tips**: **“Never hesitate to call Pharmacy if unsure/questions”**
  - **BMI**: BMI = 30-35, second loading dose of 2g may replace first maintenance dose, or give maintenance dose one interval earlier
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Dosing of Other Antimicrobials:
- **For more information on renal dosing for other antimicrobials (including CVVH dosing)**: See http://handbook.partners.org/pages/3805. Can also search Partners Handbook for “renal dosing,” click first link, then “antimicrobial renal dosing guidelines”
- **For more information on antibiotic penetration into different tissues**: See https://hospitalpolicies.ellucid.com/documents/view/13863
- **Abx with equivalent IV/PO availability**: Azithromycin, clindamycin, doxycycline, fluconazole, linezolid, levofloxacin, ciprofloxacin, metronidazole, TMP/SMX. Some of the oral to IV doses may vary (e.g. cipro 400 mg IV q12h –> ~ 500 mg PO q12h).
- **For information on aminoglycoside dosing**:
  - See https://hospitalpolicies.ellucid.com/documents/view/11354 and consult pharmacy
**Hematology**

**Anemia & Pancytopenia**

**GENERAL APPROACH TO ANEMIA** *(Williams Hematology 2018)*

- **Presentation:** Hypoxic sx (fatigue, dizziness, DOE, pallor, angina, claudication, retinal hemorrhage), nonspecific sx (cramps, abd pain, nv), compensatory mechanisms (hyperventilation, tachycardia, palpitations, orthostasis, ↑pulsion, flow murmur, bruit)

- **Associations:** Jaundice (hemolysis), glossitis (folate / B12 def), motor / sensory deficits (B12 def), PICA / kollionychias / angular chelitis (Fe def), splenomegaly (cirrhosis, inflm), constipation / bone pain (meloma), melena / +FOBT (GIR, CRC), Mediterr / Asian / Black (thal/SS), unusual thromboses (PNH), petechiae / ecchymoses (coagulopathy, pancytopenia)

- **Initial labs (draw/add on labs prior to transfusion):**
  - CBC (other cell lines, MCV, RDW), retic count, special slide, T&S
  - Determine hypo- (retic index [RI] <2%) vs hyper-proliferative (RI >2%)
  - Very low RI (<0.1%) indicative of aplastic anemia or red cell aplasia

- **Additional labs depend on retic index:**
  - RI <2% - "Anemia labs": Fe/TIBC/ferritin, folate / B12 (in last 6 mo.), Cr, LFTs, TSH
  - RI >2% - "Hemolysis labs": LDH, bilirubin, haptoglobin,DAT, UA, Coags

**CLASSIFICATION OF ANEMIA** *(NEJM 2014;371:1324, Lancet 2018;391:155, Williams Hematology 2018)*

<table>
<thead>
<tr>
<th>UNDERPRODUCTION (RI &lt;2%)</th>
<th>Normocytic (MCV 80-99 µm³)</th>
<th>Macrocytic (MCV ≥ 100 µm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia of inflammation</strong></td>
<td>Organ-specific: Renal (CKD/ESRD): ↓ Epo (should ↑10x per 10% Hct drop) Endocrine (thyroid, pituitary, adrenal, parathyroid, testosterone): ↓ Epo</td>
<td></td>
</tr>
<tr>
<td><strong>Thalassemias</strong></td>
<td>Marrow (red cell aplasia, AA, MDS, myelofibrosis, myelophthysis, PNH, MM): SPEP, serum FLC, BMBx</td>
<td></td>
</tr>
<tr>
<td><strong>Sideroblastic anemia</strong></td>
<td>Retinocytosis</td>
<td></td>
</tr>
<tr>
<td>↑ ferritin, Fe/TIBC nl, basophilic stippling (Pb), ringed sideroblasts (BM)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DESTRUCTION / LOSS (RI >2%)**

**Extrinsic (transfused RBC has shortened life span):**

- **MAHA (-DAT, +schisto):** see *Thrombocytopenia: TMA*s for DDx
  - Smear (≥2 schisto/HPF); PLT ~25K, LDH ↑↑, indir bili ↑, hapto ↓

- **Immune (+DAT, +spherocytosis):** Ab- and/or complement-mediated

- **Warm autoimmune (CLL, HIV, lymphoma, SLE): +DAT anti-IgG/C3**

- **Cold autoimmune (EBV, CMV, Mycoplasma): +DAT anti-C3**

- **Alloimmune:** acute v. delayed hemolytic transfusion rxn

- **Drug:** PCN, ophalo, quinine, amphi B, NSAIDs, procainamide

- **Non-immune (-DAT, +/- RBC inclusion):**
  - Infection: babsa, malaria, bartonella, C. perfringens, H. flu (type B)
  - Toxin: lead, copper, insect / spider bites, hypotonic infusion

**Intrinsic (transfused RBC has normal life span):**

- **Heredity:**
  - Hb disease (SS, HbC, thal): Hb electrophoresis
  - Enzyme deficiency (G6PD, PK): levels often nml in attack; check 4wk later & repeat in 3mo if neg.

- **Membrane defect:** spheroctysis, elliptocytosis

- **Acquired (new onset):**
  - PNH (paroxysmal nocturnal hemoglobinuria): flow cytometry +/- FLAER for GPI anchor, smear nml, UA (hgb/hemodin), thrombosis (intra-abd/cerebral)

- **Acute blood loss:** GI blood loss, hematoma

**APPROACH TO PERIPHERAL BLOOD SMEAR** *(NEJM 2005;353:498)*

- **Low power (200x):** Scan slide for WBC distribution. Identify the “thick” edge and the “feathered” or thin edge.

- **Med power (400x):** Examine feathered edge for rouleaux, parasites, abnormal WBC, platelet aggregation / micros pellets.

- **Oil Immersion (1000x):** Assess the size, shape, and morphology of major cell lineages:
  - RBC: Examine where RBCs are close but not touching, compare to lymphocyte nucleus size for scale
  - WBC: Concentrate on edges and thin end of film, normal WBC include PMN, eos, basos, lymphocytes, monocytes

**IRON DEFICIENCY ANEMIA** *(NEJM 2015;372:1832; Blood 2019;133:30)*

- **Etiology:** ↑loss due to chronic bleeding (PUD/UGIB ↑BUN), colon CA/LGIB, menses, intravascular hemolysis), ↑demand (Epo, pregnancy, blood donation), ↓intake (malnutrition) or ↓absorption (IBD/post-gastrectomy/celiac). If unexplained or refractory to PO iron, eval. for celiac, AI gastritis, H. pylori, which accounted for 5%, 27%, 19% of unexplained IDA *(Haematologica 2005:90:585).*
Hematology

**Anemia & Pancytopenia**

- **Treatment**: PO 325 mg FeSO₄ x 3 QD or QOD (↑ absorption w/ QOD; *Lancet Haematology* 2017;4:e524). ~6wk to correct anemia, ~3-6mo to replete stores. Absorp. ↑ on empty stomach, w/ ViC, ↓ w/ Ca foods, antacids. GI SE: constipation, epigastric pain, N/V.
  - IV repletion (if excessive SEs, CKD, malabsorption, IBD, intolerant to PO, or CHF). Calc. iron deficit (weight (kg) x 2.3 x [target Hb – pt Hb) + 500] & replete up to 1000mg. Typical dose: iron sucrose 200mg QOD x 5 or 300mg QOD x 3. SE: n/v, pruritus, flushing, myalgia/arthritis, CP; typically resolve in 48h. Anaphylaxis rare w/ Fe-glucuronate & Fe-sucrose.

**ANEMA OF CHRONIC DISEASE / INFLAMMATION** (*NEJM 2005; 352:1011, Blood 2019:133:40*)

- **Etiology**: autoimmune, infection, malignancy, chronic disease (HF, CKD); inflammatory cytokines (IL-1, IL-6 & TNFα) → ↑ hepcidin → ↑ ferroportin degradation/internalization → ↓ intestinal Fe absorption, ↓ Fe recycling by macrophage & hepatic Fe mobilization
- **Treatment**: Tx underlying dz. Fe only if concomitant Fe deficiency (Tsat <15-20%, ferritin <100, or no response to EPO).

**MACROCYTOSIS/MEGALOBLASTIC ANEMIA**: macrocytosis = RBC size > nl, megaloblastic = incr RBC size 2/2 abnl cell division in BM;

- **Folate ↓**: folate, 3mo. stores; ↓ intake (EIOH use), ↓ absorption (celiac, S-FU, MTX, TMP, phenytoin), ↑ demand (pregnancy, hemolysis, met. cancer); severe form a/w hemolytic anemia & pancytopenia, ↑↑ homocysteine, MMA nl; Tx: 1-5 mg PO folate QD

- **B12 ↓**: beef, 3yr. stores; ↓ intake (EIOH use, vegan), pernicious anemia (Ab to IF, gastric parietal cells), ↓ absorption (gastrectomy, celiac, Crohn’s, bacterial overgrowth, tapeworm, chronic pancreatitis); severe form a/w pancytopenia & subacute combined degeneration (dorsal columns, corticospinal tract) w/ dementia, ataxia, paresthesia, ↑↑ homocysteine, ↑↑ MMA Tx: 1-2 mg PO B12 QD (as effective as IM if not 2/2 malabsorption) (*Blood 1998;92:1191*). Post-bx, neurom sx start to improve 3mos-1yr (*NEJM 2013:368:149*).

**AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)**

- **Mechanism**: antibody- or complement-mediated RBC destruction. DAT detects IgG and C3 bound to RBCs.

- **Etiology**: (hemolysis + DAT, ↑ spherocytes):
  - Warm AIHA (CLL/lymphoma, SLE, Evans, HIV, CVID, post-transplant, prior allo-blood transfusion): +DAT anti-IgG/anti-C3, extravascular hemolysis in spleen; treat w/ steroids: prednison 1-1.5 mg/kg/d for up to 3 weeks (effective 50–90% of cases), splenectomy, Rituximab, immunosuppressants, IVIG, notify Blood Bank if rapid hemolysis
  - Cold AIHA: paroxysmal cold hemoglobinuria (cold-reacting IgG, often after viral infection) and cold agglutinin disease
    - Cold hematologic: +DAT anti-C3 at room temperature (can check thermal amplitude, cold agglutinins, ↑↑ IgG dir act at 4°C), has intravascular hemolysis; Tx: avoid cold; if sx/transfusion-dependent, plasmapheresis/IVIG as extravascular hemolysis in spleen; treat w/ steroids: prednisone 1-1.5 mg/kg/d for up to 3 weeks (effective 50–90% of cases), splenectomy, rituximab, immunosuppressants, IVIG, extravascular hemolysis in spleen; treat w/ steroids: prednison 1-1.5 mg/kg/d for up to 3 weeks (effective 50–90% of cases), splenectomy, rituximab, immunosuppressants, IVIG, notify Blood Bank if rapid hemolysis
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  - Warm AIHA: positive DAT, ↑ IgG (IVIG/RhIg/myeloma), CTD (eg: controlled SLE)

**SICKLE CELL ANEMIA** (*NEJM 2017; 376:1561*)

- **Mechanism**: Hbs → sickling when ↓O₂ → hemolysis + microvascular occlusion (ACS, CVA, pain crises, splenic sequestration, hand-foot syndrome, renal papillary necrosis, priapism); risk of aplastic anemia w/ parvo B19, encapsulated inxn, osteo

- **Gen**: hydroxyurea (↑ HbF), folate & MVI, vaccines for encapsulated bacteria, VTE ppx for all admitted to hospital

- **Pain crises**: pain ctrl (opioids + PO NSAIDs; if unknown prior dose: IV morphine 0.1-0.15mg/kg [max 10mg] or Diliaid 0.02-0.05mg/kg [max 1.5mg] → PCA, IVF if hypovolemic, O2 if <95%)

- **Acute chest syndrome**: fever, ↑WBC, pulm. infiltrate; r/o PE, ACS, PNA; Tx: O2 if <95%, transfusions (goal Hb >10); simple vs. exchange, pain ctrl (see above), abx (CTX/azithro or FQ), bronchodilators, incentive spirometry

- **Transfusion**: indicated in acute stroke, multorgan failure, acute chest syndrome, goal Hb >10. Exchange > simple if Hb near baseline, high HbS % (≥50%) due to risk of hyperviscosity.

- **Hyperhemolytic crisis**: rare complication (1%); presentation: pain, fever, worsening anemia w/in 7-15 days of transfusion, dropping reticulocyte count, CAT may be negative. Tx: Notify blood bank, hydration +/- steroids, IVIG, rituximab.

**PANCYTOPEANIA**

- **Etiology**: BM: ↓cellular (aplastic, myelofibrosis, chemo, PNH, mets), cellular nl (MDS, PNH), ↑cellular (leukemia, lymphoma, MM)

- **Systemic**: ↑spleen (cirrhosis), toxin (EtOH, cocaine), nutrition (↓B12/folate, Cu), CTD (SLE, RA), sepsis, HLH/MAS

- **Medications**: NSAIDs, PPIs, sulfas, antihistamine, chemo, anticonvulsants, antiprotozoals, heavy metals, many others

- ↑Infection: viral (HIV, HBV/HCV, CM/EVEB; parvo), bacterial (Brucella, TB), fungal (Histoplasmosis, parasitic (leish, malana, schisto)

- **Work-up**: Initial/Mild: ↑ meds & repeat CBC diff. retic. smear, LFTs, TSH, B12 / folate, PT / PTT, fibrinogen, HIV, HBV / HCV

- **Severe**: ↑ Hcy / MMA, Cu, LDH / DAT, ANA / RF / CCP, ESR / CRP, SPEP, CMV / EBV / Parvo, Tox, Abd US+Doppler

- **Heme**: ↑↑ BMBx (highly consider if pancytopenic w/o obvious systemic causes), flow cytometry (if c’t PNH)

*Effitan Akam, Charlotte Lee* 126
Hematology

Thrombocytopenia

THROMBOCYTOPENIA (Hematology 2012;2012:191)

Definition: Platelet count < 150k. Risks: <50k w/ surgery, <20k spont. bleed (less so in ITP), <10k severe bleed

<table>
<thead>
<tr>
<th>↑ PRODUCTION</th>
<th>↑ DESTRUCTION</th>
<th>SEQUESTRATION / POOLING / DILUTIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Infxn: late HIV/HCV, parvo, sepsis</td>
<td>- Infxn: early HIV/HCV, H, pylori &gt; HIV/VZV/CVM/EBV, tick-borne illness</td>
<td>- Splenomegaly (e.g. cirrhosis &amp; portal HTN): may sequester 90% of circulating platelets</td>
</tr>
<tr>
<td>- Nutrition: ↓B12/folate/Cu ETOH</td>
<td>- Immune: ITP (+AIHA+Evan’s), SLE/APS, RA, CLL, HIT, CVID, post-transfusion purpura</td>
<td>• Massive transfusion → 10U pRBC ↓ plt by 50%</td>
</tr>
<tr>
<td>- Drugs: see list in margin</td>
<td>- Drug-induced: immune (DITP, vanc)</td>
<td>• Hypothermia</td>
</tr>
<tr>
<td>- Malignancy: leukemia, MDS, PMF, aplastic anemia, infiltrate</td>
<td>- MAHA: DIC, TTP/HUS, mHTN, HELLP</td>
<td>• Gestational</td>
</tr>
<tr>
<td>- Congenital: Bernard Soulier, vWD (specific types), other rare causes</td>
<td>- Shearing/aggregation: CVH, CPB, IABP, vasculitis, hemangioma (Kasabach-Merritt)</td>
<td></td>
</tr>
</tbody>
</table>

Workup: initial labs: CBC w/ diff (Δ other cell lines), review special slide (schistos, other), HIV, HCV (if not recently)
- If c/l hemolytic anemia (↓Hgb & ↓Plts) → also LDH / hapt / bili, DAT (AIHA), retic count.
- If schistocytes on slide → also coags, D-dimer, fibrinogen (eval for DIC vs. TTP/HUS), consider heme consult
- Consider ANA (SLE), ACL/ALA (APLS) if appropriate based on other clinical signs/symptoms.
- If ↓> 30 yo, splenomegaly, or systemic sx → consider BMxB to r/o MDS, AA, leukemia, infiltrate.
- Rule out pseudo-thrombocytopenia → platelet clumping 2/2 EDTA (can order Platelet Count, Citrated in Epic)

PRIMARY IMMUNE THROMBOCYTOPENIA (ITP) (Blood 2017;129:2829)
Pathophys: thrombocytopenia/di auto Ab-mediated megakaryocyte destruction and ↓ plt production
Presentation: Presents w/ mucocutaneous bleeding; defined by isolated plt <100k, dx of exclusion; 10% have ITP + AIHA = Evans Syndrome; BMxB: ↑ megakaryocytes (performed in >60yo to r/o MDS); anti-plt Ab testing not useful.

Management: (Lancet Haematol 2016;3:e489)
- Tx: plasma exchange, no plt unless bleeding; role of steroids & rituximab still debated. (Blood 2017;129:2836)
- HUS (plt <30K): Shiga-toxin-mediated bloody diarrhea w/ abd pain (O157:H7 E. coli, Shigella). S/sx: severe AKI; severe neuro sx (SZ, coma, hemiparesis) rare. Dx: stool+ for organism or toxin; Tx: supportive care often including HD, unclear role for Abx in prevention
- Atypical HUS: complement-mediated TMA; S/sx: severe AKI + 20% w/ extra-renal sx (CNS, cardiac, pulm hemorrhage, pancreas); Dx: complement genotyping, anti-complement Ab; Tx: plasma exchange, eculizumab (terminal comp. inhib, $$$, NEJM 2013;368:2169)
- Drug-Induced: 1) Immune-mediated (gemcitabine, oxaliplatin, quetiapine, quinine) → acute fc, abd pain, n/v, AKI
- Dose-Dependent (Genticin, tacrolimus, sirolimus, cyclosporine, cyclophosphamide, cyclosporin, DACA) → subacute fatigue, HTN

Secondary Etiologies: SLE, APLAS, HELLP syndrome, scleroderma, ↑↑↑ HTN and the following:
- DIC: 2/2 various inflammatory etiologies (sepsis, metastatic cancer, infection, trauma, pancreatitis). ↑PT/PTT, ↑D-dimer, ↓fibrinogen.
- Often normal coags in chronic DIC. DIC score: plt <50K, ↑D-dimer, ↑PTT (>6 sec), fibrinogen <100 mg/dL (score 5-8 consistent w/ DIC). Tx underlying cause, transfuse plt if <10K (or serious bleeding <50K), cryo if fibrinogen <100, FFP if INR >2.

Anti-infectives:
- TMP/SMX
- Vancomycin
- Penicillin
- Ampicillin
- Piperacillin
- Ceftriaxone
- Rifampin
- Ethambutol
- Quinine

Anti-platelets:
- Aboximab
- Epptibatide
- Tirofiban

Others:
- Heparin (HT)
- Ranilindine
- Simvastatin
- Haloperidol
- Amiodarone
- Oxaliplatin
- Irintiecann
- Acetaminophen
- Naproxen
- Ibuprofen
- Furosemide
- OTC/Herbal

Direct | BM:
- Linezolid
- Thiazide
- Chemo/XRT
- ETOH

Eftitan Akam

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- Eosinophils: myeloid lineage-derived granulocytes that act as innate effector cells in Th2 immune responses. Pathology mediated by release of granule contents such as major basic protein (MBP), peroxidases (→ ROS), cytokines/chemokines, & enzymes
  - Eosinophils are quickly eliminated by steroids → eosinophilia may be unmasked as pts taper off chronic glucocorticoids.
  - Either primary and due to clonal expansion (HES/leukemia) or secondary (reactive) due to infection, atopy, meds, rheum dz, etc.

Malignancy  | Primary HES (PDGFRA-assoc.), eosinophilic leukemia, NHL, HL, mastocytosis; less common with solid tumors.
Autoimmune  | EGPA (see Vacculitits), PAN, eosinophilic fasciitis, RA, IBD, lgG4, GVHD, blistering disease.
Allergic     | Drug or food allergy, DRESS Syndrome, ABPA, atopy, hyper IgE syndrome, AIN, episodic angioedema (Glyc Synd.).
Misc         | Adrenal insufficiency, cholesterol emboli syndrome, acute arterial thrombosis.


- Hx: meds/supplements (<6 wks), diet, travel, occupational exposures, atopy, infxn, malignancy, rheumatic dz, full ROS
- Exam: assess for rashes, cardiac/pulmonary abnormalities, nasal/sinus involvement, LAD, hepatospplenomegaly, neuropathy
- Initial diagnostics: CBC w/ diff, special slide, BMP, LFTs, LDH, ESR/CRP
  - If AEC 500-1500: check troponin, B12/tryptase, CXR as clinically indicated
  - If AEC >1500, assess for HES: check U/A, CK, troponin, EKG, CXR, PFTs, CT C/A/P (for adenopathy, organomegaly, masses, organ infiltration), tissue biopsy of affected organs; also obtain B12, troptase, serum Ig levels
- Additional diagnostics (as clinically indicated): Strongyloides serology & stool O&P, other serologies if potential exposure; ANCA if ?EGPA; ANA, RF, CCP if ?rheum dz; IgE levels + allergy testing if ?allergic; imaging/bronch, serologies (e.g. aspergillus IgE) if ?pulm. dz; imaging/endoscopy if ?GI dz; TTE/CMR if ?cardiac dz; periph. flow +/- BM sx if ?MPD or >1500 & no obvious 2nd cause

TREATMENT (Hematology 2015;2015:92)

- Urgent Tx: if cardiac, neuro, or thromboembolic complications, AEC >100,000/rapidly rising, or s/sx of leukostasis → 1mg/kg to 1g solumedrol (+empirc ivermectin 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 identifiable cause to treat; consider resolution & organ damage

ORGAN-SPECIFIC PATHOLOGY


- Eosinophilic endomyocarditis: necrosis → thrombus formation (→ embolic events) → fibrosis → restrictive CM, valve involv.
  - May be due to hypersensitivity myocarditis, parasitic infections, malignancy, idiopathic HES
  - Dx: TTE (LV/RV apical dysfunction, signs of restriction, intracardiac thromb) and cardiac MRI (+subendocardial LGE) → transient/migratory pulm. opacities, 1Es/2/2 helminth larvae in lung; Dx: larvae in resp secretion (stool usually -)
- Eosinophilic coronary arteritis: rare complication of EGPA; may mimic ACS.
  - Acute eosinophilic PNA: <7d fever, cough, SOB; a/w smoking; 1periph. Eos often absent at presentation; Dx: BAL Eos ≥25%
  - Chronic eosinophilic PNA: subacute fever, cough, SOB, wt loss; a/w asthma; Dx: BL periph/pleural infl, UL-predom; BAL Eos>25%
  - Allergic bronchopulmonary aspergillosis (ABPA): asthma/CF c/b recurrent exacerbations w/ fever, malaise, brown mucus plugs; Dx: 1Es, 1total IgE, 1Aspergillus IgE & IgG, imaging w/ central bronchiectasis, UL/ML consolidations; Tx: steroids + itraconazole
  - Loeffler syndrome: transient/migratory pulm. opacities, 1Es/2/2 helminth larvae in lung; Dx: larvae in resp secretion (stool usually -)
  - Eosinophilic esophagitis (EoE): dysphagia, food impaction, GERD-like sx/refractory GERD, assoc w/ allergic conditions; Dx: EGD w/ bx, exclude other causes (GERD, motility d/o, Crohn’s, infxn, CTD, etc.); Tx: dietary Δs, PPI, topical steroids (MDI/neb, PO liquid)
  - Eosinophilic gastroenteritis (EGE): stomach/duod. +/- esoph., colon; Sx: N/V/D, abd. pain, ascites; Tx: dietary Δs, PO steroids


- Myelodysplastic HES: acute/chronic eosinophilic leukemia, PDGFRA-associated MPN → clonal expansion of Eos; 80% pts have FIP1L1-PDGFRα fusion gene; remainder have PDGFRα, FGFR1, JAK2 rearrangements
  - Dx: anemia, thrombocytopenia, 1 tryptase, 1 B12, special slide (dysplastic eosinophils), flow cytometry (PDGFRα, BCR-ABL1, JAK2, FGFR1, KIT), BM Bx (fibrosis, hypercellularity)
  - Tx: if PDGFR+, imatinib; if JAK2+, JAK2 inhibitor; if FGFR1+, chemo; 2nd line or no rearrangement: hydroxyurea, IFN-α, other TKI/empirc imatinib
- Lymphocytic HES: clonal lymphocyte expansion → 1 cytokines that stimulate eosinophil differentiation. Often present w/ skin/skin tissue manifestations. Up to 25% risk of progression to lymphoma.
  - Dx: flow cytometry for CD3, CD4
  - Tx: steroids; 2nd line: IFN-α, hydroxyurea, mepolizumab (anti-IL-5; NEJM 2008;358:1215, alemtuzumab
- Idiopathic HES: eosinophilia without identified cause and evidence of end-organ damage → consider ANCA-neg EGPA (50% cases)
  - Tx: steroids; 2nd line: hydroxyurea, IFN-α, mepolizumab, alemtuzumab

Jacqueline Henson

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## Coagulation Disorders

### Coagulopathy

1st hemostasis (↓ platelet # or function, VWD → mucocutaneous bleeding, petechiae) or 2nd (prolonged PT/PTT → deep tissue bleeding)

- Rule out artifact, anticoagulant use, or systemic disease (cirrhosis, DIC, abx, malnutrition, renal dz, cancer)
- If prolonged PT/PTT and etiology is not clinically apparent, order mixing study w/ normal plasma
  - If PT/PTT corrects: supports clotted factor deficiency (confirm w/ factor specific assays)
  - If no (or partial) correction: supports presence of inhibitor (confirm w/ inhibitor specific assays)
    - Drug inhibitor (e.g. heparin), acquired factor inhibitor (VIII, V->IX, XI), nonspecific inhibitor (e.g. LA)
  - If work-up is unrevealing, think VWD, platelets, can check FXIII (most commonly presents w/ delayed surgical bleeding)
- Tx: replace missing factor, eliminate inhibitor (immunosuppressants), treat underlying condition

<table>
<thead>
<tr>
<th>Coagulation Defect:</th>
<th>Normal aPTT</th>
<th>Prolonged aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal PT</td>
<td>Platelet dysfunction (VWD, other platelet disorders) ↓ Factor XIII</td>
<td>Intrinsic pathway: ↓ Factor VIII, IX (hemophilias), or XI (Ashkenazi) VWD ↓ Factor VIII</td>
</tr>
<tr>
<td>Prolonged PT</td>
<td>Extrinsic pathway: ↓ Factor VII (liver, congenital, early DIC) Vit K deficiency/warfarin</td>
<td>Common pathway: Liver, DIC, warfarin OD/rat poison Rarely common pathway deficiency/inhibitor</td>
</tr>
</tbody>
</table>

### Hypercoagulable States (NEJM 2017;377:1177)

### Workup of First VTE

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Provoked by strong trigger</th>
<th>Unprovoked OR Provoked by weak trigger</th>
<th>Unusual site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ex: major surgery, trauma, immobility, CA, pregnancy/OCP, SLE, IBD, nephrotic sx, Paget-Schroetter (UES), May-Thurner (LES)</td>
<td>(e.g. minor surgery) in a young pt (&lt;45 yo) or strong FH or recurrent thrombosis</td>
<td>Arterial thrombosis</td>
</tr>
</tbody>
</table>

- Consider age-appropriate cancer screen
- No role for hypercoag. testing
- Test for inherited conditions (below)
- Test for APLAS if extensive VTE, recurrent events, or arterial clot
- Cerebral veins: test for inherited conditions + APLAS
- Splanchic veins: test for inherited conditions + APLAS + MPN + PNH

- Provoked → A/C x 3 mo. DOAC>VKA>LMWH (LMWH favored if cancer), if persistent risk factor can extend (CHEST 2016;149:315)
  - Catheter-associated → no need to remove catheter if functional and able to tolerate A/C
- Unprovoked → at least 3 mo A/C. Consider indefinite if: low-moderate bleeding risk AND unprovoked proximal DVT or symptomatic PE, recurrent VTE, or cancer (reassess annually); unprovoked have significantly higher recurrence risk (10% <1yr off A/C, 30% <5yr)
  - No evidence that “hypercoag workup” improves outcomes, rarely changes mgmt, $$$, do NOT perform at time of event
    - Panel includes: APC resistance (reflexes to FVL), protein C/S (reflexes to FVIII/fibrinogen), ATIII, LA, prothrombin G20210A (PTG), cardiolipin. Does NOT include anti-β2 glycoprotein.
    - Only FVL and PTG are reliable in acute VTE or on A/C → wait to send entire panel until 2 wks after A/C d/c’d

### Condition

<table>
<thead>
<tr>
<th>CLINICAL PEARLS</th>
<th>TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited Conditions</td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden/ APLS resistance</td>
<td>Most common inherited cause of hypercoagulability</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>2nd most common cause of hypercoagulability</td>
</tr>
<tr>
<td>Protein C/S deficiency</td>
<td>Activated protein C + protein C/S inactivate FV aand FVIIIa; ↓ level (more common) or function leads to hypercoagulability</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>↓ level or function</td>
</tr>
<tr>
<td>Others</td>
<td>↑ FVIII, dysfibrinogenemia, fibrinolytic deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>APLAS</td>
</tr>
<tr>
<td>Clinical criteria: venous/artrial thrombosis, pregnancy complications (eg: spont. abortion, premature birth 2/2 preeclampsia, eclampsia, or placental insufficiency)</td>
</tr>
<tr>
<td>- LA unreliable on A/C, but anti-cardiolipin and β2GP IgM/IgG not affected</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>NB: HypercT, HIT &amp; APLAS, are the only hypercoagul. assoc. w/ arterial thrombosis</td>
</tr>
</tbody>
</table>

Will Simmons 129
### Hematology

#### Parenteral Anticoagulation

**PARENTERAL ANTICOAGULANTS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Monitoring</th>
<th>Bridging</th>
<th>Reversal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin (UFH)</td>
<td>- Ac: bolus 0U/kg, gtt</td>
<td>- PTT</td>
<td>- To LMWH: give</td>
<td>- Protamine: 1 mg</td>
<td>- Preferred in renal failure (CrCl &lt;30), procedure soon, poor absorption, pregnancy</td>
</tr>
<tr>
<td></td>
<td>12U/kg/hr, goal PTT 63-83</td>
<td>ACT at high doses (cath lab)</td>
<td>LMWH &amp; stop UFH at same time</td>
<td>per 100U heparin (contains ATIII, which potentiates A/C effect of UFH)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- VTE: bolus 80U/kg, gtt</td>
<td>- Anti-Xa if baseline</td>
<td>To warfarin: stop</td>
<td>Do NOT give FFP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18U/kg/hr, goal PTT 70-100</td>
<td>↑PTT, very high doses: goal 0.3-0.7</td>
<td>UFH once therapeutic INR ≥2d</td>
<td>(contains ATIII, which potentiates A/C effect of UFH)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- PPX: 5,000U SC q8-12h</td>
<td></td>
<td>- Protamine: 1mg per</td>
<td>- Acute VTE: LMWH &gt; UFH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1mg/lm/kg to max 50mg, provides</td>
<td>(thrombus regression, fewer comp, mortality same)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>~60% reversal, most</td>
<td>(Cochrane Rev 2017;2:1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>effective if last dose</td>
<td>- Prolonged t1/2 in renal failure</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>within 8 hr</td>
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</tr>
<tr>
<td>Enoxaparin (LMWH, Lovenox)</td>
<td>- Ac: 1mg/kg SC BD</td>
<td>- No need for routine monitoring</td>
<td>- To UFH: stop LMWH &amp; start UFH</td>
<td>- No need for reversal agent</td>
<td>- Only dabigatran (PO) has antidote (idarucizumab)</td>
</tr>
<tr>
<td></td>
<td>1mg/kg SC BD</td>
<td>- Anti-Xa (4th after dose)</td>
<td>w/bolus 1.2 h before the next</td>
<td>t/2 4h after every dose change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- PPX: 40mg SC QD (30mg</td>
<td>- No need for routine monitoring</td>
<td>LMWH dose would have been</td>
<td>for goal 1.5-3x baseline PTT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BID if high risk)</td>
<td>- Anti-Xa (3h after dose)</td>
<td>due</td>
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<tr>
<td>Fondaparinux (Araxtra)</td>
<td>- VTE: wt-based dosing</td>
<td>- No need for routine monitoring</td>
<td>- To warfarin: stop</td>
<td>- No reversal agent</td>
<td>- Only dabigatran (PO) has antidote (idarucizumab)</td>
</tr>
<tr>
<td></td>
<td>&lt;50kg → 5mg QD 50-100kg</td>
<td>- Anti-Xa (3h after dose)</td>
<td>fondaparinux once therapeutic</td>
<td></td>
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<tr>
<td></td>
<td>&gt;100kg → 10mg QD</td>
<td></td>
<td>INR ≥2d</td>
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<tr>
<td></td>
<td>- PPX: 2.5mg SC QD</td>
<td></td>
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<tr>
<td></td>
<td>- GFR &lt;30: contraindicated</td>
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<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>- HIT: 1-2mcg/kg/min</td>
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<tr>
<td></td>
<td>- Caution w/dosing in critically ill, cardiac dysfunction, liver disease</td>
<td></td>
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<tr>
<td></td>
<td>- PTT (2h after every dose change)</td>
<td></td>
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</tbody>
</table>


**Risk Factors**

- **Nonvalvular AF (ACC 2017)**
  - CHA2DS2-VASc ≥7
  - CVTIA, or systemic embolism <3mo.
  - Bridge unless major bleed/LICH <3mo.
  - VTE <3 mo.
  - Prot. C/S or ATII deficiency
  - Multiple thrombophilic abnormalities
  - Bridge
  - AF w/ CHADS2 ≥4 and prior CVA/TIA or valvar AF
  - All mech. MV, caged ball/lilt disc AVR, or any mech. valve w/ CVA <6mo.
  - VTE <3mo. or APLAS

- **VTE (ASH 2018)**
  - VTE 3-12mo.
  - Heterozygous factor V Leiden
  - Prothrombin 20210 mutation
  - Recurrent VTE
  - Active malign.
  - No bridge
  - AF w/ CHADS2 3-4 (CHA2DS2-VASc 5-6)
  - Bileaflet AVR w/ CVA risk factors
  - VTE 3-12mo., recurrent VTE, non-severe thrombophilia, active malignancy
  - Consider bridging based on risk of bleeding in patient/from procedure

- **Other Indications (ACCP 2012)**
  - AF w/ CHADS2 0-2 w/o prior CVA
  - Bileaflet AVR w/o CVA risk & no AF
  - VTE >1yr and no risk factors

**Risk Factors**

- **High Risk**
  - CHA2DS2-VASc ≥7
  - CVTIA, or systemic embolism <3mo.
  - Bridge unless major bleed/LICH <3mo.

- **Mod. Risk**
  - CHA2DS2-VASc 5-6
  - CVTIA or systemic embolism >3mo.
  - Likely bridge if prior CVA/TIA and if not ↑ risk of bleeding

- **Low Risk**
  - CHA2DS2-VASc ≤4
  - No prior CVA/TIA or systemic embolism
  - No bridge

**Bridge**

- **NeJM 2015;373:373 823** demonstrated ↑ risk of bleeding w/ bridging in pts with AF undergoing invasive procedure requiring interruption of VKA (NB: excluded pts w/ mech. valves, stroke/TIA <12wk, major bleeding <6wk, CrCl <30, Ptt <100k)

- **Bridging VKA w/ UFH or LMWH**
  - Stop VKA 5d prior to procedure if therapeutic INR. Start UFH or LMWH when INR <2.
  - Stop UFH 4-6h prior to surgery and LMWH 12 or 24hrs prior to surgery (depending on dosing interval).
  - Restart UFH/LMWH at 24hrs postop if low postprocedural bleeding risk or 48-72hrs if high risk. D/C when INR >2.
  - Resume VKA w/in 24hrs postop if no bleeding complications (will not ↑ early bleeding risk because effect takes 24-72hrs).

- **DOACs** generally no bridging required
  - Most can be stopped 24-72h prior to surgery, depending on renal function (see JACC 2017;69:871)
  - If low bleeding risk, can resume 24hrs after procedure. If high bleeding risk, wait 48-72hrs. If unable to take PO for prolonged period or second procedure is anticipated, start UFH/LMWH at the above time points instead.

Charlotte Lee

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Hematology

Oral Anticoagulation


<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing/Monitoring</th>
<th>Bridging/Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong> (Coumadin)</td>
<td><strong>Dose:</strong> Initiation: 5mg QD x2d; if frail, HF, kidney/liver dz: consider 2.5mg; if BMI &gt;40: consider 7.5mg</td>
<td><strong>Bridging:</strong> To parenteral A/C: start IV w/o bolus when INR &lt;2</td>
</tr>
<tr>
<td>- Vitamin K antagonist: inhibits vitamin K-dependent gamma-carboxylation of F II, VII, IX, X, Protein C, S</td>
<td><strong>Adjust by INR, which lags 48h behind dose Δ</strong></td>
<td>- From parenteral A/C: see <strong>Parenteral Anticoagulation Reversal:</strong> (IV vitamin K faster than PO at 6h, same at 24h)</td>
</tr>
<tr>
<td>- t½ 40h (variable)</td>
<td><strong>Monitoring:</strong> (UW Dosing Nomogram)</td>
<td>- <strong>Active bleeding:</strong></td>
</tr>
<tr>
<td></td>
<td>- INR &lt;2: T up to 10-20%/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- INR 2-3: no change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- INR 3-4: ↓10%/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- INR &gt;4: hold until INR 2-3, restart ↓5-15%/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- If overlap w/ direct thrombin inhibitor, check chromogenic FXa: goal 20-40%</td>
<td></td>
</tr>
</tbody>
</table>

**Dabigatran** (Pradaxa)

<table>
<thead>
<tr>
<th>Dose:</th>
<th>Non-valvular AF: 150mg PO BID if GFR &gt;30, 75mg PO BID if GFR 15-30 (RE-LY NEJM 2009;361:1339)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE:</strong> 150mg PO BID after 5d UFH/LMWH (RE-COVER NEJM 2009;361:2342)</td>
<td></td>
</tr>
<tr>
<td>- PPX: 220mg PO QD (RE-NOVATE II Thromb Haemost 2011;106:721)</td>
<td></td>
</tr>
</tbody>
</table>

**Rivaroxaban** (Xarelto)

<table>
<thead>
<tr>
<th>Dose:</th>
<th>NV AF: 20mg PO QD if GFR &gt;30, 15mg if GFR 15-30 (ROCKET-AF NEJM 2011;365:883)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE:</strong> 15mg PO BID x21d, then 20mg QD (EINSTEIN-DVT NEJM 2010;363:2499; EINSTEIN-PE NEJM 2012;366:1267)</td>
<td></td>
</tr>
<tr>
<td>- PPX: 10mg PO QD (MAGELLAN NEJM 2013;368:513)</td>
<td></td>
</tr>
</tbody>
</table>

**Apixaban** (Eliquis)

<table>
<thead>
<tr>
<th>Dose:</th>
<th>NV AF: 5mg PO BID if GFR &gt;30, 2.5mg BID if 2/3: GFR 15-30, Wt ≤60kg, age &gt;80 (ARISTOTLE NEJM 2011;365:981)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE:</strong> 10mg BID x7d, then 5mg BID x6mo, then 2.5mg BID if need (AMPLIFY NEJM 2013;369:799)</td>
<td></td>
</tr>
<tr>
<td>- PPX: 2.5 mg BID (NEJM 2009;361:594)</td>
<td></td>
</tr>
</tbody>
</table>

**Edoxaban** (Savaysa, Lixiana)

<table>
<thead>
<tr>
<th>Dose:</th>
<th>NV AF: 60mg PO QD, 30mg QD if CrCl 30-50 or wt ≤60kg (ENGAGE-AF NEJM 2013;369:2093)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE:</strong> 60mg QD after 5d UFH/LMWH; 30mg QD if CrCl 30-50 or wt ≤60kg or taking P-gp inhibitors (NEJM 2013;369:1406)</td>
<td></td>
</tr>
<tr>
<td>- PPX: not FDA-approved (15-30mg PO QD)</td>
<td></td>
</tr>
</tbody>
</table>


- VTE: DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) > VKA > LMWH
- VTE & active malignancy: LMWH or edoxaban (NEJM 2018;367:615) > other DOACs, VKA; apixaban may be > LMWH (ADAM-VTE ASH 2018); DOAC ppx ↓INR risk in inh/high risk ambulatory pts w/ CA (AVERT NEJM 2019;360:711; CASSINI NEJM 2019;380:720)
- VTE & obesity (BMI ≥40, weight ≥120 kg): VKA, LMWH, or rivaroxaban > other DOACs
- Recurrent VTE on non-LMWH A/C: switch to LMWH; Recurrent VTE on LMWH: increase LMWH dose
- Mechanical valve: VKA; VKA > dabigatran (RE-ALIGN NEJM 2013;369:1206)
- Non-valvular AF: DOAC > VKA; Valvular AF: VKA
- AF + PCI: dual therapy (P2Y12 + OAC) vs. triple therapy (ASA + P2Y12 + OAC): triple therapy ↑bleeding, ↓ ischemic events
  - Dual therapy options: (1) P2Y12 (clopidogrel or ticag) + VKA (WOEST Lancet 2013;381:1107); (2) P2Y12 (clopidogrel) + low dose rivaroxaban 15mg QD (PIONEER AF NEJM 2016;375:2423); ↓bleeding, similar CV death/MI/CVA; (3) P2Y12 (clopidogrel) + dabigatran 150mg QD (RE-DUAL PCI NEJM 2017;357:1517); ↓bleeding, similar MI/CVA/death/unplanned revascularization
  - If triple therapy chosen, consider transition to dual therapy at 4-6 weeks
- APS: VKA; VKA > rivaroxaban in high-risk APS (TRAPS Blood 2018;132:1365)
- Stable ischemic CAD: very lose dose rivaroxaban (2.5mg BID) + ASA → ↓MACE compared to ASA alone; ↑ major bleeding but no difference in ICH or fatal bleeding (COMPASS NEJM 2017;377:1319)
**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
- Therapeutic apheresis: extracorporeal treatment that selectively removes cells or other abnormal substances
  - Plasmapheresis: removes plasma. Indications: TTP, hyperviscosity sx, cryo, Guillain-Barre, CIPD, MG, ANCA, anti-GBM.
  - Plasma exchange: similar but w/ replacement (donor plasma). Indications: TTP (replace ADAMTS13, NEJM 1991:325:393)
  - Cytapheresis: removes abl or excessive # blood cells; indications: hyperleukocytosis, thrombocytosis (goal WBC <100 and plt <1000), sickle cell crisis, severe babesiosis (high grade parasitemia >10, severe hemolysis, or pulm/liver/renal dz)
- Direct antiglobulin test (DAT/Coomb's Test): tests for Ab or complement on RBCs (RBCs + Coomb's reagents [anti-IgG, anti-C3])

**BLOOD PRODUCTS**

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red Blood Cells</strong></td>
<td>1U = 330cc = $895 Processing <em>See transfusion restrictions below.</em> 1. Leukocyte reduction 2. Irradiation 3. Washing</td>
<td>- Hgb &lt;7 (NEJM 2014:371:1381, NEJM 2013:368:11) - Hgb &lt;8 if CAD/ACS ortho/cardiac surgery - AlHA and MDS (no specific Hgb threshold) - Sickle cell disease (see Anemia: Sickle Cell Disease)</td>
<td>- Response: 1U ↑ Hgb 1 - pRBCs will not exert same onotic effect as hyperoncotic colloid (25% albumin) (Hct ≈55% diluted in saline)</td>
</tr>
<tr>
<td><strong>Fresh Frozen Plasma</strong></td>
<td>1U = 250cc = $460 1 Dose ~ 10-20 cc/kg Noncellular portion of blood that is separated and frozen after collection. Contains all coagulation factors with max correction INR 1.7</td>
<td>Low platelets or functionally abnormal platelets - &lt;10,000: PPX spont bleeding. Consider antifibrinolytics in refractory thrombocytopenia in CA (NEJM 1997:337:1870) - &lt;50,000: major bleed, intra- or post-op surgical bleed, ppX prior to invasive operative procedures (no data) - &lt;100,000: post-bypass bleed, ICH/ophthalmic (no data) - ITP: if life-threatening CNS/GI/GU bleed; fatal hemorrhage is often preceded by wet purpura (mucus membrane bleeding). Otherwise pltts not beneficial. - HIT: TTP: avoid PLTs unless bleeding</td>
<td>- Effect &lt; 6H due to short half of FVII - Assess response: 1U ↑ coagulation activity = 10%</td>
</tr>
<tr>
<td><strong>Cryoprecipitate</strong></td>
<td>10U = 150 ccs = $2850 Contains factor VIII, factor XIII, VWF, and fibrinogen</td>
<td>Low platelets or functionally abnormal platelets - &lt;10,000: PPX spont bleeding. Consider antifibrinolytics in refractory thrombocytopenia in CA (NEJM 1997:337:1870) - &lt;50,000: major bleed, intra- or post-op surgical bleed, ppX prior to invasive operative procedures (no data) - &lt;100,000: post-bypass bleed, ICH/ophthalmic (no data) - ITP: if life-threatening CNS/GI/GU bleed; fatal hemorrhage is often preceded by wet purpura (mucus membrane bleeding). Otherwise pltts not beneficial. - HIT: TTP: avoid PLTs unless bleeding</td>
<td>- Fibrinogen replacement: 0.2 bag/kg → 100 mg/dL fibrinogen w/ 1/2 3-5d - FVIII or vWF replacement: cryo is last resort therapy</td>
</tr>
<tr>
<td><strong>Coagulation Factors</strong></td>
<td>1-factor: VIII, IX, rF Vila (NovoSeven), ATIII 3-factor (II, IX, X) 4-factor PCC (II, VII, IX, X; Kcentra) FIBELA (anti-inhib. complex) vWF/FVIII (Humate-P)</td>
<td>Low platelets or functionally abnormal platelets - &lt;10,000: PPX spont bleeding. Consider antifibrinolytics in refractory thrombocytopenia in CA (NEJM 1997:337:1870) - &lt;50,000: major bleed, intra- or post-op surgical bleed, ppX prior to invasive operative procedures (no data) - &lt;100,000: post-bypass bleed, ICH/ophthalmic (no data) - ITP: if life-threatening CNS/GI/GU bleed; fatal hemorrhage is often preceded by wet purpura (mucus membrane bleeding). Otherwise pltts not beneficial. - HIT: TTP: avoid PLTs unless bleeding</td>
<td>- Blood Transfusion Service approval required - S/E: Allergic rxn, thrombosis</td>
</tr>
<tr>
<td><strong>Antifibrinolytics</strong></td>
<td>Contains Lysine derivatives that bind to plasminogen to fibrinolysis and hemostasis Types (topical, PO, IV) 1. Aminocaproic acid (Amicar) 2. Tranexamtic acid (TXA)</td>
<td>Fibrinogen &lt;100; 50-100mg/dL, give 10U; &lt;50, give 20U Advanced liver disease (consider antifibrinolytics instead) Massive transfusion w/ fibrinogen or abl ROTEM/TEG Complex cardiac surgery (JAMA 2017:217:738) Postpartum hemorrhage (Br J Anaesth 2015: 114:623) FVIII deficiency, VWD, uremia</td>
<td>- Amicar: 4-5 g/hr → 1g/hr for 8h until bleeding controlled - TXA: 1 g → 1g/8h - S/E: Risk of seizures w/ TXA</td>
</tr>
</tbody>
</table>
**Hematology**

### Transfusion Medicine

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Types</th>
<th>~$40/bottle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. 5% (iso-oncotic)</td>
<td>5% if hypovol/intravasc depl., 25% if fluid/Na restricted</td>
</tr>
<tr>
<td></td>
<td>2. 25% (hyper-oncotic)</td>
<td>- Cirrhosis: HRS, SBP, LVP (see End Stage Liver Disease)</td>
</tr>
<tr>
<td></td>
<td>Both contain 12.5g albumin &amp; 154 mEq Na (isotonic)</td>
<td>- Shock: 4% albumin similar to 0.9% NS for IVF resuscitation (when alb. &gt;2) (SAFE NEJM 2004;350:2447)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ARDS: 25% albumin (25g) q8h x3d + laxis gt 3x3d → ↑O2, neg. TBB (when alb. &lt;2) (Crit Care 2005;33:1681)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- C/T: traumatic brain injury (SAFE trial subgroup)</td>
</tr>
</tbody>
</table>

### TRANSFUSION RESTRICTIONS*

- **Leukoreduction (LR):** filters leukocytes to (1) ↓ HLA sensitization in chronically transfused pts / heme malignancies, bone marrow / kidney / lung transplant candidates (not liver transplant) (2) ↓ CMV risk & (3) ↓ febrile non-hemolytic transfusion rxn (FNHTR)
- **Irradiation:** prevents proliferation of donor T lymphocytes from attacking host marrow (TA-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:** (1) hx severe anaphylaxis, (2) IgA def & anaphylaxis

### MASSIVE TRANSFUSION

**Page Transfusion Medicine Resident p21829 (x63623) and run down pick-up slip**

- **Activate when anticipate transfusing 50% TBV (~5U pRBC) in 2h OR 100% TBV (~10U pRBC or 5L plasma) in 24h**
- **Complications:** dilutional coagulopathy, hypothermia, hypocalcemia (citrate), metabolic alkalosis (citrate metabolized to bicarb)
- **Emergency release un-crossmatched pRBCs (O- for pre-menopausal females, O+ ok for males and older females)**
- **Transfuse 1U FFP for every 3-4 pRBCs (if >6 U pRBCs anticipated), 6-pk PLT (PLT<100,000 anticipated), 10U cryo (fibrinogen <100)**
  - No evidence for 1:1 transfusion protocol, combat trauma studies confounded by survival bias (JAMA 2015;313:471)
  - Excessive FFP a/w higher ARDS in pts not requiring massive transfusion
  - Goals: Hb >7-10, PLT >50,000, INR <2, fibrinogen >100
- **Correct coagulopathy (A/C, liver dz) → IV vit K, FFP 15cc/kg; platelet dysfunction (ASA, plavix, uremia) → PLTs, DDAVP 0.3 mcg/kg**
- **Consider IV aminocaproic acid @ 5g bolus over 1h, then 1g/hr gt x 8h or IV TXA @ 1g bolus over 10min, then 1g over 8h**

### PLATELET REFRACTORINESS

**Failure to achieve acceptable ↑ platelet count following transfusion. Normal t1/2 of 3 days.**

- **Causes:**
  - Alloimmune: Ab to class-I HLA antigens (e.g. +PRA) or PLT-specific antigens. Risk factors: multiple pregnancies, prior transfusions with non-leukoreduced blood products, and organ transplants (NEJM 1997;337:1861)
  - Non-alloimmune: 2/3 of cases; Ddx: sep/sps/DIC, HIT, TTP, CVH/CPB/IABP, splenomegaly, HSCT, viral infection (HIV/HCV) and medications (sulfa, vanc, linezolid, piperacillin, rifampin, amphotericin, heparin, thiazide, anti-GI/pro/B12)
- **Evaluation:** check plt 30min post-transfusion on 2 occasions and assess plt recovery (15min-1hr later) & plt survival (18-24hr later)
  - ↑ plt recovery (↑ <10k on 2 occasions) → alloimmune refractoriness
  - ↓ 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; test for alloreactivity against HLA antigens. Normal is 0%, range 0-100%. To order in Epic: HLA Lab, MGH (choose: Blood > Platelet Refractory > Platelet Refractory Workup, HLA class I Ab screen). Test is only run on Tuesdays and Fridays. 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 within 15-60 minutes of completion.
  - ABO/HLA-matched apheresis single donor pRBCs from Red Cross. Takes days to process. Each unit costs approximately $3000 and has a shelf life ~3 days.
  - Consider aminocaproic acid if bleeding (contraindicated in thrombotic DIC); correct coagulopathy with DDAVP if e/o uremia

### MANAGEMENT OF ANEMIA IN JEHOVAH’S WITNESSES

- **Am J Hematol 2017: 92-1370**
  - Discuss management with patients on a case-by-case basis
  - **Acceptable products:** hematinsics (iron, folate, B12, recombinant human EPO), non-blood volume expanders (NS, LR, hydroxyethyl starches), hematostatic agents (amin, tranexamic acid, DDAVP, albumin-free clotting factors)
  - **Acceptable to some:** autotransfusion, HD/apheresis/CPB/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
**Hematology**

**Transfusion Reactions**

### INITIAL EVALUATION:
- Blood Bank (x63623, p21829)
- Sx: fever / chills, hives / flushing / jaundice, infusion site pain, shock / oliguria, wheezing / rales, DIC

#### 1. STOP transfusion, ABCs, VS q15min, clerical check
#### 2. If only urticarial sx → treat symptomatically, resume transfusion once Sx resolve
#### 3. If suspected rxns → Purple Top (10cc EDTA tube for hemoglobinemia, DAT, repeat ABO/Rh), UA (for hemoglobinuria), crossmatch, smear
   - High suspicion for hemolysis: bilis, LDH, haptoglobin, crossmatch, smear
   - High suspicion for sepsis: GS/Bx of both pt & blood product
   - High suspicion for TRALI/TACO: JVP, BNP, ABG, portable CXR

### ACUTE TRANSFUSION REACTIONS (<24 HRS)

<table>
<thead>
<tr>
<th>Reaction / Incidence</th>
<th>Presentation / Diagnosis</th>
<th>Pathophysiology</th>
<th>Treatment / Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Hemolytic (AHTR)</strong> 76,000–137,000</td>
<td>Sx: 1st 15 min; fever / chills, back / flank pain, bleeding / DIC</td>
<td>- ABO / Kidd incompatibility (preformed Abs) → intravascular hemolysis (IgM), cytokine / complement activation&lt;br&gt; - Rh / Kell / Duffy incompatibility → less severe extravascular hemolysis</td>
<td>Tx: NS (+/- lasix) for goal UOP &gt; 100 cc/hr x 24h&lt;br&gt; - Monitoring: HoTN, AKI, DIC, mortality ↓ volume transfused&lt;br&gt; PPX: vigilance</td>
</tr>
<tr>
<td><strong>Febrile Non-Hemolytic (FNHTR)</strong> 200–2,500 (RBC) 50–1,600 (PLTs)</td>
<td>Sx: 1–6h: low-grade fever, chills, HA, flushing&lt;br&gt; Dx: hemolysis workup negative</td>
<td>- Donor WBCs produce TNFα, IL1, IL6&lt;br&gt; - RBC: donor WBCs activated by recipient anti-HLA Abs&lt;br&gt; - PLT: donor WBCs make cytokines before transfusion</td>
<td>Tx: APAP +/- meperidin&lt;br&gt; PPX: leukoreduction (LR), little evidence for pre-medication</td>
</tr>
<tr>
<td><strong>Sepsis (Bacterial Contamination)</strong> 75,000 (PLTs)</td>
<td>Sx: 15–60 min: high fever, rigor, abd sx, HoTN / shock&lt;br&gt; Dx: GS / Bx of both pt &amp; bag</td>
<td>- Bacteria &gt;&gt; Viruses in donor blood&lt;br&gt; - RBC: Yersinia, PsA (endotox-GNRs)&lt;br&gt; - PLTs: Staph epi (GPCs)</td>
<td>Tx: antibiotics, quarantine all other similar products&lt;br&gt; PPX: routine screening</td>
</tr>
<tr>
<td><strong>Urticaria / Hives</strong> 33-100</td>
<td>Sx: any time during / after transfusion; localized or diffuse hives &amp; redness&lt;br&gt; Dx: no work-up necessary</td>
<td>- IgE-mediated hypersensitivity to donor plasma proteins</td>
<td>Tx: pause → diphenydramine&lt;br&gt; → resume if urticaria resolves&lt;br&gt; PPX: washed products, no evidence for pre-medication</td>
</tr>
<tr>
<td><strong>Anaphylactic Anaphylactoid</strong> 20,000 – 50,000</td>
<td>Sx: within min: acute HoTN, angioedema, urticaria, wheezing, abd pain&lt;br&gt; Dx: clinical; consider IgA deficiency</td>
<td>- IgE-mediated hypersensitivity in recipient lacking IgA or haptoglobin&lt;br&gt; - Bradykinin-mediated flushing/HoTN in pt taking ACEi or neg charged filters (e.g. TPE w/ albumin)</td>
<td>Tx: ABCs, O2, IVF +/- pressors, epi IM Q15min, methylprednisolone 125 mg, diphenhydramine 25-50 mg&lt;br&gt; PPX: washed products</td>
</tr>
<tr>
<td><strong>Transfusion-Related Acute Lung Injury (TRALI)</strong> 5,000 (FFP &gt; PLT &gt; RBC)</td>
<td>Sx: 1–6h: fever, SpO2 &lt; 90%, PaO2/FiO2 &lt; 300, normal JVP, HoTN&lt;br&gt; Dx: BNPl, b/l CXR infiltrates w/o CHF</td>
<td>- Pre-transfusion stress activates lung endothelial cells &amp; primes PMNs&lt;br&gt; - Donor anti-HLA Abs/bioactive factors attack primed PMNs of recipient</td>
<td>Tx: ABCs, O2, intubation&lt;br&gt; PPX: male donor plasma (fewer anti-HLA, anti-PMN Abs); defer donors w/ prior assoc TRALI cases</td>
</tr>
<tr>
<td><strong>Transfusion-Associated Circulatory Overload (TACO)</strong> 350–5,000</td>
<td>Sx: 1–6h (cardiogenic edema); dyspnea &amp; hypoxemia, elevated JVP, HTN&lt;br&gt; Dx: elevated BNPl, CXR</td>
<td>- Highest risk in elderly, HF, CKD, chronic anemias</td>
<td>Tx: O2, IV diuretics&lt;br&gt; PPX: slower rate (1cc/kg/hr)</td>
</tr>
<tr>
<td><strong>IVIG Transfusion Reactions</strong> 5-15% of infusions</td>
<td>- Inflammatory rxn: fever, chills, flushing, myalgias&lt;br&gt; - Anaphylactoid rxn: urticaria, flushing, chest pain, N/V, HTN</td>
<td>- Inflammatory rxn: Ab/Ag interaction i/o concurrent fxn&lt;br&gt; - Anaphylactoid rxn – unknown, potentially kinin-mediated, rare</td>
<td>Tx: IVF, sx mgmt&lt;br&gt; PPX: slow, space out infusions</td>
</tr>
</tbody>
</table>

### DELAYED TRANSFUSION REACTIONS (>24 HRS, <28 DAYS)

<table>
<thead>
<tr>
<th>Reaction / Incidence</th>
<th>Presentation / Diagnosis</th>
<th>Pathophysiology</th>
<th>Treatment / Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delayed Hemolytic (DHTR)</strong> 2,000</td>
<td>Sx: 3d; fever, anemia, jaundice, flu-like illness&lt;br&gt; Dx: +DAT, +DBili / LDH, +smear w/ spherocytes</td>
<td>- Anamnestic IgG against previously exposed antigen (Kidd / Duffy / Kell) → extravascular hemolysis</td>
<td>NB: Delayed Serologic&lt;br&gt; Transfusion Reaction is the same except w/o hemolysis</td>
</tr>
<tr>
<td><strong>TA-GVHD</strong> Rare (typically immunosuppressed)</td>
<td>Sx: 3-30d; fever, rash, mucositis, diarrhea, hepatitis, pancytopenia</td>
<td>- Donor T cells attack non-HLA matched recipient organs i/o immunosuppression or 1st degree relative donor</td>
<td>PPX: irradiation</td>
</tr>
<tr>
<td><strong>Post-Transfusion Purpura (PTP)</strong> Rare (women&gt;&gt;men)</td>
<td>Sx: 3-14d; purpura, mucocutaneous bleed&lt;br&gt; Dx: plt &lt; 10,000, anti-HPA-1A</td>
<td>- HPA-1A neg women develop anti-HPA-1A Abs, which is common in donor PLTs</td>
<td>Tx: 1st line: IVIG / 2nd: PLEX&lt;br&gt; PPX: HPA-1A negative PLTs</td>
</tr>
</tbody>
</table>
Oncology

Acute Leukemia

General Diagnostic Approach on Admission
- **History:** Note sibling status (for donor search), and if pre/peri menopausal, obtain date of last LMP, full ROS
- **Laboratory workup:**
  - Peripheral smear: Anemia, thrombocytopenia, variable WBC, circulating blasts, Auer rods (indicates myeloid origin)
  - Peripheral flow cytometry: Collect in yellow top tube, label “new leukemia rush,” bring to Warren 506
  - Screening labs: CBC w/ diff, BMP, LFTs, coags, UA, dHCG, HBV/HCV, CMV IgG, T&S
  - DIC labs: CBC, PT/PTT/INR, fibrinogen, D-dimer (esp if concern for APL)
  - TLS labs: BMP, LDH, Uric acid, Ca, Mg, Phos; diagnosis requires 2 lab (↑Uric acid, ↑K, ↑PO4, ↓Ca) + 1 clinical (AKI, arrhythmia, sz) criteria
- BM Bx: >20% blasts, flow cytometry, cytogenetics (karyotype, FISH), molecular testing (FLT3 ITD/TKD, NPM1, IDH1/2)
- **Studies:** EKG, CXR, TTE (needed prior to induction due to cardiotoxic chemotherapies), +/- CT head (if CNS sx)
- **Access:** double-lumen Hickman vs. triple-lumen PICC in anticipation of chemotherapy. Coordinate central access with attending.
- LP +/- intrathecal chemo: Indications for LP include 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:** HSCT work-up (if ≤80 yo): Collect in 2 yellow top tubes, send to American Red Cross; siblings>parent/children as donor

Troubleshooting Orders on Admission
- Utilize the Leukemia Admission Order Set (includes Neutropenic precautions, BMT diet, PRNs, among others)
  - TLS pxpx: Allopurinol 300mg QD
  - GI ppx: Omeprazole 20mg QD
  - VZV reactivation ppx: Famvir 500 mg QD
  - Hibiclens daily and peridex mouthwash BID
  - No VTE ppx: given thrombocytopenia and risk of DIC
- **How to send “Peripheral Flow”:** (do not delay ordering, even overnight)
  - Orders → Flow cytometry (not bone marrow flow), must fill in flow cytometry clinical history and click “flow cytometrycbc and differential, special slide box, leukemia panel;” Inpt Leukemia Attnd manages results, but CC outpt Onc; **Rush samples**
  - Send in Yellow top tube, then hand-carry specimen to the Warren 506 flow lab and inform this is RUSH for New Leukemia
- **How to send HLA/PRA:**
  - Orders → HLA Lab → Specimen Type: Blood → Pt: Recipient → Test: Allotransplant, if HLA, to AmRedCross → if PRA, Class I/II Ab screen

General Treatment Approach

1) **Induction Chemotherapy:** Starts on “day 1”
   - Usually standard regimen with addition of targeted agents for patients with certain cytogenetic abnormalities. This regimen will kill both leukemia and bone marrow (BM) cells, but will not completely ablate the marrow. The goal is for healthy BM cells to recover more quickly and restore normal marrow function. Older patients (≥60 yrs) receive lower-intensity therapy.

   ![Diagram](https://via.placeholder.com/150)

   2) **Day 14 Bone Marrow:**
   - Day 14, BM biopsy is performed to check for residual dz.

   3) **No Residual Leukemia**
   - If BM is ablated (i.e. sufficiently acellular without evidence of residual leukemia), check for complete remission (CR) at day 28.

   4) **Residual Leukemia and Re-Induction Chemotherapy:**
   - If there are residual leukemia cells, a second round of chemotherapy (re-induction) may be administered.

5) **Count Recovery and Assessment for CR**
   - During days 21-25, expect count recovery (may be delayed w/ addition of experimental therapies). Repeat BM Bx to check for CR.

6) **Consolidation Therapy:**
   - Initiated soon after remission is achieved. Goal to eradicate residual disease and sustain a lasting remission. Options include chemo or allogeneic stem cell transplant (allo-SCT), depending on patient- and disease-specific factors. In general, allo-SCT is preferred in higher-risk disease, if patient is medically able to tolerate it. Chemo in lower-risk disease and in pts who are not allo-SCT candidates.

7) **Surveillance:**
   - CBC every 1-3 months for 2 years, then every 3-6 months up to 5 years.

<table>
<thead>
<tr>
<th>Acute Myelogenous Leukemia (AML)</th>
<th>Risk Category</th>
<th>Cytogenetic and Molecular Features</th>
<th>NEJM 2016;374:2209</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epi: Most common leukemia in adults (80%). Median age of dx: 68yo.</td>
<td>Favorable</td>
<td>t(8;21): RUNX1/RUNX1T1 t(16;16) or inv(16): CBFB-MYH11 NPM1 mutation w/o FLT3-ITD</td>
<td></td>
</tr>
<tr>
<td>S/sx: Pancytopenia (fatigue, petechiae, ecchymoses, infections), myeloid sarcoma (i.e. chloroma), leukemia cutis (non-tender red/brown papules/nodules), neutrophilic dermatosis (i.e. Sweet syndrome - tender red/violet papules/plaques), gingival hypertrophy (due to leukemic infiltration), joint swelling (leukemic infiltration, gout) leukostasis (WBC &gt; 50K; dyspnea, HA, blurry vision, stroke)</td>
<td>Intermediate</td>
<td>Normal cytogenetics, t(9;11) NPM1 mutation w/ FLT3-ITD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unfavorable</td>
<td>del(5q), -5, -7, -17, t(6;9), t(9;22), 11q23, complex karyotype RUNX1, ASXL1, or TP53 mutation NPM1 WT w/ FLT3-ITD</td>
<td></td>
</tr>
</tbody>
</table>
Acute Leukemia

- **Subtypes:** t-AML (therapy-related from radiation, chemo), s-AML (secondary from preceding heme disorder, e.g., MDS, MPN, PNH)

- **Risk stratification:** Based on **cytogenetics**, mutations, performance status (Karnofsky/ECOG). Worse if t-AML or s-AML.

- **Treatment** ([NEJM 2009;361:1249])
  - Induction (Day 1) – **“T+3”,** cytarabine continuous infusion x 7d + ida/daunorubicin (bolus/short infusion) days 1-3
    - Midostaurin (tyrosine kinase inhibitor) added to T+3 in AML with FLT3 mutations ([NEJM 2017;377:474])
    - Liposomal cytarabine/daunorubicin (Vyxeos); improved survival in therapy- and MDS-related AML compared w/ standard T+3 ([J Clin Oncol 2016;38:2684])
    - Gemtuzumab ozogamicin added to 7+3 in CD33-positive AML ([Blood 2017;130:2373])
  - Elderly/trail pts: can consider hypomethylating agents (azacytidine, decitabine) +/- venetoclax (BCL2 inhibitor)
  - **Day 14 BM biopsy** – check for BM ablation → **reinduction:** if residual leukemia detected on Day 14 BM
  - **Day 28 BM biopsy** – check for complete remission (CR) (<5% blasts, nl CBC; 70-80% if < 60 yo; 40-50% if > 60)
  - Consolidation – Based on risk stratification ([Blood 2017;129:424])
    - Favorable risk: HIDAC (high dose AraC) x 3 cycles vs. standard dose AraC
    - Intermediate risk: chemo vs. allo-HSCT
    - Unfavorable risk: allo-HSCT vs. clinical trial

- **Complications:**
  - 1) **DIC** (if present → strong suspicion for APL); 2) **Febrile neutropenia**; 3) TLS → allopurinol, fluids, consider rasburicase if Uric Acid > 10; 4) **Leukostasis** → hydroxyurea, consider leukapheresis

**Acute Promyelocytic Leukemia (APL):** subtype of AML ([NEJM 2013;369:111])
- S/sx: Pancytopenia sx (fatigue, anemia, ecchymoses, infections). Especially high risk for DIC and bleeding
- **Smear:** Atypical promyelocytes (large, “dirty” granular, bilobed nuclei, +Auer rods)
- **Cytogenetics:** t(15;17) → PML-RARα (>97%), rarely t(11;17), t(5;17)
- **Treatment:** early tx w/ ATRA CRITICAL given high early mortality 2/2 to coagulopathy; should start ATRA if there is even mild suspicion for APL as there is low drug toxicity and high mortality with delayed treatment
  - **Induction**
    - Low-risk (WBC≤10K): ATRA (all-trans retinoic acid) + ATO (arsenic trioxide) ([JCO 2017;35:583])
    - High-risk (WBC>10K): ATRA + idarubicin or daunarubicin/cytarabine
  - **Consolidation**
    - ATRA + (daunorubicin vs. ATO), may depend on induction therapy
    - After completion, check for remission; goal complete molecular remission (absence of PML-RARα on RT-PCR)
- **Complications of ATRA therapy:**
  - Differentiation syndrome: SIRS, hypoxemia, edema, pulmonary infiltrates, AKI → high-dose steroids (dexamethasone 10mg q12h), consider temporary cessation of ATRA
  - Hyperleukocytosis: see Oncologic Emergencies
  - Idiopathic intracranial hypertension: headache, vision loss, papilledema → hold ATRA, pain control +/- steroids/acetazolamide

**Acute Lymphocytic Leukemia (ALL)**
- Epi: Bimodal. Peak incidence in 3-5 y/o, another peak in >45 yo (68% 5-year survival), Most common cancer in children.
- S/sx: Pancytopenia sx, bone pain (if acute disease), masses (LAD, HSM, anterior mediastinal mass in T-ALL), CNS sx (CN palsy, N/V, HA), TLS
- **Smear:** Lymphoblasts with scant cytoplasm, large nuclei containing nucleoli
- **Subtypes:** Precursor B-cell ALL, mature B-cell ALL, mature T-cell ALL
- **Risk stratification:**
  - **Precursor B-cell ALL** (cytogenetics >> WBC/age effect on risk)
    - **Favorable:** WBC < 30k, age < 35 years; hyperdiploidy (trisomy 4, 10 or 17 most favorable), t(12;21); rapid response to treatment (<0.01% minimal residual disease on Day 29 BM)
    - **Unfavorable:** WBC ≥ 30k, age ≥ 35 years, KM72A rearrangement, t(9;22) Philadelphia, Ph-like, hypodiploidy, CNS or testicular involvement, slow response to treatment (>0.01% minimal residual disease on Day 29 BM)
  - **Mature T-cell ALL:** poorer prognosis than precursor B cell, associated with t(8;14)
  - **Mature B-cell ALL:** poor prognosis, generally in elderly and with elevated WBC

- **Treatment** ([NEJM 2006;354:166; JCO 2011;29:532])
  - **General** – No single superior regimen, many regimens. Involves 1) induction, 2) consolidation (can be multiple rounds), 3) intensification (if needed), 4) CNS therapy (if needed), 5) maintenance, 6) allo-HSCT (high risk dz).
    - AYA versus adult: if patient is AYA (age 15-39), pediatric-inspired regimen is used
  - **CNS ppx** – Intrathecal MTX/cytarabine vs. systemic high-dose MTX w/ leucovorin rescue
  - **Maintenance** – Weekly MTX/6-MP + monthly Vinc/Pred x2-3 yrs; ↑prognosis if young, WBC < 30K, T-cell type, early CR
  - For refractory/relapsed ALL, blinatumomab (Blincyto) (B-ALL) and anti-CD19 CAR-T Cell Therapy

Amy Yu
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Lymphadenopathy (LAD) Evaluation (Am Fam Phys 2016;94:896)
- Generalized LAD DDx: HIV, EBV, mycobacteria (TB), SLE, medications (e.g. phenytoin), sarcoma, lymphoma/malignancy
- Localized LAD DDx: cervical (EBV, CMV, toxo, TB, lymphoma), supraclav (malignancy), axillary (inflx, breast ca), inguinal (STDs)
- Rx: exposures, travel, meds, B sx (fevers/drenching night sweats, >10% unintentional wt loss in 6 mo), other sx/sx of inflx or malig
- Exam: localization (think about area of nodal drainage), size (abnormal >1 cm), consistency, fixation, tenderness (inflammation)
- Labs: CBC, HIV (RNA if acute), LDH, HBV/HCV, PPD/TSpot, RPR, ANA, heterophile Ab; consider HTLV and EBV serologies
- Imaging: CT C/A/P, PET (can define node size and distribution, more helpful for monitoring of disease treatment/progression)
- Biopsy: consider if large node (>2cm), persistence 4-6 wks, or increase in size, with immunohistochemical and cytogenetics
  - Excisional (open) biopsy: reveals abnormal cells and nodal architecture (THIS IS THE PREFERRED METHOD)
  - Core needle biopsy: tissue for molecular studies, alternative to open if node inaccessible; ask IR to use large-bore needle
  - FNA: can be used as initial screening test for LAD, not diagnosis; no info on tissue architecture, high false neg rate

Lymphoma Staging: for Hodgkin lymphoma (HL), add “B” if presence of B symptoms
- Stage I: ≥ 1 LN in a single LN group, or single extralymphatic organ
- Stage II: ≥ 2 LN groups on same side of diaphragm
- Stage III: LN groups above and below diaphragm
- Stage IV: disseminated ≥ 1 extralymphatic organs
- BM biopsy, PET (except in HL clinical stage IA/IIA w/ favorable features, CLL by flow cytometry), labs above, HBV serologies if Ritux

Hodgkin Lymphoma: Reed-Sternberg cells (CD15+ CD30+ CD20-) in inflammatory background; bimodal age distribution (Lancet 2012;380:836)
- WHO classification (classical HL, separate from NLPHL):
  - Nodular Sclerosis (70%): mediastinal mass, good prognosis
  - Mixed Cellularity (25%): peripheral LAD, HIV/EBV, poor resource areas
  - Lymphocyte Rich (5%): peripheral LAD, good prognosis
  - Lymphocyte Depleted (<1%): worst prognosis (late stage @ pres)
- Treatment: note risk of late effects – cardiotox, 2 malignancy, pulm tox
  - Stage I-II: ABVD + XRT (curative intent)
  - Stage III-IV: ABVD x 6 cycles vs. escalated BEACOPP + XRT
  - Refractory/relapsed: salvage chemo + auto-SCT, followed by maintenance Brentuximab; PD1/PD-L1 blockade (JCO 2018; 36:1426)

Non-Hodgkin Lymphoma (NHL): a/w immunosup (e.g. HIV, bp), autoimmune dz (e.g. Sjogren), infxn (e.g. H. pylori, HCV, HTLV1, EBV) (Lancet 2012;380:848)
- Indolent: incurable but better prognosis, follicular lymphoma international prognostic index (FLIPI) (Blood 2004;104:1258)
- Aggressive: higher chance of cure but worse prognosis, aggressive NHL revised international prognostic index (IPI) (Blood 2007;109:1857)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>Prevalence</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>70</td>
<td>25-35%</td>
<td>Aggressive, rapidly growing, nodal/extranodal site; BCL-2, BCL-6 or MYC translocations common.</td>
<td>Limited disease: R-CHOP + RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Double-hit lymphoma (DHL): more aggressive subtype w/ both MYC and BCL-2 or 6 translocations</td>
<td>Extensive disease: R-CHOP +/- targeted tx (lenalidomide, irbritinib, bortezomib-based on subtype, CD47 Ab (NEJM 2018;379:1711); CAR-T in relapsed/refractory disease</td>
</tr>
<tr>
<td>Follicular</td>
<td>60</td>
<td>20-25%</td>
<td>Indolent, painless LAD</td>
<td>- Stage I &amp; II: observation or RT +/- Immunotherapy (bulky)</td>
</tr>
<tr>
<td>SLL/CLL</td>
<td>65</td>
<td>&lt;5%</td>
<td>Indolent, painless LAD</td>
<td>- Stage I: RT vs observation</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>60-70s</td>
<td>&lt;5%</td>
<td>Aggressive, splenogemaly</td>
<td>- Advanced: Ibrutilin +/- Rituxan vs chemo (i.e. FCR)</td>
</tr>
<tr>
<td>MALT</td>
<td>65</td>
<td>&lt;5%</td>
<td>Good prognosis, mucosal sites (GI) associated with H. pylori</td>
<td>- Gastric: triple therapy if H. Pylori+</td>
</tr>
<tr>
<td>Splenic MZL</td>
<td>70s</td>
<td>&lt;5%</td>
<td>Indolent, splenomegaly associated with H. pylori</td>
<td>- Splenectomy; if Rx: BR, R-CHOP, R-CVP, R (elderly)</td>
</tr>
<tr>
<td>Adult Burkitt</td>
<td>45</td>
<td>&lt;1%</td>
<td>Aggressive, rapidly growing, extranodal sites (jaw-African, abdomen-American)</td>
<td>- R-CALGB, R-CODOX-M, R-EPOCH or R-HyperCVAD</td>
</tr>
</tbody>
</table>

Diagnosis: DBCL, follicular, mantle, mantle cell, splenic MZL, adult Burkitt

Hodgkin Lymphoma International Prognostic Score (IPS) (JCO 2012;30:383)

<table>
<thead>
<tr>
<th>Points</th>
<th>Sy PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;45</td>
<td>Male 0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>1</td>
</tr>
<tr>
<td>Albumin &lt;4</td>
<td>2</td>
</tr>
<tr>
<td>Hb &lt;10.5</td>
<td>3</td>
</tr>
<tr>
<td>WBC ≥15,000</td>
<td>4</td>
</tr>
<tr>
<td>Lymphocytes &lt;600 or &lt;8%</td>
<td>≥5</td>
</tr>
</tbody>
</table>

Helen D’Couto

- **Serum protein electrophoresis (SPEP):** detects & quantifies monoclonal M-proteins
  - M-protein (paraprotein, monoclonal protein): monoclonal Ig secreted by abnormally expanded clone of B-cells and plasma cells, seen in monoclonal B-cell proliferative disorders, cryoglobulinemia, and autoimmune disease (e.g. RA, SS)

- **Immunofixation (IF):** confirms polyclonal or monoclonal nature of serum proteins, and determines the type of M-protein, based on its heavy (IgG, IgM, IgA) and light (κ/λ) chain composition

- **Serum free light chain (sFLC):** detects polyclonal & monoclonal free light chains (κ/λ) (200-500x more sensitive than IF)
  - Normal: κ/λ light chain ratio of 0.26-1.65 confirms normal B-cell differentiation
  - Abnormal κ/λ ratio: monoclonal plasma (MM, primary amyloidosis) and B-cell (lymphomas) aberrations
  - **Polyclonal decrease:** immunosuppression and immunodeficiency states
  - ↑ sFLC & relatively unchanged κ/λ ratio: chronic infection, inflammatory disorders, polyclonal autoimmune disease
  - NB: Renal failure results in increased sFLC levels with κ/λ ratio up to 3 due to clearance of FLC → determine urine Bence Jones protein (monoclonal light chains) by UPEP+IF κ/λ ratio 1.7-3.0, to determine if FLC are monoclonal

- **UPEP (24h):** similar to SPEP but more sensitive in detecting FLC (BJP); if M protein detected, it is confirmed by IF

  - **Specific indications:**
    - SPEP & Ig levels: send if suspect primary hypogammaglobulinemia (primary B-cell immunodeficiencies, e.g. CVID) or secondary immunodeficiencies (e.g. lymphoma, myeloma, immunosuppressive therapy, post-irradiation)
    - SPEP+IF & sFLC: send if suspect clonal B-cell abnormalities (e.g. myeloma, Waldenstrom, amyloidosis, paraproteinemia)
      - SPEP+IF alone is insensitive for primary amyloidosis, nonsecretory/oligosecretory myeloma, light-chain myeloma
    - UPEP+IF: Not needed to screen for plasma cell disorders, as SPEP/IF/sFLC combination is sufficiently sensitive. Generally used after diagnosis is established to detect nephrotic FLC concentrations and monitor response to therapy.

