

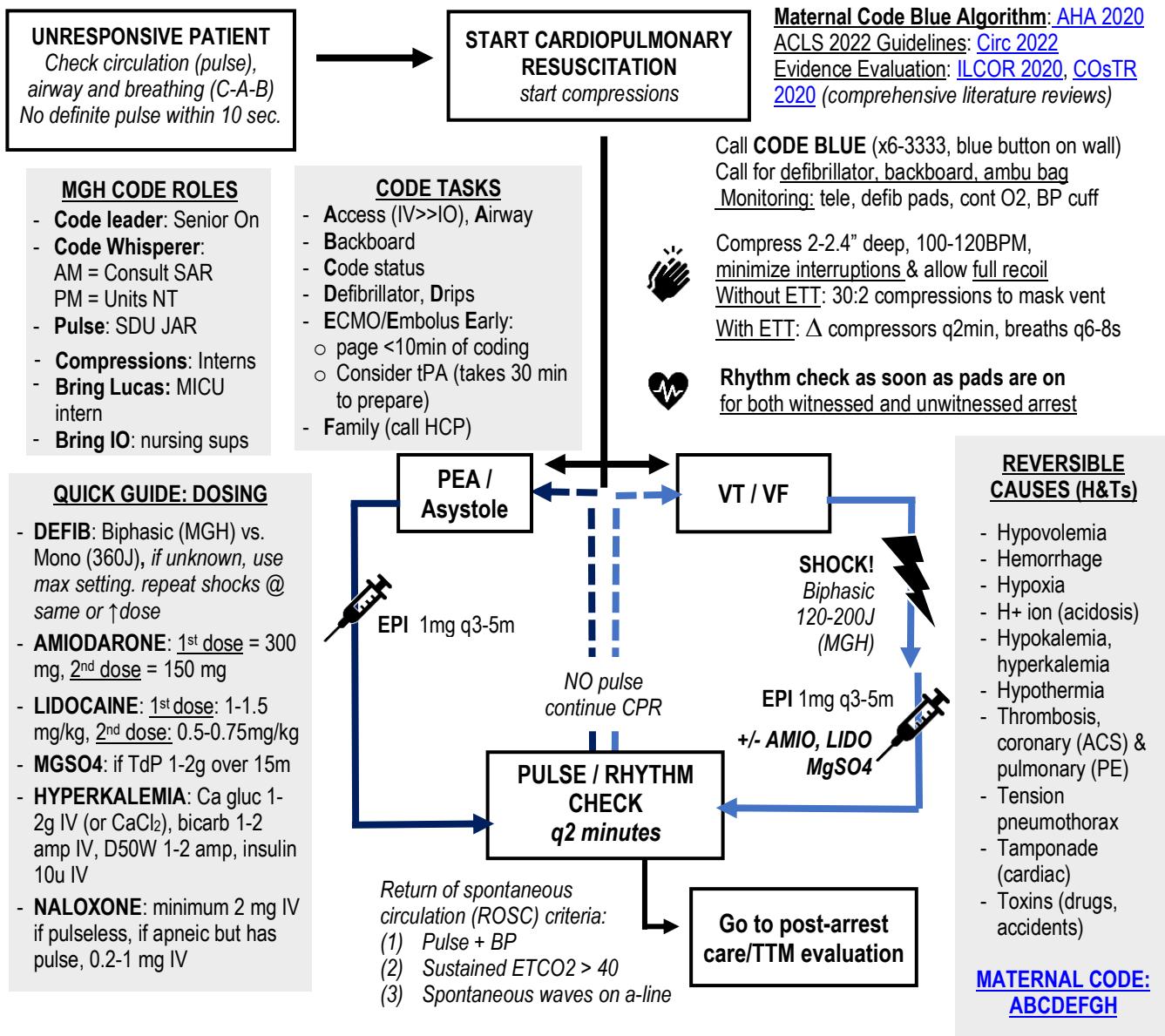
# MGH Housestaff Manual

# Table of Contents

<b>CARDIOLOGY</b>					
ACLS: Cardiac Arrest & TTM	1	Glomerular Disease	95	Calcium Disorders	180
ACLS: Bradycardia	3	Chronic Kidney Disease	96	Osteoporosis & Vitamin D	181
ACLS: Tachycardia	4	Dialysis & Transplant	97	Thyroid Disorders	182
ACLS: Defibrillation/Cardioversion/Pacing	5	Advanced Diuresis	98	Male Hypogonadism	183
EKG Interpretation	6	Acid-Base Disorders	99	<b>ALLERGY &amp; IMMUNOLOGY</b>	
Narrow Complex Tachycardia	8	Sodium Disorders	101	Drug & Contrast Allergy	184
Wide Complex Tachycardia	9	Potassium Disorders	102	Angioedema & Anaphylaxis	186
Atrial Fibrillation & Flutter	10	Magnesium & Phosphorus Disorders	103	Mast Cell Disorders	187
QTc Prolongation	12	IV Fluids & Electrolyte Repletion	104	Primary Immunodeficiency	188
Chest Pain	13	Urinalysis & Nephrolithiasis	105	<b>NEUROLOGY</b>	
Acute Coronary Syndrome	14	<b>INFECTIOUS DISEASE</b>		Altered Mental Status	189
MI Complications	16	Empiric Antibiotics	106	Delirium	190
Cardiac Catheterization	18	Multidrug Resistant Organisms	108	Dementia	191
Non-Invasive Cardiac Testing	19	Community Acquired Pneumonia	109	Headache & Vertigo	192
Echocardiography	21	HAP/VAP & Aspiration Pneumonia	110	Stroke & TIA	193
Heart Failure	22	Viral Respiratory & Head & Neck Infections	111	CNS Emergencies	195
Right Ventricular Failure	25	Urinary Tract Infections	112	Seizures	196
Mechanical Circulatory Support	26	Skin & Soft Tissue Infections	113	Weakness & Neuromuscular Disease	197
Pulmonary Artery Catheterization	27	Osteomyelitis	114	Neuroprognostication	198
Cardiac Devices: PPM, ICD, & CRT	28	Bloodstream Infections & Endocarditis	115	<b>PSYCHIATRY</b>	
Valvular Heart Disease	29	Meningitis & Encephalitis	116	Consent & Capacity	199
Pericardial Disease	31	C. Difficile Infection	117	Agitation	200
Aortic Disease	32	Invasive Fungal Infections	118	Psychosis	201
Syncope	34	Tuberculosis	119	Catatonia, NMS, & Serotonin Syndrome	202
Severe Asymptomatic HTN & Emergency	35	HIV/AIDS & Opportunistic Infections	120	Depression	203
Peripheral Artery Disease	36	Transplant ID	121	Anxiety Disorders	204
Cardio-Oncology	37	STIs & Travel Medicine	122	Alcohol Use Disorder & Withdrawal	205
Outpatient CV Health	38	Tick-Borne Diseases	123	Opioid Use Disorder & Withdrawal	207
Anti-Arrhythmic Medications	41	Mpox & Ectoparasites	124	Other Substance Use	208
Telemetry & Physical Exam	42	Fever of Unknown Origin	125	Drug Testing	209
<b>PULMONOLOGY &amp; CRITICAL CARE</b>			126	<b>PRIMARY CARE</b>	
Respiratory Distress	43	Rare Diseases at MGH	127	Health Screening & Maintenance	210
Hypoxemia & Hypercapnia	44	Infection Control	128	Transgender Health	212
Noninvasive Oxygenation/Ventilation	45	Antimicrobial Dosing	129	Women's Health	213
Interpretation of Chest Imaging	46	<b>HEMATOLOGY</b>		Men's Health	216
PFTs & Asthma	47	Pancytopenia & Anemia	130	Sleep Medicine	217
COPD	48	Sickle Cell Disease	131	HEENT Concerns	218
Bronchiectasis & Hemoptysis	49	Thrombocytopenia	132	Nodules	220
Interstitial Lung Disease	50	Eosinophilia	133	Musculoskeletal Pain	221
VTE Diagnostics	51	Coagulation Disorders	134	Immigrant & Refugee Health	223
VTE Management	52	Anticoagulation Agents	135	Climate Change & Health	224
Pulmonary Hypertension	53	Anticoagulation Management	136	Health Equity & Insurance	225
Mechanical Ventilation	54	Transfusion Medicine	137	<b>CONSULTANTS</b>	
ARDS	56	Transfusion Reactions	138	Calling Consults	226
ECMO	58	Peripheral Smear Interpretation	139	Perioperative Medicine	227
Sedation	59	<b>ONCOLOGY</b>		Dermatology	229
Shock	60	Acute Leukemia	140	Surgery	232
Sepsis	61	Lymphadenopathy & Lymphoma	141	Urology	233
Vasopressors	63	Plasma Cell Disorders	143	ENT	234
Toxicology	64	MDS & MPN	144	Ophthalmology	235
Lung Transplant	65	Hematopoietic Stem Cell Transplantation	145	OB/GYN	236
<b>GASTROENTEROLOGY</b>			146	<b>RADIOLOGY</b>	
Upper GI Bleeding	66	CAR T cell Therapy	147	Radiology Basics	237
Lower GI Bleeding	67	Solid Organ Malignancies	148	Contrast	238
Abdominal Pain	68	Immune Checkpoint Inhibitors	149	Protocols	239
GERD & Peptic Ulcer Disease	69	Oncologic Emergencies	150	Interpretation of Common Studies	241
Nausea & Vomiting	70	Febrile Neutropenia	151	<b>PROCEDURES</b>	
Diarrhea	71	Inpatient Leukemia & Lymphoma Regimens	152	Ultrasound Basics	243
Constipation, IBS, & Colonic Disorders	72	<b>GERIATRICS &amp; PALLIATIVE CARE</b>		Contrast	238
Esophageal & Upper GI Disorders	74	Pain Management	153	Ultrasound-Guided Peripheral IV	245
Inflammatory Bowel Disease	75	Adv Care Planning & Code Status	154	Central Line	246
Intestinal Disorders	77	Death & Pronouncement	155	Arterial Line	248
Nutrition & Feeding	78	End of Life Care & Hospice	161	Intraosseous Line	249
Weight & Weight Loss	79	Frailty & Polypharmacy	162	Paracentesis	250
Pancreatitis & Pancreatic Masses	80	Geriatric Assessment & Elder Abuse	163	Lumbar Puncture	251
Liver Chemistry Tests	81	<b>RHEUMATOLOGY</b>		Thoracentesis	252
Biliary Disease	82	Approach to Rheumatologic Disease	165	Pericardial Drain	253
Acute Liver Injury & Failure	83	Arthritis	166	Fluid Analysis	254
Viral Hepatitis	84	Connective Tissue Diseases	168	Tube Management	255
Alcohol-Related Liver Disease	85	Vasculitis	169	Exposures & Needle Sticks	258
NAFLD	86	Miscellaneous Rheumatologic Diseases	171	<b>LOGISTICS</b>	
End Stage Liver Disease	87	Autoantibodies	172	Monitoring & Prophylaxis	259
Hepatorenal Syndrome	91	Rheumatologic Medications	173	Peri-Procedural Anticoagulation	260
Liver Transplant	92	<b>ENDOCRINOLOGY</b>		Senior On Encounters	261
<b>NEPHROLOGY</b>			174	Post-Acute Care	262
Acute Kidney Injury	93	Adrenal Insufficiency	175	Microaggressions/Bias, Patient-Directed	263
		Pituitary Disorders	176	Discharge, ICE	264
			177	MGH Directory	264

# Cardiology

# ACLS: Cardiac Arrest & TTM



## ACLS LOGISTICS & UPDATES

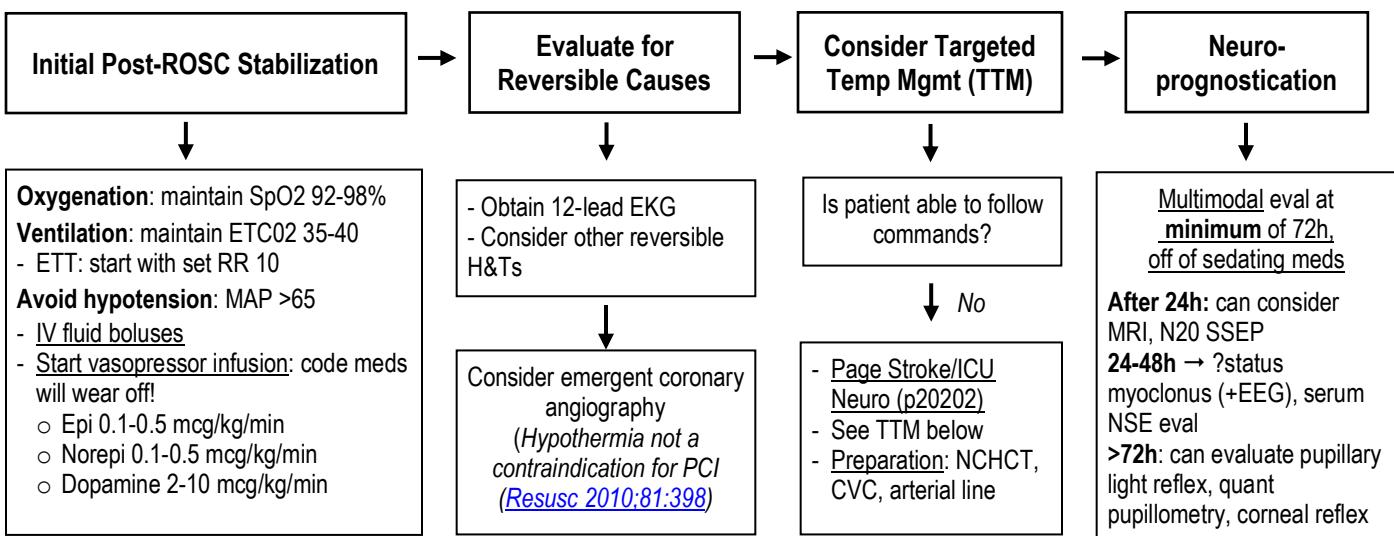
- ACCESS: try IV first, IO if necessary or IV not feasible; c/f reduced drug delivery esp with pre-tibial placement ([AHA 2020 ACLS](#))
- STAT LABS: ABG with K & Hgb, CBC, BMP, LFTs, lactate, T&S, coags, fibrinogen, cardiac enzyme
- MONITORING: recommend wave capnography during CPR, keep ETCO<sub>2</sub> at least >10mm H<sub>2</sub>O, ideally >20
- PROGNOSTICATION: ETCO<sub>2</sub> <10 mmHg in intubated pts after 20min CPR ~90% sensitive for no ROSC
- PREGNANT WOMEN: Apply left lateral uterine displacement, IVs above diaphragm, if receiving IV Mg, stop and give CaCl or Ca gluc, prep for perimortem delivery early, suggest delivery if no ROSC within 5min, TTM should still be considered with ROSC
- VSE PROTOCOL: vasopressin 20U with first 5 doses of epi + hydrocortisone 200mg x1; not currently used at MGH

## Thrombolysis for Known or Suspected PE During Code

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

## ECMO for Cardiac Arrest

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



## TARGETED TEMPERATURE MANAGEMENT AFTER CARDIAC ARREST ([Circ 2020:S266-468](#))

**Rationale:** Hyperthermia/fever is associated with worse neurological outcomes and neuronal damage due to inflammatory changes and biochemical cascades that develop following ischemia and reperfusion injury associated with cardiac arrest ([Arch Intern Med 2001](#)). Goal is to avoid fevers and to be aggressive about diagnosing/treating infections.

**Causes of fever:** Infection (high risk of aspiration/pneumonia, global ischemia -> gut ischemia -> bacterial translocation). Pan-culture and consider aggressive antibiotic treatment. Drug fever

**\*Importantly\***: Previously low-quality data; many new trials and evolving MGH guidelines. After ROSC discuss with ICU attending and consult neuro to discuss TTM plan (hypothermia at 33°C vs normothermia at 36°C)

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

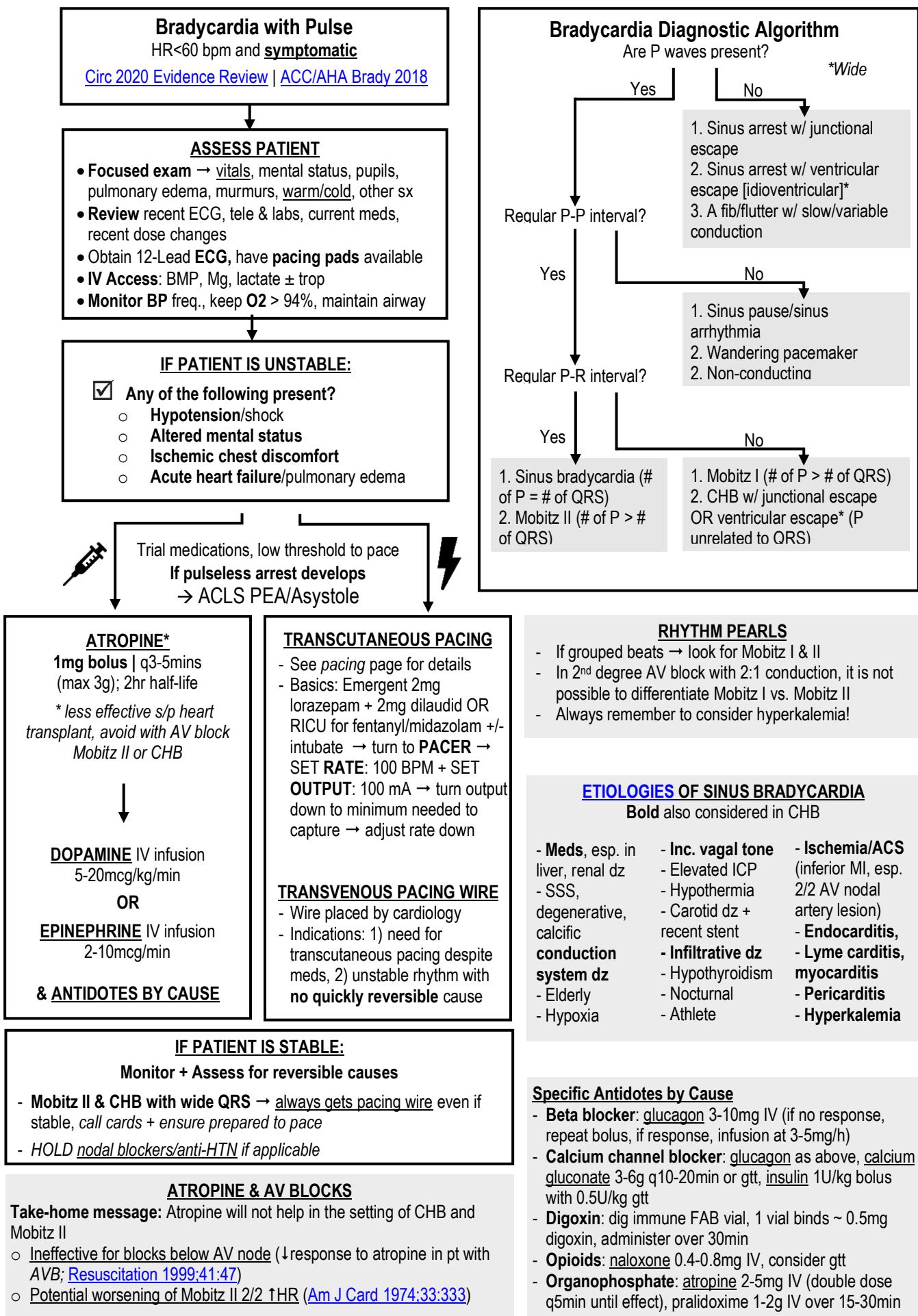
- **Hypothermia (33°C)**
  - European and American society guidelines recommend ([Circ 2020:142:S366](#)) ([Int Care Med 2015:41:2039](#))
  - Improves neurologic outcomes (NNT 6) & survival to discharge (OR 5.25) following out-of-hospital cardiac arrest from VF, pulseless VT, or PEA/asystole of presumed cardiac cause ([NEJM 2002;346:549](#); [NEJM 2002;346:557](#); [NEJM 2013;369:2197](#); [Circ 2015;132:2146](#); [NEJM 2019;381:2327](#))
  - Unclear if benefit is from hypothermia or avoidance of hyperthermia
- **Normothermia (36°C)**
  - TTM2 Trial: no difference in mortality or functional outcome at 6 months for out of hospital cardiac arrest w/ hypothermia vs normothermia, more hemodynamically significant arrhythmias in hypothermia arm ([NEJM 2021;384:2283](#))
  - Since TTM2, MGH protocol has changed so patients admitted after out of hospital cardiac arrest will be started on the normothermia protocol in the Emergency Room (see [Ellucid](#))
  - Normothermia helps avoid use of paralytics and lower required sedation, but some patients may still require medication to avoid shivering

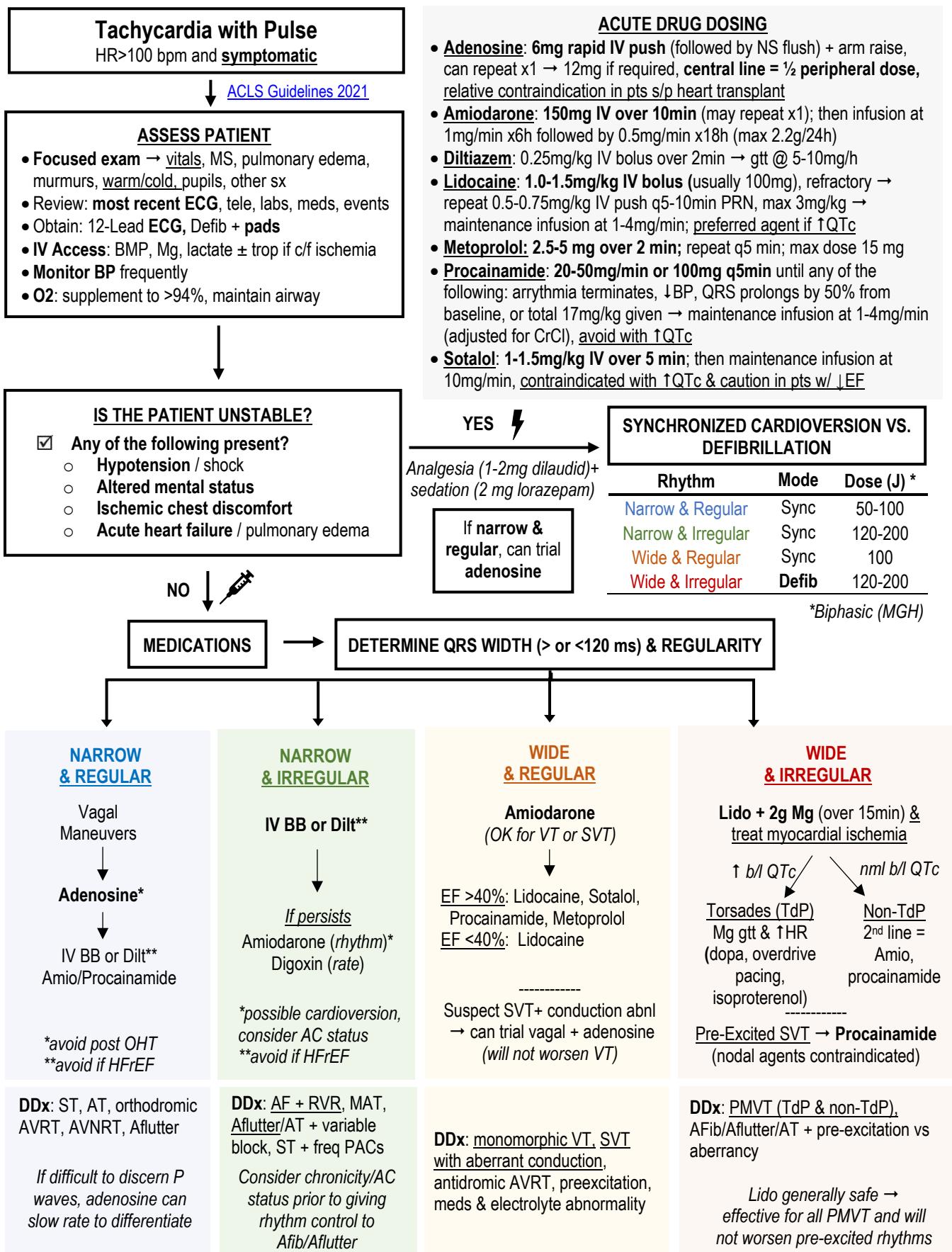
**Methods of temperature control:** Foley catheter temperature monitoring, cold saline injection, external cooling device (Arctic Sun), shivering management (Mg, acetaminophen, meperidine, buspirone, dexmedetomidine, dantrolene, paralysis)

**Duration of TTM:** Multiple considerations including age of patient, existing neurologic damage, risk of infection, etc. Discuss with ICU attending and neuro about duration of TTM and rate of temperature change ([NEJM 2022](#))

- Normothermia: per Ellucid, 36°C for 24 hours then 37°C for at least 48 hours
- Hypothermia: per Ellucid, 33°C for 24 hours, then rewarm at rate of 0.25°C per hour and maintain at 36°C for 48 hours

**Neuro-prognostication** see [Neurology - Neuroprognostication](#) section





## VAGAL MANEUVERS:

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

# Cardiology

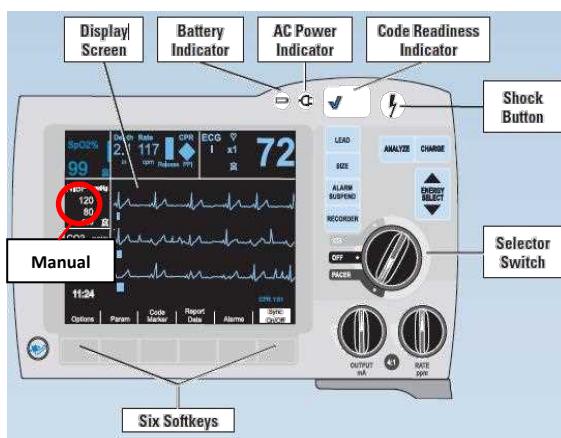
# ACLS: Defibrillation/Cardioversion/Pacing

## EXTERNAL DEFIBRILLATION/CARDIOVERSION/TRANSCUTANEOUS PACING

- About the device:** the Zoll R Series is on all code carts & ICUs at MGH. This device allows for external defibrillation, cardioversion, and pacing with additional benefits (e.g. display ET-CO<sub>2</sub>, CPR quality feedback, & upload rhythm strips into Epic)
- Additional supplies/resources:** Ambu bag, intubation equipment, RICU staff, backboard, suction
- Medications:** use procedural sedation (typically 50mcg **fentanyl** → 2mg **midazolam**) when possible, requires **Cardiac Anesthesia/RICU**. In emergent situations, **Dilaudid** 1-2mg → **lorazepam** 2mg are reasonable alternatives (often readily available).