TYPES OF PLASMA CELL DISORDERS (Lancet Oncol 2014;15:e358)

- **MGUS:** 3% population > age 50, 7.5% > age 85; abnl sFLC ratio predicts prog to MM (~1% progress/yr); SPEP in 6 mo, then yearly.

- **MM** (IgG or IgA): M-protein > 3 g/dL and/or 10-60% BM clonal cells + CRAB; or > 60% BM plasma cells, sFLC ratio > 100, or ≥1 focal lesion (plasmacytoma) on imaging w/ CRAB. [CRAB: Ca (>11 mg/dL), Renal dz (Cr > 2 g/dL), Anemia (Hb < 10 g/dL), Bone lesions (≥1 focal lesion on survey, CT, or PET)].
  - **Smoldering MM:** absence of CRAB sx; treat if high risk (BM ≥ 10% with any M-protein, IgA, hypogammaglobulinemia, t(4;14), del(17p), MRI with bone marrow changes); 10% progress to MM per year.

  - **Waldenstrom’s (IgM):** Very rare; lymphoplasmacytic lymphoma in the bone marrow with IgM monoclonal gammapathy in the blood; anemia, mucocutaneous bleed, HSM, hyperviscosity (IgM = pentamer, thus more clumped → check viscosity), cryoglobulinemia.

  - **AL amyloidosis:** 1) amyloid-related systemic syndrome, 2) (+) amyloid by Congo red, 3) amyloid is light-chain related, 4) monoclonal plasma cell d/o. Sx: cardiomyopathy, purpura, nephrotic syndrome, peripheral neuropathy, orthostasis, hepatomegaly, macroglossia.

  - **POEMS syndrome:** (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes), a/w ↑VEGF, sclerotic bone lesions, and Castleman’s disease.

<table>
<thead>
<tr>
<th>MGUS</th>
<th>Smoldering MM</th>
<th>Multiple Myeloma</th>
<th>Waldenstrom’s</th>
<th>AL amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal BM plasma cells (%)</td>
<td>&lt; 10</td>
<td>10-60</td>
<td>≥ 10 (or plasmacytoma)</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>M protein in serum (g/L)</td>
<td>&lt; 3</td>
<td>≥ 3 [IgG or IgA]</td>
<td>Present</td>
<td>&gt; 3 [IgM]</td>
</tr>
<tr>
<td>Clinical signs</td>
<td>Absent</td>
<td>Absent</td>
<td>Present (CRAB)</td>
<td>Present</td>
</tr>
</tbody>
</table>

MULTIPLE MYELOMA (MM) WORKUP AND MANAGEMENT (Nat Rev Dis Primers 2017;3:17046; NCCN 2019 MM guidelines)

- Lab findings/workup: ↑AG, ↑globulin, ↑ESR, peripheral smear (rouleaux RBCs), ↑LDH, ↑β2M, SPEP/IF/sFLC, whole body low-dose CT +/- PET (more sensitive than skeletal survey), BM biopsy (IHC, flow, cytogenetics, FISH)

- Prognosis: depends on pt age, performance status, comorbidities, R-ISS staging (incorporates cytogenetics, LDH, β2M, albumin)

- Treatment Agents: most common induction regimens combine a proteasome inhibitor, immunomodulator and steroids:
  - Proteasome inhibitors: bortezomib (velcade - V), carfilzomib (Cz), ixazomib (ix)
  - Immunomodulatory agents (IMiDs): lenalidomide (revlimid - R), pomalidomide (Pom), thalidomide (T),
  - Steroids, chemo: dexamethasone (D), prednisone (P), melphalan (M), cyclophosphamide (C), doxorubicin (dox)
  - Proteasome inhibitors: bortezomib (velcade - V), carfilzomib (Cz), ixazomib (ix)

- Induction & consolidation: NOT curative
  - Induction: Triplet therapy with RVD most common, other combos also seen; CyBorD used if renal failure at presentation.
  - If candidate for autologous SCT → consolidation w/ auto-SCT; consider early SCT if > standard risk
    - Well-established PFS benefit with auto-SCT; improved OS also seen in most RCTs (NEJM 2017;367:1311)
  - Early (SCT after recovery) vs. delayed SCT (at time of early relapse): better PFS, but no clear OS benefit
  - Maintenance therapy (e.g. single agent R or V) following SCT or if not SCT candidate
  - Relapsed/refractory myeloma: combinations of above agents or repeat auto-SCT; CAR-T also under investigation

- Complications and adjunctive therapies
  - Bone disease: all patients should receive ppx bisphosphonate (pamidronate preferred over zoledronic acid) or denosumab; palliative XRT/vertebroplasty/kyphoplasty for path fracture/cord compression (consult Neuro-IR)
  - Anemia: consider erythropoietin; Renal failure: cast nephropathy, Type II RTA, nephrotic syndrome, hyperCa, urate nephropathy, type I cryoglobulinemia
  - Hyperviscosity: usually when IgM > 4 g/dL, IgG > 5 g/dL, IgA > 7 g/dL
  - ID PXP: consider PCP/HSV/fungal PXP if high-dose dexamethasone, VZV PXP if bortezomib; IVIG if recurrent infection
  - VTE PXP: consider if receiving immunomodulator (lenalidomide, pomalidomide)-based therapy (higher risk of thrombosis)

David Qualls
**Oncology**

### MYELODYSPLASTIC SYNDROME (MDS): Clonal stem cell mutation → ineffective/dysmorphic hematopoiesis → risk of AML
- Presentation: Age > 50, cytopenia sx (fatigue, bleed, infxn's), most are asymptomatic with unexplained cytopenias (~90% anemia)
- Risk factors: Male, exposure (benzene, tobacco), tx-related (alkylating agents, XRT), genetic (Down, Li-Fraumeni, Diamond-Blackfan)
- **Diagnosis:**
  - Smear: hypogranulated PMNs, pseudo-Pelger-Huet (hypolobated PMNs), ovalomacrophagocytosis, blasts (<20%)
  - BM bx: usually hypercellular w/ single- or multi- lineage dysplasia, +/- blasts <20%, +/- ring sideroblasts, +/- fibrosis
  - Exclude other reasons for cytopenias: ANA, HIV/HCV, EBV/CMV/Panv, ETOH, B12/folate/copper, ↑Zinc, TSH, Fe/TIBC/ferritin, DAT, SPEP/SFLC, CD55/59 flow (PNH), erythropoietin, review meds (e.g. MTX, Mycoprolenone Mofetil, Cyclophosphamide)
- **Prognosis:** Based on IPSS-R; median survival ranges from 0.7 yr in “very high” risk, to 8.8 yrs in “very low” risk
- **Treatment:** Based on IPSS-R, performance status & age; see NCCN 2019 MDS Guidelines
  - Neutropenia: abx prophy +/- G-CSF (if infxn). Thrombocytopenia: if suspect ITP, TPO agonist +/- steroids
  - Intermediate/High risk: hypomethylating agent (decitabine, azacitidine) to prolong time to transplant or if poor SCT candidate
    - If good PS: allogenetic HSCT (only curative tx, though with high up-front toxicity)
  - Special variants: del (5q) = lenalidomide; hypoplastic MDS with PNH+ cells, HLA-DR15 or age <60 = ATG + Cyclosporine

### MYELOPROLIFERATIVE NEOPLASMS (MPN): Clonal expansion of one or more myeloid lineages. Most common: CML, polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Sequelae vary depending on lineage; PV and ET can progress to secondary MF; all can transform to AML. Goals of tx are to improve symptoms, prevent thrombosis, prevent transformation to AML; only potentially curative therapy for any MPN is allogeneic HCT.

**NCCN 2019 MPN Guidelines, NCCN 2019 CML Guideline**

| MPN | PV (↑Hgb | WBC ↑Plt) | ET (↑Plt) | Primary Myelofibrosis (MF) (↑Hgb | WBC ↑Plt) | CML (↑Hgb | WBC ↑Plt) |
|-----|----------|----------|----------|---------------------|---------------------|---------------------|
| Sx  | Hyperviscosity (HA, dizziness, Δ vision, abdominal pain, ruddy complexion), Thrombosis (VTE, stroke, Budd-Chiari), Aquagenic pruritus, Erythromelalgia | Similar to PV, Bleeding (2/2 acquired vWF disorder, consider if plt > 1 million) | Fatigue, night sweats, weight loss, abd pain, satiety, hepatosplenomegaly, anemia, thrombotic/ hemorrhagic events | Often asymptomatic; fatigue, night sweats, bleeding, abd pain, weight loss, splenomegaly (most common physical exam finding) |
| Dx  | Major WHO criteria: Hgb >16.5 (Men), Hgb >16 (Women) BM bx showing trilineage proliferation Mutations: JAK2 V617F or JAK2 exon 12 mutation Minor WHO criteria: Low new WHO criteria: Major WHO criteria: PLT >450k BM bx shows enlarged megakaryocytes with hyperlobulated nuclei Mutations: JAK2 50%, CALR 30%, MPL 5% Minor WHO criteria: Other clonal markers Major WHO criteria: BM bx w/ ‘dry’ tap showing reticulin or collagen fibrosis Mutations: JAK2 50%, CALR 40%, MPL 5% Minor WHO criteria: Leukoerythroblastic smear (left-shift, nucleated and teardrop RBCs), ↑LDH, anemia, splenomegaly |
| Tx  | All: Phlebotomy (goal HCT < 45), ASA 81 if no bleeding, allapurinol, antihistamine; if age >60, ↑ risk thrombosis: Hydroxyurea (but risk AML transformation) > interferon-α, 2nd line: Ruxolitinib (NEJM 2015;372;426) | All: ASA 81 (unless vWF disorder) If age >50 or ↑risk thrombosis: hydroxyurea > interferon-α > anagrelide (NEJM 2005;353;33) | Allo-HSCT (only cure), transfusion, hydroxyurea, ruxolitinib (JAK2 inhibitor, primary benefit is symptom reduction) (NEJM 2012;365;787) | BCR-ABL inhibitors: Imatinib, Nilotinib, Dasatinib. Allo-HSCT if resistant or in accelerated/blast phase |
| Ddx | ↑/−: hypoxia-induced (heart/lung dz, carboxy-Hb, smoking) vs. epo-producing tumor. ↑: epo: activating epo receptor mutation (rare) | Infection, inflammation, iron deficiency, splenectomy, neoplasm | Other MPNs (especially ET); MDS; hairy cell leukemia; other marrow-infiltrating malignancies | Leukemoid nx (↑LAP), drugs (steroids, GCSF, ATRA), infection (C. diff, mono), severe hemorrhage, splenectomy, DKA, organ necrosis |

**Other MDS/MPN Types:**
- Chronic myelomonocytic leukemia (CMLL): MDS/MPN overlap syndrome w/ monocytosis >1000 & splenomegaly
- Systemic mastocytosis: rare, mast cells and precursors (CD34+): Dx: skin bx (cutaneous), BM bx (systemic), ↑tryptase, KIT D816V mutation; Sx: flushing, pruritus, anaphylaxis, eosinophilia; Tx: no cure, treat sx; hydroxyurea, interferon-α; c-kit inhibitor Masitinib
- Hypereosinophilic syndrome: peripheral eosinophilia (>1500) w/o other etiology; Dx: abs eos >1500 measured 2x, 1+ month apart +/− tissue bx; Sx: skin lesions, neuropathy, clots, HSM; Tx: steroids, imatinib if FIP1L1-PDGFRα fusion gene, meloprolizumab, HSCT

**Hemophagocytic lymphohistiocytosis (HLH):** "cytokine storm" syndrome, 1° or 2° (infectious, inflammatory, neoplastic – esp lymphoma); Dx: pathologic mutation or 5+ fever, cytopenia, splenomegaly, ↑TGN, ↑ferritin, ↓NK cells, ↓CD25, hemophagocytosis in BM/Spleen/LNs; Sx: fever, HSM, rash, sepsis; Tx: HLH-94 protocol (dexamethasone/etoposide then Cyclophorine A +/- IT MTX if CNS involvement), survival ~2 mo w/o therapy

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Stem Cell Transplantation

TERMINOLOGY:
- One-liners include: underlying malignancy; day since transplant (transplant day = day 0, day before = day -1, day after = day +1); conditioning/cytoreduction regimen (conventional/myeloablative vs reduced-intensity/non-myeloablative); autologous vs allogeneic transplant; donor type (matched related/unrelated, haploidentical, umbilical cord) and source (bone marrow, peripheral stem cells, cord blood); GVHD prophylaxis regimen
- Example one-liner: “35M w/AML (FLT3-mutated) who is now day +4 from his myeloablative (flu/mel) matched related donor (MRD) peripheral blood stem-cell transplant (PBSCT) with tacrolimus/methotrexate GVHD prophylaxis (day 0 = 1/1/19).”

<table>
<thead>
<tr>
<th>AUTOGENEIC TRANSPLANT</th>
<th>ALLOGENEIC TRANSPLANT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Transplant of self (patient)-mobilized and harvested stem cells</td>
</tr>
<tr>
<td><strong>Goals</strong></td>
<td>Reconstitute hematopoiesis after high-potency chemo to kill all cells in BM (tumor abnormal); intent is mostly curative except for myeloma (goal deep remission)</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>1st relapsed lymphomas (40-50% 5YS) &amp; all myelomas (35% 5YS); also for consolidation bx in amyloidosis, relapsed Waldenström, germ cell tumors</td>
</tr>
<tr>
<td><strong>Source of cells</strong></td>
<td>Usually peripheral blood stem cells (PBSC) – less invasive, more rapid engraftment than BM harvest</td>
</tr>
<tr>
<td><strong>Global timeline</strong></td>
<td>Mobilization (G-CSF; chemo) → harvest cells from self → high-dose chemo to kill disease → transplant → recovery of counts in 7-10 days (engraftment) → monitor for infectious &amp; transplant-related complications</td>
</tr>
<tr>
<td><strong>Graft-versus-host disease (GVHD)</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Graft-versus-tumor (GTV) effect</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Immunosuppresion</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Time to engraftment</strong></td>
<td>7-10 days</td>
</tr>
</tbody>
</table>

TIMELINE (NEJM 2006;354:1813)
- Cell mobilization/collection (or harvest of bone marrow): few weeks prior to transplant admission; chemo + G-CSF to mobilize
- Conditioning: day -8 to -3; varies based on conditioning regimen and donor type (Blood 2014;124:344)
  - Goal: Eradicate/debulk tumor & create space for donor cell engraftment
  - Agents: Chemo (ex. alkylating agents - busulfan, cyclophosphamide, melphalan) ± total body irradiation ± mAb
- Transplantation: day 0, infusion of stem cells
- Engraftment: day +7 to +30, defined as persistent ANC >500 & Pit >100k after nadir (3-6 days after completion of conditioning)
  - Autologous: PBSC (7d) vs Allogeneic: PBSC (14d), BM (18d), dUCB (28d)
  - G-CSF (neupogen/fligrastim) accelerates neutrophil engraftment by a few days: 10 mcg/kg/d (Day +1 to ANC >500)
  - Transusions (irradiated & leukoreduced), Hct>25, Plt>10K (>50K if bleeding), attending-dependent
    - Check post-tx CBC in 15-60 min

ALLOGENEIC STEM CELL TRANSPLANT SPECIAL CONSIDERATIONS:
- Stem cell donor source: donor cells are matched to pt by HLA typing to minimize GVHD: matching at alleles A, B, C, DR, DQ
  - Matched-related donor (MRD) preferred, compatible siblings, matched at 10/10 HLA alleles
  - Matched-unrelated donor (MUD): common, NMDP database, matched at 8-9/10 HLA alleles
  - Haploidentical: any parent/sibling/child is a match, match 9/10 HLA alleles, TGVHD; post-SCT cyclophosphamide (PTCy) removes allorreactive donor T-cells, reduces GVHD (Blood Rev 2015;29:63)
  - Stem cell collection: MUD, MRD, haploidentical stem cells can be collected via peripheral blood or direct from bone marrow; PBSCT has more GVHD but less graft failure, BM has less GVHD but higher graft failure
  - Umbilical Cord Blood (UCB): immature SC from fetus – allows for more HLA disparity and quick to obtain, but delayed engraftment and ↑txp-mortality compared to MUD (similar DFS/OS, ↑ severe GVHD) (Blood 2013;122:491)
- Pre-transplant preparative (conditioning) regimen:
  - Myeloablative conditioning: complete tumor eradication & ablation of host BM/immune cells prior to transplant
    - ↑toxicity, ↑immunosuppr, ↑txp-mortality, ↓relapse; consider in young healthy patients, with MRD or no CR

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Stem Cell Transplantation

- **Reduced intensity conditioning (RIC):** tumor debulking, create space in host BM/ immunosuppress enough to allow graft to be accepted; rely on **Graft vs Tumor** effect for cure (host and donor hematopoiesis coexists in mixed chimeric state and ↓GVHD; %donor cells in chimeric state predictive of relapse)
  - ↓ toxicity, ↓ bxp-mortality, ↑ relapse, consider in elderly w/ co-morbidities
- **GVHD PPX:** day -3 to indefinite (tapered after months to years), goal is to prevent graft rejection & acute/chronic GVHD
  - **Immunosuppression regimens:** combined Tacrolimus/Methotrexate or Tacrolimus/Sirolimus most common; in haploidentical transplants, post-transplant cyclophosphamide (PTCy) and Tacro/Cellexct is used.
    - **Tacrolimus (FK506):** calcineurin inhibitor, goal trough: 5-10 ug/L
      - Toxicity: AKI, ↑K, ↓Mg, ↑LFTs, N/V, TMA, tremor, ↑risk of DM
    - **Sirolimus (Rapamycin):** mTOR inhibitor; goal trough 3-12 ug/L
      - Toxicity: AKI, Sinusoidal obstruction syndrome (SOS), leukopenia, TMA, HLD, TCP
    - **Methotrexate (MTX):** anti-metabolite (inhibit thymidine), given at D1,3,6,11 w/ cyclosporine or tacrolimus
      - Toxicity: mucositis, myelosuppression, hepatotoxicity, AKI
    - **Mycophenolate (MMF/Cellexct):** anti-metabolite (inhibits purine synthesis)
      - Toxicity: myelosuppression, N/V/D
  - **Post-transplant cyclophosphamide (PTCy):** days +3 and +4; kills early alloreactive T-cells
  - **T-cell depletion regimens:** (ATG, decreased T-cell dose) no longer favored; decreased GVHD but no effect on OS

**INFECTIOUS COMPLICATIONS:** due to chemo-related pancytopenia & immunosuppression (ASBMT/IDSA Recommendations)

- **Infectious PPX:** **items with asterixis have well-established benefit and are employed at all institutions**
  - **Bacterial:** Cipro 500 BID or Levofoxacin 500 QD (Day -1 to ANC > 500)
  - **Viral (HSV/VZV):** Acyclovir 400 TID/800 BID or Famiclovir 500 BID (Day -1 to +365 [auto]; 2 yrs min & until off IS [allo])
  - **Fungal:** Fluconazole 400 QD or Vori 200 BID or Posaconazole 200 TID (Day -1 to ANC>500 [auto], until 3-6 mo [allo])
  - **PCP/Toxo:** Bactrim DS QD or Vori 200 BID or Posaconazole 200 TID (Day -1 to ANC>500 [auto], until 3-6 mo [allo])
  - **CMV:** no ppx, if CMV+ pre-emptive treatment with IV ganciclovir or PO valganciclovir (Day -1 to +100)
    - Letemovir is a novel anti-CMV drug approved for use in high-risk allo-HCT patients
  - **Day 0-30 (Pre-engraftment – neutropenic)**
    - **Bacterial:** GPCs & GNRs (F&N); neutropenic enterocolitis (typhilitis): pip/tazo vs. -penem vs. cefepime/flagyl + surgery c/s
    - **Viral:** resp/enteral (adeno, flu, RSV, parainfluenza), HSV
    - **Fungal:** aspergillus, candida
  - **Day 30-90 (Early post-engraftment – poor cellular immunity)**
    - **Bacterial:** GPCs & GNRs
    - **Viral:** resp/enteral (adeno, flu, RSV, parainfluenza), EBV (post-transplant lymphoproliferative disorder/PTLD), CMV, HHV6 (screen CMV/EBV if allo, adeno if T-cell depleted, HHV6 if UCB)
    - **Fungal:** aspergillus, candida, PCP
    - **Parasitic:** Toxo
  - **Day 90+ (Late post-engraftment – chronic GVHD, poor cellular & humoral immunity)**
    - **Bacterial:** encapsulated bacteria (SHIN)
    - **Viral:** resp/enteral (adeno, flu, RSV, parainfluenza), EBV (PTLD), VZV, BK (hemorrhagic cystitis), JC (PML)
    - **Fungal:** aspergillus (nodular), PCP (interstitial)
    - **Parasitic:** Toxo (can mimic PCP PNA)

**NON-INFECTIOUS COMPLICATIONS:** due to immune-mediated organ damage, toxic effects of chemo, or immunosuppression

- **Non-infectious PPX:**
  - **Tumor Lysis Syndrome:** Allopurinol 300 QD (Admit to Day -1, but much lower risk in SCT than with induction chemo)
  - **Hepatic veno-occlusive disease:** Ursodiol 300 TID (Admit to Day +30)
  - **Day 0-30 (common to have mucositis, nausea/vomiting, alopecia, rash, diarrhea)**
    - **Nausea/Vomiting:** optimal management varies based on timing relative to chemo initiation
      - **Immediate (day 0-1):** 5-HTs blockade (Zofran, Aloxai), Neurokinin-1 antagonists (Emend), decadron
      - **Delayed (day 2-5 post chemo):** dopamine (D2) blockade (Compazine, Reglan, Haldol)
      - **Late (5+ days post chemo):** Alivan, steroids, Marinos (more helpful in younger pts, marijuana users)
    - **Mucositis:** most HSCT patients get some degree of mucositis; duration and severity are worse in allogeneic HSCT. Treatment is focused on pain and caloric intake.
      - **Pain:** topical/IV opiates; low threshold for PCA
      - **Nutrition:** TPN initiated if PO intake impaired by mucositis, and expected to continue for ≥ 1 week
      - **Palliferman:** (recombinant keratinocyte growth factor) can reduce duration, severity of mucositis
  - **Liver – Sinusoidal obstruction syndrome/veno-occlusive disease:**
    - **Cause:** direc cytotoxic injury to hepatic venules leading to hypercoaguable state and microthrombi
    - **Sx:** RUQ pain, jaundice, ascites/edema; ↑ALT/AST/TBili, ↑INR/Cr (if acute liver failure or HRS)
Day 30+
- **Acute GVHD**: ~40% in MRD, ~60% in MUD (cellular immune response, TH1 cell-mediated) (NEJM 2017;377:2167)
  - Risk factors: ↑ HLA mismatch, ↑ age, female donor/male recipient, TBI-myeloablation, PBSC > BM
  - Cause: donor T-cell recognizes and attacks recipient native cells (usually day 0 to +100, but can be later)
  - Dx: plasma EBV DNA monitoring can raise suspicion for PTLD (thousands of copies/microL compared with hundreds); biopsy with immunophenotyping for true dx
  - Rx: prior acute GVHD, HLA mismatch, ↑ age, PBSC > BM
- **Chronic GVHD**: 30-70% of patients s/p allo-HSCT (humoral immune response, TH2 cell-mediated) (NEJM 2017;377:2565)
  - Cause: both donor T-cell & B-cell mediated attacks on recipient after day +100
  - Risk factors: prior acute GVHD, HLA mismatch, ↑ age, PBSC > BM
  - Sx: resembles scleroderma (sicca, dysphagia, arthritis, skin tightening, malar rash), lung (obliterative bronchiolitis), liver (cholestasis), cytopenias/immunodeficiency; any organ system can be affected
  - Rx: steroid +/- broad immunosuppression, photopheresis (ECP) for skin; novel agents including ruxolitinib (Jakafi), ibrutinib, rituximab have been shown to be effective in steroid-resistant disease
  - **PTLD** (post-transplant lymphoproliferative disease): ~1% in allo-SCT; median day +70-90 (NEJM 2018;378:549)
    - Cause: IS leads to EBV reactivation (dormant in B cells) & clonal B cell proliferation (usually donor-derived)
    - Risk factors: T-cell depleted donor graft, treatment with ATG, HLA-mismatch, cord blood transplant
    - Rx: plasma EBV DNA monitoring can raise suspicion for PTLD (thousands of copies/microL compared with hundreds); biopsy with immunophenotyping for true dx
    - Rx: reduce IS, anti-viral, RTX-based chemo (if systemic) vs surgery/RT (if localized)

### QUICK REFERENCE

**Day -8 conditioning to Day +30 engraftment**

<table>
<thead>
<tr>
<th>S/Sx monitor</th>
<th>DDx fever</th>
<th>DDx abdominal pain/ascesis</th>
<th>DDx dyspnea/hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo toxicity: mucositis, N/V/D, s/sx infection</td>
<td>Infection (bacterial, viral, fungal, parasitic)</td>
<td>Infection: typhilitis (abx, urgent surgical consult)</td>
<td>Existing disease: CHF, COPD, asthma</td>
</tr>
<tr>
<td>GVHD sx: rash, jaundice, diarrhea (24h volume)</td>
<td>Drug rxn</td>
<td>Veno-occlusive disease: RUQ pain, jaundice, ascites, edema</td>
<td>Infection: PNA (bacterial vs. fungal), aspiration</td>
</tr>
<tr>
<td>SOS sx: RUQ pain, jaundice, ascites, edema</td>
<td>Engraftment (day 7-9 for auto, day 14-21 for allo)</td>
<td>GVHD</td>
<td>Volume (often on maintenance IVF with chemo)</td>
</tr>
<tr>
<td>Engraftment sx: fever, dyspnea, edema</td>
<td>Tumor (initial lysis &amp; cytokine release)</td>
<td>Obstruction/ileus/ constipation</td>
<td>Drug: chemo-induced lung injury or cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td>Immobility (Atelectasis, aspiration, DVT/PE)</td>
<td></td>
<td>Engraftment (pulmonary edema from capillary leak)</td>
</tr>
<tr>
<td></td>
<td>GVHD</td>
<td></td>
<td>Pneumonitis</td>
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<td></td>
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<td>Alveolar hemorrhage</td>
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<tr>
<td></td>
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<td>PE, TRALI, GVHD</td>
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</tbody>
</table>
CAR T-Cell Therapy

MECHANISM OF ACTION
- Chimeric antigen receptor T cells (CAR T cells): type of autologous therapy; T lymphocytes collected from the patient, genetically modified via transfection with a gene encoding a chimeric antigen receptor (CAR) that directs the T-cells against a selected antigen on the patient’s tumor
- CARs: consist of an extracellular domain that targets and binds a tumor antigen (i.e. CD19 in B-cell NHL and ALL) attached to intracellular domains that signal for T-cell activation (see figure)

FDA-APPROVED THERAPIES: ANTI-CD19 cell-based therapies
- Yescarta (axicabtagene ciloleucel; aka axi-cel)
  - Aggressive, refractory adult B-cell lymphoma: ZUMA-1, Phase II trial (NEJM 2017;377:2531)
- Kymriah (lisagenleucel)
  - Relapsed/refractory B-ALL in patients <25 yrs old: ELIANA, Phase II trial (NEJM 2018;378:439)
  - Adults with relapsed/refractory DLBCL: JULIET- Phase II trial (NEJM 2019;280:45)
- Other CAR-Ts for hematologic malignancies (CD19 target) and solid malignancies (other antigen targets) under investigation (JCO 2017;35:30) (NEJM 2016;375:2561) (J Immunol 2018;200:459)
- Also under investigation: combination of immune checkpoint blockade (anti-PD, anti-PD-L1) with CAR-T (Int J Mol Sci 2018;19:online)

TOXICITIES (Nat Rev Clin Oncol 2018;15:47)
- Cytokine-release syndrome (CRS)
  - Most common toxicity, usually within 1st wk; fulminant cytokine release (IL-2, sIL2R, IFNγ, IL-6, GM-CSF) triggered by CAR-T engagement of antigen and T cell proliferation. Trisk in bulky disease, specific constructs
  - Signs/Sx: fever, malaise, anorexia, myalgia, can affect any organ system (CV, lung, GI, liver, renal, CNS)
  - Diagnosis: monitor for at least 7 days after CAR-T infusion: vitals, tele, basic labs, ferritin, CRP, TLS labs; exclude infection
  - Therapy: if plan to treat CRS with steroids or anti-IL6, first get clear approval by the treating attending
    - Empiric broad-spectrum antibiotics if febrile until infection is ruled out
    - MGH: we give tocilizumab (anti-IL6R); siltuximab (anti-IL6) also exists; 2nd line: glucocorticoids
  - CAR-T-cell-related encephalopathy syndrome (CRES)
    - Etiology is unclear; passive cytokine diffusion into brain (IL-6, IL-15 a/w neurotoxicity) vs CAR-T trafficking into CNS
    - Timing/Duration: typically lasts for 2-4 days, but can vary in duration from hours to weeks.
    - Can have biphasic presentation: 1st phase w/ fever and CRS (first 5 days); 2nd phase after fever/CRS subsided with delayed neurotoxicity/seizures in 10% (3-4 weeks after infusion)
    - Diagnosis: monitor for at least 7 days after CAR-T infusion: vitals, tele, basic labs, ferritin, CRP, TLS labs; exclude infection
    - Therapy: if plan to treat CRS with steroids or anti-IL6, first get clear approval by the treating attending
      - Empiric broad-spectrum antibiotics if febrile until infection is ruled out
      - MGH: we give tocilizumab (anti-IL6R); siltuximab (anti-IL6) also exists; 2nd line: glucocorticoids

Cytokine-release Syndrome (CRS) Management guideline based on CRS grade. Adapted from Blood 2014;124:188-195.
- Grade 1 CRS: Fever, constitutional symptoms
- Grade 2 CRS: Hypotension: responds to fluids or one low dose pressor
  - Hypoxia: responds to <40% O2
  - Organ toxicity: grade 2
- Grade 3 CRS: Hypotension: requires multiple pressors or high dose pressors
  - Hypoxia: requires >40% O2
  - Organ toxicity: grade 3, grade 4 transaminis
- Grade 4 CRS: Mechanical ventilation
  - Organ toxicity: grade 4, excluding transaminis

- Vigilant supportive care
  - Assess for infection (Treat fever and neutropenia if present, monitor fluid balance, antinfectives as needed)
  - If cerebral edema: acetazolamide, glucocorticoids; HOB>30
  - If failure to improve in 48h, consider etoposide as in HLH-94 treatment protocol; consider intrathecal cytarabine

- Vigilant supportive care
  - Tocilizumab / corticosteroids

- Extended co-morbidities or older age?

CAR T-Cell Therapy

Amy Yu, Shawn Li
<table>
<thead>
<tr>
<th>Organ</th>
<th>Risk factors/ screening</th>
<th>Staging/diagnostics</th>
<th>Treatment</th>
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</thead>
</table>
| **Prostate** | ● Adenocarcinoma (95%)  
● Transitional cell carcinoma, carcinosarcoma, basal cell carcinoma, lymphomas, or stromal sarcoma (~5%)  
● Androgen deprivation therapy (ADT): orchiectomy, LHRH agonist (goserelin, histrelin, leuprolide, triptorelin)  
● Androgen disruption: abiraterone + prednisone, or enzalutamide | ● Age, AA race, genetic factors (BRCA1/2 and family history), smoking  
● Discuss PSA with men >50 (DRE not recommended) | Low risk (T1c/T1-T2a + Gleason score ≤6 + PSA ≤10)  
● Active surveillance (PSA, DRE +/- repeat bx), external beam radiation therapy (EBRT) +/- brachytherapy (BT), or radical prostatectomy (RP) +/- EBRT & ADT  
Intermediate risk (T2b-T2c or PSA 10-20 or GS 7)  
EBRT & ADT or EBRT & BT +/- EBRT, RP +/- pelvic lymph node dissection (PLND) +/- EBRT +/- ADT  
High risk (T3a/T3b-T4a or GS ≥8)  
EBRT & ADT, ERBT & brachy, or RP with extended PLND +/- EBRT +/- ADT | |
| **Breast** | ● Infiltrating ductal (76%)  
● Invasive lobular (8%)  
● Ductal/lobular (7%)  
● Mucinous (colloid) (2.4%)  
● Tubular (1.5%)  
● Medullary (1.2%)  
● Papillary (1%)  
● TCH(P): Docetaxel, carboplatin, trastuzumab +/- pertuzumab  
AC-TH(P): doxorubicin/cyclophosphamide followed by weekly paclitaxel + trastuzumab +/- pertuzumab  
Aromatase inhibitor (AI): anastrozole, letrozole, exemestane | ● Age, genetics (BRCA1/2), FHx, obesity after menopause, menopause >55y chest RT, 1st birth >30y, nulliparity, HRT, menarche <13y, ETOH, benign breast disease, smoking  
Screening: q1-2y mammography after 50 (or 5-10y before earliest FHx, whichever is earlier), discuss before starting age 40. | Castration sensitive: ADT (LHRH agonist +/- antiandrogen, LHRH antagonist or orchiectomy) + abiraterone + prednisone vs. docetaxel  
Castration resistant: ADT (testo<50ng/dl) + docetaxel (chemo naive) or cabazitaxel (docx exposed), mitoxantrone + prednisone, androgen disruption; sipuleucel-T, and bone-targeted radium-223 or denosumab/zoledronic acid (bone mets, no visceral mets) (NCCN Guidelines Version 1.2019) | |
| **Pancreas** | ● Exocrine/ adenoca (94%)  
● Endocrine (6%)  
● FOLFIRINOX: leucovorin, 5-FU, irinotecan, oxaliplatin  
ChemOR: capectabine or CI 5-FU + RT | | |
| **Risk factors:**  
Smoking, ETOH, obesity, DM, chronic pancreatitis, age, male, FH pancreatic CA, HNPCC, BRCA1/2  
**Diagnostics:**  
CT C/A/P pancreas protocol, EUS, MRCP, ERCP if indicated, CA19-9  
**Determine resectability based on vascular involvement** | Resectable: surgery + adjuvant chemOR  
Borderline resectable: neoadjuvant chemo & surgery +/- adjuvant chemOR  
Locally adv: chemoRT or stereotactic body radiation therapy (SBRT)  
Metastatic (NEJM 2011;364:1817): FOLFIRINOX or gemcitabine +/- nab-paclitaxel +/- palliative RT  
BRCA: FOLFIRINOX or gemcitabine/cisplatin, +/- chemoRT  

Lauren Banks
### Colon and rectum
- Adenoca (96%)
- Neuroendocrine
- Lymphoma

#### Risk factors
- FOLFOX: oxaliplatin, leucovorin, 5-FU
- CAPEOX: capecitabine, oxaliplatin
- FOLFIRI: irinotecan, leucovorin, 5-FU
- FOLFOXIRI: irinotecan, oxaliplatin, leucovorin, fluorouracil
- EGFR inhibitor: cetuximab, panitumumab

#### Staging
- Staged I-IV using TNM system
- Colon: Stage I: surgery + observation
- Stage II: surgery + neo- vs. adjuvant chemo (5-FU/leucovorin or capecitabine, add oxali if high-risk features)
- Stage III: surgery + adjuvant FOLFOX/CAPEOX
- Stage IV: resection of limited liver or lung mets + FOLFOX/CAPEOX/FOLFR1/FOLFOXIRI +/- bevacizumab
- KRAS/NRAS wt and left-sided tumors: FOLFOX/FOLFR1 + EGFR inhibitor
- MSI-H/dMMR: immunotherapy (pembrolizumab, nivolumab or nivolumab + ipilimumab)

#### Recital
- Stage I: low anterior resection (LAR) or abdominopereineal resection (APR) +/- neo- vs. adjuvant chemoRT
- Stage II-III: resection with neoadjuvant chemoRT (NCCN Guidelines Version 2.2019 Colon Cancer)

### Lung
- NSCLC (84%) – adenoca, large cell > SCC
- SCLC (13%)
- Chemoradiation:
  - cisplatin/etoposide, cisplatin/vinblastine, carboplatin/pemetrexed, cisplatin/pemetrexed, paclitaxel/carboplatin with RT
  - EGFR inhibitors: osimertinib, erlotinib, afatinib, gefitinib, dacomitinib
  - T790M assoc w/ TKI resistance
- ALK/R0S1 inhibitors: crizotinib, ceritinib, alectinib, brigatinib
- BRAF/MEK inhibitors: dabrafenib/trametinib
- TRK inhibitor: larotrectinib

#### Risk factors
- Smoking, asbestos, occupational exposures, lung fibrosis, age, male, AA race, lower SE status
- 25% lung cancer worldwide not due to smoking (50% of women with NSCLC are never smokers, 60-80% in Asian populations are women) → more likely single mutation (ALK, EGFR, ROS1)

#### Screening
- Annual low dose CT chest for pts 55-74 yo with ≥30 pack-yr hx and smoking within last 15 yrs

#### Staging
- NSCLC staged I-IV using TNM system
- SCLC staged as limited vs. extensive using TNM system

#### Diagnostics
- CT chest/upper abd, PET/CT, brain MRI
- Molecular testing for NSCLC (EGFR, ALK, ROS1, PD-L1)

#### Targeted tx
- EGFR inhibitor (EGFR sensitizing mutations); ALK/R0S1 inhibitors (ALK or ROS1 rearrangement), BRAF/MEK inhibitors (BRAF V600E), TRK inhibitor (NTRK gene fusion)

#### Immunotherapy (if no driver mutation)
- KEYNOTE-010, NEJM 2018;379:2078: pembrolizumab (1st line for ≥50% tumor PD-L1 expression); pembrol + chemo (1st line option regardless of tumor PD-L1 expression level);
- alternative agents: nivolumab, atezolizumab

#### Initial systemic tx
- Platinum agent + docetaxel, pemetrexed, gemcitabine, or ramucirumab

#### SCLC
- Limited: surgery + chemo +/- mediastinal RT
- Extensive (NEJM 2018;379:2220): chemo & atezolizumab +/- RT for lobar obstruction, SVC synd, bone/brain mets vs pal/supp care

### Melanoma
- Superficial spreading (75%)
- Nodular (15-30%)
- Lentigo maligna (~5%)
- Acral lentiginous (<5%)
- Ocular (5%)

#### Risk factors
- Sun exposure (UVB > UVA), atypical nevi, high nevi count, family or personal hx, immuno-suppression

#### Staging
- TNM system
- Factors include: Breslow thickness, ulceration, mitotic rate, lymphatic involvement, and distant metastases
- Serum LDH is an important prognostic factor used in active surveillance and treatment

#### Surgical excision
- Appropriate margins based on tumor thickness +/- sentinel LN bx vs. complete regional LN dissection

#### Adjuvant treatment or for metastatic disease
- Immunotherapy (NEJM 2015;373:23, NEJM 2015;372:2521): anti-PD-1 monotherapy (pembrolizumab or nivolumab); combination nivolumab/ipilimumab
- Targeted tx (NEJM 2014;371:18): BRAF/MEK inhibitors (BRAF V600 activating mutations), KIT inhibitor imatinib (KIT-mutant tumors)
- Radiation: considered with symptomatic localized disease (e.g. brain mets)
Oncology

Chemotherapy & Toxidities

Common Chemotherapy Toxidities:
- **Severe N/V**: any AC combinations (doxo/epi/id/daunorubicin+ifos/cyclophosphamide), carmustine, dacarbazine, cisplatin, methotrexate, streptozotocin; HIDAC (AraC), aldesleukin/IFNα, amifostine > 300, ATO, azacitidine, bendamustine, busulfan, clofarabine, daclomycin, irinotecan, melphalan, methotrexate > 250, temozolomide; refer to NCCN Guidelines for management
- **Severe BM**: busulfan, carmustine, cyclophosphamide, dacarbazine, ifosfamide, 5-FU, methotrexate, doxorubicin (daunorubicin), taxotere, taxol, carboplatin, melphalan, fludarabine

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS</th>
<th>TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>Breast, colorectal, pancreatic, gastric, esophageal, H&amp;N</td>
<td>Coronary vasospasm, acute cerebellar ataxia, hand-foot syndrome, stomatitis, hemorrhage, GI ulcers/bleeding, hiccups, diarrhea, BM↑*</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Breast, colorectal</td>
<td>Monitor INR (if on Coumadin), hand-foot syndrome, SJS-TEN, N/V/D, cytopenias (worse with stage IV breast CA), liver toxicity</td>
</tr>
<tr>
<td>Cytarabine (HiDAC)</td>
<td>AML, ALL, CLL, meningeal leukemia</td>
<td>Acute cerebellar ataxia, PRES, BM↑*, chemical conjunctivitis (Rx dexamethasone eye drops), ↑LFTs, cutaneous tox, hand-foot syndrome</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Breast, ovarian, NSCLC, pancreas, bladder</td>
<td>Capillary leak syndrome, PRES, TMA/HUS, ARDS, ↑LFTs, N/V, hematuria</td>
</tr>
<tr>
<td>Mercapturine (HiDAC)</td>
<td>ALL (w MTX), CML</td>
<td>Biliary cholestasis &amp; hepatocellular necrosis, BM↑*, (Consider TPMT SNP testing if severe BM↑), N/V/D</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>CLL, NHL, AML</td>
<td>BM↑, autoimmune hemolytic anemia, neurotoxicity, fatal pulm toxicity (when used w/ pentostatin for CLL)</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>CML, cervical, sickle cell, H&amp;N</td>
<td>BM↑, cutaneous tox, N/V/D, ↑LFTs, ↑Cr, ↑BUN</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>ALL, breast, H&amp;N, CTCL, SCLC, NSCLC, NHL, osteosarcoma</td>
<td>BM↑, aplastic anemia, AKI, ↑LFTs, hepatic fibrosis/cirrhosis, cutaneous tox, IS (PCP), pneumonitis/PF, teratogenic, ulcerative stomatitis/diarrhea, IF</td>
</tr>
<tr>
<td>Pemethystrex</td>
<td>Mesothelioma, NSCLC</td>
<td>BM↑, desquamating rash, pneumonitis, renal tox</td>
</tr>
</tbody>
</table>

**Alkylation Agents (all cause BM↑, infertility & increased risk of MDS/AML)**
- Busulfan: HSCT conditioning, CML
- Ifosfamide: Testicular, breast, lung, HL, NHL, bone
- Melphalan: MM, ovarian
- Carmustine: CNS tumors, HL, NHL, MM
- Cyclophosphamide: Leukemia, MM, breast, NHL, ovarian, retinoblastoma
- Dacarbazine: HL, melanoma
- Cisplatin: Bladder, ovarian, testicular, H&N
- Carboplatin: Ovarian, lung, H&N, CNS tumors
- Oxaliplatin: Colorectal, pancreatic

**Antifolates**
- Methotrexate: ALL, breast, H&N, CTCL, SCLC, NSCLC, NHL, osteosarcoma
- Pemetrexed: Mesothelioma, NSCLC

**Antibiotics**
- Bleomycin: HLNHL, testicular, ovarian, H/N
- Mitomycin: Gastric, esoph, anal, bladder, pancreas

**Hormonal Therapy**
- Tamoxifen: Breast
- Raloxifene: ER+ Breast
- Anastrozole: ER+ Breast (post-menopausal)
- Fulvestrant: ER+ Breast (post-menopausal)
- Megestrol: Breast, endometrial
- Leuprolide: Prostate, breast (goserelin)
- Fulvestrant: Prostate
- Bicalutamide: Prostate

**Topoisomerases Inhibitors**
- Anthracyclines (Dauno/Epi/ Doxorubicin): Breast, ALL, AML, MM, lung, bladder
- Mitoxantrone: Breast, ALL, AML, breast
- Irino/Topotecan: Irinotecan: colorectal, SCLC, Topotecan: cervical, ovarian, SCLC
- Etoposide: SCLC, testicular, KS, glioblastoma

**Late Pulmonary Toxicities**
- Fludarabine: BM↓, pulmonary fibrosis, mucositis, rash, IF
- Oxaliplatin: BM↓, renal/pulmonary tox, neurotoxicity, BM↓, rhabdo, ↑QT, PRES
- Pemetrexed: BM↓, renal/cardiac tox, HUS, interstitial pneumonitis, ARDS, bladder fibrosis

**Common Chemotherapy Toxicities:**
- **Severe N/V:** any AC combinations, carmustine, dacarbazine, cisplatin, methotrexate, streptozotocin; HIDAC (AraC), aldesleukin/IFNα, amifostine > 300, ATO, azacitidine, bendamustine, busulfan, clofarabine, daclomycin, irinotecan, melphalan, methotrexate > 250, temozolomide; refer to NCCN Guidelines for management
- **Severe BM:** busulfan, carmustine, cyclophosphamide, dacarbazine, ifosfamide, 5-FU, methotrexate, doxorubicin (daunorubicin), taxotere, taxol, carboplatin, melphalan, fludarabine

**Drug Toxicities:**
- **5-FU:** breast, colorectal, pancreatic, gastric, esophageal, H&N, coronary vasospasm, acute cerebellar ataxia, hand-foot syndrome, stomatitis, hemorrhage, GI ulcers/bleeding, hiccups, diarrhea, BM↑*
- **Capcitabine:** breast, colorectal, monitor INR (if on Coumadin), hand-foot syndrome, SJS-TEN, N/V/D, cytopenias (worse with stage IV breast CA), liver toxicity
- **Cytarabine (HiDAC):** AML, ALL, CLL, meningeal leukemia, acute cerebellar ataxia, PRES, BM↑*, chemical conjunctivitis (Rx dexamethasone eye drops), ↑LFTs, cutaneous tox, hand-foot syndrome
- **Gemcitabine:** breast, ovarian, NSCLC, pancreas, bladder, capillary leak syndrome, PRES, TMA/HUS, ARDS, ↑LFTs, N/V, hematuria
- **Mercapturine (HiDAC):** ALL (w MTX), CML, biliary cholestasis & hepatocellular necrosis, BM↑*, (Consider TPMT SNP testing if severe BM↑), N/V/D
- **Fludarabine:** CLL, NHL, AML, BM↑, autoimmune hemolytic anemia, neurotoxicity, fatal pulm toxicity (when used w/ pentostatin for CLL)
- **Hydroxyurea:** CML, cervical, sickle cell, H&N, BM↑, cutaneous tox, N/V/D, ↑LFTs, ↑Cr, ↑BUN
- **Methotrexate:** ALL, breast, H&N, CTCL, SCLC, NSCLC, NHL, osteosarcoma, BM↑, aplastic anemia, AKI, ↑LFTs, hepatic fibrosis/cirrhosis, cutaneous tox, IS (PCP), pneumonitis/PF, teratogenic, ulcerative stomatitis/diarrhea, IF
- **Pemetrexed:** Mesothelioma, NSCLC, BM↑, desquamating rash, pneumonitis, renal tox

**Alkylation Agents (all cause BM↑, infertility & increased risk of MDS/AML):**
- **Busulfan:** HSCT conditioning, CML
- **Ifosfamide:** Testicular, breast, lung, HL, NHL, bone
- **Melphalan:** MM, ovarian
- **Carmustine:** CNS tumors, HL, NHL, MM
- **Cyclophosphamide:** Leukemia, MM, breast, NHL, ovarian, retinoblastoma
- **Dacarbazine:** HL, melanoma
- **Cisplatin:** Bladder, ovarian, testicular, H&N
- **Carboplatin:** Ovarian, lung, H&N, CNS tumors
- **Oxaliplatin:** Colorectal, pancreatic

**Anti-Folates:**
- **Methotrexate:** ALL, breast, H&N, CTCL, SCLC, NSCLC, NHL, osteosarcoma, BM↑, desquamating rash, pneumonitis, renal tox

**Antibiotics:**
- **Bleomycin:** HLNHL, testicular, ovarian, H/N
- **Mitomycin:** Gastric, esoph, anal, bladder, pancreas

**Hormonal Therapy:**
- **Tamoxifen:** Breast, ER+ Breast
- **Raloxifene:** ER+ Breast (post-menopausal)
- **Anastrozole:** ER+ Breast (post-menopausal)
- **Fulvestrant:** ER+ Breast (post-menopausal)
- **Megestrol:** Breast, endometrial
- **Leuprolide:** Prostate, breast (goserelin)
- **Flutamide:** Prostate
- **Bicalutamide:** Prostate

**Topoisomerases Inhibitors:**
- **Anthracyclines (Dauno/Epi/Doxorubicin):** Breast, ALL, AML, MM, lung, bladder, cardiotoxicity (DCM, myopericarditis); BM↑, IS, 2nd malignancies, local tissue necrosis in setting of extravasation, liver/renal tox, typhlitis, “chemo brain”
- **Mitoxantrone:** Breast, ALL, AML, breast
- **Irino/Topotecan:** Irinotecan: colorectal, SCLC, Topotecan: cervical, ovarian, SCLC
- **Etoposide:** SCLC, testicular, KS, glioblastoma, BM↑, acute infusion rxn (HoTN), metallic food taste, SJS/TEN

Lauren Banks
**Oncology**

**Chemotherapy & Toxicities**

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<tr>
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<td>Panitumumab</td>
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<td>Denileukin</td>
<td>MM, MDS (lena)</td>
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<td>Lena/poma/ thalidomide</td>
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<td>ATRA</td>
<td>APL</td>
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<td>Arsenic</td>
<td>MDS</td>
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<tr>
<td>Azacytidine</td>
<td>MDS</td>
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<td>Decitabine</td>
<td>AML, CML, MDS</td>
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<td>BCR-ABL: Ph+ CML/ALL (I, D), GIST (I), MDS (I), HES/CEL (I)</td>
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<td>Nilotinib</td>
<td>BCR-ABL: Ph+ CML/ALL</td>
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<td>Gefitinib</td>
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<td>Vemurafenib + Cabotinib</td>
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<td>Dabrafenib + Trametinib</td>
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<td>Lapatinib</td>
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<td>Sorafenib</td>
<td>VEGF: RCC, HCC, thyroid</td>
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<tr>
<td>Sunitinib</td>
<td>VEGF: RCC, GIST, pancyt, neuroendo</td>
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<td>Bortezomib</td>
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<td>Cabozantinib</td>
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<td>Olaparib</td>
<td>BRCA-mutant ovarian (3rd line), breast</td>
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<tr>
<td>Rucaparib</td>
<td>BRCA-mutant ovarian (2nd line)</td>
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<tr>
<td>Niraparib</td>
<td>Ovarian, peritoneal</td>
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<tr>
<td>Palbociclibilicliblil</td>
<td>HR+ metastatic breast</td>
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<tr>
<td>Abemaciclibin</td>
<td>HR+ metastatic breast</td>
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*Key: BM↓ = myelosuppression, IS = immunosuppression, N = nausea, V = vomiting, D = diarrhea, IF = infertility, DHFR = dihydrofolate reductase, HES = hypereosinophilic syndrome, hand-foot syndrome = palmar-plantar erythrodysesthesia

**Table does not include all off-label clinical indications

**See “Immune Checkpoint Inhibitors” chapter for immunotherapy-associated toxicities

Lauren Banks

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Immune Checkpoint Inhibitors

**IMMUNE CHECKPOINT INHIBITORS (ICIs)**
- **Indications:** melanoma, NSCLC, RCC, urothelial, gastric, HCC, H&N, HL, numerous other indications are under investigation including breast cancer. PD-1 inhibitors are FDA-approved for any microsatellite instability-high (MSI-H) or mismatch-repair deficient cancers (dMMR) (NEJM 2017;377:1345, NEJM 2018;378:1277).
  - Pre-existing autoimmune disease is NOT an absolute contraindication to the use of ICIs. Can be associated with flare but rarely treatment-limiting (J Clin Oncol 2018;36:1905, Ann Oncol 2017;28:368).

- **Definition:** systemic autoimmune or inflammatory events due to immune system activation by ICIs
- **Risk factors:**
  - Combination immunotherapy (anti-CTLA-4+anti-PD-1): associated with earlier, higher incidence, and severity; significantly less with anti-PD1 compared with anti-CTLA-4.
  - No predictors of who will develop irAEs. Patients with pre-existing autoimmune disease can flare (see above).
- **Timing:** highly variable based on organ system involved, drug target, monotherapy vs combination. Can present over weeks to years.
- **Clinical presentation:** Dermatologic toxicity (rash, vitiligo), hepatitis, thyroiditis, colitis, myocarditis, pneumonitis, DM1, neurotoxicity (aseptic meningitis, encephalitis, transverse myelitis, neuropathy/mononeuritis, GBS, myasthenia), arthralgias>arthritis, Sicca syndrome. See below for organ-specific details.
- **Treatment:** Absence of prospective data, treatment recommendations based on expert consensus, see ASCO guidelines (J Oncol Pract 2018;14:247).
  - Systemic glucocorticoids (PO, IV) are first-line.
  - Other immunosuppressive agents are used in treatment-refractory cases (infliximab [except hepatitis], MMF, tacrolimus, MTX, ATG, IVG/plasmapheresis in autoAb-mediated/neurologic irAEs).
  - Can continue therapy with close monitoring for Grade 1 toxicities; hold for Grade 2, consider resuming if back to Grade 1.
  - Grade 3 irAE typically requires holding immunotherapy, generally rechallenge is not advised.
  - Grade 4 irAE warrants permanent discontinuation of immunotherapy (except in endocrinopathies controlled with hormone replacement); in some cases, change to different agent may be safe.

Skin toxicity:
- Typically manifest as rash, pruritis, rarely SJS/TEN. Common, up to 30-40% of patients (higher with CTLA-4 than PD-1/L1 blockade). Vitiligo seen only in melanoma, associated w/ response to tx (JAMA Dermatol 2016;152:45).
- **Timing:** Early, within the first few weeks of treatment initiation.
- **Signs/sx:** Four types of skin reactions:
  1. Inflammatory (psoriasiform or lichenoid reactions)
  2. Immunebullous (dermatitis herpetiformis or bullous pemphigoid)
  3. Keratinocyte alteration (acantholytic dyskeratosis)
  4. Immune reaction mediated by alteration of melanocytes (regression of nevi, tumor melanosis, vitiligo)
- **Diagnosis:** Exam; r/o other etiologies (i.e. infection, DRESS, TEN/SJS); grade grossly based on BSA coverage (<10% grade 1, 10-30% grade 2, >30% grade 3)
- **Treatment:** Topical steroids, oral antihistamines for inflammatory/pruritic reaction. If severe, consider systemic steroids and derm consult. Often does not require treatment interruption.
Oncology | Immune Checkpoint Inhibitors

Hypophysitis (JAMA Oncol 2018;4:173)
- Primarily seen with anti-CTLA-4, estimated prevalence of 3.2%. Rarely with anti-PD-1/PD-L1 agents (0.5%).
  - Mechanistically distinct from other irAEs; thought to be mediated by direct binding of ipilimumab to CTLA-4 expressed on normal cells of the anterior pituitary (Sci Transl Med 2014;6:230).
- Timing: Median onset is 8 weeks
- Signs/sx: Headaches (can be severe) most common; fatigue, N/V, dizziness, weight loss, hot flashes, cold intolerance, hyponatremia (anterior hypopituitarism); not associated with central diabetes insipidus (posterior pituitary spared)
- Diagnosis: MRI brain/pituitary shows transient (generally resolved by 2 months), diffuse pituitary enlargement; test hormonal axes: 8AM serum cortisol + ACTH and/or cort stim; TSH w/ ft4/T4/T3; PRL; LH/FSH, serum testosterone/SHBG (in men); IGF-1.
- Treatment: Symptoms resolve with appropriate hormone substitution; hormone deficiencies tend to persist
  - Hypocortisolism: physiologic glucocorticoid replacement (prednisone 3-5mg daily equivalent; increase x2-3 with infection/illness), high-dose glucocorticoids do not improve outcomes (may be associated with reduced survival); counsel about adrenal crisis; obtain medical bracelet (Cancer 2018;124:378, Oncologist 2016;21:804)
  - Hypothyroidism (can also occur independent of hypophysitis): thyroid hormone replacement with levothyroxine (hypercortisolism can also occur, but rarer; consult endocrine)
  - Hypogonadism: consider testosterone replacement if persists
  - GH deficiency: GH theoretically contraindicated due to active malignancy, although no supportive evidence (Nat Clin Pract Endocrinol Metab 2006;2:532)

Colitis
- More commonly seen with anti-CTLA-4; Grade 3/4 colitis is higher with ipilimumab (<10%) than with anti-PD-1 agents (1-2%).
- Timing: 6-8 weeks (median) after initiation of therapy.
- Signs/Sx: Diarrhea, abdominal pain
- Diagnosis: CBC; BMP; CRP; ANCA; consider lactoferrin/calprotectin; flex-sig and/or colonoscopy; rule out alternative etiologies: Clostridium difficile, bacterial or viral pathogens (stool Cx, O&P, CMV PCR, cryptosporidia); CTAP can show mild diffuse bowel thickening or segmental colitis associated with diverticulosis; GI consult for EGD/colo (can affect upper/lower) for grade 2 sx (4-6 BM/d >baseline), pathology shows active acute colitis.
- Treatment: Symptomatically with anti-diarrheal agents after exclusion of infection; Grade 1/2 (<3/4-6 BM >baseline): antidiarrheal; budesonide 9 mg PO or prednisone PO if fails to improve (G1>14d; G2>3d); Grade 3/4 (>6 BM over baseline): systemic glucocorticoids (prednisone 1-2 mg/kg or methyl/prednisolone 1-2 mg IV) with taper, infliximab in refractory cases

Pneumonitis
- More common w/ anti-PD-1, but serious toxicity rare. Combination therapy confers significantly higher risk. (Chest 2017;152:271, J Clin Oncol 2017;35:709): risk also increased in combination with targeted therapy for lung ca.
- Timing: Highly variable onset, later than other irAEs.
- Signs/sx: Dyspnea (53%), cough (35%), increased sputum production; life-threatening presentations include acute interstitial pneumonia/ARDS; 1/3rd of patients asymptomatic (J Clin Oncol 2017;35:709, Clin Cancer Res 2016;22:6051)
- Diagnosis: Low threshold to obtain CT/HRCT, CXR often not helpful; workup Ddx (viral and bacterial PNA, COP, COPD exacerbation, heart failure, lymphangitic carcinomatosis/disease progression, PE): VBG, influenza/RSV PCR, resp viral panel, BCx, SpCx and smear, sputum for PCP if at risk, consider BAL; NT-proBNP, troponin, TTE, CTPE/LENI. Imaging non-specific: GGOs, NSIP-like, COP-like, HP-like.
- Treatment: Oxygen, glucocorticoids (prednisone 1-2 mg/kg or methyl/prednisolone 1mg/kg) prolonged taper, consider empiric abx, diuretics

Myocarditis (J Am Coll Cardiol 2018;71:1755)
- Rare, but serious adverse event of ICI associated with high mortality (46% death in severe myocarditis); risk much higher with combination therapy
- Timing: Generally within 3 months (Oncologist 2018;23:874, Lancet 2018;391:933)
- Signs/sx: Sx of heart failure (SOB, LE edema), chest pain, palpitations, arrhythmia
- Diagnosis: EKG/tele; troponin, CK-MB, NT-proBNP, ESR/CRP; TTE; consider myocardial bx; CPK/aldolase; EMG/muscle bx
- Treatment: pulse-dose glucocorticoids (1g IV x3d, then PO pred 1mg/kg); second line consider ATG/IVIG (if unstable), or infliximab/MMF/tacro (if stable) (Oncologist 2018;23:879); BB, ACEi/ARB (EF low)

Hepatitis (Oncologist 2018;23:991)
- Timing: Median onset 6-14 weeks after treatment initiation
- Signs/sx: Usually asymptomatic
- Diagnosis: LFTs, r/o other etiologies such as viral hepatitis, ingestion/EtOH, drugs. Rarely consider liver bx if severe
- Treatment: If LFTs ≥ 3-5 ULN, hold therapy and monitor labs closely. If persists >1-2 weeks, treat with methylprednisolone (1mg/kg/day); 2nd line MMF (Cellcept), 3rd line ATG (Cancer Treat Rev 2016;44:51)

Charlotte Lee
Tumor Lysis Syndrome (NEJM 2011;364:1844, JCO 2008;26:2767)

- **Pathophys:** Tumor lysis (iso of cytotoxic tx initiation, rarely spontaneous in NHL and acute leukemia) causes release of intracellular components (nucleic acids catabolized to uric acid, K+, PO4+). **Clinical effects (can be deadly):** renal failure (↑uric acid precipitates in renal tubules); seizure/Ca-phos crystal deposition (↑phos → ↓Ca); arrhythmias (↑K);

- **Risk factors:**
  - **Malignancy risk:** High: ALL/AML (WBC ≥ 100k), CLL (on venetoclax & ↑uric acid), stage 3/4 Burkitt’s/lymphoblastic NHL, bulky DLBCL. **Intermediate:** ALL (WBC < 100k), AML (WBC 25-100k or < 25k & ↑LDH), Burkitt’s, DLBCL, CLL (chemo-specific & ↑WBC), rare chemo-sens bulky solid tumor. **Low:** HL, indolent NHL, CML, CLL (on alkylation tx & WBC <50k), MM

- **High risk substrate:** WBC > 50k, LDH > 2x ULN, bulky tumor (>10 cm), hypervolemia, uric acid > 7.5, renal failure

- **Diagnosis (Cairo-Bishop criteria):**
  - Laboratory diagnosis: 2+ criteria within 3d before or 7d after cytotoxic therapy: uric acid ≥ 8 mg/dL, K ≥ 6 mEq/L, phos ≥ 4.5mg/dL, or Ca ≤ 7mg/dL. Criteria also satisfied if 25% change from baseline.

- **Clinical diagnosis:** lab TLS + 1+ criteria: Cr 1.5x ULN, arrhythmia, seizure, death (not attributable to chemo agent)

- **Prophylaxis and treatment:** While treating, labs should be checked Q2-Q4H, patient should be on telemetry given electrolyte abn

  - Hydration: Maintain UOP >600 cc/hr to offset as much as possible uric acid and phos; can use diuretics prn
  - Use bicarb only with marked acidosis, as ↓urine ph will ↓uric acid crystals but ↑Ca-phos crystals

- **Electrolyte abnormalities:**
  - Use bicarb only with marked acidosis, as ↓urine ph will ↓uric acid crystals but ↑Ca-phos crystals

  - Uropathy: ↓K (hyperK tx), ↓phos (binders), ↓Ca (avoid until phos wnl or sx of ↓Ca)

- **Allopurinol:** 100mg/m2 PO q8h or 200-400mg/m2 IV, administer 24-48 hr before chemo, cont until hyperuricemia resolved

  - Renal dose, note reduced clearance of other meds (ie: cyclophosphamide, MTX, 6-MP, azathioprine, ampicillin)

- **Rasburicase** (discuss with attending): 0.2 mg/kg IV, administer if high risk or baseline uric acid ≥ 8 mg/dL

- **Risk of anaphylaxis, hemolysis. Contraindicated in G6PD deficiency (risk of methemoglobinemia)

- **Renal replacement therapy:** indicated if Ca-phos product ≥70 mg2/dL2

### Hyperviscosity Syndrome/Leukostasis (Blood 2012;119:2205)

- **Etiology:** 1) hyperproteinemia from monoclonal gammapathies mostly commonly Waldenström’s macroglobulinemia (IgM), uncommonly myeloma; 2) hyperleukocytosis/leukostasis seen in AML with blasts > 50k (uncommon in ALL/CLL unless very high counts); 3) other diseases such as rheumatoid disease, polycythemia, sickle cell, spherocytosis

- **Signs/symptoms:** Most common: pulmonary (SOB) and CNS (blurry vision) venous engorgement, headache, dizziness, ataxia, confusion, coma, fever → if concerned, page hematology fellow on call and clinical pathology resident for EMERGENCY VISCOSITY STUDY, p21828, (notify attending ASAP as pheresis will involve attending-level decision)

- **Diagnosis:** ↑Ostwald tube serum viscosity, light chains, SPEP, WBC (often >100k, but can be lower in blast crisis)

- **Lab artifacts from hyperleukocytosis:** spurious ↑TK (use ABG K), falsely low arterial PO2 (use 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: leukopheresis; cytoreduce (hydroxyurea); induction chemo; avoid RBC & pt transfusion (↑Viscosity)


- **Primary CA:** lung > prostate, breast > non-Hodgkin’s lymphoma, renal cell, multiple myeloma, lymphoma

- **Location:** TS (60%) > LS (25%) > CS (15%); multiple sites in 20-35%; ESCC score for spinal level (JNCCN 2016:14:70)

- **Symptoms:** back pain (usually 1st sx; radicular, localized, worse at night/recumbent/valsalva → weakness, gait instability → sensory deficits (saddle anesthesia in cauda equina lesions), bowel/bladder dysfxn

- **Exam:** pain precedes other sx by ~7 wks, weakness/ataxia, paresthesia, ↑reflexes, Babinski, ↓anal sphincter tone

- **Diagnosis:** STAT vs. urgent full spine MRI with cord compression/metastasis protocol, alternative is CT myelography

- **Treatment:** Call Spine Surgery & Radiation Oncology ASAP → more effective than chemo (except for heme, germ cell malignancies)

  - Severe deficits: dexamethasone 96mg x1, then 24mg IV q6hr x3d, then taper x10d

  - Minimal deficits: dexamethasone 10mg IV x1, then 4mg IV q6hr

### Brain Metastases with Increased Intracranial Pressure (Ann Palliat Med 2015;4:225, JCO 2015;33:3475)

- **Intracranial tumors present in ~10-30% of patients with metastatic disease:** call Neurosurgery & Radiation Oncology

- **Primary CA:** lung (48%), breast (15%), melanoma, RCC, osteosarcoma, head and neck, thyroid, colorectal

- **Symptoms:** headaches (40-50%); “tension”, worse w/ Valsalva, N/V), focal neuro deficits (20-40%, hemiparesis most common), cognitive dysfunction (30-35%), new onset seizures (10-20%), stroke (5-10%)

- **Diagnosis:** contrast MRI ↑sensitivity > non-enhanced MRI, CT +

- **Treatment:** control vasogenic edema (dexamethasone 10mg IV x1, then 8mg BID), consider AED (usually not recommended for 1st pp); avoid AC if c/t active hemorrhage; definitive treatment will ↓local recurrence: stereotactic radiosurgery > whole-brain XRT (↑neurocognitive impairment; hippocampal sparing helpful) > surgery

### Superior Vena Cava Syndrome (SVC syndrome) (NEJM 2007;356:1862)

- **Etiology:** External compression of SVC from a mediastinal mass (commonly lung CA or NHL) causing ↑upper body venous pressure

- **Symptoms:** cerebral edema (HA, confusion, herniation), narrowing of larynx/pharynx (dyspnea, stridor, cough, dysphagia, hoarseness), head/neck swelling (visually striking, often not clinically significant), hemodynamic instability ↓venous return

- **Diagnosis:** venography, CT chest w/contrast, obtain/ensure tissue diagnosis to guide tx (extremely important!)

- **Treatment:** secure airway, RT/chemo, intravascular stent (emergent/refractory), steroids (stridor/resp distress only, clear with onc)
Oncology

Febrile Neutropenia

DEFINITIONS AND ETIOLOGY (J Oncol Pract 2019:15:19, NCCN Prevention and Treatment Guidelines):

- **Fever**: single temperature ≥101°F (38.3°C) orally or ≥100.4°F (38°C) >1h
- **Neutropenia**: defined as ANC <500 or <1000 and predicted nadir ≤500 within 48h
  - Functional neutropenia: defective PMNs, common in leukemia (↓ neutrophil function despite ANC>500)
- **Microbiology**:
  - Only 40-50% have infectious source identified (others attributed to translocation of intestinal bacteria)
  - 25% organism identified: 40% GNRs (E. coli, Klebs > PsA); 60%GPCs (CoNS > MSSA/MRSA, strep, enterococcus/VRE) esp w/ indwelling lines or mucositis; fungal (Candida, Aspergillus) more likely w/ prolonged ↓ANC, broad-spectrum abx use, or TPN

EVALUATION:

- **H&P**: prior micro data, time since last chemo, recent antibiotic therapy/ppx, major comorbid illness, use of devices
- **Exam**: mouth (mucositis), skin (erythema), perineum/rectal (visual inspection, avoid DRE)
- **Studies**: BCx x2 sites (≥1 periph, 1 per CVC lumen), UA/UdC, CBC, BMP, LFTs, CXR, Sputum Cx/GS, viral panel, CMV PCR (SCT)
- **Further site-specific studies to consider**:
  - Diarrhea: stool culture, O&P, C. diff; abdominal pain: CT AP (may not have abdominal pain iso neutropenia, consider imaging)
  - Pulmonary symptoms: Influenza/RSV PCR, CXR/CT chest, +/- bronch/BAL (especially if prolonged F&N)
  - HA/sinus pain: CT face/sinus
  - HA/sinus pain: CT face/sinus
  - Fungal markers: LDH, beta-D-glucan; galactomannan if high risk for Aspergillus (SCT, GVHD, neutropenia >10-14d)
  - **MASCC Risk Index score** (JCO 2000;18:3038): identifies cancer patients with febrile neutropenia at low risk of complication
  - **High risk**: anticipated ANC ≤100 for ≥7d, inpt status, MASCC <21, co-morbidities/infections (renal/hepatic impairment, PNA, central line infxn), allogeneic HSCT, mucositis grade 3-4, alemtuzumab use within past 2 months → Inpatient management
  - **Low risk** (JCO 2013:31:794): anticipated ANC ≤100 for <7d, no co-morbidities, good performance status (ECOG 0-1), MASCC ≥21 can be treated with PO antibiotics after brief inpatient stay versus strictly outpatient (oncologist’s discretion)

TREATMENT/PROPHYLAXIS (NCCN Prevention and Treatment Guidelines):

- **Empiric abx**: within 1hr, up to 70% mortality if delayed abx (Antimicrob Agents Chemother 2014:58:3799)
  - **Gram-negatives (PSA dosing)**: broad gram negative coverage within 60 min of presentation
    - Cefepime 2g q8h (or ceftazidime 2g q8h), pip/tazo 4.5g q6h, or meropenem 1g q8h
    - PCN allergy: Confirm allergy; use Penicillin Hypersensitivity Pathway and test-dose cefepime or meropenem; consider allergy consult. If true allergy, use aztreonam (avoid in ceftazidime allergy) + levofloxacin.
    - High-risk ESBL: meropenem 1g q8h (2g q8h if meningitis)
    - Low risk (JCO 2013:31:794): cipro PO + augmentin vs. clinda (if PCN allergy)
  - **Gram-positives**:
    - First line: Vanc; VISA/VRSA or VRE: daptomycin (unless pulmonary process, poor lung penetration) or linezolid
    - Indications: hypoTN/severe sepsis, GPC bacteremia, catheter-related infxn (rigors with infusion), SSTI, PNA on imaging, MRSA colonization (esp in HSCT), severe mucositis + prior FP ppx + GNR coverage with ceftaz
    - Vancomycin NOT part of FN empiric regimen (JAC 2005:55:438); indwelling lines, mucositis alone, FO pp, and persistent fever despite GN coverage are NOT indications
  - **Anaerobic**
    - Indications: intra-abd source, C. diff, oral ulcer/periportal infxn, post-obstructive PNA, necrotizing ulceration
  - **Fungal (invasive molds)**
    - Indications: F&N >4-7d, +fungal biomarkers, + CT chest (circumscribed, air crescent, cavity), + BAL fungal cx
    - Micafungin 100mg q24h or Amphotericin 3mg/kg (admin after 500cc NS)
    - Indications: F&N >4-7d, +fungal biomarkers, + CT chest (circumscribed, air crescent, cavity), + BAL fungal cx
    - Vancomycin NOT part of FN empiric regimen (JAC 2005:55:438); indwelling lines, mucositis alone, FO pp, and persistent fever despite GN coverage are NOT indications
  - **Resolution of fever**:
    - Documented infxn: narrow abx and tx for recommended course, then switch to FO pp until ANC >500
    - Culture negative: continue empiric treatment until ANC >500 vs. narrow to FO pp if afebrile x4-5d
  - **Fever continues >4-7d**:
    - Clinically stable: do not broaden abx or add vanc, consider other causes (ie: engraftment, differentiation, GVHD, TLS, drug fever, thrombophlebitis, hematoma, hepatoportal candidiasis)
    - Clinically worsening: broaden abx +/- fungal coverage, consider CT chest +/- branch to evaluate for fungal infxn
  - **Catheter-associated infxn**:
    - Coag-negative staph, non-VRE Enterococcus: can keep line if IV abx + abx lock x2 wks
    - Staph aureus, PsA, fung: must remove line. For gram negative, d/w attending; line removal vs. lock therapy.
    - Complicated infxn (endocarditis, septic thrombosis, bacteremia/fungemia >72 h): remove line, abx x4-6 wks
  - **Prophylaxis**
    - **Antimicrobial ppx**: Refer to NCCN guidelines (citation above) for more specific indications
      - **Antibacterial (FLQs)**: high-risk pts and attending discretion for intermediate-risk pts
      - **Antifungal (azole vs echinocandin)**: heme malignancies during neutropenia and 75 days post-allo HSCT
      - **PCP (TMP-SMX)** ppx recommended for equivalent of ≥20 mg prednisone daily for ≥1 month and allo/auto HSCT
      - **HSV/ VZV (acyclovir vs. famvir)**: sero+ undergoing tx while neutropenic, or 1 yr post-auto and 2 yrs post-allo HSCT
    - **G-CSF**: recommended if risk of F&N >20% → shortens duration of F&N, but does NOT decrease mortality (JCO 2006:24:3187)
Geriatrics & Palliative Care

Frailty & Polypharmacy

Richard Newcomb

Frailty
Consider on all admissions >75-80 years old, or admissions billed as “failure to thrive”

- Reframe “failure to thrive” as frailty, which has evidence-based assessment criteria and diagnostic approach
- Consensus frailty definition: “Medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability” for developing increased dependency and/or death” JAMDA 2013;14:392

- **FRAIL screen:** Frail = 3 or more positive answers; Pre-Frail = 1-2 positive answers (J Nutr Health Aging. 2012;16:601)
  - Fatigue: “In the past four weeks, do you feel tired all or most of the time?”
  - Resistance: “By yourself, do you have any difficulty walking up 10 steps without resting?”
  - Ambulation: “By yourself, do you have any difficulty walking a city block?”
  - Illnesses: Does patient have more than 4 comorbidities?
  - Loss of weight: Greater than 5% weight loss over past year?

Inpatient frailty assessment: find the root cause!

- Thorough H&P and workup to evaluate for new/progressive illness (cancer, CHF, COPD, cirrhosis, CKD, etc.)
- Physical Functioning – goal is to identify ADL/IADL deficits for targeted intervention
  - Katz ADL Scale (“Does anyone help you with: walking, feeding, dressing, bathing, grooming, toileting?”)
  - Instrumental ADLs (“Does anyone help you with: cooking, cleaning, shopping, driving, medications, finances?”)
- Cognition and Mental Health
  - Rule-out delirium with Confusion Assessment Method (see Mental Status Exam in “Psychiatry” Section).
  - If negative, proceed to Mini-Cog evaluation to screen for dementia; If any deficits, refer for outpatient evaluation
  - Always screen for depression with PHQ-2 (see Health Screening & Maintenance in “Primary Care” Section)

Interventions for frailty (Age Ageing 2017;46:383)

- **Exercise:** inpatient and outpatient PT; exercise programs as outpatient can reduce fall risk (JAMA 2018;319:1705)
- **Nutrition:** consider nutrition consult for vitamin, protein, and fat supplementation; education
- **Cognition** training (outpatient OT consult): improve short-term memory, information processing, problem-solving
- **Home environment** assessment and modifications: consider social work consult, OT consult, iCMP referral

Polypharmacy and inappropriate medications for elderly patients

- No consensus definition of polypharmacy (“you know it when you see it”). High prevalence: >50% inpts >75yo (BMC Geriatr 2017;17:230).
- Polypharmacy increases likelihood of Adverse Drug Reactions (ADRs), Drug-Drug Interactions, delirium, falls, and other negative outcomes. Should communicate with PCP about simplifying med list.
- **Medication classes to (usually) AVOID in geriatric patients:**
  - Anticholinergics: Risk of delirium, falls, and other side effects. Avoid antihistamines, TCAs, MAOIs, antimuscarinics (oxybutynin), muscle relaxants (cyclobenzaprine), prochlorperazine.
  - Benzodiazepines: avoid due to risk of delirium, falls, cognitive impairment, etc. (also risk w/ non-BZD hypnotics)
  - Antipsychotics: concern for increased mortality with antipsychotics in the elderly (JAMA Psych 2015;72:438)
  - Peripheral alpha blockers and central alpha-agonists: -zosins and clonidine confer risk of orthostasis and falls
  - Long-acting sulfonylureas: risk of hypoglycemia
  - PPIs: attempt switch to H2 blockers unless clear indication for PPI (risk of C. diff, bone loss/fracture)
  - NSAIDs (especially in elderly patients with decreased CrCl): risk of GI bleed and AKI

- See American Geriatric Society Beer’s List and STOPP-START for further details on potentially inappropriate meds
- Parkinson’s disease: ondansetron is anti-emetic of choice. Avoid metoclopramide and prochlorperazine (as well as antipsychotics)
- Dosage adjustments: ensure appropriate renal dose adjustment for anticoagulants (enoxaparin, apixaban, rivaroxaban, and dabigatran), antibiotics, etc.

Verifying and coordinating medications

- **Verify the Preadmission Medication List (PAML)** on admission → Boston-area 24/7 pharmacies: CVS: 781-894-1600 (dial 2, 2); Walgreens: 617-389-2188 (dial #, 0)
- **Coordinate discharge Rx planning** and education with patient, pharmacy, and PCP → Lower risk of readmission with intensive pharmacist intervention (med rec and education) and coordination with PCP (JAMA IM 2018:178:375)
Geriatrics & Palliative Care  

Pain Management

- Pain history and etiology can help guide therapy. Goal is to maximize level of functioning and quality of life.
  - Time course, location, radiation, quality, severity, exacerbating/relieving factors, associated symptoms, side effects from prior analgesics, functionality (e.g., ADLs, ambulation)
  - Use adjuvant medications and non-pharmacologic: PT/exercise/activity, heat or ice, CBT, treating comorbid psych dx, addressing existential issues, massage, acupuncture or other integrative therapies
- Step-wise approach to pain management: (Principles of Analgesic Use, CDC guidelines)
  - Mild to Moderate Pain – non-opioids and adjuvants are first line
    - Acetaminophen: max dose 3 g daily (2 g safe in liver disease)
    - NSAIDs: celecoxib if GI risk ↓, naproxen if CV risk ↓, ketorolac if severe pain
  - Moderate to Severe Pain – consider short-acting opioids
  - Severe Pain requiring around the clock opioids – consider adding extended release (ER) medications
    - Avoid ER opioids if pain source expected to resolve (e.g., bone fracture, hematoma)

Pain archetypes and useful adjuvant analgesics
- Somatic/Musculoskeletal – easily localized, sharp, aching, gnawing
  - Bony pain – high dose NSAIDs or steroids*. Consider palliative XRT or surgery.
  - Muscle spasm – topical lidocaine, capsaicin, metyl salicylate-menthol ointment (Bengay); muscle relaxants such as benzos, 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
- Inflammatory – associated with other signs of inflammation (swelling, erythema, warmth)
  - NSAIDs, steroids*
- Neuropathic – burning, stinging, alldynia (perceiving innocuous stimuli as painful), hyperalgesia
  - Topical lidocaine and diclofenac gel (NB: often short-term benefit, often not covered by insurance as outpatient)
  - Pregabalin, gabapentin, clonidine, SNRIs (duloxetine, venlafaxine), TCAs (amitriptyline, nortriptyline, desipramine)

Opioids
- Opioid-tolerant defined as total daily dose (TDD) x7 days: morphine 60 mg/oxycodone 30 mg/hydromorphone 8 mg/fentanyl 25 mcg/h
- Patients on suboxone or methadone for OUD → consult ACT for assistance with pain management
- No max dose. Goal is to find minimum dose needed to control sx w/ minimal SE
- Avoid use combo pills (limits titration flexibility)
- Treat constipation prophylactically
- Rotate opioids if side effects, dose reduce by 25-50%

Converting opioids
Ex: Pt takes morphine ER 60 mg PO q12h and uses two morphine IR 15 mg PO breakthrough doses per day
Step 1) Calculate total daily opioid requirement
TDD = (60 mg x 2 doses) + (15 mg x 2 doses) = 150 mg morphine per day
Step 2) Convert TDD to equivalent dose of new opioid
30 mg morphine = 150 mg morphine
  x = 100 mg oxycodone
20 mg oxycodone
Reduce dose by 25-50% to account for incomplete cross-tolerance → ~60 mg oxycodone total daily dose
Step 3) Divide TDD by number of doses per day
- If initiating or converting to long-acting opioid, divide TDD into ER doses and add breakthrough dose (10-20% of TDD of ER opioid)
Final dose: oxycodone ER 30 mg q12h with 10 mg oxycodone q4h pm breakthrough

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<tr>
<th>Opioid Equivalent Doses</th>
<th>PO (mg)</th>
<th>IV (mg)</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>n/a</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>20</td>
<td>n/a</td>
</tr>
<tr>
<td>Hydromorphine</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Fentanyl*</td>
<td>n/a</td>
<td>0.1 (100 mcg)</td>
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</table>

<table>
<thead>
<tr>
<th>Fentanyl patch (mcg/hr)</th>
<th>Morphine PO (mg/day)</th>
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<tbody>
<tr>
<td>25</td>
<td>50</td>
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<td>50</td>
<td>100</td>
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<tr>
<td>75</td>
<td>150</td>
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</table>

*Use caution converting to Fentanyl - short duration of action

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Route</th>
<th>Onset (min)</th>
<th>Peak Effect (min)</th>
<th>Duration of Effect (hr)</th>
<th>Clearance/Metabolites</th>
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<tr>
<td>Morphine</td>
<td>IV</td>
<td>5-10</td>
<td>10-30</td>
<td>3-5</td>
<td>AVOID in renal disease</td>
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<tr>
<td></td>
<td>PO</td>
<td>15-60</td>
<td>90-120</td>
<td>4</td>
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<tr>
<td>Hydrocodone</td>
<td>IV</td>
<td>5-20</td>
<td>15-30</td>
<td>3-4</td>
<td>Safer in renal disease</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>15-30</td>
<td>90-120</td>
<td>4-6</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>PO</td>
<td>15-30</td>
<td>30-60</td>
<td>4-6</td>
<td>2nd line for renal disease</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>30</td>
<td>90</td>
<td>3-4</td>
<td>AVOID in renal disease</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV</td>
<td>&lt;1</td>
<td>5-7</td>
<td>45 min to 2+ hr</td>
<td>Safest in renal and liver disease</td>
</tr>
<tr>
<td>Methadone</td>
<td>IV</td>
<td>10-20</td>
<td>60-120</td>
<td>4-6</td>
<td>Safest in renal disease</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>30-60</td>
<td>90-120</td>
<td>4-12</td>
<td></td>
</tr>
</tbody>
</table>

Patrick W. Malecha

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Methadone and Fentanyl: Initiate only with assistance of Palliative Care or Pain consult!

- **Methadone** – both a mu agonist and NMDA antagonist
  - Beneficial in neuropathic pain
  - Cannot be converted linearly from other opioids
  - Safety concerns: bimodal short and long half-life (up to 150 hours), QTc prolongation
  - Not as useful for dyspnea
- **Fentanyl**
  - Safer in both liver and renal dysfunction
  - Safety concerns: must remove patch if febrile (cutaneous vasodilation → faster transdermal absorption)
  - Requires 18-24h for therapeutic level (patch)

**Pain crisis management:** Severe worsening of pain. While treating, pursue reasonable diagnostic workup for etiology (e.g., bowel perforation/peritonitis, procedural complication, bleeding). **Goal is reduction in pain score by >50%**.

1) **Opioid-naive:** give morphine IV 2-5 mg or hydromorphone IV 0.2-0.4 mg 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 15 min
   - 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 2-3 hours, use this dose as new breakthrough dose
   - Side effects with no pain relief → rotate to different IV opioid (no dose reduction if uncontrolled pain)

**Uptitration:** if pain only moderately controlled with scheduled doses (not in pain crisis), ↑ total daily dose by 30-50%
- If taking ER opioid and needing >3-4 rescue doses daily, ↑ ER dose by 50-100% of total rescue dose used in past 24 hrs

**Patient-Controlled Analgesia (PCA):** appropriate for patients who are AAO and able to use equipment. Families may NOT use PCA by proxy at MGH.
- Medicine residents can order “General PCA” (for opioid-naive patients) or “High Risk PCA” (BMI >40, hx OSA, RAAS -2 to -5, Age >65). If opioid-tolerant or pain difficult to control, consult Palliative Care or Pain.
- Components to PCA pumps: PCA bolus dose, lockout interval (in minutes), one-hour dose limit, RN/clinician bolus (for breakthrough pain), and continuous infusion rate (only use after consulting Palliative Care or Pain)
  - Example for opioid-naive patient:
    - Morphine PCA bolus: 1.5 mg
    - Lockout interval: 10 minutes
    - One-hour limit: 6 mg
    - Clinician bolus: 2 mg q30min PRN
    - Continuous rate: 0 mg/hr

**Adverse effects of opioids and management**
- **Respiratory depression** – hold opioid, consider low doses of naloxone but CAUTION if on high dose ER opioids.
  - Dilute 0.4 mg naloxone (1 ml) in 9 ml saline, give 1-2 ml q2 min until ↑ RR or mental status improves
  - Half life is shorter than many opioids, watch for recurrence of resp depression
- **Constipation** – ALWAYS start standing senna 1-4 tabs qhs or bid and miralax qd when initiating opioids; lactulose, bisacodyl and other laxatives if needed; methylaltrexone qod if failed laxative therapy (dosed by weight)
- **Myoclonus** – reduce dose or rotate opioid, consider gentle IVF; can give ativan 0.5-1 mg PO/IV qid
- **Nausea/vomiting** – prochlorperazine, metoclopramide, haloperidol. Avoid ondansetron (constipating)
- **Pruritus** – Nalbuphine 5 mg IV q6h (pruritus mediated by mu receptor unless rash/allergic reaction).
- **Sedation** – consider CNS stimulants (dextroamphetamine, methylphenidate)
- **Delirium** – reduce dose or rotate opioid; haldol 0.5-1 bid-qid or zypréxa 2.5-5 mg PO qd-bid
- **Allergic reaction** – very rare; rotate opioid

**Opioid use and aberrant use definitions**
- **Addiction:** neurobiologic disease with environmental and psychosocial factors, manifested by impaired control over drug use, compulsive use, continued use despite harm, and cravings. See Psychiatry section
- **Misuse:** intentional or unintentional use in a way that is contrary to directions (e.g., not taking as directed, altering route of delivery, obtaining drugs from other sources)
- **Diversion:** redirection of a drug from its lawful purpose to illicit use
- **Tolerance:** adaptation from exposure to a drug resulting in diminished effect from the drug over time
- **Physical dependence:** state of adaption manifested by withdrawal syndrome in response to abrupt cessation of a drug, rapid dose reduction, or drug antagonist
  - Tolerance and physical dependence are expected with long-term opioid use and should not be confused with addiction
- **Pseudoaddiction:** can be difficult to distinguish from true addiction. Occurs when pain is undertreated and behaviors resolve when pain is adequately treated.
**Geriatrics & Palliative Care**

**Non-pain Symptom Management**

**Searchable Resources:** Palliative care network of Wisconsin (www.mypcnow.org/fast-facts), www.capc.org, Pink and Green Books

**Palliation in serious illness and end of life** can be challenging and often is helped by a Palliative Care consultation.

- “Comfort measures only” is NOT a one-size-fits-all set of orders (e.g., indwelling Foley may be more tolerable than frequent urinary incontinence, diuretics may still be indicated for relief of dyspnea or edema, etc.)
- For persistent/recurrent sx meds should be made standing, with additional PRNs for breakthrough

**Anxiety:** often exaceriated by medications (steroids, appetite stimulants, etc.), undertreated pain, and dyspnea

- Treat underlying causes, use non-pharmacologic strategies (integrative therapies c/s, SW & spiritual care for coping/support)
- For acute anxiety: clonazepam 2.5-5mg q6hr prn, lower doses if elderly. Avoid BZDs due to delirium risk.
- For longer-term management, consider usual meds (SSRIs, SNRIs, TCAs)

**Depressed mood:** Can be difficult to distinguish between MDD, demoralization, and adjustment disorder. See Psychiatry section

- Treat uncontrolled symptoms, especially pain. Screen for delirium.
- CBT/psychotherapy may be better for existential demoralization than in MDD (Am J Hosp Palliat Care. 2016;33(1):93)
  - Some amount of depressed mood is expected, doesn’t necessarily need medication but benefits from psychosocial support
- If nearing end-of-life, CNS stimulants (dexamethasone, dextroamphetamine) > SSRIs due to faster onset of action

**Delirium:** common and often multifactorial

- Prevention: remove unnecessary lines/catheters/restraints; lights on, shades & pt up during day; limit nighttime interruptions and lights/TV; frequent reorientation, use signage; minimize staff/room changes; manage other symptoms
- No FDA-approved delirium med, but if hallucinations or agitation interfering w/ staff or pt safety → Haldol 0.5-1mg IV q4hr PRN. Consider atypical antipsychotics. See Neuro section on delirium for further details.

**Nausea/vomiting:** See relevant GI sections

**Xerostomia:** side effect of chemo/XRT, head/neck surgery, or medications

- Oral hygiene, oral hydration, saliva substitutes such as Biotene

**Anorexia/Cachexia:** common in AIDS, heart failure, COPD, advanced cancer. Often highly concerning for family > patient.

- Rule out reversible causes (other sx causing poor PO intake). In general, allow PO for comfort if near end-of-life.
- Meds to consider: dexamethasone, megestrol (VTE risk), dronabinol, mirtazapine
- NB: during dying process, artificial nutrition and hydration risk may outweigh benefit

**Fatigue:** often related to disease progression, medications, other treatments, deconditioning, malnutrition, sleep disturbances, sx’s


**Dyspnea:** exacerbated by deconditioning, cachexia, worsens at EOL, exacerbates anxiety. Does not always correlate w/hypoxemia.

- Treat underlying causes depending on etiology; consider bedside fan
- For refractory dyspnea, opioids are gold standard (often at lower doses than required for pain). BZDs less supported by evidence; can be used for associated anxiety and must weigh risk of delirium

**Secretions:** pooled secretions → “death rattle”. Disturbing to observers, less bothersome to pt

- Stop feeds/fluids, don’t deep suction (uncomfortable to pt), continue oral care
- Glycopyrrolate 0.2-0.4mg IV q4 PRN. Less deliriogenic than other anti-cholinergics
- Other alternatives: scopolamine patch, atropine, hyoscymamine (may cause delirium)

**Insomnia (inpatient management)**

- Avoid BZDs and non-BZD hypnotics (e.g., zolpidem, zaleplon, eszopiclone) for inpatient management due to delirium risk. Avoid H1 blockers (diphenhydramine, hydroxyzine) due to risk of delirium, next-day sedation, anticholinergic side effects.
- Use non-FDA approved treatments on a short-term basis: melatonin (3-5mg Q6PM), trazodone (12.5-50mg QHS, QTc prolonging), mirtazapine (7.5mg QHS)
- Use with caution: quetiapine (12.5-25mg QHS, QTc prolonging) – there is concern for increased mortality with antipsychotics in the elderly (JAMA Psych. 2015;72:438). Reserve for patients with additional indication (e.g., patients who require pharmacologic tx for agitated delirium).

**Catastrophic hemoptysis or hemorrhage:** often preceded by “sentinel” small bleed. Be sure to prep pt/family for possibility.

- Dark linens/basins present in the room (contrast w/ blood). PPE for caregivers, suctioning, warm blankets (hemorrhage → chills)
- Consider pre-drawn crisis meds, goal is rapid anxiolysis and sedation (BZDs q5-10 min +/- opioids, though bleeding usually painless)

**Meg Allison**
Serious illness conversations

- **When?** Preferred early in disease course as outpatient, but in the inpatient setting some scenarios include:
  - New or progressive serious medical illness such as advanced cancer, ESRD, ESLD, HF, COPD
  - Prognosis trigger: “Would I be surprised if this patient died in the next year?” (J Palliat Med 2010;13:837)
  - Indicator of life expectancy < 6 months (calculator, J Palliat Med 2012;15:175)
  - Age > 80 and hospitalized; see Geriatrics -> Frailty section
- **Why?** Ascertain how the patient wants to live; more than just end of life care preferences
- **How?** Often best to plan patient or family meeting (NEJM 2014;370:2506)

**Preparation**
- Identify time and location to accommodate all meeting participants in an appropriate manner
- Include patient and their preferred participants, primary team, RN, SW, and other providers as appropriate
- If complex decisions/psychosocial issues/family conflict, consider a palliative care consult
- Pre-meet with team to decide meeting leader, discussion goals, unified assessment of clinical scenario, treatment options, and team recommendation

**Serious Illness Conversation – suggested outline / prompts** (adapted from Ariadne Labs SICG)

<table>
<thead>
<tr>
<th>Step</th>
<th>Suggested Prompts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open the conversation</td>
<td>&quot;I'd like to talk about what is ahead with your illness. Would that be ok?&quot;</td>
</tr>
</tbody>
</table>
| Assess prognostic awareness | "What is your understanding of your illness?"  
"Looking to the future, what are your hopes about your health?"  
"What are your worries?" |
| Share hope and worry | "Would it be ok if we talked more about what lies ahead?"  
"I hear you’re hoping for ______ and I worry the decline we’ve seen will continue"  
"I hear you’re hoping for ______ and I worry something serious may happen in next (time window: weeks, months, years)" |
| Align | "I wish we didn’t have to worry about this" |
| Explore what’s important | "If your health worsens, what is most important to you?"  
"How much do your family or friends know about your priorities and wishes?" |
| Close the conversation | "It sounds like ______ is very important to you"  
"Given what’s important to you, I would recommend" |

**Next Steps**
- Debrief with team: **How did that feel?** What went well? What could have gone better?
- Document Serious Illness Conversation in Epic:
  - Patient ID banner (top of chart): click “Code: ___” -> “Advance Care Planning Activity” -> “Serious Illness Conversation” in left tab; fill out SIC form -> “Close”
  - Write ACP note: Within “Advance Care Planning Activity” -> “ACP Notes” -> “Create ACP Note” -> type .ACPSICDOCUMENTATION; write rest of the note

**Code status discussions**

**General Considerations**
- Ideally, code status should be confirmed and reflected in Epic at the time of admission → do not presume full code
- Confirm directly with the patient/HCP, MOLST, and/or prior documentation by outpatient providers
- Readress if a patient’s clinical status changes, or if code status is deemed inappropriate for the clinical setting
- Code status should reflect a patient’s values and preferences and is not equivalent to ACP (it is a specific medical procedure for which harms/benefits should be weighed given clinical context)

**Survival Outcomes** (Circulation 2019;139:e56)
- Out-of-hospital cardiac arrest: survival to hospital discharge: 10.4%; survival with good neurologic function 9.9%
- In-hospital cardiac arrest: survival to discharge 25.6%; survival with good neurologic function 22%
  - Favorable outcomes: ACS, drug overdose, drug reaction (up to 40% survival)
  - Unfavorable outcomes: age >80 (<10% survival), multiorgan failure, sepsis, advanced cancer, ESRD, ESLD, dementia
  - Post-arrest complications include hypoxic-ischemic brain injury, rib fractures, pulmonary contusion, prolonged ICU care

*Richard Newcomb*
Conducting Code Status Discussions (JAMA 2012: 307:917)

- Initial tips:
  - Be prepared: Plan the conversation ahead of time. Know details of your patient’s condition and prognosis.
  - **Do not offer DNI alone**, as resuscitation almost always requires intubation.
  - Suggested framing of CPR for patients: “CPR is a medical procedure that we would do if you were to die, that is if your heart were to stop and you were to stop breathing. CPR includes pressing on your chest to pump the heart and the use of a breathing machine to help you breathe.”

- Two main types of code status discussions:
  - Information-gathering code status discussion
    - **Who?** Patients you would expect and would recommend to be full-code.
    - **Suggested Prompt**
      - Introduce: "Would it be okay if we did some emergency planning? I want to talk about a procedure called CPR."
      - Assess patient understanding: "What do you know about CPR?"  "Do you have any personal or family experience with CPR?"  "Have you spoken with other doctors about CPR?"
      - Share information / confirm goals: Describe CPR as above. "Right now, if your heart were to stop, you would receive CPR. Is this consistent with your goals?"
      - Forecast the future: "In the future, your doctor may no longer recommend CPR because it would be unlikely to help. At that time, your team will talk with you more."

- Decision-making code status discussion
  - **Who?** Patients you would recommend to be DNR/DNI.
  - Often may require serious illness conversation. Use clinical judgement based on acuity of illness prior to engaging in conversation; may be preferable to discuss w/ outpatient providers first.
  - **Reference guide above for opening conversation (Introduce and Assess understanding steps).**

<table>
<thead>
<tr>
<th>Step</th>
<th>Suggested Prompt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduce</td>
<td>&quot;Would it be okay if we did some emergency planning? I want to talk about a procedure called CPR.&quot;</td>
</tr>
</tbody>
</table>
| Assess patient understanding | "What do you know about CPR?"  "Do you have any personal or family experience with CPR?"  "Have you spoken with other doctors about CPR?"
| Share information / confirm goals | Describe CPR as above. "Right now, if your heart were to stop, you would receive CPR. Is this consistent with your goals?"
| Forecast the future | "In the future, your doctor may no longer recommend CPR because it would be unlikely to help. At that time, your team will talk with you more." |

Advance care planning forms

- MOLST (MA Medical Orders for Life-Sustaining Treatment; hot-pink forms available on all medical units): medical orders for patients with advanced serious illness and limited prognosis that documents preferences for CPR, intubation, hospital transfer, artificial nutrition, and more.
  - Transferrable to outside facilities; complete MOLST prior to discharge to rehab/SNF if patient DNR/DNI
- 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).
- Health Care Proxy (HCP) / medical power of attorney: an advance directive document that designates a healthcare agent to make future medical decisions if patient loses capacity. Expressly authorized in MA by statute.
  - If no HCP: surrogate hierarchy: see Section 3, bullet 6 of MA: An Act Improving Medical Decision Making
- Links to MOLST/HCP forms are found in banner at the top of a pt’s Epic chart or scanned into the Media tab.

General Inpatient Hospice (GIP)

- Pts with terminal dx and prognosis of <~2wks, transitioned to CMO, with sx mgmt needs requiring inpatient care (eg: high flow O2, uncontrolled symptoms requiring IV medications, high RN needs for wound care/suctioning)
  - Discuss w/floor CM team (to perform insurance benefit screen and coordinate w/ hospice liaison) and consult Pall Care
  - If admitted to GIP, pt transitions off housestaff team, Pall Care attending becomes AOR, Pall Care clinician becomes RC.

Richard Newcomb
Geriatrics & Palliative Care  Death Management & Pronouncement

Practical steps for making a patient CMO:
- D/c all unnecessary lines and tubes (usually maintain IV access but d/c central line if possible; discuss Foley w/ RN)
- D/c labs, routine vitals, and other interventions that do not contribute to comfort
- Run order list and d/c unnecessary medications. Continue medications that contribute to comfort, that will prevent uncomfortable events (e.g., maintain rate control to avoid AFRVR), or that have a withdrawal syndrome (e.g., SSRIs).
- Generally avoid artificial nutrition and hydration – may cause volume overload without meaningful benefit (J Clin Onc 2013:31:111)

Prior to Death:
- Involve family +/- chaplaincy (available 24/7), other care team members (e.g., PCP). Ask about religious/cultural traditions.
- Consider early contact of the New England Organ Bank (NEOB) @ 800-446-6362. The NEOB determines eligibility for donation. They are trained in how to discuss donation with the family; you DO NOT need to discuss with the family. See also Organ Donation page.
- When passing off a patient who may pass away, prep the “Report of Death” form – at minimum the cause of death section

Withdrawing ventilatory support (palliative extubation or discontinuation of BIPAP/HFNC):
- Prior to extubation (see also MGH MICU Policy and ATS Guidelines for more detail; Am J Resp Crit Care Med 2008:177:912):
  - Allow family time with patient (if desired). Ask family if they would like to see a Chaplain or Social Worker or have last rites.
  - Discuss with family the extubation process, expected dying process (e.g., agonal breathing), plans for symptom control, and expected timeline (death usually occurs in minutes to hours; see Chest 2010:138:289)
  - Have a plan/medications ready to address air hunger, pain, and anxiety aggressively. Discuss plan/orders w/ RN.
  - Do not withhold appropriate symptom management because of concern for hastening death (remember the Principle of Double Effect – your focus should be on managing symptoms, including palliative sedation if no other reasonable options). If in doubt, involve SAR/fellow/attending/pall care.
  - Discuss with RT (and SAR/fellow/attending PRN) vent withdrawal plan (immediate withdrawal vs down-titration of vent support). In some cases, may continue full vent support if death expected rapidly from pressor wean.
- Medications (see also Non-Pain Symptom Management page):
  - STOP paralytic agents (cisatracurium) and Propofol
  - opioids: Dilaudid or morphine gtt, with frequent PRN bolus from gtt (if not already on gtt, give bolus when starting gtt. If increasing gtt, bolus as well – otherwise won’t reach new steady state for hours). Work w/RN to provide anticipatory dosing.
  - Benzodiazepines: High dose Ativan IV PRN or start Ativan/midazolam gtt (bolus when starting or increasing gtt, as with opioids)
  - Consider Haldol IV PRN (anxiety/delirium) and glycopyrrolate (secretions)

Catastrophic bleeding: see Non-Pain Symptom Management page

DEATH PRONOUNCEMENT

PRONOUNCEMENT: Introduce yourself to the family, explain what you are doing, express condolences
- FEEL for pulse, LISTEN for heart sounds/breath sounds (> 60 sec), SHINE light to determine absence of pupillary light reflex, and NOTE time at the end of your exam, which becomes the time of death

QUESTIONS FOR NEXT OF KIN (Not HCP, but Next of Kin (NOK): Husband/Wife > Children > Other Family)
- If no NOK in room, call NOK to notify of patient’s death.
- Ask the family if they would like to see a CHAPLAIN or SOCIAL WORK
- Ask if family would want an AUTOPSY?
- If family accepts autopsy, ask about DISPOSITION OF ORGANS. Consider recommending the option of MGH retaining organs for further testing, education, research (if not, value of info from autopsy lower)
- Are there OTHER FAMILY MEMBERS they would like you to inform?
- Will anyone else be COMING TO VIEW THE BODY prior to morgue?
- What can you tell family: body is kept at MGH until the funeral home calls MGH (path: 617-726-2967) and arranges for pick-up. Advise family to contact their funeral home, and tell the funeral home that patient passed away at MGH (Social Work can assist).

ONCE YOU LEAVE THE ROOM:
Step 1: Notify ATTENDING and PCP. Email acceptable, if death was expected.
Step 2: Obtain “Report of Death” form from OA. Fill out in BLACK ink. If any mistakes, you will need to START OVER.
Step 3: Log into Epic before calling the numbers listed on the form.
Step 3: Call the Medical Examiner if necessary or in doubt (most cases not necessary). Document the first name of the staff member.
Step 4: Call New England Organ Bank: 800-446-6362: will need patient’s demographics, cause of death. May require: history of cancer, recent infections, recent labs, hx dementia, other PMHx.
Step 4: Call the Admitting Office (6-3393) to inform them of the death. They will ask cause/time of death, Med Examiner, NEOB.
Step 5: The “Report of Death” goes to admitting with the chart. Chart cannot leave the floor until the Report of Death is completed. Patient is transported down to the morgue by nursing.
Step 6: Document a brief “note of patient death”: SmartPhrase “MGHDOMDEATHNOTE”.

James (“Jay”) Miller
Organ donation after brain or circulatory death

- ~75% of transplanted organs are from deceased donors, including donation after brain death (DBD) and donation after circulatory death (DCD). DCD represents ~8% of organs procured nationally, ~20% in the Boston area (NEJM 2007;357:209)
- DBD = death based on neurologic criteria ("brain death," or irreversible loss of all functions of the brain, including the brain stem)
- DCD = death based on cardiopulmonary criteria (irreversible cessation of circulatory and respiratory function and mechanical ventilatory support is no longer medically indicated, but criteria for brain death are NOT fulfilled)
  - Organs from DCD and DBD donors have similar long-term outcomes (NEJM 2002;347:248)

Eligibility for organ donation

- Medical team determines that discontinuation of medical support is appropriate and discusses this with the HCP or legal next-of-kin
- DO NOT broach the topic of potential organ donation with family; New England Organ Bank (NEOB) is specifically trained to do this.
- If family wishes for withdrawal of support, the medical team notifies NEOB (800) 446-6362 who will coordinate the process for consent and donation (NB: this process can take up to 24 hours)

Care of the patient prior to organ donation

- Patients with potential for organ donation need to maintain organ viability in response to potentially severe autonomic and inflammatory responses that occur after severe neurologic insult or brain death.
- Interventions often require a delicate balance to preserve multiple organs: (Crit Care Med. 2015;43:1291, NEJM 2004;351:2730)
  - Continuous temperature monitoring, telemetry, and lab monitoring for renal function, electrolytes, acid-base status
  - Hemodynamics – goal MAP 60-110 (JAMA Surg. 2014;149:969)
    - Fluids and vasopressors for hypotension/vasoplegia. Consider vasopressin before catecholamines (helps w/ DI)
    - Dobutamine for reduced EF
  - Maintenance of normothermia via external warming or cooling
  - Urine output monitoring – goal 0.5-1.0 cc/kg/hr. Monitor for DI with severe neurologic injury or brain death.
  - Proper ventilatory support and pulmonary toilet – lung-protective LTVV as in ARDSNet. Prevent pneumonia with head elevation, etc. (JAMA. 2010;304:2620)
  - Maintenance of eunatremia, euvolemia, and acid-base status
  - Consider glucocorticoids for adrenal insufficiency; thyroid hormone for EF <45% or hemodynamic instability (limited evidence)
  - Empiric antibiotics if concern for infection

Death pronouncement in the operating room for DCD patients

- Generally, withdrawal of medical support, including extubation, occurs in the OR after pt is prepped by surgical team
- All members of the organ recovery teams must be outside of the room from the time of withdrawal of support to declaration of death; otherwise this poses a conflict of interest. Family may be present in the OR if they wish.
- Medical team (MD and RN) are present to coordinate end of life care from time of withdrawal of support to death, including PRN palliative medications. NEOB staff may not participate in the administration of medications or declaration of death
- Death must occur and be declared within 2 hours of extubation, otherwise organs are deemed nonviable.
  - “Dead-donor rule” (DDR) = recovery of organs cannot be the cause of death, and organs should be taken only from persons who are already dead (NEJM 2013;369:1287)
- MD declares death based on the irreversible cessation of circulatory and respiratory function (checks carotid artery for pulsations and auscultates for breath sounds using a sterile ultrasound cover over stethoscope)
  - PEA arrest meets criteria for cessation of circulatory function so long as there is no pulsatile flow on arterial line. Death can be declared even if cardiac electrical activity persists.
  - After death is declared, a 5-minute observation period begins to ensure no ROSC
- Death paperwork should be signed by declaring MD in the OR (i.e., bring prepped death paperwork with you)
**Rheumatology**

**Approach to Rheumatologic Disease**

**Overview:** rheumatologic diseases may be roughly separated into 4 categories:

<table>
<thead>
<tr>
<th>Arthritis</th>
<th>Connective tissue disease</th>
<th>Vasculitis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA, spondyloarthropathies, PMR, crystalline arthritis, OA</td>
<td>SLE, Sjögren’s, scleroderma, MCTD, UCTD, myositis (DM/PM)</td>
<td>small, medium, and large vessel vasculitides (e.g., GCA, PAN, GPA, EGPA)</td>
<td>Autoinflammatory diseases, bone/tendon/bursal disease, sarcoid, IgG4-related disease</td>
</tr>
<tr>
<td>RF, anti-CCP</td>
<td>ANA, C3/C4, anti-Sm, anti-dsDNA, anti-Sc170, anti-histone, anti-U1RNP, anti-Ro/La, antiphospholipid Abs</td>
<td>ANCA, cryoglobulins</td>
<td>(limited role for ACE, IgG4)</td>
</tr>
</tbody>
</table>

NB: Always consider malignancy and infection as alternative diagnoses prior to initiation of immunosuppressants unless at risk of permanent organ damage (i.e., do not withhold glucocorticoids when suspecting GCA, mononeuritis multiplex, RPGN, etc.).

**Rheumatologic ROS:** Fevers, rashes/photosensitivity, alopecia, nail/nailfold abnormalities, sicca symptoms, conjunctivitis, uveitis, episcleritis, scleritis, Raynaud’s, oral/genital ulcers, polychondritis, enthesitis, serositis sx, thromboses, neuropathy, pregnancy loss.

**Basic Labs:** CBC w/ diff, BMP, LFTs, UA, random urine protein:Cr ratio, ESR/CRP, CK, aldolase, TSH, hepatitis B/C serologies

**Inflammatory Arthritis**

<table>
<thead>
<tr>
<th>Arthritis</th>
<th>Sex</th>
<th>Age</th>
<th>Serology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>F &gt; M</td>
<td>35-65</td>
<td>RF+/CCP+ (70%-80%)</td>
<td>Symmetric chronic inflammatory polyarthritis</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>M = F</td>
<td>30-55</td>
<td>RF+ (2%-10%)</td>
<td>Asymmetric, large joints; 50% w/ RA distrib; majority w/ history of psoriasis, examine nails</td>
</tr>
<tr>
<td>Reactive arthritis (post-inf)</td>
<td>M &gt; F</td>
<td>16-50</td>
<td>RF-, HLA-B27+ (50%-80%)</td>
<td>a/w enthesitis, LBP, ocular sx, GU/GI sx</td>
</tr>
<tr>
<td>Enteropathic arthritis</td>
<td>M = F</td>
<td>All ages</td>
<td>RF-</td>
<td>a/w enthesitis, oral ulcers; 20% w/IBD</td>
</tr>
<tr>
<td>Axial spondyloarthritis (e.g., ankyllosing spondylitis)</td>
<td>M &gt; F</td>
<td>15-45</td>
<td>HLA-B27+ (&gt;50%)</td>
<td>Asymmetric, large joints; LE&gt;UE, enthesitis, dactylitis; a/w “silent” GU infxn (e.g., GC/Chla)</td>
</tr>
<tr>
<td>Gout</td>
<td>M &gt; F</td>
<td>&gt;25</td>
<td>RF-</td>
<td>Intermittent inflammatory; usu. monoarticular</td>
</tr>
<tr>
<td>Pseudogout</td>
<td>F = M</td>
<td>&gt;60</td>
<td>RF-</td>
<td>5% w/ RA-like arthritis lasting for wks to months</td>
</tr>
</tbody>
</table>

| Viral arthritis | F > M | All ages | RF+ (<10%); consider Parvovirus B19 Ab | Acute symmetric polyarthritis w/ RA distribution; <10% develop chronic polyarthritis |

1Seronegative spondyloarthropathy (SpA)

<table>
<thead>
<tr>
<th>Connective Tissue Disease</th>
<th>Sex</th>
<th>Age</th>
<th>Serology/Tests</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>F &gt; M</td>
<td>15-40</td>
<td>ANA+ (&gt;95%), anti-dsDNA (70%), anti-Sm/ RNP (30%), anti-histone, C3/4</td>
<td>Sx: rash, oral ulcers, arthritis, serositis, renal dz, neuro d/o, heme abnormalities. ↑ CK suggests myositis</td>
</tr>
<tr>
<td>Sjögren’s syndrome (SS)</td>
<td>F &gt; M</td>
<td>40-60</td>
<td>Anti-Ro(SSA)/La(SSB), [often ANA1:320 and RF+], lip bx</td>
<td>Sx: sicca sx, parotid gland inflam, dental caries; RA/SLE a/w 2° SS; if dx uncertain, perform lip bx; if salivary gland enlarged, consider IgG4</td>
</tr>
<tr>
<td>Systemic sclerosis (SSc), (a.k.a., scleroderma)</td>
<td>F:M 4:1</td>
<td>30-50</td>
<td>ANA+ (&gt;95%), anti-Scl-70*, ACA*, anti-RNP-pool 3* any are &gt;99% specific</td>
<td>Types: Local (linear/morphea) vs. systemic (dcSSc, lcSSc, SSC sine scleroderma) Sx: CREST; scleroderma renal crisis; ILD</td>
</tr>
<tr>
<td>Mixed connective tissue dz</td>
<td>80% F</td>
<td>20-30</td>
<td>ANA (speckled), anti-U1RNP (100%)</td>
<td>Sx: clin. ft. of SLE, SSC, myositis overlapping over many yrs.; pHTN</td>
</tr>
<tr>
<td>Dermatomyositis/polymyositis</td>
<td>F:M 2:1</td>
<td>40-50</td>
<td>ANA+ (up to 80%), cytoplasmic (e.g., anti-Jo1)</td>
<td>Sx: Proximal muscle weakness, rashes, GERD/dysphagia; may cause antisynthetase syndrome (ILD, myopathy, arthritis)</td>
</tr>
</tbody>
</table>

**Vasculitis**

**Large-vessel vasculitis**

- Takayasu arteritis; giant cell arteritis (GCA)

**Medium-vessel vasculitis**

- Polyarteritis nodosa; Kawasaki disease (usually in children, can affect large vessels)

**Small-vessel vasculitis**

- ANCA-associated: (Granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis)
- Immune complex-associated; (Cryoglobulinemic, IgA [Henoch-Schönlein purpura], hypocomplementemic urticarial (anti-C1q)

Julie Fiore, Mazin Abdelghany
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen</th>
<th>ANA pattern</th>
<th>Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory polyarthritis:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF (IgM)</td>
<td>Fc gamma</td>
<td>negative</td>
<td>RA (50-75%), Sjogren’s (30%), chronic infection</td>
<td>Unspecific despite name: RA, CTD, cryoglobulinemia, chronic infection</td>
</tr>
<tr>
<td>CCP</td>
<td>Citrullinated</td>
<td>negative</td>
<td>RA (75-85%), HCV</td>
<td>Most specific test for RA, positive in 75-85% (“seropositive RA”), a/w erosive dz and extraarticular manifestations; used for dx only, NOT marker of dz activity</td>
</tr>
<tr>
<td><strong>Connective tissue diseases (SLE, Sjogren’s, SSC, MCTD, UCTD, DM/PM):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>- ANA = Antinuclear antibodies (specific ANA Abs listed below). If positive, order specific autoantibodies guided by clinical presentation. Titors present in normal pts at 1:40 (20-30%), 1:80 (10%), 1:160 (5%), 1:320 (2.5%). Levels ≥1:320 most convincing. - (+) ANA: MCTD (100%), SLE (98%), scleroderma (95%), Sjogren’s (60%), RA (45%), PM/DM (35%) - Ddx for (+) ANA: Autoimmune: autoimmune hepatitis, PBC, UC, myasthenia gravis, Graves’, Hashimoto’s; ID: malaria, SBE, syphils, HIV, HSV, EBV, HCV, Parvo-B19; Systemic inflammation: lymphoproliferative disorders, IPF, asbestosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dsDNA</td>
<td>ds/mtDNA</td>
<td>homogeneous</td>
<td>SLE (40-60%)</td>
<td>Specific for SLE, a/w SLE activity and lupus nephritis</td>
</tr>
<tr>
<td>dsDNA</td>
<td>dsDNA</td>
<td>homogeneous</td>
<td>SLE, DIL (90%), Felty’s</td>
<td>Sensitive, but not specific for drug-induced lupus (DIL); common meds: procainamide, hydralazine, infliximab, phenytoin, lithium</td>
</tr>
<tr>
<td>RNP</td>
<td>U1-snRNP</td>
<td>speckled</td>
<td>MCTD (100%), SLE (30%)</td>
<td>MCTD: high-titer anti-U1 RNP</td>
</tr>
<tr>
<td>RNP</td>
<td>U1-RNP</td>
<td>homogeneous</td>
<td>SLE (40-60%)</td>
<td>MCTD: high-titer anti-U1 RNP</td>
</tr>
<tr>
<td>Smith</td>
<td>snRNP</td>
<td>speckled</td>
<td>SLE (30%)</td>
<td>Specific for SLE, a/w sev. manif. (renal, psych., heme, vasculitis), red indic of dz activity</td>
</tr>
<tr>
<td>SS-A/Ro</td>
<td>Ro52, Ro60</td>
<td>speckled</td>
<td>Sjogren’s (75%), SLE (40%), SSC</td>
<td>Can be seen with myositis; in SLE, a/w pulmonary disease, photosensitivity, lymphopenia, and congenital heart block</td>
</tr>
<tr>
<td>SS-B/La</td>
<td>La</td>
<td>speckled</td>
<td>Sjogren’s (40%), SLE (10-15%)</td>
<td>a/w congenital heart block in SLE, late-onset SLE, and 2nd Sjogren’s</td>
</tr>
<tr>
<td>ACA</td>
<td>CENP A-F</td>
<td>centromere</td>
<td>lcSSc (15-40%)</td>
<td>a/w limited systemic sclerosis, ↑ risk of P&amp;H, esophageal disease</td>
</tr>
<tr>
<td>Scl-70</td>
<td>topo-I</td>
<td>speckled</td>
<td>dcSSc (10-40%)</td>
<td>a/w diffuse systemic sclerosis; ↑ risk of ILD, Raynau’ds</td>
</tr>
<tr>
<td>RNA pol III</td>
<td>RNA pol. III</td>
<td>nucleolar</td>
<td>dcSSc (4-25%)</td>
<td>a/w scleroderma renal crisis, skin disease, malignancy</td>
</tr>
<tr>
<td>Fibrillarin</td>
<td>U3-RNP</td>
<td>nucleolar</td>
<td>dcSSc (&lt;5%)</td>
<td>a/w PAH, pulmonary fibrosis, and myositis, esp. in African-Americans</td>
</tr>
<tr>
<td>PM-Scl</td>
<td>exosome</td>
<td>nucleolar</td>
<td>SSc (5-10%)</td>
<td>a/w limited systemic sclerosis, ↓ risk of pulmonary and renal dz, ↑ risk inflammatory myositis</td>
</tr>
<tr>
<td><strong>Myositis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jo-1*</td>
<td>tRNA (His)</td>
<td>cytoplasmic</td>
<td>PM/DM (30%), ASS (~20%)</td>
<td>Antisynthetase syndrome (ASS); myositis (DM/PM), ILD (70%), polymyositis, mechanic’s hands, Raynaud’s, fever</td>
</tr>
<tr>
<td>Mi-2*</td>
<td>Mi-2</td>
<td>homog/speckli</td>
<td>DM (15-20%)</td>
<td>More likely in acute DM, a/w classic shawl rash</td>
</tr>
<tr>
<td>MDA-5*</td>
<td>MDA-5</td>
<td>negative</td>
<td>DM</td>
<td>Clinically amyopathic dermatomyositis (CADM), rapidly-progressive ILD</td>
</tr>
<tr>
<td>TIF1g*</td>
<td>TIF1g</td>
<td>fine speckled</td>
<td>Juvenile DM</td>
<td>a/w malignancy in adult DM</td>
</tr>
<tr>
<td>SRP*</td>
<td>signal recog. particle</td>
<td>cytoplasmic</td>
<td>myositis</td>
<td>Immune-mediated necrotizing myopathy (degenerating, regenerating, and necrotic cells on bx), rapid progressive disease course</td>
</tr>
<tr>
<td>PL-7*, PL-12*, EJ*, OJ*, KS*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMGCR</td>
<td>HMG CoA reductase</td>
<td>negative</td>
<td>myositis</td>
<td>Immun-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 reported</td>
</tr>
<tr>
<td>PR3 (c-ANCA)</td>
<td>proteinase 3</td>
<td>negative</td>
<td>GPA (80-90%), DIV (50%)</td>
<td>Poor correlation of titer with disease flare/remission; Antibody frequency lower in GPA with limited disease</td>
</tr>
<tr>
<td>MPO (p-ANCA)</td>
<td>myeloperoxidase</td>
<td>negative</td>
<td>MPA (70%), EGPA (50%), GPA (Asians), DIV (95%)</td>
<td>Poor correlation of titer with disease flare/remission; Drug-induced vasculitis; high-titer positive for MPO or PR3/MPO double positive (e.g., levamisole vasculitis 2/2 cocaine use)</td>
</tr>
<tr>
<td>Cryoglobulins</td>
<td>Fc gamma</td>
<td>negative</td>
<td>cryoglobulinemic vasculitis</td>
<td>HCV &gt; HBV, HIV, CTDs, lymphoproliferative disease; a/w hypocomplementemia, palpable purpura, glomerulonephritis</td>
</tr>
</tbody>
</table>

*ordered as part of the myositis panel; §Extractable nuclear antigens (ENAs)
**Approach to the Patient with Joint Pain:** Assess (1) articular or non-articular, (2) inflammatory or non-inflammatory, (3) acute or chronic, (4) joint pattern, and (5) associated signs or symptoms

<table>
<thead>
<tr>
<th>(1) Articular</th>
<th>Non-articular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain with all joint ROM</td>
<td>Pain with only some joint ROMs</td>
</tr>
<tr>
<td>Most painful at the limit of joint ROM</td>
<td>May not be most painful at the limit of joint ROM</td>
</tr>
<tr>
<td>All passive ROMs in joint reduced equally</td>
<td>1 or several passive ROMs reduced more than others</td>
</tr>
<tr>
<td>Examples: True hip joint = anterior groin</td>
<td>Examples: Tendinitis, enthesitis, bursitis, ligament injuries, muscle problems</td>
</tr>
<tr>
<td>True ankle joint = anterior tibiotalar joint line</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(2) Inflammatory vs. non-inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory articular</strong></td>
</tr>
<tr>
<td>Warmth</td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>Redness</td>
</tr>
<tr>
<td>Tenderness</td>
</tr>
<tr>
<td>Stiffness</td>
</tr>
<tr>
<td>Examples:</td>
</tr>
<tr>
<td>In AM, ≥30m and gelling§</td>
</tr>
<tr>
<td>(3) Acute vs. chronic</td>
</tr>
<tr>
<td>&lt;6 weeks</td>
</tr>
<tr>
<td>Dx: infectious arthritis (e.g., septic, gonoccal, viral), injury (e.g., hemarthrosis), reactive arthritis, crystal-induced arthritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(4) Joint pattern‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small:</strong> wrist, MCP,PIP, DIP, ankle, midtarsal, MTP)</td>
</tr>
<tr>
<td>Monoarticular: 1 joint</td>
</tr>
<tr>
<td>Axial skeleton: thoracic spine, lumbar spine, sacroiliac joints or anterior costochondral joints</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(5) Extra-articular features of rheumatologic disorders that cause arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
</tr>
<tr>
<td>ILD, rheumatoid nodules, scleritis, pleural effusion, rarely ulcers (rheumatoid vasculitis)</td>
</tr>
<tr>
<td>Connective tissue disorders (include SLE, Sjogren’s, SSC, MCTD, DM/PM)</td>
</tr>
<tr>
<td>Seronegative spondyloarthropathies</td>
</tr>
<tr>
<td>Gout</td>
</tr>
<tr>
<td>Fibromyalgia</td>
</tr>
</tbody>
</table>

**Common Arthritis Syndromes:**

**Pattern of joints**

<table>
<thead>
<tr>
<th>Gout</th>
<th>CPPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoarticular (podagra = 1st sx in 50% pts) &gt; oligo/polyarticular (hindfoot, fingers, ankle, knee)</td>
<td>Monoarticular &gt; polyarticular (knee &gt; wrist, shoulder, ankle)</td>
</tr>
<tr>
<td>Ddx: Trauma, CPPD, septic arthritis; consider cellulitis</td>
<td>Ddx: As above for gout; can overlap with gout flares</td>
</tr>
<tr>
<td>Triggers: diuretics, meat, seafood, alcohol, HTN, DM2, CKD</td>
<td>Mimics any arthritis (OA, gout, RA, CTD, neuropathic joints); can be asx, acute (pseudogout; complicates OA most commonly), chronic (<em>pseudo-RA</em> ~5%), severe DJD (pseudo-neuropathic)</td>
</tr>
<tr>
<td>Course: acute flares → chronic arthropathy (tophi)</td>
<td>Extra-articular Sx: Tophi, urate nephrolithiasis, chronic nephropathy</td>
</tr>
</tbody>
</table>

**CPPD:** calcium pyrophosphate disease; LE: lower extremity; OA: osteoarthritis; RA: rheumatoid arthritis; CTD: connective tissue disease; DJD: degenerative joint disease; MCP: metacarpophalageal joint; asx: asymptomatic

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Julie Fiore, Mazin Abdelghany

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## Rheumatology

### Arthritis

<table>
<thead>
<tr>
<th>Pattern of joints</th>
<th>Clinical presentation, extra-articular disease, and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RA</strong></td>
<td>Symmetric, pred. small (peripheral) polyarthritis (MCP,PIP, wrists, MTP)</td>
</tr>
<tr>
<td></td>
<td>Ddx: HCV/HBV, Lyme, crystal, SLE, psoriatic arthritis, sarcoid arthropathy. Typical Sx: palindromic rheumatism (episodic sx, migratory, 30-60% develop RA), monoarthritis (eventual polyarthritis in days-wks) Extra-articular: Anemia, rheumatoid nodules, I LD, pleural effusion, scleritis/scleritis, splenomegaly (Felty’s), a/w Sjogren’s, rarely vasculitis</td>
</tr>
<tr>
<td><strong>Ankylosing spondylitis</strong></td>
<td>Spine and SI joints</td>
</tr>
<tr>
<td></td>
<td>Gradual onset; low back pain, buttock pain, impaired spine mobility Extra-articular: Synovitis, enthesitis, dactylitis, uveitis, psoriasis, IBD</td>
</tr>
<tr>
<td><strong>Psoriatic arthritis</strong></td>
<td>See 5 patterns in right column; axial (spine) involvement 42%</td>
</tr>
<tr>
<td></td>
<td>Ddx: RA, OA, 70% w/ psoriasis; 5 patterns: distal (DIP), asymm. oligo., symm. poly., arthritis mutilans, spondyloarthritis (sacroilitis, spondylitis). Extra-articular: Synovitis, enthesitis, dactylitis, nail pits/onycholysis, uveitis</td>
</tr>
<tr>
<td><strong>Enteropathic arthritis</strong></td>
<td>Axial (spondylitis/sacroilitis) and/or periph</td>
</tr>
<tr>
<td></td>
<td>Ddx: Behçet’s, celiac, pseudomembranous colitis, Whipple’s, parasitic, 6-46% of IBD pts. Extra-articular: Enthesitis, dactylitis, E nodosum</td>
</tr>
<tr>
<td><strong>Reactive arthritis</strong></td>
<td>Asymm. oligo &gt; mono &gt; small polyarthritis; LE slightly &gt; UE</td>
</tr>
<tr>
<td></td>
<td>1-4 wks post-infxn, a/w enteric: Salmonella, Shigella, Yersinia, Campylobacter, C. diff; GU: Chlamydia, E. coli, Ureaplasma, Mycoplasma. Extra-articular: Conjunctivitis, GU sx, oral ulcers, keratoderma, E nodosum</td>
</tr>
<tr>
<td><strong>Septic arthritis</strong></td>
<td>Monoarth. (50% knee)</td>
</tr>
<tr>
<td></td>
<td>Usu. hematogenous; pts w/ RA ↑risk; Staph &gt; strep &gt; GNRs</td>
</tr>
<tr>
<td><strong>Osteoarthritis</strong></td>
<td>Knees/hips, 1st MTP, PIP, D-, and L-spine</td>
</tr>
<tr>
<td></td>
<td>Limits ROM, bony swell, joint deforms/unstab., stages (1) pain limits high-impact activity → (2) pain constant, affects ADLs → (3) intense pain</td>
</tr>
</tbody>
</table>

### Other arthritis: Viral polyarthritis (mimics RA), CTD (e.g., SLE, Sjogren’s, SSC), vasculitis, adult-onset Still’s, sarcoidosis, osteochondroma, osteoid osteoma, pigmented villonodular synovitis, amyloidosis, hemophilia, sickle cell disease

*All Seronegative spondyloarthropathies should be considered in ddx for each other*

### Diagnosis

| Arthrocentesis: Negatively birefringent needle-shaped crystals, 10k/WBC<100k, diagnostic score (Arch Intern Med 2010;170:1120); culture as septic arthritis can co-exist. If any suspicion for septic arthritis, start empirical abx until Cx negative. |
| Acute: Rx depends on pt’s comorbidities. Colchicine (1.2mg x1, 0.6mg 1h later, then 0.6mg QD until 2-3d after resolu), PO GC (pred 40mg until resolu., then taper), NSAIDs (until 1-2d after resolu. [usu. 5-7d]), or intra-articular GC injection Chronic: Urate lowering if: ≥2 attacks/yr, CKD, urate nephrothiasis, tophi (urate goal <6); Δdiet; d/c diuretics. Do not stop urate lowering therapy during acute attack. |
| **Gout**               | **Treatment** (non-pharm management for all-PT/OT, exercise) |
| Arthrocentesis: Small pos. birefringent rhomboid crystals, 10k/WBC<100k; XR: chondrocalcinosis, crowned dens |
| Acute: ≤2 joints → intra-articular GC injection 1st line; 2nd is same as gout (prefer colchicine w/in 24h of sx onset) Chronic: Consider HCO, low-dose GC, MTX |
| **CPPD**               | Exclude other dz (esp. psoriatic, viral, polyarticular gout/CPPD, SLE). RF (70% sn, 85% sp), anti-CCP (75% sn, 95% sp), 30% ANA+, extremely XRs. |
| Acute/flares: GC or NSAIDs and initiate DMARD if not on Chronic: DMARD (MTX > HCO, SSZ, leflunomide); if pt fails monotherapy, consider combination; if fails combo, transition to biologic (infliximab, abatacept, tocilizumab) |
| **RA**                | Exclude other dz (esp. psoriatic, viral, polyarticular gout/CPPD, SLE). RF (70% sn, 85% sp), anti-CCP (75% sn, 95% sp), 30% ANA+, extremely XRs. |
| Acute/flares: GC or NSAIDs and initiate DMARD if not on Chronic: DMARD (MTX > HCO, SSZ, leflunomide); if pt fails monotherapy, consider combination; if fails combo, transition to biologic (infliximab, abatacept, tocilizumab) |
| **Ankylosing spondylitis** | Sacroilitis (XR or MRI), LBP, ↑ESR/CRP, HLA-B27 (90% sn/sp) |
| NSAIDs 1st line, no GC, DMARDs not effective TNFα inh. 2nd (infliximab, etanercept, adalimumab) |
| **Psoriatic arthritis** | Clinical dx, ↑ ESR/CRP (40%), HLA-B27, CASPAR criteria (91%sn;99%sp) |
| NSAIDs 1st line; if mod/sev, MTX > SSZ, leflunomide Sev. and erosive: TNFα inh. (inflix, adalimumab, golimumab) |
| **Enteropathic arthritis** | Joint pain, LBP, always exclude septic arthritis, HLA-B27 (50-75%) |
| Usually improves w/ Rx of IBD. NSAIDs 1st line, d/w GI as can ↑IBD inflam. 2nd SSZ > MTX, azathioprine. 3rd TNFα inh. |
| **Reactive arthritis** | Presence of preceding infection, arthrocentesis, stoole culure, GC/Chla |
| Treat GI inflxn; GI inflxn may not need Rx. Acute: 1st NSAIDs, 2nd intra-articular GC, 3rd PO GC, Chronic: >6mo, SSZ+MTX |
| **Septic arthritis** | Arthroc: Fluid GS/Cx, joint WBC usually 50-150k |
| Antibiotics (3-4 wks) and joint drainage/wash out (ortho c/s) |
| **Osteoarthritis** | Clinical, age>45, AM stiff <30m, slow progression, no warmth, musc wasting |
| PT, braces, PRN NSAIDs, consider duloxetine (60-120mg), intra-articular GC injection, severe sx → refer to ortho |

*Seronegative spondyloarthropathies: GC: glucocorticoid; MTX: methotrexate; CTD: connective tissue disease; SLE: systemic lupus erythematosus; HCO: hydroxychloroquine; SSZ: sulfasalazine; LBP: low back pain"
<table>
<thead>
<tr>
<th>Dz</th>
<th>Clinical presentation</th>
<th>Work-up</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>Discoid/malar rash (spares nasolabial fold), photosensitivity, serositis, nephritis, oral/nasal ulcers, psychosis, arthritis, cytophenias, constitutional sx (fever, weight loss, fatigue)</td>
<td>+ANA, +anti-dsDNA (up to 70% pts, a/w SLE activity and lupus nephritis), +anti-Sm (30% pts, high specificity, remains + in remission), +anti-RNP (25%), +anti-SS-A/Ro (30%), +anti-SS-B/La, (20%). 2012 SLICC criteria (Arthritis Rheum 2012: 64: 2677)</td>
<td>Initial: hydroxychloroquine/ chloroquine for all ± steroids 2nd line: MMF, AZA, MTX, RTX, cyclophosphamide</td>
<td>- High risk VTE/ATE - CNS, Renal dz - 40% w/ APLAS - Osteonecrosis (both 2/3 SLE and steroids)</td>
</tr>
<tr>
<td>Sjögren's</td>
<td>Sicca sx (dry mouth/eyes), caries, parotid enlargement, vasculitis, interstitial nephritis, neuropathy, cytophenias</td>
<td>+ANA, +anti-SS-A (Ro, 70% pts), +anti-SS-B (La, 50-70%), +RF consider salivary biopsy</td>
<td>Sicca only: sx mgmt Systemic: Hydroxychloroquine/ chloroquine, MTX, AZA, RTX, cyclophosphamide, glucocorticoids</td>
<td>5-10% lifetime risk of NHL</td>
</tr>
<tr>
<td>Myositis (polymyositis, dermatomyositis, inclusion body myositis)</td>
<td>Proximal &gt; distal muscle weakness: difficulty with stairs, standing from seated position, reaching above head</td>
<td>Abs: +anti-Jo1 (a/w ILD, mechanic hands, arthritis), +anti-Mi2 (15-20%, a/w acute onset, shawl sign, good prognosis), +anti-MDA5</td>
<td>Initiation: prednisone 1mg/kg (up to 100mg/d) x4-6wk, then taper Maintenance: AZA/MTX Resistant/severe: pulse steroids, AZA, MTX, MMF, IVIG, RTX, cyclophosphamide (if ILD)</td>
<td>(DM) occult malignancy (9-32% incidence): commonly ovarian, breast, colon, lung, NHL, nasopharygeal cancer Additional: ILD in 10%; upper esophageal involvement; increased risk of MI</td>
</tr>
<tr>
<td>Systemic Sclerosis (aka scleroderma)</td>
<td>Localized: (affects skin only): linear (e.g., en coup de sabre), morphea Systemic: may be limited cutaneous [lcSSc] (67% pts; skin thickening in hands/face only, commonly with CREST sx) or diffuse cutaneous [dcSSc] (33% pts; diffuse skin thickening, more significant multi-organ dz, less commonly with CREST sx) CREST sx: Calcific nodules, Raynaud’s, Esophageal dysmotility, Sclerodactyly, Telangiectasias Other systemic sx: renal crisis, ILD (&gt;70%), PAH (10-40%) NB: systemic sclerosis sine scleroderma→pts with scleroderma but w/o skin findings</td>
<td>+anti-centromere (a/w lcSSc, only seen in 5% pts with dcSSc) +anti-Scl-70 (a/w dcSSc), +RNA-pol-II (a/w dcSSc and scleroderma renal crisis), +fibrilin (a/w severe dcSSc, esp. in African-Americans (Arthritis Rheum 1996:39:1151)</td>
<td>Skin: MMF, MTX G: PPIs, motility agents Lung: CCBs, endothelin-1 antag., PDE inhibitors, prostacyclin agonists MSK: Low dose pred, hydroxychloroquine, MTX Raynaud’s: CCBs</td>
<td>Increased risk of multiple cancers Scleroderma renal crisis (up to 20%): AKI, abrupt HTN; a/w anti-RNA-pol III; treat with ACEi (captopril) + avoid steroids</td>
</tr>
<tr>
<td>MCTD</td>
<td>Overlap of SLE, systemic sclerosis, and polymyositis; Raynaud’s; non-erosive arthritis;</td>
<td>+anti-RNP by definition</td>
<td>SLE features: glucocorticoids, RTX Scleroderma features: less responsive to steroids</td>
<td>Main cause of death is PAH</td>
</tr>
<tr>
<td>UCTD/Overlap syndromes</td>
<td>Early Raynaud’s, ILD, inflammatory arthritis not meeting classification criteria for RA, non-specific rash</td>
<td>Diagnosis of exclusion; does not meet criteria for diagnosis of specific disease</td>
<td>Managed according to symptoms</td>
<td>According to dominant clinical presentation</td>
</tr>
</tbody>
</table>

Sneha Kannan, Avanthi Raghavan

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DIAGNOSTIC OVERVIEW (Arthritis Rheum 2013;65:1)

- Classified by size and type of blood vessel involved, e.g., large vessels (aorta and its branches) vs. medium-sized vessels (main visceral arteries = named) vs. small vessels (vessels without names such arterioles, capillaries, venules)

STEP 1 – SUSPECT VASCULITIS

Overview:
- No "typical" presentation but consider in constitutionally ill patient with evidence of multisystem organ involvement and evidence of inflammation.
- LARGE vessel: aorta/branches, e.g., external carotid, temporal, ophthalmic → limb claudication, bruits, asymmetric BP, absent pulses, HA, visual loss
- MEDIUM vessel: renal/hepatic/mesenteric arteries, etc. → cutaneous nodules, "punched out" ulcers, livedo racemosa, digital gangrene, mononeuritis multiplex (e.g., foot/wrist drop), renovascular HTN
- SMALL vessel: vessels of skin, small airways, glomeruli → palpable purpura, urticaria, glomerulonephritis, alveolar hemorrhage, scleritis

General Testing:
- Inflammation? → CBC w/ diff (ACD, thrombocytosis, neutrophilia, eosinophilia), ESR, CRP
- Organ involvement? → BMP, LFTs, CPK, stool guaiac, CXR, brain MRI (if neurologic symptoms), CT chest, CTA (if GI/claudication)

Presentation-specific Testing (i.e., small-vessel s/s):
- Immune complex formation? → complement levels (C3, C4, consider CH50), ANA, RF/Cryoglobulins
  - ANA/RF are NOT positive in 10 vasculitis; +RF could suggest cryoglobulinemia or endocarditis (in addition to RA)
  - C3/C4 ↓ in cryoglobulinemia, SLE, and 25% of PAN; normal complement levels in all other vasculitides (rarely low in HSP)
- ANCA-associated? → send ANCA for IIF; will reflex to MPO (p-ANCA) and PR3 (c-ANCA) antibody ELISA if positive

STEP 2 – RULE OUT MIMICS

- Ddx: Infections (SBE, HIV, HBV, HCV, EBV, Neisseria, Syphilis), malignancies (leukemia, lymphoma, myeloma, MDS, solid tumors), IgG4-Related Disease (IgG4-RD, NEJM 2012;366:538, Mod Pathol 2012;25:1181), cocaine / levamisole, other drug-induced vasculitides, hypercoagulable states (APLAS, TTP)
  - If skin necrosis of lower extremities → consider cholesterol emboli or calciphylaxis
  - If renal artery, internal carotid artery, vertebral artery involvement → consider fibromuscular dysplasia
- Tests: BCx, HBV, HCV, HIV, SPEP/UPEP/SFL/UFL, tox screen, consider IgG4

STEP 3 – CONFIRM DIAGNOSIS

Tissue biopsy: typically required to secure diagnosis
- Skin, sural nerve and muscle (PAN, EGPA, first prove abnormal NCS), temporal artery (GCA), muscle (PAN), kidney (GPA, MPA), lung (GPA, MPA)
- Less common: testicle (PAN), rectum/gut, liver, heart, brain (10 CNS vasculitis), sinus (GPA)

Angiography: particularly if tissue biopsy is unfeasible
- Celiac/superior mesenteric, renal (PAN), aortic arch (Takayasu, GCA), extremities (Buerger disease), brain (10 CNS vasculitis)

GENERAL TREATMENT APPROACH

- Remove inciting agents (meds, drugs), treat primary conditions (infections)
- Induction: often steroids + cyclophosphamide (CYC) or biologic, i.e., rituximab (RTX) for ANCA-associated (Lancet 2006;368:404) nephrology at MGH tends to use steroids + CYC + RTX
- Maintenance: Less well defined, typically azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), RTX
- Prevention of treatment complications: PPD, HBV serologies, Pneumovax (and other vaccines), glucocorticoid prophylaxis (PPI, TMP-SMX, calcium/vitamin D)
## Large-Vessel Vasculitides
*“large vessels” = aorta and main branches, NEJM 2003;349:160*

**GIANT CELL ARTERITIS:** Inflammation of the aorta & its extracranial branches (i.e., spares ICA), often involves temporal artery (TA), most common primary systemic vasculitis; Epi: age >50, 2:1 M:F, rare <50 = consider alternative diagnoses, mimics.

- **Sx:** constitutional (low grade fevers, fatigue, wt loss, anorexia), new/different HA, abrupt visual disturbance (amaurosis fugax, blindness, diplopia), jaw claudication (most specific sign – L>R), AMS, 10% w/ URI sx, aortic dissection

- **Exam:** asymmetric BP/pulse; tender, thickened or pulseless TA; jaw claudication (gum test, r/o TMJD), ischemia on fundoscopy

- **Dx:** Gold standard = temporal artery biopsy; TESR (ESR usually >100 but <50 in 10%), TCRP (more sensitive, correlates with disease activity), TIL-6 (rational for tocilizumab); may use Doppler ultrasound as initial screen, but sensitivity varies
  - **TA biopsy:** start w/ unilateral; if (-), consider b/l (only ↑ yield by 5-10%); up to 30-40% of bx may be false (-) due to “skip areas”
  - **If concern if large vessel GCA (e.g., aorta, subclavian):** pursuing imaging (CTA vs. MRA)

- **Rx:** Start prednisone 1mg/kg/d immediately if high suspicion; NEVER delay Rx for Bx (>14d window for Bx after starting prednisone)
  - **Dose:** prednisone 1mg/kg (start with methylpred 1g IV x3d if visual changes) with slow taper; full course usually 9-12 months (Arthritis Rheum 2006;54:3310)
  - **ASA 81mg QD can help prevent cranial ischemic complications (vision loss, TIA/stroke).** (Arthritis Rheum 2004;50:1332)

**POLYMyalgia Rheumatica (PMR):** seen in 50% of GCA pts; 10% of pts w/ PMR develop GCA, peak occurrence at 70-80 yrs old

- **Sx:** symmetrical AM stiffness/pain (NOT weakness) in neck, shoulders/prox arms, hips/prox thighs; if weak, consider other etiologies

- **Rx:** prednisone 12.5-25 mg/day with slow taper, consider early addition of MTX (Ann Rheum Dis 2015;74:1799)

**Takayasu Arteritis:** “pulseless disease,” inflammation of thoracoabdominal aorta & branches: Epi: age <40, 8:1 M:F, esp Asians

- **Sx:** inflammation (fever, arthralgias/myalgias, weight loss, night sweats) → vessel inflammation (carotidynia, limb claudication)

- **Exam:** unequal pulses & BP (upper extremities), ± pulses, bruits, formal eye exam

- **Dx:** MRA or CTA; arteriography will show occlusion, stenosis, aneurysms; consider carotid ultrasound/Doppler studies

- **Rx:** prednisone 1mg/kg; 50% of patients will need 2nd agent for chronic sx (MTX, leflunomide, MMF, CYC, Aza, tocilizumab)

## Medium-Vessel Vasculitides
*“medium vessels” = named artery*

**POLYarteritis Nodosa:** kidneys, skin, muscles, nerves, GI, joints (almost always spares lungs); Epi: 40-60yo; associated with HBV

- **Sx:** mononeuritis multiplex (in up to 70% of pts), GI distress (post-prandial), myalgias, weight loss, night sweats

- **Exam:** HTN, skin lesions (erythematous nodules, purpura, livedo reticularis, ulcers, bullous eruption, palpable purpura), neuropathy

- **Dx:** gold standard = biopsy; HBV/HCV serologies, C3/C4, CTA/MRA showing focal stenosis or microaneurysm (renal/mesenteric vessels)

- **Rx:** prednisone 1mg/kg ± CYC 2 mg/kg/d PO or IV pulse (if mod-severe or steroid-refractory); antivirals if HBV-related

**Thromboangiitis Obliterans (Buerger’s Disease):** Segmental inflammation of small-med arteries and veins of extremities; occlusive intravascular thrombosis; Epi: age ≤45yo, 70-90% ♀, strongly associated with tobacco use, associated with Raynaud’s in 40% of patients

- **Dx:** clinical → 1) age 2-3 tobacco use; 2) distal ischemia (diabetic findings) 5) exclusion of autoimmune, thrombophilia, DM, embolism

- **Rx:** Smoking cessation! Iloprost (PG analog) for pain; CCB (for Raynaud’s); intermittent pneumatic compression (when painful ulcers)

**ANCA-Associated Small-Vessel Vasculitides (Pauvi-Immune)**

- **c-ANCA = cytoplasmic staining (antigen primarily proteinase 3 [PR3]); p-ANCA = perinuclear staining (antigen commonly myeloperoxidase [MPO])**

**Microscopic Polyangiitis (MPA):** necrotizing vasculitides of small vessels usually *without* granulomas (capillaries, venules, arterioles); Epi: all ages (mean 50-60yo), M>F, ↑ in Caucasians; most common cause of pulmonary-renal syndrome (NEJM 2012;367:214)

- **Dx:** +p-ANCA 70%, +c-ANCA rare, BAL, gold standard = skin/renal biopsy; r/o HIV, cryo, hype B/C

- **Rx:** similar to GPA → methylprednisolone or cyclophosphamide or RTX (NEJM 2010;363:221)

**Granulomatosis with Polyangiitis (GPA; Wegener’s Granulomatosis):** necrotizing granulomatous inflammation of arteries, capillaries, and veins, usually involving upper and lower airways (30%) and kidney (80%), +/- cutaneous (leukocytoclastic vasculitis)

- **Dx:** sinus CT (+/- bone erosions), Bx w/ granulomatous inflammation of vessel walls, 90% + c-ANCA

- **Rx:** limited disease: MTX + prednisone; severe disease: IV pulse steroids x3 days (with oral taper) + RTX or CYC (+/- plasma exchange)

**Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss Syndrome):** necrotizing granulomatous inflammation of vessels in lungs, skin, nerves; strongly associated with asthma/allergic rhinitis and peripheral eosinophilia (asthma precedes vasculitis); may lead to hypereosinophilic syndrome with multi-organ involvement (e.g., heart/myocarditis, lungs)

- **Dx:** >4 of following: asthma, >10% peripheral eos, neuropathy, pulmonary opacities, paranasal sinus disease, consistent biopsy

- **Rx:** IV pulse steroids x3 days (with oral taper) ± CYC or RTX (if severe disease); do not delay rx if mononeuritis → nerve infarction

## Immune Complex-Associated Small-Vessel Vasculitides

**Henoch-Schönlein Purpura (HSP):** 90% in children; ☻☻; often after URI; in adults, more severe presentation, possible a/w malignancy

- **Sx:** classic tetrad of 1) palpable purpura (100%, usually on LEs/buttocks =dependent areas), 2) colicky abdominal pain (60%), 3) arthritis (75%), 4) renal involvement (40-50%, proteinuria, microscopic hematuria to RPGN)

- **Rx:** children: supportive, usually self-limited; adults may require immunosuppression: steroids, dapsone. NSAIDs if mild GI/arthralgias

**Cryoglobulinemia:** immunoglobulins that precipitate at low temperatures and re-dissolve on rewarming

- **Type 1: Monoclonal** (usually IgM or IgG), associated with Waldenstrom’s, MM
  - **Sx:** peripheral neuropathy, renal impairment, hyperviscosity (Raynaud’s, digital ischemia, livedo), vasculitis

- **Type 2: “Mixed” monoclonal Ig against polyclonal IgG** (often IgM with RF activity), associated with HCV, HIV, HBEV

- **Type 3: “Mixed” polyclonal Ig (IgM or IgG) against polyclonal Ig (IgM or IgG), associated with CTDs, lymphoproliferative disorders, HCV
  - **Sx:** palpable purpura, arthralgias, myalgias

- **Rx:** treat underlying cause (e.g., HCV); prednisone ± 2nd immunosuppressive agent (RTX, CYC); consider plasma exchange for Type 1
Rheumatology

Miscellaneous Rheumatologic Diseases

**Behcet's Disease**: Autoinflammatory condition characterized by recurrent aphthae, vasculitis, and skin/GI/neuro/joint sx
- **Epi**: W > M, 20-40 y/o, ↑ Turkey, Middle East, and Asian countries
- **Sx**: Recurrent painful oral ulcers and ≥2 of the following: painful genital ulcers (specific), ocular disease (most commonly uveitis or retinitis), skin lesions (pustules, folliculitis, papules, erythema nodosum), negative pathergy test (skin pustule formation to needle prick [NB: not sensitive in Caucasians])
- **Rx**: Colchicine 1-2 mg daily, low dose prednisone. Apremilast (PDE-4 inhibitor) for ulcers
- **Dx**: Clinical dx only, no specific laboratory tests exist; may have ↑ ESR/CRP

**Familial Mediterranean Fever (FMF)**: Autoinflammatory disorder due to mutations in MEFV gene; autosomal recessive inheritance; characterized by recurrent bouts of fever and serosal inflammation
- **Epi**: Most common in Jews, Armenians, Turks, and Arabs. Onset <10 yrs old (65% pts), <20 yrs old (90% pts)
- **Sx**: Recurrent acute attacks (1-3 days, resolve spontaneously) of fever associated w/ peritonitis (often mistaken for surgical abdomen), unilateral pleuritis, arthritis (monoarticular, sterile joint), or skin lesions (erysipelas-like). **Other manifestations include**: exertional myalgia, pericarditis, testicular pain, and aseptic meningitis.
- **Rx**: Colchicine 1-3 mg/day (to prevent acute attacks and progression to amyloidosis). 5 -10% colchicine resistant, add on IL-1 inhibitors

**Adult Onset Still's Disease (AOSD)**: Systemic inflammatory disorder characterized by fevers, arthritis, and rash. Can present as single episode (wks-mos), multiple flares, or be persistently active.
- **Epi**: W = M. Bimodal → 15-25 yrs old and 36-46 yrs old
- **Sx**: fever; arthralgias; evanescent, salmon-colored maculopapular rash that coincides w/ fever, usually on the trunk, may be precipitated by trauma (Koebner phenomenon); pericarditis; pleural effusions; macrophage activating syndrome
- **Dx**: **Yamaguchi criteria** → requires 25 features, including ≥2 major criteria:
  - Major: Fever ≥39ºC for ≥1 week, arthralgias/arthritis ≥2 weeks, salmon-colored rash, ↑ WBC (≥10K + ≥80% PMN)
  - Minor: Sore throat, LAD, HSM, ↑ AST/ALT, ↑ LDH, negative ANA/RF
  - Other labs (not part of criteria): ↑ ESR/CRP, ferritin >3000 ng/mL (if >10,000, consider MAS spectrum), ↑ plt, ↓ Hgb
- **Rx**: MTX, anti-TNF, anti-IL6R, anti-IL1

**Fibromyalgia**: *NOT* a rheumatic disease. Chronic widespread musculoskeletal pain, often w/ fatigue, sleep disturbance, and multiple somatic symptoms.
- **Epi**: W > M, generalized MSK pain in often 20-55 years of age. Often coexists with other inflammatory diseases like SLE, other CTDs, RA. Often psychiatric comorbidities.
- **Sx**: widespread MSK pain, fatigue, cognitive disturbance (decreased attention & ability to perform complex tasks), psychiatric sx (depression), headache, parasthesias, IBS. Pan-positive ROS not uncommon.
- **Dx**: clinical diagnosis, multiple tender points often used to assess, but specific number NOT needed for diagnosis. Newer criteria involve widespread pain index (WPI) and symptom severity (SS) scale
- **Rx**: Initial therapy: patient education, exercise program; Pharmacologic therapy: first-line includes amitriptyline, duloxetine, or milnacipran; also may consider cyclobenzaprine, gabapentin, and pregabalin (monotherapy > combo therapy). Avoid narcotics.