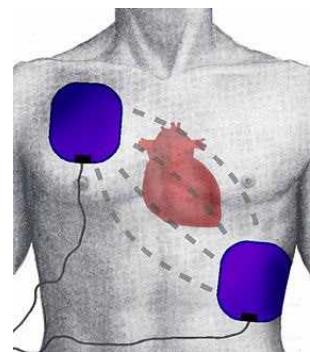
## DISPLAY/OPERATION OF ZOLL R SERIES

- Remove all clothing covering the patient's chest. Dry chest if necessary. If the patient has excessive chest hair, shave it to ensure proper adhesion of the electrodes. Can rip off hair with extra set of pads if razor not readily available in acute situations.
- Attach hands-free therapy electrodes in anteroapical position (pictured) or anteroposterior position



### Pearls:

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



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

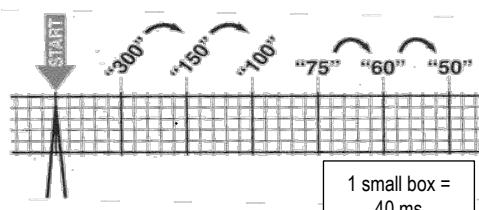
# Cardiology

# EKG Interpretation

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

## RATE (atrial, ventricular)

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

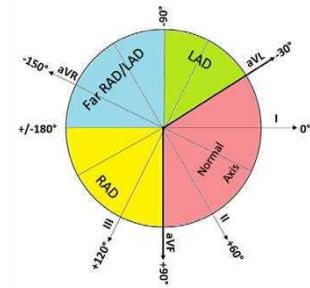


## RHYTHM (regular or irregular; sinus vs non-sinus)

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

## QRS AXIS (use direction of QRS complex)

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



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

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

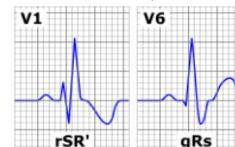
- P wave**: right and left atrial depolarization. Normal duration <120ms
- PR interval**: atrial depolarization, AV node and His-Purkinje conduction. Normally 140-200ms, changes with rate (shortened at faster rates, longer at lower rates) d/t autonomic effects on AV nodal conduction
- QRS**: ventricular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

**LAFB**: left axis deviation, QRS <120, qR in I, aVL and rS in II, III, aVF. Common, nonspecific

**LPFB**: right axis deviation, QRS <120, rS in I, aVL and qR in II, III, aVF. Rare to see in isolation, usually occurs with RBBB

**Bifascicular block**: RBBB with either LAFB or LPFB

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



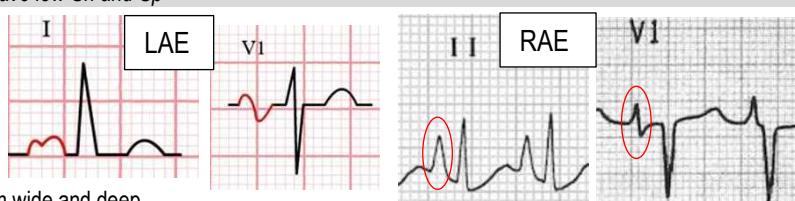
**LBBB**: QRS >120, wide negative QS in V1, wide tall R in I, aVL, V5, V6. Causes: primarily dilated cardiomyopathy (ischemia, infection, valvular, infiltrative).



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

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

- LVH**: Sokolow-Lyon criteria: S in V1 + R in V5 or V6 ≥35mm **OR** R in aVL ≥11mm. Cornell criteria: S in V3 + R in aVL >28mm (M) or >20mm (F). For non-voltage based criteria consider [Romhilt-Estes score](#)
- RVH**: R>S or R ≥7mm in V1, S ≥7mm in V5 or V6
- LAE**: P wave duration ≥120ms (>2.5mm), widely notched P (≥40ms), negative component of P in V1 >1mm wide and deep
- RAE**: P wave height >2.5mm in II ("P-pulmonae"), initial positive P wave in V1/V2 ≥1.5mm



## ISCHEMIA/INFARCTION (JACC 2009;53:1003)

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

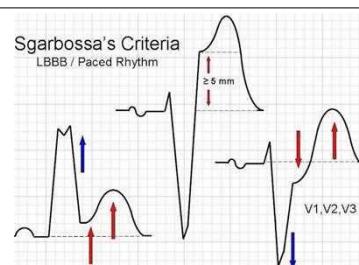
Diagnosis w/ STE	Characteristic ECG Findings
Acute STEMI	STE in $\geq 2$ contiguous leads in coronary distribution (see table), reciprocal STD
LVH	Concave STE in V1-V3 with STD and TWI in I, aVL, V5-V6, voltage criteria as above
LBBB	Concave STE in V1-V3, discordant with negative QRS
Acute pericarditis	Diffuse STE (usually $<5\text{mm}$ ), PR depression, amplitude of STE:T wave (in mm) $>0.26$ is specific
Printzmetal's angina/vasospasm	Transient STE in coronary distribution as in STEMI
Acute PE	STE in inferior and anteroseptal leads, mimics acute MI, complete or incomplete RBBB
Stress-induced cardiomyopathy (Takotsubo's)	Diffuse STE in precordial leads w/o reciprocal inferior STD, STE followed by deep TWI
Ventricular aneurysm	Persistent STE after MI, often with abnormal Q waves
Early repolarization	J point elevation $\geq 1\text{mm}$ in 2 contiguous leads (esp V4), amplitude of STE:T wave (in mm) $<0.25$
Brugada syndrome	rSR' and downsloping STE in V1-V2 (see below)
Male pattern	1-3mm concave STE, often highest in V2
Normal variant	STE in V3-V5, TWI, short QT, high QRS voltage
Cardioversion	Marked (often $>10\text{mm}$ ) and transient following DCCV

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

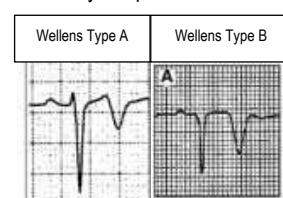
### Modified Sgarbossa Criteria:

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

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

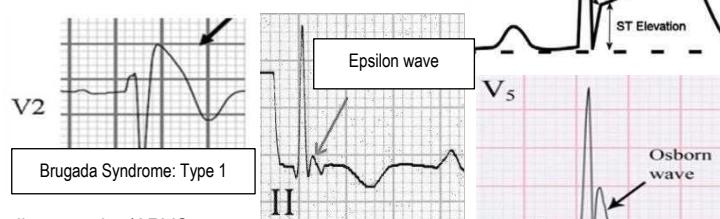


- Q wave:** usually a marker of scar, pathologic Q waves must be deep ( $>1\text{mm}$ ), 25% height of QRS, and 40ms long. More likely 2/2 prior MI if inverted T wave in same lead. Small "septal" Q physiologic in V5, V6, I, aVL
- Wellens Syndrome:** sign of **critical proximal LM or LAD lesion**, 75% MI in  $<2\text{w}$ . Often pain free with h/o angina. Normal/slightly elevated troponin. Type A: 25% biphasic (up then downsloping morphology) T waves in V2 and V3. Type B: 75% symmetric, deeply inverted precordial T waves. Isoelectric or minimally elevated ( $<1\text{mm}$ ) ST segment. No precordial Q waves ([Am J Emerg Med 2002;20:7](#); [Am Heart J 1982;103:730](#))



## OTHER

- Acute PE:** 10-25% nml EKG, nonspecific: sinus tach ( $\uparrow Sn$ ), RBBB, RAD/LAD, TWI V1-V4, inferior STE;  $\uparrow Sp/\downarrow Sn$ : S1Q3T3. High PPV when dx PE vs ACS: TWI in III+V1 ([Am J Card 2007;99:817](#); [Am J Emerg Med 2001;19:514](#))
- J-Point Elevation Syndromes:** J point is when QRS transitions to ST segment
  - Early repolarization pattern:** benign STE in absence of chest pain, terminal QRS slur, or terminal QRS notch
    - Suspicious features: FH of sudden cardiac arrest or early unexplained death, eval and workup suggestive of channelopathy, h/o unheralded syncope suggestive of arrhythmogenic pathogenesis ([Circ 2016;133:1520](#))
  - Brugada Syndrome:** autosomal dominant SCN5A loss of function mutation in 10-30%, M>F, more common to have nocturnal cardiac arrest, p/w VT/VF or sudden cardiac death ([Circ Arrhythm Electrophysiol 2012;5:606](#))
  - Osborn wave:** hypothermia  $T < 93^\circ\text{F}$ , elevation of J point height ~ proportional to degree of hypothermia. More dome-shaped compared to Epsilon wave.
  - Epsilon wave:** found in arrhythmogenic right ventricular cardiomyopathy (ARVC); inherited, age 10-50, fibro-fatty replacement of RV myocardium → ventricular arrhythmias [[Circ 2005;112:3823](#)]), most Sp in V1 (30% with ARVC), low frequency, positive terminal deflection in V1-V3
- Electrolyte Abnormalities**



Abnormality	Characteristic ECG Findings
Hypokalemia	Prolonged QT, ST depression, flattened T wave, prominent U wave
Hyperkalemia	Peaked, <b>symmetric</b> T wave → flat P → prolonged PR $\pm$ AVB → widened QRS $\pm$ BBB (severe) → sinusoidal
Hypocalcemia	Prolonged QT, unchanged T wave
Hypercalcemia	Shortened QT

# Cardiology

## NARROW COMPLEX TACHYCARDIA (QRS <120ms)

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

Diagnostic approach & general principles:

1. Determine the width of the QRS complex
2. Determine if the rhythm is regular or irregular
3. Assess for the presence of p-waves (noting location, axis and morphology)
4. Compare to baseline ECG
5. Treatment (See ACLS: Tachycardia and Atrial Fibrillation/Flutter)
  - If unstable → synchronized cardioversion
  - If stable → vagal maneuvers (carotid massage/valsalva/ice water on face). Adenosine can resolve diagnostic dilemmas and treat AVNRT and AVRT (adenosine is blocked by theophylline/caffeine & potentiated by dipyridamole)
  - Acute treatment for all others is BB, CCB or amiodarone (use caution with pharmacologic cardioversion and consider ruling out intra-atrial clot if pt has been in Afib/flutter for > 48 hours and has not been anticoagulated for 3 weeks prior to cardioversion)

## Narrow Complex Tachycardia

Regular	Irregular
P-waves Characteristics	
Normal P	= Sinus
Abnormal P	= AT
Retrograde P	= AVRT, (or not visible) AVNTR, JT
Flutter waves	= AFL w/ variable block
	No P's = AFib
	≥3 different P's = MAT
	Flutter waves = AFL w/ variable block

### Regular, narrow complex tachycardias

#### Sinus Tachycardia (rate >100, maximum HR = 220-age)

Gradual onset

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

#### Ectopic Atrial Tachycardia (AT) (atrial rate 100-200)

Due to abnormal automaticity at a single atrial focus, other than the SA node or due to a reentrant circuit within the atria

Discrete P waves present, but of abnormal morphology +/- axis (i.e. p wave inverted in

Classic digoxin toxicity is AT w/ variable AVB

Usually seen in otherwise normal hearts

#### Junctional Tachycardia

Due to increased automaticity within the AV node (or due to re-entrant rhythms, e.g., AVNRT)