Yousef Badran

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### Rheumatologic Medications

<table>
<thead>
<tr>
<th>DRUG/CLASS</th>
<th>INDICATIONS</th>
<th>COMMON TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine (AZA; Imuran)</td>
<td>DM/PM, RA, SLE nephritis, vasculitis</td>
<td>GI, bruising, myelosuppression, lymphoproliferative d/o, hepatotoxicity; <strong>test for TPMT deficiency as low levels can ↑ toxicity</strong> (TPMT metabolizes 6-MP to inactive metabolites → deficiency increases circulating 6-MP levels); do not give with xanthine oxidase inhibitors (allopurinol, febuxostat)</td>
</tr>
<tr>
<td>Cyclophosphamide (CYC; Cytoxan)</td>
<td>SLE (LN), vasculitis (most severe)</td>
<td>myelosuppression, hemorrhagic cystitis (MESNA for ppx), lymphoma, infertility (cumulative dose, leuprolide ppx)</td>
</tr>
<tr>
<td>Hydroxychloroquine (HCO; Plaquenil)</td>
<td>RA, SLE, Sjogren’s</td>
<td>N/V, retinopathy (q1y retinal exam), dizziness, alopecia, myelosuppression; G6PD</td>
</tr>
<tr>
<td>Leflunomide (LFM; Arava)</td>
<td>PsA, RA</td>
<td>N/V, alopecia, rash, diarrhea, HTN, hepatotoxicity, URI, dizziness/HA, teratogen</td>
</tr>
<tr>
<td>Methotrexate (MTX; Rheumatrex, Trexall, Otrexup, Rasuvo)</td>
<td>RA (first line), PsA</td>
<td>myelosuppression, hepatotoxicity (give with folate), pneumonitis, stomatitis, rash, teratogen</td>
</tr>
<tr>
<td>Mycophenolate Mofetil (MMF; CellCept)</td>
<td>AAV, DM/PM, PsA, Scleroderma, SLE</td>
<td>Cardiac (HTN, edema, CP, tachycardia), HA, insomnia, diarrhea, rash, pain, fever, stomatitis</td>
</tr>
<tr>
<td>Sulfasalazine (5-ASA; Azulfidine)</td>
<td>AS, IBD, JRA, psoriasis, RA</td>
<td>sore throat, stomatitis, myelosuppression, N/V, rash, HA</td>
</tr>
<tr>
<td>Apremilast (Otezla); PDE4 inhibitor</td>
<td>PsA, severe psoriasis</td>
<td>N/D, URI, depression</td>
</tr>
<tr>
<td>Tofacitinib (Xeljanz); JAK inhibitor</td>
<td>RA, AS, psoriasis</td>
<td>Infection, lymphoma, diarrhea</td>
</tr>
</tbody>
</table>

### BIOLOGIC, non-TNF†‡

<table>
<thead>
<tr>
<th>DRUG/CLASS</th>
<th>INDICATIONS</th>
<th>COMMON TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept (Orensa); CTLA-4</td>
<td>PsA, RA</td>
<td>URI, HA, nausea, HTN, dizziness, dyspesia</td>
</tr>
<tr>
<td>Anakinra (Kineret); anti-IL1R</td>
<td>AOSD/MAS, gout, Schnitzler syndrome</td>
<td>myelosuppression (neutropenia), rash/injection reactions, HA, arthralgia, fever</td>
</tr>
<tr>
<td>Belimumab (Benlysta); anti-BAFF</td>
<td>SLE</td>
<td>Depression, HA, infusion reaction, PML, GI</td>
</tr>
<tr>
<td>Canakinumab (Ilaris); anti-IL-1b</td>
<td>CAPS, CAD (CANTOS trial)</td>
<td>Infection, HA, vertigo, GI, MSK pain, nasopharyngitis</td>
</tr>
<tr>
<td>Rituximab (Rituxan); anti-CD20</td>
<td>APLAS, GPA/MPA, IgG4-RD, Scl-ILD, (SLE)</td>
<td>URI, HTN, infusion reaction, TLS, PML, fever, rash/pruritis, LE edema</td>
</tr>
<tr>
<td>Tocilizumab (Actemra); anti-IL-6R</td>
<td>GCA, RA</td>
<td>URI, hepatotoxicity, HLD</td>
</tr>
<tr>
<td>Secukinumab (Cosentyx); anti-IL17A</td>
<td>AS, PsA, psoriasis</td>
<td>URI</td>
</tr>
<tr>
<td>Ustekinumab (Stelara); anti-IL-12/23</td>
<td>PsA, psoriasis</td>
<td>URI, PRESS, seizures</td>
</tr>
<tr>
<td>IVIG</td>
<td>APLAS, DM/PM, IBM, IMNM, Kawasaki’s</td>
<td>transfusion reactions/anaphylaxis, aseptic meningitis, thromboembolism, HA</td>
</tr>
</tbody>
</table>

### BIOLOGIC, TNF inhibition†‡

<table>
<thead>
<tr>
<th>DRUG/CLASS</th>
<th>INDICATIONS</th>
<th>COMMON TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira); anti-TNF</td>
<td>AS, IBD, PsA, psoriasis, RA</td>
<td>HA, nausea, rash, URI, CPK elevation, infection, drug-induced lupus</td>
</tr>
<tr>
<td>Infliximab (Remicade); anti-TNF</td>
<td>AS, IBD, PsA, psoriasis, RA</td>
<td>HA, nausea, diarrhea, ALT elevation, infection, drug-induced lupus</td>
</tr>
<tr>
<td>Golimumab (Simponi); anti-TNF</td>
<td>AS, IBD, PsA, RA</td>
<td>injection reactions, URI, drug-induced lupus</td>
</tr>
<tr>
<td>Certolizumab (Cimzia); anti-TNF</td>
<td>AS (axial), IBD, RA</td>
<td>Nausea, infection, URI, drug-induced lupus (rare)</td>
</tr>
<tr>
<td>Etanercept (Enbrel); sol. TNF-α</td>
<td>AS, PsA, psoriasis, RA</td>
<td>HA, rash, nausea, diarrhea, infection, okay w/ HCV; drug-induced lupus</td>
</tr>
</tbody>
</table>

†‡ All can cause HBV /TB reactivation (check hepatitis serologies, PPD and/or IGRA prior to starting); if positive, start antiviral prophylaxis with entecavir (HBV reactivation) and prophylaxis with INH (latent tuberculosis) as per ID/rheum. (NB: TNF-alpha inhibitors are **safe** in HCV infection → may even be beneficial, as TNF-alpha promotes liver fibrosis, **Expert Opin Biol Ther 2012;12:193**)

AAV (ANCA-associated vasculitis), AOSD (Adult-onset Still's disease), APLAS (Anti-phospholipid antibody syndrome), AS (Ankylosing spondylitis), DM (dermatomyositis), EGPA (eosinophilic granulomatosis with polyangiitis), GCA (giant cell arteritis), GPA (Granulomatosis with polyangiitis), IBD (inflammatory bowel disease), IMNM (Immune-mediated necrotizing myopathy), JRA (juvenile rheumatoid arthritis), MAS (Macrophage activating syndrome), MPA (Microscopic polyangiitis), PM (polymyositis), PsA (Psoriatic Arthritis), RA (rheumatoid arthritis), SLE (systemic lupus erythematosus), UC (Ulcerative colitis)
Endocrinology

Outpatient Type 2 Diabetes Management

Pre-Diabetes (Diab Care 2019:42:S13)
- **Diagnosis:** A1c 5.7-6.4%; fasting plasma glucose (FPG) 100-125; or OGTT w/ 2hr plasma glucose (PG) 140-199
- **Monitoring:** A1c at least q1y; if A1c 6.6-4.4%, screen q6mo (25-50% 5-year risk of progression to diabetes if A1c 6.5-6.6%)
- **Treatment:** Lifestyle interventions most effective; metformin also effective, esp. if BMI ≥ 35 or age <45 (DPP, NEJM 2002;346:393)

Diabetes (Diab Care 2019:42:S13)
- **Diagnosis:** A1c > 6.5%; FPG >126; 75g OGTT with 2hr PG >200; or random glucose >200 & symptoms. Unless diagnosis is made by symptoms & random glucose >200, **confirm with repeat or additional test.** (NB: for T1DM, check TSH, celiac screen at diagnosis).
- **Treatment:** Goal A1c 7%; liberalize to < 8-8.5% if life expectancy <10 years or high risk for hypoglycemia.

Screening: Beginning at age > 45 years OR if BMI > 25 (or ≥ 23 in Asian-Americans) + risk factors (1st degree relative with DM, nonwhite, history of CVD, hypertension, HDL<35, triglycerides>250, PCOS, sedentary); screen q3y if normal (ADA Guidelines 2018)

### Healthcare Maintenance for Diabetic Patients

<table>
<thead>
<tr>
<th>Every visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Review blood sugar log → goal AM fasting blood glucose 80-130</td>
</tr>
<tr>
<td>• Blood pressure → goal SBP &lt;140; ACEi/ARB first line</td>
</tr>
<tr>
<td>• Weight, BMI → weight center referral if BMI &gt; 40 or &gt; 35 with poor control; nutrition referral for all patients</td>
</tr>
<tr>
<td>• Foot exam (inspect skin, joints, pulses, sensation) esp if known neuropathy or PVD; ABIs/vascular referral if PVD</td>
</tr>
<tr>
<td>• Smokingcessation counseling (Advise, Assist, Arrange)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3-6mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A1c Q6 months if controlled; Q3-6 months if A1c above target</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Lipids:</strong> moderate-intensity statin if 40-75 yrs old w/ ASCVD&lt;7.5%; high-intensity statin if ASCVD≥7.5%; ASA for 2° prevention of CVD (limited evidence for 1° prevention)</td>
</tr>
<tr>
<td>• Urine mAlb/Cr, BMP → consider ACEi/ARB if hypertensive w/ either proteinuria or GFR&lt;60; refer to renal if GFR&lt;30</td>
</tr>
<tr>
<td>• Monofilament exam → if fail to feel at 4/10 specific sites, + for neuropathy (see PCOI for specific sites)</td>
</tr>
<tr>
<td>• Retinopathy screen w/ dilated eye exam or retinal photography; can consider Q2-3yr if normal exam(s)</td>
</tr>
<tr>
<td>• LFTs → consider elastography and/or hepatology referral if elevated to evaluate for NASH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Influenza annually</td>
</tr>
<tr>
<td>• Hepatitis B series if age &lt;60 and not immune</td>
</tr>
<tr>
<td>• PPSV23 x1 age &lt;65; re-dose x1 &gt;65 with at least 5 years between doses</td>
</tr>
</tbody>
</table>

### Basal insulin management

- **Criteria for initiation:** Consider if A1c ≥ 9%, random BG ≥ 300, fasting BG ≥ 250, or if symptomatic; also if < 65yo on two agents with A1c >8% (or ≥ 65yo and A1c > 8.5%) on two occasions at least three months apart; or when the A1c is quickly rising
- **Initial dose:** Starting dose: 0.1-0.2U/kg/day or 10U/day (if weight >80kg, may consider starting at 20U/day)
- **Choice of agent:** choose long-acting (glargine, detemir QD) or intermediate-acting (NPH BID → cheaper) |
- **Route:** pen (easier to use, more expensive) vs. needle/syringe

### Prandial insulin management

- **Criteria:** Consider if A1c still not at goal with basal insulin 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
  - **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. Counsel to avoid missing meals to avoid hypoglycemia.
- **Titration:** Increase dose by 1-2U or 10-15% q3d until target glucose reached (pr-preprandial: 80-130; 1-2h post-prandial < 180)
- **If A1c still not controlled:** add rapid-acting insulin to another meal and titrate as above
- **If hypoglycemia occurs or FPG < 80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater

### Insulin supplies

- **Needles:** Come as universal pen needles, or attached to syringes, made by many companies. 32G 4mm - less painful (higher gauge thinner and shorter needle), but obese patients and high insulin doses often require deeper/wider needle.
- **Syringes:** Boxes of 100. Pt on basal/bolus insulin needs 4 syringes/day (4 boxes/3 months). Pt on long-acting insulin only needs 1 box/3 months. Choose the smallest syringe that will hold the dose (smaller barrel → clearer scale markings).

<table>
<thead>
<tr>
<th>Use this barrel size...</th>
<th>With this dose range...</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/10 mL</td>
<td>30 units or less</td>
</tr>
<tr>
<td>1/2 mL</td>
<td>31-50 units</td>
</tr>
<tr>
<td>1 mL</td>
<td>51-100 units</td>
</tr>
</tbody>
</table>

- **Alcohol swabs** (or patients can wash hands/skin with soap and water)
- **Glucometer & test strips:** Many choices (insurance dependent), each with own strip brand. Most test strips come in boxes of 50-100.
- **All durable medical equipment including test strips and glucometers, require an ICD-10 code on the script itself**

Max Petersen
# Endocrinology

## Outpatient Type 2 Diabetes Management

### Non-Insulin Agents

<table>
<thead>
<tr>
<th>Drug/Dose Range</th>
<th>% ↓ A1c</th>
<th>Contraindications</th>
<th>Patients (pts) who benefit/Pros</th>
<th>Side Effects/Considerations</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (Glucophage) 500-1000mg BID</td>
<td>1-2</td>
<td>GFR cutoffs: - &lt;45mL/min don’t initiate - &lt;30mL/min discontinue</td>
<td>- First line therapy - Weight loss - Improve lipids</td>
<td>- Diarrhea/GI (nausea, bloating) - B12 deficiency - Lactic acidosis in patients with severe liver/renal disease; hold 48 hrs s/p IV contrast</td>
<td>$5 (IR) $8 (ER)</td>
</tr>
</tbody>
</table>

**Metformin pearls:** To increase adherence, warn patients about GI side effects and educate patients that side effects go away with time for most; can be minimized by taking WITH food. Start with 500mg daily and increase by 500mg each week to a dose of 1000mg BID; each dose increment helps – no diminishing returns. If GI side effects occur at a higher dose (side effects are dose-dependent), decrease and try at later date. Many patients tolerate the ER formulation better than IR.

### Insulin Secretagogues:

- stimulate release of insulin from pancreatic beta cells, thus only effective in pts who still have beta cell function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas: Glipizide 2.5-20mg QD Glimepiride 1-8mg QD</td>
<td>1-2</td>
<td>Severe renal or hepatic impairment - NOTE: cross-reactivity in pts with allergy to sulfa abx is low</td>
</tr>
<tr>
<td>Meglitinides: Repaglinide (Prandin) 0.25-4mg QAC</td>
<td>0.5-0.7</td>
<td>Mod to severe hepatic impairment - Concurrent gemfibrozil therapy</td>
</tr>
</tbody>
</table>

### GLP-1 Receptor Agonists:

- stimulate glucose-dependent insulin release from beta cells, therefore lower risk of hypoglycemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta) 5-10mg BID</td>
<td>0.5-1.1</td>
<td>FDA Black Box Warning: risk of thyroid C-cell tumors (e.g., medullary), so avoid if hx of thyroid cancer or if pt w/ MEN2</td>
</tr>
<tr>
<td>Liraglutide (Victoza) 0.6-1.8 QD Dulaglutide (Trulicity) 0.75-1.5 Qwk</td>
<td>0.5-0.8</td>
<td>- No contraindications, but very weak</td>
</tr>
</tbody>
</table>

### DPP-4 Inhibitors:

- inhibit degradation of DPP4, increasing glucose-dependent insulin secretion and decreasing glucagon secretion

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin (Januvia) 25mg-100mg QD Saxagliptin (Onglyza) 2.5-5mg QD Linagliptin (Tradjenta) 5mg QD</td>
<td>0.5-0.8</td>
<td>GFR cutoffs: - &lt;45mL/min don’t initiate - &lt;30mL/min discontinue - History of bladder cancer (dapagliflozin)</td>
</tr>
<tr>
<td>Canagliflozin (Invokana) 100-300mg QD Empagliflozin (Jardiance) 5-10 mg QD Dapagliflozin (Farxiga) 5-10 mg QD</td>
<td>0.8-0.9</td>
<td></td>
</tr>
</tbody>
</table>

### SGLT-2 Inhibitors:

- block renal glucose reabsorption, increasing glucosuria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Side Effects/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone (Actos) 15-30mg QD</td>
<td>1-1.6</td>
<td>Avoid use in pts w/ history of bladder cancer</td>
</tr>
</tbody>
</table>

### Thiazolidinediones:

- increase insulin sensitivity by acting on adipose, muscle, and liver to ↑ glucose uptake, ↓ ectopic lipid deposition

- Monthly costs in Boston area pharmacies (GoodRx)

**PEARLS FOR CHOOSING A SECOND NON-INSULIN AGENT**

- If prominent ASCVD: GLP-1RA or SGLT2i
- If prominent heart failure or CKD (but eGFR > 45 mL/min): SGLT2i
- If weight loss desired: GLP-1RA or SGLT2i
- If cost is a major concern: SU or TZD

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Max Petersen 170
Endocrinology

Inpatient Diabetes Management

### Inpatient Management

**Glycemic targets**
- **Floor:** fasting 100-140 mg/dL, random <180 mg/dL
- **ICU:** 140-180 mg/dL (NOT stricter) *(NICE-SUGAR, NEJM 2009;360:1283)*

Check FSBG AC & QHS (at least for 24-48h) in (1) known diabetics, (2) non-diabetics with BG > 140 mg/dL, (3) those receiving therapies a/w hyperglycemia (corticosteroids, octreotide, tube feeds, TPN)

* Note: FSBGs inaccurate in hypotension (esp. on pressors) and hypothermia due to altered blood flow to skin. Confirm w/ serum glucose.

**Hypoglycemia**
- **↑ Risk:** T1DM, malnutrition, emesis, ↓ body weight, ↓ PO intake, ↓ steroid dose, AKI *(↓ insulin clearance)*, CKD *(esp. dialysis)*
- **Manifestations:** < 70: Shakiness, anxiety, diaphoresis, visual Δ, HA, AMS
- **< 55:** Seizure, coma

**Beware of hypoglycemia unawareness in T1DM and longstanding T2DM**
- **Tx:** PO if able (15g gel, tabs, juice); IV (0.5-1 amp D50 = 12.5-25g), recheck in 15 min and chase with PO if due to insulin OD
- **Tip:** If sulfonylurea OD → **Tx:** 50-75 mcg octreotide subQ

**Review and adjust insulin regimen if hypoglycemia (BG<70) or BG<100 occurs while inpatient, even if asymptomatic**

**Admission Orders** *(NEJM 2006:355:1903)*
1. Hold home oral antihyperglycemic agents *(NEVER hold basal insulin for T1DM)*
2. Continue home insulin regimen with dose reduction *(~25-50% reduction)* given expected change in diet while hospitalized.
3. Hypoglycemia is associated with increased mortality in elderly, so reasonable to be cautious.
4. If not on home insulin, and **well controlled**, reasonable to start with ISS and T2D as listed below.
5. If not on home insulin, and not well controlled, **start with basal-bolus**!
   - TDD 0.5 U/kg/day (0.2-0.3 if age>75, lean, ESRD, ESLD, frail): 50% basal, 50% prandial + ISS
6. If NPO: no need to ↓ basal if truly only covering basal needs, but this is unusual. Consider 50% dose reduction or 0.2 U/kg/day for basal insulin. Be sure to change correctional ISS and FSBG from TID AC to q6h.
7. Correctional insulin sliding scale: use low-dose if insulin-sensitive/ESRD/ESLD/frail, otherwise moderate-dose for most T2DM

**Adjusting Insulin Dosing:** In general increase by no more than 20% of total daily insulin requirement every day

**Special Situations:**
1. **Glucocorticoids:** rule of thumb → give NPH 0.1U/kg/d for every 10mg pred, up to 0.4U/kg/d; if dexamethasone, use glargine instead
2. **Tube Feeds:** If not on insulin already, start with RISS q6h. Convert to NPH BID based on needs. If on insulin, use ½ basal (NPH BID) + ½ bolus (regular insulin q6h) + correctional. If TF stopped, give D5W at TF rate until next NPH dose, and ↓ NPH dose by 50% or more based on pre-TF insulin requirements. TPN: regular insulin can be added to TPN (discuss w/ nutrition), does not cover basal!

**Disposition:** If new home insulin → nutrition c/s + floor RN teaching and arrange outpatient f/u. Using discharge order set, send rx for MGH outpatient pharmacy and bring up to floor for RN teaching.

Max Petersen

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DKA: DIABETIC KETOACIDOSIS

Pathophysiology: Think about each element of Diabetic Keto-Acidosis
- Diabetes: ↓ insulin & ↑ opposing hormones (glucagon, catechols, cortisol) → hyperglycemia → osmotic diuresis
- Ketones: ↓ insulin → ↑ lipoysis → ↑ free fatty acids → ↑ ketones [acetocetate, β-hydroxybutyrate, acetone (fruity breath)]
- Acidosis: ↑-hydroxybutyrate and acetocetoacetate, and contraction alkalosis with total body HCO₃⁻ deficit (NEJM 2015;372:546)

Precipitants (the “Ts”): infection (30-40% of cases), initial presentation of DM (20-25% of cases), insulin non-adherence, inflammation (pancreatitis – but ↑ amylase / lipase in DKA even w/o this), ischemia/infarction (MI, CVA, gut), intoxication (EtOH, cocaine), iatrogenesis (e.g., SGLT2 inhibitors, steroids, thiazides, dobutamine/terbutaline, atypical anti-psychotics), infant (pregnancy)

Presentation: dehydration, polydipsia/polyuria, N/V/abd pain, weakness, AMS, Kussmaul’s respirations, fruity breath (acetone)

Dx: BG 250-800, pH <7.3, AG >10, urine/serum ketones. Consider euglycemic DKA in pt on SGLT2i, EtOH liver dz, pregnancy.
- Check BMP, CBC + diff, UA, serum osm, serum β-hydroxybutyrate, ABG/VBG. Consider TnT, EKG, BCx, UCx, CXR, lipase/amylase.

Note: sodium correction represents what the sodium will be once glucose is corrected. NOT what the sodium currently is! When to use absolute sodium value: when calculating anion gap. When to use corrected value: to assess for underlying hypotonic hypoNa.
- Correction Formula: add 1.6 mEq/L for every 100 mg/dL of serum glucose > 100 mg/dL (e.g. if 300 mg/dL, add 3.2 mEq/L)
- Note: UA ketone does not test for β-hydroxybutyrate (BOHB), which is the predominant ketone in DKA (must measure from serum)

Management: *Prioritize ABCs, volume status, identifying precipitant → THEN electrolytes → THEN glucose

- Labs: BMP g2h 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)
- Bolus NS (15-20cc/kg/hr) [unless CHF, ESLD, ESRD, hypoxemia] for initial resuscitation
- Calculate corrected Na → if Na low, start NS ± K⁺ at 250-500cc/hr; if Na normal/high or hyperCl acidosis, start ½NS ± K⁺ at 250-500cc/hr
- Add D5 to IVF once BG<200 (DKA) or <300 (HHS)

Step 2: Potassium repletion
- Potassium Action
  - K<3.3 ➔ Give 20-40 mEq KCI IV per hour + hold insulin!
  - 3.3<K<5.3 ➔ Add 20 mEq K to IVF
  - K>5.3 ➔ Continue to monitor q2h

  - Step 3: Insulin therapy (Diab Care 2009;32:1335)
    - Pearls:
      - The #1 goal of insulin therapy in DKA is to stop ketogenesis and close the AG; glucose correction is secondary
      - Don’t start insulin until you have control of K⁺
      - Don’t stop the insulin gtt unless true hypoglycemia (<65 mg/dL) or hypokalemia (<3.3 mM) occurs
    - Initial: Bolus 0.1 U/kg, then start 0.1 U/kg/hr IV gtt; OR no bolus and start 0.14 U/kg/hr IV gtt
      - Goal is to ↓ BG by 50-75 mg/dL each hour
      - For mild DKA, subcutaneous insulin regimens may be used instead of IV (Cochr Dat Syst Rev 2016;1:CD011281)
    - Titrating Insulin Drip: MICU insulin dtt protocol is for general glycemic management, NOT for DKA
      - If BG does not ↓ by 50-75 mg/dL in the first hour, rebolus (DKA) or double the gtt (HHS)
      - No evidence for hourly titration of the insulin infusion rate in DKA while BG>200
      - Once BG <200 (DKA) or <300 (HHS), ↓ gtt to 0.02-0.05 U/kg/hr
      - Goal is to maintain BG at 150-200 (DKA) or 250-300 (HHS)

    - For BG < 150 mEq/L: Δ Insulin gtt and glucose source
      - BG 91-149 ➔ ↓ gtt by 25% + ↑ D5 gtt 50 ccr/hr
      - BG 66-90 ➔ ↓ gtt by 50% + ½ amp D50 + continue D5 gtt
      - BG ≤ 65 ➔ hold insulin + 1 amp D50 + continue D5 gtt

Other Electrolytes:
- HCO₃⁻: no proven benefit w/ pH > 6.9. If pH < 6.3, give 2 amps HCO3 dissolved in 400mL sterile water w/ 20mEq KCI over 2h
- Phos: Total body deficit but serum phos may be ↑ / nml; will ↓ w/ insulin; only replete if < 1.0 to prevent cardiac dysforn

Transitioning to SQ Insulin: Start if BG < 200 and pt is able to eat and two of the following are met: AG<12, HCO3>15, pH>7.3. Start basal regimen w/ either: home glargine dose OR glargine at 0.25-0.4 U/kg/d OR glargine at (# units on IV gtt over past 6h x 4 x 0.7). Start bolus regimen w/ either: 0.25-0.4 U/kg/d divided (if T1DM or unknown) OR ISS only (if T2DM). Overlap IV/SQ insulin by 2-4h.

HHS: HYPEROSMOLAR HYPERGLYCEMIC STATE

Pathophysiology: Hyperglycemia → osmotic diuresis → volume depletion; ketogenesis suppressed by low (but present) insulin levels

Precipitants: Same as DKA (NB: pts w/ T2DM and burned-out pancreas can also present with DKA)

Presentation: AMS (25-50%), seizures, focal neuro, volume depletion, after days-weeks of evolution (versus hours-days in DKA)

Diagnosis: Glucose > 600 mg/dL (frequently >1000), osmolality > 320 mOsm/kg, pH > 7.3, absent or minimal ketones

Treatment: As above for DKA w/ modifications: more aggressive IVF (~8-10 L deficit); goal glucose 250-300 mg/dL (in DKA, 150-200); transition to SQ insulin when BG<300 and mental status improved and patient is able to eat

Max Petersen
Endocrinology

Adrenal Insufficiency


Primary AI
• Mechanism: ↓ adrenal hormone → ↑ ACTH. Lesion localizes to the adrenal gland.
• Causes: Autoimmune (80-90%), cases in developed countries; anti-21-hydroxylase Ab in 86%, autoimmune polyglandular syndromes) >> infxn (TB, HIV, CMV, hist, meningoccocus), bilateral adrenal hemorrhage (infxn, DIC, APLAS), malignancy (mets), genetic (CAH, adrenal leukodystrophy), meds (keto/fluconazole, etomidate, phenobarb, phenytoin, rifampin, opioids)

Secondary AI
• Mechanism: ↓ ACTH → ↓ adrenal hormone. Lesion localizes to pituitary gland.
• Causes: Chronic glucocorticoids, opioids, medroxyprogesterone and megestrol. Ask about topical, inhaled and intra-articular steroids.

Clinical Manifestations
Primary AND Secondary:
• Signs/symptoms: weakness, fatigue, anorexia, N/V, abd pain, weight loss, orthostatic hypotension, vasodilatory shock
• Labs abnormalities: hyponatremia, hypoglycemia, hypercalcemia, non-AG acidosis, anemia, eosinophilia, lymphocytosis

Primary only (low serum ald): hyperK, salt craving, hyperpigmentation (mucous membranes, creases, pressure areas)
Secondary only (normal serum ald): ± hypopituitarism

Diagnosis

Screening test: AM cortisol. Diagnostic test: Cosyntropin stimulation test (aka “cort stim”) (JCEM 2016;101:364)

6-AM cortisol: Define AI if ≤ 3 µg/dL (some sources say <5 µg/dL suggestive); definitely not AI if ≥ 18 µg/dL

Cort stim protocol: Check serum cortisol and ACTH → give cosyntropin (ACTH) 250 µg IV/IIM → serum cortisol 30-60 min later
- Normal response: serum cortisol at 30-60 min is ≥ 18 µg/dL (note: this rules out all cases of 1° AI + chronic cases of 2° AI)
  - o In acute 2° AI, adrenal glands have not had time to atrophy; so cort stim test will be normal!
  - Can be performed at any time of day; initial cortisol check will be higher in the morning but stim will always be appropriate
  - If positive cort stim, consult endocrine.

Falsely low serum cortisol: ↓ albumin (e.g., cirrhosis), nephrotic syndrome, malnutrition, critical illness; ↓ bound and total cortisol, but free cortisol may be nil; PM testing (cortisol responses are greatest in morning)

Falsely high serum cortisol: Pregnancy, PO estrogens (↑ cortisol binding globulin, ↑bound/total cortisol, free cortisol may be ↓

Additional labs for primary AI: ↑ACTH >2x ULN, ↓aldo; in addition, check plasma renin/aldo, 17-OH-Prog, 21-OH Ab

Additional labs for secondary AI: ↓ ACTH, nl aldo

Adrenal Crisis

Acute-onset AI with distributive shock i/s/o major stressor (infxn, trauma, major surgery, critical illness)

No known AI + not taking chronic steroids: Do not delay empiric therapy for testing; defer testing until clinically stable

Known AI or taking chronic steroids: Start therapy (see below); dx can be presumed by hx; no role for cort stim test

Consult endocrine if concerned for adrenal crisis.

Treatment (JCEM 2016;101:364)

Adrenal crisis → Stress dose steroids (Hydrocortisone 100 mg IV or dexamethasone 4mg IV x1) + fluid resuscitation. Follow with hydrocortisone 50mg IV q8hr or dexam 4mg IV q24hr ± fludrocortisone 0.1mg QD when off saline infusion if 1° AI.
- May taper once patient’s clinical status improves and underlying precipitant is adequately addressed
- Dexamethasone not detected in cortisol assay; steroid of choice if considering early cort stim dx (Clin Chem 2004;50:2345)
- ***Remember to treat adrenal insufficiency BEFORE treating hypothyroidism otherwise you may precipitate adrenal crisis

Chronic AI → Glucocorticoid: hydrocortisone 15-25 mg PO QD (2/3 AM, 1/3 early PM) or prednisone 3-5 mg PO QAM; Mineralocorticoid (only in 1° AI): fludrocortisone 0.05-0.1 mg PO QD
- Chronic AI + illness → Sick Dose: “3x3 rule” = 3x daily dose for three days for outpatient / floor patients w/ minor illnesses (stress dose as above for severe illness)
- Also supply patients with medical alert bracelet if new diagnosis

Steroid Pearls

• Taper: not necessary if steroid use < 3 wks (independent of dose) → low risk of HPA suppression
• Side effects of supra-physiologic doses: ↑ weight, insomnia, skin thinning, AMS, hyperglycemia, edema, osteoporosis, gastritis
• Prophylaxis: PJP: if taking prednisone >20mg for >4 weeks plus second reason for immunocompromise; PUD: if also taking aspirin/NSAIDs; Osteoporosis: start calcium 1200mg/day + vitamin D 800IU/day if on glucocorticoids (any dose) > 3 months (consider bisphosphonates for pts at intermediate to high risk of fracture); DM2: monitor glucose/A1C, consider NPH dose (0.1U/kg/day up to 0.4U/kg/day) with glucocorticoid if BG/A1C high

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Equivalent Anti-inflam Dose (mg)</th>
<th>Relative Anti-inflam Activity</th>
<th>Relative Na Retention Activity</th>
<th>Duration (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>2</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>0.8</td>
<td>12-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0.5</td>
<td>12-36</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30</td>
<td>0</td>
<td>36-72</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>n/a</td>
<td>10</td>
<td>125</td>
<td>12-36</td>
</tr>
</tbody>
</table>
Endocrinology

Pituitary Disorders

**HYPOTHYROIDISM**
Definition: ↓ pituitary hormone production/release resulting from diseases of pituitary (1°) or hypothalamus/stalk (2°)

**Etiology:**
- Both 1° and 2°: Surgery, radiation, infections (meningitis), infiltration (sarcoid, hemochromatosis), trauma, tumors (primary pituitary tumors / mets in 1° disease; external stalk compression e.g., craniopharyngioma, meningioma, mets in 2° disease)
- 1° only: Sheehan’s (infarction), apoplexy (hemorrhage), meds (ipilimumab), autoimmune (classically in 3rd trimester/postpartum)

**Clinical Manifestations & Diagnosis:**

<table>
<thead>
<tr>
<th>Hormone Deficiency</th>
<th>Symptoms and Signs</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>Reduced lactation</td>
<td>PRL</td>
</tr>
<tr>
<td>ACTH (2° adrenal insufficiency)</td>
<td>Fatigue, weight loss, nausea, orthostatic dizziness, muscle/joint pain, hypotension</td>
<td>8 AM cortisol, cort stim test, ACTH</td>
</tr>
<tr>
<td>GH</td>
<td>Fatigue, low energy, central obesity, ↓ bone mineral density</td>
<td>IGF-1, insulin tolerance test</td>
</tr>
<tr>
<td>TSH (2° hypothyroidism)</td>
<td>Fatigue, weight gain, constipation, bradycardia, hair loss, dry skin, hyporreflexia</td>
<td>TSH, free T4</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>Amenorrhea, decreased libido, ED, infertility</td>
<td>LH, FSH, estradiol, AM testosterone</td>
</tr>
</tbody>
</table>

**Treatment:** Replace deficient hormone (JCEM 2016;101:3888) with endocrine consult assistance. Most sensitive issue is cortisol/thyroid hormone replacement: if concurrent deficiencies, treat AI before hypothyroidism as can otherwise precipitate adrenal crisis.

**HYPERPITUITARISM**
Definition: excess of any of the hormones secreted by the anterior pituitary gland (PRL, ACTH, GH, TSH, LH/FSH)

**Etiology:**
- Hyperfunctioning pituitary adenoma
- Elevated prolactin due to disruption of pituitary stalk, drugs (antipsychotics, antidepressants, antiemetics, verapamil, opioids, cocaine)

**Clinical Manifestations:** If pituitary adenoma → headaches, visual field deficits

<table>
<thead>
<tr>
<th>Hormone Excess</th>
<th>Symptoms and Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin (Prolactinoma)</td>
<td>Infertility, amenorrhea, galactorrhea, ED</td>
</tr>
<tr>
<td>ACTH (Cushing’s disease)</td>
<td>Weight gain, fatigue, irritability, anxiety, depression, insomnia, easy bruising, poor wound healing, central obesity, acne, hirsutism, wide violaceous striae, prox muscle weakness, HTN</td>
</tr>
<tr>
<td>GH (Acromegaly)</td>
<td>Arthralgias, fatigue, paresthesias (carpal tunnel syndrome), hyperhidrosis, OSA, CHF, enlarged jaw, hands, feet, coarse facial features, deepening of voice, skin tags, hirsutism, HTN</td>
</tr>
<tr>
<td>TSH (2° hyperthyroidism)</td>
<td>Fatigue, exertional intolerance, irritability, palpitations, diarrhea, tachycardia, tremor, hyporreflexia</td>
</tr>
</tbody>
</table>

**Diagnosis:**
- Labs: Should be targeted based on symptoms – Prolactinoma (PRL), Cushing’s disease (overnight 1 mg dexamethasone suppression test, late-night salivary cortisol, 24 hr urinary free cortisol excretion), Acromegaly (IGF-1, confirm with GH level after glucose tolerance test), 2° hyperthyroidism (TSH, free T4, total T3)
- Imaging: MRI brain with and without contrast, pituitary protocol

**Management:**
- Prolactinoma: If >1cm or symptomatic, first-line treatment is a dopamine agonist (cabergoline first choice, bromocriptine preferred in preconception setting). If <1cm or asymptomatic, can monitor closely with MRI and prolactin levels (JCEM 2011:96:273).
- For all other hypersecreting pituitary adenomas, treatment is transphenoidal pituitary surgery +/- radiation therapy
- For GH secreting adenomas in patients who are poor surgical candidates, can treat with somatostatin analog (octreotide)

**SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)**
Definition: Impaired free water secretion due to excessive secretion of ADH

**Causes:** Cerebral pathology (CVA, infxn, trauma), malignancy (SCC → ectopic ADH), meds (carbamazepine, oxcarbazepine, opioids, cyclophosphamide, SSRI), pulmonary pathology (PNA, atelectasis), pain, surgery (intrathoracic/abdominal), AI, HIV

**Management:** See Sodium Disorders. Treat underlying infection or pain, remove offending drugs, replace deficient hormones

- Mild/moderate sx: fluid restriction (goal <800mL/d), salt tablets (3g TID), loop diuretic (e.g., furosemide → diminishes medullary reabsorption gradient), demeclocycline/lithium (rarely used)
- Severe sx (seizure): hypertonic (3%) NS, tolvaptan

**DIABETES INSIPIDUS (DI)**
Definition: Polyuria (>3L/day) in setting of insufficient amount of ADH (central) or insufficient response to ADH (nephrogenic)

**Etiologies:**
- Central – hypothalamic or posterior pituitary damage by trauma, surgery, vascular (hemorrhage, infarction), neoplasm, infiltrative (sarcoidosis, histiocytosis), infection (meningitis, encephalitis), autoimmune, drugs (EtOH, phenytoin)
- Nephrogenic – most frequently 2/2 drugs (lithium, cisplatin), hypercalcemia, or hereditary (children); also infiltrative (sarcoidosis, amyloidosis, MM), sickle cell
Diagnosis:
- **Water restriction test:** *Normal physiology*: water restriction → ↑SOsm → ↑ADH → ↑UOsm (*JCEM 2012;97:3426*)
  - Check Na, SOsm, UOsm, UVol q2hr
    - If UOsm > 800 mEq/kg, stop test due to appropriate vasopressin response (dx: primary polydipsia)
    - If (1) SOsm > 295 mEq/kg, (2) Na > 145 mEq/L (adequate ADH stimulus) OR (3) UOsm stable on several checks despite ↑ SOsm (ADH response plateaued), administer vasopressin 4 mcg IV, then check UOsm, UVol q30min x 2hr
      - UOsm < 300 mEq/kg prior to vasopressin suggests complete DI
      - > 50% ↑ UOsm following vasopressin = central
      - < 50% ↑ UOsm following vasopressin = nephrogenic
      - UOsm 300 - 800 mEq/kg prior to vasopressin suggests partial DI (vs. primary polydipsia)

Treatment:
- Correct hypernatremia (see Sodium Disorders). Allow patient to drink to thirst and if unable to drink, oral or nasogastric water is preferred to avoid rapid changes in serum sodium.
- **Central:** first line = desmopressin (exogenous ADH); usually give intranasally (5mcg qHS + 5mcg 1-3x/day); additional meds (listed below) may be used as adjunctive therapy
- **Nephrogenic:** if partial, may try desmopressin; if complete, use one of the meds listed below
- **Salt/protein restriction:** low solute intake reduces thirst, thereby reducing free water intake
- **Adjunctive Meds:**
  - HCTZ: volume depletion → increases proximal sodium/water reabsorption, decreasing distal sodium delivery (where ADH acts)
  - Amiloride: mechanism similar to HCTZ; also beneficial in lithium-induced nephrogenic DI by blocking entry of lithium across ENaC into collecting tubule cells, thereby preventing toxicity
  - NSAIDs: enhance renal response to ADH (prostaglandins antagonize ADH)
  - Chlorpropamide: enhances renal response to ADH

Osteoporosis

Definitions:
- **Osteoporosis:** history of fragility fracture or T-score ≤-2.5 on DXA. **Osteopenia:** T-score -2.4 to -1.
  - **T-score:** SD compared to mean for normal, healthy young adults
  - **Fragility fracture:** fracture from a fall from standing height or less, particularly spine, hip, wrist, humerus, rib, and pelvis

Etiology:
- **Primary** osteoporosis is the most common. Risk factors include age ≥65, low body weight (<57.6 kg), FH osteoporosis or fractures, smoking, early menopause, excessive EtOH intake
- **Secondary** osteoporosis caused by: hyperthyroidism, hyperPTH, vit D deficiency, hypogonadism, glucocorticoids (>5mg prednisone for >3mos), myeloma, malabsorption (celiac, IBD), RA, COPD, drugs (PPI, AED, long-term heparin, leuprolide, aromatase inhib, MTX)

Diagnosis:
- Screen women with DXA scan at age 65 or younger if risk similar to that of a 65-year-old white woman with no additional risk factors (i.e. FRAX 10-year risk of major osteoporotic fracture ≥9.3%) (*USPSTF guidelines*)
- Labs for secondary causes: CBC, CMP, 25(OH)D, TSH, PTH, SPEP

Management:
- **Inpatient following fragility fracture:** assess need for surgical treatment, consult fracture liaison service (p25656), can start medical management (bisphosphonates); bisphosphonates have been shown to decrease mortality post-hip fracture in the HORIZON trial.
- **Lifestyle measures:** weight-bearing exercises, smoking cessation, decrease EtOH intake, RDA 800-1000 IU vitamin D (goal level >30), calcium 1200 mg ideally from diet
- **Pharmacologic therapy:**
  - **Bisphosphonates** – must have normal vit D and calcium levels prior to initiating therapy
    - Indicated for: all patients with osteoporosis, osteopenia in men and postmenopausal women with FRAX 10-yr risk >20% for any fracture, >3% for hip; consider when initiating glucocorticoids in pts with med-high risk of fracture (*ACR 2017;69:1095*).
    - PO alendronate 75mg or PO risendronate 35mg weekly for 5-10 yrs. Avoid if GFR<30. Provide strict instructions to prevent pill esophagitis: take on empty stomach w/ full glass of water, sit upright and wait 30 min prior to taking other meds or food.
    - Monitor with DXA scan q1-2 yrs until findings are stable (*AACE guidelines*)
  - **Denosumab** (monoclonal antibody with affinity for RANKL) – option for patients with renal dysfunction or other contraindication to bisphosphonates, q6month injection; treat with teriparatide first if severe osteoporosis
  - **Anabolic agents** (*teriparatide*): recombinant PTH, *abaloparatide*: PThrP analog – for severe osteoporosis and/or for patients with contraindications to bisphosphonates, daily SQ injection

Hawra Al Lawati
HYPERCALCEMIA

***MAKE SURE TO CORRECT CALCIUM FOR ALBUMIN: Corrected Ca = Serum Ca + 0.8 x (4-Alb)***

**Definition:**
- Mild (corrected Ca < 12)
- Moderate (corrected Ca 12-14)
- Severe (corrected Ca >14)

**Clinical Signs and Symptoms:**
- **MSK ("bones")** → Osteitis fibrosa cystica (1° hyperPTH), bone pain, weakness; **renal ("stones")** → Polydipsia, polycystosis, nephrolithiasis; **neuropsych ("overtones")** → fatigue, depression, anxiety, cognitive dysfunction to confusion, stupor, coma; **CV** → brady, short QTc, AV block, valve/vessel calcification

**Diagnostic Approach:**

**Management:** (BMJ 2015;305:h2723, NEJM 2005;352:373)
- In general, asymptomatic mild-moderate hyperCa can be managed conservatively as outpatient; patients with symptomatic or severe hyperCa (>14) should be admitted for treatment and endocrine consult.
- **Conservative measures:** avoid contributory meds; oral hydration; oral PO4 repletion to 2.5-3.0 (IV could lead to hypoCa)
- **Volume resuscitation:** patients are typically very dehydrated; bolus NS then gtt @ 200-300cc/hr with goal UOP 100-150cc/hr
- **Loop Diuretics:** use **ONLY** if concurrent HF, CKD (and only once volume replete); otherwise, avoid, as they can worsen dehydration
- **Calcitonin:** 4-8U/kg SC BID for 48 hours (will lower Ca by 1-2mg/dL). Tachyphylaxis usually occurs within 48-72h.
- **Bisphophonates:** best studied in malignancy; zoledronate >> pamidronate (except in MM; more ATN). Takes 2-4d.

**Side effects:** hypoCa (check 25-OH-D & replete prior to admin), flu-like illness. Reduce dose if CKD. Avoid if CrCl < 30.
- **Denosumab:** monoclonal Ab against RANKL → blocks pre-osteoclast maturation; studied in bisphosphonate-refractory hyperCa
- **Other:** Glucocorticoids (effective in calcitriol [1,25-OH-vit D]-mediated etiologies), HD (if refractory or life-threatening)
  - **Special considerations for 1° hyperPTH:** (JAMA Surg 2017;152:878, JCEM 2014;99:3607) Surgery is curative. Indicated if (a) symptomatic OR (b) asymptomatic with Ca > 11.5, osteoporosis/vertebral fracture, CCl < 60, nephrolithiasis, or age < 50. If poor surgical candidate, consider cinacalcet, bisphosphonate, tamoxifen

HYPOCALCEMIA

**Clinical Signs/Symptoms:** (BMJ 2008;336:1298) Neuromuscular (paresthesias, muscle cramps/spasms, tetany, Trousseau sign [carpal spasm with BP cuff inflation; 94% sens; 99% spec], Chvostek sign [circumoral muscle twitch with facial nerve tapping; poor sens; 85% spec]; seizures; ↑ QTc

**Diagnostic Approach:**

**Management:**
- **Replete magnesiam** (hypoca can be hard to correct without first correcting hypoMg → causes PTH resistance and ↑ secretion)
- **IV Ca repletion:** If severe (corrected Ca < 7.5, iCa < 1), symptomatic, or prolonged QT
  - 1-2g IV Ca gluconate OR CaCl2 (in codes; via central line, risk of skin necrosis if extravasates) over 10-20 min
  - IV therapy ↑ serum levels for only 2-3h (chase w/ gtt or PO); telemetry recommended w/ IV repletion as arrhythmias may occur
- **PO Ca repletion:** If Ca > 7.5 or ASx; 1.5-2 g elemental Ca/day in divided doses; Ca citrate better absorbed vs CaCO3 esp if pt on PPI
- **Vitamin D repletion:** 800-1000IU Vit D3 daily (if severely deficient, start with 50,000IU Vit D2 or D3 qweek x 6-8wks); in patients with poor conversion of 25-OH-D (e.g., hypoparathyroidism, CKD), use calcitriol (starting dose: 0.25mcg PO QD)
**Thyroid Disorders**

### IN PATIENT TFTS
- If thyroidal illness is suspected, TSH alone is inadequate — should also test for FT4 and T3. Half-lives: TSH 1hr, T4 7d, T3 1d.
- **Sick Euthyroid**: Alterations in thyroid function due to nonthyroidal illness rather than 1st endocrine disorder; may be adaptive (anti-catabolic); no indication to treat; most likely cause of abnormal TFTs among inpatients (Lancet Diabetes Endocrinol 2015;3:816).
  - **Typical pattern**: (1) Acute illness: ↓↓ T3, ↓ T4, ↓ fT4, ↓ fTSH. (2) Recovery phase: ↑ TSH → recovery of T4, T3.
  - **Sequential T4** should ↑ in recovering sick euthyroid but remains low in 1st hypothyroid. rT3 can differentiate central hypothyroidism (↓) from sick euthyroid (↑), but rarely needed. FT3 is useless except to dx hyperthyroidism w/ altered TBG.
  - **NB**: Undetectable TSH (<0.01) suggests true hyperthyroidism, and TSH>20 + Low T4 suggests true hypothyroidism.
- Biotin supplementation can interfere with TSH and other assays, ensure pt off biotin 1 week before testing.
- ↓ TSH also seen with glucocorticoids, dopamine, dobutamine, octreotide, ↑ HCG levels.

### HYPOTHYROIDISM
**Signs/Sx**: Fatigue, cold intolerance, ↑ weight, constipation, dyspepsia, dry skin, myalgias, abnl menses, cognitive dysfunction, depression, carpal tunnel, bradyarrhythmia, diastolic HTN, delayed relaxation of DTRs, lateral eyebrow thinning, non-pitting edema, macroglossia, froggy voice

**Labs**: ↑ LDL, ↑ triglycerides, ↓ Hgb (↓ MCV), ↑ CPK, ↓ Na

**Primary**

<table>
<thead>
<tr>
<th>TSH</th>
<th>FT4</th>
<th>Total T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Subclinical*</td>
<td>High/normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Differential Dx:**
- 1°: Hashimoto's (most common, + TPO ab), infiltrative dz (hemochromatosis, sarcoid), transient thyroiditis (lymphocytic, granulomatous, postpartum), drugs (lithium, amio, TKIs, contrast), iatrogenic (thyroidectomy, radiation), iodine deficiency
- 2°: see Hyperpituitarism section

**Hyper T4 requirement**: pregnancy, estrogen (↑ THBG), weight gain, malabsorptive states (e.g., celiac dz), nephrotic syndrome (↑ excretion), rifampin, phenytoin, carbamazepine, phenobarbital

**Treatment**:
- Levothyroxine (T4): starting dose ~1.6 mcg/kg/d PO (use 25-50 mcg QD for elderly or comorbidities); IV = 50-75% PO
- Take on empty stomach 1h before eating/meds; several hrs apart from PPI, aluminium hydroxide, iron, cholestyramine
- Check TSH q6wks and adjust dose by 12-25 mcg until normal TSH achieved

### HYPERTHYROIDISM
**Signs/Sx**: ↓ weight, ↑ appetite, tremor, palp, heat intolerance, hyperdefection, weakness, dyspnea, sweating, anxiety, emotional liability, urinary freq, abnl menses, osteoporosis, aib, systolic HTN, lid lag, exophthalmos and pretibial myxedema (Graves' only), hyperreflexia, thyroid bruit, "apathetic thyrotoxicosis" = depression, weakness, seen in elderly

**Labs**: ↓ HDL, ↑ LDL, ↓ Hgb (ml MCV), ↑ Ca, ↑ AlkP, ↑ Glu, ↑ Ca (bone resorption and hypervolemia from insensible losses)

**Primary**

<table>
<thead>
<tr>
<th>TSH</th>
<th>FT4</th>
<th>Total T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>High/normal</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Subclinical</td>
<td>Low/normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Differential Dx:**
- 1°: Graves' disease (most common, T3:T4 ratio >20-25), toxic adenoma, toxic multinodular goiter, transient thyroiditis (lymphocytic, granulomatous, postpartum), drugs (amio, contrast, lithium), iatrogenic (radiation, palpation), exogenous T3 or T4 ingestion (low thyroglobulin), HCG-mediated, struma ovarii
- 2°: see Hyperpituitarism section

**Workup**: TSI and TBII (Graves'), RAIU (not for amio-induced or if recent iodine e.g. IV contrast), thyroid ultrasound with Doppler

**Treatment**: βB for adrenergic symptoms (e.g. metop, propranolol)
- Graves' disease: thionamides (methimazole > PTU due to hepatotoxicity w/ PTU), radiiodine (risk of ↑ ophthalmopathy, surgery. Monitor total T3 and T4 q6wks.
- Toxic adenoma or multinodular goiter: radioiodine, surgery, less commonly thionamides

### THYROID CRISES (COMA / STORM)

**COMA**
- Hypothermia, bradycardia, ventricular arrhythmias, HypoTn
- Most common cause of death is hypercapnic resp failure
- Careful with IVF if hypoNa. Patients are hypometabolic; use lower drug doses at lower frequency, avoid MS-altering meds.
- **Test and Empirically Treat AI**: If concern for AI, give hydrocort 50-100mg before thyroid hormone (if concomitant AI, replacing thyroid hormone first will catalyze residual cortisol and cause hypoTn/death)
- **Tx**: T4 12.5-50mcg IV QD in elderly or at risk for MI, up to 200mcg if sick and young. T3 (5-10mcg Q8H) only given if pt is critically ill (T4 conversion to T3 takes several days), give only with endo guidance, can cause rebound hypermetabolism
- **Recheck FT4 in 3-7d; if giving T3, monitor peak levels**

**STORM**
- Hyperthermia, tachycardia, tachy-CM, atrial arrhythmias, HyperTn
- Treat the underlying precipitant
- Patients are hypermetabolic and will clear drugs quickly
- **BB**: Only propranolol decreases T4→T3 conversion, may require high doses (2g/day). Titrate to sx and HR (i.e. <80).
- **Anti-Thyroid Meds**: Only stop formation of new hormone, not release of stored hormone. Methimazole (20mg Q4-Q6) is preferred unless pt is critically ill. PTU (200mg Q4-Q6) decreases T4→T3 but higher rates of fulminant hepatic necrosis. Iodine (100-250mg Q6-Q6H) must be given at least 1hr after thionamide; can cause Jod-Basedow in toxic adenoma and Wolff-Chaikoff in Graves.

### AMIODARONE-INDUCED THYROID DISEASE
Check TSH prior to tx, q4-6 mo while on amio, and for 1 yr after amio discontinued.
- Typical response to amio acutely: ↑ TSH (2-3x nl), ↑ T4 and FT4, ↓ T3, ↑ rT3 → levels return to normal in 3-6 months
- May cause hypothyroidism (due to Wolff-Chaikoff effect or destructive thyroiditis) OR hyperthyroidism (Type 1 → ↑ synthesis due to ↑↑ iodine load; Type 2 → direct toxicity of drug on thyroid gland, causing thyroiditis and stored hormone release)
Adverse Drug Reactions (ADRs): (J Allergy Clin Immunol. 2010; 125: S126)

- **Type A = Predictable** (~85-90%): dose-dependent, related to drug’s known pharmacological action, & occur in otherwise healthy pts if given sufficient dose / exposure (e.g., diarrhea from antibiotics, gastritis from NSAIDs, aminoglycoside nephrotoxicity)
- **Type B = Unpredictable** (10-15% of ADRs): usually dose independent; unrelated to pharm action; occur only in susceptible pts
  - **Drug Intolerance** (undesirable pharmacologic effect @ low / subtherapeutic doses without underlying disorder of metabolism/excretion/bioavailability of drug) – e.g., tinnitus after aspirin
  - **Drug Idiosyncrasy** (abnormal effect caused by underlying abnormalities of metabolism/excretion/bioavailability) – e.g., hemolysis after antioxidant drug in G6PD deficiency
  - **Pseudo-allergic reaction - Anaphylactoid** (drug causes direct release of mediators from mast cells/basophils) – e.g. flushing during vancomycin infusion, exacerbation of asthma/rhinitis w/ aspirin in AERD
  - **Drug Allergy** (immunologically mediated Hypersensitivity Reactions – see table below)

### Hypersensitivity Reactions (Gell and Coombs Classification):

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction</th>
<th>Mechanism</th>
<th>Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Immediate, min - 1 hr)</td>
<td>IgE</td>
<td>Ag-IgE complex-mediated activation of mast cells &amp; basophils → release of histamine, prostaglandins</td>
<td>Anaphylaxis (WHEAL: Wheezing, Hives, Edema [laryngeal], Angioedema, Low BP)</td>
</tr>
<tr>
<td>II (Delayed, variable)</td>
<td>Cytotoxic</td>
<td>Ab binds to Ag-coated cells → cell injury</td>
<td>Hemolysis, thrombocytopenia, neutropenia</td>
</tr>
<tr>
<td>III (Delayed, 1-3 wks)</td>
<td>Immune-complex</td>
<td>Ag-Ab complex deposition in vessels/tissue → complement activation and inflammation</td>
<td>Serum sickness, arthus reaction, vasculitis</td>
</tr>
<tr>
<td>IV (Delayed, 2-7 days)</td>
<td>T Cell-mediated</td>
<td>Ag exposure activates T cells → cytokine release leading to tissue injury</td>
<td>Contact dermatitis, SJS/TEN, DRESS</td>
</tr>
</tbody>
</table>

### Desensitization:
- Drug is administered in increasing doses over hours → mast cells/basophils eventually become unreactive to Ag activation. Once desensitized, pt can safely receive drug at usual intervals for a **continuous period**
- Only induces **TEMPORARY tolerance**. After drug is stopped, desensitization ends over days-weeks
- ONLY appropriate for **Type I HSRs (NOT for Type II-IV)**
  - Consult Allergy/Immunology for advice on dosage, admin and monitoring instructions, management of acute reaction
  - Perform in ICU except low-risk oral desensitization w/ hx of mild rxn: ASA, Bactrim, allopurinol, clopidogrel

### Drug Provocation Testing (i.e., Test Dose):
- Used to assess pt’s reaction to a drug to which they may be allergic (i.e., to exclude drug allergy)
  - Absence of reaction to test dose → drug can be safely administered. **Monitor for delayed Type 4 HSR.**
  - Does NOT assess cross-reactivity of structurally-related drugs
  - **Contraindication:** h/o severe non-IgE mediated HSR (i.e., Type II-Type IV)

#### Test Dose Procedure:
- **Step 1:** Test dose is 1/10 of treatment dose for IV meds; 1/4 of treatment dose for oral meds (Order name: “Test Dose”)
  - VS (by RN): before, 30mins, and 60mins after test dose
  - Orders: Epi 1:1000 IM (0.3 mg) PRN, Benadryl 50 mg IV/PO PRN
  - Hold: beta blockers (inhibit Epi) and ACE inhibitors (increased risk of allergic rxn) on day of procedure
  - Positive reaction: page the Allergy fellow (p13042) and file incident report
- **Step 2:** If asymptomatic after 60 minutes, administer full treatment dose
  - VS (by RN): 30mins, 60mins after full dose

### Common Drug Reactions:
- **PCN & Cephalosporin Allergy (Type I HSR)**
  - PCN allergy highly over-reported: 90% patients w/ h/o PCN allergy can tolerate PCN (J Allergy Clin Immunol. 2010; 125: S126)
  - Cross-reactivity between B-lactams often mediated by R-group sidechain (J Allergy Clin Immunol 2015;3:1006)

### B-Lactams by shared R-groups:

<table>
<thead>
<tr>
<th>R-Groups</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red</td>
<td>Amoxicillin, Ampicillin</td>
</tr>
<tr>
<td>Blue</td>
<td>Ceftriaxone, Ceftazidime</td>
</tr>
<tr>
<td>Purple</td>
<td>Cefadroxil, Cephalexin</td>
</tr>
<tr>
<td>Green</td>
<td>Cefpodoxime, Aztreonam</td>
</tr>
<tr>
<td>Brown</td>
<td>Cefotaxime</td>
</tr>
</tbody>
</table>

**Jessica Plager**  
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Allergy & Immunology

**Drug & Contrast Allergies**

- **Taxanes/Platinum-based Chemotherapy (Type I HSR)**
  - Must differentiate *infusion reaction* (SIRS response to chemo agent) from anaphylactic reaction (i.e., Type I HSR)
  - Rates differ between agents; infusion reaction occurs in 19.5% with carboplatin and up to 30% with taxanes (NEJM 1995;332:1004); increased frequency of infusion reactions occur with subsequent infusions (AAAI 2009; 102: 179)
  - Refer patient to Chemotherapy Allergy Clinic for skin testing or desensitization

- **Allopurinol (non-Type I HSR)**
  - **Allopurinol Hypersensitivity Syndrome (AHS):** rash, fever, hepatitis, and/or renal impairment after exposure. Usually occurs 4-8 wks after initiation (Drug Saf 2013;36:953)
  - In patients of East Asian descent, unless initiating for TLS, consider sending HLA-B*5801 genotyping (high risk for AHS)
  - Can also lead to drug-mediated ANCA vasculitis or SJS/TEN

- **Aspirin/NSAID**
  - 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, refer to Allergy/Immunology for outpatient desensitization.
  - **Aspirin Exacerbated Respiratory Disease (AERD), aka Samter’s Triad:** chronic medical condition defined by triad of asthma, rhinosinusitis w/ nasal polyps, and ASA/NSAID sensitivity (usually nasal congestion, bronchospasm). Tx: ASA desensitization

- **IV Radiocontrast Media (RCM):** (ACR guidelines; 2018; 10.3: 22)

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Pathogenesis</th>
<th>Epidemiology</th>
<th>Presentation</th>
<th>Clinical pearls</th>
<th>Pre-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoallergic (Anaphylactoid)</td>
<td>RCM directly stimulates mast cells / basophils (NB: minority of pts have + skin tests indicating that minority of pts have IgE mediated rxn)</td>
<td>1-3% patients with ionic RCM &amp; 0.5% pts w/ non-ionic RCM. Severe rxs occur in 0.22% for ionic RCM, 0.04% for non-ionic RCM</td>
<td>Immediate pruritus, urticaria, angioedema, airway obstruction, HoTN, abdominal pain</td>
<td>No evidence that iodine levels in seafood or topical solutions are related to adverse events from RCM; Seafood allergy is not a contraindication to RCM. Oral contrast is NOT contraindicated in a patient with IV contrast allergy, though rarely can cause a reaction</td>
<td><strong>Elective</strong> (13 h protocol) -Prednisone 50 mg PO @ 13, 7, &amp; 1 h prior AND -Diphenhydramine 50 mg PO 1 h prior <strong>Accelerated</strong> (4-5 h protocol) -Methylprednisolone 40 mg IV now &amp; q 4 until scan AND -Diphenhydramine 50 mg IV 1 h prior <strong>Emergent</strong> -Methylprednisolone 40 mg IV 1 h prior AND -Diphenhydramine 50 mg IV 1 h prior</td>
</tr>
<tr>
<td>Delayed</td>
<td>T cell mediated</td>
<td>2% of patients</td>
<td>&gt;1 hr – 1 week -Usually mild, skin eruption -Rare: SJS, TEN</td>
<td>Tx: Supportive care</td>
<td></td>
</tr>
</tbody>
</table>
**Angioedema** *(NEJM; 2008; 359: 1027)*

- **Definition:** Localized non-pitting swelling of the skin or mucosal tissue due to interstitial edema; may affect face, extremities, genitals, bowels. Often asymmetric. Occurs in min-hrs and resolves within 24-48hrs.

- **Classification/Etiology:**

<table>
<thead>
<tr>
<th>Type</th>
<th>Urticaria?</th>
<th>Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast Cell</td>
<td>Usually</td>
<td>ASA, NSAID, CCB, platinum-based chemo, B-lactams, metoprolol, siro/everolimus, risperidone etc</td>
</tr>
<tr>
<td>Histamine</td>
<td>Rarely</td>
<td>Idiopathic / spontaneous</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Never</td>
<td>ACE/ARB: 0.1-0.7% pts on ACE; may occur any time during therapy and last 6 mo after cessation</td>
</tr>
</tbody>
</table>

- **Treatment:** ALL comers: ABCs, secure airway
  - If urticaria → identify & remove exposure → tx with antihistamines, glucocorticoids, +/- epi if breathing affected
  - If no urticaria →
    - On ACE-I → stop ACE inhibitor → supportive care (if severe, consider icatibant)
    - Known hereditary or acquired angioedema → Page allergy for C1-inhibitor, icatibant. FFP is 2nd line
    - Not on ACE-I, no known disorder → antihistamines & glucocorticoids

- **Hereditary angioedema:** autosomal dominant C1 esterase deficiency/dysfunction. Screen: ↓ C4


- **Definition:** Acute, life-threatening, multi-system syndrome caused by type I HSR (IgE-mediated)
- **Causes:** meds (beta-lactams, ASA/NSAIDs), latex, food, insect venom, cold/heat, exercise
- **Clinical Manifestations:** skin/mucosal swelling, rash/urticaria, bronchospasm/stridor, GI sx (N/V/D/pain), angioedema, HoTN/shock
  - Associated with biphasic reaction in 4-23% pts → return of symptoms 8-72 hrs after initial symptom resolution
- **Diagnostic Criteria:** one of three must be met
  1. Skin/mucosal involvement AND either respiratory compromise OR reduced BP after exposure to POTENTIAL allergen
  2. Two or more of the following after exposure to LIKELY allergen: skin/mucosa swelling, respiratory sx, HoTN, GI sx
  3. Low BP (SBP<90 or >30% drop from baseline)
- **Labs:** consider histamine (within 10-30 min of symptom onset) and tryptase (within 15 min-3 h of symptom onset and 24h after symptoms resolve to assess baseline).
- **Treatment:** establish and maintain airway, administer oxygen/IVF
  - Epinephrine: Only medication that reverses airflow obstruction & prevents cardiovascular collapse
    - **Dosing:** 0.3-0.5mg IM/SQ
    - **May repeat:** Dosing: (1mg/mL)
      - **Clinical:** Ocular itching/watering/burning
      - **Diagnosis:** Sneeze, rhinorrhea, post-nasal drip, cough
      - **Treatment:** Topical antihistamines, glucocorticoids, +/- epi if breathing affected
      - **Adjunctive Agents:** Albuterol for bronchospasm (stacked nebs x 3), H1 blockers for hives/pruritis (diphenhydramine 50mg IV/IM, glucocorticoids to prevent biphasic reaction (methylprednisolone 125mg IV QD x 2)

**Common Allergic Disorders by Organ System**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Epidemiology / Path</th>
<th>Presentation</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT</td>
<td>Allergic conjunctivitis: IgE mediated mast cell degranulation</td>
<td>Ocular itching/watering/burning</td>
<td>Clinical</td>
<td>Topical antihistamine w/ mast cell stabilizer</td>
</tr>
<tr>
<td></td>
<td>Allergic rhinitis: Seasonal (pollen) or perennial (dust miles, cockroach, mold, dander)</td>
<td>Sneeze, rhinorrhea, post-nasal drip, cough</td>
<td>Clinical</td>
<td>Intranasal glucocorticoid, nasal antihistamine</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Acute: &lt;4 wks, Subacute: 4-8 wks, Chronic: &gt;8 wks</td>
<td>Nasal congestion, obstruction, tooth/ sinus pain</td>
<td>CT sinus if chronic</td>
<td>Acute: supportive +/- abx Chronic: nasal steroids/ saline lavage</td>
</tr>
<tr>
<td>Pulm</td>
<td>Hypersensitivity pneumonitis: Acute (4-6hrs), subacute, chronic (only partially reversible)</td>
<td>Cough, SOB, fever, if chronic, fatigue &amp; wt loss</td>
<td>IgG Abs, PFTs, HRCT, BAL</td>
<td>All: Avoid antigen, Subacute/chronic: steroids +/- immunosup</td>
</tr>
<tr>
<td></td>
<td>Occupational lung disease: Exposure to mineral dust / metal (major: asbestos, silica, coal, beryllium)</td>
<td>DOE, cough, chest tightness, wt loss</td>
<td>CXR, high-res CT</td>
<td>Avoid exposure, O2, pulm rehab, bronchodilators, oral steroids for beryllium</td>
</tr>
<tr>
<td>GI</td>
<td>Eosinophilic esophagitis or gastroenteritis: Higher rates in young males 3 subtypes w/ unique features Food allergies common</td>
<td>Food impaction, dysphagia, GERD failing PPIs</td>
<td>Dx criteria: 1. Symptoms 2. ≥ 15 eos/HPF on endoscopy 3. Exclude other cause</td>
<td>Eliminate allergens, PPIs, topical glucocorticoids, esophageal dilation if stricture or fail conservative tx</td>
</tr>
<tr>
<td>Skin</td>
<td>Atopic dermatitis (eczema): Atopic triad – eczema, allergy, asthma 2-fold increase in depression/SI compared to general pop (J Am Acad Derm 2019:80:402)</td>
<td>Dry skin, pruritis, excoriation Skin flexures most common in adults, can affect any area</td>
<td>Clinical</td>
<td>Topical steroid, emollient 2nd gen oral antihistamines ineffective (Cochrane 2019 CD012167)</td>
</tr>
</tbody>
</table>
### Allergy & Immunology

#### Delayed Rash & Organ Injury

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dx</th>
<th>Description</th>
<th>Onset</th>
<th>Culprit Meds</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>DILI (Drug-Induced Liver Injury)</td>
<td>Acute liver injury (hepatocellular or cholestatic). Other sx include fever, rash, eosinophilia. May progress to acute liver failure.</td>
<td>5-90 days (peak &gt;4 weeks)</td>
<td>Allopurinol Sulfamethoxazole Augmentin Macrolides AEDs Vit K antagonists</td>
<td>Unclear benefit of systemic steroids, NAC</td>
</tr>
<tr>
<td>Kidney</td>
<td>AIN (Acute Interstitial Nephritis)</td>
<td>AKI. 10% with triad of fever, rash, eosinophilia. Urine eos: Sens 40%, Spec 72% (NOT a good test).</td>
<td>&gt;2-3 weeks</td>
<td>Penicillins Cephalosporins NSAIDs PPIs</td>
<td>Usually supportive; consider glucocorticoids if refractory</td>
</tr>
<tr>
<td>Skin</td>
<td>Morbilliform rash</td>
<td>~95% of skin reactions. Pruritic, maculopapular rash</td>
<td>4-12 days (2-3 d if prior exposure)</td>
<td>Aminopenicillins Cephalosporins Other antibiotics AEDs</td>
<td>Symptomatic tx of pruritus (oral H1 blocker, anti-itch cream)</td>
</tr>
<tr>
<td></td>
<td>AGEP (Acute Generalized Exanthematous Pustulosis)</td>
<td>Many pinpoint pustules that start in intertriginous regions, facial edema, fever, neutrophilia. <em>May resemble sepsis without infectious source</em>. Overexpression of IL-36 (J Invest Dermatol 2018;18:32779)</td>
<td>Hrs-2 days (antibiotics), 4-12 days (other drug)</td>
<td>Aminopenicillins Pristinamycine Diltiazem Hydroxychloroquine Quinolones Sulfamethoxazole Terbinafine</td>
<td>Symptomatic tx of pruritus (as above); topical steroids; systemic steroids vs cyclosporine if severe/systemic (case reports)</td>
</tr>
<tr>
<td></td>
<td>SJS/TEN (Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis)</td>
<td>Targetoid lesions, bullae, sloughing, erosions, desquamation, skin pain. Mucosal involvement in ~90% (ocular, oral, GI, urogenital, tracheobronchial necrosis, tubular nephritis). High fever. Up to 30% mortality. SJS: &lt; 10% BSA involved. TEN: &gt;30% BSA involved. Note: BSA measured in sloughed skin</td>
<td>1-3 weeks</td>
<td>MCC is Bactrim (J Invest Dermatol 2018;138:2315), Allopurinol Lamotrigine Sulfamethoxazole Phenyooin Carbamazipine Nevirapine Phenobarbital NSAIDs</td>
<td>IV fluids (similar to burns), monitor for infection, nutritional support. Consider: IVIG, cyclosporine, steroids, etanercept (J Clin Invest 2018;128:985)</td>
</tr>
<tr>
<td>Multi-Organ</td>
<td>DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)</td>
<td>Morbilliform eruption, facial edema, purpules, exfoliative dermatitis, tense bullae, lymphadenopathy w/ systemic organ involvement (liver, kidney, lung, heart, thyroid) Leukocytosis with eosinophilia, fever, elevated inflammatory markers. Assoc w/ viral reactivation (HHV6, HHV7, EBV, CMV). DRESS scoring system linked <a href="#">here</a>.</td>
<td>2-6 weeks (unlikely if med taken for &gt;3mo)</td>
<td>Carbamazipine Oxcarbazepine Allopurinol Lamotrigine Salazopyrine Sulfasalazine Phenyooin Vancomycin</td>
<td>Consider glucocorticoids if severe organ involvement. If no response, IVIG. Antivirals if herpesvirus reactivation</td>
</tr>
<tr>
<td>Drug-Induced Vasculitis</td>
<td>Purpura, arthralgias, myalgias. May have kidney, lung involvement. <em>May be PANCA</em>+, ANA+, anti-histone+, anti-cardiolipin+, ↓C4</td>
<td>7-10 days</td>
<td>Propylthiouracil Other antithyroid Anti-TNFa Cefotaxim Minocycline Hydralazine</td>
<td>If internal organ involvement, 1mg/kg/day prednisone x 4-8 wk, then taper over 6-12 mo</td>
<td></td>
</tr>
</tbody>
</table>

**General Treatment Principles** *(Immunol Allergy Clin North Am 2014;34:473)*

- For all reactions: cessation of offending agent, supportive care, consider derm consult for frozen section “jelly roll” vs biopsy of severe skin reaction
- SJS/TEN: consider burn, ophtho, OB/GYN consults for evaluation of mucosal involvement
Primary Immunodeficiency (PI)

- **Definition:** relative susceptibility to infection w/o clear 2° cause (e.g., HIV, immunosuppression, rheum disease, infection)
- **H&P:** developmental hx, fam hx, and exam w/ attn to syndromic features, age at onset, frequency & type of infections
- **General Principles of Management:** Vaccination, antibiotic prophylaxis, IVIG, Hematopoietic SCT

---

**Immune Localization of Prototypical Primary Immunodeficiency Syndromes**

<table>
<thead>
<tr>
<th>Complement</th>
<th>Phagocytic</th>
<th>T-cell Subsets</th>
<th>Combined</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C9, factor D, or Properdin</td>
<td>CGD, LAD, SCN</td>
<td>Chediak-Higashi</td>
<td>SCID, WAS, DiGeorge,</td>
<td>IgA Def, CVID, XLA, Hyper-IgM</td>
</tr>
</tbody>
</table>

**Definition**

Deficiency in one of the 3 complement pathways (classical, lectin, and alternative) Usually autosomal recessive

**Signs & Symptoms**

Sinopulmonary infection and meningitis from encapsulated bacteria, esp *Neisseria* in MAC def (C5-C9) and properdin. SLE seen in C1-C4 def

**Advanced W/U**

CH50 (test for ability of plasma to lyse sheep RBC). Note: cryos can cause false + AH50 for properdin, factor B, factor D

---

**Phagocytic Defects**

Defects in neutrophil production, destruction, or dysfunction

**Signs & Symptoms**

Bacterial and fungal SSTI and PNA Not viral

**Advanced W/U**

CGD: superoxide production by DHR fluorescence; nitroblue tetrazolium test

---

**T cell Subset Defects**

T cells have different phenotypes (Th1, Th2, Th17, Treg) based on the cytokines they secrete

**Signs & Symptoms**

Mutations in cytokines/receptors predispose to specific infections

**Advanced W/U**

Th1 (Interferon-γ IL-12 defects): Mendelian Susceptibility to Mycobacteria (MSM) Th17 (IL-17A/F and IL-22): mucocutaneous candidiasis

**Cytokine and receptor gene sequencing** (PCR or Exome)

*In vitro* assays can show signaling or cytokine production defects

---

**Combined T and B cell**

Diverse set of defects in T cell subset frequency or function; since T cell help is required for B cell Ab production, a humoral defect is often also seen, hence "combined"

**Signs & Symptoms**

Predominantly neonatal onset and severe Viral infections, particularly herpesviruses

**Advanced W/U**

B cell testing: as above

**T cell testing:**

*Number:* flow cytometry

*Function:* anergy/prolif testing (Candida)

Note: r/o HIV, autoimmune, malignancy

---

**Antibody Deficiency**

CVID (most common PID):
1) Hypogammaglobulinemia
2) Recurrent sinopulmonary infxn
3) Inadeq Ab response to vaccine challenge

**Signs & Symptoms**

IgA deficiency: low IgA X-linked Agamagamma: absent B cells

**Advanced W/U**

**B Cell Testing:**

*Number:* SPEP, serum Ig, flow cytometry

*Function:* vaccine response

- Protein: tetanus titer
- polysaccharide: PPSV23 titer

Note: Ig levels should be measured off IVIG or at trough

---

**Anti-Cytokine Auto-Antibodies**

Abs against Interferon-γ: seen in SE Asia (NEJM 2012;367:725)

**Signs & Symptoms**


**Advanced W/U**

Abs against Interferon-γ: disseminated atypical mycobacterial dz and OI's

**Abs against IL-17A/F and IL-22:** mucocutaneous candidiasis

**Non-CLIA research testing**
Neurology

Altered Mental Status

Causes of AMS: Major buckets: 1) Metabolic, 2) Infectious, 3) Drugs/Toxins/Medications, 4) Primary CNS, 5) Delirium

• Pathophysiology: Diffuse neuronal dysfunction (due to metabolic/structural factors) causing dysfunction of ascending reticular activating system which connects midbrain/pons to cortex and controls arousal/attention.

• Acute (min-hr): trauma, vascular, 1CP, meds/toxins, metabolic; Subacute (hr-day): infectious, AI, neoplastic, metabolic

• AEIOU TIPS: Alcohol (intox, HE, withdrawal, DTs, Wernicke’s); Arrhythmia, Electrolyte/Endocrine (gluc, thyroid, adrenal), Infection, Oxygen (hypoxia, hypercarbia); Overdose (opiate), Uremia/Urinary retention, Trauma/Tumor/ITP/Temp, Iatrogenic (meds - anticholinergics, bzs, anti/dopaminergics, etc), Psych/Poison, Seizure (incl. post-ictal)/Stroke/Syncpe

Approach to Acute AMS:

• ABCs & Vitals:
  o If unresponsive & pulseless call Code Blue; if hypoxemic & GCS < 8 call Rapid Response & RICU for intubation
  o Check RR (hypercarbia – opiates, COPD), BP (hypertensive encephalopathy), EKG (hypoperfusion, arrhythmia)

• Bedside Exam:
  o Establish arousal (GCS), command following, attention (days of wk backwards); look for focal weakness (stroke).
  o If not following commands: brainstem reflexes: pupils (CN 2/3), Doll’s eyes (CN 3/4/6/8), corneals (CN 5/7), symmetric grimace (CN 7), cough/gag (CN 9/10); withdrawal to pain in all extremities, posturing (JNPN 2001;71:13)
  o Pupil clues: absent light rfx, (intracranial bleed/mass, morphine, anoxic encephalopathy, eye drops); b/l fixed, dilated (severe anoxia); b/l fixed, dilated (hemiation w/ CN III compression); pinpoint (narcotic, ICH)
  o Trauma (c-spine), asterixis/myoclonus (metabolic), volume status, infectious/meningeal signs, cherry red coloration (CO), toxidromes (e.g. thyrotoxicosis: ↑ T, BP, HR; ↑CP; ↑HR, ↑BP, papilledema, N/V; heat stroke), tongue bite, incontinence (sz), tenderness (hip fx, fat embolus)

• STAT Orders:
  o ALWAYS check fingerstick glucose for acute change in mental status
  o Consider: ABG; if focal sign, c/f stroke, non-con head CT (see Stroke)

• Primary/Acute AMS Work-Up:
  o Review meds: hypoglycemic (insulin, benzo, opioid, steroid, anticholinergic (TCA), antihistamine, antihypertensive (methyl dopa, reserpine), antiepileptic, OTC’s, anti/dopaminergics, antibiotics (esp w/AKI, incl. cefepime, other CSP’s, PCN’s, FQs (Neurology 2016;86:963))
  o Check Chem 10, LFTs, CBC w/diff (infxn, PV, blast crisis, high/low plts), lactate, NH3, B12, TSH/FT4, VBG, UA/Uo/Cx/Bx, CXR, bladder scan (retention)
  o Consider ESR, CRP, drug levels, serum/urine tox screen, CK (rhabdo/NMS), nutritional deficiency (B1, B12)
  o Consider TTP (classic: jptls, anemia, renal failure, fever, neuro changes). Check LDH, STAT smear for schistocytes
  o Consider substance use or withdrawal, serotonin syndrome (elevated T, HR, BP, RR, mydriasis, hyperactive bowel sounds, hypertonia esp in LE’s; e.g. SSRI + tramadol, MAOIs, linezolid (NEJM 2005;352:1112)). neureiatric malignant syndrome (elevated T, HR, BP, RR, rigidity; e.g. antipsychotic, toxic drug levels (salicylate, valproate, dig, lithium)

• Secondary/Subacute AMS Work-Up: Consider neurology consult prior to further extensive work-up
  o Consider EEG with LTM: eval for interictal seizures or non-convulsive status if routine EEG shows seizures
  o Consider MRI w/ Gad (check CrCl first); eval for stroke, malignancy, infxn/inflammatory process, Wernicke’s
  o Consider LP: image to r/o hemiation first. Eval for cancer, infxn (if c/f infxn, neuro c/s should not delay LP or Abx)
    ▪ Standard studies: opening pressure, cell count, protein, glucose, GS/Cx
    ▪ Malignancy: cytology, flow cytometry, IgH gene rearrangement (for CNS lymphoma), paraneoplastic panel (d/w Neuro before sending)
    ▪ Infection: HSV, VZV, RPR, HIV (requires consent), Cryptococcal Ag, AFB stain/Cx, fungal Cx, Whipple PCR
    ▪ Other: AI encephalitis panel (d/w Neuro first), IgG index and oligoclonal bands (will need SPEP to compare)
  o Consider infection (HIV, Lyme, autoimmune (anti-NMDA, sarcoid), metabolic (thyroid, B1, B3, B12, Wilson’s), med (MTX), HTN enceph, PRES (tacro/cyclosporine), Addison’s crisis, porphyria (urine PBG)
  o Consider neurodegenerative disease if more chronic presentation (see Dementia)

Treatment of AMS: treat underlying cause; see disease-specific pages

• Hypovolemia: IVF: Hypoglycemia: D50 1-2 amps; Hypoxemia: O2, CXR, ABG, Seizure: protect airway, IV Ativan 2mg if GTC > 2 min, else consider Ativan 1mg; Trauma: stabilize C-spine; Meningitis: LP, empiric abx; EtOH toxicity: Thiamine 500 mg IV TID x 3d (Wernicke dosing) before sugar, then 100 PO QD; EtOH w/ft: Ativan vs Phenobarb; Opiate toxicity: Naloxone IV/IM/SC bolus q3min (0.04 dilution if mild, 0.4-2 bolus if coding); Benzo toxicity: Flumazenil 0.2 mg IV q1min (max total dose 3 mg); Hepatic encephalopathy: Lactulose 30 ml q4h titrate to BM + Rifaximin 550 mg BD, consider SBP tx (get para)

• Acute agitation: consider antipsychotics - Haldol! (IV/IM/PO, check QTc; if dystonic rnx, give benadryl 25-50 IM IV, olanzapine (SL/PO/IM; QTc less affected), quetiapine (PO, check QTc) (Psych Clin Neurosci 2013;67:323)
Avoid having to treat delirium by preventing it in your vulnerable patients:

- Minimize deliriogenic meds: anti-cholinergics, anti-histamines, benzodiazepines, opioids (optimize pain w/ non-opioids)
- Precautions: frequent reorientation, mobilize with PT/OT, OOB to chair, glasses/hearing aids, minimize lines/telemetry/catheters, early volume repletion if c/f dehydration. Avoid: room changes, physical restraints
- Anticipate circadian dysfunction: standing melatonin 3-5 mg q6PM, lights on during day and off at night, schedule rx for earlier in evening, avoid late diuresis, reduce noise.

Delirium or “Acute Brain Failure” An acute disturbance of attention with fluctuating severity over the course of the day or week & concomitant disturbance in cognition, neither of which are better explained by pre-existing/evolving neuro-cognitive disorder or newly developed reduction in arousal. Presentation is a direct consequence of a medical condition, intoxication, or withdrawal (DSM-5)

- Risk factors: Hx delirium/TIA/CVA/dementia, long hospitalization, EtOH, age >65 (~50% get delirious inpatient), infection, visual/hearing impairment, comorbidity/severe illness, depression, HIV, h/o TBI
- Associated with RR mortality of 2 ↑ institutionalization (Lancet 2014; 383:911), ↓ cognition (NEJM 2012; 367:30); leading cause of post-hospitalization decline in ADLs
- Both HYPERactive and HYPOactive delirium warrant treatment

Causes, Workup: see Altered Mental Status

Management (of HYPERactive and HYPOactive Delirium):

- Behavioral management (see top of page)
- Identify & treat UNDERLYING CAUSE w/ special attention to life-threatening conditions (see Altered Mental Status)
- Daily EKG to monitor QTc (<550msec); Daily repletion of K>4 & Mg>2 (in anticipation of pharmacotherapies)

Medication Management (for dangerous behavior ONLY): 1:1 sitter (re-orients) >> meds >> restraints (deliriogenic)

- For HYPERactive delirium/AGITATION → start PRN, escalate to scheduled (Nat Rev Neur. 2009; 5:210)
  - Haloperidol 2-5mg IV q3h PRN vs. 0.5-1mg PO q4h PRN vs. IM q1h PRN (can lead to EPS, acute dystonias in Parkinsonism)
  - Quetiapine 12.5-50 mg PO q6-12h PRN
  - Olanzapine 2.5-10 mg SL/PO/IM qd-q4h PRN
  *QTc prolong severity: Haloperidol > Quetiapine > Olanzapine; △ tx if QTc ↑ by 25-50%, QTc>500, +U-wave/T-wave flattening

- If continued severe agitation → consider Psych/Geri consult:
  - Haloperidol PRN; double PRN dose q20 min till effective; ~5-20 mg IV, consider standing or gtt (ICU);
  - Quetiapine PRN, standing 25-50 mg TID, extra dose HS.
  - Olanzapine PRN; standing 2.5-10 mg BID, extra dose HS

Discontinue when able, avoid benzos. Prolonged antipsychotic use in elderly can increase mortality.

When to Consider Psychiatry/Geri Consultation:

- Escalating/persistent delirium, Hx agitated delirium, underlying neurodegen disorder (esp PD), hx TBI
- Co-morbid EtOH or other substance use disorders
- Mult med co-morbidities (esp CV dz)/critical illness
- At risk for disinhibition/impulsivity

When to Consider Neurology Consultation:

- New focal finding <24h: Acute Stroke p21723
- New focal finding >24h: Stroke/ICU p20202
- Other concerning findings (convulsions, meningismus, e/o elevated ICP, abnl spot EEG/LP); General p20702
- Make sure to do full neuro hx and exam before calling!
Neurology

**Dementia**

**INITIAL EVALUATION:** Should almost always be in outpatient setting where can assess over time without acute illness or delirium

- Obtain collateral (family member or friend), ADLS/IADLS, assess safety, screen for depression
- Review medications for those with cognitive s/e’s (e.g., analgesics, anticholinergics, psychotropic medications, sedative-hypnotics)
- Assess cognitive impairment (MOCA > MMSE), track score at subsequent visits
- Labs: CBC, TSH, BMP; consider: RPR, Lyme, HIV, UA, hvy metals, ESR, LFT, folic acid, B1, B6, B12 (Amer Fam Phys 2005;71:1745)
- Neuroimaging: NCHCT or MRI brain (preferred) to r/o structural lesion (tumor), assess atrophy pattern, eval for vascular dementia and microhemorrhages (CAA). PET can be considered if dx unclear but often unnecessary.
- Formal neuropsych testing: pattern of deficits can suggest particular dementia syndrome; also helpful to r/o comorbid psych dz
- **Inpatient evaluation is almost never appropriate**, but should be considered for any rapidly progressing dementia syndrome or a new dementia diagnosis in pts <55 (consult Neuro for ?LP, consider RT-QuIC >14-3-3 [CJD], ACE [sarcoid], AI encephalitis, paraneoplastic encephalitis [only after d/w Neuro]), new focal neurologic deficits (?stroke), fall with head trauma or LOC
- Outpatient Neurology referral to Memory/Cognitive clinic

### DEMENTIA SYNDROMES

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Presentation</th>
<th>Exam</th>
<th>Imaging</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer Dementia</td>
<td>Amnesia earliest sx; also language and visuospatial deficits</td>
<td>Normal neuro exam (excluding MS)</td>
<td>Hippocampal (+/- global) volume loss; microhemorrhages (CAA)</td>
<td>AChE-inhibitors (mild-severe dz)</td>
</tr>
<tr>
<td>Lewy Body Dementia</td>
<td>Fluctuations in attention/alarmness</td>
<td>Parkinsonism: resting tremor (can be absent in LBD), cogwheel rigidity, bradykinesia, stooped/shuffling gait – named Parkinson’s dementia if sx present for &gt;1 yr before onset of dementia</td>
<td>Global volume loss</td>
<td>AChE-inhibitors (specifically rivastigmine) for memory sx</td>
</tr>
<tr>
<td>Frontotemporal Dementia</td>
<td>Behavioral variant most common: Changes in personality (disinhibition, apathy)</td>
<td>May have frontal release signs (non-specific)</td>
<td>Atrophy predominantly in frontal and temporal lobes</td>
<td>Sx management of autonomic dysfxn</td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>Abrupt focal sx, stepwise progression</td>
<td>Focal deficits (depending on stroke location), can include: weakness, dysarthria, ataxia, gait changes</td>
<td>Cortical or subcortical punctate lesions and volume-loss on MRI</td>
<td>Secondary stroke prevention and risk factor modification</td>
</tr>
<tr>
<td>Prion Diseases (Sporadic, Variant Creutzfeldt-Jacob Disease)</td>
<td>Rapidly progressive sx in memory, concentration, judgment</td>
<td>Myoclonus, exaggerated startle response</td>
<td>MRI: Cortical ribboning on DWI, subcortical hyperintensity on FLAIR EEG: 1-Hz periodic epileptiform discharges</td>
<td>No tx</td>
</tr>
<tr>
<td>Limbic Encephalitis (Autoimmune, Paraneoplastic)</td>
<td>Sx evolve days-weeks (more indolent possible)</td>
<td>Prominent psych features</td>
<td>MRI: FLAIR hyperintensity or contrast enhancement (esp in temporal lobe) EEG: extreme delta brush very specific</td>
<td>Immunotherapy: steroids, IVIG, PLEX, rituximab, cyclophosphamide</td>
</tr>
</tbody>
</table>

**TREATMENT:** treat sx but do not slow the progression of disease

- AChE inhibitors: Donepezil (first line), Rivastigmine (patch), Galantamine. Small effect on cognition, ADLS. Major s/e: 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 sig behavioral sx)

*Natalia Festa, Kathleen McFadden, Pavan Vaswani, Méabh O’Hare*
Neurology

Headache & Vertigo

PRIMARY HEADACHES: ~90% of benign headaches are either tension (#1) or migraine (#2)

Tension: most common (~40% population), <P> band-like, radiate forehead to occiput, mild-moderate severity, 30m to 7d. Rarely seek eval. (Am Fam Physician 2002;66:797).

• Abortives: NSAIDs. TYLENOL. Can add caffeine/bulbitalbital, antiemetic (metoclopramide, promethazine). Avoid med overuse: no more than 2 d/wk.

• Preventatives: amitriptyline, nortriptyline, SSRI, tx OSA, smoking cessation

Migraine: sx >3/5 criteria POUND (Pounding, Photo/phonophobia, Onset 4-72hrs, Unilateral, N/V, Disabling) (JAMA 2006;296:1274)

• Migraine w/aura: 1 reversible sx: visual (scintillating scotoma, visual loss/field deficit), sensory (tingling, numbness), speech lang, motor (weakness, hemiplegic migraine), basilar (dysarthria, vertigo, ataxia, diplopia), vestibular (vertigo), retinal (monocular field deficit).

Can mimic stroke. Aura without migraine headache possible (acephalgic migraine)

• Abortives: Avoid overuse HA (maximum 2d/wk). Tx early, escalate stepwise.
  - Mild/Mod pain: TYLENOL, Mg (2g IV), NSAIDs, IVF (Headache 2012;52:467)
  - Mod/Sev pain: sumatriptan (frovatriptan) 2.5mg q6h/BID (begin 2d premenstrually, for total 6d/month)

• Preventives: if >3 d/mo, long aura, or disability (Neurology 2012;78:1337)
  - BB/CCB: Propranolol 20mg Bid, Inc to 40-160mg/day. Metoprolol 25mg Bid, Inc to 50-200mg/day. Verapamil 80mg TID, increase gradually.
  - Antidepressants: Amitriptyline/nortriptyline 10mg qHS, Inc to 150mg. Venlafaxine 37.5 mg qd, Inc to 75-150 mg.
  - Anticonvulsants: Topiramate 25mg qD, Inc gradually 100mg BID. VPA 500-1500 mg qD (avoid both of these if young♀).
  - Supplements: magnesium 400mg QD, riboflavin 400mg QD, feverfew (JAMA 2006;296:1274).

• Botox: referrals required to headache clinic

VERTIGO Illusion of motion of self or world 2/2 vestib dysfxn; a/w NV, postural/gait instability. Important to distinguish: central vs peripheral (Am Fam Physician 1983;38:1625)

- Hx/Exam: duration, episodic/persistent, triggers (position Δ), prior sx, assoc sx (5D’s for brainstem: dysarthria, diplopia, dysphagia, dysphonia, dysmetria). Orthostatics. Dix-Hallpike HINTS.

- HINTS+ Exam: Everything must be c/w peripheral to be reassuring. In acute vertigo, Sn 97% Sp 85% for stroke (better than MRI!!)

- Head impulse (pt looks at your nose, passively rotate head. No saccade = ambiguous. Catchup saccade = peripheral).

- Nystagmus (unidirectional e.g. always left-beating = peripheral; L-beating in L gaze, R-beating in R gaze, any vertical = central).

- Test of skew (cover one eye then other, any vertical skew/correction = central) (Acad Emerg Med 2013;20:986)

Peripheral

Sx: Usually severe nausea, mild imbalance, hearing loss/tinnitus.

Ddx: benign positional paroxysmal vertigo (BPPV), infection: labyrinthitis, vestibular neuritis, herpes zoster oticus, Meniere’s disease, vestibular migraine, otoclerosis, trauma (perilymphatic fistula)

Imaging: if exam reassuring, none required

- Treatment: metoclopramide, prochlorperazine, mecclazine (2 wks max, vestib suppresion), lorazepam, diazepam AND Vestibular PT

Central

Sx: Usually mild nausea, severe imbalance, rare hearing sx.

Ddx: cerebral infarction (vertebrobasilar ischemia), TIA, hemorrhage, toxic, cerebellopontine mass (vestib schwannoma, ependymoma, brainstem glioma, medulloblastoma, neurofibromatosis), multiple sclerosis, vestibular migraine

Imaging: MRI Brain W/VO, coronal DWI, MRA H&N

Vessel imaging (MRA Head and Neck): vestibular, brainstem, retinal sx, motor sx

Indications for Imaging (MRI Brain W/ VO): >35 yo, abn neuro exam, acute, severe, positional, w/ exercise, immunosuppressed, wakes at night

Approach to Acute Dizziness

Episodic

Position triggered

Dix Hallpike + Supine Roll Test

Orthostatics

Nystagmus?

Other / None: Image to r/o central lesion

Acute dizziness

Add sx of medical etiology

Med w/u

Ongoing

HINTS+ exam

No catchup saccade OR Vertical skew OR New unilateral hearing deficit

+catchup saccade AND Unidirectional nystagmus AND No vertical skew AND No new unilateral hearing deficit

Likely peripheral

Simona Nedelcu, Pavan Vaswani 186
### Neurology

#### ACUTE STROKE ACTIVATION

1. **If high suspicion and onset of sx within past 24h**, call x6-3333 and activate acute stroke code. This will page both Neuro ICU/Stroke Fellow (p21723) and Stroke Resident (p20020).

2. **BE AT BEDSIDE. Consider this a code-equivalent.** Ensure 18g PIV is in place and bed is ready for travel, with travel monitor in place.

3. ABC/Vitals: check vitals, EKG, telemetry, FSG, keep NPO & HOB > 30°. **Do not treat HTN** unless BP >220/120, ACS, or ICH (see below).

4. Be ready to provide the following History/Physical:
   - **Last seen well (LSW) time** (last time seen normal by family, nursing, or anyone on team) – this is NOT the time that symptoms were noticed by you or patient
   - A/C and/or antiplatelet's?, renal function, allergies, code status, mRS
   - CI to tPA (see box) - even if CI's to tPA are present, must still call an acute stroke (patient may be candidate for IAT)
   - Use NIH stroke scale (NIHSS) to quantify severity
   - Most predictive physical exam findings: facial paresis, arm drift/weakness, and abnormal speech (JAMA 2005;293:239)

5. **STAT non-contrast CT head + CTA Head and Neck** (only need to order CTA; it includes NCCTH). If unable to receive contrast and/or LSW ≥ 6 hrs, STAT MRI +/- MRA will be considered by stroke team.

6. Labs: check Chem 10, CBC, PT/INR/PTT, TnT, UA/Uc, tox screen & AED levels (if appropriate)

#### IV tPA Criteria

- **Inclusion:**
  1. Clinical dx w/ measurable deficit, age ≥ 18
  2. Sx onset/time since LSW < 4.5 hrs (may extend to 9h soon)

- **Exclusion:**
  History: stroke/head trauma in last 3 mo; recent head/spine surg; prior ICH; intracranial malignancy, AV malformation, aneurysm; incompressible arterial puncture last 7 days

### Stroke & TIA

#### IV tPA Criteria

- **Inclusion:**
  1. Clinical: NIHSS ≥ 6, LSW ≤ 24 hrs, age 18-85, baseline mRS ≤ 1, life expectancy > 12 mo
  2. Radiological: ICA or MCA M1/2 occlusion, basilar or dominant vert occlusion, small infant core volume (CT: ASPECTS ≥ 6 + collaterals; MRI: 70 cc by DWI)

- **Exclusion:**
  Clinical: BP ≥ 185/110 (treat!), BG <50 or >400
  Heme: Pt < 40k, INR > 3

#### INPATIENT POST-STROKE CARE

- Frequent neuro checks q-1-2 hr x 24 hrs if unsteady/ICU; q4 hr if stable/ floor pt, STAT head CT if change in exam.

- Consult PT, OT, SLP (NPO until bedside swallow eval). Keep euglycemic (antypiretics), euglycemic (FSG <140), Mg ≥.2

- If received tPA: NCCTH 24 hrs post-tPA → if no/eo hemorrhagic transformation, start antiplatelet + DVT ppx.

- If did not receive tPA: ASA 325 mg x1, followed by long-term antiplatelet or A/C (wait 2-4 wks for A/C for large ischemic strokes). Start DVT ppx if ischemic stroke (unless large hemorrhagic conversion).

- **Antiplatlet long-term 2nd prevention**
  - ASA 81mg QD (50-325 mg/d effective; ≤200 mg/d lower risk of major bleed) (Am J Cardiol 2005;95:1218)
  - Plavix 75mg QD (may be superior to ASA in patients with atherosclerotic vascular dz) (CAPRIE Lancet 1996;348:1329)
  - DAPT (ASA+Plavix)
    - For TIA or minor stroke: consider in patients w/ NIHSS<4 or TIA, ASA+Plavix for 3-4 wks followed by Plavix (or ASA) alone (CHANCE NEJM 2013;369:11 & POINT NEJM 2018;379:215). Can consider Plavix load (300-600 mg) w/ 24 hrs of symptoms.
    - For symptomatic intracranial stenosis: can consider ASA/Plavix for 3 mo (SAMMPRS NEJM 2011:365:993)
    - For recurrent stroke on ASA or Plavix alone + sign athero; some use DAPT long-term; no clear evidence & higher bleed risk (CHARISMA NEJM 2006:354:7106 & MATCH Lancet 2004:364:331) – should be d/w neurology.
  - **Anticoagulation long-term 2nd prevention** (embolic infarcts from AFib, paradoxical embolus, LV thrombus or hypercoagulable state)
    - Warfarin or DOAC for pts w/ AF (hold off x 2-4 wk if hemorrhagic conversion or large hemispheric stroke)
    - No need for both antiplatelet & anticoagulation
  - Start Atorvastatin 80 mg w/ LDL goal < 70 (SPARCL NEJM 2006;355:549)

Mariel Kozberg
Consider Fluoxetine 20 mg daily x 90d for motor recovery if ischemic stroke w/ hemiparesis/plegia (FLAME Lancet Neurol 2011;10:123), but recent data does not support this use (FOCUS Lancet 2019;383:265).

Work up cause/secondary prevention: (see additional details below in Special Considerations by Stroke Type)

- **Labs**: lipids, A1c, TSH, ESR/CRP; if <60 y/o, send tox screen (cocaine), hypercoagulability w/u (if recommended by neuro)
- **Imaging**: head and neck CTA or MRA (can do TOF if low GFR); carotid US as alternative
- **Cardiac workup**: EKG, TTE, inpatient telemetry followed by 30-day MCOT vs. LINQ if tele is negative for AFib

### SPECIAL CONSIDERATIONS BY STROKE TYPE

#### CARDIOEMBOLIC STROKE

<table>
<thead>
<tr>
<th>SUSPECT WHEN:</th>
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</thead>
<tbody>
<tr>
<td>ACA/MCA/PCA occlusion w/o sig vascular dz</td>
</tr>
<tr>
<td>Infarcts in multiple territories or cerebellar stroke</td>
</tr>
<tr>
<td>Known risk factors (LA/LV thrombus, AFib, LVEF&lt;25%, aortic disease, intracardiac shunt)</td>
</tr>
<tr>
<td>Hypercoagulability/hyperviscosity (solid organ or heme malignancy, HbSS, cryo, cloting d/o)</td>
</tr>
</tbody>
</table>

**DIAGNOSTIC WORKUP:**

- TTE (w/ bubble if pt < 60 y/o) - if PFO, r/o venous thrombus (LENIs/ MRV pelvis), can consider closure (RESPECT NEJM 2017;377:1022)
- Inpatient telemetry followed by 30-day MCOT vs. LINQ at discharge (unless known AFib)

**ACUTE MANAGEMENT CONCERNS:**

- Avoid immediate AC unless known intracardiac thrombus or mechanical valve. Transition to long-term AC in 2-4 weeks.

#### SYMPTOMATIC CAROTID STENOSIS

**DIAGNOSTIC WORKUP:**

- CTA vs. MRA head & neck usually sufficient
- Alternatives: carotid US (typically need carotid US prior to consideration of CEA)

**ACUTE MANAGEMENT CONCERNS:**

- If ≥50% symptomatic carotid stenosis consider carotid revascularization (sten/t angioplasty/endarterectomy) – ideally w/in 2 weeks of sx (NASCET II NEJM 1998;339:1415)
- Consider anticoagulation if territory to be saved (d/w neurology)
- Consider induced HTN if symptoms fluctuate with BP

#### INFECTIVE ENDOCARDITIS

**DIAGNOSTIC WORKUP:**

- Unexplained fever w/ stroke in pt with valvular dz

**ACUTE MANAGEMENT CONCERNS:**

- Immediate antibiotics; caution with IPA
- Early cardiac surgery if small non-hemorrhagic stroke; delayed cardiac surgery (2-4 wk) if large or hemorrhagic stroke
- Avoid anticoagulation or antiplatelet w/o a separate indication

#### CAROTID AND VERTEBRAL DISSECTIONS

**DIAGNOSTIC WORKUP:**

- <60 y/o or posterior circulation stroke in pt w/o RFs
- Neck pain, HA, or Horner’s syndrome
- Trauma (vertebral fx), chiropractor, coughing spells

**ACUTE MANAGEMENT CONCERNS:**

- Goal of tx is to prevent stroke: highest risk in first few days
- Immediate anticoagulation (if early) followed by antiplatelet. Prefer antiplatelet if: sx onset >3d ago, dissection extends intradurally (no AC due to risk of SAH), large infarct (risk of hemorrhage) (CADISS Lancet Neurol 2015;14:361)
- High rate of recanalization → Tx 3 months then re-image vessel

#### CEREBRAL VENOUS SINUS THROMBOSIS

**DIAGNOSTIC WORKUP:**

- Positional HA, vomiting, papilledema, vision Δ
- P/w SZ (common, may be difficult to control)

**ACUTE MANAGEMENT CONCERNS:**

- Immediate anticoagulation even in presence of hemorrhage
- AEDs if seizures (not indicated for ppx)
- IV fluids, avoid dehydration, modify risk factors (smoking, OCPs)

### TRANSIENT ISCHEMIC ATTACK (TIA)

**Definition:** Transient neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia w/o acute infarction or end-organ injury as assessed clinically or by imaging

**Causes:** Atherothrombotic stenosis (ICA, vertebral, basilar, small vessel), embolic (arterial, aortic, cardiac, paradoxical), dissection (ICA, vertebral) - identification will guide tx (antiplatelet therapy vs. search for underlying arrhythmia +/- anticoagulation)

**Imaging:** MRI (w/ DWI/ADC) w/in 24hr of sx onset and vessel imaging of head and neck for large vessel occlusive disease (e.g. MRA (time of flight if low GFR) vs. CTA vs. carotid ultrasound)

**Cardiac w/u:** TTE to excl thrombus & PFO (age <60) & tele/MCOT vs. LINQ monitoring to exclude AFib if suspected embolic TIA

**ABCD² score** (Age, BP, Clinical features, Sx Duration, Diabetes) used to identify pts w/ high risk of ischemic stroke w/in 1 week of TIA

**Management:** Immediate intervention reduces the risk of recurrent stroke (1.5-3.5% risk within 48h), see 2° Prevention above

Mariel Kozberg

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**Neurology**

**CNS Emergencies**

**Intracranial hemorrhage (ICH):** epidural (EDH), subdural (SDH), subarachnoid (SAH), intraparenchymal hemorrhages (IPH)

- **Causes:** trauma (all), HTN (IPH), ruptured aneurysm/AVM (SAH, IPH), cerebral amyloid (IPH), tumor (IPH; most common w/ met breast Ca, lung Ca, melanoma, RCC, choroid, thyroid CA’s), cortical vein thrombosis (IPH), venous sinus thrombosis (IPH)

- **Presentation:** typically acute focal neuro deficit, +/- progressive & conscious, 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 head for all; +CTA head if SAH/IPH), coags/PLTs; need f/u scan at 6h to assess progression

- **STAT Management:**
  - STAT Neurosurg (p21111) if SAH/SDH/EDH; otherwise, Neuro (acute stroke: p34282; non-acute stroke: p20202; in ED: p20000).
  - Elevate HOB to 30-45° to reduce ICP and prevent aspiration.
  - **BP control:** SBP < 140 (studied in SAH or ICH due to ruptured aneurysm/AVM), use IV labetalol or nicardipine drip (avoid hydralazine if possible), place arterial line (INTERACT Lancet Neurol 2008;7:391, ATACH Crit Care Med 2010;38:637).

- **Correct coag:** warfarin/INR>1.5: tx [vitamin K 10 mg IV x 1] AND [3-5U FFP or Kcentra] (call blood bank); ↓Plt (transfuse, goal >50); uremia/antimal use: consider DDAVP 0.3mcg/kg IV, heparin/LMWH (protamine), s/p ICA (check fibrinogen, give cryo, +/- amicar), rivaroxaban or apixaban: give Andexanet Alfa (Andexxa); dosing based on size and timing of last dose (call pharmacy)


- **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 if stable after 48hrs, but confirm with consultants**

**Elevated Intracranial Pressure (ICP) / Herniation**

- **Etiologies:** Mass (tumor, abscess, hemorrhage), cerebral edema (massive infarction, hyperammonemia, DKA), hydrocephalus (tumor, intraventricular hemorrhage, leptomeningeal disease, meningoitis), PRES. If ICP severely elevated then herniation (displacement and compression of brain tissue) ensues. LP in setting of significantly raised ICP may also result in herniation.

- **Signs of herniation:** fixed/dilated/asymmetric pupil (often 1 first) accompanied by nausea, somnolence/confusion, limited upgaze; flexor/extensor posturing; ipsilateral hemiparesis (uncal herniation): Cushing’s triad (bradycardia, HTN, & irregular breathing)

- **Tests:** STAT head CT (x63050)

- **Management:**
  - STAT Neurosurg. (p21111) (for ICP monitor/EVD placement/decompressive hemicraniectomy)
  - Secure ABCs, elevate HOB to 30-45°, keep head midline (to secure venous drainage), treat pain/agitation
  - Neuro-ICU level monitoring (p20202 can help coordinate)
  - Hyperventilate to PaCO2 ~ 30-35 mmHg (if suspect herniation, transiently reduces ICP), only for short-term management
  - IV mannitol therapy 1g/kg q6h (use with caution in pts on HD & warfarin), place arterial line (INTERACT Lancet Neurol 2008;7:391, ATACH Crit Care Med 2010;38:637)
  - If related to edema from malignancy or bacterial infection, give 10mg IV dexamethasone x 1, then 4mg q6hrs
  - **Complications during LP:** if sx of herniation/opening pressures > 40 cm H2O, consider STAT head CT. Immediately replace stylet into needle, only drain CSF in the manometer, STAT Neurosurgery (p21111).

**Hypertensive Encephalopathy: PRES (“posterior reversible” encephalopathy syndrome)**

- **Typically associated with:** severe HTN, but also relative HTN in setting of preeclampsia/eclampsia, cytotoxic/immunosuppressive drugs (Cyclosporine, Tacrolimus, Cisplatin, Bevacizumab), acute/chronic renal failure, uremia, sepsis, vasculitides, TTP → due to impaired cerebral autoregulation and endothelial dysfunction, hypomagnesemia (NEJM 1996;334:494.9)

- **Symptoms:** HA, confusion, decreased consciousness, visual disturbances, seizures, can result in ICH and ↑ICP

- **Tests:** Brain MRI +gad: FLAIR shows vasogenic edema w/in white matter in the posterior cerebral hemispheres; DWI/ADC normal (but also can have strokes); additional regions can be involved including brainstem, cerebellum, basal ganglia, frontal lobes

- **Management:** ICU if severe, strict BP control (reduce 25% daily, if severe use nicardipine or labetalol drip), treat seizures, Mg2+ (esp in eclampsia), remove inciting factor

- **Prognosis:** Often fully reversible; complications include progressive cerebral edema, ICH, stroke, death

**Cord Compression:** High level of suspicion in cancer patients with back pain, urinary sx or LE weakness

- **Etiologies:** Subacute (tumor/mets, abscesses) vs acute (disc herniation, trauma, hemorrhage)

- **Symptoms:** Back pain, motor weakness, hyperreflexia below lesion (“can be hypo in acute or w/cauda equina”), +Babinski, loss of sensation (typically c/w dermatome or level), bowel/bladder incontinence OR retention, loss of rectal tone, saddle anesthesia

- **Tests:** STAT whole spine MRI w/contrast (cord compression protocol), call ED MRI (x63050) or inpt MRI (x64226)

- **STAT page NSG/Ortho spine +/- Rad Onc (x68652) for possible XRT if tumor-related**

- **Dexamethasone** (10mg IV x 1 then 4mg q6h), esp in malignancy: solumedrol in acute cord injury 2/2 trauma is controversial

**Other CNS Emergencies**

- **Respiratory failure is/o neuromuscular disorders: See Weakness & Neuromuscular Disorders**

- **NMS and serotonin syndrome: See Catatonia/NMS/Serotonin Disorder**

- **Status epilepticus:** See Seizures/Epilepsy

- **Stroke:** See Stroke.

*Michael Young*
Neurology

Seizures


- Epilepsy: brain d/o characterized by enduring predisposition to generate seizures (unprovoked)
- Status Epilepticus: at least 5 mins of continuous seizure or 2+ seizures w/ incomplete recovery of consciousness in between
- Non-convulsive Status Epilepticus: non-convulsive electrographic seizure ≥10s or rhythmic EEG responsive to seizure treatment
- Tonic: persistent flexion/extension; Clonic: limb jerking; Atonic: loss of postural tone; Myoclonic: sudden brief muscle contraction
- Psychogenic Non-Convulsive Epileptic Seizures (PNES): Important to distinguish from epileptic events. Features that are common in PNES but rare in epilepsy: opisthotonus (arched back), undulating/asynchronous motor activity, eyes closed with resistance to lid opening, and side-to-side head movements (Epilepsy & Behav 2003;3:205)

Classification (Epilepsia 2010:4:676):

- Focal: Unilateral, occurring in one hemisphere +/- impaired consciousness (formerly simple partial, complex partial)
- Generalized: Occurring in and rapidly engaging b/l distributed networks (formerly tonic-clonic, atonic, myoclonic, absence)

Etiology: Provoked vs Not? Primary epilepsy, vascular (stroke/ischemia/hemorrhage), withdrawal (EtOH/BZDs), mass lesions (tumor, abscess), trauma, metabolic (↓ glc, TCO2, ↓O2, ↑Ca), meds, infection (systemic and CNS), HTN or HoTN, high fever, eclampsia, PRES

Ddx: syncope, TI, migraine, PNES (~30% also have epilepsy), myoclonus, dystonia

H&P: Previous sz history, prodrome (palpitation, sweating, N/V, aura), med list (many lower threshold), triggers (exertion, pain/fatigue/emotional stress, cough/urination/defecation), tongue biting, incontinence, lateralizing signs, alcohol. GET ABCs

Previous sz history, prodrome (palpitation, sweating, N/V, aura), med list (many lower threshold), triggers (exertion, pain/fatigue/emotional stress, cough/urination/defecation), tongue biting, incontinence, lateralizing signs, alcohol. GET ABCs

Labs: FSBG, TOX, AED levels, Lfts, CBC, albumin, HTN, AKI, lactate, troponin, blood cx, b-hcg. Prl Sn ~50%

Monitoring: Tele (↑ risk for fatal cardiac arrhythmias during ictal/post-ictal period; ictal arrhythmias ↑ risk of sudden death)


LP/BCx: If febrile, HIV/immunocompromised, or if no clear etiology

EEG: Within 24-48h if not seizing, emergent EEG if seizing: DO NOT wait to manage. If emergent, contact EEG fellow (p16834)

<table>
<thead>
<tr>
<th>Treatment of status epilepticus:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCs: VS, O2, EKG; Assess pt safely; Place 2 PIVs (BZD + PHT incompatible)</td>
</tr>
</tbody>
</table>

Persistent SZ (10-30min): Levetiracetam, VPA, fosphenytoin/phenytoin, phenobarb, +/− lacosamide (need pre/post EKG to check PR)  |

Refractory SZ (30-60 min): Intubate, continuous EEG  Midaz (if HD unstable) +/- propofol gtt |

Seizure P Px: No AED in 1st seizure unless abnormal EEG OR abnormal imaging (Epilepsia 2008;49:13). Early AED only reduces short term recurrence risk (<2yr) and is unlikely to change prognosis of sustained remission (3+ yrs) (Neuro 2015:86:7)54

EtOH seizure: Pnx not well when intoxication or withdrawal is the cause of seizure (Neuro 2006;67:45)

Brain tumor: No px. If seizures occur, start AEDs: Keppra > Lacosamide (fewer chemo interactions)

TB: Keppra 500-750 mg BID x 7 days (Neurosurg Focus 2008:25:E3)

ICH: AED only if clinical seizure or traumatic etiology, Keppra 500mg BID x 7days

PNES: Treatment with outpatient Cognitive Behavioral Therapy (CBT), psychiatry involvement. In acute setting it may be helpful to educate patients about functional neurologic symptoms (http://www.neurosymptoms.org), and place social work consult.

In MA, No Driving for LOC event until 6 mos seizure free. Counsel pt and include in discharge summary.

<table>
<thead>
<tr>
<th>AED</th>
<th>Loading</th>
<th>Dosing</th>
<th>Goal Level</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>60mg/kg</td>
<td>1:1 PO:IV</td>
<td>No goal, level to check adherence</td>
<td>Psychiatric sx (irritability, anxiety, depression, sedation, psychosis).</td>
</tr>
<tr>
<td>Valproic acid (Depakote)</td>
<td>20-40mg/kg</td>
<td>1:1 PO:IV</td>
<td>50-100 mcg/mL (&gt;1h post load)</td>
<td>Teratogenic. Abnormal LFTs, weight gain, N/V, encephalopathy (↑ NH3), pancreatitis, thrombocytopenia. Good for mood disorders.</td>
</tr>
<tr>
<td>Phenytoin (Dilantin), Fosphenytoin</td>
<td>20 pheny equiv/kg</td>
<td>1:1 PO:IV</td>
<td>10-20 mcg/mL, correct for alb, (2h post load)</td>
<td>Teratogenic. Gingival hypertrophy, hair growth, rash, AMS, diplopia, ataxia, slurred speech, hypotension/arrhythmia (if run faster than 50mcg/min; Fosphenytoin is less cardiotoxic).</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>No Load</td>
<td>1:1 PO:IV</td>
<td>1-13 mcg/L</td>
<td>Rash, SJS, nausea, somnolence, dizziness, ataxia. Good in mood disorders.</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>No Load</td>
<td>Only PO</td>
<td>N/A</td>
<td>Weight loss, fatigue, teratogenic. Nephrolithiasis, cognitive, anxiety, anorexia, tremor</td>
</tr>
<tr>
<td>Lacosamide (Vimpat)</td>
<td>200-400mg</td>
<td>1:1 PO:IV</td>
<td>N/A</td>
<td>Headache, diplopia, dizziness, nausea, hypotension. Obtain EKG after load, and watch for PR prolongation.</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>No Load</td>
<td>Only PO</td>
<td>4-12 mcg/mL</td>
<td>SIADH, N/V/D, rash, pruritus, fatigue, blurred vision, diplopia, lethargy.</td>
</tr>
</tbody>
</table>

Amrit Misra & Sattar Khoshkhoo 190
MYASTHENIC CRISIS:
• Tx in the evening. Typically involves ocular (ptosis, diplopia), bulbar, respiratory, neck and proximal>distal limb muscles.

MYASTHENIA GRAVIS/LAMBERT EATON (MG/LEMS):
• Weakness of voluntary muscles, worse w/exertion & repetitive movements and

Elective intubation w/ 20-30-40 Rule:
• EMG/NCS:
  • Tx: IVIg or plasmapheresis (equiv. outcomes); monitor respiratory function with NIF/VC TID to qD (done by RT)-more frequent if crisis

• Cause: Auto-Abs against postsynaptic ACh-R in skeletal muscle (MG) or Voltage Gated Calcium Channels (LEMS)
  • Dx:
    • Associated Sx:
      • Autonomic Sx:
        • Associated Sensory Sx:
          • Absent reflexes (may be present acutely), facial weakness, autonomic instability, weakness. Associated Sx/Signs: proximal (many myopathies), bulbar (dysphagia, dysarthria, diplopia)

Neurology

APPROACH TO WEAKNESS
• Ask about functional issues (getting out of chair, tripping over curbs/stairs)

UMN signs: spasticity, increased tone, hyperreflexia, + Babinski | LMN signs: fasciculations, atrophy, decreased tone, hyporeflexia

Pattern: UMN (extensors in UEs, flexors in LEs), proximal (many myopathies), bulbar (dysphagia, dysarthria, diplopia)

Associated Sensory Sx: reduced sensation, tingling, burning, allodynia, hyperalgesia, decreased temperature sense, imbalance

Autonomic Sx: orthostasis, constipation, urinary retention, erectile dysfunction, changes in sweating, hair loss, post-prandial nausea

EMG/NCS: Can be helpful with localization, determining fiber type involved, determining if disease is axonal vs demyelinating (which guides tx), and determining injury extent (which guides prognosis). Often higher yield at least 2-3 weeks into illness and as outpt.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Associated Sx/Signs</th>
<th>Diagnostics</th>
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<td>Brain</td>
<td>Cortical signs (language/visual field/neglect), cerebellar sx, UMN signs</td>
<td>MRI Brain best initial test (+gado if c/f cancer, infxn, demyelinating dz)</td>
<td>Vascular (hemorrhage or ischemia), tumor, trauma, demyelinating</td>
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<td>Spinal Cord</td>
<td>Sensory level, bowel/bladder dysfxn, UMN signs.</td>
<td>MRI Spine (level based on sx, +gado if c/f cancer, infxn, demyelinating dz)</td>
<td>Transverse myelitis (MS, NMO, connective tissue dz), infxn (viral myelitis, HTLV), compression (tumor/disc/abscess), vascular, trauma, paraneoplastic, toxic, ↓B12/Cu</td>
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<td>Anterior horn cell</td>
<td>LMN signs. If motor neuron dz: both UMN and LMN signs.</td>
<td>NCS/EMG +/- MRI brain and spine; LP</td>
<td>ALS, SMA, polio, acute flaccid myelitis (pediatric)</td>
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<td>Radiculopathy</td>
<td>Motor/sensory sx corresponding to nerve root. +Radiating pain.</td>
<td>MRI Spine (level based on sx)</td>
<td>Nerve root compression (disc herniation, spondylodiscitis) by far most common; radiculopathy: GBS, iatrogenic (post-op, chemo); ischemic, infxn (HIV, Lyme, CMV, EBV), DM (typically thoracic), sarcoal, malig.</td>
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<td>Peripheral Neuropathy</td>
<td>Sensory symptoms; autonomic dysfxn if small fibers affected. Often symmetric and length dependent. GBS is ascending.</td>
<td>Labs: highest yield = A1c, B12 + MSA, SSEP + immunofixation Add’l labs (in select pts): Lyme, RPR, HIV, malnutrition (B1, B6, vit E, B3, Cu), vasculitis (ANCA, ANA, ESR, CRP, RF, C3/C4), celiac, ACE</td>
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<td>Ice pack test, tension (rarely) Labs: myasthenia panel (see below) NCS/EMG: repetitive stimulation, single fiber EMG CT chest</td>
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<td>Myopathy</td>
<td>Proximal weakness most common. Pain uncommon.</td>
<td>Initial Labs: CK, aldolase, LDH, LFTs, TSH/T4, PTH, ESR/CRP EMG: e/o muscle irritability, chronicity May need muscle biopsy</td>
<td>Critical illness, medication-related (steroids, statins, colchicine, cyclosporine, NRTI), inflammatory myopathies (Inclusion Body Myositis, Dermatomyositis, Polymyositis)</td>
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GUILLEMIN-BARRÉ SYNDROME (Acute Inflammatory Demyelinating Polyradiculoneuropathy): Symmetric, ascending numbness & weakness. Absent reflexes (may be present acutely), facial weakness, autonomic instability, acute resp failure in 30% of patients.

Causes: Often recent infection (Campylobacter jejuni, HIV, CMV, EBV, Zika) or vaccination (rare)

Dx: LP w/ albuminocyt. dissoci. (high protein, norm WBCs). Anti-GQ1B in CMF variant. NCS/EMG: highest yield 2-3wks after sx onset

Tx: IVig or plasmapheresis (equiv. outcomes); monitor respiratory function with NIF/VC TID to qD (done by RT)-more frequent if crisis

Elective intubation w/ 20-30-40 Rule: VC <20mL/kg, NIF weaker than -30cm H20, MEF <40 cm H20, CRP, RF, ESR, C3/C4), celiac, ACE |

Original yield of testing = 80% acute GBS/CIDP, DM, Lyme; Mononeuropathy: compression/trauma; Mononeuropathy multiplex: vasculitis, amyloid, sarcoal, HNPP |

Important/Common Causes | Associated Sx/Signs | Diagnostics | Important/Common Causes |
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Neuroprognostication

Neurological prognostication after cardiac arrest is challenging and uncertain (Seminar in Neurology 2017;37:040). The introduction of therapeutic hypothermia alters the timeframe for neurological recovery and the interpretation of prognostic markers. Studies of neurological prognostication are hampered by heterogeneous patient populations and variable definitions of “coma”. We will discuss the clinical predictors of recovery and available diagnostics – clinical exam, electrodiagnostic testing, and neuroimaging.

Cerebral performance category (CPC)

- **Good Outcome:**
  - CPC 1. Mild deficits. Able to work. May have mild neurologic/psychologic deficits.

- **Poor Outcome:**
  - CPC 4. Coma (no wakefulness) or vegetative state (wakefulness but unawareness).
  - CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

**Therapeutic hypothermia:** Post-cardiac arrest patients are cooled within 6 hours of return of spontaneous circulation (ROSC), to 32–34°C, where they are maintained for 24 hours via surface or endovascular cooling methods (Nat Rev Neurol 2014;10:190). Targeted temperature management (36°C), has equivalent efficacy (NEJM 2013;369:2197). During this period, patients can be paralyzed with neuromuscular blocking agents to prevent shivering, and are commonly maintained on propofol, midazolam, fentanyl and other sedatives. After completion of 24 hours of TH, patients are typically rewarmed in a controlled fashion over 8-12 hours, with discontinuation of paralytics (if used) only once the shivering threshold—estimated at around 36°C—is passed; sedative-hypnotics are continued while patients are paralyzed.

**Timeframe post cardiac arrest diagnostics:**

- **Day 1-2 Therapeutic hypothermia and rewarming**
  - Electroencephalography (EEG)
    - Timing: started during TH and continued for 24 hours post normothermia.
    - Poor prognosis: absence of EEG activity, seizures, burst suppression (Neurology 2013;80:339).
    - Positive prognosis: continuous background pattern and reactivity at day 3 or later.
  - Clinical exam
    - Poor prognosis: Status myoclonus at <48 hours post cardiac arrest or normothermia. Defined as spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs and axial musculature. There may be no EEG correlate. Absent brainstem reflexes: bilateral pupillary, corneal, and oculocephalic reflexes. Absent brainstem reflexes, along with apnea and other criteria (depending on local guidelines), may signify brain death.

- **Day 3-5**
  - Somatosensory evoked potentials (SSEP) – measurement of brain activity in response to somatosensory stimulation
    - Timing: 48 hours post cardiac arrest or normothermia.
    - Poor prognosis: bilateral absence of N20, which reflects the integrity of thalamocortical projections.
  - Neuron specific enolase (serum) – non-specific marker of neuronal injury (misnomer as it is found in RBC and platelets).
    - Timing: 24-72 hours post cardiac arrest or normothermia.
    - Poor prognosis: >33 ug/l and increasing daily NSE levels (Neurology 2011;77:623). NSE is prognostic in the pre-therapeutic hypothermia era but is not well validated in patients who received therapeutic hypothermia. Not part of MGH neuroprognostication guidelines.
  - CT head, 48 hours post cardiac arrest or normothermia
    - Poor prognosis: wide spread hypodensity, loss or reversal of grey-white differentiation.
  - Brain MRI, 72 hours post cardiac arrest or normothermia
    - Poor prognosis: DWI and ADC changes suggestive of ischemic injury (Ann Neurrol 2009;65:394). Quantitative ADC values may correlate with severity. MRI can be insensitive to lesions if not performed during normothermia.

**Combining prognostic indicators** (MGH neuroprognostication guidelines, 2017): Prognostic value of at least 2 of the following findings (measured after completion of re-warming following TH, between 36-72 hours post cardiac arrest) – *bilaterally absent SSEP, unreactive EEG Background, early myoclonus, incomplete recovery of brainstem reflexes.*

<table>
<thead>
<tr>
<th>Prediction</th>
<th>In-Hospital Mortality</th>
<th>Poor 3-6 Month Neurological Outcomes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>79 (67-88)%</td>
<td>62 (51-72)%</td>
</tr>
<tr>
<td>FPR (95% CI)</td>
<td>0 (0-8)%</td>
<td>0 (0-14)%</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>100 (93-100)%</td>
<td>100 (93-100)%</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>76 (63-86)%</td>
<td>44 (31-58)%</td>
</tr>
</tbody>
</table>

FPR = false positive rate (probability of ≥2 findings not leading to outcome). PPV = positive predictive value (probability of ≥2 findings leading to outcome). NPV = negative predictive value (probability of <2 findings not leading to outcome).

* Poor outcome defined as severe disability/dependency, coma, or death.
MENTAL STATUS: (document daily for pts w/ new AMS or worsening psychiatric sx) 

APPEARANCE/BEHAVIOR: grooming/hygiene, eye contact, attitude/cooperation, abnormal mvmt (fidgeting, tics, TD)

SPEECH/LANGUAGE: mechanics (rate, volume, prosody, articulation, fluent or not → if pt can place 5 words together = fluent); paucity of speech, mutism, echolalia (copying provider’s speech), verbigeration (repeating meaningless phrases)

THOUGHT PROCESS: presence of disorganization (including derailing/tangentiality); also note vague use of references (common in psychosis); thought blocking (pt appears unable to produce responses to questions)

MOOD/AFFECT: pt’s own description, observed affect, future views, self-attitude (worthlessness, grandiosity)

THOUGHT CONTENT/PERCEPTIONS: SI/HI, delusions, hallucinations, overvalued ideas, obsessions, poverty of content

COGNITION: level of consciousness, orientation, MOCA

INSIGHT/JUDGMENT: give examples (insight: patient recognizes sx as pathological/accepts dx; judgment: pt takes

PSYCHOSIS

• Characteristics: delusions, hallucinations (auditory>visual), thought disorganization

• Ddx: schizophrenia, schizoaffective, MDD w/ psychosis, bipolar w/ psychosis, malingering, substance-induced (cocaïne, amphetamines, MJ, bath salts, hallucinogens, EtOH), less frequently OCD/PTSD/borderline PD, intellectual disability, dementia, due to another medical condition (delirium, epilepsy, AIP, paraneoplastic limbic encephalitis)
  o New onset psychotic disorders in patients >50 is fairly rare. Medical cause of psychotic symptoms in this age group (delirium, CNS pathology, dementia) is more likely unless known psych diagnosis.

• Labs: CBC, BMP, UA, Utox+VPAIN, serum tox including EtOH, UA, med levels, delirium workup (see neuro page)

• Refer to psych: outpatient = always, inpatient = if decompensated (can be associated with fear, agitation, aggression)

Treatment Basics:

Confirm home antipsychotics/mood stabilizers early in admission, continue only if patient reliably taking; otherwise, dose reduce. Ask if patient on long-acting injectable medication/date of last injection, ask which PRN medications work well for patient. Obtain Depakote, lithium, clozapine levels.

• Antipsychotics:
  o Best practice is generally to avoid multiple antipsychotics in 1 patient. If med list includes >1 antipsychotic, be sure to confirm before ordering as it is unlikely they're taking all in outpatient setting. Continue patient’s home Cogentin (benztropine) if prescribed to reduce EPS sx (particularly common in 1st gen high potency antipsychotics like Haldol). Clozapine is typically prescribed for treatment resistant schizophrenia/schizoaffective in the US but has the notable side effect of agranulocytosis. If patient on clozapine, consult psychiatry early to continue medication in house.

• Mood Stabilizers:
  o Include lithium, Depakote, lamotrigine, some antipsychotics. Confirm compliance with lamotrigine given risk of SJS
  o Consider lithium toxicity in patients who present with n/v/AKI/new NSAID/ARB/diuretic use: sx include nausea, vomiting, diarreha, tremor, ataxia, confusion/agitation → seizures, nonconvulsive status, encephalopathy if severe

AGITATION IN DELIRIUM: (see Delirium in neuro section)

• Safety: #1 priority is patient and staff safety. LISTEN to nursing concerns.
  o Very low threshold to page security, particularly if patient has a history of violence
  o Can always page psychiatry (page APS resident after 6PM on weekdays/5PM on weekends)
  o Offer oral medications early. Consider lorazepam 1st line if strong suspicion for stimulant intoxication or catatonia
  o If patient requires restraints, ensure appropriate sedation as agitated patients are at risk of rhabdo/MSK injury
  o 2nd generation antipsychotics carry a black-box warning for increased all-cause mortality in pts with dementia (who commonly present with superimposed delirium) – goal is lowest effective dose for shortest time possible

• Treat underlying cause:
  o Carefully review pts’ medications and assess risk/benefit of continuing anticholinergics & benzodiazepines. If opiates are required, consider preferably using PO oxycodone or hydromorphone if IV needed

• Management
  o Use behavioral strategies (including frequent re-orientation& light/physical activity (OOB/PT) cues) as first-line
  o If medication is required for adults with QTc<550ms, can trial oral quetiapine (initial doses 12.5-25mg q6 hrs)
  o If requires IV, trial IV haloperidol (initial dose 2.5-5mg, 1-2mg in elderly/frail). May be effective and is less associated with dystonia than IM or PO dosing. Prefer early psych consultation for pts requiring higher/more frequent doses.
  o Monitor QTc, replete mag ≥2.0 and K ≥4.0 while using antipsychotics.
  o AVOID antipsychotics in patients with Parkinsonian syndromes, catatonia, NMS

• IM medications: Use only as a last resort in case of emergencies. Consult psychiatry for pts requiring IMs.
  o IM haloperidol (5mg) should be co-administered with either IM diphenhydramine (25-50mg) or IM benzotropine (0.5-1mg) to reduce risk of dystonia although these medications may temporarily worsen delirium.
  o IM olanzapine or thorazine may be given alone but should be used cautiously in elderly pts given risk of orthostasis
  o IM olanzapine cannot be administered with IM benzos/barbiturates due to risk of cardiorespiratory depression
Consent, Capacity, & Legal

Three Elements of Valid Informed Consent: 

1. Relevant Clinical Information: At minimum: diagnosis, proposed intervention, its purpose, its risks/benefits, alternatives, and risks/benefits of alternatives (including no intervention)
2. Voluntary Decision: The decision must be voluntary and without coercion from hospital staff or family/friends
3. Capacity: Confirm patient has the ability to make a decision about the specific question being addressed (see below)

Exceptions to Informed Consent

1. Emergency: Imminent risk of serious harm or without medical intervention. All attempts should be made to find HCP/other surrogate decision-maker. Always discuss with Attending of Record. Document emergent situation, lack of capacity, lack of available surrogate, need for emergent intervention. Consider 2nd opinion/consulting MGH lawyer-on-call.
2. Lack of Capacity or Competency: Turn to the appropriate HCP, guardian or other surrogate decision-maker (see below)

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 judge. Determines a person’s ability to make decisions in multiple areas of life.
- Any physician can make a determination of capacity. Psychiatry should be consulted only for capacity assessment in complex cases, such as when neuropsychiatric illness may be impairing decision-making or when the pt, family, and medical team disagree on decision-making. Before consulting psychiatry, explain risks/benefits to patient and know patient’s expressed decision. If consult required, have risks & benefits of each intervention available to consultant.
- 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 patient to have capacity): NEJM 2007; 357:1834 NEJM 1988; 319:1635

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Approach in Physician’s Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicate a clear and stable choice</td>
<td>Ask patient to indicate a choice. No expression is a presumption of incapacity. Frequent reversals of choice may indicate lack of capacity.</td>
</tr>
<tr>
<td>Understand relevant information</td>
<td>Ask patient to describe his/her understanding of the information given by the physician (diagnosis, proposed intervention, purpose of intervention, risks/benefits, risks/benefits of alternatives including no intervention).</td>
</tr>
<tr>
<td>Appreciate the situation and its consequences</td>
<td>Ask patient to describe views of diagnosis, interventions, and likely outcomes. Is patient aware of her illness? Its seriousness? Consequences?</td>
</tr>
<tr>
<td>Be able to manipulate information provided in a rational fashion</td>
<td>Ask patient to compare treatment options, consequences, and reasons for choice. Does the patient weigh the risks and benefits logically?</td>
</tr>
</tbody>
</table>

Documenting Capacity Assessment: “Based upon my evaluation of the pt, he/she does/does not express a consistent preference regarding the proposed treatment, does/does not have a factual understanding of the current situation as evidenced by [example], does/does not appreciate the risks and benefits of treatment and non-treatment, and is able/unable to rationally manipulate information to make a decision as evidenced by [example]. Therefore, in my opinion, this pt has/lacks capacity to make this medical decision.” If capacity present: “We should respect the patient’s right to make this decision to [details].” If lacks capacity: “Surrogate decision-maker needed.”

Surrogate Decision-Makers

- Encourage each pt to sign legal HCP form specifying surrogate. Surrogate should be activated when pt lacks capacity.
- Surrogate’s job is to make the decision pt would have made for herself if she were able—not what the surrogate wants
- 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 Guardianship team.
- Guardianship: Legal process by which the MA Probate Court grants a guardian the authority to make decisions on behalf of someone whom a judge has ruled is not competent. Guardianship required when there is no HCP identified & pt is unable to designate a HCP. Note: a patient may not have capacity to make a certain medical decision and still be able to designate a HCP. For help: contact ‘Guardianship team’ of Lisa Lovett, LICSW, & Mary Lussier-Cushing, RN/PC
- Rogers guardianship: Granted by court, allows guardian to authorize the use of specifically approved antipsychotics
- For emergent or life-threatening situations in which a patient lacks decisional capacity, emergency guardianship is not required to provide lifesaving treatment & should not delay care. Consult MGH lawyer-on-call if any questions arise

Temporary Involuntary (Psychiatric) Hospitalization (Section 12 in MA - MGL ch.123 §12): Consult psych for all pts on 12a

- Section 12a (the front of the "pink paper"): MD uses this form to apply for involuntary psych hospitalization of a pt who, based on MD’s exam & opinion, requires hospitalization to avoid likelihood of serious harm by reason of mental illness

- Authorizes pt’s transport to psych facility and, if necessary in the process, the use of restraint of the pt to maintain safety.

- Issued when likelihood of serious harm to self &/or others is imminent (general rule of thumb is within <24-72 hrs) and:
  1. is the result of a serious mental illness (which must be supported in writing with specific evidence; “symptoms caused solely by alcohol or drug intake, organic brain damage or intellectual disability do not constitute a serious mental illness”)
  2. Substantial risk of physical harm to others; (3) Very substantial risk of physical self-injury or injury as manifested by evidence that the person’s judgment is so affected (i.e., by serious mental illness) that he/she is unable to protect himself/herself in the community.

- Section 12b (reverse side of the "pink paper", "72 hr hold"): Completed by evaluating MD at receiving psychiatric facility

Civil Commitment for Substance Use Disorder Treatment (Section 35 in MA - MGL ch.123 §35)

- Process by which the court may involuntarily commit someone to inpatient substance use disorder treatment when there is likelihood of serious harm as a result of the disordered substance use; must be pursued via petition filed at courthouse

Laura DiCola
Psychiatry

Catatonia, NMS, & Serotonin Syndrome

**CATATONIA**: behavioral syndrome that occurs in the context of underlying psychiatric or general medical diagnosis, marked by inability to move normally despite full physical capacity; pathophysiology incompletely understood

- **Subtypes**:
  - retarded: immobility, mutism, withdrawal
  - excited: mania, hyperkinesis, stereotypy, disorientation
  - malignant: accompanied by hyperthermia, autonomic instability, rigidity & delirium ([Arch of Gen Psych 2009;66:1173](https://doi.org/10.1001/archgenpsychiatry.2009.51))

**Etiology**: ([Schizophr Bull 2010;36:239, Behav Brain Sci 2002;25:555](https://doi.org/10.1017/S0140525X03000179))
- Psychiatric: mood disorders > thought disorders (schizophrenia, autism) > dissociative disorders
- Medical: seizures (including NCSE), PRES, CNS lesion, infection, TBI, PLE, delirium, anti-NMDAR encephalitis, SLE
- Drug: dopamine-blockers, dopamine withdrawal, sedative/hypnotic withdrawal, hallucinogens, synthetic MJ, opiates

**Diagnosis**: DSM-V or Bush-Francis Catatonia Rating Scale ([BFCRS](https://www.duke.edu)), diagnose w/ ≥ 2 of 1st 14 ([Psych Scand 1996;93:129](https://doi.org/10.1111/j.1398-9987.1996.tb01795.x))

- **Most common signs** in order of decreasing frequency in recent study ([World J Psych 2016;6:391](https://doi.org/10.3978/j.issn.2090-8252.2015.10.01)) include:
  - 80%+: immobility, mutism, withdrawal & refusal to eat, staring
  - 50%+: negativism (oppose/no response to instruction), posturing/catalepsy (spontaneous maint of posture), rigidity
  - 10%+: waxy flexibility (ability to mold limbs with initial resistance), stereotypy (repetitive, purposeless mvmts), echophenomena (repetition of examiner's words or mvmts), veriberation
  - Other signs: automatic obedience, mitigation, ambidity (motorically stuck in indecisive movement), grasp reflex

- **Exam**: Observe for 30s outside pt room • Attempt to engage in conversation • Scratch head or gesture in exaggerated manner (echopraxia)
  - Exam for cogwheeling in arms, alternate force, attempt to reposture • Test for mitgehen • Extend hand & say, “Do not shake my hand” (ambidexterity, pt will appear stuck)
  - Reach into pocket & say, “Stick out your tongue. I want to put a pin in it” (automatic obedience)
  - Check for grasp reflex

- **Ddx**: catatonia: delirium, dementia, stroke, PD, stiff person & locked in syndromes, NCSE, akinetic & elective mutism, anti-NMDAR encephalitis; malignant: NMS, malignant hyperthermia, SS, DTs, CNS infection/vasculitis, antichol toxicity

**Treatment**: ([Schizophr Bull 2010;36:239](https://doi.org/10.1093/schbul/bsp115))
- Hold D2 blockers (e.g., typical/atypical antipsychotics; prochlorperazine, promethazine, metoclopramide)
- Ativan Challenge: 2mg IV x1 (1mg in frail elderly). If response, 2mg standing IV Ativan q6-8h, uptitrate as tolerated.
- DO NOT HOLD FOR SEDATION (signs of catatonia can be mistaken for sedation → write hold for resp depression)
  - If no response, then ECT
  - Adjunctive agents: Amantadine (100mg QD up to 600 QD), memantine (10-20mg QD), zolpidem, AEDs

**NEUROLEPTIC MALIGNANT SYNDROME**: ([Am J Pysch 2007;164:870](https://doi.org/10.1176/appi.ajp.2007.06071094))

- **Overview**: abrupt onset of 1) mental status Δ 2) rigidity 3) fever & 4) autonomic dysfunction associated with DA blocking agent or withdrawal of pro-dopamine agent ([List of Meds Associated with NMS](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3849861/))
- **Risk Factors**: initiation/increase of above agent (typically occurs within hours/days but can be idiosyncratic), hx of NMS/catatonia, withdrawal from EtOH/sedatives, basal ganglia disorders, exhaustion, dehydration, agitation
- **Labs**: ↑ WBC and CK = most common lab abnormalities (↑ CK only seen in 50% of cases). Low serum iron is 92-100 % sensitive for NMS but not specific. *May also see*: mild elevations in LDH, alk phos, AST, ALT, electrolyte abnormalities
- **Ddx**: serotonin syndrome, malignant hyperthermia, malignant catatonia (significant overlap), CNS infection, spinal cord injury, seizure, heat stroke, acute dystonia, CNS vasculitis, thyrotoxicosis, drug intoxication/toxicity, withdrawal states

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td></td>
</tr>
<tr>
<td>Mild rigidity, confusion, T&lt;100.4F, HR &lt;100</td>
<td>1. D/c offending agent &amp; ?contributors (serotonergics, Li, anticholinergics) 2. Aggressive fluids 3. Lorazepam 1-2mg IM/IV Q4-H</td>
</tr>
<tr>
<td>Moderate (may require ECT)</td>
<td>4. ADD cooling measures +/- ICU 5. ADD bromocriptine 2.5-5mg PO Q8H or amantadine 100mg PO Q8H</td>
</tr>
<tr>
<td>Severe (may require ECT)</td>
<td>6. ICU level of care (if intubation required, consider versed/protopol for sedation) 7. ADD dantrolene 1-2.5 mg/kg IV Q6H x 48hr</td>
</tr>
</tbody>
</table>

**SEROTONIN SYNDROME**: ([NEJM 2005;352:1112](https://doi.org/10.1056/NEJMoa042766))

- **Overview**: exposure to serotonergic agent leading to triad of 1) mental status Δ 2) neuromuscular hyperreactivity (tremor, hyperreflexia, clonus) & 3) autonomic instability (tachycardia, tachyphnea, diaphoresis, mydriasis, hyperthermia, shivering, sialorrhea, urinary incontinence, diarrea). *Note*: n/v/d common in SS prodrome but rarely seen in NMS
- **Causative Agents**: amphetamines, buspropion, buspirone, carbamazepine, carbidopa-levodopa, cocaine, cyclobenzaprine, diphenhydramine, fentanyl, levodopa, linezolid, lithium, LSD, MAOIs, MDMA, meperidine, methadone, methylene blue, metoclopramide, ondansetron, SNRIs, SSRIs, TCAs, tramadol, trazodone, triptans, tryptophan, VPA
- **Diagnosis**: Can use *Hunter's criteria for diagnosis of serotonin toxicity* if diagnostically unclear ([QJM 2003;96:635](https://doi.org/10.1093/qjmed/hcg029))
- **Treatment**: 1) Hold offending agent (generally will resolve w/in 24 hrs) 2) Use BZDs if agitation present (lorazepam 2 mg IV, repeat PRN) 3) If unsuccessful, can use cyproheptadine 12 mg x1 then 2mg Q2h until clinical response seen. Very severe cases with hyperthermia may require ICU level of care with intubation, sedation, and paralysis.

Fiona Gispen
MAJOR DEPRESSIVE DISORDER (MDD)

Overview:
- Epi: Common in general population; lifetime U.S. prevalence 17% (Arch Gen Psych 2005;62:617).
- Screening: USPSTF (2013) recommends universal screening of adult primary care patients (Grade B).
  - PHQ-2: In last month, has pt: 1) felt down/depressed/hopeless? 2) had little interest/pleasure in doing things?
    - ≥1 = pos. screen. 97% sens/67% spec for MDD → PHQ-9 to grade severity. (AFP 2012;85:139).
- DSM-5 Criteria: Must have depressed mood and/or loss of interest/pleasure + ≥4 of following sx: ↑or↓ weight/appetite, ↑or↓ sleep, psychomotor agitation/slowing, fatigue, worthlessness/guilt, poor concentration, thoughts of death or SI; sx must be present over same 2 wk period and cause significant impairment/distress.
  - dx: drugs/meds, OSA, hypothyroid, stroke, TBI, dementia, MS, HIV, bipolar, schizoaffective.
- Treatment: Drugs + therapy more effective than either alone, but monotherapy of either acceptable (APA 2010).
- Consider escitalopram & sertraline as 1st line (better efficacy/acceptability profile vs duloxetine, paroxetine) (Lancet 2009;373:746).
  - TCAs and MAOIs not recommended 1st line (SEs, safety).

Side Effect Profiles of Commonly Prescribed Antidepressants

<table>
<thead>
<tr>
<th>Drowsiness</th>
<th>Insomnia/Agitation</th>
<th>GI upset</th>
<th>Weight gain</th>
<th>Sexual dysfn</th>
<th>Orthostatic HoTN</th>
<th>QTC Prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>↓↑</td>
<td>↑↑↑↑ (fluox, sert)</td>
<td>↑↑↑↑ (sertraline)</td>
<td>↑↑ (paroxetine)</td>
<td>↑↑↑↑ (paroxetine)</td>
<td>↑</td>
</tr>
<tr>
<td>SNRIs</td>
<td>↓↑</td>
<td>↓↑</td>
<td>↑↑↑↑ (paroxetine)</td>
<td>↑↑↑↑ (venlafaxine)</td>
<td>↑↑↑↑</td>
<td>↑</td>
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<tr>
<td>Bupropion</td>
<td>↓</td>
<td>---</td>
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<td>↑</td>
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<td>↑</td>
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<tr>
<td>Mirtazpine</td>
<td>↑↑↑↑</td>
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<td>↑↑↑↑</td>
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<td>↑</td>
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<tr>
<td>Trazodone†</td>
<td>↑↑↑↑</td>
<td>---</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑</td>
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</tbody>
</table>

*Bu propion lowers the seizure threshold; contraindicated in pts w/ seizure disorder, anorexia/bulimia nervosa.
†Trazodone is rarely (1/1,000-1/10,000) associated w/ priapism (e.g., urological emergency).

Dosing of Common Antidepressants:
Adequate trial is 6-12 wks at full dose; if poor tolerance/response after 4-6 wks, augment or class switch.

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Usual (Max) Dose</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>20mg QD</td>
<td>↑ 20mg Qwk</td>
<td>20-40mg QD (40)</td>
<td>Taper over 2-4 wks</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10mg QD</td>
<td>↑ 10mg after ≥1wk</td>
<td>10-20mg QD (20)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>50mg QD</td>
<td>↑ 25-50mg Qwk</td>
<td>50-200mg QD (200)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20mg QD</td>
<td>↑ 20mg Q3-4wk</td>
<td>20-80mg QD (80)</td>
<td>0-2 wks (long t1/2)</td>
</tr>
<tr>
<td>Paroxetine – IR</td>
<td>20mg Qam</td>
<td>↑ 10mg Q ≥1wk</td>
<td>20-50mg QD (50)</td>
<td>3-4 wks (short t1/2) withdrawal effects more common/severe</td>
</tr>
<tr>
<td>Paroxetine – CR</td>
<td>25mg Qam</td>
<td>↑ 12.5mg Q ≥1wk</td>
<td>25-50mg QD (62.5)</td>
<td></td>
</tr>
<tr>
<td>Duloxetine (SNRI)</td>
<td>40-60mg QD or divided BID; ≥60mg QD w/o additional benefit</td>
<td>75mg Q≥4d, 75-375mg daily or divided</td>
<td>37.5-75mg QD x4wks</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (SNRI)</td>
<td>37.5 QD or in 2-3 divided doses; 175mg Q≥4d, 75-375mg daily or divided</td>
<td>37.5-75mg QD x4wks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Refer to psych: Concern for Bipolar Depression, failure of 2 adequate rx trials, severe MDD w/ SI/HI, psychosis, or catatonia.

GENERALIZED ANXIETY DISORDER (GAD)

Overview:
- Epi: US lifetime prev is 7.7% & 4.6% (AFP 2015;91:617). 90% will meet criteria for at least 1 co-morbid psych condition in their lifetime (MDD, dysthymia, AUD, simple phobia, social anxiety) (J Clin Psych 2009;70:10).
- Screening: GAD-7: score ≥5 indicates mild GAD (97% sens/57% spec, LR 2.2); score ≥10 indicates moderate GAD (89% sens/82% spec, LR 5.1) (Arch Intern Med 2006;166:1092). Commonly done annually with PHQ-2; no USPSTF recs.
- DSM-5 Criteria: A) Excessive anxiety/worry occurring most days for ≥6 months 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.
- Treatment: 1st line therapy = SSRIs/SNRIs and/or CBT, based on availability/pt preference; no head-to-head trials (meta-analyses have found effect sizes ≈ equivalent).
  - No individual SSRI/SNRI shown more effective; select based on SEs, DDIs, and pt treatment history/preference; titrate & adjust as for MDD above.
  - In general, SSRIs have lower risk of insomnia/agitation over SNRIs. Citalopram, escitalopram, paroxetine cause least agitation; sertraline and fluoxetine cause more agitation.
- Refer to psych: failure of 2 adequate next-step trials or severe GAD w/ recurrent panic.

Sam Wainwright

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Alcohol Withdrawal

Initial Evaluation:
- H&P; last drink time, hx complex w/d (sz, ICU/intubation, DTs), AMA, co-ingestions
- Labs: CMP, CBC, serum osm if HCO₂ <15 or AG, CPK if found down, tox screen w/consent, BAL (clear ~15-35 mg/dL/hr, chronic= faster metabol, higher tolerance) (J Forensic Sci 1993;38:104)
- Chronic use: low K/Mg/Co/Phos/VitD – EtOH toxic to renal tubules, lowers GI absorb; ketoacidosis – EtOH metab → less gluconeogenesis → rel hypoglycemia → low insulin state → FFA to ketones

Initial Tx for all EtOH Withdrawal (w/d):
- IV thiamine (See Wernicke’s below) – FFA to ketones

Decide: Phenobarb vs Benzo protocol:
Use Phenobarb if:
- Hx DTs, seizures, BZD-resistance, success w/phenobarb, or prior ICU admissions for w/d; current Sx of DTs; not responding to BZDs: risk of paradoxical response to BZDs (chronic CNS dz) AND no contraindications (greater than 30 mg ativan equivalents; high likelihood of leaving AMA; Hx SJS/TEN; tx AIP; unstable respiratory status

Use Benzos if:
- mild-mod w/d sx, no hx complicated w/d, phenobarb contraindicated

Phenobarbital Protocol:
- for moderate-severe w/d
  - IM load+PO taper. Binds GABA-A and glutamate, t1/2 = 1-4d.
  - NO MORE BENZOS after phenobarb started
  - Side Effects: apnea, hypoventilation, hypotension, bradycardia, laryngeal spasm
  - To calculate doses: Use http://stagehandbook.partners.org/pages/4281
  - Input: 1) Height (IBW) 2) High-risk withdrawal?: Past DTs +/- sz AND [EtOH use in <2wks OR active w/d sx OR +BAL with labs predictive of severe w/d (low plt, high MCV, K)] 3) High-risk sedation?: age>65, liver dz, head injury, recent benzos, concurrent sedatives
  - *If cirrhosis: slower excretion/metabolism, max load 8mg/kg, check level and adjust taper. Stop taper after 2d

ED IV Phenobarb Load:
- active severe w/d, CIWA >15, 2+ of (HR>110, SBP >140, diaphoresis, tongue fasc). Must stay 1hr in ED after IV load.

Troubleshooting:
- Serum level not required. Check 5h after load if considering re-load
- Assess frequently! IM loading dose is split to allow monitoring: 40% @0h, 30% @3h, 30% @6h. Peak plasma concentration 30m-4h post-IM dose and 2-8h post-IV
- NO MORE IM unless re-load (see below). Start PO 8hrs after IV load, dose per sheet excel.
- Consider Reload:
  - for breakthrough sx despite IV or IM load. If 5h<15, OK to reload, Target level 12-15. Consult psych, ACT, or pharmacy. 2 Options:
    1) Reload IM. eg if serum level 6, give equivalent IM load again to target 12
    2) Increase taper: jump up to PO doses for higher serum target
- Discharge: Phenobarb increases receptor sensitivity to benzos/EtOH: drinking after IV/M load can be fatal. Will autotaper over days. If exam/VS stable, ok to d/c patient before all doses complete, no earlier than day 3. No PO doses on d/c.

Wernicke-Korsakoff Syndrome:
Wernicke’s (acute): Clinical diagnosis w/ Caine Criteria (85% S) requires ≥2 dietary deficiency, oculomotor dysfxn, cerebellar dysfxn (LE ataxia), & either AMS or poor memory. Untreated, can progress to coma, death. Note: Serum B1 level NOT diagnostic (Journal of Neurology, Neurosurgery, and Psychiatry 1997:62:51)
Tx: thiamine IV 500mg TID x5d (1st dose before glucose), then PO ppx 100mg QD

Benzodiazepine Protocol:
- for mild-mod w/d
  - Use Epic Alcohol Withdrawal Order Set!
  - Route: PO Ativan if able to take PO>IV Ativan>>Valium>Lumbar (long half-life, delayed toxicity, cleared by the liver)
  - PRN: use CIWA scale, NOT HR, BP alone (poor predictors of DTs) (JGIM. 1996:11:410). PRN protocol inappropriate if AMS, DTs, or severe w/d
  - Standing: if likely to have severe w/d
    - Beware paradoxical response, resistance (>6mg ativan/hr), or BZD toxicity (similar to DTs) w/escalating dose
    - Consider switch to phenobarb if CIWA consistently >16 and bzd dose <30mg ativan equivalents
OPIOID USE DISORDER (OUD): chronic, relapsing d/o of opioid use due to dysfunction of brain reward circuits (J Addict Med 2015;9:358)
- Screen all patients with single question: “How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?” Confirm diagnosis using DSM-5 Criteria for opioid use disorder. Use ≠ addiction.
- Addiction History: 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 per day, recent withdrawal
  - Assess treatment readiness: treatment history (medications, counseling, mutual-aid organizations), social circumstances (housing, food security, legal issues). Understand patient’s current goals, including safer use vs abstinence.
  - Assess for high-risk injection practices: History of bacterial/fungal complications (endocarditis, SSTIs, bone/join infections) viral complications (HIV, HCV, HBV). If currently injecting, use PCOIG harm reduction conversation guide to review injection practices.
  - Assess risk of overdose: h/o non-fatal OD, ↑tolerance from recent incarceration or abstinence-based treatment, access to naloxone, high-dose Rx’d opioids and/or other sedatives (check MassPAT), injection use (Ann Intern Med 2013;159:592; Addiction 2015;110:996)
- Labs: Serum/urine tox, LFTs, HIV, HBV/HCV, TB, RPR, EKG. NB: urine fentanyl separate order, takes days to result
  - Pain Control: pts w/ OUD and/or chronic opioids likely have developed tolerance and require higher doses of opioids to treat pain
  - In pts using non-prescribed opioids: (Can initiate methadone for withdrawal & add short-acting opioids titrated to pain
  - In pts taking methadone: Give usual dose once confirmed & add short-acting opioids (e.g., oxycodone) titrated to pain
  - In pts taking buprenorphine: There are several available strategies:
    - For pain of short duration, may continue daily bup & add short-acting opioids (may need high doses, consider PCA)
    - Give TDD of bup divided 3-4x daily (e.g. 4-8 mg q6-8h for mod-severe pain)
    - Naloxone: goal is to improve mental status, oxygen saturation, and ensure RR>10, NOT to achieve normal level of consciousness
      - Dose: 0.04mg IV, if no response increase dose q2 min: 0.5mg→2mg→4mg→10mg→15mg.
      - Administer intranasally or IM if no IV access
      - NB: Too much naloxone will precipitate opioid withdrawal. Consider diluting 0.4 mg in 10 ml saline and push 1 ml q2-3min.
      - If failing to respond, call Rapid Response and consider endotracheal intubation (STAT RICU consult)
  - Post-resuscitation: Continuous 02 monitoring (naloxone lasts 30-60m while t1/2 of opioids longer in OD ), APAP level. Consider naloxone gtt if recurrent OD.