P waves may be absent (e.g. buried within the QRS complex), inverted and/or retrograde

#### Atrioventricular Nodal Re-entrant Tachycardia (AVNRT) (rates 150–250)

Arises from functional re-entry within AV node

P wave, if visible, is retrograde (may be seen as a pseudo R-wave in lead V1, or pseudo S wave in lead II) – note that retrograde P waves appear earlier in AVNRT than in AVRT

Short RP (when conducting fast-slow), however more commonly no RP (when conducting slow-fast)

Trigger PAC (slow-fast) > PVC (fast-slow)

Young adults, F>M, usually arises within structurally normal hearts

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

Ventricular depolarization occurs via the AV node, however an accessory tract allows for retrograde conduction to the atria (if ventricular depolarization occurs via the accessory tract, the resultant QRS is wide and is termed "anti-dromic, see WCT)

Retrograde P waves may be present (if so, they appear later than those seen in AVNRT)

### Irregular, narrow complex tachycardias

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

Discrete P waves present, of ≥3 morphologies Irregular due to varying PP, PR, and RR intervals Seen in COPD, pHTN, CAD, electrolyte disarray, aminophylline/theophylline use

#### Atrial Fibrillation (AF)

No coordinated atrial activity (P wave absent), irregular, fibrillatory waves present

Arises from numerous re-entrant tracts in atria or pulmonary veins

If associated with pre-excitation, the result is an irregular, WCT

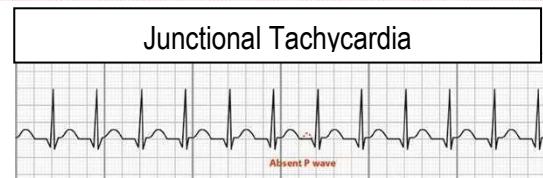
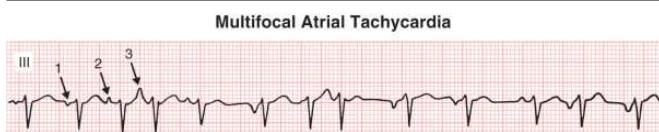
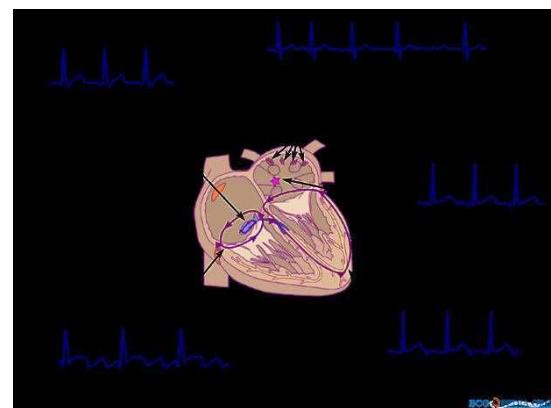
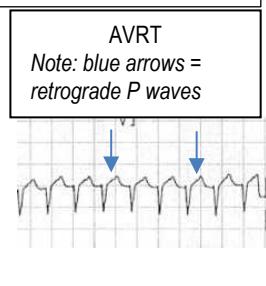
#### Atrial Flutter (AFL) (P waves present at rate of 250-300)

Arises from true (isthmus-dependent, typical) or functional (isthmus-independent, atypical) re-entry in R atrium May be regular (e.g. 2:1, 3:1, 4:1, etc.) or irregular (if variable AV block)

Counterclockwise: negative flutter waves in II, III, aVF

Clockwise: positive flutter waves in II, III, aVF

No isoelectric baseline, atrial rate ~300, always >250, usually with 2:1 conduction but can have variable conduction



# Cardiology

# Wide Complex Tachycardia

## WIDE COMPLEX TACHYCARDIA (QRS $\geq 120$ ms)

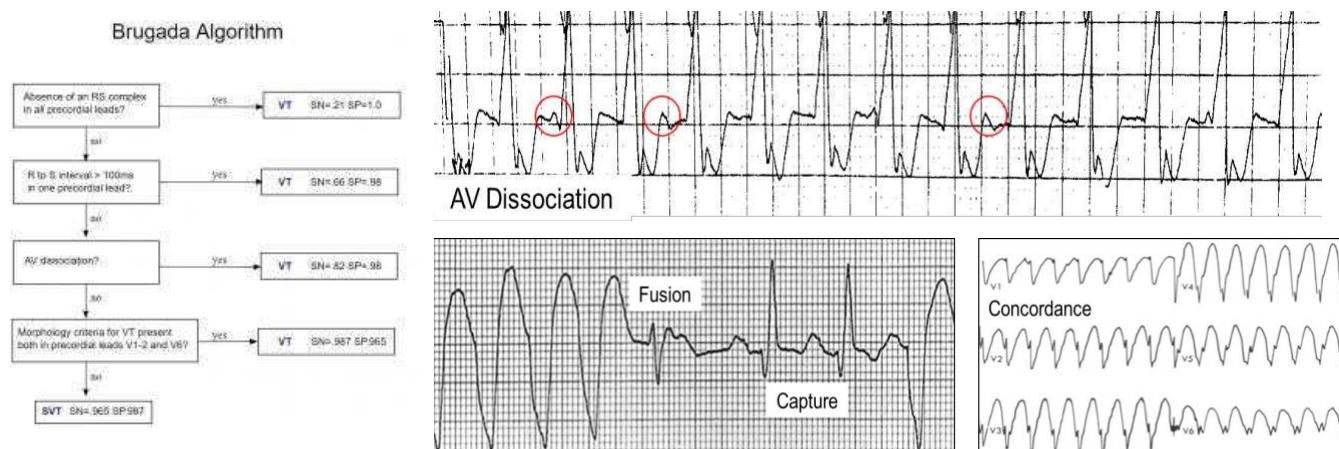
### Etiology

- Ddx: VT (80%), SVT with aberrant conduction, and pacemaker-mediated tachycardia

ECG Factors that Favor VT	ECG Factors that Favor SVT with Aberrancy
<ul style="list-style-type: none"> <li><b>Very wide QRS</b> (<math>&gt;160</math> msec)</li> <li><b>Superior axis</b> (II, III, aVF neg) or <b>northwest axis</b> (I, aVF neg)</li> <li><b>AV dissociation</b> (often V rate <math>&gt;</math> A rate) <math>\rightarrow</math> diagnostic of VT</li> <li><b>Concordance</b>: all QRS across precordium completely positive or completely negative</li> <li>Partial (<b>fusion beat</b>) or complete (<b>capture beat</b>) depolarization of ventricle by underlying supraventricular rhythm</li> <li><b>R wave peak time <math>\geq 50</math> msec</b> (measured in lead II)</li> <li>Brugada criteria (<a href="#">Circ 1991;83:1649</a>) (only applicable if rhythm is regular); R-wave peak time criteria (<a href="#">Heart Rhythm 2010;7:922</a>); VT score (<a href="#">Europace 2016;18:578</a>)</li> </ul>	<ul style="list-style-type: none"> <li><b>Pre-existing BBB</b> <math>\rightarrow</math> functional/rate-dependent BBB d/t encroachment on bundle refractory period; RBBB <math>&gt;</math> LBBB</li> <li>QRS with sharp initial deflection followed by broad terminal deflection</li> <li><b>Pre-excitation</b> on baseline ECG <math>\rightarrow</math> antidromic AVRT or pre-excited atrial fibrillation</li> <li><b>R wave peak time <math>&lt; 50</math> msec</b> (measured in lead II)</li> </ul>

### Other important considerations:

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

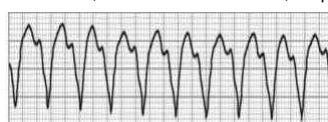


## MANAGEMENT OF VT (also see ACLS: Tachycardia)

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

### Monomorphic VT

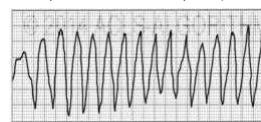
DDx: ischemia, structural heart disease, idiopathic



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

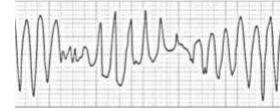
### Polymorphic VT

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



- Evaluate for **ischemia** & need for revascularization
- Stable**  $\rightarrow$  magnesium 2-4g over 10-15min, 1HR above intrinsic rate (dopa, epi, iso, burst overdrive pacing),  $\downarrow$  QTc (**lido**), avoid bradycardia (amio, CCB/BB)
- Unstable**  $\rightarrow$  defibrillation

### Torsades de Pointes



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

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

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

# Cardiology

# Atrial Fibrillation & Flutter

## ATRIAL FIBRILLATION

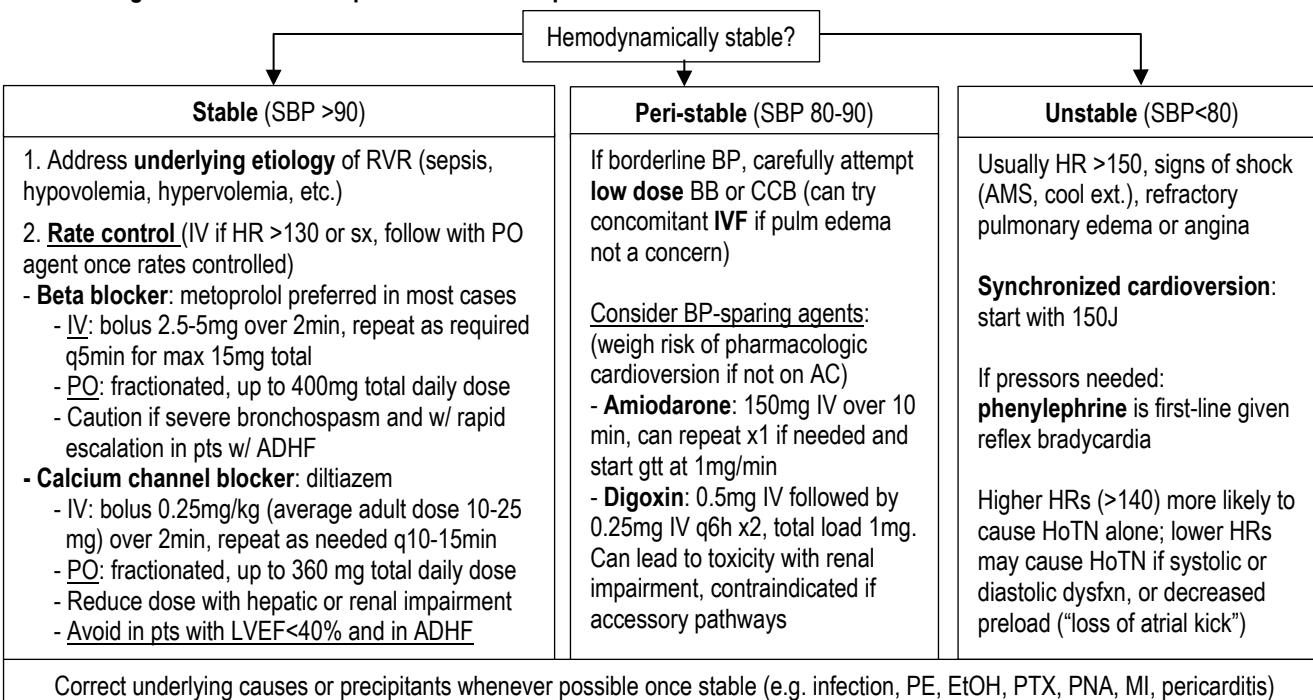
Epidemiology ([Heart Rhythm 2012;9:632](#))

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

## Clinical Evaluation of New-Onset AF

- H&P: presence & timing of sx, HTN, DM, valve dz, HF, angina, congenital heart disease, OSA, FH of AF, acute precipitants (e.g. EtOH, thyrotoxicosis, sympathomimetic drugs, surgery, MI, myocarditis, PE, acute pulmonary disease, infection)
- ECG: absence of discernible p waves, irregularly irregular R-R intervals (if regularized, may represent escape rhythm and CHB)
- TTE: LV function, LA/RA size, valve function, pulmonary HTN, LA thrombus (better visualized with TEE)
- CXR: evaluate for pulmonary parenchymal processes, pulmonary vasculature/edema
- Labs: TFTs, LFTs, BUN/Cr, CBC, NT-proBNP
- May also need longer term rhythm monitoring (Holter, Zio patch). Consider stress test if signs/sx of ischemic heart disease.
- Smartwatch notification has PPV 0.84 for AF on subsequent simultaneous EKG in patients > 65 ([NEJM 2019; 381:1909-1917](#))