ACUTE OPIOID OVERDOSAGE (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
  - Naloxone: high-dose Rx’d opioids and/or other sedatives (check MassPAT), injection use (Ann Intern Med 2013;159:592; Addiction 2015;110:996)
  - In pts taking buprenorphine: There are several available strategies:
    - Wait until Clinical Opioid Withdrawal Scale (COWS) >10, usually 10-12h after last heroin use/short acting opioids.
      - Avoid precipitated withdrawal—rapid, intense induced if buprenorphine given too early.
      - First dose: 4mg/1mg (1/2 of an 8mg/2mg Suboxone tablet)
      - Second dose: If continued withdrawal sx, give another 4mg/1mg after 45-60 minutes
      - Third dose: If recurrent withdrawal sx, give another 4mg/1mg after 6-12 hours
      - Maximum dose for Day #1 is 12mg suboxone.
    - Prescribe total from Day 1 for Day 2, then reassess later in the day. Can give additional 4mg/1mg for withdrawal symptoms, but max dose for Day #2 is 16mg suboxone.
  - Methadone: Full agonist. Check and trend EKG for QTc, as methadone may further prolong QTc.
    - Day 1 Initial dose: 10-20mg x1. COWS q2h. If <6 ➔ observe; if 6-12 ➔ 5mg dose x1; if ≥12 ➔ 10mg dose x1. REQUIRED to call ACT if ≥40 mg daily dose.
    - Day 2 Stabilization: Day 1 dose if COWS ≤5, increase by 20% if COWS 6-12.
    - If not planning to transition to methadone maintenance, decrease dose by 20% per day
  - NB: If unable to initiate Suboxone/methadone, offer symptomatic medications and short-acting opioids for pain
    - Autonomic dysregulation: Clonidine 0.1-0.2mg TID PRN (monitor BP); avoid w/ 1st Suboxone/methadone dose
    - GI upset: Bentyl 10-20mg Q6H PRN abd cramps; promethazine 25-50mg IM PRN N/V; loperamide 2mg PRN diarrhea
    - Anxiety: Hydroxyzine 25mg Q8H PRN or trazodone 50-100mg q8h PRN
  - Discharge planning: Ensure pts have insurance, PCP, suboxone provider, and list of shelters/needle exchanges (if needed)
    - Last dose letter for patients on methadone maintenance (includes date/amount of last methadone dose)
    - Prescribe naloxone and teach OD response. Emphasize that Narcan reverses OD for ~30m. After OD ➔ EMS to the ED.
    - Bridge clinic: Founders 8th Floor, pts can call 617-643-8281 Mon-Fri 8am-4pm to schedule appt or present as walk-in
  - Obstetrics: For pain of short duration, may continue daily bup & add short-acting opioids (may need high doses, consider PCA)

Opioid Use Disorder & Withdrawal

John Weems

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**Psychiatry**

**Substance Use Disorders**

**MGH Tox Screens:**

- **Basic Serum Toxicology Screen:** Quantitative assay for ethanol, salicylates, acetaminophen; Qualitative assay for TCAs
- **Drug Screen, Prescription/OTC (“Full tox”):** Send out to Mayo, will take >3 days to return ([www.mayomedicallaboratories.com](http://www.mayomedicallaboratories.com))
  - Common OTCs: Caffeine, acetaminophen, salicylates, ibuprofen, naproxen, dextromethorphan, diphenhydramine, guaiifenesin
  - **Psychoactive Drugs:** Barbiturates, AEDs (incl. carbamazepine, lamotrigine, levetiracetam, topiramate), propofol, TCAs, SSRIs, SNRIs, bupropion, phenothiazines (incl. chlorpromazine, thioridazine), clozapine, muscle relaxants (cyclobenzaprine, metaxalone), sleep meds (incl. zolpidem, zaleplon)
  - Others: Lidocaine, trazodone, theophylline, some pesticides
  - Limited use for illicit drugs: Benzos, some opiates (incl. codeine, meperidine, methadone, oxycodone, fentanyl), amphetamines
- **Drugs Not on screen:**
  - THC
- **Urine Toxicology Screen:** Amphetamines, barbiturates, benzodiazepines, THC, cocaine, opiates, phencyclidine
- **VPAIN (“Urine pain panel”):** Buprenorphine, oxycodone, methadone, 6-monoacetyl morphine (heroin metabolite)
  - NB: urine fentanyl is an add-on test—consider sending for suspected opioid OD (esp. with PEA arrest) given prevalence of high prevalence of synthetic fentanyl analogues in the community
- **Oral Fluid Drug Test:** Differentiates specific TYPE of benzo (eg, lorazepam v diazepam), opiate (eg, codeine v heroin), amphetamine


<table>
<thead>
<tr>
<th>Class</th>
<th>Detection Time (days)</th>
<th>False Positives</th>
<th>False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>1-2d after use</td>
<td>bupropion, labetalol, tramozone, rantidine, pseudoephedrine, selegiline</td>
<td>Ritalin &amp; atomoxetine won’t test +</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>2-20d after use</td>
<td>Fioricet (contains butalbital)</td>
<td></td>
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<tr>
<td>Benzodiazepines</td>
<td>1-5d (most); 2-30d after diazepam</td>
<td>oxaprin (NSAID)</td>
<td>lorazepam, clonazepam &lt;1mg/day</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>1-7d after use, up to 1mo heavy chronic use</td>
<td>hemp products, Marinol</td>
<td>synthetic cannabinoids</td>
</tr>
<tr>
<td>Opiates (NOT methadone, fentanyl, meperidine)</td>
<td>1-3d after use, 6-8d after heavy use</td>
<td>poppy seeds (unlikely); At MGH, methadone, naloxone, fluorquinolones do NOT interfere</td>
<td>oxycodone, oxymorphone, Suboxone</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2-4d after use, 1-3wks after heavy use</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>7-14d after use</td>
<td>Lamictal, Effexor, Tramadol, dextromethorphan, doxylamine</td>
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<tr>
<td>Buprenorphine</td>
<td>5-10d</td>
<td>high doses of opiates/methadone/tramadol; quinine, hydroxychloroquine, naltrexone</td>
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</tr>
<tr>
<td>Methadone</td>
<td>1-5d</td>
<td>quetiapine, diphenhydramine, doxylamine</td>
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</tr>
<tr>
<td>Oxycodone</td>
<td>2-4d</td>
<td>substances that change urine color (e.g., Flagyl) will cause refusal</td>
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</tbody>
</table>

**Cocaine Intoxication/Withdrawal:**

- **Intoxication:** Grandiosity, euphoria, hyperactivity, anorexia, anxiety, psychotic sx (formication, paranoia, AH/VH), fever, mydriasis. Vasosospasm can cause HTN emergency, stroke, MI and seizures. **Tx:** labetalol, phenotolamine (AVOID unopposed alpha stimulation)
- **Withdrawal:** Depression, fatigue, nightmares, cravings, ↑ sleep/appetite. **Tx:** propranolol, quetiapine for severe sx; Chronic: consider topiramate and/or baclofen for cravings/dependence (consult ACT) ([Psychiatry 2005;24](http://www.psychotherapynews.com/articles/2005/24/2411115.html))

**Benzodiazepine Withdrawal:** Manage withdrawal per EIOH protocol (see “Alcohol Withdrawal” section). Higher risk for delirium with BZD withdrawal. If possible, initiate taper with same BZD agent (eg due to extremely short half-life, alprazolam requires alprazolam taper).

<table>
<thead>
<tr>
<th>Commonly used benzos</th>
<th>Comparative dosages (approx)</th>
<th>Half-life (hours) (approx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam (Xanax)*</td>
<td>0.5mg</td>
<td>6-27 (oral peak 1-2)</td>
</tr>
<tr>
<td>clonazepoxide (Librium)*</td>
<td>25mg</td>
<td>5-30 (oral peak 0.5-4)</td>
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<tr>
<td>clonazepamine (Klonopin)*</td>
<td>0.25mg</td>
<td>18-50 (oral peak 1-2)</td>
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<tr>
<td>diazepam (Valium)*</td>
<td>5mg</td>
<td>20-50 (oral peak 0.5-1)</td>
</tr>
<tr>
<td>lorazepam (Ativan)*</td>
<td>1mg</td>
<td>10-20 (oral peak 2-4)</td>
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<tr>
<td>temazepam (Restoril)*</td>
<td>10mg</td>
<td>3-19 (oral peak 1-2)</td>
</tr>
<tr>
<td>triazolam (Halcion)*</td>
<td>0.25mg</td>
<td>2-3 (oral peak 0.7-2)</td>
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</table>

*Most common illicit usage bc most commonly prescribed

**Spice/K2/Bath Salt Intoxication:** Agitation/violence, hallucination/paranoia, anxiety, tachycardia, arrhythmia, myoclonus, diaphoresis.

- **TX:** low stimulation environment, IVF, consider IV BZDs to reduce agitation and prevent seizure ([Curr Psychiatry Rep 2016;18:52](http://www.clinicaljournalofpsychiatry.com/article/S1521-6549(16)30052-0/abstract))

**THC Intoxication:** Euphoria followed by relaxation; tachycardia; hallucinations (especially w/ high potency THC, e.g., wax/dab)

- **Cannabinoid hyperemesis syndrome:** Chronic user with recurrent NV, abdominal pain; symptom relief w/ hot showers; mild leukocytosis. **Tx:** IVF, antiemetic, and THC cessation; consider BDZ, followed by antipsychotic and capsaicin ([J Med Toxicol 2017;13:71](http://www.jmedicaltoxicology.com/article/S1556-9527(17)30012-6/abstract))

Julia Cromwell, Meghan Musselman
### General Screening Guidelines (USPSTF*, ADA*, AACF/acea, ACC/Aha*, ACCP*, CDC, ACS†) [Evidence Grade]

#### Cardiovascular Screening / Preventative Health Recommendations

<table>
<thead>
<tr>
<th>Age</th>
<th>18</th>
<th>19</th>
<th>20</th>
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<th>75+</th>
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</thead>
<tbody>
<tr>
<td>CVD Risk</td>
<td>Assess RFs q4-6y [B]†&lt;sup&gt;1&lt;/sup&gt; (age, sex, total chol/HDL, SBP, DM, smoking)</td>
<td>Estimate risk w/ ASCVD calculator q4-6y [B]‡</td>
<td>If ASCVD risk ≥10% w/ ≥1 CVD RF*&lt;sup&gt;‡&lt;/sup&gt;, consider statin [B]§</td>
<td>ASA for 1° ppx*&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1° ppx for CV events, colon CA if ≥10% 10-yr ASCVD risk, no risk bleeding, &amp; life exp ≥10 years [B]†‡&lt;sup&gt;‡&lt;/sup&gt;; recent RCT w/ no sig benefit in elderly (NEJM 2018;379:1509)</td>
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<tr>
<td>Diabetes</td>
<td>If HTN or BMI ≥25 (≥23 Asian) w/ ≥1 DM RF*&lt;sup&gt;‡&lt;/sup&gt; [B]‡</td>
<td>Q3y, 1° interval if abnl result, annually in pre-DM*</td>
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<td>HLD</td>
<td>Q3-5y: Q1y if borderline high BP, obese, AA [A]†</td>
<td>Q1y [A]§</td>
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<tr>
<td>HCV</td>
<td>One-time screening age &lt;20</td>
<td>Men 20-45, women 20-55: screen Q5yr, ↑ if RF [C]†; Q 3-5y in DM if wnl at dx</td>
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<tr>
<td>LTCA</td>
<td>Men &gt;45, women &gt;55 Q1-2y if no RF*&lt;sup&gt;‡&lt;/sup&gt; [A]: Q1y in DM [B]§</td>
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<tr>
<td>Skin CA</td>
<td>Insufficient evidence for routine skin exams by clinicians [I]§</td>
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<td>Obesity</td>
<td>Annual BMI → refer for or offer intensive behavioral intervention if ≥30 (obese) [B]‡</td>
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<tr>
<td>Diet</td>
<td>Intensive behavioral counseling if CVD RF* [B]‡</td>
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<tr>
<td>Exercise</td>
<td>150 min/wk mod exercise (30 min 5x/wk); 75 min/wk intense exercise (25 min 3x/wk)/†</td>
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</table>

#### Universal Cancer Screening

| **Colorectal CA** | Start 10 years prior to age of affected family member at dx*** | Colo Q10y, flex sig Q5y, FIT Q1y [A]† |
| **Lung CA** | Q1y low-dose CT if 50 yrs & quit w/in last 15y [B]§ |

#### Infectious Disease Screening

| HIV | Screen at least once; repeat based on risk assessment [A]† |
| HCV | Screen x1 if born 1945–1965, additional screening based on risk assessment [B]‡ |
| HBV | Born in endemic region, getting HD or immunosuppression, HIV+, IVDU, MSM, close contact w/ HBV+ person [B]§ |

#### Psych/SUD/Social Risk Factor Screening

| Depression | Q1y [B]‡; PHQ-2: in 2 wk how often (a) little interest/pleasure doing things & (b) down/depressed/hopeless |
| EtOH Misuse | Screen regularly with AUDIT-C [B]‡ |
| Tobacco | Every encounter [A]§; Advise to quit, Assist doing so (plan, quit date, QuitWorks, meds), Arrange f/u. |
| Intimate Partner Violence | Screen regularly in women of reproductive age [B]§; HITS screen well-validated. Assess immediate safety & consider HAVEN referral. |
| Fall Risk | No data but consider ongoing IPV, elder abuse screening |

* CVD RFs: DM, HTN, personal Hx of any athero, FHx (<50 in male relatives, <60 in female relatives), BMI (30+), smoking
† DM RFs: prior abnl testing (A1c≥5.7), FHx, AA/Latinx/Asian/NA ancestry, Hx GDM, PCOS, CVD, HLD<35 or TG>250, physical inactivity
** Age 40 if ≥1° degree relative dx <65; Age 45 if AA or 1° degree relative dx <65; Age 50 for others expected to live ≥10yrs
*** Age 40 if ≥1° first-degree relative with history of prostate cancer

#### Additional Screening Guidelines for Men (USPSTF*, ACS†) [Evidence Grade]

<table>
<thead>
<tr>
<th>Age</th>
<th>18-40</th>
<th>40</th>
<th>45</th>
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<th>60</th>
<th>65</th>
<th>70</th>
<th>75+</th>
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<tbody>
<tr>
<td>AAA</td>
<td>If +tobacco hx [B]§</td>
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<tr>
<td>Prostate CA</td>
<td>FHx* Q2y&lt;sup&gt;3&lt;/sup&gt;</td>
<td>FHx, AA Q2y&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Screen all men Q2y if life expectancy ≥10-15yrs&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>PSA 55-69yo if pt preference [C]&lt;sup&gt;3&lt;/sup&gt;, recommend against if &gt;70yo [D]&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Testicular CA</td>
<td>Recommend against routine screening in all men [D]&lt;sup&gt;3&lt;/sup&gt;</td>
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#### Additional Screening Guidelines for Non-Pregnant Women (USPSTF*) [Evidence grade]

<table>
<thead>
<tr>
<th>Age</th>
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<th>19</th>
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<th>21</th>
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<th>65</th>
<th>70</th>
<th>75+</th>
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</thead>
<tbody>
<tr>
<td>Breast CA</td>
<td>Consider BRCA counseling if +FHx. Screening tools available. [B]†</td>
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<tr>
<td>Individualized screening by risk (Gail Model)</td>
<td>Q2y mammography age 50-74. Stop if &lt;10yrs life expectancy. [B]‡</td>
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<tr>
<td>Cervical CA</td>
<td>Q3y [A]§</td>
<td>Q3y or Q5y + HPV co-testing [A]§</td>
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<tr>
<td>STIs</td>
<td>≤24: GC/CT annually [B]§</td>
<td>Screen based on risk assessment</td>
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<tr>
<td>Contraception</td>
<td>Discuss with everyone. Start folic acid at reproductive age if planning/capable of pregnancy [A]§</td>
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<tr>
<td>Osteoporosis</td>
<td>Consider earlier screening based on FRAX assessment [B]§</td>
<td>DEXA [B]§</td>
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<tr>
<td>2: Stop if 3 consecutive neg paps or 2 consecutive neg co-tests within 10 yrs w/ most recent test within 5 years. Continue x20 yrs s/p dx pre-cancerous lesion regardless of age. Do not resume age ≥65 for new sexual partner only.</td>
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</tbody>
</table>
ADDITIONAL SCREENING GUIDELINES FOR SPECIAL POPULATIONS

- MSM (men who have sex with men) and SMW (sexual minority women): see LGBTQ Health
- Immigrants and refugees: see Immigrant & Refugee Health

Note that there is considerable discrepancy between societal guidelines created using the same evidence. Examples include:

- Breast Cancer – USPSTF: biannual screening age 50-74 [B]; discussion of risks/benefits age 40-49 [C]; no recommendation for women >75 given insufficient evidence [I]; ACS: annual mammography age 45-55; discuss transitioning to biennial screening at 55 until life expectancy <10 years; discuss initiation of annual screening starting at age 40. ACOG: offer screening mammography at 40; start screening at 50; discuss cessation at 75; screen Q1-2 years.
- Diabetes – USPSTF: screen overweight and obese adults aged 40-70; no specific interval guidance. We have selected the ADA guidelines because they account for additional risk factors and recommend a specific screening interval.

MANAGEMENT OF ABNORMAL PAP SMEAR (ASCP Consensus Guidelines, 2012)

<table>
<thead>
<tr>
<th>Abnormal Pap Cytology Results</th>
<th>ASCUS</th>
<th>LSIL</th>
<th>HSIL</th>
<th>AGC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 21-24</td>
<td>Preferred: Management as per LSIL (annual cytology). Alternative: HPV reflex. If HPV-, repeat regular screening; if HPV+, manage as LSIL</td>
<td>Repeat cytology in 1 year: if neg, ASC-US, or LSIL, repeat in 12 mos; if neg repeat in 12 months; if neg x2 resume regular screening vs. if ≥ ASC-US on any repeat → colpo</td>
<td>Colpo w/ endocervical curettage</td>
<td>For AGC-NOS, AGC-endocervical, or adenocarcinoma in situ (AIS) → colpo w/ biopsy &amp; endocervical sampling, w/ additional endometrial sampling if ≥ 35yo or younger w/ endometrial neoplasia RFs (unopposed estrogen, tamoxifen, early menarche, late menopause, PCOS, DM, obesity) or sux (AUB) For AGC-endometrial → endometrial &amp; endocervical sampling</td>
</tr>
<tr>
<td>Age 25-29</td>
<td>Preferred: HPV reflex. If HPV+ → colpo. If HPV- repeat co-testing in 3 years. Alternative: Repeat cytology in 1 year. If neg, resume routine screening. If ≥ ASC-US → colpo</td>
<td>HPV reflex: If HPV- repeat co-testing in 1 year and if neg repeat co-testing in 3 years vs. if pos (cytology or HPV) → colpo. If HPV reflex or unknown → colpo</td>
<td>Option 1: Colpo w/ endocervical curettage Option 2: Immediate LEEP (not if pregnant or desiring pregnancy)</td>
<td></td>
</tr>
<tr>
<td>Age 30+</td>
<td>Preferred: HPV reflex. If HPV+ → colpo. If HPV- repeat co-testing in 3 years. Alternative: Repeat cytology in 1 year. If neg, resume routine screening. If ≥ ASC-US → colpo</td>
<td>HPV reflex: If HPV- repeat co-testing in 1 year and if neg repeat co-testing in 3 years vs. if pos (cytology or HPV) → colpo. If HPV reflex + or unknown → colpo</td>
<td>Option 1: Colpo w/ endocervical curettage</td>
<td></td>
</tr>
</tbody>
</table>

VACCINES - [https://www.cdc.gov/vaccines/schedules/hcp/adult.html](https://www.cdc.gov/vaccines/schedules/hcp/adult.html)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age</th>
<th># of Doses/ Special indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>All, q1Yr</td>
<td>No live vaccine (intranasal): immunocompromised/pregnant</td>
</tr>
<tr>
<td>Tdap / Td</td>
<td>All, q10Yrs (substitute Tdap for Td once)</td>
<td>Extra dose Tdap for pregnant women</td>
</tr>
<tr>
<td>PCV13/ PPSV23</td>
<td>All ≥25; PCV13, then PPSV23 12 mo later; if PPSV23 already given &lt;65, re-dose x1 at ≥ 5yrs. Age 19-64: if CHF/CM, chronic lung dz, cirrhosis, DM, ETOH d/o, smoking; redose x1 at ≥ 65 (if &gt;5y from 1st PPSV23 &amp; 12mo from PCV13)</td>
<td>Special pops: CSF leak, cochlear implant, functional asplenia, immunocompromised (incl: immunodeficiency d/o, HIV, nephrotic syndrome, malignancy, tx; full list at CDC) Age &gt;18: give PCV13 x1 → PPSV23 8 wks later and redose x1 at 5yrs if asplenia or immunocomp &amp; again at age 65 (if &gt;5yrs from 1st)</td>
</tr>
<tr>
<td>Varicella*</td>
<td>Only if no evidence of immunity (presumed immune if U.S.-born pre-1980)</td>
<td>2 doses at least 1mo apart</td>
</tr>
<tr>
<td>Zoster*</td>
<td>50+ (regardless of varicella infxn hx)</td>
<td>2 doses RZV 2-6 mo apart if &gt;50yo (if received ZVL, at least 2 mo after dose). If &gt;60, give RZV (preferred) or ZVL</td>
</tr>
<tr>
<td>HPV</td>
<td>Women &lt;27, Men &lt;22 (or MSM, HIV &lt;27)</td>
<td>3 doses at 0/1-2/6 months</td>
</tr>
<tr>
<td>MMR*</td>
<td>Only if no evidence of immunity</td>
<td>1-2 doses at least 28 days apart, 1 dose in women of childbearing age</td>
</tr>
<tr>
<td>Hep A</td>
<td>Likely unvaccinated if born before 1991</td>
<td>2 doses at 0/6-12 mo for travel to endemic countries, MSM, any drug use (not just IVDU), liver dz, clotting d/o, household contacts of those at risk</td>
</tr>
<tr>
<td>Hep B</td>
<td>Likely unvaccinated if born before 1991</td>
<td>3 doses at 0/1-6 mo for mult partners, STI, MSM, + partner, IVDU, DM, ESRD, any liver dz, HIV, health worker/occup exposure, travel to endemic country, household contacts</td>
</tr>
<tr>
<td>Meningococcus (MenACWY/ MenB)</td>
<td>Usually vaccinated as teen. May need booster q5y if risk of infxn remains.</td>
<td>1-3 doses depending on type for living in dorms, asplenia, HIV, MSM, complement def, military, occup exposure, travel</td>
</tr>
<tr>
<td>Hib</td>
<td>Usually vaccinated as child</td>
<td>1 dose if not immune for asplenia, SCD</td>
</tr>
</tbody>
</table>

* Hold in pregnancy, malignancy, immunocompromised
Vulvar/Vaginal Complaints (Obstet Gynecol 2008;5:1243)

- Presentation: vaginal discharge, odor, pain, pruritus
- Infectious vaginitis: more likely to present acutely
  - Bacterial vaginosis (BV): malodorous discharge, most common and most pts asymptomatic, high prevalence in WSW
    - Dx: 3/4 Amسل criteria (homogenous/thin-grey-white discharge smoothly coating vaginal walls, clue cells, fishy smell on KOH, pH >4.5 (less reliable if post-menopause) → order “Genital culture female” in Epic, collected with rayon swab, gram stain assesses for clue cells (0-3 consistent with normal flora, 7-10 consistent with BV)
    - Tx: Flagyl 500mg BID x7d, clinda 300mg BID x 7d, or secnidazole 2gm x 1; can opt not to tx if not pregnant
  - Candida: curd-like discharge, pruritus
    - Dx: pH nl, order “Genital culture female” in Epic, collected with rayon swab, add on anti-fungal sens. if recurrent
    - Tx: Monistat 7 (vaginal miconazole 2% 5g daily x 7d) OTC, fluconazole 150mg PO X 1 requires Rx (cheaper)
  - Trichomonas: purulent malodorous discharge, inflammation on exam (DDx includes gonorrhea and chlamydia)
    - Dx: pH >5-6, trichomonads on microscopy, order “Trichomonas vaginalis antigen” collected with rayon swab
    - Tx: Flagyl 2gm x1 for patient and sexual partners
- Dermatoses: more likely to present chronically, often require GYN referral and biopsy
  - Contact dermatitis: erythema, swelling, fissures, erosions → r/o Candida, remove offending agent
  - Vulvar atrophy: 50% postmenopausal 2/2 decreased vaginal secretions, Δ vaginal flora → moisturizers, topical estradiol
  - Lichen simplex chronicus: intense pruritis + lichenified plaque i/s/o atopic dermatitis hx → antihistamines, steroids
  - Lichen sclerosis: onset 50-60s, cigarette paper skin + porcelain white papules i/s/o autoimmune dz, may lead to labia minora fusion, clitoral hood phimosis, fissures, perianal dz, 5% incidence of malignancy → high potency steroids x4 wks
  - Lichen planus: “purple, papular, pruritic,” while lacy Wickham striae → high potency steroids, monitor for SCC


- Hx: quantity, pattern (breakthrough, intermenstrual, irregular), sexual/ OB hx, trauma, FH, cancer risks, meds (hormones, A/C)
- Dx: pelvic exam; CBC, coags, hCG, TSH, PRL, UA, GCCT; +/- transvaginal pelvic US (TVPU5), hysteroscopy, endometrial bx (EMB)
- DDx:
  - Structural: polyps (↑ risk of endometrial CA if post-menopausal, on tamoxifen, >1.5cm → resection, Mirena), leiomyomas (fibroids → resection, hysterecomy, GnRH agonists), adenomyosis (boggy uterus → hormonal bx, hysterecomy)
  - Malignancy/hyperplasia: must be excluded in any peri- or post-menopausal ≥ 40y with AUB or younger pts with risk factors (unopposed estrogen, early menarche, late menopause, nulliparity, PCOS, obesity, DM, tamoxifen, Fx) → dx with bx and EM B +/- imaging → tx with progesterone for hyperplasia + EMB Q3-6mo OR hysterecomy
  - Ovarian dysfunction: endocrine d/o, PCOS, obesity → OCP, progestin-only (Mirena), endometrial ablation, hysterecomy
  - Coagulopathy: disorders of hemostasis or oral A/C
  - Iatrogenic: common with progestin-only contraceptives, especially initially

Polycystic Ovary Syndrome (PCOS): affects 5-10% of women of reproductive age (NEJM 2005;352:1223; J Clin Endo Met 2013;98;4565; Obstet Gynecol 2009;114;936)

- Criteria: 2/3: oligo/ anovulation, clinical/ biochemical hyperandrogenism (i.e. hirsutism), polycystic ovaries on pelvic US
- Workup: testosterone; exclude other dx (hCG, FSH, 17-OHP (pre-8AM), prolactin, TSH), screen for metabolic d/o, OSA, mood d/o
- Tx: weight loss, OCP/ Mirena, spironolactone, metformin (if insulin resistant), fertility referral if/ when pt desires pregnancy

Infertility: Evaluate after 12 mo unprotected intercourse in <35 yo, 6 mo in >35 yo (Fertil Steril 2015;103:e44)

- DDx: ovulatory dysfunction, fallopian tube abnormalities, uterine abnormalities, cervical factors, endometriosis
- Hx: duration of infertility, prior OB/GYN hx (menstrual hx, pregnancies, PID, fibroids, cervical dysplasia, endometriosis, contraceptive use, DTE exposure in <35 yo, 6 mo in >35 yo (Fertil Steril 2015;103:e44)
- Dx:
  - Test ovulation: mid-luteal progesterone (day 21, 1 wk before expected menses, goal >3), home kit to check for LH surge
  - Test ovarian reserve: FSH estradiol (day 3, goal FSH <10, estradiol <80), clomiphene challenge test
  - Additional workup: chlamydia PCR, HSG (fallopian tubes), saline infusion sonohysterography (uterus)
  - Partner: semen analysis
- Tx: if testing abnormal, refer to reproductive endocrinology for specific induction of ovulation, IVF, or donor oocytes

Menopause: amenorrhea x12 mo w/o alt etiology (no need to check labs), avg onset age 51, suspect 1° ovarian insuff if <40 yo (Obstet Gynecol 2014;123:202)

- Vasomotor sx (hot flashes): Systemic hormone tx (estrogen + progestin, estrogen monoxif hysterecomy): most effective therapy but only recommended if <60 yo and for <5 yrs duration (J Clin Endo Met 2008;93:4567); start at 0.5 mg/day; side effects include breast tenderness, vaginal bleeding; ↓CRC, fracture risk; ↑breast CA, CVD, VTE; Ø inc risk of mortality after 5-7 yrs (JAMA 2017;318(10):927); Alternatives: SSRIs (paroxetine), SNRIs (venlafaxine), gabapentin, clonidine
- Vaginal sx (dryness, burning, pain w/ intercourse)
  - Lubricants (KY): prior to intercourse; Moisturizers (Replens): longer-term relief
  - Topical estrogen therapy; ring, tablet, cream; start at 0.3 mg/day; Ø inc risk of endometrial hyperplasia
  - SERM (ospemifene): for sx atrophy not relieved by nonpharm tx or not amenable to topical bx; adv effects incl ↓ hot flashes
**Contraception:** see Quick Start Algorithm (Contraceptive Technology 20th Ed CDC USMEC 2016)

- 45% of pregnancies are unplanned → rule out pregnancy before initiating contraception → IUD, implant are first line
- Hormonal methods take ~1 wk to work → use backup method for 7 days

<table>
<thead>
<tr>
<th>Use</th>
<th>1y Failure Rate*</th>
<th>Pros/Cons</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td><strong>Estrogen-progestin</strong></td>
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<tr>
<td>Pill</td>
<td>Daily</td>
<td>9% (0.3%)</td>
<td>- Pros: ↓menses, PMS, cramps, acne, endometrial/ovarian CA</td>
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<td></td>
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<td>- Cons: N/V, breast tenderness, libido, spotting, require patient adherence</td>
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<tr>
<td>Ring (Nuva-Ring)</td>
<td>3 wks in, 1 wk out</td>
<td>9% (0.3%)</td>
<td>- Pros: effective, long-acting</td>
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<td>- Cons: VTE, thrombogenic mutation</td>
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<tr>
<td>Patch (Xulane)</td>
<td>Weekly x3 wks, 1 wk off; apply to arm, torso, or buttck</td>
<td>9% (0.3%)</td>
<td>- Active breast or liver CA</td>
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<td>- Migraine w/ aura, &gt;35 yo + any migraine</td>
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<td>- Uncontrolled HTN, DM w/ vasc complications, CVD, valvular dz</td>
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<td>- &gt;35 yo + &gt;15 cig/day</td>
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<td></td>
<td></td>
<td></td>
<td>- ESLD</td>
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<tr>
<td>IUD (hormone content Mirena &gt; Kyleena &gt; Skyla)</td>
<td>0.2%</td>
<td>- Pros: effective, long-acting, ↓ bleeding, physical complications (rare)</td>
<td>- Abn uterine cavity, G/C at time of insertion, PID, endometrial/cervical/breast/liver Ca, APLAS, pregnancy, ESLD</td>
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<tr>
<td>Implant (Nexplanon)</td>
<td>Q3Y to upper inner arm</td>
<td>0.05%</td>
<td>- Pros: long-acting</td>
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<td></td>
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<td>- Cons: irregular bleeding</td>
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<tr>
<td>Injection (Depot-Provera)</td>
<td>Q3mo IM/SQ to buttck</td>
<td>6% (0.2%)</td>
<td>- Pros: few contraindications</td>
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<td>- Cons: irregular bleeding</td>
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<td></td>
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<td>- Must take at same time daily</td>
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<tr>
<td>Pill (Micronor)</td>
<td>Daily</td>
<td>9% (0.3%)</td>
<td>- Bariatric surgery</td>
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<td></td>
<td></td>
<td>- Breast/liver CA, APLAS, ESLD</td>
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<tr>
<td><strong>Progestin-only</strong></td>
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<tr>
<td>Copper IUD (Paraguard)</td>
<td>Q12Y</td>
<td>0.8%</td>
<td>- Pros: effective, long-acting, safe in ESLD, emergency contraceptive</td>
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<td>- Cons: heavier bleeding, cramping</td>
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<td></td>
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<td></td>
<td>- Abn uterine cavity, G/C at time of insertion, PID, endometrial/cervical/breast/liver Ca, pregnancy</td>
</tr>
<tr>
<td>Male condom</td>
<td>Every encounter</td>
<td>18% (2%)</td>
<td>- Pros: STI prevention</td>
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<td></td>
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<td></td>
<td>- Cons: require patient adherence</td>
</tr>
<tr>
<td>Sterilization</td>
<td>Permanent</td>
<td>0.15%</td>
<td>- Surgical risk, patient unsure of decision</td>
</tr>
</tbody>
</table>

* Typical use – i.e. % women who will have unplanned pregnancy in 1 year on this method; (% Perfect use – not realistic for most)

**Oral Contraceptives (OCPs): (CDC MMWR 2013;62(RR05):1)**

- Types: monophasic vs multiphasic/ triphasic; combined (estrogen + progestin) vs progestin-only
- OCP selection:
  - 2nd generation progestin-containing (levonorgestrel, norethindrone): ↓ VTE risk
  - 3rd generation progestin-containing (norgestimate, desogestrel): ↓ androgenic SE, higher VTE risk
  - Progestin-only (norethindrone 0.35 mg): if contraindication to estrogen, if lactating
- Switching OCPs due to SEs:
  - HA, nausea, breast tenderness → 2/3 estrogen excess → decrease estrogen dosing, change to QHS
  - Weight gain, acne, hirsutism, ↓ libido, mood Δ → 2/3 androgen or progestin excess → change to 3rd gen progestin
  - Breakthrough bleeding → increase estrogen dosing if early cycle bleeding; increase progestin or change to triphasic if late
  - Amenorrhea → rule out pregnancy, otherwise continue with same pill

**Emergency Contraception:** (Obstet Gynecol 2010;115:1100)

- Sexual assault cases should be referred to the ED for an exam by a trained SANE RN
- Plan B (levonorgestrel 1.5mg x1 or 0.75mg x2): OTC, use within 72 hrs, less reliable if BMI >30
- Ella (ulipristal acetate 30 mg): requires rx, use within 120 hrs, more reliable in higher BMI
- Paragard (copper IUD): requires office visit, ideally placed within 120 hrs (okay up to 160), most effective

**Abortion:** (Guttmacher Institute Fact Sheet; Am J Public Health 2017;107:1904; Obstet Gynecol 2014;123:676)

- See PCOI for list of providers in MA. Ave cost ~$500, 50% pay out of pocket. 1/4 will have abortion by age 45 in USA.
- Workup: confirm pregnancy/ LMP/ TVPUS, check CBC/ Rh, offer STI testing and immediate post-abortion contraception
- Medical abortion (performed up to 10 wks gestation, 92% effective): mifepristone x1 → buccal misoprostol in 24-48 hr → pt passes pregnancy at home over hrs, a/w cramping and bleeding, tx with NSAIDs → f/u bHCG or TVPUS usually in 14d
- Surgical abortion (performed up to 24 wks gestation, 99% effective): same-day office procedure → no f/u unless complications
- Counseling: 1-866-4-EXHALE
Primary Care

Musculoskeletal Pain

Urinary incontinence: Very common (25% young women → 75% of older women). Most women do not seek help.

- Types: stress (leakage with coughing, laughing, etc.), urge (loss of urine preceded by feeling of urgency), mixed (most common, stress + urge), overflow, and functional (impaired mobility/cognition/neurologic).
- Dx: History: Review meds (anticholinergic, diuretics, etc.), bowel habits, caffeine/ETOH use, 72h voiding diary. Physical exam: check for prolapse, fistula, diverticulum; cough stress test (can be supine, but standing w/ full bladder ↑ sensitivity); urethral mobility (w/pt bearing down, displacement >30° or movement >2cm); rectal exam (fetal impaction, sphincter tone); neuro exam. Diagnostics: UA/ox, PVR (if suspect overflow, abnl >150cc), specialized urodynamic studies not indicated in initial eval of uncomplicated UI.
- Tx: All types: bladder training (timed voiding, use PCOI handout), lifestyle interventions (eg weight loss, ↓ fluid/caffeine intake) and pelvic floor muscle exercises (eg Kegels, use PCOI handout, consider referral to pelvic floor PT). Stress/mixed: Pessaries (mixed data, best for women who wish to avoid therapy/behavioral therapy, refer to urogyn for fitting), vaginal estrogen (in post-menopausal women w/ vaginal atrophy), and surgeries/procedures (eg midurethral sling, urethral bulking agents). Urgency: antimuscarinics (numerous side effects), beta-agonists (eg mirabegron, avoid w/uncontrolled HTN, ESRD, liver disease), and intravesicular botox

MUSCULOSKELETAL PAIN

KNEE PAIN

- Pathophysiology: Detailed hx, incl: trauma, acute vs. chronic, constitutional sx, BMI, orthopedic hx. Elicit history of swelling, stiffness, instability, popping or catching sensation, sensory/motor changes. Have pt point to area of pain with one finger.

<table>
<thead>
<tr>
<th>Location</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>Quadriceps or patellar injury, patellofemoral syndrome, Osgood-Schlatter, bursitis, RA, gout, pseudogout, septic joint</td>
</tr>
<tr>
<td>Lateral</td>
<td>Lateral meniscal tear, lateral collateral ligament injury, iliotibial band, lateral OA</td>
</tr>
<tr>
<td>Medial</td>
<td>Medial meniscal tear, medial collateral ligament injury, tibial plateau fracture, anserine bursitis, medial OA</td>
</tr>
<tr>
<td>Popliteal</td>
<td>Popliteal/Baker cyst, PCL injury, DVT</td>
</tr>
</tbody>
</table>

- Knee Exam:
  - Test | Maneuver | Positive in |
  - Lachman (similar to anterior drawer) | Pt supine with knee flexed, one hand on pt's femur, just above knee. Other hand on pt's tibia. Apply slight flexion and pull sharply towards your abdomen. If tibia feels unrestrained, positive test. | ACL injury |
  - Posterior drawer | Pt supine with knee flexed, can stabilize foot by sitting on it. Place hands around tibia, apply pressure backward in place parallel to femur. If unrestrained motion, positive test. | PCL injury |
  - McMurray | One hand over medial joint line with knee fully flexed. Evert foot, apply valgus stress and gently flex/extend knee. If clicking around medial joint line, positive test. | Meniscal injury |

- XR Imaging: if trauma <1wk old & c/f fracture, follow Ottawa Rules, Se 98%, Sp 49% (Ann Int Med 2004;140(2):121). [obtain if any of the following: >55yo, isolated patellar tenderness, tenderness at head of fibula, cannot flex to 90°, or cannot bear weight for 4 steps (limp doesn’t count)]. If eval of chronic OA, get weightbearing views of both knees; add patellar view for patellar problems.

- Reserve MRI until 4 weeks conservative care unless suspect fracture, infection, or internal derangement (e.g. ACL, meniscal tear in younger patients). Asymptomatic meniscal tears: 13% younger than 45 yo, 36% older than 45 yo (Clin Ortho Rel Res 1992;282:177)

- Treatment: Limited benefit of arthroscopy, especially in degenerative meniscal tears in age > 45 yo, patients with OA (BMJ 2017;357:j1982). Start with NSAIDs, PT, weight loss first even with clicking, catching. Consider glucosamine+chondroitin or platelet-rich-plasma (AHRQ 2017;17-EHC011-EF)

SHOULDER PAIN

- Pathophysiology: R/O neck etiology; neck pain, pain radiating to beyond elbow, numbness, tingling. Hx: Age, trauma, acute vs. chronic, constitutional sx, orthopedic hx. Get precise pain location, day/night, provoking activity, loss of ROM, weakness.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Hx/PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacromial bursitis</td>
<td>Referred pain to lateral upper arm. Impingement signs, painful arc 70°-120° abduction. Overuse; overhead</td>
</tr>
<tr>
<td>Glenohumeral Arthritis/Adhesive Capsulitis</td>
<td>Aching, stiff; chronic loss of active and passive motion in all planes. OA: crepitus, age &gt; 60 yo. Capsulitis: risk w/diabetes, thyroid disease, immobilization, often 40-60 yo.</td>
</tr>
<tr>
<td>Labral Tears &amp; Instability</td>
<td>Young athletes. “Click, pop, catch.” Ant inferior → shot-blocking arm pulled back. Posterior → push-up. SLAP (Superior Labrum Anterior Posterior) → baseball pitching, throwing, overhead weight lifting.</td>
</tr>
<tr>
<td>AC joint pain</td>
<td>Young: traumatic sprain, fall with separation. Older: AC evolves into OA (can contribute to impingment) Pain, tenderness, possibly swelling over AC joint, positive cross arm test</td>
</tr>
</tbody>
</table>

- Shoulder Exam:
  - Test | Maneuver | Positive in |
  - Drop-arm | Ask patient to abduct arm at 90°. Test is positive if they cannot smoothly adduct shoulder to waist-level. | Rotator cuff tear |
  - Neer | Fully pronate forearm (thumb pointing backwards) then bring shoulder to full forward flexion. Test is positive if there is any pain. | Subacromial impingement, rotator cuff tear or tendonopathy |
  - Hawkins | Forward flex shoulder to 90°. Then flex elbow to 90°. Then internally rotate the shoulder. Test is positive if there is pain. | Teres minor & infraspinatus |
  - External rotation | Flex elbow to 90°. Patient externally rotates the shoulder while examiner |
Following is the primary care management of musculoskeletal pain:

### Imaging:
- **X-ray** of the affected area may be needed to rule out bony lesions or joint dislocations.
- **MRI** may be used to assess soft tissue damage.
- **CT scan** can provide detailed imaging of bones and soft tissues.
- **Ultrasound** is useful for assessing soft tissue abnormalities like bursitis or tendinopathies.

### Therapies with Questionable Evidence:
- **Pharmacological therapies**:
  - **NSAIDs** for acute pain: ibuprofen, naproxen.
  - **Opioids**: Considered for severe pain, usually in combination with non-opioids.
  - **Non-opioids**: Acetaminophen, NSAIDs, tramadol.
- **Non-pharmacological therapies**:
  - **Physical therapy**: Includes exercise, massage, and ultrasound.
  - **Psychological interventions**: CBT, mindfulness.

### Pathophysiology of MSK Pain:
- **Acute pain**: Typically resolves in 4-6 weeks in the majority of patients. Avoid bed rest! Activity as tolerated.
- **Chronic pain**: Persistence beyond 12 weeks suggests a poor prognosis. Multimodal therapy is recommended.

### Possible Effective and Lower-Risk Therapies:
- **Non-pharmacological therapies**:
  - **Physical therapy**: Acetaminophen, NSAIDs, tramadol.
  - **Physical therapy**: Massage, hydrotherapy, acupuncture.
- **Psychological interventions**: CBT, mindfulness.

### Therapies with Questionable Evidence and/or Higher Risk of Harm:
- **NSAIDs**: Use with caution; may increase bleeding risk.
- **Opioids**: Risk of addiction, dependency, and long-term use may exacerbate pain.

### Extended Opioid Use:
- **Screening**: Pain agreement, tox screens.
- **Prescribing**: Consider opioid-sparing strategies. Avoid long-term high-dose opioid use.
- **Monitoring**: Regular follow-up to assess pain control, side effects, and adherence.

### Long-term Opioid Use:
- **Screening**: Pain agreement, tox screens.
- **Prescribing**: Consider opioid-sparing strategies. Avoid long-term high-dose opioid use.
- **Monitoring**: Regular follow-up to assess pain control, side effects, and adherence.

### Follow-up for Longer-term Opioids:
- **See patients in office at least q1-3 months to review pain, function, side effects, compliance, and re-evaluate plan.**
- **Early refill requests** should trigger an appointment to assess reason, obtain tox screen, discuss proper use.
Primary Care

LGBTQ Health

Preventive Health Care for MSM (Am Fam Physician 2015;91:844)

- Background:
  - MSM face health inequities in the following areas: HIV/AIDS, STIs, cancer screening, immunizations, substance & tobacco use, mental health, domestic violence (IOM 2011)
  - 2006-2009: 34% increase in HIV incidence among MSM ages 13-29 (48% among African American MSM). In 2011 67% of new cases of HIV were among MSM (PLoS One 2011;6:e17502)
  - LGBTQ individuals: 1.5-fold risk depression and anxiety, 2.5-fold risk suicide attempts (BMC Psych 2006;18:70)

- Recommendations:
  - Annual STI Screening; HIV; TrepAb for syphilis; site-specific GC/CT NAAT based on sexual history (urine, rectal, pharyngeal); urine NAAT as sensitive as urethral, no need to swab urethra; self-collected rectal swabs as sensitive as provider-collected rectal swabs; testing pharyngeal swabs for CT not recommended
  - Screen Q3-6mo if multiple/anonymous partners, sex in conjunction w/ drug use
  - HAV vaccine recommended (focal-oral transmission, don’t need to check immunity); HBV SAg & SAb once, vaccinate if non-immune; HCV Ab once if born 1945-1965; check HCV Ab Q1y if high risk or HIV+
  - HPV vaccination if <27, no clear anal pap guide: HIV- consider q2-3y; HIV+ q1y (high-grade AIN 29%) (Clin Infect Dis 2006;43:223)
  - PrEP: Consider if high-risk sexual activity, nl Cr, able to take daily; TDF-FTC QD is only FDA approved option (CDC 2017)
  - Educate on how to access PEP within 72h of high-risk exposure – can page 36222 at MGH


- Breast cancer: increased risk & incidence in SMW, possibly 2/2 higher rates of obesity, nulliparity, EtOH use
- Cervical Cancer: SMW at risk for HPV infection from both male & female partners but have lower screening rates & higher rates of cervical cancer than heterosexual women (2.2% vs 1.3%). Offer regular pap schedule to everyone w/a cervix regardless of gender or sexual orientation. See HCM section for pap algorithm.
- STIs: Limited data on risk of female-to-female transmission. Screen SMW as usual based on age/risk (see HCM).

Transgender Medicine: 1 in 300 adults in the U.S. identify as transgender or gender non-conforming (Am J Public Health 2017;107:e1)

- Gender Terminology
  - Sex assigned at birth: based on external anatomy vs Gender identity: internal sense of one’s gender
  - Transgender/trans: when one’s assigned sex at birth and gender are not congruent
  - Transgender/transgender: when one’s assigned sex at birth and gender identity are congruent
  - Non-binary, gender non-conforming, genderqueer: gender identity not w/in society’s M/F binary
  - When in doubt, ask your patient! (How do you prefer to be called, what pronouns do you use, etc.)

- Health inequities: mental illness (suicide attempts, depression, anxiety, cervical cancer (counsel that less likely to obtain adequate sample), HIV (trans women w/ 22% HIV infection rate vs 10% of MSM in the US) (J Adolesc Health 2015;56:274; J Gen Intern Med 2014;29:778; Lancet Infect Dis 2012;13:214)
- Discrimination prevents trans patients from seeking health care (US Trans Survey 2015)
- Basic concepts: honor pt’s gender identity, provide anatomy-based screening, multidisciplinary care w/ mental health access
- Gender-Affirming Care: see WPATH Standards of Care, UCSF Center for Excellence in Transgender Health, Fenway guide
  - Informed consent is needed for hormone therapy
  - Discuss fertility preservation needs prior to starting hormones
  - Feminizing hormone therapy cornerstones: Estradiol + concomitant androgen blocker
    - Estradiols (oral/sublingual, transdermal patch, estradiol valerate/estradiol cypionate IM)
    - Androgen blockers (spironolactone most common, can decrease required estrogen dose)
  - Masculinizing hormone therapy cornerstones:
    - Testosterone (T) (testosterone cypionate/enanthate IM/SQ or testosterone topical gel)

<table>
<thead>
<tr>
<th>Potential Risks</th>
<th>Irreversible changes</th>
<th>Reversible changes</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| Masculinizing Therapy (testosterone) | - Breast or uterine cancer  
- Erythrocytosis  
- Liver dysfunction | - Voice changes  
- Facial and body hair  
- Possible male pattern baldness  
- ↑ in size of clitoris | - Cessation of menses  
- ↑ sex drive  
- ↑ muscle mass  
- Possible acne, mood changes | - CBC, lipids, LFTs at 6 mos, then q6-12 mos  
- Consider A1c q6-12 mos if PCOS or risk of DM  
- Serum T after 6-12 mos |
| Feminizing Therapy (estrogen, spironolactone) | - Infertility, erectile dysfunction  
- Breast cancer  
- Blood clots (DVT, PE)  
- Increased risk of CAD, HTN, stroke, liver dz  
- Migraines | - Breast growth  
- Decreased testicle size  
- Infertility | - ↓ muscle mass  
- Weight gain  
- Hair/skin softens  
- ↓ sex drive  
- ↓ libido, erections | - If on spironolactone, BUN/Cr 2-8 wks after start or dose change  
- Lipids, glucose, BMP at 6 mos, then q6-12 months  
- Consider yearly prolactin |

(J Clin Endo Metab 2009:94:3132)

- Pregnancy prevention for transmasculine pts: T suppresses period but may not prevent pregnancy
- Additional practices to alter appearance: binding, tucking, hair removal, silicone injections

Sarah Axelrath, Seth Tobolsky

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Chronic Cough (Am Fam Phys 2017;96:575): Subacute (3-8 weeks) vs. Chronic (>8 weeks)

- Most common causes: upper airway cough syndrome (UACS), asthma, GERD; 18-62% pts have combo.
  - Other causes: post-infxn (self-limiting but can last up to 3+ months, treat sx), nonasthmatic eosinophilic bronchitis, chemical irritant (eg. cigarette smoke), psychogenic/habitual cough, bronchiectasis, cancer, TB, sarcoidosis.
  - Normal CXR usually excludes bronchiectasis, persistent PNA, sarcoidosis, TB.

- General approach: 1) Obtain good history (smoking status, URI hx, ACE-i use); consider CXR if no ACE-i or irritant exposure (except smoking) and ↓ suspicion for UACS/asthma/GERD; 2) Remove possible offending agent; 3) Start empiric tx for UACS/asthma/GERD sequentially until resolution → tx should be added to initial regimen; 4) Consider PFTs, esophageal pH monitoring, chest CT, sputum tests, cardiac studies if sx persist despite treatment of usual causes.

### Etiology

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment</th>
</tr>
</thead>
</table>

#### Upper Airway Cough Syndrome (UACS)
- Formerly post-nasal drip syndrome. Most common cause of subacute and chronic cough. 2/2 nasal secretions stimulating cough receptors. PE of throat/ nose may reveal cobblestoning. Common causes: allergic/non-allergic rhinitis, sinusitis.
- Avoid environmental triggers of allergic rhinitis.
- Intrasinal steroids, antihistamine nasal spray, oral antihistamine, oral decongestants, or saline nasal rinse can be used for symptom relief.

#### Asthma
- Typically w/ episodic wheezing & dyspnea. Cough variant asthma pt w/ only cough. Pt may have h/o atopy. PE may reveal nasal polyps. Need spirometry w/ bronchodilator response & bronchoprovocation (eg. metacholine challenge) for dx.
- PRN bronchodilators +/- inhaled corticosteroids.
- Some pts may use only seasonally. See “Asthma” in pulmonology section for stepwise therapy.

#### GERD
- Epigastric burning sensation, sour taste in mouth, but sxns absent in >40% of patients.
- Lifestyle modifications, moderate dose PPI (omeprazole 40 mg). 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 (cetrizine) or 3rd gen (lofex/adenaline) antihistamine. If bronchial hyperreactivity, tx w/ usual asthma care.

#### ACE Inhibitor
- Produces cough in 3-20% of pts. 2/2 ACEI mediated increase in bradycardin. Sxs can occur 1wk – 6 mos after starting.
- Withdraw ACEI (resolves within 1-4 weeks), change to ARB (not associated with cough).

### Rhinosinusitis (Otolaryngol Head Neck Surg 2015;152:598)
- Acute (<1mo) vs. subacute (1-3mo) vs. chronic (>3mo, usually w/ anaerobes); recurrent (4 or more annual episodes)

#### Dx
- Rhinorrhea (viral - clear, bact - purulent) + nasal obstruction or facial pressure/pain/fullness. A/w anosmia, ear fullness, cough, H/A

#### Treatment

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Time Frame</th>
<th>Treatment</th>
</tr>
</thead>
</table>

| Bacterial: S. pneumo (41%), H. flu (35%), M. catarrhalis (4%), S. aureus (3%), anaerobes (7%), strep (7%) | >10 days, or worsening within 10 days after initial improvement (“double worsening”) | Watchful waiting* in pts w/ good follow-up vs. Augmentin 875mg BD** (Doxy 100mg BD in PCN-allergic) x 5-7d |

#### Viral
- 7-10 days
- Symptom control, oral decongestant

#### Fungal: Mucor (invasive) in DM, immunocompromised
- Acute(invasive) to more chronic (>3mo)
- Surgical removal of fungal mucin or “fungal ball” (mycetoma). ENT emergency if invasive (destruction of sinus, erosion into orbit or brain)
- NSAIDs/Tylenol for pain
- Saline irrigation/Netipot
- Topical nasal steroids
- Topical decongestant (oxymetazoline) x 3d
- Expectorants/(guaifenesin)

#### Pharyngitis (IDSA Guidelines/JAMA 2012;308:1307): Most cases are viral (suspect if + conjunctivitis, coryza, cough, diarrhea, hoarseness, discrete ulcerative stomatitis, viral exanthema). Only 5-15% of adult sore throat visits are Group A Strep (GAS).

- Exclude dangerous etiologies: epiglottitis, peritonsillar abscesses, infx in submandibular or retropharyngeal space, primary HIV

- Identify & treat GAS w/ Risk of suppurative complications (peritonsillar abscess, cervical lymphadenitis, mastoiditis), prevent rheumatic fever (lower risk in adults), ↑transmission, & improve sx. ASO liters useful only in dx of non-suppurative sequelae of GAS.
  - Center Criteria: 1 pt for each – tonsillar exudates, tender ant. cervical LAD, fever, ℃ cough.
    - 0-2: No testing, treat sx.
    - 3-4: Send Rapid Strep antigen detection test (Sens 70-90/Spec 90) + throat culture (if neg rapid but ↑clinical suspicion)
  - Tx: PO Penicillin V 250mg QID vs 500mg BIDx10d; amoxicillin 500mg BIDx10d; IM Pencillin G benzathine 1.2 mill Ux1
    - PCN-allergic: Cephalexin 500mg BIDx10d
    - Beta-lactam sensitivity: Clinda 300mg TiDx10d; Azithromycin 500 mg QDx1d, then 250 mg QDx4d
  - 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, primary HIV, GC/chlamydia) or suppurative complications such as tonsillopharyngeal cellulitis of abscess.
- Is it malignant? ↑Risk: diameter >4 cm, increased vascularity, irregular shape, high T2 signal on MRI, delayed contrast washout. ↓Risk: if ≤10 HU on CT, homogenous and lipid-rich.
- Is it functionally active? Clinical exam & lab testing for all nodules (unless obvious myelolipoma) to r/o pheo & Cushing’s (see table). Also test for hyperald in hypertensive pts. Only test for production of excess sex hormones if clinical stigmata. AVOID testing inpatients due to high false positive rates.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Suggestive Clinical Features</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma</td>
<td>HTN, palpitations, headache, diaphoresis</td>
<td>Serum metanephrines, 24H urine fractionated metanephrine and catecholamines</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Central obesity, prox muscle weakness, facial plethora</td>
<td>1 mg dexamethasone suppression test is first line for screening in this population</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>HTN, hypokalemia</td>
<td>Plasma aldo and PRA (d/c aldo antagonists before testing). May req. Adrenal Vein Sampling.</td>
</tr>
<tr>
<td>Adrenocortical cancer</td>
<td>Sxs related to excess glucocorticoid, mineralocorticoid, androgen/estrogen secretion</td>
<td>Serum DHEA-S and measure any other clinically indicated steroid based on clinical features</td>
</tr>
</tbody>
</table>

- Indications for adrenalectomy: > 4 cm on CT scan, malignant, or hormonally active; surgery after hormonal eval
- Follow up: If indeterminate, repeat CT scan in 6-12 mos, then as clinically indicated. Consider cortisol & catechol testing yearly x 4-5yrs (effectiveness of this practice unknown). EJE guidelines don’t recommend). Adrenalectomy if nodule grows by 20% or > 1 cm.

Thyroid Nodules (Thyroid 2016;26:1, Endo Pract 2016;22:622)
- Is it malignant? ↑Risk: pt h/o irradiation to head/neck, +family hx, or h/o thyroid cancer syndromes (i.e. MEN 2)
- Workup: obtain ultrasound and check TSH (low TSH=less likely CA, high TSH=more likely CA)
  - Low TSH - measure FT4 and FT3, obtain Thyroid radionuclide (^23) scan.
    - If “hot nodule,” consider Tx for hyperthyroidism if symptomatic. No biopsy necessary.
    - If “cold nodule,” refer for US-guided FNA
  - If normal or high TSH, measure FT4 and TPO antibody, refer for thyroid U/S and FNA based on US findings.
- FNA: All nodules >2cm or >1cm with moderately suspicious qualities. No FNA for purely cystic nodules.
- Follow up: Based on U/S characteristics. If neg FNA but highly suspicious U/S findings, repeat US/FNA within 12 mo. If low-moderate suspicious U/S findings, repeat U/S 12-24 mo, consider FNA if change. Can stop f/u after 2 neg FNAs.

Incidental Pulmonary Nodules (Radiology 2017;284:228, Chest 2013;143(Suppl 5), Thorax 2015;70:Suppl 2)
- NB: these guidelines are for incidental findings; recommendations for f/u of nodules found on LDCT for lung cancer screening are different as that population is high risk (see Lung-RADS classification tables online)
- Is it malignant? Pt characteristics: ↑Risk w/ h/o smoking, emphysema, pulmonary fibrosis, extra-thoracic cancer, asbestos exposure, age. Nodule characteristics: Quality (subsolid/ground glass>solid), size, rate of growth, borders (irregular/spiculated border>smooth border), calcification (eccentric>popcorn/concentric/diffuse), location (upper>lower lobe),
- Follow up: Tailored to patient and type of nodule. Subsolid (ground glass): if <6 mm, no routine f/u. If >6 mm, CT at 6-12 months, then CT every 2 yrs until 5 yrs. Part solid: if <6mm, no routine f/u. If >6 mm, CT at 3-6 mos, then annual CT for 5 yrs if unchanged and solid component <6 mm. Solid nodules: see below.

<table>
<thead>
<tr>
<th>Nodule type</th>
<th>&lt;6mm</th>
<th>6-8mm</th>
<th>&gt;8mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single solid nodule</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>No routine follow up</td>
<td>CT at 6-12 months, then consider CT at 18-24 months</td>
<td>Consider CT at 3 months, PET/CT, or tissue sampling</td>
</tr>
<tr>
<td>High risk</td>
<td>Optional CT at 12 months</td>
<td>CT at 6-12 months, then CT at 18-24 months</td>
<td>Consider CT at 3 months, PET/CT, or tissue sampling</td>
</tr>
<tr>
<td><strong>Multiple solid nodules</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>No routine follow up</td>
<td>CT at 3-6 months, then consider CT at 18-24 months</td>
<td>CT at 3-6 months, then consider CT at 18-24 months</td>
</tr>
<tr>
<td>High risk</td>
<td>Optional CT at 12 months</td>
<td>CT at 3-6 months, then CT at 18-24 months</td>
<td>CT at 3-6 months, then CT at 18-24 months</td>
</tr>
</tbody>
</table>

- Consider referral to the Pulmonary Nodule Clinic: refer in Epic or call x38728 for appointment
Medical examination for newly arrived refugees and immigrants (CDC checklist)

Introduction
- Health system in US: describe role of PCP, how to obtain prescriptions/refills/labs/imaging/referrals, how to use ER
- Know your Rights: Handouts re ICE (English) (Spanish); Red Cards (rights cards in different languages); compiled resources

History & Physical: obtain prior medical records if possible
- Mental health: PTSD, anxiety, depression: R-HS-15 (screen at 2nd visit to minimize effect of re-traumatization)
- Legal Status Screen: Do not document in medical record. “Do you have any questions about your immigration status?”
  - If yes → Refer to Advice & Counsel session, e.g. LINC program MGH Chelsea or through local legal aid organizations
  - If possible asylum case → May refer directly to organization providing legal services, e.g. PAIR; MIRA

Vaccinations:
- Age-appropriate vaccines as indicated (see Health Screening & Maintenance section)
- If no vaccine documentation, check titers (including childhood vaccines such as MMR) or assume pt not vaccinated.

Screening:
- General screening: CBC w/ differential (eos, anemia), UA (hematuria), glucose, gen chem, pregnancy test if appropriate; hepatitis, lead, micronutrient, chronic disease
- Tuberculosis: eval sx, h/o sick contacts, PE; send T-spot (preferred with prior exposure to BCG vaccine) or PPD
- STIs: Syphilis (TrepAb at MGH, VDRL/RPR elsewhere); HIV; GC/CT (urine NAAT) if \( < 25 \) & sexually active or \( > 25 \) + risk (h/o sexual assault, LE h/o on UA, sx, new or > 1 partner, partner w/ STI)
- Malaria (PCR most sensitive, blood films less sensitive if C/sx)
  - Test pts from Sub-Saharan Africa (SSA) who did not receive pre-departure presumptive Rx w/ artesunate-combination (e.g. pregnant when Rx was C/I)
  - Any pt from malaria-endemic country w/ sx infection
- Intestinal/Tissue Invasive Parasites: Test if no pre-departure Rx (albendazole, ivermectin) or incomplete: \( \geq 2 \) stool O&P, Strongy loidiasis, filariasis, schistosomiasis
- Hematia, infertility, chronic pelvic pain
- Splenomegaly
- Chronic rash or itching
- Esophageal dysmotility
- Seizures, CNS sx

Parasitic Infections

<table>
<thead>
<tr>
<th>Type</th>
<th>Basis</th>
<th>Work Permit</th>
<th>Green Card</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPR</td>
<td>Varied</td>
<td>Yes</td>
<td>Yes</td>
<td>Lawful Permanent Resident: Green card recipient; pathway to citizenship. Can apply for family members to get green card “family based” immigration.</td>
</tr>
<tr>
<td>U-Visa, T-Visa</td>
<td>Crime</td>
<td>Yes</td>
<td>Yes</td>
<td>Eligible if victim of human trafficking (T) or victim of certain types of crime (U). Violence Against Women Act: Eligible if abused by spouse, child or parent who is LPR/citizen.</td>
</tr>
<tr>
<td>TPS</td>
<td>Country</td>
<td>No</td>
<td></td>
<td>Temporary Protected Status: Short list of countries, designated by Homeland Security, where conditions preclude safe return. Cannot be deported while country of origin on list.</td>
</tr>
<tr>
<td>Cancellation of Removal</td>
<td>Discretionary</td>
<td>Yes</td>
<td>No</td>
<td>Based on exception hardship to self or LPR/citizen spouse, parent, child if deported: ineligible with certain criminal convictions.</td>
</tr>
<tr>
<td>DACA</td>
<td>Age</td>
<td>Yes</td>
<td>No</td>
<td>Deferred Action for Childhood Arrivals: Obama administration program deferring immigration cases of undocumented youth. Eligible for in-state tuition and work permits.</td>
</tr>
<tr>
<td>Refugee</td>
<td>Fear</td>
<td>Yes</td>
<td>Yes</td>
<td>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).</td>
</tr>
<tr>
<td>Asylum</td>
<td>Fear</td>
<td>180-days s/p filing</td>
<td>After 1-yr</td>
<td>Well-founded fear of being persecuted based on race, religion, nationality, membership in social group or political opinion. Application due within 1yr date of entry. If granted, may also apply to spouse and children if in United States.</td>
</tr>
<tr>
<td>Withholding of Removal</td>
<td>Fear</td>
<td>No</td>
<td>No</td>
<td>Asylum/CAT/Withholding all part of same application. No 1yr rule; may apply at any time. Ineligible with certain criminal convictions.</td>
</tr>
<tr>
<td>CAT</td>
<td>Fear</td>
<td>No</td>
<td>No</td>
<td>Convention Against Torture: similar to Withholding, but still eligible with criminal convictions.</td>
</tr>
<tr>
<td>Undocumented</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td>Patients should seek legal counsel to ensure no options to apply for alternative statuses.</td>
</tr>
</tbody>
</table>

Helen D’Couto

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Primary Care  Outpatient Disease Management Index & Decision Aids

Index of Outpatient Disease Management

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Calculators, Decision Aids, and Apps

Calculators and Decision Aids for Providers:
- AUDIT Alcohol Use Questionnaire: [http://auditscreen.org/using-audit](http://auditscreen.org/using-audit)
- CAGE Questions for Alcohol Use: [https://www.mdccalc.com/cage-questions-alcohol-use](https://www.mdccalc.com/cage-questions-alcohol-use)
- CDC Adult Vaccine Schedule: [https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html](https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html)

Patient-Provider Shared Decision Aids:

Primary Care Apps:
- American Diabetes Association Standards of Care App: [https://professional.diabetes.org/content-page/standards-care-app-1](https://professional.diabetes.org/content-page/standards-care-app-1)
- Apps available in iTunes or Google store: AHRQ ePSS (repository of USPSTF guidelines and recommendations), ASCVD Risk Estimator, ACP Clinical Guidelines, CDC MEC Contraception Guide
Consultants

Calling Consults

TIPS FOR CALLING CONSULTS

- **To do BEFORE you call:**
  - Place **order** in Epic for consult
  - Existing **outpatient specialist** (e.g. cardiologist, oncologist) should be called first. You should also know name of the outpatient provider before calling an inpatient consult.
  - **Know your patient** – you may be asked to provide additional information (current status, **exam**, workup). Briefly review the admit note and **briefly see/examine the patient** if you have not done so previously.
    - GI: melena/hematochezia, stoll, current/prior Hct, coags, transusions, past EGD/colo, vitals, IV access, NSAID/ASA use
    - **Cards**: EKG/tele, prior stress/echo/cath (know anatomy), dry weight, biomarkers, current cardiac meds, outpt cardiologist
    - Renal: Baseline Cr, CXD stage, on/off HD, dialysis access, electrolyte mgmt, current UOP, nephrotoxins, outpt nephrologist
    - Onc: known cancers w/ stage hx history, biopsy results (for new dx), current anticoagulants, special slide, outpt oncologist
    - **ID**: current/past micro data, possible sources, current/prior abx (incl # of days), fever curve, hardware, travel, exposures
  - **Know your question** – Bigelow JAR should specify consult question in task list. If not there, **ASK. It is always OK to clarify.**

- **To do DURING the page/call:**
  - Call as early in the day as possible (ideally before noon). The paging directory: **ppd.partners.org** or “Phone Directory” in **Epic**
  - **In your page to consulting team, include:** pt name, MRN, location, call back #, brief consult question +/- level of urgency
  - Avoid “curbside” questions. If there is a specific question about management, call a formal consult.
  - **Tell the consultant a brief HPI, a clear explanation of the team’s thinking and a clear and specific question**

- **To do AFTER the call:**
  - Invite the consultant to find you to relay their recommendations or tell them who will be covering for you

CALLING EMERGENT CONSULTS

- **Surgery:** STAT to surgeon means life-threatening emergency (eg: hemorrhage, lost airway, perforated or ischemic bowel) → include reason for consult in your page to help expedite urgency
  - Page **Senior Resident on call** under **Emergency Surgery/Trauma (Churchill) Team (Red/Blue/White/Green)**
  - **Psychiatry** (eg: pt trying extremely to leave AMA w/ unclear capacity; security concerns, major behavioral issues)
    - **8am-6pm:** p33061 (Emergency Consult Resident). If weekend/Holiday: p17911 (weekend rounding psychiatrist)
    - **6pm-8am:** Call APS (6-2994) or page APS resident at 27792
  - **Ophtho:** Go through Partners Paging Directory. Backup/emergency number is 617-573-4063 (MEEI ED back desk).
  - **Toxicology (ingestions/overdoses/exposures/interactions):** Call Poison Control Massachusetts (617-355-6607 or 800-222-1222).

CALLING SURGICAL CONSULTS AT MGH

- All surgical consults are considered urgent. For a non-urgent consult overnight, wait to page until AM.
- **In the ED:** speak directly to (do not page) the surgery team that sits in Acute. Once patient on floor, page intern on the **consulting team**. Do NOT page the ED Surgery resident who placed initial consult note. Do NOT page surgery attending.
- **New Ward consult** → Page “Senior Resident on call” under **Emergency Surgery/Trauma (Churchill) Team (Red/Blue/White/Green)**
  - Existing ward consults, page the intern for that Churchill service, not the team on call that day
  - **New Private consult** (patient had prior operation by MGH surgeon) → Page **Senior** for new consult on **Baker** surgery services
    - (Teams 1-6); team depends on which surgery attending is requested.
    - **Team 1 (Surg Onc)** → Paging Directory: “Surgical Oncology (Baker Team 1)”
    - **Teams 2-6** (Berger, Colorectal, Pancreas, MIS, Endocrine) → Paging Directory: “General/Gastrointestinal Surgery”
  - **Cardiac Surgery consult** → Page **In-House Fellow** under “Cardiac Surgery” – you will usually be directed to the NP
  - **Ortho consult** → Page 20296 or “Orthopedics In-house” under “Orthopedics”
  - **Transplant Surgery consult** → Page “**Intern**” (6a-6p) or “House officer on call (6p-6a)” under “Transplant Surgery”
  - **Vascular Surgery consult** → Page “On-Call Resident” under “Vascular and Endovascular Surgery”

CALLING OTHER SUBSPECIALTY CONSULTS

- **ACT (Addiction Consult Team):** Place consult in Epic (no need to call), for EIOH or other substance use disorders, suboxone, etc.
- **AMS (Anticoagulation Management Service):** For established pts: p30104, or click AMS icon in Epic to determine existing AMS RN; Inpatient for discharge – place Epic consult, if urgent or questions, page Discharge Pathway Service: p30103
- **Cardiology:** login to Amion under “mghcardiology” to identify appropriate fellow
- **Chronic pain (cancer pain, pain in addiction):** p17246; **Acute pain service (epidurals and periop pain):** p27246
- **Diabetes nurse educator:** Service NP: p20737; MD: p14364
- **ENT:** Call the MEEI ED at 617-573-3431 and they will page the consult resident
- **Optimum Care Committee (“OCC,” Ethics):** Page ethics support pager: p32097 (Mon-Fri, 8am-4pm, except holidays)
- **Ophtho:** **Weekday 8am-5pm (routine):** p23555 or look up through Partners Directory; **Weekday 5pm-8am or Weekend/Holiday:** p23666 or call MEEI ED Back Desk 617-573-4063. Determine whether patient can travel to MEEI for an exam prior to calling consult.
- **Psychiatry:** For **non-emergent floor consult:** start with order for psych consult in Epic
  - **Weekday, Weekend Night, Holiday Night:** Call CL coordinators (6-2984). These consults will be seen within 24 hours.
  - **Weekend or Holiday 8am-5pm:** p17911 (weekend rounding psychiatrist)
- **Transfusion reactions:** Page blood bank resident: p21829, or fellow: p24346
Peri-operative Cardiac Risk Stratification and Risk Reduction:

**GOAL:** To estimate and optimize risk of peri-operative cardiac events, **NOT to “clear for surgery”**

- Peri-op cardiac events: MI (usually clinically silent, NSTEMI > STEMI, usually POD#0-3, not intraop), CHF, VT/VF, card arrest, death
  - Major determinants include: (1) condition of patient (2) risk of procedure (3) functional capacity
- Emphasis on risk stratification. **Very few patients need non-invasive/invasive testing** unless they would change management in the absence of surgery.

Peri-Operative Cardiovascular Evaluation for Non-Cardiac Surgery (JACC 2014;64e77)

Operative Risk without Adjustment for Patient Factors

<table>
<thead>
<tr>
<th>High Risk &gt;5%</th>
<th>Intermediate Risk 1-5%</th>
<th>Low Risk &lt;1%</th>
</tr>
</thead>
</table>
| - Emergent major surgery, esp in elderly
  - Aortic, peripheral, or major vascular |
| - HEENT, CEA
  - Intrathoracic, intraperitoneal, prostate
  - Orthopedic                          |
| - Superficial, cataract, breast
  - Endoscopy                             |
| - Ambulatory                            |

Revised Goldman Cardiac Risk Index (RCRI): Six independent predictors (risk factors) of major cardiac complications

Retrospectively derived in cohort of 2900 and prospectively validated in another cohort of 1400 (Circulation 1999;100:1043)

<table>
<thead>
<tr>
<th>#RCRI Predictors</th>
<th>Rates of event (95% CI)</th>
<th>#RCRI Predictors</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.4-0.5% or ~0.5%</td>
<td>1</td>
<td>1.1 (1.0-1.3)</td>
</tr>
<tr>
<td>1</td>
<td>0.9-1.3% or ~1%</td>
<td>2</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>2</td>
<td>3.6-6.6% or ~5%</td>
<td>3</td>
<td>0.7 (0.6-0.9)</td>
</tr>
<tr>
<td>≥3</td>
<td>9.1-11.0% or ~10%</td>
<td>≥4</td>
<td>0.6 (0.4-0.8)</td>
</tr>
</tbody>
</table>

Active Cardiac Conditions
- Unstable Coronary Syndromes: unstable/severe angina, acute (< 7d) or recent (< 30d) MI
- Decompensated HF
- Significant Arrhythmias: symptomatic/new ventricular arrhythmias, SVT with HR >100 at rest. Symptomatic bradycardia, high-grade AVB.
- Severe Valvular Disease: severe sx AS (mGrad >40, AVA < 1.0 cm²), sx MS (progressive DOE, presyncope, HF)

2 Surgical Risk Calculators
(1) Revised Cardiac Risk Index
(2) Gupta MICA NSQIP Risk Prediction

Operative Cardiac Risk Stratification and Risk Reduction:

- Emergency non-cardiac surgery?
  - Yes
    - Proceed with surgery
  - No
    - Active cardiac condition that requires eval/tlx before surgery?
      - Yes
        - Treat/Test/Stabilize and reassess risk-benefit of surgery
      - No
        - Estimated peripertative risk of major adverse cardiac events based on combined clinical/surgical risk
          - Low risk (<1% per NSQIP calculators or RCRI score 0-1)
            - Proceed to surgery
          - Elevated risk
            - Able to achieve ≥4 METs?**
              - Yes
                - Proceed to surgery
              - No/unknown
                - Utilize RCRI and Gupta surgical risk calculators to assess clinical risk factors, consider stress testing, and reduce risk

*4+ METs: 12 flights stairs; walk 4 blocks; golf, bowl, dance
**Alternatives Cardiac Risk Assessment:** Gupta Perioperative Cardiac Risk (Circulation 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 Creatinine >1.5
- Derived RF from "prospective" cohort of 211k; validated on cohort of 257k. Compared to RCRI, better discriminative predictive value.

**Preoperative Coronary Revascularization (CARP: 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 of CARP RCT: EF<20%, unstable angina, LMCA disease >50%, severe AS.

**Peri-operative β-Blockade and Other Cardiac Drugs:**

- Evaluate for peri-operative β-blockade (Circulation 2009;120:e169)
  - Continue β-blocker: if already taking for other indication (e.g. CAD, arrhythmia, HTN) for goal HR 55-65 (Class I, LOE C)
  - Initiate β-blocker: ≥ 3 RCRI risk factors or if pt has indication for β-blocker otherwise (Class IIa, LOE B).
- Never start on day of surgery!
- Uncertain role of β-blocker: if no known CAD but either +stress test or high risk factors

**Anti-platelet management (POISE-2: NEJM 2014;370:1494; Anesth Analg 2015;120:570)**

- DAPT post PCI: POBA <14d, BMS <30d, DES <6-12mo → delay elective surgery. If urgent, continue ASA, hold P2Y12i x5d.
- ACEi/ARB: Pts have more transient peri- and post-operative episodes of HoTN; no diff in death, post-op MI, stroke; ↑ or ↓ AKI unclear
  - Discontinue ACEi/ARB night before surgery (unless used for HF and BP ok), failure to restart ARB within 48h → 30-d mortality (Anesthesiology 2015;123:288).
- Other: All other anti-hypertensives should be continued perioperatively to goal BP <180/100 to avoid bleeding.

<table>
<thead>
<tr>
<th>Risk Levels</th>
<th>Risk Factors for Thromboembolism</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>- AF w/ CHA2DS2-VASc ≤ 4, no prior embolism</td>
<td>- No bridging recommended</td>
</tr>
<tr>
<td></td>
<td>- VTE ≥1year ago and no additional risk factors</td>
<td>- BRIDGE: increased risk of bleeding, note exclusion criteria below</td>
</tr>
<tr>
<td></td>
<td>- Bileaflet AVR w/out risks for stroke and no history of AF</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>- AF w/ CHA2DS2-VASc 5-6 or prior embolism (≥ 3 mo. ago)</td>
<td>Consider bridging based on individualized patient bleeding/embolism risk and procedure</td>
</tr>
<tr>
<td></td>
<td>- VTE w/in 3-12 months, recurrent VTE, non-severe thrombophilia, active malignancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Bileaflet AVR w/ risk factors for stroke</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>- AF w/ CHA2DS2-VASc ≥ 7, recent embolism, or valvar AF</td>
<td>Bridge with LMWH or UFH</td>
</tr>
<tr>
<td></td>
<td>- VTE w/in 3mos, or antiphospholipid antibody syndrome</td>
<td>- Enoxaparin should be stopped ~24h prior to surgery</td>
</tr>
<tr>
<td></td>
<td>- All mitral valves, caged ball/tilt disc AVR, or any mechanical valve w/ CVA ≤ 6 months</td>
<td>- UFH should be stopped 4-6h prior to surgery</td>
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<tr>
<td></td>
<td></td>
<td>- Ideal to resume ≤ 24 h post-op if bleeding stabilized</td>
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</tbody>
</table>

- BRIDGE: Notably ~90% were low-risk/outpatient surgeries. Exclusion criteria included: mechanical valves, stroke/TIA w/in 12 weeks, major bleeding w/in 6 weeks, CrCl <30, Pt <100k
- More data needed on DOACs but generally do not bridge; see ACC guidelines re: timing of interruption and re-initiation

**VTE Prophylaxis (Mayo Clin Proc 2014;89:394)**

- Postop VTE risk assessment: Caparini Score
- Non-orthopedic surgeries: those undergoing general or abdominal/pelvic surgery are at highest risk
- Orthopedic surgeries: all pts at high VTE risk 2/2 tourniquet time + immobilization; minimum duration 10-14d (35d if higher risk)

**Peri-operative Monitoring and Considerations:** (NEJM 2015;373:2258)

- ACS: Most Ms occur w/in 48h while patients are on analgesics that mask pain→ some data show benefit of troponin monitoring (Ann Intern Med 2011;154:523; JAMA 2012;307:2295)
- In a meta-analysis of 2179 patients, an elevated post-op NT-proBNP was the single strongest predictor of post-op MI and death (JACC 2014:63:170)
- AF: may be a more important risk factor than CAD for 30-day post-op mortality (Circulation 2011;124:289)
- 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 (Ann Intern Med 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: High risk of peri-op death; MELD predicts survival (>15 median survival ~2 months); Child-Pugh C very high risk (>80% in-hospital mortality) (J Gastroenterol Hepatol 2012;27:1569)
- Low albumin: independent predictor of 30-day post-op morbidity and mortality (Arch Surg 1999;134:36)

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Dermatology

Before Consulting Dermatology: Please upload photo of rash to the media tab of EPIC using Haiku

- If consulting regarding drug rash, please note exact timing of suspect medications
- There is overlap between dermatology, allergy, infectious disease, rheumatology, wounds, and burn services. Please consider initial dermatology consult for skin processes to confirm diagnosis; additional services can be added as needed.

Quick Steroid Guide:

- **Face/intertriginous areas**: hydrocortisone 2.5% cream, hydrocortisone valerate 0.2% cream
- **Body**: fluocinolone 0.025% cream if mild, clobetasol 0.05% ointment if severe to mid strength to super potent depending on severity
- **Scalp**: 0.01% fluocinolone scalp solution or oil (dermasmoothe); oil better for dry scalp

**Counsel patients**: Use daily x 2 weeks then 1 week “off”, avoid face, risk = skin thinning

<table>
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<tr>
<th>MGH topical steroid formulary by level of potency:</th>
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<tbody>
<tr>
<td>- <strong>Super potent</strong>: clobetasol C 0.05%, betamethasone dipropionate O 0.05%</td>
</tr>
<tr>
<td>- <strong>Potent</strong>: fluocinonide-emollient C, O, G 0.05%</td>
</tr>
<tr>
<td>- <strong>Upper-mid strength</strong>: betamethasone valerate O 0.1%</td>
</tr>
<tr>
<td>- <strong>Mid strength</strong>: fluocinolone O 0.025%</td>
</tr>
<tr>
<td>- <strong>Lower-mid strength</strong>: fluocinolone C 0.025%, betamethasone valerate C 0.1%</td>
</tr>
<tr>
<td>- <strong>Mild</strong>: hydrocortisone valerate C 0.2%, fluocinolone scalp oil 0.01%</td>
</tr>
<tr>
<td>- <strong>Least potent</strong>: hydrocortisone 2.5%, hydrocortisone O 1.0%</td>
</tr>
<tr>
<td>- <strong>Over the counter</strong>: hydrocortisone C 0.5%, 1.0%</td>
</tr>
</tbody>
</table>

**Common Dermatologic Conditions**: (alphabetical, most common are underlined)

- **Allergic contact dermatitis**: Identify and remove suspected trigger; tx depends on severity; high potency topical steroid for limited body surface area (BSA); low to mid potency for face; consider prednisone taper for more extensive BSA involvement or significant discomfort (taper >1 wk to avoid rebound flare)

- **Calciphylaxis**:
  - Extreme pain (may precede skin lesion), violaceous retiform patch/plaque → necrosis, ulcer, eschar formation
  - Dx: Ca²⁺ x P product, skin biopsy (gold standard, not always needed); bone scan can show increased radiotracer uptake (specificity >90%)
  - Tx: Normalize serum Ca²⁺, phosphate and PTH levels via non-calcium based phos binders (i.e. sevelamer) and cinacalcet; IV and/or intralesional sodium thiosulfate; treat secondary infections (high risk of sepsis), pain control, wound care. Discontinue warfarin if possible. Consider addition of anticoagulation if appropriate.
  - Development of calciphylaxis = indication to start RRT in CKD pts; often converting PD to HD

- **Cellulitis**: (see Infectious Disease: Skin and soft tissue infection) Consult derm if not improved in 48h to distinguish cellulitis mimickers (30% of all cases); calculate ALT-70 Score, [https://www.mdcalc.com/alt-70-score-cellulitis](https://www.mdcalc.com/alt-70-score-cellulitis)
  - ALT-70 Score of 5-7, indicates 82.2% likely cellulitis ([J Am Acad Dermatol 2017;76:618](https://www.mdcalc.com/alt-70-score-cellulitis));
  - If ALT-70 score 3-4, consider derm c/s especially if no improvement by 48h with abx → c/s shown to reduce abx use and duration ([JAMA Derm 2018;154:529](https://www.mdcalc.com/alt-70-score-cellulitis))

- **Cutaneous GVHD**:
  - Skin pain/pruritus can precede eruption, starts on acral surfaces (range of eruptions from folliculocentric or morbilliform to TEN-like); acute vs. chronic based on morphology, not time course
  - Acute: follicular erythematous papules; chronic: asteeotic, LP-like, eczematous, sclerosdermoid, poikilodermatous
  - Stage 1: <25% BSA, stage 2: 25-50% BSA, stage 3: >50% BSA, stage 4: erythroderma w/ bullae (TEN-like)
  - Tx: immunosuppression with corticosteroids +/- cyclosporine or tacrolimus, supportive care

- **Eczema/atopic dermatitis**: 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 2 wks; for face, use least potent to lower mid-strength steroids BID x 1-2 wks; for scalp, mid- to high-potency steroid in solution, foam, or oil vehicles; for erosions/fissures, consider petrolatum or mupirocin ointment BID x 1-2 weeks

- **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 2 weeks; typically triggered by infection (90%): HSV, mycoplasma, GAS, EBV, less commonly drug reaction
  - Tx: treat underlying infxn, NSAIDs, cool compresses, topical steroids, antihistamines; systemic steroids only if severe

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- **Erythroderma:** Diffuse redness > 90% BSA.
  - **Causes:** psoriasis, atopic derm, mycosis fungoides, cutaneous T cell lymphoma, pityriasis rubra pilaris, drug, other.
  - **Work-up:** CBC w/ diff, BMP, detailed med rec, +/- HIV. Tx: liberal emollients or mid-potency topical steroids and antihistamines; correct fluid/electrolyte imbalance; monitor for 2nd infections, discontinue offending meds, c/s derm

- **Hypersensitivitis:** see above
  - **Urticaria (acute):** Treatment includes antihistamines, topical steroids, and for severe cases, oral steroids.
  - **Tinea pedis:** Treatment includes topical antifungals such as terbinafine or econazole.
  - **Stasis dermatitis:** Treatment includes compression therapy, topical emollients, and for severe cases, oral steroids.
  - **Seborrheic dermatitis:** Treatment includes topical steroids, antifungals, and for severe cases, systemic antibiotics.
  - **Psoriasis:** Treatment includes topical steroids, calcipotriene, biologics, and for severe cases, systemic immunosuppressants.
  - **Purpura fulminans:** “DIC in skin” = true emergency
    - **Work-up:** DIC labs, blood cultures, skin biopsy w/ GS and culture; Tx: broad-spectrum abx + supportive care.
  - **Herpes zoster (shingles):** Treatment includes antiviral therapy and pain management.
    - **Uncomplicated, <72 hr (immunocompetent):** valacyclovir 1000mg PO Q8H x7d or acyclovir 800 mg PO 5x/d x7-10d
    - **Disseminated:** >20 vesicles outside two 1st dermatomes; acyclovir 10 mg/kg IV q8h; consider immunodeficiency w/u
    - **Immunosuppressed:** acyclovir 10 mg/kg IV q8h; IVFs if hypovolemic to decrease risk of acyclovir crystal nephropathy; obtain DFA/viral culture; monitor carefully for dissemination (esp. encephalitis, pneumonia, hepatitis)
    - **Herpes zoster ophthalmicus:** Urgent Ophtho consult if concern for ocular involvement
    - **Post-herpetic neuralgia:** risk ↓ w/ early antiviral treatment (<72 hr); if higher risk (>50 yo w/ moderate-to-severe acute pain) consider preventive tx w/ gabapentin 300 mg PO QD, titrate up to 3600 mg QD, divided TID as tolerated
    - **Consider high lysine, low arginine diet and post-episode vaccination to prevent herpes recurrence
  - **Pressure Injury/Ulcers:** must be documented in your H&P
    - **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
    - **Wound Consult (Plastics/Vascular collab) for:** acute wound issues such as limb ischemia, wet gangrene, any wound requiring OR debridement → IP Consult to Inpatient Wound Service; consider derm consult first to confirm etiology
  - **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 APS, CTD, malignancy, protein C/S deficiency
    - **Work-up:** DIC labs, blood cultures, skin biopsy w/ GS and culture; Tx: broad-spectrum abx + supportive care.
  - **Psoriasis:** Depends on severity; short-term tx includes topical steroids, calcipotriene, intense moisturization +/- occlusion w/ plastic wrap; long-term tx includes phototherapy, acitretin, MTX, biologics w/ outpt Derm f/u (JAAD 2011;65:137)
  - **Seborrheic dermatitis:** For face, least potent to lower mid-strength topical steroid BID x 1wk and/or ketoconazole 2% cream BID x 4 wks, then 1-2x/wk for maintenance; alternatively pimecrolimus cream, tacrolimus 0.03 or 0.1% ointment for scalp, ketoconazole 2% shampoo qHS
  - **Stasis dermatitis:** LE compression (ACE wraps, stockings) with elevation; mid-strength to superpotent corticosteroid ointment BID x 1-2 wks +/- occlusion with plastic wrap; mupirocin ointment BID x1-2 wks to erosions; intensive moisturization (hydrated petrolatum) (Note: bilateral lower extremity cellulitis extremely rare – diagnosis of exclusion)
  - **Tinea pedis:** Apply topical imidazole (econazole 1% cream QD or clotrimazole 1% cream BID x 2-4 wks) or allylamine (terbinafine 1% cream BID x 2 wks) to entire foot and webbed spaces between toes
  - **Urticaria (acute):** Identify, remove trigger; histamine-mediated itch → combination PO antihistamines (fexofenadine 180 mg PO BID with diphenhydramine or hydroxyzine PO QHS; add ranitidine BID if not improved); dry skin itch → cream-based emollients; neuropathic itch → gabapentin; adjunct → topical menthol (not on any open erosions, as it will sting)
  - **Vasculitis:** idiopathic in up to 50%; small, medium, and large-vessel
    - **Small-vessel vasculitis is also known as leukocytoclastic vasculitis (LCV):** most common
      - **Immune-complex:** HSP, erythema elevatum diutinum, urticarial vasculitis, cryoglobulinemia, cutaneous small vessel vasculitis (dx of exclusion); ANCA-mediated: GPA, MPA, EGPA; other: calciphylaxis (see above)
      - **Etiologies:** 1) Drug-induced: abx, allopurinol, thz, hydantoins, PTU; 2) Connective-tissue disease; 3) Infections: HBV, HCV, Strep, URI, HIV, CMV, Mycobacteria, Neisseria spp.; 4) Malignancy
      - **Workup:** UA w/ microscopy, CBC w/diff, BUN LFTs, HBV, HCV, cryos, complements, ANA, dsDNA, RF, ANCA
**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

<table>
<thead>
<tr>
<th>Urticaria/Anaphylaxis</th>
<th>Immediate (min-hr) – delayed (days)</th>
<th>Pruritic, well-circumscribed, erythematous papules/plaques with central pallor.</th>
<th>+/- angioedema, wheezing, GI sx, tachycardia, HoTN,</th>
<th>Any</th>
<th>Antihistamines (benadryl + H2) + Steroids if severe + IM epinephrine if s/s anaphylaxis - c/s allergy immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed Drug Eruption</td>
<td>Minutes-hours</td>
<td>Solitary sharply demarcated round red-brown patch or edematous plaque recurring in <strong>same location</strong> each time drug ingested. Can evolve to bullae. Oral/anogenital mucosa common sites.</td>
<td>Usually asymptomatic</td>
<td>Abx (sulfa, TMP, FQs, TCNs), NSAIDs, barbiturates</td>
<td>-Topical steroids if symptomatic</td>
</tr>
<tr>
<td>Acute Generalized Exanthematous Pustulosis (AGEP)</td>
<td>2-14 days</td>
<td>Small non-follicular pustules on erythematous/edematous plaques, begin on face or intertriginous areas then become widespread. Usually within 24-48 hours of medication exposure. Burning, pruritus common.</td>
<td>Fever, marked neutrophilia +/- oral mucosal erosions, facial edema</td>
<td>Abx (PCN, macrolides) <strong>Can occur after only one exposure</strong></td>
<td>-Anti-pyretic -Topical steroids</td>
</tr>
<tr>
<td>Exanthematous</td>
<td>4-14 days</td>
<td>Pruritic, erythematous macules/papules start on trunk, spread centrifugally to symmetric extremities. May lead to erythroderma.</td>
<td>+/- low grade fever</td>
<td>Abx (PCN, sulfa), allopurinol, phenytoin, <strong>Requires repeat exposures</strong></td>
<td>-Topical steroids, antihistamines (Note: may take 7-14d after stopping drug to resolve)</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>4-21 days</td>
<td>Prodromal fevers, malaise, myalgias/arthritis. Pruritic atypical targetoid (amorphous, 2 color zones) macules → bullae → desquamation</td>
<td>Mucosal bullae, erosions &amp; crusting, conjunctivitis + Nikolsky sign Complications: 2° infection, resp. compromise, GIB, visual impairment</td>
<td>Abx (sulfa), AEDs, allopurinol, phenobarbital</td>
<td>-Cyclosporine (preferred at MGH) -Steroids possible mortality benefit (<a href="https://doi.org/10.1001/jamadermatol.2017.153514">JAMA Derm 2017;153:514</a>)but controversial -IVIG, anti-TNF -Burn level care if &gt;30% BSA</td>
</tr>
<tr>
<td>DRESS</td>
<td>3-6 wks</td>
<td>Morbilliform rash spreads downward symmetrically from face, can see SJS/TEN-like lesions and mucosal involvement.</td>
<td>Fever, arthralgias, eosinophilia, internal organ involvement (liver, kidney; rarely lung, heart), LAD.</td>
<td>Abx, AEDs, ARV (nevirapine, abacavir), carbamazepine</td>
<td>-Supportive care -IV Solumedrol (decreased risk of bowel edema vs. PO), SLOW taper (3-6 wks)</td>
</tr>
</tbody>
</table>
Consultants

Surgery

See Calling Consults for details on how to call the appropriate surgical service.

Small Bowel Obstruction: ([J Trauma Acute Care Surg 2015;79:661]

- **Causes:** adhesions from any previous abdominal surgery, hernias, cancer, intussusception, volvulus, foreign bodies, stricture
- **Dx:** abdominal distension, vomiting, obstipation. Labs normal or hypokalemic metabolic alkalosis from repeated emesis. Examine for evidence of hernias and prior abdominal scars. If severe pain, consider strangulation (lactate, leukocytosis).
- **Imaging:** KUB - air-fluid levels; CT A/P + gastrografin - dilated bowel proximal to and decompressed bowel distal to obstruction
- **Tx:** NPO, large bore NGT (18Fr) to continuous low wall suction; consider surgical exploration if signs of strangulation/bowel ischemia, s/p gastric bypass (high risk of internal hernia), closed loop obstructions, or if no improvement in 72 hours


- **Definition:** progressive, rapidly spreading, infection in deep fascia with secondary necrosis of skin and subcutaneous tissues
- **Microbiology:** 70-90% of cases are polymicrobial (anaerobes, *S. Aureus*, Clostridium, Peptostreptococcus, Enterobacteriaceae, Proteus, Pseudomonas, Klebsiella, Vibrios spp.), less commonly mono-microbial.
- **Clinical signs:** rapidly spreading erythema (hrs to days) → evidence of soft tissue necrosis; pain disproportionate to exam.
  - Suggestive features: rapid expansion of erythema on serial exams, pain extending beyond border(s) of erythema, dusky/violaceous skin, undermining of skin and subcutaneous tissues, turbid (“dishwater”) discharge, palpable crepitus
- **Dx:** i+ CT helpful, has a ~95-100% NPV. Labs for LRINEC (CRP, WBC, Hg, Na, Cr, Gluc) – score ≥ 6 has a 96% NPV.
- **Tx:** IV abx ([Vanc or Linezolid] + [Pip/Tazo or carbapenem] + Clinda to inhibit toxin production) + urgent surgical consultation

Ischemic Limb: ([NEJM 2012; 366:2198]

- **6 P’s** Pain, Poikilothermia (cool), Paresthesia, Pallor, Pulselessness, Paralysis suggest arterial thrombotic/embolic occlusion

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Sensory Loss</th>
<th>Motor Loss</th>
<th>Arterial Doppler</th>
<th>Venous Doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Viable</td>
<td>None</td>
<td>None</td>
<td>Audible</td>
<td>Audible</td>
</tr>
<tr>
<td>II (a/b)</td>
<td>Threatened</td>
<td>Minimal, painful</td>
<td>None or Mild</td>
<td>Variably inaudible</td>
<td>Audible</td>
</tr>
<tr>
<td>III</td>
<td>Irreversible</td>
<td>Profound</td>
<td>Profound</td>
<td>Inaudible</td>
<td>Inaudible</td>
</tr>
</tbody>
</table>

- **Dx:** check and document pulses and/or Doppler signals
  - Obtain ankle-brachial indices, Dopplers at bedside—if stage I, non-urgent, obtain formal studies
- **Tx:** consider IV heparin; surgical emergency: consult Vascular Surgery immediately


- **Definition:** excessive pressure within a muscle compartment, impairing perfusion
- **Etiology:** crush injury, ischemia → edema, bleed, etc.
- **Clinical signs:** tight, tender skin; pain out of proportion to known injuries; pain with passive ROM; ↑ lactate or CPK
- **Dx:** measurement of compartment pressures at bedside using Stryker transducer needle (call Churchill Service for assistance)
  - Arterial flow diminished once compartment pressure within 30 mmHg of DBP, 20 mmHg in hypotensive patients
  - Nevertheless, compartment syndrome is a clinical diagnosis, regardless of measured compartment pressure(s)
- **Tx:** surgical emergency (fasciotomy/decompression); consult Churchill Surgery immediately

Abdominal Compartment Syndrome (ACS) and Intra-Abdominal Hypertension (IAH): ([Intensive Care Medicine 2013;39:1190]

- **Definition:** IAH = IAP >12. ACS = IAP > 20 AND clinical evidence of organ dysfunction (e.g. high airway pressures, decreased venous return, elevated CVP/PCWP, ↑UO/AKI, elevated lactate, acidemia). IAP measured via bladder pressure.
- Typically occurs after massive resuscitation in ICU patients with trauma, burns, s/p liver tx, severe ascites, pancreatitis, sepsis.
- **Tx:** if IAP 12-20 w/o clinical instability:
  - Evacuate lumenal contents (NGT/rectal tube/enema)
  - Increase pain control/sedation (to level of paralysis if necessary)
  - Head of bed tilted up
  - LVP if ascites
  - Decrease tidal volume, permissive hypercapnia
  - Avoid over-resuscitation
- True ACS (IAP >20, organ dysfunction despite medical management): surgical decompression provides definitive management

Raghu R. Chivukula

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**Symptomatic Urolithiasis (kidney stones):**

- **Evaluation/Management:**
  - Imaging: Non-contrast Stone Protocol CT (I, O): evaluates position, hydronephrosis, hints at composition; alternative is KUB and ultrasound (requires both), without non-diagnostic studies prompting CT
  - UA/UCx: In all patients except those with ureteroscopies. If positive cx, need decompression by stent (Urology) or percutaneous nephrostomy/PCN (GU IR)
  - Rehydration: Normal Saline @ 150 mL/hr if tolerated (↑ ureteral peristalsis)
  - Alpha-Blockers: Tamsulosin 0.4mg PO QD (hold for SBP < 90) (ureteral relaxation)
  - Analgesia: Opioids preferred; NSAIDs/Ketorolac more effective but risk bleeding and AKI
  - Preoperative workup if requiring intervention: NPO / EKG / Coags / Type & Screen

- **Consider Urology Consult:** solitary or transplanted kidney, DM, immunosuppression, AKI, +UA/UCx, sepsis, inadequate pain control

- **Urosepsis Management:** image ASAP, BCx/UCx, urgent Urology consult; IV abx to cover GNRs + enterococcus

- **Clinical Pearl:** Patients with an acute abdomen lie still, pts with renal colic writhe in pain

- **Hematuria / Obstructed Catheter:** microscopic hematuria defined as UA with >3RBC/hpf; consider glomerular source in proper context

  - DDx: UTI, INR>3, traumatic catheter placement, bladder CA (5th most common neoplasm), upper urinary tract CA, prostate CA

  - Workup: “The Three C’s”: 1) Hematuria protocol CT (3-phase: non-con, arterial phase, delays to assess ureters); 2) Urine cytology once hematuria clears (blood interferes with test); 3) Outpatient cystoscopy

  - Tx: if obstructed (can’t void or catheter not draining / “clot retention”) or significant hematuria: Irrigate bladder via Whistle-Tip catheter using a 60 cc catheter-tipped syringe – flush in and out with saline to remove clots until urine is clear; then place 3-Way Foley on continuous bladder irrigation (CBI, AKI Murphy drip)

  - Start CBI after clot extraction; titer to keep urine cranberry juice color or lighter

**Urinary Retention**

- **Urethral/bladder pathology:**
  - Etiology: BPH, UTI, constipation, neurogenic (MS, SC injury), DM, immobility, anticholinergics, opioids, benzos, pelvic surg
  - Treatments (improvement may take 3-12 months):
    - Aggressive bowel regimen, treat UTI, minimize narcotics and anticholinergics, encourage ambulation
    - Alpha blockers (Finasteride does not help acute retention, takes 4-6 months to work)
    - Clean intermittent catheterization (CIC) with bladder scans to ensure low residual volume vs chronic Foley/SPT

- **Ureteral pathology:** typically external compression on ureter by mass or LN → hydronephrosis. Often due to underlying malignancy, portends poor prognosis. Management depends on GOC, prognosis, GFR, need for nephrotoxic chemo. Options: PCN, ureteral stent.

**Urinary Incontinence**

- **Classifications:** stress (leakage w/ coughing, etc.), urge (proceeded by urgency), mixed (most common), overflow (PVR >150), functional (neurologic, impaired mobility/cognition)

- **Treatment:**
  - All types: lifestyle interventions, bladder training (timed voiding), Kegel pelvic floor exercises
  - Stress: vaginal estrogen (post-menopausal women w/ vaginal atrophy), pessaries (mixed data), surgery (midurethral sling)
  - Urge: antimuscarinics (oxybutynin, tolerodine, beware of side effects), beta agonists (mirabegron, avoid w/ uncontrolled HTN)
  - Alpha blockers (Finasteride does not help acute retention, takes 4-6 months to work)
  - Kegel pelvic floor exercises

**Tubes and Drains**

- **Foley Catheter:** externally placed tube which travels through urethra and into bladder
  - Placement: lay patient flat, sterile prep, hold penis upright, instill 10cc’s of 2% viscous lidocaine (order “UroJet”) into urethra, always insert Foley catheter to the hub. Inflate balloon only after return of urine with 10 cc’s of sterile water; gently withdraw catheter to bladder neck and feel the balloon settle. May need to flush catheter with 60cc’s to verify position: easy flush w/ drainage = in bladder
  - Foley Size: Hx BPH → large Foley (18 Fr Coudé or larger). Keep curve up / nub on hub pointed toward umbilicus. Hx instrumentation or urethral stricture → small Foley (14 Fr or smaller)
  - Use Coudé catheter for elderly men/BPH or difficult placement—has a gentle upward curve to pass through the prostate (Coudé catheters can be ordered from Central Supply, ED or Ellison 6)
  - Urethral trauma: leave catheter in for at least 5 days to allow for urethral healing

- **Suprapubic Tubes (SPT):** externally placed tube which travels through the overlying skin and directly into the bladder
  - Placed by GU IR. Once tract formed (after 1-2 changes by IR), change q6-12wks similar to Foley
  - Staph aureus becomes a more common organism involved in infections

- **Percutaneous nephrostomy tube (PCN):** externally placed tube which travels through the overlying skin directly into the renal pelvis
  - Placed by GU IR usually under local anesthesia. Cannot be coagulopathic, thrombocytopenic, or on ASA/Plavix
  - Urine collects in external bag. If low UOP into bags, passage of blood or concern for malposition - obtain CT A/P, call GU IR

- **Ureteral stent:** internally placed stent which maintains ureteral patency from level of renal pelvis to bladder
  - Placed by Urology in OR with general anesthesia, requires change every 3-6 months. May cause urinary urgency. Is NOT changed in setting of infection

  - If stents/PCNs/Chronic Foley or SPT/ileal conduit or neobladder – UTIs should be treated only if symptomatic, NOT based on UA/UCx
Epistaxis (Nosebleed)

- **Acute Management:**
  - Have pt lean forward, pinch nostrils, hold pressure for 20 min
    - Do not lean head back or hold bony part of nose
    - Hold over basin, measure blood loss as possible
    - Do NOT “peek” – hold continuous pressure for 20 min
    - Usually a patient will not pinch hard enough – best for RN/MD to do so
  - Oxymetazoline 0.025% nasal spray (after gently clearing clots)
  - Control SBP (goal < 120) if much > baseline (coagulation if suspect massive posterior bleed)
  - Correct coagulopathy if present
  - Consult ENT if continued bleed
    - If bleed visualized, may consider silver nitrate cauterization, nasal packing, or Neuro IR embolization
    - Nasal packing (by ENT): risk of Toxic Shock very low but may prescribe prophylactic cephalexin or clindamycin; packing typically removed after 5d by ENT (whether in or outpt)
  - Location: most are anterior bleeds; posterior are more rare/serious/difficult to manage
  - Hx: side, duration, EBL, prior episodes (and txs), trauma (fingers, fists, foreign body, etc), prior nasal surgery, nasal trauma hx, HTN, anticoagulant meds, nasal steroid spray use
  - Exam: rapidity of bleeding, inspect nasal septum and oropharynx for originating site; suction clots from OP to protect airway
  - Tests: coags, CBC, type & screen; crossmatch pRBC if brisk bleed

- Location: most are anterior bleeds; posterior are more rare/serious/difficult to manage
- Hx: side, duration, EBL, prior episodes (and txs), trauma (fingers, fists, foreign body, etc), prior nasal surgery, nasal trauma hx, HTN, anticoagulant meds, nasal steroid spray use
- Exam: rapidity of bleeding, inspect nasal septum and oropharynx for originating site; suction clots from OP to protect airway
- Tests: coags, CBC, type & screen; crossmatch pRBC if brisk bleed

- **Stridor**
  - **Acute Rx:** IV access, racemic epinephrine nebulizer x 1 STAT if concern for supraglottic source, 10 mg dexamethasone IV x 1
    - If concern for subglottic source, consider IM/IV epinephrine and benadryl if allergy suspected (see Angioedema & Anaphylaxis in “Allergy & Immunology” Section); consider Heliox
      - If unstable → Call RICU & trauma surgery (x-3333) for possible surgical airway
      - If stable → Call ENT for airway evaluation
  - Epinephrine dosing: If allergic reaction suspected: 0.3mg IM (1:1,000 solution) or 0.1mg IV (1:10,000 solution)
  - Hx: timing/evolution, inspiratory/expiratory/biphasic, inciting events, prior episodes, evidence of infection, allergy, hx EtOH/tobacco (cancer risks), hx of known head and neck, radiation
  - DDx (in adults): iatrogenic/post-intubation (laryngeal/vocal cord edema/praxis of the recurrent laryngeal nerve from ET tube); infectious (epiglottitis, laryngitis, laryngotracheitis [croup], bacterial tracheitis, Ludwig’s angina); allergic; tumor/mass of larynx or trachea; neurological (vocal cord spasm or immobility); foreign body/truma
  - Imaging: If stable consider CT scan with contrast of head/neck/chest to localize source

**Acute Sinusitis** *(Otolaryngol Head Neck Surg 2007;137:S1)*

- See Respiratory Complaints in “Primary Care” Section for outpatient management
- Primarily a clinical diagnosis – CT usually not necessary, and CT findings alone (usually) not sufficient as 40% of asymptomatic people have CT abnormalities of sinuses *(Otolaryngol Head Neck Surg 1991;104:480)*
- **Signs/symptoms:**
  - Complicated (extra-sinus extension): visual changes, proptosis, mental status changes, severe HA, facial soft tissue changes on exam. In immunocompromised or critically ill, consider invasive fungal sinusitis (IFS), a surgical emergency. *(See Invasive Fungal Infections in “Infectious Disease” Section)*
- **Workup:** Uncomplicated → no testing required. Complicated → CT with contrast +/- nasal endoscopy to look for evidence of purulence.
  - If needing to rule out IFS, nasal biopsy with STAT pathology required
- **Inpatient Treatment:**
  - If requires hospitalization, use levofloxacin or amp/sulbactam IV +/- surgery if complicated / drainable extra-sinus collection
  - Invasive fungal sinusitis: liposomal amphotericin, surgical debridement, ID consultation

To call an ENT consult: page the ENT consult resident p22220.
To transfer a patient to MEEI: Call the MEEI ED at 617-573-3431.
Consultants

Ophthalmology

Basic Eye Exam: “Ocular Vital Signs”
- Visual Acuity (e.g. 20/200, CF, etc)
- Pupils (4mm -> 2mm OD, No APD)
- Visual Fields
- Extra Ocular Movements
- Intraocular pressure
- Color vision testing (Ishihara cards)

Common Abbreviations:
APD = Afferent pupillary defect
AT = Artificial tears
cc/sc = With/without refractive corr.
CE = Cataract extraction
CF = Count fingers (VA)
CWS = Cotton wool spot
DES = Dry eye syndrome
EOM = Extraocular movement
HM = Hand motion (VA)
IOL = Intraocular lens
IOP = Intraocular pressure
LP = Light perception (VA)
MGD = Meibomian gland dysfunction
NLP = No light perception (VA)
NPDR = Non-prolif. diabetic retinopathy
NS = Nuclear sclerosis
OU = Both eyes
PDR = Prolif. diabetic retinopathy
PVD = Posterior vitreous detachment
RD = Retinal detachment
RG = Retinal ganglion
c/s = With/without contact lens
SPK = Superficial punctate keratitis
SLE = Slit lamp exam
VA = Visual acuity
VF = Visual fields

High-Yield Pearls for the Wards:
- Vision Loss: acute (requires urgent evaluation) vs. chronic (outpt referral) - assess patient with their glasses on!!
- Glaucoma drops: prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, or alpha 2 agonists; all lower IOP
  - If brand-name combo meds unavailable, fractionate combo meds, ask phrm for substitution advice, or have pt bring in home meds
- Ophthalmoscope: Available on most floors. Tropicamide (dilating drop) is available to order. Can make pt light-sensitive for 4 hours.
- Dilating drops: 0.5% tropicamide (parasympathetic antagonist), 1-2 drops placed 15-20 minutes before exam
- Finding the retina: dilate the eye and use the ophthalmoscope as in http://stanfordmedicine25.stanford.edu/the25/fundoscopic.html

Common Eye Pathology
- The Red Eye: typically benign; refer to optho if no improvement or any "ocular vital sign" changes (see above)
  - Viral conjunctivitis: eyes “stuck shut” in AM, itchy, crusty discharge, ± URI symptoms, ± pre-auricular nodes, winter time
    - Tx: supportive/isolation (typically adenovirus, highly infectious). Wash hands thoroughly if you suspect this!
  - Allergic conjunctivitis: olopatadine 0.1% gtt bid x 5d. Clear Eyes/Visine not rec’d (rebound redness/2/2 alpha agonism)
  - Anterior uveitis: pain and true photophobia must be present ± eye injection. Refer to MEEI ED.
  - Contact lens keratitis: Have patients remove contact lens when admitted! Use glasses. P/w red/uncomfortable eye; infection until proven otherwise. Refer to MEEI ED.
- Blepharitis (inflamm of eyelids): p/w crusting/red eye/gritty feeling
  - Tx: baby shampoo, warm compresses, abx ointments x 2 weeks, then daily lid hygiene. Tx Hordeolum ("sty") the same.
- Dry Eye Syndrome (DES): p/w eye pain or "grit"/paradoxical tearing ±vague "blurliness."
  - Tx: artificial tears q1hrs pm first line tx, refer if no improvement
- Corneal abrasion/exposure keratopathy: unilateral, redness, mild light sensitivity, common after sedation
  - Dx: apply fluorescein (order in Epic) to the affected eye, illuminate with a blue light (e.g. ophthalmoscope, or smartphone screen with Eye Handbook App), abrasion will light up green; keratopathy will look like “sandpaper” instead of smooth glass.
  - Tx: abx ointment (Erythromycin 0.5%/bacitracin ophthalmic QID) + Lacrilube qhs. Consult if no improvement after 24 hrs.
- Anisocoria (unequal pupils): old (20% population has at baseline) vs. new (can be trivial 2/2 anticholinergic vs. catastrophic from herniation). NB: always ask for h/o ocular surgery as surgical pupil is a common benign cause.

<table>
<thead>
<tr>
<th>Miosis (Constricted Pupil)</th>
<th>Mydriasis (Dilated Pupil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Cholinergic (eg: morphine, pilocarpine)</td>
<td>↑ Sympathetic (eg: atropine, CNIIII paralysis)</td>
</tr>
<tr>
<td>↓ Sympathetic (eg: Horner’s)</td>
<td>↓ Cholinergic (eg: epinephrine, cocaine)</td>
</tr>
</tbody>
</table>

- If clinical suspicion for herniation (known bleed, CN3 palsy, obtundation, hemiparesis) → STAT head/neck CT A
- Horner’s Syndrome: ptosis, miosis, ± anhidrosis. Wide ddx along pathway from posterior hypothalamus → C8-T2 → superior cervical ganglion → up sympathetic chain along internal carotid and into orbit. Will require head and neck angiographic imaging to n/o potential carotid dissection.
- Retinal detachment: Presents with flashes/floaters/curtain coming over vision. Risk factors: myopia (near-sighted), trauma, diabetic retinopathy, prior eye surgery.
  - Tx: Refer to MEEI ED. Will likely require vitrectomy surgery.
- Subconjunctival hemorrhage: blood between conjunctiva and sclera from ruptured vessel. No vision changes, not painful. Can be 2/2 associated blood dyscrasia, vascula, trauma, spontaneous. Will resolve spontaneously. No need to consult optho.
- Endophthalmitis: Infection within globe. Can be 2/2 trauma, surgery, or endogenous source (bacteremia/fungemia).
  - Tx: Ophtho c/s, antibiotics/antifungals that will penetrate blood-brain barrier. May require vitrectomy (surgery).

Yasmin Islam

To call an Ophtho consult: Check vision using vision card and pupils prior to calling consult! General Inpatient Consult: page 21004; for Emergent/Overnight 617-573-4063 or MEEI Operator 617-523-7900.
# Radiology

## Contact Information & Life Images

<table>
<thead>
<tr>
<th>Main Number</th>
<th>617 – (643 / 724 / 726) – XXXX</th>
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## Reading Rooms

<table>
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<tr>
<th>Room Type</th>
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<td>Teleradiology</td>
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<td>PET</td>
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<tr>
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## Technologists

<table>
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<tbody>
<tr>
<td>CT Blake 2</td>
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<tr>
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## On Call Pagers

<table>
<thead>
<tr>
<th>Radiology Type</th>
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<tr>
<td>Cardiac CT</td>
<td>22122</td>
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<tr>
<td>Cardiac MRI</td>
<td>33133</td>
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<tr>
<td>IR GI/GU</td>
<td>34071</td>
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<td>IR Neuro Spine</td>
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<td>IR Vascular</td>
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<tr>
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<td>Neuro Inpatient</td>
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<td>Pediatrics</td>
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## Consults – Weekdays

<table>
<thead>
<tr>
<th>8am</th>
<th>12pm</th>
<th>5pm</th>
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<th>8am</th>
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<tbody>
<tr>
<td>Cardiac CT</td>
<td>Dodd</td>
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<td>XXXXXXXXXX</td>
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<tr>
<td>Chest</td>
<td>Dodd</td>
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<td>ED</td>
<td></td>
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<tr>
<td>GI</td>
<td>Dodd</td>
<td></td>
<td>ED</td>
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<tr>
<td>Neuro</td>
<td>Neuro Consult (730am – 430pm)</td>
<td>Neuro ED</td>
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<tr>
<td>Vascular</td>
<td>Dodd</td>
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<td>ED</td>
<td></td>
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<td>Other</td>
<td>Reading Room</td>
<td>ED</td>
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## Consults – Weekends & Holidays

<table>
<thead>
<tr>
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<th>5pm</th>
<th>7pm</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
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<tr>
<td>Chest</td>
<td>Dodd</td>
<td>ED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Dodd</td>
<td>ED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuro</td>
<td>Neuro ED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>ED</td>
<td></td>
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</tbody>
</table>

- **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
  - Send images to MGH PACS: upload to MGH ➔ request read
  - Retrieve images from The Cloud: ISDrequests.partners.org ➔ file an urgent 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
    - Exams will not be read if: requisition was for a different body part than the uploaded images; study >6 months old; a more recent LifeImage is available; US, fluoroscopy, or mammography

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Craig Audin, Reece Goiffon
**Radiology Basics**

- **X-ray:**
  - **5 Radiographic Densities**
    - Air
    - Fat
    - Soft Tissue
    - Bone
    - Metal

  - **Silhouette Sign:** loss of the margin between two opposing structures of the same radiographic density
    - RUL – right paratracheal stripe
    - RML – right heart border
    - RLL – right hemidiaphragm
    - LUL – aortic arch
    - Lingula – left heart border
    - LLL – left hemidiaphragm

- **Computed Tomography (CT):**
  - **Hounsfield Units (HU):** measurement of CT attenuation
  - **Windowing and leveling:** adjusting contrast and brightness to highlight structures
    - **Window (contrast):** range of Hounsfield units displayed across the grayscale
      - Wide window – best for large differences in attenuation
      - Narrow window – best for subtle differences in attenuation
    - **Level (brightness):** HU that corresponds to mid-gray
      - High level – best for structures with high attenuation
      - Low level – best for structures with low attenuation

  - **Phases of contrast:**
    | Phase       | Time After Injection | Structures Evaluated                  |
    |-------------|----------------------|---------------------------------------|
    | CTPE        | 15 s                 | Pulmonary arteries                     |
    | Arterial (CTA) | 30 s              | Aorta, systemic arteries, renal cortices |
    | Late arterial | 60 s               | Routine chest                          |
    | Portal Venous | 70 s               | Routine abdomen                        |
    | Nephrographic | 100 s              | Renal medulla                          |
    | Venous      | 120 s               | Peripheral veins                       |
    | Delayed (Urogram) | 10-15 min   | Ureters, bladder                       |

- **Magnetic Resonance Imaging (MRI):**
  - **T1 & T2 Signal**
    - **Evolution of Blood**
      - Hyperacute: <1 day OxyHb
      - Late subacute: 7-28 days Extracellular metHb
      - Chronic: >28 days Hemosiderin
      - Acute: 1-2 days DeoxyHb
      - Early subacute: 2-7 days Intracellular metHb

  - **Protein Signal**

- **MRI safety:**
  - Device compatibility: www.mrisafety.com
**Indications:**
- **IV:** whenever possible, particularly for *infection, tumors, and vessel imaging*
- **PO positive (hyperdense):** bowel obstruction, bowel wall pathology, differentiate bowel from other abd. structures
- **PO negative (hypodense):** inflammatory bowel disease, GI bleed, mesenteric ischemia
- **Rectal:** appendicitis, penetrating abdominal trauma

**Pregnancy and breast feeding:** *(ACR 2018)*
- **Pregnancy:**
  - **Iodinated:** no need to withhold contrast *(no data to suggest potential harm to fetus)*
  - **Gadolinium:** unknown risk to fetus → consider noncontrast or alternative study
- **Breast feeding:** mother’s informed decision to “pump and dump” for 12-24 h after scan

**Renal function:** *(ACR 2018, MGPO 2017)*
- **Age >60 years, dialysis, kidney transplant, single kidney, renal cancer, renal surgery, HTN on medication, DM, metformin**
- **Outpatient:** GFR within 30 d
- **Inpatient:** GFR within 24 h

<table>
<thead>
<tr>
<th>Screening</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age &gt;60 years, dialysis, kidney transplant, single kidney, renal cancer, renal surgery, HTN on medication, DM, metformin</strong></td>
<td><strong>GFR ≥ 45: contrast per protocol</strong></td>
</tr>
<tr>
<td><strong>Outpatient:</strong> GFR within 30 d</td>
<td><strong>GFR 30-44: pre-hydrate</strong></td>
</tr>
<tr>
<td><strong>Inpatient:</strong> GFR within 24 h</td>
<td><strong>GFR &lt; 30: non-contrast or alternative study</strong></td>
</tr>
</tbody>
</table>

**MGH prehydration protocol:** *(MGPO 2017)*
- **PO (preferred):** 1-2 L PO non-caffeinated beverage 12-24 h prior to scan
- **IV (outpatient):** NS 250 mL IV bolus @ 1 h prior to scan
- **IV (inpatient):** NS 100 mL/h IV 6-12 h before and 4-12 h after scan *(ACR 2018)*

**Contrast reactions:** *(ACR 2018)*
- **Mild**
  - Limited urticaria
  - Itchy throat
  - Nasal congestion
  - URI symptoms
  - N/V, flushing/warmth
  - HA/dizziness
  - Mild HTN
  - Transient vasovagal reaction

- **Moderate**
  - Diffuse urticaria
  - Facial/laryngeal edema w/o dyspnea or hoarseness
  - Bronchospasm w/o hypoxia
  - Protracted N/V
  - HTN urgency
  - Isolated CP
  - Vasovagal reaction requiring tx

- **Severe**
  - Anaphylaxis
  - Facial/laryngeal edema w/ dyspnea or hoarseness
  - Bronchospasm w/ hypoxemia
  - HTN emergency
  - Arrhythmia
  - Seizure
  - Protracted vasovagal reaction

**Indications for Premedication**
- **Prior mild-moderate allergic reaction**
- **None for prior physiologic reactions**
- **None for shellfish allergies**
- **No cross-reactivity between iodinated contrast and gadolinium**

**Corticosteroid Dose Equivalents**

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>PO:IV 1:1</th>
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<tbody>
<tr>
<td>Prednisone 50 mg PO</td>
<td>Hydrocortisone 200 mg</td>
</tr>
<tr>
<td>Methylprednisolone 40 mg</td>
<td>Dexamethasone 7.5 mg</td>
</tr>
</tbody>
</table>

**Adult premedication protocol:** *(ACR 2018)*
- **Elective (13 h protocol)**
  - Prednisone 50 mg PO @ 13, 7, and 1 h prior; **AND**
  - Diphenhydramine 50 mg PO @ 1 h prior
- **Accelerated (4-5 h protocol)**
  - Methylprednisolone 40 mg IV now and q4h until scan; **AND**
  - Diphenhydramine 50 mg IV @ 1 h prior
- **Emergent (1 h protocol) – no evidence of efficacy, only if no alternatives**
  - Methylprednisolone 40 mg IV @ 1 h prior; **AND**
  - Diphenhydramine 50 mg IV @ 1 h prior
• Ordering Studies:
  - All cross-sectional studies are protocolled by radiology – simply provide the necessary information:
    - Body part and modality
    - Indication: clinical history relevant to the study
    - Contrast: “per radiology discretion” unless specific reason otherwise
    - Contraindications for contrast: kidney injury or prior allergic reaction (see Contrast)
  - Questions: call the appropriate division or page the appropriate on-call radiologist (see Contact Information)
• Level of Urgency:
  - Routine: order of interpretation depends on acquisition time
  - Urgent: takes priority over routine studies
  - STAT: means NOW, high acuity/life threatening emergencies
    - Patient must be ready for immediate transport
    - Patient must be accompanied by a responding clinician capable of providing emergency care
    - Responding clinician must be present for the entire exam
    - Radiology will provide preliminary read: phone call for XR/US, at the scanner for cross-sectionals
• Overnight Reads:
  - Studies with full interpretations overnight: all ED studies, STAT studies, and acute CTPEs
  - Verbal preliminary reads:
    - Typically done for ICU studies only
    - Inpatient studies are only reviewed overnight if there is an urgent clinical question (i.e., one that would alter overnight management). Consider face-to-face consult in ED.
    - After communication w/ the primary team, all verbalized prelim reads will be documented in the chart
    - A full interpretation will be generated the following morning for all prelim reads
• Cardiovascular Protocols:
  - DVT imaging: US is initial test of choice (Cardiovascular Diagnosis and Therapy 2016;6:493)
    - CTV/MRV: primarily used for central venous thrombosis when initial US is equivocal or non-diagnostic
  - Arterial imaging:
    - CTA: three phases (noncontrast, arterial, delays) → stenosis, dissection, aneurysm
    - Requisition: specify vessel of interest, field of view, and indication
  - Coronary CTA:
    - ECG-gated study of the heart → only performed by CV CT on-call radiologist during normal hours
    - Specify if body parts other than the heart should be imaged (thoracic aorta, CABG grafts, etc.)
  - Other EKG-gated CTAs:
    - Indications: any evaluation of the heart or ascending aorta
    - EKG-gating is unnecessary for the descending thoracic aorta, abdominal aorta, and pulmonary arteries
  - Noncontrast vascular studies:
    - RP hematoma, pre-op aortic calcifications, coronary calcium score, follow-up aortic size
• ED Protocols:
  - Trauma: I+, single phase (arterial for chest, portal venous for abdomen/pelvis – images checked at the scanner by radiology for possible delays)
    - Blunt trauma: includes bone kernel reformats for improved visualization of bones
    - Penetrating trauma: O+R+ for increased sensitivity of bowel injury
  - Cervical spine: I-, need for CTA determined by radiology, bone kernel reformats in all 3 planes
    - Images checked at the scanner by radiology only if IV contrast is required for another body part
  - Appendicitis: I+ and O+/R+ (please specify PO or PR), kidneys through pelvis only
  - Neuro ED: call reading desk @ x68188
• GI/GU Protocols:
  - Stone protocol: I-O-, low dose
    - Order contrast-enhanced CT if there is concern for ANYTHING else (stones may still be visualized)
  - Routine abdomen/pelvis vs renal mass vs bladder cancer vs hematuria:
    - Routine abdomen/pelvis: I+O+, single phase (portal venous) → workhorse protocol
    - Renal mass: I+O+, two phases (noncontrast, nephrographic), abdomen only → renal masses or cysts
    - Bladder cancer: I+O+, two phases (portal venous, delayed) → workup or monitoring of GU malignancy
    - Hematuria: I+O+, “three” phases (noncontrast, nephrographic, urogram) → hematuria, hydrenephrosis
  - CT urogram vs CT cystogram:
    - Urogram: antegrade filling of ureters and bladder with IV contrast (delayed phase)
    - Cystogram: retrograde filling of bladder with contrast via Foley catheter → evaluation of bladder rupture
Arterially-enhancing tumors:
- MR CHIT: melanoma, RCC, choriocarcinoma, HCC, islet cell (neuroendocrine) tumors, thyroid

Does my patient need to be NPO?
- IV contrast CT: 2 h
- Abdomen/pelvis CT: 8 h
- Non-contrast CT: no NPO

Fluoroscopy protocols:
- Requisition: specify indication, h/o surgery or aspiration
- Barium swallow vs modified barium swallow vs UGI series vs SB follow-through:
  - Barium swallow: esophagus, GE junction, proximal stomach ➔ dysphagia, GERD
  - Modified barium swallow: mouth, pharynx, upper esophagus ➔ dysphagia, aspiration
  - UGI series: barium swallow plus stomach, pylorus, and duodenal bulb ➔ bariatric surgery
  - SB follow-through: small bowel, terminal ileum, and proximal LB +/- UGI series beforehand

Musculoskeletal Protocols:
- Questions: page MSK IR on-call radiologist @ p36321

Nuclear Medicine Protocols:
- Overnight studies:
  - Tagged RBC study: BRBPR (NOT guaiac positive stools, melena, or massive bleeding)
    - Requirements: consult IR first for possible angiogram if study is positive
  - VQ scan: acute PE (NOT chronic PE), ONLY if results will alter management (i.e. AC tonight)
    - Requirements: CXR within 24 h, patient stable for duration of scan (~4 h)
  - HIDA scan: acute cholecystitis, ONLY if results will alter management (i.e. OR tonight)
    - Requirements: NPO 4-24 h prior to study, no opiates 12-24 h prior to study, bilirubin <10

PET:
- Fasting: hold everything but meds and water
  - Overnight is ideal, but AT LEAST 6 hours for non-DM patients
  - AT LEAST 4 hours for DM patients
    - Continue long-acting insulin, hold short-acting insulin 4 h prior to scan
  - Blood sugar thresholds
    - FDG-PET brain < 175 mg/dL
    - FDG-PET whole body < 250 mg/dL

Neuroradiology Protocols:
- Inpatients: page Neuro IP on-call radiologist @ p32535
  - Acute stroke:
    - Inpatients/ICU: page acute stroke consult fellow @ p21723
    - ED: activate ED2CT via the group pager
  - Head CT: typically noncontrast
    - Indications for contrast-enhanced head CT: infection and/or tumor AND contraindication for brain MRI
  - Spine MRI: for more than 1 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
    - Not to be used as an anesthesia service for unruly patients (typically performed without conscious sedation, although this can be arranged if required for patient safety)

Thoracic Protocols:
- All chest CTs are high resolution – traditional “high res chest CT” is now the diffuse lung disease CT (see below)
  - Routine chest vs CTE vs CTA chest:
    - Routine chest: single phase (late arterial) ➔ workhorse protocol
    - CTE: single phase (pulmonary arterial) ➔ pulmonary arteries
    - CTA chest: three phases (noncontrast, arterial, delays) ➔ systemic arteries
  - Double rule out studies:
    - Clinical concern for PE and aortic dissection
    - Contrast can only be optimized for one (must pick CTE or CTA)
  - Diffuse lung disease (a.k.a. misnomer “high res CT”):
    - Indications: ILD, lung transplant, air trapping
  - Nodule follow-up: (Radiology 2017;284:228)
    - Indications: incidental nodule on prior CT, age >35 y, AND no history of malignancy or recent infection
    - Fleischner Society 2017 Guidelines
• **CXR – line placement:**
  - SVC: between right tracheobronchial angle and right heart border (*Chest* 1998;114:820)
  - Cavoatrial junction: two vertebral bodies below the carina (*JVIR* 2008;19:359)
  - **Line positioning:**
    - Central line: tip in the SVC or at the cavoatrial junction
    - HD catheter: tip in the right atrium
  - **Post placement:** check for pneumothorax (see below)
• **CXR – pulmonary edema:** (*Core Radiology* 2013)
  - Vascular redistribution (first sign): increased caliber of pulmonary vessels in upper lobes (cephalization)
  - Interstitial edema: increased interstitial opacities, indistinctness of pulmonary vasculature, Kerley B lines, peribronchial cuffing
  - Alveolar edema: perihilar/central opacities, pleural effusions, cardiomegaly
  - Pearls: typically bilateral and symmetric, rapid appearance/resolution of radiographic findings
  - Pitfalls: low lung volumes can mimic increased interstitial opacities
• **CXR – pneumothorax:** (*UpToDate* 2018)
  - **Sensitivities:**
    | Imaging Position | Detectable PTX Size | Imaging Findings                      |
    |------------------|---------------------|---------------------------------------|
    | Supine/Portable  | 500 cc              | Deep sulcus sign, lucency along mediastinal border |
    | Upright          | 50 cc               | Sharp visceral pleural line, absence of distal lung vessels |
    | Lateral decubitus| 5 cc                | Nondependent collection of air         |
  - Tension: contralateral mediastinal shift, collapse of ipsilateral lung, flattening of ipsilateral hemidiaphragm, widening of ipsilateral rib spaces
    - Medial border of scapula: in continuity with rest of bone
    - Skin folds: form an interface (not a line), extension beyond rib cage, presence of distal lung vessels
• **KUB – line placement:** (*Pediatric Radiology* 2011;41:1266)
  - GE junction: within 1 vertebral body of the T10-T11 disc space, <16 mm from left spine border
  - **Pylorus:** C-loop of duodenum is only reliable indicator of post-pyloric placement
    - Right side of spine is unreliable
  - **Line positioning:**
    - Decompression: gastric fundus or dependent portion of stomach
    - Feeding: distal duodenum or proximal jejunum
  - **Post placement:** check for endobronchial placement
• **KUB – small bowel obstruction:** (*RadioGraphics* 2009;29:423)
  - **KUB:** preferred initial examination
    - **Assess for:** small bowel dilatation >3 cm, air-fluid levels, stacked loops of bowel, transition point
  - **CT:** equivocal cases or for further evaluation
    - **Assess for:** SB dilatation, collapse of distal bowel loops, transition point
    - **Severity:**
      - Partial: passage or air or contrast beyond the obstruction
      - High grade partial: 50% difference in caliber between dilated and collapsed SB loops
      - Complete: no passage of air or contrast beyond the obstruction
    - **Transition point:** look for small-bowel feces sign (fecal material mixed with gas bubbles in small bowel)
    - **Cause:** adhesions, Crohn’s, malignancy, hernias
    - **Complicated SBO:**
      - Closed loop obstruction: radially oriented bowel loops, engorged mesentery, whirl sign
      - Strangulation: bowel wall thickening, lack of bowel wall enhancement, pneumatosis intestinalis, portal venous gas
• **KUB – pneumoperitoneum:** (*AJEM* 2009;27:320)
  - **Upright:** air beneath the diaphragm
  - **Left lateral decubitus:** air over the liver
  - **Supine (insensitive):**
    - Anterior superior oval sign: gas bubbles projecting over liver
    - Hyperlucent liver sign: free air overlying liver
    - Rigler’s sign: air on both sides of the bowel wall
    - Falciform ligament sign: linear density projecting over liver
• **US – cholecystitis:** *(AJR 2011;196:W367)*
  - US is preferred initial examination
  - Gallstones: echogenic foci with posterior shadowing
  - Common findings: gallbladder wall thickening >3 mm, gallbladder distension >40 mm, peri-cholecystic fluid
  - Sonographic Murphy’s sign: 92% sensitivity (analgesics reduce sensitivity)
  - Gallstones and gallbladder wall thickening: 95% positive predictive value for acute cholecystitis

• **US – deep venous thrombosis:** *(Cardiovascular Diagnosis and Therapy 2016;6:493)*
  - Compression US: noncompressibility of vein, echogenic thrombus within vein, venous distension
  - Venous duplex US: absence of color Doppler signal within vein, loss of flow phasicity, loss of response to augmentation maneuvers
  - CT venogram:
    - Alternative to US in critically ill patients who have undergone CTPE
    - 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:**
  - Anatomy: [http://www.radiologyassistant.nl/](http://www.radiologyassistant.nl/)
  - CT and MRI basics: see *Radiology Basics*
  - Search pattern: see below

<table>
<thead>
<tr>
<th>CT Head</th>
<th>MRI Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Brain parenchyma</td>
<td>1. Brain parenchyma</td>
</tr>
<tr>
<td>a. Mass lesion: brain windows</td>
<td>a. Mass lesion: T1, T2, FLAIR</td>
</tr>
<tr>
<td>b. Intracranial hemorrhage: brain and subdural windows</td>
<td>b. Intracranial hemorrhage: SWI, T1, T2</td>
</tr>
<tr>
<td>c. Infarction: stroke windows</td>
<td>c. Infarction: DWI, ADC</td>
</tr>
<tr>
<td>2. Vessels</td>
<td>2. Vessels: T2 for flow voids, T1 post-contrast, TOF if noncontrast MRA</td>
</tr>
<tr>
<td>3. CSF spaces: ventricles, sulci, cisterns</td>
<td>3. CSF spaces: T2</td>
</tr>
<tr>
<td>4. Midline shift or herniation</td>
<td>4. Midline shift or herniation: coronals helpful</td>
</tr>
<tr>
<td>5. Soft tissues (great place to start for trauma head CTs)</td>
<td>5. Soft tissues</td>
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<table>
<thead>
<tr>
<th>CT Chest</th>
<th>MRCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lines and tubes (scout can be very helpful)</td>
<td>1. Choledocholithiasis: hypointense filling defect within CBD surrounded by hyperintense bile</td>
</tr>
<tr>
<td>2. Abdomen</td>
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</tr>
<tr>
<td>3. Soft tissues</td>
<td></td>
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<tr>
<td>4. Bones</td>
<td></td>
</tr>
<tr>
<td>5. Heart and mediastinum: thyroid, lymph nodes, heart and pericardium, major vessels, esophagus</td>
<td></td>
</tr>
<tr>
<td>6. Pleura: pleural effusion, pneumothorax</td>
<td></td>
</tr>
<tr>
<td>7. Lungs: secondary pulmonary lobe is the key</td>
<td></td>
</tr>
<tr>
<td>a. Radiology Assistant ➔ Lung HRCT Basics</td>
<td></td>
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<table>
<thead>
<tr>
<th>CT Abdomen/Pelvis</th>
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<tbody>
<tr>
<td>1. Lung bases</td>
<td></td>
</tr>
<tr>
<td>2. Liver/gallbladder: focal lesions, biliary ductal dilatation</td>
<td></td>
</tr>
<tr>
<td>3. Spleen</td>
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<td>4. Pancreas: focal lesions, pancreatic ductal dilatation</td>
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<td>5. Adrenals</td>
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<td>6. Kidneys/ureters: hydronephrosis, stones, focal lesions</td>
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<td>7. Bladder/pelvic organs</td>
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<td>8. Peritoneum: free air or fluid</td>
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<td>10. Vessels</td>
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<td>11. GI tract: bowel distension, bowel wall thickening</td>
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<td>12. Soft tissues</td>
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Procedures

Ultrasound Basics

**Equipment:** (NEJM 2011;364:749)

**Basic Terminology:**
- **Frequency:** 1Hz = 1cycle/sec; Medical U/S typically between 2-15MHz (derm U/S up to 100MHz).
  - 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.
- **Depth:** Depth of field of view (FOV). Excessively large FOV ↓ spatial resolution; tight FOV limits view of nearby structures.
- **Attenuation:** Reduced signal transduction through a medium = ↓ signal intensity behind it (bone/air have high attenuation)

**Transducer (probe):** Converts electricity into sound waves → transmits sounds wave into tissue → receives sound waves echoed back from tissue. Indicator (denoted by light or notch on probe) displays on **left of the screen.** **Exception:** echocardiography → indicator displays on **right side.**
- **SECTOR (cardiac) probe:** Good for looking in small sonographic windows (i.e., between intercostal spaces for cardiac or pulm imaging); low resolution, produces fan-like image.
- **LINEAR (vascular) probe:** Good for shallow structures (i.e., vascular, soft tissue). Uses high frequency with good resolution, produces rectangular image.
- **CURVED (abdominal) probe:** Good for deeper structures (i.e. intra-abdominal). Uses lower frequency; combines linear and sector probe image qualities.

**Commonly Used Modes:**
- **B-mode** (brightness mode): Standard 2D gray-scale image.
- **D-mode** (doppler): Detects flow to or away from transducer. Useful to find and define vessels, flow across valves
  - 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 (echogenic or hyperechoic)
- **Fat and muscle** are dark, though varies depending on the tissue (hypoechoic)
- **Fluid** (e.g. blood, effusion) appears black on ultrasound (anechoic), though thick fluids (pus) can be brighter than typical fluid
- **Tendons and nerves** are bright / hyperechoic when perpendicular to probe, but dark / hypoechoic when angle is changed (anisotropy).
- **Bone** has a bright hyperechoic rim (due to reflection) around a black / anechoic image with a shadow behind it

**Artifacts:** Elements seen on ultrasound image that do not exist in reality
- **Reflection:** Proportional to the difference in acoustic impedance between two tissues
  (↑ difference = ↑ reflection)
  Relative acoustic impedance: bone >> solid organ > fat >> lung >> air.
- **Shadowing:** ↓ signal beyond a strongly attenuating OR reflecting structure (e.g. stones, bone)
- **Enhancement:** ↑ signal posterior to weakly attenuating (hypo or anechoic) structure (e.g., cysts)
- **Mirror image:** Structures in front of strong reflector (e.g. diaphragm) appear to lie behind it as well
- **Reverberation:** Evenly spaced lines at various depths beyond a strong reflector (e.g. A lines beyond pleura)
- **Comet tail:** Tiny, narrow reverberations beyond very strong reflector (e.g. metal pellet) blending into a line
Procedures

Imaging and Tips:

Diagnostic Use:

- **Pneumothorax:** Use SECTOR probe. With patient supine, look in the 3rd intercostal space on the anterior chest. Identify the hyperechoic rims of the ribs with posterior shadowing; within the intercostal space identify the hyperechoic stripe that is the pleura. A normal lung will slide along the pleural line with respiration, a 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 (see pictures). Sens 91%, Spec 98%, superior to CXR. A lung point is not sensitive but is 100% specific. ([J Emerg Trauma Shock 2012;5(1):76, Ann Emerg Med 2013 61(2):207]).

- **Pulmonary embolism:** SECTOR probe. Bedside ultrasound can be used to identify right heart strain. Look for RV size ≥ LV size, septal bowing, though note sens/spec for PE 53%/83%. RV/LV ratio is most easily visualized in the apical 4 chamber view, but can be misleading based upon slight changes in plane. Assess with septum vertical in line with midpoint of probe. Combine with the parasternal axes for better reliability. ([J Am Soc Echocardiogr 2017;30:714]).

- **Pulmonary Edema:** Use SECTOR probe to evaluate the lung between rib spaces as above, across lung fields as for auscultation. Look for B-lines: comet like artifacts that shine perpendicular from the pleural line and obliterate A-lines. ≥3 in one interspace is consistent with interstitial fluid, and bilaterally suggests pulmonary edema. Operator dependent but can outperform CXR. ([Am J Emerg Med 2015;33(5):620]).

- **Pericardial Effusion:** Use SECTOR probe. Look for an anechoic stripe between the heart and the hyperechoic pericardium, though hemorrhagic or purulent effusions can appear more complex. On parasternal long axis this will be anterior to the descending aorta, while a pleural effusion would be posterior. All four views are important, but often only subxiphoid used in emergencies. Look for chamber collapse indicating tamponade: RA is more sensitive; RV is more specific. ([Resuscitation 2011;82(6):671]).

- **Volume Status:** Use the SECTOR probe. IVC collapsibility has been proposed as a proxy for CVP and fluid responsiveness, though data is mixed and 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 ≤2.1cm and 2) IVC collapses ≥½ its diameter. Can use M mode to track variation, cycles are inverted if spontaneously breathing vs mechanical ventilation, more accurate in the latter. ([Crit Care 2012 8:16(5):R188, Crit Care Med 2013;41(3):833, Shock 2017 47(5):550]).

Procedural: Refer to white book pages on specific procedures for more details

- **Paracentesis:** Use CURVED probe. Locate largest fluid collection, often in LLQ. Try rolling patient to side to increase pocket size. LINEAR probe can help identify any overlying vessels to your approach, particularly the inferior epigasitcs. Hyperechoic finger-like projections are bowel within the anechoic ascites. Measure the depth of the abd wall and compare to your needle to determine when to expect flash, though with tenting this will be a slight underestimation.

- **Central venous access:** Use LINEAR probe. Reduces complications and quality of placement compared to landmark approach ([Crit Care 2017;21:225]).
  - **In-plane** (long axis): Can view entire tip, but harder to keep needle in view
  - **Out-of-plane** (short axis): Easier to center needle, may underestimate depth

- **Peripheral IV:** Use LINEAR probe. Most of your time should be in finding the best vein to go for, often in the medial groove between biceps/triceps. Track along vessel length to determine trajectory, look for large, superficial, compressible vessels that are not adjacent to pulsatile, non-compressible arterial vessels. As above, in plane vs out of plane.
Procedures

Ultrasound-Guided Peripheral IV

Indication: Non-emergent access in a patient for whom 2+ attempts at blind PIV placement have failed or have a history of difficult access. If emergent, obtain IO or central access.

Equipment: IV catheter: Use a “straight” IV, not a “butterfly”; 20G or larger (smaller IVs not well visualized on US); Standard length (30mm) or if superficial edge of the vein < 0.8 cm deep; Long IVs (48mm+) best if depth ≥0.8 cm. (Long 20G IVs only available in ED); IV starter pack (includes tourniquet, chlorhexidine, Tegaderm, gauze and tape), sterile lubricant (what you use for a rectal exam is fine), Tegaderm to cover the ultrasound probe, and extension tubing, which should be primed and attached to a saline flush. Ultrasound machine with a vascular probe. Optional: additional tourniquet (stacked, not serial), tubes for labs and vacutainer adapter (if you need labs).

Preparation:
Place a tourniquet high, near axilla. Using a transverse view (short axis) and shallow depth (about 2 cm), scan forearm. Anatomy is variable. Upper arm is more predictable, see diagram. Success is predicted primarily by the diameter of the vein (>0.5 cm is preferred) and the superficial edge of the vein should be < 1.6 cm deep. A vein should be fully compressable and pulseless. Scan its course to learn trajectory. Use minimal pressure to avoid collapsing vein and accurately assess depth. It is important to estimate depth correctly because if IV is too short, it will come out. Keep little finger on skin to stabilize probe. Clean the site and probe with alcohol or chlorhexidine. Cover the probe with a sterile Tegaderm. Apply sterile lubricant.

Transverse Technique (Short Axis) – Pros: requires less finesse with the ultrasound probe and allows visualization of adjacent structures. Faster. Cons: harder to visualize the needle tip.
Select the point where you intend for the catheter to enter the vein. Prepare to puncture the skin distal to this point (distance = depth of vein). Hold the needle at 45˚ to the skin. Puncture the skin just enough to identify the tip of the needle on the screen. Advance the probe until you lose the needle tip. Then advance the needle until it reappears. When you are right above the vein it will likely compress under the pressure of the needle. Make a quick, but very small jab to enter the vein without puncturing the back wall. You should see a bright spot the in the center of the dark vessel. Drop the angle of the needle. Advance the probe until the needle tip is no longer visible. Then advance the needle again so that is reappears in the center of the vessel. After you have advanced the needle tip 3-5mm within the vein you can either advance the catheter until hubbed or proceed advancing the needle by the same method until hubbed. Then retract the needle, attach extension tubing, remove tourniquet, and ensure blood return/flush before securing catheter.

Longitudinal Technique (Long axis) – Pros: improved visualization of the needle tip helps to avoid going through the back wall of the vein and you can advance the catheter under direct visualization. Cons: challenging to maintain probe, vein and needle in plane; cannot see adjacent structures.
Identify your target vein in the transverse view, then slowly rotate the probe to obtain a longitudinal view with the indicator towards your needle. Align your needle in the plane of the probe, puncture the skin at a 45˚ and visualize the needle tip. Advance the needle until it begins to compress the vein. Very small jab to enter the vein. Advance the needle until you can see that the tip of the catheter itself is fully within the vein. Do not go through the back wall. At this point you can advance the catheter under direct visualization.

Troubleshooting – Cannot see needle: bounce the needle tip to generate artifact. Too much loose tissue: ask someone to assist by putting tension on the tissue without applying pressure over your target vein. Vein rolls: reposision to make sure you are directly over the middle of the vein and 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

Central Line Placement

General Considerations

Indications: Hemodynamic monitoring (CVP, CVO2); admin. of noxious meds (pressors, chemo, hypertonic solution, TPN); rapid large volume resuscitation; inadequate peripheral access; HD/CVVH/pheresis; to introduce other devices (PA line, temp wire).

Contraindications: Vein thrombosis or stenosis should prompt another site. Coagulopathy/thrombocytopenia are relative contraindications, if severe coagulopathy, avoid subclavian (not a compressible site + difficult to effectively monitor for bleed).

Site selection: General preference at MGH is RIJ > LIJ > subclavian > femoral due to historical concern for infection. However, more recent data suggests no difference between these sites with proper attention to sterile technique.

Catheter selection: Select based on number of lumens and speed of infusion; if rapid infusion required → large bore, short length Cordis Alternatives: PICC (if no concern for bacteremia) or IO (should not be used for > 24h, but in extreme circumstances OK for 48h).

Scheduled exchange of catheters without evidence of infection is NOT indicated

Cultures drawn from indwelling catheter have ↑ false (+) rate; generally not done aside from time of sterile placement (NEJM 2003;348:1123)

Internal Jugular Vein


Advantages | Disadvantages
---|---
Compressible vein | Carotid artery puncture 2-10%
Lower risk of pneumothorax (< 1%) than subclavian | Less patient comfort
Ability to use real-time ultrasound | Anatomy not as consistent as subclavian

All IJ CVCs placed with real-time US guidance @ MGH: ↓ first attempt failure, procedure time, and failure / complication rate.

Positioning: Supine + Trendelenburg to engorge veins, maximize target, ↓risk of air embolus

Entry:
- Locate triangle formed by medial and lateral portions of SCM with the clavicle as base
- Find IJ → superficial and lateral to carotid, compressible, larger, thinner
- RIJ generally preferred (direct course to SVC; LIJ ↑ risk of PTX and thoracic duct injury)

Entry:
- Bevel up at the apex of SCM / clavicule triangle, about 4-5 cm above suprasternal notch
- Aim at ipsilateral nipple, 45 degrees (map out trajectory of vessel using ultrasound)

Aim at ipsilateral nipple, 45 degrees (map out trajectory of vessel using ultrasound)

1) Preparation and positioning are essential; ensure someone is available to help at all times
2) Obtain consent; perform TIME-OUT; complete checklist (usually RN)
3) Use 2% chlorhexidine solution to prep (in the kit); drape the entire patient in sterile field
4) Open kit, place caps on CVC (except brown port), flush all lines with sterile saline (leave cap on the saline flush for ease at end of procedure); ensure guide wire advances easily and syringe comes off needle easily
5) Anesthetize area with lidocaine (aspirate before injecting!)
6) Locate IJ vein & carotid artery using ultrasound
7) Insert and advance the large bore needle → bevel up, 45°, towards ipsilateral nipple, visualizing tip with US; aspirate / apply negative pressure; once flash of blood is obtained → stop advancing the needle, continue to draw back venous flow (dark, non-pulsatile)
   * If arterial flow seen, remove needle and compress ~10 min
   * If air drawn back, suspect PTX → STAT CXR, 100% FiO2, decompress if tension
8) Once flow obtained, stabilize needle with your non-dominant hand, remove syringe from locator (occlude hub with thumb to minimize risk of air embolism in non-ventilated patients)
9) Feed the curved end of the wire into the needle (never feed the opposite end).
   NEVER LET GO OF THE WIRE.
   * If any resistance, draw back wire, assess for flow w/ syringe; If good blood flow, try twisting wire or lowering angle of needle
   * For R-sided IJ → feed 30cm of wire (three dark lines) → watch for ectopy
   (suggests wire in RV → withdraw)
10) Withdraw needle
11) Confirm wire is in vein using US in transverse and longitudinal planes
12) Perform manometry confirmation → advance 20G angiocath over wire, remove wire, connect to manometer → venous blood should be < 20cm → replace wire, remove angiocath
13) Extend puncture site with scalpel (face cutting edge away from wire to prevent cutting wire)
14) Thread dilator over wire (using twisting motion) until about 1/3 is inserted, then remove; goal is to dilate skin/subcutaneous tissue, NOT the vessel itself (increased bleeding); ensure the wire moves back and forth freely while dilating (may otherwise be kinked)
15) Advance catheter over wire (comes out brown port, which is why it must be uncapped); remove wire
16) Draw back off all ports using saline flush (only need to see small amount of flash), flush all lines clean, clamp ports, place caps
17) Secure with sutures; place biopatch prior to securing with dressing
18) Order CXR (ASAP) to assess position, rule out PTX and hemothorax; look at the CXR yourself ASAP; 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.

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Central Line Placement

Subclavian Vein

Positioning: Some place a roll of towels between scapula to expose subclavicular area... others say this distorts anatomy; place in Trendelenburg to engorge vein

Entry: @ MGH → infraclavicular approach (as opposed to supraclavicular); puncture skin 1cm caudal to junction of medial 1/3 and middle 1/3 of clavicle (where vein flows just under the bone)

Target: Bevel up and aim toward sternal notch, 30° to the skin; needle should advance just on the underside of the clavicle (~3-5cm depending on anatomy); some people “walk down” the clavicle to ensure this, but may lead to dulling or bending of needle as well as perioseal 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

Positioning: head of bed flat; abduct lower extremity and externally rotate the hip

Entry: Bevel up, 2-3 cm below inguinal ligament, 1cm medial to palpated pulse → femoral vein lies medial & inferior to the femoral artery

- If non-urgent use ultrasound 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 → risk for RP bleed & peritoneal perforation

Target: Directly superior at 30-45°.

Cordis (aka venous introducer sheath)

Combined dilator and sheath w/ side port for IV access

Indications:
- Rapid resuscitation (shorter length, wider diameter)
- Introducer sheath for PA catheter
- Introducer for temp wire placement.

Sites: IJ (R preferred for PA line), subclavian vein, femoral vein

Placement technique: Uses Seldinger technique (advance catheter over a wire) but dilator and sheath are advanced over wire together; dilator and wire removed together; side port aspirated and irrigated prior to use.