## Acute Management of AF with Rapid Ventricular Response



**Cardioversion** (ALWAYS consider high risk of embolic stroke if any breaks in AC for 3 weeks prior)

- Indications**: Urgent: ischemia, end-organ hypoperfusion, symptomatic hypotension, severe pulmonary edema; Elective: new-onset AF or unacceptable symptoms from persistent AF
- Synchronized Electrical Cardioversion** (DCCV): start with 150J (biphasic), increase energy stepwise if sinus rhythm not achieved. See ACLS: *Cardioversion*.
- Chemical Cardioversion**: success rate significantly higher for acute (<7d) compared with longer duration AF
  - Pill-in-pocket (flecainide, propafenone, dofetilide, ibutilide)
  - Amiodarone (IV infusion weakly effective for cardioversion, PO load over 3-4w, 27% rate of cardioversion)
- Anticoagulation** (applies to BOTH chemical and electrical)
  - Pre-cardioversion: if definitive new onset **<48h**: may proceed without anticoagulation. If Afib onset **>48h or unclear**: anticoagulate for 3w prior to cardioversion or obtain TEE immediately prior to cardioversion ([NEJM 2001;344:1411](#))
  - Post-cardioversion: anticoagulate for at least **4 weeks after cardioversion** (risk of myocardial stunning and AF recurrence, but unproven efficacy). Anticoagulation 4 weeks after reversion to sinus rhythm is based on CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores

## Risk Assessment

- CHA<sub>2</sub>DS<sub>2</sub>-VASc**: 1pt for **CHF**, **HTN**, **Age 65-74**, **DM**, female **Sex**, **Vascular disease**; 2pt for **Age≥75**, **Stroke/TIA**. CHA<sub>2</sub>DS<sub>2</sub>-VASc > CHADS<sub>2</sub> in "truly low risk" subjects ([Thromb Haemostasis 2012;107:1172](#))

# Cardiology

# Atrial Fibrillation & Flutter

- Score 0 = no AC or ASA; Score 1 (in women) = no AC vs oral AC based on clinical judgment → how high is risk from specified risk factor? (e.g. HTN, DM, age bring greater risk compared to female sex, vascular dz); Score ≥2 (≥3 in women) = oral AC
- NOT used to guide decision making for HOCM or mitral stenosis (MS) with moderate severity or greater.
- **HAS-BLED**: risk stratification of bleeding risk w/ oral AC. HTN (SBP>160); abnl renal function (CrCl<50); liver disease (cirrhosis or Bili 2x ULN or AST/ALT/AlkPhos 3x ULN); stroke; bleeding history; labile INR (<60% in Rx range); elderly (>65y); antiplatelet meds (ASA, NSAID); alcohol (>8 drinks/w) or other drug use. Score ≥3 suggests caution and regular follow-up
- **SPARCTool** can aid in risk/benefit assessment and choice of anticoagulation

## Anticoagulation (AHA/ACC/HRS: [Circ 2019;140:e125](#), [Stroke 2010;41:2731](#))

- Tx recommended for all pts except CHA<sub>2</sub>DS<sub>2</sub>-VASc 0 or contraindications to anti-coagulation
- Subclinical AF is also associated w/ increased stroke/systemic embolism ([NEJM 2012;366:120](#))
- **DOACs vs warfarin**: DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) recommended > warfarin in all except w/ mod-severe mitral stenosis, HOCM, or mechanical valve. Warfarin may be > rivaroxaban in rheumatic heart dz ([NEJM 2022;387:978-988](#)). DOACs: ↓ risk of stroke, mortality, & ICH, ↑ risk of GIB ([Lancet 2014;383:955](#)), apixaban lowest GIB risk ([Annals 2022;175:1515-1524](#))
- **Dosing**: see *Anticoagulation Agents* for dosing. Dose-reduce apixaban to 2.5mg BID if 2/3: Cr ≥1.5, Wt ≤60kg, age ≥80
- **Renal impairment**: for pts w/ CrCl<15 or on dialysis, can use either warfarin or apixaban
- **Bridging AC**: see *Anticoagulation Management*
- Pts at low risk for thromboembolism may be maintained on ASA alone (see above), no reliable data to guide between 81 vs 325mg

## Left Atrial Appendage (LAA) closure

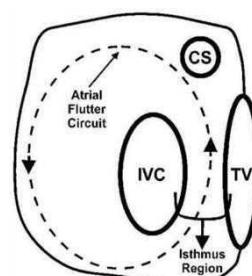
- LAA is the source of at least 90% of thrombi in pts with CVA and AF
- **Watchman device**: in non-valvular AF, device placement → comparable stroke prevention to warfarin with ↓ bleeding risk & improved mortality ([JACC 2017;70:2964](#)). AC can be discontinued 6w after LAA closure per MGH protocol
- **Surgical occlusion**: decreases risk of stroke and systemic embolism. Grade 1B recommendation for surgical occlusion only for patients undergoing cardiac surgery for another indication w/ CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥ 2 ([NEJM 2021;38422:2081](#))

## Long-Term Rate vs Rhythm Control

- Rate control noninferior to rhythm control for AF sx, CV mortality, & stroke risk ([AFFIRM](#), [RACE](#), [PIAF](#), [STAF](#), [HOT CAFÉ](#), [AF-CHF](#))
- Rhythm control (antiarrhythmics and AF ablation) superior to usual care (rate control) for patients with recently diagnosed AF (within 1 year) and concomitant CV conditions in decreasing CV mortality, stroke, and hospitalization for HF or ACS ([EAST-AFNET 4](#))
  - Consider **rhythm control** if persistent AF sx impairing quality of life, age <65, or comorbid HF (esp if systolic dysfxn)
  - Restoration of NSR may lead to increased quality of life & exercise performance ([NEJM 2005;352:1861](#); [JACC 2004;43:241](#))
- **Rate Control**
  - BB > CCB in achieving rate control (70% vs 54%), either alone or in combination with digoxin
  - **Digoxin** alone is moderately effective in controlling V-rate at rest (time to onset 3-6 hrs), ineffective w/ high adrenergic tone
    - Long-term digoxin a/w increased mortality in AF patients ([JACC 2018;71:1063](#))
  - **Targets**: lenient rate control (resting HR <110) non-inferior to strict (HR <80) w/ similar outcomes in CV death, stroke, bleeding, arrhythmia, & hospitalization for HF ([RACE II](#)). Strict HR (or rhythm) control may be beneficial in younger pts or pts w/ HF
  - Contraindications/Warnings: evidence of pre-excitation on ECG (in these patients, IV procainamide is 1<sup>st</sup> line), cautious use in high-degree AVB. CCB should not be used in pts with LVEF <40% given negative inotropy
- **Rhythm Control** ([Circ 2012;125:381](#))
  - **Choice of Agents:**
    - No structural heart disease: “pill-in-pocket” (flecainide/propafenone), dofetilide, dronedarone, sotalol, amiodarone
    - Structural heart disease: **CAD**: dofetilide, dronedarone, sotalol, amiodarone; **HF or LVH**: amio, dofetilide
  - “Pill-in-Pocket”: for pts with recent pAF and infrequent and well-tolerated episodes, ppx may have risk>benefit. PRN flecainide or propafenone at sx onset is safe and effective ([NEJM 2004;351:2384](#))
  - **Catheter ablation** (pulmonary vein isolation [PVI]): ↓ long-term AF recurrence rate vs AADs in both pAF ([MANTRA-PAF](#), [RAAFT-2](#)) & persistent AF ([EHJ 2014;35:501](#)). Ablation in pts w/ HF ↓ morbidity/mortality ([CASTLE-AF](#)). Ablation more effective than antiarrhythmic for maintaining sinus rhythm for pts w/ pAF. Cryoablation not yet established 1<sup>st</sup> line ([STOP-AF](#), [EARLY-AF](#))
  - **AV nodal ablation with PPM**: indicated when pharmacologic rate/rhythm control not achievable ([JACC 2014;64:2246](#))

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

- ECG: “sawtooth” P waves (F waves), atrial rate typically 250-300bpm w/ 2:1 conduction (~V-rate 150), though can be variable block, 3:1, or 4:1. 1:1 conduction can briefly precede VT/VF
  - **Type 1 (typical)**: reentrant loop in RA via cavo-tricuspid isthmus
    - Counterclockwise: more common, inverted flutter waves II, III, aVF + upright flutter waves V1
    - Clockwise: less common, upright flutter waves in II, III, aVF + inverted flutter waves in V1
  - **Type 2 (atypical)**: does not meet criteria for Type 1; is typically faster and often refractory to ablation
- **Anticoagulation**: risk of thromboembolism lower than AF ([J Stroke Cerebrovasc 2018;27:839](#)) but anticoagulation management is similar to AF ([Chest 2012;141:e531S](#))
- **Rate control**: similar strategies (BB, CCB) to AF, but more difficult to successfully rate-control
- **Rhythm control**: cavo-tricuspid isthmus (CTI) ablation for typical flutter >90% effective at 1y ([Circ Arrhythmia EP 2009;2:393](#))

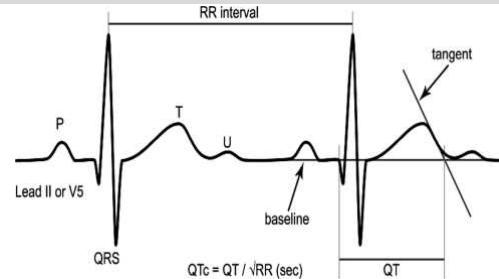


# Cardiology

# QTc Prolongation

## DEFINITION ([Circ 2009; 119: e241](#))

- QT interval correlates with repolarization time of ventricles
- Normal: ≤460ms; Borderline (adult): 460-479ms (female), 450-459ms (male)
- Measure from beginning of QRS to end of T wave in a lead with T wave > 2mm (best in II, V5), define end point using tangent from peak of steepest slope to isoelectric line; can use ECG or caliper function on telemetry
- QTc is QT corrected for HR; linear (i.e., Hodges/Framingham) formulas are recommended by [AHA \(J Electrocardiology 2004;37:81\)](#)
- Can be calculated using [MDCalc](#) or with formulas below:  
 $\text{Framingham} = \text{QT} + 0.154 * (1-\text{RR})$  |  $\text{Fridericia} = \text{QT}^{3/2}/\text{RR}$  |  $\text{Hodges} = \text{QT} + 1.75 * (60/\text{RR}-60)$  |  $\text{Bazett} = \text{QT}/\sqrt{\text{RR}}$  |  $\text{Rautaharju} = \text{QT} * (120+\text{HR})/180$ 
  - Framingham and Fridericia provide best rate correction and mortality prediction ([JAHA 2016;5:e003264](#))



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

- Bundle branch blocks [lengthen QT interval](#); can calculate using [Mayo calculator](#), or obtain rough estimate using QT - (QRS-120)
  - $\text{JT prolongation index} = \text{JT} * (\text{HR} + 100)/518$  where JT is distance between J point and end of T, with a JTI ≥112 identifying repolarization prolongation in all ventricular conduction defects ([J Electrocardiology 1992;25:131](#))

## CONGENITAL LONG-QT SYNDROMES

- Majority of pts are asymptomatic, often discovered on ECG or QTc prolonged more than should be expected by drugs, etc.
- Sx: presyncope/syncope, hemodynamic compromise, sudden cardiac death; triggered by exercise, stress
- Tx: beta blockers, ICD if previous cardiac arrest and expected survival >1y ([Circ 2006;114:e385](#))

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

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

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

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

Class of Drug	QT-Prolonging Drugs: [common, high-risk, (low-risk)] ( <a href="#">NEJM 2004;350:1013; Br J Clin Pharm 2010;70:16</a> )
Antiarrhythmics	CLASS IA/C: <a href="#">quinidine</a> , <a href="#">disopyramide</a> , <a href="#">procainamide</a> , flecainide, propafenone CLASS III: <a href="#">sotalol</a> , <a href="#">dofetilide</a> , <a href="#">ibutilide</a> , <a href="#">dronedarone</a> , <a href="#">amiodarone</a> - oral <a href="#">amiodarone</a> rarely associated w/ TdP due to uniform delay in repolarization across myocardium
Antimicrobials	ANTIBIOTIC: <a href="#">azithromycin</a> , erythromycin, clarithromycin, <a href="#">levofloxacin</a> , moxifloxacin, ( <a href="#">ciprofloxacin</a> ), ( <a href="#">metronidazole</a> ) ANTIFUNGAL: <a href="#">fluconazole</a> , voriconazole, ( <a href="#">ketoconazole</a> ) ANTI-MALARIAL: <a href="#">quinine</a> , <a href="#">quinidine</a> , chloroquine, (hydroxychloroquine)
Antipsychotics	<a href="#">haloperidol IV</a> , <a href="#">thioridazine</a> , <a href="#">chlorpromazine</a> , <a href="#">ziprasidone</a> , <a href="#">quetiapine</a> , <a href="#">risperidone</a> , <a href="#">olanzapine</a> , haloperidol oral, clozapine
Antidepressants	Clomipramine, imipramine, <a href="#">citalopram</a> , <a href="#">escitalopram</a> , ( <a href="#">fluoxetine</a> ), ( <a href="#">sertraline</a> ), ( <a href="#">trazodone</a> ), ( <a href="#">mirtazapine</a> )
Anti-emetics	<a href="#">ondansetron IV&gt;oral</a> , droperidol, ( <a href="#">metoclopramide</a> )
Others	<a href="#">Methadone</a> , <a href="#">propofol</a> , <a href="#">hydroxyzine</a> , ( <a href="#">loperamide</a> ), ( <a href="#">albuterol</a> ), ( <a href="#">donepezil</a> )

## MONITORING FOR QT/QTC PROLONGATION

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

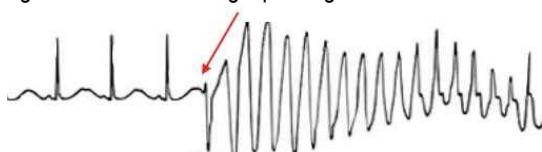


Illustration: Modified from Circ EP 2019;12:12

## MANAGEMENT OF ACQUIRED LONG QT

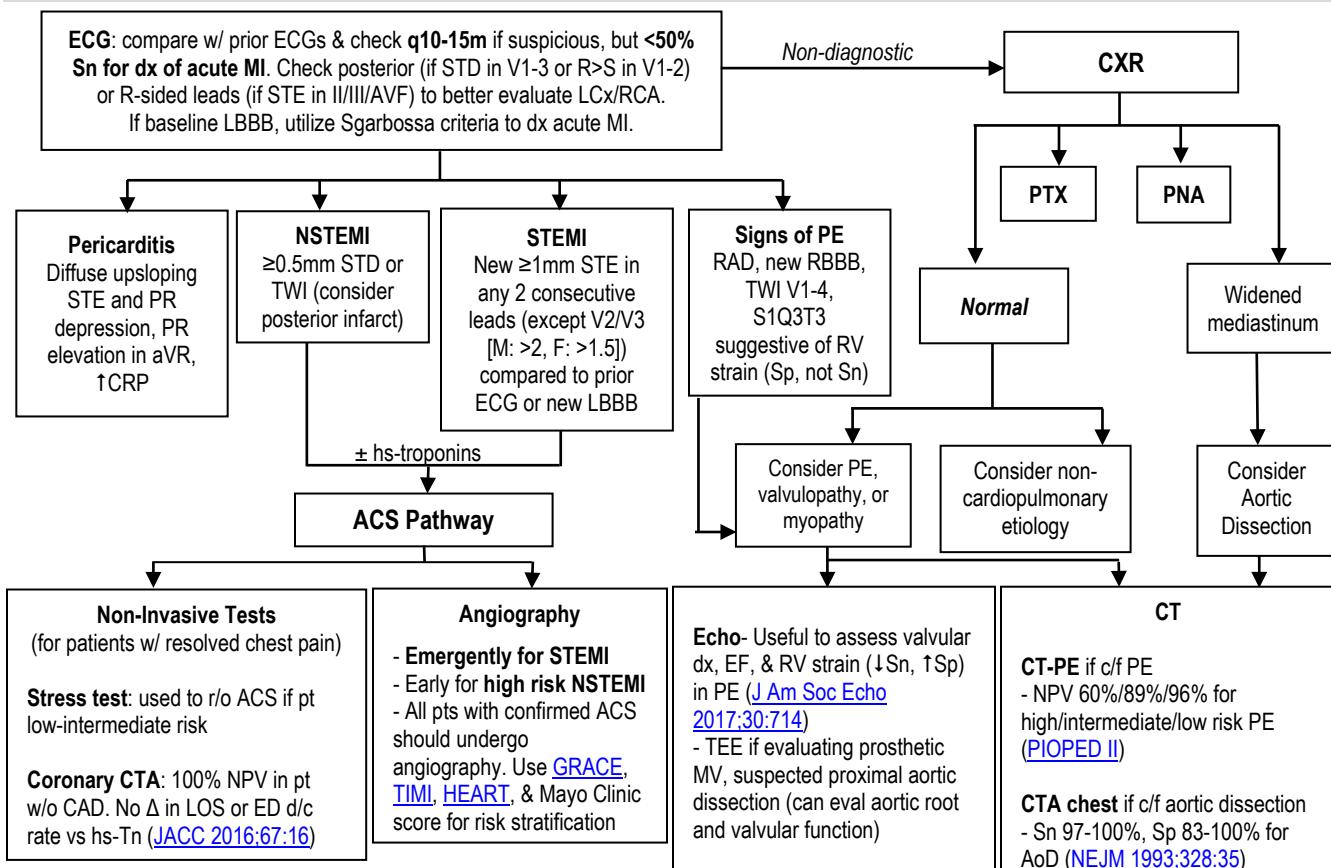
- Stop offending drug if QTc > 500ms or increase in QTc of > 60ms
- ECG should be checked for bradyarrhythmias & signs of impending TdP ([RonT](#), above). Stop drugs causing bradycardia.
- Check electrolytes & consider repleting (K > 4, Mg > 2). Supratherapeutic repletion of K to 4.5-5.0 can be used in pts on QT-prolonging drugs who have had TdP

# Cardiology

# Chest Pain

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

## BASIC CHEST PAIN ALGORITHM



# Cardiology

# Acute Coronary Syndrome

## DEFINITIONS AND EVALUATION

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

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

- **Type 1 MI:** spontaneous plaque rupture, ulceration, fissure, erosion, dissection → intraluminal thrombus
- **Type 2 MI:** supply-demand mismatch that is not atherothrombosis – most commonly due to sepsis/infection, arrhythmias, severe anemia, renal failure, surgery, hypertension, and heart failure; other causes include vasospasm, microvascular ischemia (e.g. Takotsubo), non-plaque thromboembolism (e.g. infectious via PFO), aortic dissection, vasculitis, steal ([Circulation 2019;140:1661](#)).
  - Must have a **clear** precipitating factor. If not, treat as a type 1 MI until further evaluation
  - 50-70% have obstructive CAD – reasonable to initiate ASA, BB, and high-intensity statin

Evaluation of CP with hsTnT				
Emergency Department – CP onset ≥3h PTA	Inpatient or Emergency – CP onset < 3h			
Check hsTnT <b>immediately</b> and at <b>1h</b>	Check hsTnT <b>immediately</b> and at <b>3h</b>			
<u>Rule in:</u> hsTnT ≥52 OR Δ ≥5 from baseline → consider ACS	<u>Rule in:</u> hsTnT ≥10 (F) or ≥15 (M) AND Δ ≥7 from baseline AND sx or ECG changes or concerning imaging (CCTA, cath) → consider ACS			
<u>Rule out:</u> hsTnT <10(F) or <12(M) AND Δ <3 from baseline → <b>unlikely ACS</b>	<u>Rule out:</u> no significant Δ in 3h → <b>unlikely ACS</b>			
Intermediate: calculate <a href="#">HEART score</a> , repeat hsTnT in 3h and apply inpatient criteria (right)				
STEMI	NSTEMI	Unstable Angina		
<ul style="list-style-type: none"> <li>• 1mm STE in two contiguous leads (if V2-V3: &gt;2.5mm in M&lt;40, 2mm in M&gt;40, 1.5mm in F) OR new LBBB AND <math>\oplus</math> biomarkers</li> <li>• If baseline LBBB, use Sgarbossa's criteria: ≥1 mm concordant STE, 1 mm STD V1-V3, ≥ 5 mm discordant STE</li> <li>• Electrically Silent: LCx or RCA lesions. Consider posterior V7-V9 leads, in which STE&gt;0.5mm is diagnostic. Other changes: large R in V2-V3, STdep in anterior leads (mirror image effect)</li> </ul>	$\oplus$ ECG or hx, $\oplus$ biomarkers	$\oplus$ ECG or hx, $\ominus$ biomarkers		
<b>RESPONDING CLINICIAN or MED SR</b> <b>READ ECG</b> <b>ESCALATE</b>	<b>STEMI CRITERIA</b> <ul style="list-style-type: none"> <li>✓ NEW ST elevation:           <ul style="list-style-type: none"> <li>▪ ≥ 1 mm in at least two contiguous leads</li> <li>▪ ≥ 2 mm (men) or ≥ 1.5 mm (women) in V2-V3</li> </ul> </li> <li>✓ NEW ST depression in at least two leads V1–V4</li> <li>✓ NEW Multi-lead ST depression with ST elevation in aVR</li> <li>✓ NEW Left Bundle Branch Block with acute symptoms</li> </ul> <p> Start .AcuteMIMGH SmartPhrase in Epic to provide relevant information to clinical team</p> <p><b>ONE OR MORE STEMI CRITERIA MET?</b></p> <table border="1"> <tr> <td><b>YES</b> Call Cath Emergency STEMI Line <b>x6-8282</b></td> <td><b>UNCERTAIN</b> STAT page General Cardiology Consult*: "Suspect Acute MI"</td> </tr> </table> <p><small>*See Partners Phone Directory for on-call info</small></p>	<b>YES</b> Call Cath Emergency STEMI Line <b>x6-8282</b>	<b>UNCERTAIN</b> STAT page General Cardiology Consult*: "Suspect Acute MI"	<b>Clinical Evaluation &amp; Risk Stratification:</b> <ul style="list-style-type: none"> <li>• Consider pt's baseline CAD risk. Review prior stress test and cath data. ↑ risk of MI w/ resp infxn (esp flu) (<a href="#">NEJM 2018;378:345</a>)</li> <li>• Treat secondary causes of myocardial demand</li> </ul> <p><b>ECG:</b> (<a href="#">NEJM 2003;348:993</a>)</p> <ul style="list-style-type: none"> <li>• Obtain serial tracings (q15-30min) if initial ECG non-diagnostic in pts with compelling hx &amp; sx</li> <li>• Non-STE ischemic EKG changes: ≥0.5mm STD (horizontal, downsloping), new TWI ≥1mm or normalization ("pseudonormalization") of prior TWI in s/o sx</li> </ul> <p><b>Cardiac Biomarkers:</b></p> <ul style="list-style-type: none"> <li>• hsTnT 99<sup>th</sup> %ile among normal subjects: M 15ng/L, F 10ng/L</li> <li>• 75% of healthy individuals will have measurable hsTnT</li> <li>• hsTnT peaks within 12-48 hrs, normalizes in 5-14 days</li> </ul>
<b>YES</b> Call Cath Emergency STEMI Line <b>x6-8282</b>	<b>UNCERTAIN</b> STAT page General Cardiology Consult*: "Suspect Acute MI"			

## REVASCULARIZATION

- **PCI Indications:** recommended over fibrinolysis at a PCI-capable center in patients with STEMI <12h symptom onset
  - **STEMI:** door to device ideally <60min at PCI centers. PCI regardless of time from onset for cardiogenic shock, malignant arrhythmia (recurrent sustained VT, VF), persistent STE and/or CP. Late PCI (>48h post-event) not indicated in stable pts ([NEJM 2006;355:2395](#)); if PCI delayed (>120min from first medical contact), worse outcomes -- consider fibrinolysis ([Eur Heart J 2020;4:858](#))
  - **NSTEMI/UA:** see "Risk Stratification" above
- **PCI Strategies:** **Access:** radial > fem | **Stent:** DES > BMS ([NEJM 2016;375:1242](#))
  - STEMI without cardiogenic shock: complete revascularization strategy (culprit + non-culprit) has ↓ risk of CV death and MI at 3y (COMPLETE, [NEJM 2019;381:1411](#))
  - STEMI with cardiogenic shock: culprit-lesion only PCI has a ↓ risk of death/RRT (CULPRIT-SHOCK, [NEJM 2018;379:1699](#))
- **CABG:** preferred for 3VD ([NEJM 2009;360:961](#)), L main disease ([Lancet 2016;388:2743](#); [NEJM 2016;375:2223](#)), 2VD with prox LAD stenosis or EF <50%, DM + 2VD w/ involvement of LAD ([NEJM 2012;367:2375](#)). (Guideline: [Circulation 2022;145:4](#)).
- **Fibrinolysis:** inferior to PCI ([Lancet 2003;361:9351](#)); consider in STEMI with symptom onset <12 hours (12-24 hours reasonable) if first medical contact to device time anticipated >120 minutes. Contraindicated in ↑bleeding risk (esp ICH), suspected dissection, ischemic stroke <3 months prior, severe HTN ([Circulation 2012;127:362](#)).
  - Door to needle ideally <30 minutes. Tenecteplase (TNK-tPA), reteplase (rPA), alteplase (tPA) > streptokinase.
  - **Adjuncts:** Load with ASA (325mg; continued indefinitely at 81mg) and clopidogrel (300mg if ≤75, 75mg if >75; continued for at least 14 days to 1 year at 75mg), AC with heparin or Lovenox for 48 hours ([Circulation 2016;134:123](#)).