CVC Complications

Arterial puncture: Hold pressure x 10 mins; compress 1 inch inferior (IJ) or 2 inches superior (femoral) to puncture mark

Dilation / line placement in an artery: Consult vascular surgery BEFORE removing line; consider CT if pt stable

Pneumothorax (IJ & subclavian): Suspect if hypoxia, hypotension, difficult stick; obtain STAT CXR → thoracic surgery consult if PTX or hemoTX; if tension physiology (shock) → immediate decompression with 16G angiocath @ 5th ICS, mid-axillary line (enter above the rib)

Retroperitoneal bleed (femoral): Suspect if hematoma or hypotension; STAT CT / US → vascular medicine consult

Loss of wire or wire stuck in vessel: DO NOT use excessive force to pull out wire if it is stuck → leave in place, hold pressure to prevent exsanguination → STAT KUB / CXR if wire loss → vascular medicine consult

Air embolism: Hypoxia, chest pain, dyspnea, hypotension → can occur with insertion, removal, or while CVC is in place; administer 100% O2 (to speed air resorption); lay in Trendelenberg + left lateral decubitus position (to trap air in RV apex); STAT TTE (to assess for air in RVOT) → vascular medicine consult for potential aspiration of embolus

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Procedures

Arterial Line Placement

General Considerations:
Indications: Real-time BP monitoring (pressors, HTN emergency, CVA); frequent ABGs (≥3 per day)
Locations: Radial > dorsalis pedis > femoral > axillary; brachial not recommended given lack of collaterals unless placed by anesthesia.
Contraindications: Lack of collaterals, 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, 20G angiocaths, guide wire, Tegaderm; consider marking pen

- If pt awake — consider lidocaine (without epinephrine), small syringe and 25G needle
- Do NOT use BD Insyte Autoguard BC IV catheter (pink stripes on package → has a one-way valve)
- Alternatively, use Arrow arterial line kit; the kit's longer catheter is preferable for femoral site

Radial Technique:

1. Obtain consent and perform TIME-OUT; ask RN to prepare for A line
2. Test for collateral circulation of the hand:
   - **Allen test**: Make fist for ~30 sec, then occlude ulnar & radial arteries; pt opens hand (palm should be blanched); then release pressure from ulnar artery → palm should regain color within ~5 sec
   - **Modified Allen test**: Put sat probe 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 is key to successful placement
   - Bring bed to acceptable height
   - Put Chux under wrist; extend pt's wrist; secure arm board (bendable arm boards in CCU and MICU)
   - Consider taping hand to bed to stabilize; mark course of artery w/ pen or indent with top of pen; use US / doppler as needed
4. Use 2% chlorhexidine swabs to widely sterilize radial side of wrist; open towel packet to create sterile field
5. Drop angiocath & guide wire on sterile field; don sterile gloves and drape widely w/ sterile towels
6. If pt awake, can anesthetize superficially with lidocaine (without epi)
7. Check angiocath to ensure catheter slides easily off needle; pull one side of wire slightly out of paper casing but not all the way out
8. Palpate radial artery with non-dominant hand; plan to puncture just distal to the pulse you palpate, and aim towards that pulse
9. With bevel up, advance angiocath needle at a 45° angle toward pulse until flash is obtained (similar to ABG)
10. Once flash obtained, go "through-and-through": advance ~0.5cm through artery; hold the top of the plastic catheter (pink on 20G angiocaths) with non-dominant hand; push button to retract needle, while steadying the catheter (should be no blood flow)
11. Hold guide wire close to head of angiocath w/ dominant hand
12. Lower angiocath as parallel to skin as possible and SLOWLY pull it back until pulsatile blood flow is obtained
13. Advance 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)
14. Advance angiocath into the artery over the wire (Seldinger technique)
15. Apply pressure to the radial artery proximal to catheter; remove guide wire; occlude opening of the angiocath with finger
16. Ask RN for A-line setup and sterilely connect transducer / T-piece to angiocath; RN will flush; confirm placement w/ arterial waveform
17. Dress the area with a Tegaderm; MICU nurses will often re-dress afterwards, so ask them their preference; In ED, suture line to the wrist; NWH has special snap dressings that keep the line in place

Daily ✓ for ischemia (cool, white, purple) & infection (need for removal)

Troubleshooting and Alternatives:
- Consider using a Doppler or ultrasound to identify the location / trajectory of the vessel. If using Doppler, mark out course of artery with marking pen or indentations from top of Bic pen. If using US, once needle is withdrawn and plastic catheter visualized in the artery, it can be advanced under US guidance without use of the guide wire. This can be helpful if artery is small.
- If unable to thread guide wire AFTER ATTEMPTING TO SPIN during insertion, consider micropuncture wire (cardiac cath lab or MICU med room). May help with atherosclerotic arteries at the price of ↑ risk of perforation
- After multiple attempts, the artery may spasm. Pursue alternative site.
- Femoral artery access can be considered in difficult cases. Use the long catheter in the Arrow a line kit. Puncture must occur distal to the inguinal ligament to prevent RP bleed. Too distal, however, and the femoral artery will bifurcate into superficial and deep femoral vessels. The femoral artery usually transverses the inguinal ligament ~1/3 distance from pubic symphysis to the ASIS. Optimal point of skin puncture is 1-2 cm below the inguinal ligament at point where pulse is palpated (see above)

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Intraosseous Line Placement

General Considerations:

- **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 (shock, sepsis, status epilepticus, trauma). Used for delivery of fluids/medications; bloodwork (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 (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)
- **Note:**
  - Infusion rate roughly 160mL/min at tibia or humerus with use of pressure bag, half of that 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, 10 cc syringe with saline flush, chlorhexidine/povidone iodine, sterile gloves. If awake, 3 cc syringe with 1% lidocaine via 25G needle
- **Location:**
  - **Proximal tibia** (preferred): Find the flat surface 2 cm below tibial tuberosity, 1-2 cm medial along tibia
  - **Proximal humerus:** Position palm on abdomen (elbow flexed, shoulder internally rotated) greater tubercle 2 cm 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 cardiac 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 on the drill; turn the safety cap clockwise for removal
8. Hold drill perpendicular to bone; manually press the needle through the skin until it touches the bone
9. Confirm you see one black line on the needle (5mm mark); if not, use a longer needle
10. Apply gentle, steady, downward pressure while holding the trigger; allow drill to do the work
11. Release trigger when decrease resistance felt (“give” or “pop”) as you enter into medullary space
12. While holding catheter in place, pull straight up from the catheter 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 dressing for other size
17. Administer rapid NS bolus, blood product, pressor, etc. with a pressure bag or syringe
18. Always return the IO kit to the CCU resource nurse to refill

Removal:

- **Remove within 24 hours** of insertion once other access is obtained, or if signs of erythema, swelling or extravasation
- Disconnect infusions.
- Attach Leuer lock syringe to catheter hub.
- Stabilize extremity then rotate catheter & syringe clockwise while pulling straight back.
- Apply pressure to IO site then apply dressing
Procedures

Paracentesis

Indications:
- **Diagnostic**: New-onset ascites, unknown etiology of ascites, rule out SBP. Low threshold for inpatients with cirrhosis and often helpful to obtain concurrent RUQUS with Doppler to rule out hepatic or portal vein thrombosis
- **Therapeutic**: Large volume paracentesis (>5L) → performed for abdominal pain/discomfort, diuretic-refractory ascites, respiratory compromise, abdominal compartment syndrome, adjunctive treatment of esophageal variceal bleeding (can lower portal pressures)

Contraindications: Overlying infection (i.e. cellulitis), inability to demonstrate ascitic fluid on US, bowel obstruction/distention, acute abdomen requiring surgery, 2nd or 3rd trimester pregnancy
- \( \uparrow \) INR / \( \downarrow \) plts are NOT contraindications (INR in patients with cirrhosis is NOT reflective of the risk of bleeding). There is no need to correct coagulopathy w/ FFP or platelets unless severe DIC (Hepatology 2013;57:1651)

Materials: Sterile gloves, cap, face shield, chlorhex, sterile towels, ultrasound, 1% lidocaine (10cc syringe, SQ 25G needle, 1.5 inch 20-22G needle), two 18G needles, 60cc syringe, diagnostic assay tubes as below, gauze, bandage or Tegaderm dressing
- **Diagnostic**: 20G two-way (pink box) angiocath or 18–22G 1.5-inch needle. In obese pts, may use angiocath from femoral art line. Purple and green top tube, black top tube (for micro). Technically DO NOT need to inoculate blood culture bottles at the bedside.
- **Therapeutic**: Safe-T-Centesis kit (preferred, pigtail minimizes perforation risk) and Centesis kit (straight rigid needle) from procedure cart, 1L vacuum bottles, 25% albumin dosed 6-8g per liter of fluid removed if >5L (Hepatology 2013;57:1651)

Site Selection/Positioning:
- Position patient supine, turned slightly toward the side of the paracentesis, and angled upright at 30°
- Use abdominal probe to **identify fluid pocket at least 2-3cm in all dimensions** by rotating/fanning probe and ensure absence of bowel loops
- Avoid superficial veins or prior surgical incisions and use vascular probe with Doppler to avoid SQ vessels

Approaches:
- LLQ (1): more 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
- **Infrapubic (2)**: midline, 2cm below umbilicus; lowest risk of bleeding but must ensure bladder empty

Instructions:
1. Identify best site with abdominal US probe (as above) and mark site with pen or round base of needle
2. Open sterile OR towels package and use light blue covering as sterile field to drop sterile supplies. Don sterile protective equipment (technically only need gloves, mask, bouffant cap) and clean skin vigorously with chlorhexidine. Create sterile field over patient with deeper tissues with lidocaine in 10cc syringe. Use Z-line technique (as below) and aspirate while advancing needle; once ascitic fluid begins to fill syringe, stop advancing the needle & inject remainder of lidocaine to anesthetize the highly sensitive parietal peritoneum

**Z-line technique**: reduces risk of ascites leak. With non-dominant hand, pull skin ~2cm caudad to deep abdominal wall while para needle is being slowly inserted

Diagnostic para 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

Diagnostic Assays:

<table>
<thead>
<tr>
<th>Tube</th>
<th>Lab</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green top</td>
<td>Chem</td>
<td>Fluid albumin (send serum albumin to calculate SAAG), fluid total protein (to determine need for SBP px)</td>
</tr>
<tr>
<td>Purple top</td>
<td>Heme</td>
<td>Fluid cell count</td>
</tr>
<tr>
<td>Blood culture bottles</td>
<td>Micro</td>
<td>Can send for aerobic &amp; anaerobic fluid culture, clean top with alcohol and inoculate at bedside for max yield</td>
</tr>
<tr>
<td>Black top</td>
<td>Micro</td>
<td>Gram stain and culture plates</td>
</tr>
<tr>
<td>Other tests to consider: glucose, amylase, LDH, bilirubin, triglyceride, AFB smear, mycobacterial culture, adenosine deaminase, pH, cytology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic para 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 1/2 cm
- d) Advance catheter only 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

Complications:
- Flow stops/slow: roll patient slightly to side of para, rotate catheter, slightly withdraw catheter, flush catheter, new vacuum container
- Flash of blood in catheter: use vascular probe to avoid SQ vessels → withdraw & insert new catheter at different site
- BRB return: injury to mesentery or inferior epigastrics → stop, assess for hemotema 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 → apply pressure dressing, seal w/ Dermabond or single stitch (4-0 non-absorbable suture)

Sally Knooihuizen

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Procedures

Arthrocentesis

Indications:

Diagnostic: Evaluation of inflammatory mono/oligoarthritis or uncharacterized joint effusion. A single inflamed joint should always have diagnostic aspiration to differentiate septic arthritis, crystalline arthropathy, inflammatory arthritis, and hemorrhrosis

- Avoid if overlying cellulitis or periarticular infection; prosthetic joints should prompt Ortho/Rheum consult; safe to perform if on warfarin (Am J Med. 2012;125:265) or DOAC (Mayo Clin Proc 2017;92:1223) but consider smaller needle
- Ultrasound may be used to guide needle insertion but will also offer diagnostic information with complexity of fluid
- Hlip joint aspiration should be performed by interventional radiology

Therapeutic: Injection of corticosteroid/anesthetic in autoimmune arthritis (RA/JIA, spondyloarthropathies) or single-joint gout flare (especially when systemic therapy is contraindicated); drainage of large effusion, pus, or blood

- Avoid if overlying cellulitis, periarticular infection, septic arthritis, periarticular fracture, joint instability
- Use of intra-articular steroids in OA is falling out of favor due to progressive cartilage damage (JAMA 2017;317:1967)

Complications: iatrogenic infection (1/3500, >48h after procedure, may see systemic signs of infection), post-injection flare (mirrors infection and occurs within 24-48h of procedure), hemorrhaxis, leakage of joint fluid, local or systemic steroid effects

Technique ➔ Knee

Materials: Sterile gloves, chlorhexidine/iodine, 5cc 1-2% lidocaine 5cc w/o Epi (25G needle, 5cc syringe) or ethyl chloride spray, 18-22G needle, 20-60 mL syringe, diagnostic tubes (purple/green top, aerobic/anaerobic bottles), sterile towels/sheet, bandage

Positioning/Approach: position the knee in extension or 15-20° flexion. Approaches described below:

- Lateral (see image): 1cm lateral and 1cm superior to the superior 1/3 of the lateral patella. Angle the needle approximately 45° toward the feet and insert behind the patella at a 45° angle to the skin. More likely to yield fluid in difficult cases
- Medial: 1cm medial to the superior 1/3 of the medial patella. Angle the needle perpendicular to the leg and at a 45° angle to the skin

Protocol:

- Identify landmarks as above and mark point of entry with the base of a needle cap or pen. Sterilize the site. A sterile field is not technically required but may drape the area w/ a sterile sheet or towels. Prep needles and syringes.
- Anesthetize overlying skin using ~0.5cc lidocaine (SQ 25G needle, 5cc syringe) to make a wheal. May use remaining lidocaine along procedure tract.
- Attach 18-20G needle to 30cc syringe and position needle according to approach. Advance needle slowly (avg 1-1.5 in) and aspirate while advancing.
- Once fluid is visualized, aspirate joint fluid to fill syringe. May attach a 2nd 30cc syringe to drain additional fluid for sx relief pending size of effusion.
- Withdraw needle and apply bandage. Fill diagnostic tubes (purple OR green top for cell count/diff and crystal eval, aerobic/anaerobic ox bottles).

Diagnostic Assays: Cell count/diff, crystal analysis, gram stain/culture AND blood cultures (Am Fam Physician;2003;68:1)

- Septic arthritis: Most common locations: knee > hip > shoulder > elbow
  - If patient HDS, hold antibiotics prior to tap; 70% Staph, 17% Strep, 8% GNR (H. flu child > adult)
  - WBC count usually 50-150K but can be lower (e.g., <20K in disseminated gonorrhea); ↑WBC = ↑ risk of infection
  - Presence of crystals does not rule out septic arthritis (up to 5% of pts with crystals also have septic joint)
  - Gram stain: Sens 75% for Staphylococcus, 50% for GNR, < 25% for Gonococcus
  - Joint cx usually positive but only 50% sensitive in gonococcal arthritis (swab genitalia & pharynx for diagnosis)
- Gout: negatively birefringent needle-shaped urate crystals (yellow) on polarized microscopy (sens 63-78%, spec 93-100%)
- Pseudogout: positively birefringent CPPD rhomboid crystals (blue) on polarized microscopy (sens 12-83%, spec 78-96%)

<table>
<thead>
<tr>
<th>MEASURE</th>
<th>NORMAL</th>
<th>NON-INFLAMMATORY</th>
<th>INFLAMMATORY</th>
<th>SEPTIC</th>
<th>HEMORRHAGIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarity</td>
<td>Transparent</td>
<td>Transparent-opaque</td>
<td>Opaque</td>
<td>Bloody</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td>Clear</td>
<td>Yellow to opalescent</td>
<td>Yellow to green</td>
<td>Red to brown</td>
<td></td>
</tr>
<tr>
<td>Viscosity</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>WBC (per mm³)</td>
<td>&lt; 200</td>
<td>2,000 to 100K</td>
<td>50 to 150K</td>
<td>200 to 2,000</td>
<td></td>
</tr>
<tr>
<td>PMNs (%)</td>
<td>&lt; 25</td>
<td>≥ 50</td>
<td>≥ 75</td>
<td>50 to 75</td>
<td></td>
</tr>
</tbody>
</table>
Procedures

**Lumbar Puncture**

**Indications:**
Diagnostic: Suspicion for CNS infection, CNS malignancy/mets, SAH, or CNS demyelinating/inflammatory process

**Therapeutic:** Idiopathic intracranial hypertension, NPH, cryptococcal meningitis, intrathecal medications/chemotherapy

**Contraindications:** No absolute contraindications; high risk if skin infection over puncture site, epidural abscesses, ↑ ICP 2/2 mass lesion or obstruction (risk of brain herniation), spinal cord tumor or AVM, thrombocytopenia (<50K) or coagulopathy (INR > 1.5)

**Preparation:**
- **Hold AC:** time frame needed to hold AC prior to procedure: IV heparin (4hrs, PTT<35), LMWH therapeutic 24hrs, LMWH ppx (12hrs), Plavix (5-7 days), DOAC (3 days), warfarin (3 days) w/ 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 re-start AC), DOM policy can be found under Epic → Resource → elucid Policy Manager → Search "Anticoagulation and Neuaxial Anesthesia"

- **Head CT:** Only obtain head CT if ≥1 of the following: age > 60, hx CNS disease, seizure in last 7d, immunocompromised, AMS, aphasis, cranial nerve deficit; if none of these, then 97% NPV for no mass lesion ([NEJM 2001; 345:1727](https://www.nejm.org/doi/full/10.1056/NEJM054952))

**Technique:** ([NEJM 2006;355:e12](https://www.nejm.org/doi/full/10.1056/NEJM054952))

**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 medularis at L1–L2)**
- **Lateral** (if measuring opening pressure): Fetal position (maximize head and hip flexion), no hip / shoulder rotation; keep back parallel to edge of bed
- **Upright** (easier in obese): Sit on bed, head / arms rest on table, spine flexed
- **To identify target, place a hand firmly on each iliac crest and mark where your thumbs meet at the midline. Draw a line on the skin between the iliac crests. Before inserting the needle, place your thumb and pointer finger on either side of the spine to ensure the needle is midline**
- **Sitting while performing the procedure is often easier than standing, as the needle is in your line of sight**

**Protocol:** ([JAMA 2006;296:2012](https://jama.jamanetwork.com/))

1. **Prepare:** Sterilize and drape widely. Re-identify target. Make lidocaine wheal w/ 25G, then inject track (aspiration before injecting, goal is FREEZE CSF!)
2. **Tap:** Check needle / stylet mobility. Bevel should face ceiling when pt is lateral. Needle angles toward the umbilicus, straight at the back. Stabilize with your hand against the skin and advance with your dominant hand. Remove stylet frequently to check for CSF flow but always keep stylet in place when advancing.
3. **Troubleshoot:** If hitting bone, partially withdraw, adjust angle, and re-advance. Try another space below if no luck. If patient has pain, DO NOT withdraw → ASK “where?” If pain is shooting down the left side, withdraw slightly and go slightly more to the right.
4. **Measure OP:** 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). Pt lies flat post-procedure for as long as tolerated.

### Diagnostic Assays

<table>
<thead>
<tr>
<th>Tube</th>
<th>Lab</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1 mL)</td>
<td>Heme</td>
<td>CSF cell count</td>
</tr>
<tr>
<td>2 (1 mL)</td>
<td>Chem</td>
<td>Total protein, glucose</td>
</tr>
<tr>
<td>3 (3–5+ mL, depending on number of tests)</td>
<td>Micro</td>
<td>Gram stain/culture, Consider HSV PCR, VZV PCR, cryptococcal antigen, viral culture, AFB stain, VDRL. Ask lab to save extra CSF. If you may need flow cytometry, DO NOT FREEZE CSF!</td>
</tr>
<tr>
<td>4 (1 mL)</td>
<td>Heme</td>
<td>CSF cell count (should have fewer RBCs than tube 1 unless hemorrhage)</td>
</tr>
</tbody>
</table>

**Additional tests:** Cytology & flow cytometry (meningeal carcinomatosis), oligoclonal bands (multiple sclerosis), paraneoplastic antibodies, 14–3–3 & RT-QuIC (prion disease); may want to collect extra black top tubes for these purposes; if c/f prion disease, 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 neurosurgery 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**: Incidence 10-30%. Likely 2/2 dural leak with traction. Onset 72h, lasts 3–14 days. Give pain meds that do not affect platelets. No evidence for bed rest. If persistent, c/s anesthesia for epidural blood patch.
- **Spinal hematoma**: Suspect if on AC w/ persistent back pain or neuro sx → urgent MRI → dexameth + NSGY c/s
Thoracentesis

**Indications:**
Diagnostic: To establish etiology ≥ 1 cm pleural effusion visualized by US (not necessary for small effusions w/probable alternative dx)
- Pleural effusions visible on CXR when > 200 mL of fluid is present

Therapeutic: Large effusions → resp compromise or sx (e.g., dyspnea), hemothorax, empyema, complicated parapneumonic effusion

**Contraindications** (relative, not absolute) ([Chest 2013;144:456](https://journals.lww.com/chestjournal))
- 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% but is not a contraindication ([Crit Care 2011;15:R46](https://ccforum.com/articles/15/7/R46))

**Preparation:**
- Obtain: Skin cleansing agent, gauze, sterile gloves/drape, hemostat, 1-2% lidocaine, 10 mL syringe with 22 & 25 gauge needle
- Collection: 18-20g over-the-needle catheter, 60cc syringe, 3-way stopcock, drainage tubing, specimen tube, evacuation container, occlusive dressing
- Attending MUST be present for thoracentesis: Page IP (p23710), pulm, or call MICU x68048 to see who is on service
- Get consent, tell pt’s nurse, obtain thorac kit & ultrasound, perform timeout (verify patient identity, procedure, site)

**Technique:** ([NEJM 2006;355:e16](https://www.nejm.org/doi/full/10.1056/NEJMoa061843)), Video
1. Position: Patient on edge of bed, leaning forward, arms resting on table
2. Identify: Height of effusion determined by auscultation & percussion of chest wall. Use ultrasound to confirm location of effusion.
   - Mark 5-10 cm lateral to spine & 1-2 ICS below effusion. 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
3. Prep & drape: thoracentesis kit, put on sterile gown and gloves, sterilize patient w/chlorhexidine, then drape
4. Using 25G needle, place wheel 1% lidocaine over superior edge of the rib
5. Using 22G needle, walk the needle over superior aspect of the rib while intermittently aspirating and injecting perpendicular to the pleural space
6. When aspirated pleural fluid, withdraw slightly then anesthetize the parietal pleura (highly sensitize) with 2-3cc of lidocaine. Note penetration depth!
7. Attach 18G over-the-needle catheter to syringe & advance over superior aspect of the rib, pulling back while advancing
8. 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
9. Attach 60 cc syringe to 3-way stopcock connected to catheter, withdraw full syringe of fluid, and put in appropriate tubes for lab & micro studies
10. Attach tubing to 3-way stopcock, affixing longer tube to large evacuation container & shorter tube to the syringe (NB: tubing is all one-way)
11. 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 post-expansion pulm edema.
12. When done, withdraw catheter while patient is humming (to avoid air entry into pleural space); cover site with occlusive dressing
13. Obtain post-procedure CXR to look for pneumothorax or hemothorax

**Diagnostic Assays:**
- **Send fluid for:** TP, LDH, chol, glucose, pH, cell count, culture and Gram stain, anaerobic culture, fungal wet prep w/culture. Consider:
  - TG (chylothorax), Cr (urinothorax), amylase (pancreatitis, esophageal rupture), ADA (TB), AFB culture, modified AFB culture, 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 / patient is symptomatic and/or in distress → needle decompression with 16G angiocath at 5th ICS mid-axillary line (always above nipple); Chest tube indicated in 20% of cases → Consult IP (p23710) or thoracic surgery
3. **Vasovagal Syncope/Pleural Shock:** Caused by needle penetrating parietal pleura; supportive care
4. **Re-expansion pulmonary edema:** To avoid, stop thoracentesis if cough, OP, or dyspnea, limit volume removal (< 1.5 L). Do not attach to vacuum, remove fluid slowly without excessive negative pressure; treat w/oxygen, diuretics, BiPAP.

Dan Okin, Alex Blair
Pericardial Drain

Indications:
- Pericardial effusion with tamponade physiology (or if at high risk for development of tamponade physiology)
- Diagnostic or palliative drain of stable pericardial effusion

Relative Contraindications: No absolute contraindications
- Coagulopathy: INR>1.7, platelets<20, PTT>60 or on heparin gtt. Consider FFP/platelets when on call for procedure
- Effusion associated with aortic dissection or myocardial rupture, as decompression could lead to extension of injury
- Effusion associated with severe pHTN (controversial), as decompression could lead to RV dilation and acute RV failure (Pulm Circ 2013 3(3) 467)

Management Overview: If in doubt about management, page the cardiology team that placed the drain
- Pericardiocentesis does not completely evacuate a pericardial effusion. A pericardial pigtail catheter is often left in for 24-72h to allow for serial drainage, preventing re-accumulation and repeated procedures.
- Frequency of drainage depends on chronicity and size of the effusion, usually q6-q12h. Recommendations are often found in the report from the cath lab when the drain was initially placed.
- Give cefazolin 1g q8h (or vancomycin if PCN allergy) for prophylaxis while drain is in place.
- Monitor effusion resolution and recurrent tamponade. Check serial hemodynamics/pulsus paradoxus.
- If >100cc output/day for 3 days s/p drain placement, aggressive therapy may be indicated (i.e., sclerosing agents, pericardial window, etc.)
- Consider removal of pericardial drain if <50cc output over 24 hours. Obtain approval from cardiology prior.

Materials:
- Sterile technique: gloves, mask, hat
- Sterile towels
- Chlorhexidine swabs (at least 3)
- 60cc screw-on syringe (x2-3 if high output)
- New blue cap for 3-way stopcock
- Heparin pre-mixed syringe (10U/mL)

Technique:
1. Set up sterile field. Put on, gloves, mask and hat, gown is optional
2. Ask nursing to lift catheter off skin by flush port. Sterilize distal exposed catheter and stopcock with chlorhex swab. Holding the sterilized area, take catheter from nursing and sterilize remaining portion
3. Place sterile towels around and underneath distal catheter and stopcock, and lay catheter down
4. Ensure the stopcock is turned towards the catheter. This closes the catheter line.
5. Remove and throw away one blue cap (doesn’t matter which).
6. Sterilize open stopcock tip with iodine or chlorhex swab.
7. Hold up flush port; nursing will connect heparin syringe (syringe itself is not sterile) to open/sterilized tip, turn stopcock to the remaining capped valve, and infuse 2cc heparin.
8. Turn stopcock back towards catheter, remove (do not discard) heparin syringe, and connect 60cc syringe.
9. Turn stopcock to the remaining capped valve and slowly withdraw pericardial fluid. This may require significant negative pressure. Consider different patient positions (Trendelenberg, lateral decubitus, etc.) to mobilize pericardial effusion. Patient may experience chest discomfort. Monitor hemodynamics
10. Save/transfer pericardial fluid if needed for analysis. Otherwise discard.
11. Can stop draining once fluid flow diminishes/ceases. Turn stopcock back towards catheter and remove syringe.
12. Ask nursing to re-attach heparin syringe and infuse another 2cc heparin, again closing stopcock to the patient
13. Remove heparin syringe and attach new blue cap to open valve.
14. Consider re-sterilizing distal exposed catheter and stopcock with chlorhex swab.
15. Write procedure note. Be sure to deduct the 2-4cc infused heparin when calculating amount of fluid removed.

Fluid Studies:
- Gram stain and bacterial/fungal culture
- Specific viral studies/PCR
- Cytology
- AFB stain, mycobacterial culture, adenosine deaminase, IFN-gamma, or lysozyme (if considering TB pericarditis)
- Protein, LDH, glucose, red/white cell count not helpful for fluid characterization
### LUMBAR PUNCTURE INTERPRETATION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pressure (cm H2O)</th>
<th>WBC per mL</th>
<th>Predominant cell type</th>
<th>Glucose (mg/dL)</th>
<th>Protein (mg/dL)</th>
<th>Further CSF Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>9–18</td>
<td>0–5</td>
<td>Lymph</td>
<td>50–75</td>
<td>15–40</td>
<td>N/A</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>20–50</td>
<td>&lt;100 to &gt;10k</td>
<td>&gt; 80% PMN</td>
<td>&lt; 40</td>
<td>100–1000</td>
<td>Culture, Gram stain</td>
</tr>
<tr>
<td>Viral meningitis (Enteroviruses, HSV, VZV, arboviruses)</td>
<td>9–20</td>
<td>50–1000</td>
<td>Lymph; early echovirus / HSV can have 80% PMN</td>
<td>&gt;45; low in LCM and mumps</td>
<td>&lt;200</td>
<td>HSV/VZV PCR, consider further viral PCR or Ab if clinical suspicion; d/w ID</td>
</tr>
<tr>
<td>Lyme meningitis</td>
<td>9–20</td>
<td>10–300</td>
<td>Lymph</td>
<td>Normal</td>
<td>50–100</td>
<td>Ab testing paired with serum ab (though poor sensitivity)</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>18–30</td>
<td>50-300</td>
<td>Lymph</td>
<td>&lt; 50</td>
<td>50–300</td>
<td>MTb Cx &lt; 60% sensitive, Nucleic acid test not approved by FDA</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>18–30</td>
<td>&lt; 300</td>
<td>Lymph</td>
<td>&lt; 50</td>
<td>40–300</td>
<td>Fungal wet prep + Cx, discuss other testing with ID</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>18–30+</td>
<td>5–500</td>
<td>Lymph</td>
<td>&lt; 40</td>
<td>&gt;45</td>
<td>Fungal wet prep + culture, cryptococcal antigen</td>
</tr>
<tr>
<td>Epidural/Brain abscess</td>
<td>18–30</td>
<td>10–300</td>
<td>Lymph</td>
<td>Normal</td>
<td>50–400</td>
<td>Gram stain not sensitive</td>
</tr>
</tbody>
</table>

NB: WBC correction for RBCs (i.e., traumatic tap): corrected WBC = measured WBC – (measured RBC / 500)

### PARACENTESIS INTERPRETATION

<table>
<thead>
<tr>
<th>PMN ≥ 250/µL</th>
<th>(+) Ascites culture</th>
<th>(-) Ascites culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Bacterial Peritonitis (SBP) (Secondary Peritonitis → polymicrobial)</td>
<td>Culture Negative Neutrocytic Ascites (CNNA)</td>
<td></td>
</tr>
</tbody>
</table>

CNNA: has similar clinical presentation and prognosis as SBP, thus treat for suspected SBP after diagnostic PMN count without waiting for + cx (ddx: peritoneal carcinomatosis, tuberculosis, pancreatitis)

Calculations: # of PMNs = Total nucleated cells x % of PMNs
Correction for RBCs (RBC count > 50,000/mm³, seen in “traumatic tap”) = measured PMNs – (measured RBCs / 250)

Clues in Fluid Analysis for SBP vs. Secondary Peritonitis:
- If ≥2 present, increased suspicion for secondary peritonitis: 1) serum total protein >1 2) serum glucose < 50 3) serum LDH > upper limit of normal
- Consider repeat paracentesis after 48hrs of antibiotic treatment: if PMN ↓ and only 1 org. on prior culture, likely SBP; if PMN ↑ and multiple org. on prior culture, then likely secondary peritonitis

### SAAG ≥ 1.1 g/dL (etioloogy related to portal HTN)

- Cirrhosis
- Nephrotic syndrome

### SAAG < 1.1 g/dL (etioloogy NOT related to portal HTN)

- Chronic HB
- Budd-Chiari
- Peritoneal carcinomatosis
- TB
- Pancreatitis

SAAG = Serum Albumin – Ascitic Fluid Albumin (from samples obtained on the same day)

### PLEURAL FLUID INTERPRETATION

**Light’s Criteria:** Exudate if ≥1 criteria present (98% Sn, 83% Sp)
- Pleural fluid protein / serum protein > 0.5
- Pleural fluid LDH / serum LDH > 0.6
- Pleural fluid LDH > 2/3 ULN of serum LDH (i.e. > 140)

**NB:** Diuretics cause ~25% of transudates to be misclassified as exudates¹

If ≥1 of these, it’s an exudate with 98% Sn and 70% Sp:
- Pleural fluid protein > 2.9, LDH > 95, cholesterol > 45

**More Specific Criteria for Confirming Exudate:**
- Pleural fluid cholesterol > 60 (54% Sn, 92% Sp)
- Serum albumin – pleural albumin ≤ 1.2 (87% Sn, 92% Sp)
- Pleural NT-proBNP < 2,300pg/mL (>80% Sn, >70% Sp)

- Other tests: Adenosine deaminase, amylose, triglyceride, cholesterol, Gram stain/culture, cell count, IFN-γ, NT-proBNP, pH, tumor markers
- Complicated Parapneumonic Effusion / Emphyema = (+) Gram Stain / Cx / purulent OR pH <7.2 OR glu <60 → drainage
NASOGASTRIC TUBES

Indications:
- Decompression of SBO or minimize vomiting in ileus
- Enteral feeding / med administration; charcoal admin (ODs), oral contrast or colonoscopy prep
- Lactulose (hepatic encephalopathy)

Contraindications
- Head / maxillofacial trauma, basilar skull fracture, or recent neurosurgical intervention
- Esophageal stricture or ≥ grade 2 varices / recent banding (discuss w/ GI if uncertainty regarding varices / banding)

Supplies:
- NGT, lubricant/viscous lidocaine ("UroJet"), Chux, emesis basin, cup of water with ice and straw, 60mL syringe, tape
- If NGT needed for decompression: use 14 to 16 Fr Salem sump NGT (larger diameter, ↓ clogging)

NGT Placement:
- Assess patency and symmetry of nares by direct visualization
- Consider topical anesthetic (e.g., 4% lidocaine) pre-treatment
- Position patient in upright "sniffing" position with neck flexed and 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 inferiomedial, not upward
- After passage of NGT into oropharynx (will feel curve & ↓ resistance), have patient swallow water via straw while advancing rapidly
  - If patient excessively coughs, gags, has change in voice or dyspnea, or increased resistance, STOP (never force) and suspect improper location (in airway or coiled) and immediately withdraw. Look in posterior oropharynx for coiling.
- Advance to predetermined depth and 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 is present before securing tube w/ tape or bridle if ↑ risk removal (AMS)
- Confirming position: MUST confirm placement with KUB prior to feeding/meds given risk of placement in trachea/lungs. KUB will show NGT tip below the diaphragm. Optional for KUB if bilious return when NGT for decompression (bile = stomach).

Dobhoff tube / Enteroflex:
- Thinner, more flexible; more comfortable but ↑ risk of placement into lung
  - Requires 2-step 2-CXR placement method
  1. Measure from nose to earlobe to mid-sternum → insert tube this distance → secure → Obtain CXR
  2. If CXR shows tip (1) past carina & (2) midline → advance into stomach → Repeat CXR → remove stylette

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 Q8hr. If clogged, can try methods to unclog tube as below in "Gastrostomy Tubes"

Complications (↑ with longer duration):
- GI: malposition, coiling, knotting anywhere along course of tube, nasal/GI tract perforation. ↑ risk acid/stomach content reflux and aspiration → consider PPI. Chronic suction → gastritis/pressure necrosis: consider removal if grossly bloody
- Pulm: intubation of lung → inadvertent med, contrast, TF administration → PNA, pulm abscess, tracheal perforation, PTX, death
- HEENT: nasal irritation, epistaxis, intracranial placement, skin erosion, sinusitis,alar necrosis, tracheoesophageal fistula/perf

Removal:
- If for ileus/SBO, consider removal when passing flatus or resolved N/V. Alternatively, may remove when NGT output <1L over 24 hours. Consider clamp trial before removing (clamp 4 hours, then check residual. Remove if <150 cc)
- Remove tape. Flush tube w/ 10mL air or NS. Turn OFF suction & clamp. Fold Chux around tube insertion site. Gently remove tube
**Procedures**

**GASTROSTOMY TUBES**

- Clear, soft, graduated tubing held in place w/ plastic mushroom-shaped ring/balloon in stomach (~3 cm deeper in obese pts)
- May be replaced at bedside after epithelialized track forms (~2-4 wks; delayed by malnutrition, steroids, immunosuppression)
- Gastrojejunostomy (GJ) tubes have 3 access ports: G tube port, J tube port and 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 and elixir meds should be given through J tube
  - Attach 3cc syringe w/ warm H2O to female Leur adaptor. Push or pulse plunger to force through debris. Flush w/ 30 cc warm H2O to ensure not clogged.
  - Can also try Seltzer, ginger ale, Coca-Cola. If persistent, can try pancreatic lipase (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 (30-60 mL gastrograffin f/b KUB)
- **Falling out**:
  - replace w/ similar-sized Foey or feeding tube. Obtain tube study as above.
- **Local site infection**:
  - try topical abx +/- antifungal before PO (cephalexin, clinda)
- **Granulation tissue**:
  - check tube size (not too long or short); treat w/ warm compresses and silver nitrate (w/ barrier cream on surrounding nl skin to protect)

**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 or device, 18F/20F Coudé if BPH or high bladder neck → insert curve up / nub on hub pointed toward umbilicus
- 3-way Foleys (drainage, balloon, irrigation ports): 20F/22F used for continuous bladder irrigation (CBI) in gross hematuria

Placement:

1. Lay patient flat, prep, hold penis upright (keep on stretch while advancing)
2. Instill 10cc 2% viscous lidocaine ("UroJet") into urethra
3. Insert Foley catheter to the hub
4. As catheter reaches bladder neck, keeping penis on stretch, point phallus down towards toes (to mimic natural curve urethra).
5. After urine return AND catheter hubbed, fill balloon w/ 10cc sterile H2O
6. Gently withdraw catheter to bladder neck
7. Verify position by flushing with 60cc fluid (catheter in bladder) and withdraw. Inability to withdraw suggests:
   a. Bladder empty and sucking against bladder mucosa (instill 60 cc)
   b. Catheter in urethra or false passage
   c. Catheter outside bladder (undermined bladder neck in pt s/p prostatectomy/TURP)
8. Don’t forget to reduce foreskin (if not, may cause paraphimosis = urologic emergency)

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) +/- with clots
- Titrate flow to "fruit punch" colored urine (should be see through)
- When discontinuing, usually start with clamp trial to ensure resolution before removal

**Special Circumstances**

- **Artificial Urinary Sphincter (AUS)** - men s/p prostatectomy c/b sig. urinary incontinence. DEACTIVATE device prior to placing foley. Place smallest catheter possible (12F) and remove ASAP.

**Troubleshooting**

- **Difficulty in female patient**: likely poor positioning. Place sheets under hips & place pt in Trendelenburg
- **Urethral trauma**: blood at meatus. Leave catheter ≥3-5d
- **Foley is leaking**:
  - Bladder spasms 2/2 infection, mucosal irritation, overactive bladder. Start anticholinergic (oxybutynin 5mg TID 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 types, usually standard Foley catheter
- Know type & size catheter, who exchanges, how exchanged, how frequently
- Is this a new tract (<7d, ask urology to replace) or established (years, you can try and replace)?
- 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

Sally Knooihuizen 242
### CHEST TUBES

**Indications:** Drainage of air (PTX), blood (hemothorax), pus (empyema), or lymph (chylothorax)

**Chest Tube Logistics:**
- **Drainage:** Measured by gradations in 3 columns; if significant drainage, watch for re-expansion pulmonary edema
- **Suction control:** Adjusts negative pressure applied to pleural space
  - Suction determined by setting on the device [A], NOT at the wall; if working properly, suction verification window [E] will be orange
  - "Suction" vs. "water seal": If Pleur-evac 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

**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 BPF) vs. leak in chest tube (check tubing and connections to Pleur-evac)
  - **Note:** "Tidaling" (movement w/ respiratory variation in water seal chamber) [C] is normal – i.e., not an air leak
- **Clogging:** Look for debris in tube, lack of tidaling, can try "stripping the tube" by compressing it with your fingers while pulling TOWARDS the drainage system, helpful to have an alcohol prep pad for lubrication, might require tPA (alteplase) for clot or Pulmozyme (dornase) for fibrinolysis → involve IP / surgery (whoever placed tube)

**Removal:**
- **General criteria:** No active air leak, pt off positive pressure ventilation, < 150cc of drainage over 24h
- **Steps to removal:** place on suction (-40 mm Hg to -10 mm Hg) → place on water seal → clamp trial (clamp tube with hemostat)
  - With each step, wait 4 hours, 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 48 hrs.
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 you were doing**
2. **Immediately clean the affected area**
   - Sharp stick: Wash site immediately with soap/water. Alcohol-based agents are also virucidal to HBV, HCV, HIV.
   - Splash to open wound: Wash site immediately with soap/water
   - Splash to eye(s): Irrigate liberally for up to 5 minutes
   - Notify your department supervisor as needed; the charge nurse is often a very helpful resource
3. **Call occupational health (OHS)**
   - Monday-Friday 7am-5pm call 617-726-2217, located at 165 Charles River Plaza (CRP) Suite 404 (4th floor)
   - Outside of normal business hours, page the on-call occupational health provider at p21272
   - **Have the following information available** for the OHS staff member at the time of your call:
     - Source patient's: Name, MRN, DOB, location, MD, diagnosis, known Hx, exposure to HBV/HCV/HIV meds
     - Needle: Brand, size, gauge, specific device, device manufacturer, safety design type, part of a kit?
4. **Test the patient for HBV, HCV, and HIV**
   - HBV/HCV: One **gold top tube**
     - Order HBsAg and HCV qualitative Ab; if patient known HCV+, also send HCV RNA
     - If using paper form (available from OA), mark with BILLING NUMBER CL00009 so pt not charged
   - HIV: Another **gold top tube**
     - **By law in Massachusetts** [MGL Part I Title XVI Chapter 111 Section 70F (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 HIV tube to STAT lab (results ~60 min once received), send HBV/HCV tube to standard core lab
   - **IF the patient is CONSENTABLE**
     1. Obtain a special HIV occupational exposure consent form/lab requisition from the OA
     2. Write STAT result in the comment section
     3. Have the patient sign and then sign it yourself
     4. Ensure the form is marked with BILLING NUMBER CL00009 so the patient is not charged
   - **IF the patient is NOT CONSENTABLE**
     1. A valid and invoked health care proxy (you need paperwork!) can sign the occupational exposure consent form, OR
     2. Facility legal staff can assume temporary guardianship
     - **NB:** 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 and obtain written consent anyway. If this is not possible, consider contacting Kimon Zachary (infectious disease), the Chiefs, the program director, or the chief medical officer.
5. **Decision 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)

### PATHOGEN
- **HIV**
  - Percutaneous (blood): 0.3%
  - Mucocutaneous (blood): 0.09%
  - **There has only been 1 confirmed case of occupational transmission since 1999 (CDC)**
  - **PFP can vary but usually includes 3 anti-retroviral drugs:**
    - 2 NRTI: tenofovir PLUS emtricitabine (or lamivudine) **AND**
    - INSTI: dolutegravir (or raltegravir)
    - INSTI can be substituted with a PI (darunavir) boosted by ritonavir
  - **28 days of treatment recommended but optimal length unknown**
  - Regimen usually well-tolerated, side effects include:
    - Common but mild: N/V, diarrhea, fatigue, HA
    - Rare: hepatitis, hyperglycemia, fevers, rash, pancytopenia
  - **Serial testing at 6wk, 12wk, and 6mo if patient positive**

- **HCV**
  - Percutaneous: 1-2%
  - **No PEP; serial testing at 4wk, 12wk, and 6mo if patient positive**

- **HBV**
  - Percutaneous: 30%
  - Positive immune titers usually are an employment requirement
  - Vaccine non-responders should be seen in occupational health

6. **File a safety report!**
Cardiac Monitoring (MGH Clinical Guidelines for Cardiac Monitoring)

- Assess patient risk for life-threatening arrhythmia, ischemia, or hemodynamic instability in the next 24 hours

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Continuous cardiac</td>
<td>Continuous cardiac monitoring in presence of</td>
<td>Continuous cardiac monitoring</td>
<td></td>
</tr>
<tr>
<td>monitoring</td>
<td>licensed clinical personnel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- May be off monitor</td>
<td>only in presence of licensed clinical personnel</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pt Location</th>
<th>General care unit</th>
<th>General care unit</th>
<th>Step-down; ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel</td>
<td>- No cardiac monitor</td>
<td>- With cardiac monitor</td>
<td>- With cardiac monitor</td>
</tr>
<tr>
<td></td>
<td>- Unaccompanied</td>
<td>- Accompanied by MD, PA, NP, or RN</td>
<td>- Accompanied by MD, PA, NP, or RN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example indications*</th>
<th></th>
<th></th>
<th>Early ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Typical chest pain</td>
<td>- Acute compensated HF</td>
<td>- S/p cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>- Uncontrolled AFB</td>
<td>- 24 hrs s/p PPM/ICD placement</td>
<td>- Septis</td>
<td></td>
</tr>
<tr>
<td>- Post-stroke AFB</td>
<td>- Suspected cardiogenic syncope</td>
<td>- Acute respiratory failure</td>
<td></td>
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<tr>
<td></td>
<td>- Actual or risk of QTc prolongation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Complicated ETOH withdrawal</td>
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<td></td>
</tr>
</tbody>
</table>

* Refer to 2017 AHA guidelines on ECG monitoring for more detailed indications and monitoring duration (Circulation 2017;136:e273)

How to run telemetry: click on “Patient Data"
- Events: events sorted in reverse chronological order (eg: runs of NSVT, bradycardia)
- FD Strip: telemetry strip for a specific moment in time
- FD Page: global view useful in identifying abrupt changes that can be zoomed in on using the FD Strip view
- Graphic Trends: graphic view of HR trends over time
- Calipers: interactive calipers used to calculate intervals on telemetry strip

O2 Saturation Monitoring (MGH Clinical Guidelines for O2 Saturation Monitoring)

- Assess patient risk for hypoxemia or respiratory distress in the next 24 hours

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Spot check O2 sats as</td>
<td>Continuous O2 sat monitoring in presence of</td>
<td>Continuous O2 sat monitoring</td>
<td></td>
</tr>
<tr>
<td>frequently as clinically</td>
<td>licensed clinical personnel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>indicated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pt location</th>
<th>General care unit</th>
<th>General care unit</th>
<th>Step-down: ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel</td>
<td>- No O2 sat monitor</td>
<td>- With O2 sat monitor</td>
<td>- With O2 sat monitor</td>
</tr>
<tr>
<td></td>
<td>- Unaccompanied</td>
<td>- Accompanied by MD, PA, NP, RN, or RRT</td>
<td>- Accompanied by MD, PA, NP, RN, or RRT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example indications</th>
<th></th>
<th></th>
<th>Acute respiratory distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stable chronic respiratory disease</td>
<td>- COPD exacerbation</td>
<td>- High-risk airway</td>
<td></td>
</tr>
<tr>
<td>- Post-procedure</td>
<td>- OSA not on CPAP</td>
<td>- NIPPV</td>
<td></td>
</tr>
<tr>
<td>- Opioid naive patients</td>
<td>- PCA use</td>
<td>- Intubation</td>
<td></td>
</tr>
<tr>
<td>receiving PO narcotics</td>
<td></td>
<td>- Continuous narcotic infusion</td>
<td></td>
</tr>
</tbody>
</table>

DVT Prophylaxis (MGH Anticoagulation Management Stewardship Committee VTE Prophylaxis Guidelines)

- Assess patient risk for DVT

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ambulatory</td>
<td>Major surgery (&gt;45 min, not craniotomy,</td>
<td>Major surgery (craniotomy, ortho, spine, or for</td>
<td></td>
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<tr>
<td></td>
<td>ortho, spine, or for cancer)</td>
<td>cancer)</td>
<td></td>
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<tr>
<td>- Estimated LOS &lt;48 hr</td>
<td>Acute illness; immobility w/ est LOS &gt;48h</td>
<td>Critical illness in ICU</td>
<td></td>
</tr>
<tr>
<td>- Not meeting moderate- or</td>
<td>H/o VTE, thrombophilia (incl. hormone tx)</td>
<td>2+ moderate risk factors</td>
<td></td>
</tr>
<tr>
<td>high-risk criteria</td>
<td>- Active malignancy</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Ambulation Pharmacologic OR mechanical</th>
<th>Pharmacologic AND mechanical</th>
<th></th>
</tr>
</thead>
</table>

30 / 30 / 30 Rule
- Pharmacologic prophylaxis: can be administered if platelets >30K
- Mechanical prophylaxis: SCD boots should not be off the pt for >30% of the day
- Ambulation: pts should ambulate 30 min/shift (60 min/day)

Pharmacologic prophylaxis options:
- Enoxaparin (lovenox): 40 mg SC daily, default in patients with CrCl >30 and BMI <40
- Heparin (UFH): 5,000 units SC Q8H-Q12H, preferred in patients with CrCl <30 or BMI >40
  - Q8H dosing preferred in hospitalized cancer patients, as Q12H dosing is less effective
- Fondaparinux: 2.5 mg SC daily (can be used if concern for HIT)

GI Prophylaxis
- Indications (Crit Care Med 2016;44:1395):
  - Admitted to ICU AND one of the following: 1) Mechanically ventilated >48 hr, 2) Coagulopathy (pt <50, INR >1.5, PTT >2x ULN), 3) GI bleed in the last year, 4) TBI, spinal cord injury, or burns, 5) 2+ of the following: sepsis, occult GI bleed >6 days, steroids >60 mg prednisone daily, ICU LOS >7 days
  - Prophylaxis options (PO unless contraindicated): PPI (omeprazole, esomeprazole, pantoprazole) or H2 blocker (famotidine)
<table>
<thead>
<tr>
<th>Code:</th>
<th>Hypotension</th>
<th>Tachycardia:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – Access</td>
<td>Cardiogenic: MI, BB/CCB toxicity, acute</td>
<td>Narrow:</td>
</tr>
<tr>
<td>B – Backboard</td>
<td>myocarditis, valvular dz (AS)</td>
<td>AVRT/AVNRT</td>
</tr>
<tr>
<td>C – Code Status</td>
<td></td>
<td>Afb/Aflutter with RVR</td>
</tr>
<tr>
<td>D – Defibrillator/Drips</td>
<td></td>
<td>MAT/Atrial Tachycardia</td>
</tr>
<tr>
<td>E – Epinephrine/Electr</td>
<td>(150-200J, run tele)</td>
<td>Wide:</td>
</tr>
<tr>
<td>F – Family/Fluids</td>
<td></td>
<td>VT, PMVT</td>
</tr>
<tr>
<td>G – Glucose</td>
<td></td>
<td>SVT with aberrancy, PM mediated/tracked</td>
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<tr>
<td>Hypovolemia</td>
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<td>Hypoxia</td>
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<td>Hydrogen ion (acid)</td>
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<td>Hyper/Hypokalemia</td>
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<td>Hypothermia</td>
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<td>Hypoglycemia</td>
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<td>Tamponade</td>
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<td>Tension pneumothorax</td>
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<td>Thrombus – MI</td>
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<td>Thrombus – PE</td>
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<td>Trauma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Acute Hypoxemia:</td>
<td>Junk in the lung:</td>
<td>Synchronized Cardioversion</td>
</tr>
<tr>
<td></td>
<td>Aspiration/Mucous</td>
<td>Narrow regular – 50J</td>
</tr>
<tr>
<td></td>
<td>Plug/Pneumonia</td>
<td>Narrow irregular – 120-200J</td>
</tr>
<tr>
<td></td>
<td>Fluid in the lung:</td>
<td>Wide regular – 100J</td>
</tr>
<tr>
<td></td>
<td>Pulmonary edema/ARDS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI, HTN, Tachycardia, Volume</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
<td></td>
</tr>
<tr>
<td>Bradycardia:</td>
<td>Conduction disease Vagal</td>
<td>Adenosine:</td>
</tr>
<tr>
<td></td>
<td>Right-sided MI Hypothyroid</td>
<td>6-12mg; use if narrow + regular</td>
</tr>
<tr>
<td></td>
<td>Medication effect Hypoxemia</td>
<td>consider if wide + regular unless WPW</td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
<td>*If post-heart transplant, avoid unless</td>
</tr>
<tr>
<td></td>
<td></td>
<td>advised by heart failure/transplant team,</td>
</tr>
<tr>
<td></td>
<td>Tx:</td>
<td>will need reduced dose if used</td>
</tr>
<tr>
<td></td>
<td>Atropine: 0.5-1mg q3-5min; maximum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dopamine: 2-20mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epinephrine: 2-10 mcg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transcutaneous pacing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transvenous pacing</td>
<td></td>
</tr>
<tr>
<td>Seizure:</td>
<td>Check FSBG</td>
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</tr>
<tr>
<td></td>
<td>2-4mg IV Ativan x2, 20mg PR diazepam,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or levetiracetam (Keppra) 20mg/kg</td>
<td></td>
</tr>
<tr>
<td>Numbers:</td>
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<td></td>
</tr>
<tr>
<td>STEMI:</td>
<td>6-8282</td>
<td></td>
</tr>
<tr>
<td>PERT:</td>
<td>4-7378</td>
<td></td>
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<tr>
<td>SHOCK:</td>
<td>6-2241</td>
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<td>STROKE:</td>
<td>p34282</td>
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<td>ICU Resource:</td>
<td>p25213, 6-6718</td>
<td></td>
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<tr>
<td>Floor Resource:</td>
<td>p25101</td>
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<tr>
<td>General Triage:</td>
<td>p25205</td>
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<tr>
<td>SICU Fellow :</td>
<td>4-49041, p22256</td>
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<tr>
<td>MOD:</td>
<td>p28482</td>
<td></td>
</tr>
<tr>
<td>Intensivist:</td>
<td>p26955, 857-31-0741</td>
<td></td>
</tr>
<tr>
<td>MOD:</td>
<td>p28482</td>
<td></td>
</tr>
<tr>
<td>Intensivist:</td>
<td>p26955, 857-31-0741</td>
<td></td>
</tr>
<tr>
<td>AMS:</td>
<td>CNS: CVA, ICH, seizure, infection, PRES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metabolic toxins: NH4, CO2, BUN,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exogenous toxins: Med/drug, withdrawal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitals: Hypoperfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miscellaneous severe: TTP, Addison, Thyroid</td>
<td></td>
</tr>
<tr>
<td>tPA:</td>
<td>Pulseless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50mg over 2 min, 50mg in 30 min</td>
<td></td>
</tr>
<tr>
<td>Pulse:</td>
<td>100mg over 2 hours</td>
<td></td>
</tr>
<tr>
<td>Contraindications: prior ICH, ischemic CVA/head trauma, major surgery past 3 months, suspected aortic dissection, active bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow with heparin (bolus)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Logistics

Formulas

Recommended websites for formulas:
www.mdcalc.com
www.nephromatic.com

Drug Dosing and Body Weights

Actual Body Weight (ABW): actual weight recorded on admission (most commonly used weight for dosing)

Ideal Body Weight (IBW):
Male: 50.0kg + 2.3kg for every inch over 5 feet
Female: 45.5kg + 2.3kg per inch over 5 feet

Adjusted Body Weight (AdjBW):
AdjBW = IBW + 0.4 x (ABW – IBW); use for obese pts (i.e., if ABW>1.3x IBW)

Electrolytes and Fluids

[Na+] in fluids (mEq/L): NS = 154, ½NS = 77, 3% = 514, LR = 130

Total Body Water (TBW):
TBW = F x weight; F = 0.6 ♂, 0.5 ♀ (or 0.5 and 0.45 if elderly)

Intracellular fluid (ICF) = 2/3 TBW
Extracellular fluid (ECF) = 1/3 TBW
ECF = 3/4 interstitial, 1/4 intravascular

Free Water Deficit in Hypernatremia:
water deficit (L) = TBW x \( \frac{\text{measured Na}}{140} - 1 \)

\( \Delta \text{Na based on Infusate Sodium (per 1L infusion)} \) [use for hypoNa or hyperNa]:
change in serumNa = \( \frac{\text{infusate Na} - \text{serum Na}}{\text{TBW (in liters)}} + 1 \)

Sodium Correction in Hyperglycemia:
corrected Na = measured Na + (2.4/100 mg/dL) x (glucose–100)
**Needed for routine chemistries; not required for ABG specimen**

Calcium Correction for Hypoalbuminemia:
Corrected Ca = Ca (mg/dL) + 0.8 x (4.0 – measured alb (mg/dL))

Transtubular Potassium Gradient:
TTKG = \( \frac{\text{UUrinary}}{\text{KSerum}} \) accurate if UNa > 25, UOsm>SOsm
Normal TTKG = 8-9, but >11 with K load
Hyperkalemia: <6 suggests hypoadosteronism
Hyperkalemia: <2 suggests extrarenal loss; >7 suggests renal loss

Fractional Excretion of Sodium and Urea:
\( \text{FeNa} = \frac{\text{UNa} \times \text{PCr}}{\text{PNa} \times \text{UCr}} \)
\( \text{FeUrea} = \frac{\text{UUN} \times \text{PCr}}{\text{BUN} \times \text{UCr}} \)

Osmolality

Plasma Osmolality:
calc osm = 2 x Na (mEq/L) + 18
BUN (mg/dL) + 2.8 + EtOH (mg/dL) / 4.6

Osmolar Gap:
OG = P\text{osm} – calc osm (normal: < 10)

Stool Osmol Gap:
SOG = Osm\text{stool} – 2 x (Na\text{stool} + K\text{stool})
>125: suggests osmotic diarrhea; <50: suggests secretory diarrhea

Urine Osmol Gap:
U\text{osm} = 2(U\text{Na} + U\text{K}) + U\text{urea} / 2.8 + U\text{glucose} / 18 (normal: 10-100)
<150: shows impaired NH\text{+}+ excretion (type I/IV RTA)
>400: shows increased NH\text{+}+ excretion (type II RTA/diarrhea)

Acid/Base Physiology

Primary metabolic acidosis (Winter’s formula):
compensated pCO\text{2} = 1.5 × HCO\text{3} + 8 ± 2

Primary metabolic alkalosis:
compensated pCO\text{2} = 0.7 × HCO\text{3} + 20 ± 5

Primary respiratory acidosis:
\( \Delta \text{pH} = 0.08 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg
\( \Delta \text{HCO} \text{3} = 1 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg

Chronic:
\( \Delta \text{pH} = 0.03 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg
\( \Delta \text{HCO} \text{3} = 4 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg

Primary respiratory alkalosis:
\( \Delta \text{pH} = 0.08 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg
\( \Delta \text{HCO} \text{3} = 2 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg

Chronic:
\( \Delta \text{pH} = 0.03 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg
\( \Delta \text{HCO} \text{3} = 4 \) for each \( \Delta \text{PaCO} \text{2} \) 10 mmHg

Anion Gap:
AG = Na – (Cl + HCO\text{3}) [normal ~12]
Corrected AG = AG + 2.5 x (4 – measured alb (mg/dL))

Delta-Delta Gap:
\( \Delta \Delta \text{G} = \Delta \text{AG} \times \Delta \text{HCO} \text{3} = (\text{AG} - 12) / (24-\text{HCO} \text{3}) \)
<1 mixed hyperchloremic and anion gap acidosis;
1-2 anion gap acidosis
>2 anion gap acidosis and metabolic alkalosis

*In lactic acidosis, use 0.6*\( \Delta \text{AG} \) (due to ↓ renal clearance of lactate compared to other anions)

Urine Anion Gap:
UAG = \( U\text{Na} + U\text{K} – U\text{Cl} \) [normal: -20 to +20]
>20: Type I/IV RTA; <20: diarrhea/Type II RTA

Cardiovascular Physiology

SaO\text{2} and PaO\text{2} Correlation:
SaO\text{2} 99 98 95 90 88 80 73 60 50 40 30
PaO\text{2} 149 100 80 60 55 48 40 30 26 23 18

Arterial Oxygen Content (C\text{O} \text{2}):
C\text{O} \text{2} = (1.34 x Hb x S\text{O} \text{2}) + (0.003 x P\text{O} \text{2})

Cardiac Output: CO = HR x SV

Jonathan Salik
247
Cardiac Output (Fick): \[ CO = \frac{VO_2}{(CaO_2 - CvO_2)} \]

→ \[ VO_2 \approx 3 \times wt \text{ (kg)} \text{ or } 125 \times BSA \text{ (roughly 250 ml/min; use metabolic cart to measure precise value)} \]

Systemic Vascular Resistance (normal 800-1200):

\[ SVR \text{ (dynes} \cdot \text{sec} \cdot \text{cm}^{-5}) = \frac{MAP \text{ (mmHg) - CVP \text{ (mmHg)}}}{CO \text{ (L/min)}} \times 80 \]

Pulmonary Vascular Resistance (normal 150-250):

\[ PVR \text{ (dynes} \cdot \text{sec} \cdot \text{cm}^{-5}) = \frac{mPAP \text{ (mmHg) - PCWP \text{ (mmHg})}}{CO \text{ (L/min)}} \times 80 \]

Law of Laplace: \[ \sigma \text{ (wall stress)} = P \times r \div 2h \]

Poiselle Equation:

\[ \Delta P = \frac{8\mu \times L \times Q}{\pi r^4} \]

\( \mu \) = dynamic viscosity, \( L \) = length, \( Q \) = flow, \( r \) = radius

Bazett Formula:

\[ QTc = \frac{QT}{\sqrt{RR \text{ (♀ < 460 ms; ♂ < 440 ms)}}} \]

Friedewald Formula:

\[ \text{LDL} = \text{TC} - \text{HDL} - \frac{(\text{TG})}{5} \]

Maximum Heart Rate: Max HR = 220 – age (if unable to achieve >85% max HR, suggests chronotropic incompetence)

Transpulmonary and Diastolic Pulmonary Gradient:

\[ TPG = mPAP - PCWP; >12-15 \text{ suggests pre-cap pulm HTN} \]

\[ DPG = PAd - PCWP; >7 \text{ mmHg suggests pre-cap pulm HTN} \]

Alveolar-arterial (A-a) Oxygen Gradient:

\[ \text{Calculated A-a gradient} = \frac{PaCO_2}{R} - \frac{PaCO_2}{0.8} \]

\( FiO_2 \) = 0.21 on RA; add 0.03 for each extra L O2/min cannula

\( P_{atm} \) = atmospheric pressure (mmHg) = 760

\( P_{H2O} \) = alveolar pressure of water (mmHg) = 47

\( R \) = respiratory quotient = \( \frac{V_{CO_2}}{V_{O_2}} \approx 0.8 \)

**Normal A-a gradient = 2.5 + (0.21 x age)**

Shunt Fraction (normal: 3-8%, but ↑ 5% for every 100 mmHg drop in PaO2 below 600 mmHg):

\[ Qs = 0.0031 \times (PAO2 - PaO2) \]

\[ QT = \frac{[0.0031 \times (PAO2 - PaO2)] + (Ca - vO2)}{0.0031 \times (PAO2 - PaO2)} \]

where \( Qs \) = shunt flow, \( QT \) = total flow, \( Ca-vO2 \) assumed 5%. \( FiO_2 \) must be 1.0 in this calculation

\( R \) becomes 1.0 after breathing 100% O2 for 20 minutes because of N2 wash-out

> 15% = pathologic shunt

Minute Ventilation (V\text{e}) (volume per unit time):

\[ V\text{e} = RR \times V_t \]

Bohr Equation (i.e., dead space fraction) (normal: 0.2 – 0.4):

\[ V_d = \frac{PaCO2 - PetCO2}{PaCO2} \]

**Gastroenterology and Hepatology**

Maddrey’s Discriminant Function for Alcoholic Hepatitis

\[ \text{MDF} = 4.6 \times (PT – control PT) + \text{total bilirubin} \]

**At MGH, control PT (upper limit of normal) is 13.2s**

>32: consider treatment with glucocorticoids

MELD (Model for End-Stage Liver Disease): use online calc

**Note: MELD-Plus score with better performance over MELD and MELD-Na scores (developed at MGH in 2017)**

Correction of Ascitic PMN for Ascitic RBC

Corrected PMN_{ascites} = PMN_{ascites} – (RBC_{ascites} / 250)

**Neurology**

Correction of CSF WBC for CSF RBC

Corrected WBC_{CSF} = WBC_{CSF} - (WBC_{serum} \times [RBC_{CSF} / RBC_{serum}])

**Nephrology**

Creatinine Clearance from Timed Urine Collection

\[ CrCl = \frac{U\text{Cr (mg/dl)} \times U\text{volume (ml/min)}}{\text{serum Cr (mg/dL)}} \]

\( eGFR \): use CKD-EPI equation (if black, multiply by 1.159)

**Hematology**

Absolute Neutrophil Count: \( ANC = WBC \times (\% \text{ PMN} + \% \text{ bands}) \)

Reticulocyte Production Index (RI) (normal: 2-3):

\[ RI = \% \text{retic} \times \left( \frac{Hct \text{ (patient’s normalHct)}}{\text{maturation factor (MF)}} \right) \]

\( MF \): 1.0 (Hct > 36), 1.5 (Hct 26-35), 2.0 (Hct 16-25), 2.5 (Hct < 15)

RI: <2 in hypoproliferative state; >3 in hyperproliferative state

Statistics and Epidemiology

**Sensitivity** = TP / (TP + FN)

**Specificity** = TN / (FP + TN)

**Positive Predictive Value** = TP / (TP + FP)

**Negative Predictive Value** = TN / (FN + TN)

**Positive Likelihood Ratio** = Sensitivity / (1 – Specificity)

**Negative Likelihood Ratio** = (1 – Sensitivity) / Specificity

**Number Needed to Treat** = 1/absolute risk reduction (ARR)
Post-Acute Care: Post-hospital care of patients to help them return to baseline.

- Largest source of Medicare regional variation. High cost growth (NEJM 2014;370:689) and risk of readmission (Health Aff 2010;29:57).
- NB: Do not have capability for rapid diagnostics (CT scanners), procedures, or significant acute issues (hypoxemia, hypotension)

<table>
<thead>
<tr>
<th>Setting (most to least intensive)</th>
<th>Description</th>
<th>Patients / Diagnoses</th>
<th>Avg LOS</th>
<th>MD</th>
<th>Therapy / Ancillary Services</th>
</tr>
</thead>
</table>
| Long Term Acute Care Hospital (LTAC) | High intensity hospital-level care | - Tracheostomy  
- Chemotherapy  
≥ 3-day ICU stay required to qualify | 20+ days | Daily MD visits | - RT  
- PT/OT PRN  
- HD |
| Inpatient Rehabilitation Facility (IRF, “acute rehab”) | Intensive therapy for recovery of function | - Post-stroke  
- Spinal cord injury  
- Note: Specific dx codes required to qualify | 7-21 days | 2-4x/week MD visits; PM&Rx presence | - 3+ hours of therapy/day (pt must be able to participate) |
| Skilled Nursing Facility (SNF) | “Sub-acute” rehabilitation; looks/feels like nursing home; must have 3-night hospital stay to qualify under Medicare | - CHF, PNA, UTI  
- Generally older patients with functional decline / unsafe at home | 3-21 days | ~1x/week MD visits; very limited capacity for management changes | - 1-2 hours of therapy/day (pt must be able to progress) |
| Home Health | Home-based services post-hospitalization or via PCP referral | - Wound care  
- IV antibiotics  
- Post-hospital functional decline  
- Home safety eval | N/A | Managed by PCP or prescribing outpatient clinician | - 4-8 PT/OT visits  
- RN visits as needed |

Special Cases

- **Hospice**
  - Criteria: pt must have a terminal illness with prognosis of ≤6 months as certified by a physician. Depending on the hospice agency, pt may need to forego curative treatments (i.e., chemo, expensive antibiotics, etc.)
  - Home hospice: fully funded by Medicare. RNs visit, but patients need full-time caregiver support in the home, which can be a barrier to home hospice discharge
  - Inpatient hospice (SNF or dedicated inpatient hospice facility): room & board (~$400 per day) only covered by MassHealth, but not other insurers
  - GIP (in-hospital hospice care): fully funded by Medicare, patient must quality → discuss with Pall Care

- **Long-term care**
  - Patients residing in nursing homes with stably poor functional status and who require assistance with ADLs/IADLs, but do not require post-acute level care
  - Private pay or covered by MassHealth, but not funded by Medicare

- **Patient/family refusal of SNF/rehab:** recommend higher-quality SNFs in Partners Skilled Nursing Facility Network

- **Alternative programs:** If patient is in Partners ACO, discuss additional home-based care options with case manager
Logistics

Discharge Summaries

General Considerations

- Must be completed at the time of discharge for all patients being discharged to a facility or home with VNA services
- Can be completed within 24 hours of discharge for patients being discharged home without services
- CC copies to attending of record, PCP, and outpatient subspecialists

Discharge Summary Components

- **D/C Doc Checklist**: Checklist of all items required for patient discharge. As you go through the Discharge Summary tab, click on the “Refresh” button to move completed items from the “Not Completed” to “Completed” column. All components must be completed prior to a discharge to a facility. Only the “D/C Order Rec” needs to be completed for a patient to be discharged home.

  - **Review Prior to Admission Medications**: Update home medication list. If they were not accurately verified at the time of admission, the discharge medication list will be inaccurate and may be confusing to a patient with regards to which medications to modify, continue, or discontinue.
  
  - **Discharge Problem List**: Add all relevant hospital problems and diagnoses – this is important for a patient’s transition to outpatient providers. You can change the “Principal” diagnosis for billing purposes. “Resolved” problems will not remain on a patient’s problem list after they are discharged.
  
  - **Reconcile Meds for Discharge**: Choose whether to modify, resume, or stop taking each pre-admission medication. You can also prescribe new medications that are being given inpatient. Select patient’s preferred pharmacy for e-prescriptions.
  
  - **Place New Orders**: Select appropriate discharge disposition. Under “Order Sets and Pathways”, select “General Adult Discharge Order Set” and complete. Do NOT complete “Referral to Home Health VNA” or the “face to face” – this will be done by case management.

- **AVS Pt Instructions**:
  
  - **Reason for admission**: Briefly state the patient's medical diagnosis/reason for admission in 1-3 words using patient-friendly language (eg: pneumonia, low sodium level, urinary tract infection, fainting, etc.).
  
  - **Important events, results, medication changes, and instructions**: This is meant FOR THE PATIENT to clarify the reason for his/her hospitalization, highlight important testing/interventions, and briefly explain discharge instructions/follow-up plans. Important to consider health literacy, native language, and language fluency for each individual patient.

- **Additional Patient Instructions**: You can leave this section blank. Sometimes residents add wound care or post-procedure instructions here; specialists may leave specific instructions here as well.

- **Scheduled Partners Appts**: This will automatically populate with upcoming scheduled Partners appointments.

- **Follow-Up**: All relevant non-Partners appointments should be manually entered here. You can also enter appointments that have yet to be made with a phone number for the patient to call.

- **Brief Summary**: Update the one-liner one last time. It is helpful to make this a brief but comprehensive summary of the entire hospitalization to preface the details in the hospital course.

- **Hospital Course**: Use the admission H&P and most recent progress note to identify which problems should be included in the Hospital Course. Lump rather than split your hash-tagged problems into paragraph form. For each problem, include:1) relevant presenting symptoms and exam findings, 2) labs, imaging, and studies used to diagnose the problem, 3) consultant recommendations, 4) treatment course and discharge plan, 5) post-hospital follow-up items (including repeat labs and f/u incidentalomas). Less is more – focus on the big-picture overview and the clinical reasoning that guided your decision-making and management of each problem. Try to avoid MGH-specific abbreviations (eg: RUQUS, LENIs). Some find it helpful to copy and paste the admission H&P below the hospital course, especially if the patient is followed by a provider outside of Partners.

- **Discharge Exam**: Copy and paste exam from last progress note, but make sure this is up to date.

- **Provider Follow Ups**: Identify key lab, imaging, and other items that a provider needs to follow up after discharge. Please note that any pending pathology and send out tests should be included here as they do not automatically pull into the pending results section. Be sure to review all imaging results and consultant recommendations for follow-up. Some residents comment on medication titration suggestions and key medication changes.

- **Finalize DC Summary**: Once the discharge orders are signed, a new button appears under this section that allows you to create the actual discharge summary that will be filed in the Epic. Click the button and then click into the note writing space that opens on the right. Press F2 and select the general medicine discharge summary template from the drop-down menu. This will create a discharge summary containing the contents of the other free text fields already completed. You can edit this once signed as long as your attending has not already signed the addendum.

Ryan Flanagan

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# MGH Directory

## Main Numbers

<table>
<thead>
<tr>
<th>Main Number</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>617-726-2000 (MGH prefix: -724, -726, -643)</td>
<td>857-238-XXXX (Lunder), 617-523-XXXX (MEEI)</td>
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## See Partners Paging Directory for consult pagers

## Emergency Numbers

<table>
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<tr>
<th>Service</th>
<th>Phone</th>
<th>Fax</th>
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<tbody>
<tr>
<td>Senior On (Med Sr)/Bauer Room</td>
<td>3-1388, p22337</td>
<td></td>
</tr>
<tr>
<td>ED Triage Sr (ED Sr)</td>
<td>617-224-2599</td>
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<tr>
<td>Med Consult Pager (Code Backup)</td>
<td>p13480</td>
<td></td>
</tr>
<tr>
<td>RICU Team (intubation)</td>
<td>6-3333</td>
<td></td>
</tr>
<tr>
<td>Shock Team (ECMO activation)</td>
<td>6-2241</td>
<td></td>
</tr>
<tr>
<td>STEMI Team (CCL activation)</td>
<td>6-8282</td>
<td></td>
</tr>
<tr>
<td>PERT (massive PE)</td>
<td>4-7378</td>
<td></td>
</tr>
<tr>
<td>IV Nurse (urgent access)</td>
<td>6-3631, p26571</td>
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</tr>
<tr>
<td>ED Radiology (stat CXR)</td>
<td>6-3050</td>
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<tr>
<td>Pharmacy (on call)</td>
<td>6-4726</td>
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<tr>
<td>RT (on call)</td>
<td>p24225</td>
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<tr>
<td>Acute stroke (neurology)</td>
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<tr>
<td>ICU Nursing Supervisor</td>
<td>6-6718, p25213</td>
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## Hospital Floors

<table>
<thead>
<tr>
<th>Floor</th>
<th>Phone</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
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## CCU Fellow Back-Up – see Partners Paging Directory

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## Cardiology Studies

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**Jonathan Salik**

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### Logistics

#### Administration

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<td>Registrar’s office</td>
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<td>Security</td>
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<td>MGH Back Bay</td>
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<td>MGH Beacon Hill Health Associates</td>
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<td>MGH Charlestown</td>
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<td>MGH Downtown</td>
<td>617-726-6000</td>
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<td>MGH Everett Family Care</td>
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<td>MGH Primary Care Associates Waltham</td>
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<td>MGH Revere 300 Ocean Avenue</td>
<td>781-485-6303</td>
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<td>MGH Senior Health</td>
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#### Subspecialties

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<td>Anticoagulation (AMS)</td>
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<td>Boston Healthcare for the Homeless</td>
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<td>Breast Center</td>
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<td>Dental</td>
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#### Mass Eye and Ear Infirmary

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<td>11th floor (Inpatient)</td>
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<tr>
<td>ENT Consult (MEEI ED)</td>
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<tr>
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<tr>
<td>Ophthalmology Clinic</td>
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See “Radiology” Section for additional Radiology contact information

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Jonathan Salik | 252
## Logistics

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</tr>
<tr>
<td>Locum Tenens/Covering Intensivist</td>
<td>p57651</td>
</tr>
<tr>
<td>Hospitalist</td>
<td>p51253</td>
</tr>
</tbody>
</table>

### Hospital Floors

<table>
<thead>
<tr>
<th>Location</th>
<th>Main Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>6193 / 6194</td>
</tr>
<tr>
<td>ICU (2nd floor)</td>
<td>6587</td>
</tr>
<tr>
<td>3 West</td>
<td>6363</td>
</tr>
<tr>
<td>4 Usen</td>
<td>6459</td>
</tr>
<tr>
<td>4 West</td>
<td>6400</td>
</tr>
<tr>
<td>6 Usen</td>
<td>6307</td>
</tr>
<tr>
<td>6 East</td>
<td>1670</td>
</tr>
</tbody>
</table>

### Laboratories

<table>
<thead>
<tr>
<th>Department</th>
<th>Main Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Lab (for add-ons)</td>
<td>6300</td>
</tr>
<tr>
<td>Hematology</td>
<td>6095</td>
</tr>
<tr>
<td>Blood Bank</td>
<td>6091</td>
</tr>
<tr>
<td>Chemistry</td>
<td>8389</td>
</tr>
<tr>
<td>Urine Studies</td>
<td>6090</td>
</tr>
<tr>
<td>Microbiology</td>
<td>6096</td>
</tr>
<tr>
<td>Pathology</td>
<td>6140</td>
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</table>

### Radiology

<table>
<thead>
<tr>
<th>Department</th>
<th>Main Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Number</td>
<td>6600 / 6076</td>
</tr>
<tr>
<td>Radiology Reading Room</td>
<td>6162</td>
</tr>
<tr>
<td>ED Radiology</td>
<td>6185</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>6581</td>
</tr>
<tr>
<td>CT (main)</td>
<td>6725</td>
</tr>
<tr>
<td>CT (ED and after hours)</td>
<td>6505</td>
</tr>
<tr>
<td>MRI</td>
<td>6217</td>
</tr>
<tr>
<td>PET</td>
<td>6334</td>
</tr>
<tr>
<td>Nuclear Medicine</td>
<td>6087</td>
</tr>
<tr>
<td>Interventional Radiology</td>
<td>6800 / 3761</td>
</tr>
<tr>
<td>Night Watch</td>
<td>617-732-5657</td>
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</table>

### Cardiac Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Main Number</th>
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</thead>
<tbody>
<tr>
<td>ECG</td>
<td>6229</td>
</tr>
<tr>
<td>Echo</td>
<td>6231 / 2665</td>
</tr>
<tr>
<td>ETT or Nuclear Stress</td>
<td>5375 / 6229 / 6087</td>
</tr>
</tbody>
</table>

### Ancillary Staff

<table>
<thead>
<tr>
<th>Department</th>
<th>Main Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing Supervisor</td>
<td>p57711</td>
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<tr>
<td>Pharmacy</td>
<td>6012</td>
</tr>
<tr>
<td>Respiratory Therapy</td>
<td>6213</td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>5903</td>
</tr>
<tr>
<td>Speech Language Pathology</td>
<td>6548</td>
</tr>
<tr>
<td>Infection Control</td>
<td>6282</td>
</tr>
<tr>
<td>Case Management/Social Work</td>
<td>6695</td>
</tr>
<tr>
<td>Chaplain</td>
<td>6634</td>
</tr>
<tr>
<td>Interpreter Services</td>
<td>6098</td>
</tr>
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</table>

### Miscellaneous

<table>
<thead>
<tr>
<th>Department</th>
<th>Main Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>6289</td>
</tr>
<tr>
<td>PACU</td>
<td>6295</td>
</tr>
<tr>
<td>GI Unit</td>
<td>6151</td>
</tr>
<tr>
<td>Dialysis</td>
<td>6203</td>
</tr>
<tr>
<td>Pulmonary Lab</td>
<td>6127</td>
</tr>
<tr>
<td>EEG/EMG</td>
<td>6624</td>
</tr>
<tr>
<td>Anticoagulation Clinic</td>
<td>6147</td>
</tr>
<tr>
<td>Cancer Center</td>
<td>1230</td>
</tr>
<tr>
<td>Cardiovascular Health Center</td>
<td>7100</td>
</tr>
<tr>
<td>Infusion Clinic</td>
<td>6350</td>
</tr>
<tr>
<td>Occupational Health</td>
<td>6168</td>
</tr>
<tr>
<td>Admissions</td>
<td>5500</td>
</tr>
<tr>
<td>CareFinder (new NWH PCP)</td>
<td>6566</td>
</tr>
<tr>
<td>MDConnect (transfer to MGH)</td>
<td>877-637-3337</td>
</tr>
<tr>
<td>DOM Office (6 South)</td>
<td>6467</td>
</tr>
<tr>
<td>Chief Medical Resident</td>
<td>6470</td>
</tr>
<tr>
<td>Outside Calls</td>
<td>617-243-6841</td>
</tr>
</tbody>
</table>

### Getting to NWH (2014 Washington St, Newton, MA)

- You will receive transportation information prior to your NWH rotation
- Note that all transportation stipends are taxed
- **Driving**
  - Stipend covers gas and tolls
  - On day 1, park in patient garage for ~$10
  - Pay $15 cash/check at parking/security office for pass to park in employee garage behind West Entrance
- **Ride-sharing**
  - If using a ride-sharing service, consider carpooling to stay within stipend
- **Public transportation**
  - Take MBTA Green Line D outbound train to Riverside -> Woodland stop -> NWH is 2 blocks to the left
- **Single day/night coverage (eg: NF coverage, HIT)**
  - Use Uber for Business → MGH DOM Internal Medicine Residency Program account