# Cardiology

# Acute Coronary Syndrome

## RISK STRATIFICATION FOR PCI TIMING IN NSTEMI/UA

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

## ADJUNCTS TO REVASCULARIZATION

- ASA:** established mortality benefit, give to all pts in an immediate load/maintenance strategy (325mg/81mg) ([Lancet 1988;2:8607](#))
- P2Y12 Inhibitors:** ([pre-cath load not done at MGH](#), controversial benefit & may delay CABG by 5-7 days ([Circulation 2022;145:4](#)).
  - Ticagrelor:** ↓mortality compared to clopidogrel w/o increasing major bleeding. Reversible with platelet transfusion. Side effect: **dyspnea** (14-21%, often mild & transient, but can be severe enough to warrant discontinuation), risk of pneumonitis w/ alveolar hemorrhage. Avoid in liver disease, prior CVA, oral AC (PLATO, [NEJM 2009;361:1045](#)).
  - Prasugrel:** ↓death, MI, CVA compared to ticag ([NEJM 2019;381:1524](#)). Contraindicated if prior TIA/CVA, wt <60kg, or >75y
  - Clopidogrel:** ↓death, repeat MI when load/maintenance with PCI ([Lancet 2001;358:5271](#)). Prodrug, metabolized by CYP219, less effective in those with LOF allele ([NEJM 2009;360:354](#)). May benefit from PPI ppx for LUGIB ([NEJM 2010;363:1909](#)). ↓Bleeding compared to ticagrelor and prasugrel but ↑ischemic events ([Circulation 2020;142:150](#)).
  - Cangrelor:** IV reversible inhibitor with immediate onset and return of platelet function in 1h. Used in pts with recent PCI who are unable to take PO or are periprocedure, needs pharmacy approval
- Nitrates:** TNG SL (0.3-0.6mg) x3, if refractory → gtt (start 5-10mcg/min). Nitropaste and gtt have shorter half-life than SL if c/f HoTN. No mortality benefit. Caution in inferior MI/RVMI, SBP<100, or PDEi use in last 48h. If refractory CP indication for earlier cath.
- Anticoagulation:**
  - UFH:** usually stopped after 48h if ECG changes improving and concern for ongoing ischemia resolved ([BMJ 1996;313:652](#)). Start gtt w/ bolus and use **low intensity PTT goal** (63-83). No bolus if giving lytics or if on warfarin and INR<2
  - LMWH:** possible reduction in death w/ minimal evidence for ↑major bleeding, trials vs UFH largely null ([BMJ 2012;344:e553](#))
  - Fondaparinux:** preferred to UFH/LMWH if medically managed. Contraindicated in PCI ↑catheter thrombosis/complications ([JAMA 2006;295:1519](#))
  - GPIIb/IIa Inhibitors:** eptifibatide (Integrilin) used at MGH. Initiated in cath lab if PCI high-risk (extensive thrombus)
  - Bivalirudin/Argatroban:** direct thrombin inhibitor, preferred for patients w/ HIT, otherwise cost does not outweigh benefit
- Beta Blockers:** start within 24h (1B for STEMI, 1A for NSTE-ACS), mortality benefit. Consider early initiation if ischemic arrhythmias present. Not indicated for stable ischemic heart disease s/p cath, but rec'd after CABG ([Circulation 2022;145:4](#))
  - Caution in decompensated HF, ↑risk for cardiogenic shock (>70y, SBP <120, HR >110 or <60)
  - Contraindications: cocaine-induced MI, PR>240ms, 2nd or 3rd degree AVB, severe bronchospasm ([Lancet 2005;366:1622](#))
- ACEi or ARB:** start ACE within 24h in all patients if BP/renal function normal (2a;LOE:A for STEMI) but mortality benefit (1; LOE:A) in anterior STEMI; use ARB if intolerant of ACE. ARB > ACE in patients with HF or LVEF <40% ([Circulation 2008; 117:269](#)).
- Aldosterone antagonist:** s/p MI on ACE and BB, and have LVEF<=40 + DM or sx of HF (1;LOE:B) ([Circulation 2008; 117:269](#))
- Statins:** atorvastatin 80mg daily regardless of baseline LDL ([NEJM 2004;350:1495](#))
  - Early high-dose statin within 24-96h may reduce death/adverse cardiac events if given pre-PCI ([JACC 2009;54:2157](#); [JAMA 2018;319:1331](#)). Early anti-inflammatory effect may stabilize plaque ([JAMA 2001;285:1711](#); [JAMA 2004;291:1071](#))
- Morphine:** not recommended. Consider only if unacceptable level of pain refractory to TNG, careful if suspicious for inferior MI/RVMI
- Discontinue NSAIDs:** ↑risk of mortality, re-infarction, HF, and myocardial rupture after ACS

## SECONDARY PREVENTION

- Aspirin:** 81mg w/o enteric coating indefinitely (should be chewed) ([NEJM 2010;363:930](#))
- Dual antiplatelet therapy (DAPT):** ACS: DAPT for at least 12 months; stable ischemic disease: DAPT after DES for at least 6 months, BMS at least 1 month, CABG 12 months ([Circ 2016;134:e123](#)). Use [DAPT score](#) to help risk stratify. Evolving movement to shorten DAPT duration (TWILIGHT [NEJM 2019;381:2032](#); TICO [JAMA 2020;323:2407](#); STOPDAPT-2 [JAMA 2019;321:2414](#); SMART CHOICE [JAMA 2019;321:2428](#); GLOBAL LEADERS [Lancet 2018;392:940-949](#); MASTER DAPT [NEJM 2021;385:1643-1655](#)). Bottom line: In select patients, single agent P2Y12 inhibitor after 1-3 months (vs. longer duration DAPT) is non-inferior in reduction of cardiovascular events, with reduced bleeding risk.
- Beta blockers:** as above
- ACEi or ARB:** as above
- Statins:** high intensity statin (atorvastatin 40-80mg or rosuvastatin 20-40mg qd) indefinitely for pts ≤75y, moderate intensity in >75y
  - If very high risk clinical ASCVD w/ LDL-c>70 mg/dL, add **ezetimibe** and consider PCSK9i ([JACC 2019;73:3168](#))
- AF + PCI:** P2Y12 inhibitor + DOAC > triple therapy. ↓bleeding and non-inferior for ischemic events (AUGUSTUS [NEJM 2019;380:1509](#); RE-DUAL PCI [NEJM 2017;377:1513](#); [NEJM 2016; 375:2423](#)). (Guideline [JACC 2021;77:629](#)). See [Anticoagulation Management](#)
  - Common practice example: initiate triple therapy (ASA/clopidogrel/AC) for 1-4wks and d/c ASA → AC + clopidogrel
- Lifestyle:** smoking cessation, BP <140/90 (if DM or CKD, <130/80), cardiac rehab (1; LOE:B), depression screening

**MGH P2Y<sub>12</sub> SWITCHING GUIDELINES** ([Ellucid policy](#), does not apply to patients on triple therapy)

# Cardiology

# MI Complications

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

	Complication	Prevalence / Risk Factors	Timing / Clinical Signs	Evaluation	Treatment
EARLY COMPLICATIONS (Hours – Days)	Cardiogenic Shock (see Inpatient HF)	<ul style="list-style-type: none"> <li>STEMI ~6%</li> <li>NSTEMI ~3%</li> <li>Anterior MI, LBBB, prior MI, 3VD, age, HTN, DM, mechanical complications</li> <li>50% of post-MI death</li> </ul>	<ul style="list-style-type: none"> <li>STEMI: 50% develop shock w/in 6h of MI, 75% w/in 24h</li> <li>NSTEMI: 72-96h after MI</li> <li>New CP, cold/wet physiology, HoTN, tachycardia, dyspnea, JVD, rales, new murmur</li> </ul>	<ul style="list-style-type: none"> <li>TTE</li> <li>PAC (CI&lt;2.2, PCWP&gt;18)</li> <li>End organ hypoperfusion (lactic acidosis, AKI)</li> </ul>	<ul style="list-style-type: none"> <li>Inotropes/pressors</li> <li>Emergent PCI/CABG (&lt;75y + STEMI + shock w/in 36h of MI). SHOCK trial (<a href="#">NEJM 1999;341:625</a>)</li> <li>IABP and other MCS</li> </ul>
	Myocardial Free Wall Rupture (Pseudoaneurysm: LV defect contained by only pericardium, scar, more prone to rupture than true aneurysm)	<ul style="list-style-type: none"> <li>0.01% STEMIs &amp; NSTEMIs</li> <li>Transmural MI, 1-vessel MI, 1<sup>st</sup> MI (poor collaterals), anterior &amp; lateral MI, HTN, late thrombolysis (&gt;14h), fibrinolysis&gt;&gt;PCI, NSAIDs, female, age &gt;70</li> <li>10% post-MI death</li> </ul>	<ul style="list-style-type: none"> <li>40% w/in 24h, 85% w/in 1w</li> <li>Tamponade in 85%</li> <li>Electromechanical dissociation, aberrant T wave evolution, abrupt episodes of ↓HR/BP</li> </ul>	<ul style="list-style-type: none"> <li>TTE (pericardial effusion w/ high acoustic echoes indicating clot)</li> <li>STAT cardiac surgery consult</li> </ul>	<ul style="list-style-type: none"> <li>Emergent surgery for resection of ruptured myocardium w/ primary reconstruction</li> </ul>
	Interventricular Septal Rupture (VSD)	<ul style="list-style-type: none"> <li>0.21% STEMIs, 0.04% NSTEMIs</li> <li>1<sup>st</sup> MI, 1-vessel MI (esp. LAD), CKD, anterior infarct w/ inferior STE due to wrap-around LAD, older age, female</li> <li>5% of post-MI death</li> </ul>	<ul style="list-style-type: none"> <li>Bimodal: 24h &amp; 3-5d to up to 2w from event</li> <li>New, harsh holosystolic murmur (50% w/ thrill), S3, loud P2, hypotension, BiV failure (R&gt;L)</li> </ul>	<ul style="list-style-type: none"> <li>TTE w/ doppler (L to R shunt, RV overload)</li> <li>RHC: increase in O2 sat from RA to PA &gt;5, large V waves</li> </ul>	<ul style="list-style-type: none"> <li>Emergency surgery or transcatheter closure device</li> <li>Vasodilators (use cautiously) to decrease L to R shunt (nitroprusside or nitroglycerin)</li> <li>IABP</li> </ul>
	Papillary Muscle Rupture (leading to acute MR)	<ul style="list-style-type: none"> <li>0.05% STEMIs, 0.01% NSTEMIs</li> <li>Posteromedial (supplied by PDA, with inf. or post. MI) &gt;&gt; anterolateral (dual blood supply by LAD and LCx)</li> <li>5% of post-MI death</li> </ul>	<ul style="list-style-type: none"> <li>No reperfusion: 2-7d</li> <li>With reperfusion: median 13h</li> <li>Abrupt dyspnea, pulmonary edema, hypotension</li> <li>Hyperdynamic LV, holosystolic murmur at apex (radiates to LSB w/ posterior pap muscle rupture), murmur may be absent in torrential MR or severe HF</li> </ul>	<ul style="list-style-type: none"> <li>TTE (MR)</li> <li>CXR: edema (can be asymmetric to RUL if MR jet directed at right pulmonary veins)</li> <li>Tall c-v wave in PCWP tracing</li> </ul>	<ul style="list-style-type: none"> <li>Aggressive afterload reduction (nitroprusside or nitroglycerin)</li> <li>IABP</li> <li>Emergency surgery</li> </ul>
LATE COMPLICATIONS (Weeks – Months)	LV Aneurysm (discrete, dyskinetic area of LV with broad neck, rarely ruptures)	<ul style="list-style-type: none"> <li>No reperfusion: 10-30%</li> <li>Apical-anterior wall &gt;&gt; inferior posterior</li> <li>Steroids, NSAIDs</li> </ul>	<ul style="list-style-type: none"> <li>Days to weeks</li> <li><u>Acute</u>: diffuse, displaced PMI, S3 and/or S4, MR murmur, CHF</li> <li><u>Chronic</u>: HF, VT/VF, systemic embolization, may be asymptomatic</li> </ul>	<ul style="list-style-type: none"> <li>ECG w/ persistent STE</li> <li>TTE, other imaging (CMR, CT, ventriculography)</li> </ul>	<ul style="list-style-type: none"> <li><u>Acute</u>: management of CHF, ACEi, avoid NSAIDs/steroids, start heparin (if EF&lt;35%)</li> <li><u>Chronic</u>: ACEi, digoxin, diuretics, warfarin (if EF&lt;35%)</li> <li>Surgical repair</li> </ul>
	LV Thrombus	<ul style="list-style-type: none"> <li>5% of AMI patients post-PCI</li> <li>Usually in LV apex</li> <li>Large infarct size, severe apical akinesis or dyskinesis, LV aneurysm, anterior MI</li> </ul>	<ul style="list-style-type: none"> <li>Can form 24-72h post MI</li> <li>90% of thrombi are formed by 2w</li> <li>Embolization risk persists for 6mo but most by 3-4mo; risk 10% if not on warfarin</li> </ul>	<ul style="list-style-type: none"> <li>TTE w/ contrast</li> <li>CMR or CT</li> </ul>	<ul style="list-style-type: none"> <li>Warfarin (INR 2-3); DOAC may be a reasonable alternative (<a href="#">Circ. 2022;146:e205-e223</a>)</li> <li>When to stop AC unclear, check for resolution of thrombus on TTE at 3-6mo</li> </ul>
Pericarditis	<ul style="list-style-type: none"> <li>5% of pts in the ED w/ CP and no MI, M &gt; F</li> <li>85-90% idiopathic (viral/post viral), infectious, post-MI, uremic, autoimmune, malignancy, XRT, drugs</li> </ul>	<ul style="list-style-type: none"> <li>10% at 2-4d post-transmural MI</li> <li>May be focal or diffuse</li> <li><u>Dressler's syndrome (1-6wks)</u>: malaise, fever, leukocytosis, late autoimmune carditis, rare</li> </ul>	<ul style="list-style-type: none"> <li>ECG (diffuse STE, PR depressions)</li> <li>TTE (effusion)</li> <li>CMR and/or cardiac CT</li> </ul>	<ul style="list-style-type: none"> <li>ASA + colchicine</li> <li>Avoid NSAIDs and steroids post MI as can impair infarct healing</li> </ul>	
Coronary Artery In-Stent Thrombosis	<ul style="list-style-type: none"> <li>Highest risk is absence of P2Y12 inhibitor</li> <li>1% at 1 year, then ~0.2% per year thereafter</li> </ul>	<ul style="list-style-type: none"> <li>Most cases occur within 30d of PCI irrespective of stent type</li> <li>ACS symptomatology</li> </ul>	<ul style="list-style-type: none"> <li>ECG</li> <li>Biomarkers (troponin/CKMB)</li> </ul>	<ul style="list-style-type: none"> <li>PCI</li> <li>Long term anti-platelet therapy, adherence to therapy</li> </ul>	

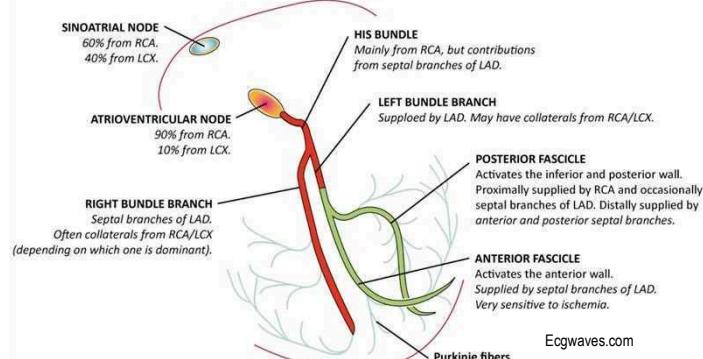
# Cardiology

# MI Complications

## URGENT ASSESSMENT OF POST-MI COMPLICATION (page Cardiology)

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

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

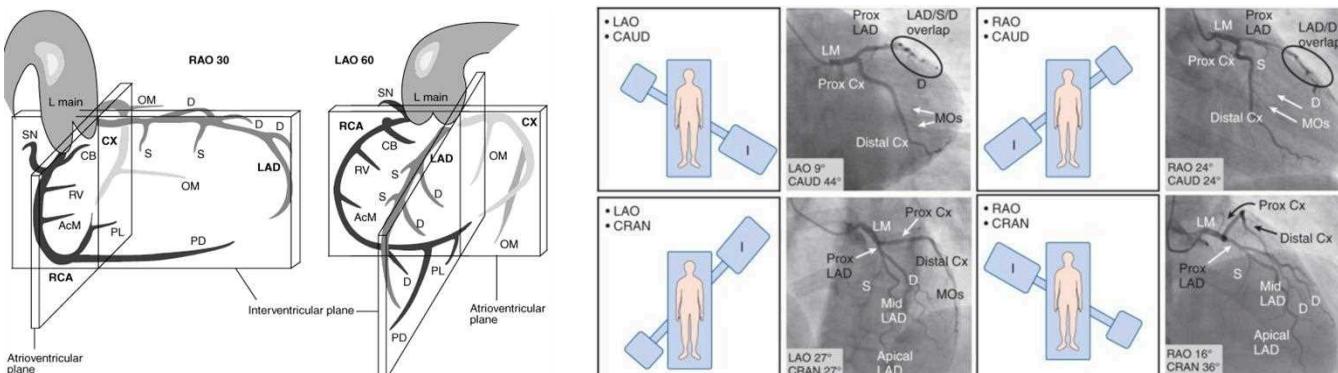


## ELECTRICAL COMPLICATIONS

### Overview

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

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



## LEFT VS RIGHT HEART CATHETERIZATION

- LHC (often used to describe Cor Angio): Arterial access (radial, fem). Assess coronary anatomy/lesions, LV & Ao pressures. PCI.
- RHC: Venous access (IJ, fem). Assess hemodynamics (see *Pulmonary Artery Catheterization*); cardiac biopsies (usually RV)

## CORONARY ANATOMY

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

## PREPARATION FOR CATHETERIZATION

- NPOpMN; INR<2; monitor Cr, no ppx abx. Continue ASA, statin, BB. UFH gtt (hold when on call), LMWH (hold 24h prior; see *Peri-Procedural AC*), hold DOACs >48hr or >72hr if CrCl<30. Hold metformin (usually 1d pre-, 2d post-proc), may hold/delay starting ACEi
- Document b/l radial, femoral, popliteal, DP pulses, & Allen's test. Check for bruits. Note history of HIT, PVD, Ao aneurysm/dissection
- Contrast allergy:** pre-tx w/ steroids & benadryl if patient has documented allergy. See *Contrast Allergy* for MGH protocols. Consult *Allergy for expedited protocol if the cath is required emergently*
- Respiratory distress:** patient will need to lie flat; consider intubation if prohibitive hypoxemia/pulmonary edema
- Pre-hydration** w/ crystalloids and NAC/bicarb have *not* been shown to prevent CIN in most patients with moderate CKD ([Lancet 2017;389:1312](#); [NEJM 2018;378:603](#)); [CIN risk calculator](#); See *Contrast*

## PERCUTANEOUS CORONARY INTERVENTION CONSIDERATIONS

- Access:** fewer bleeding/vascular complications if **radial** (vs femoral), possible ↓ death in ACS ([JACC 2018;71:1167](#)); due to radial vasospasm, CCB and/or nitroglycerin is administered along with UFH to prevent arterial occlusion
- BMS vs DES:** ↓ in-stent thrombosis with **DES** with subsequent ↓ MI/revascularization and ↓ CV death; however, ↑ **risk of late stent restenosis so requires longer duration of DAPT** ([JAH 2021;10:e018828](#); [Lancet 2019; 393: 2503](#))
- Can identify HD significant lesions via:** fractional flow reserve (FFR), Instant Wave Free Ratio (iFR), intravascular ultrasound (IVUS)
- Contraindications to stents:** predicted DAPT non-adherence, anticipated major surgery within treatment time, elevated bleeding risk
- Antiplatelet:** 81mg ASA indefinitely ([Circ 2016;134:e123](#)). P2Y12 inhibitor added after cath (prasugrel, ticagrelor or clopidogrel)
  - Not high bleeding risk:** ACS, 12mo DAPT (DES/BMS); stable IHD, ≥6mo DAPT if DES or ≥1mo if BMS
  - High bleeding risk:** ACS, 6mo DAPT (DES/BMS). In select patients, DAPT 1-3 months followed by P2Y12 monotherapy ([NEJM 2019; 381:2032](#)); stable IHD, ≥3mo DAPT if DES or ≥1mo if BMS (also consider 1-3mo DAPT followed by P2Y12 monotherapy)
  - Triple therapy: see ACS. Usually, 1 wk triple therapy and transition to P2Y12 inhibitor + DOAC.

## POST-PROCEDURE CARE

- Femoral access:** 4-6h bedrest after procedure. Closure devices decrease time needed for bedrest
  - Groin checks immediately, 6h, 8h post-procedure: **check b/l pulses, palpate for pulsatile masses, auscultate for bruits**
  - Sheaths: usually removed when PTT<60, confirm with interventional fellow; **only fellows (page access fellow) remove**
- Radial access:** TR band for 4-6h. Driven by RN protocol; if paresthesias/numbness, examine, check finger sat probe for perfusion. Can remove several mLs of air from band if necessary and if no complications. NOTE: if hematoma do not remove until fellow assesses.

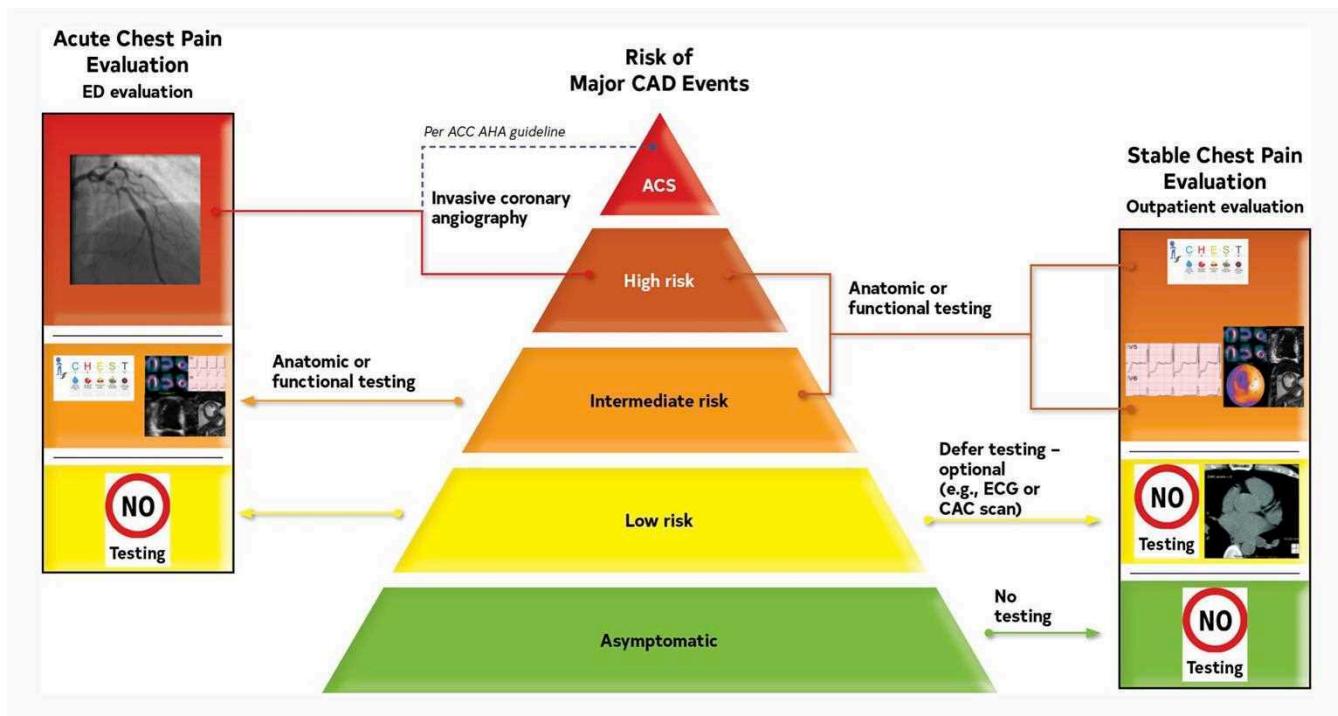
## POST-CATHETERIZATION COMPLICATIONS

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

## STRESS TESTING BASICS

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

## ROLE OF NONINVASIVE CARDIAC TESTING IN CHEST PAIN EVALUATION



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

### When deciding between CCTA (anatomic) and stress (functional) imaging in an intermediate risk patient:

- If known <50% nonobstructive CAD, or age<65 years old, prior functional study without conclusive results, bypass graft assessment, and to rule out obstructive CAD, consider evaluation with CCTA FFR
- If >50% obstructive CAD, age>65, to assess for specific areas of ischemia, or prior CCTA without conclusive results, consider evaluation with stress imaging. If high concern for ischemia after inconclusive stress, consider CCTA for balanced ischemia.

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

# Cardiology

# Non-Invasive Cardiac Testing

## STRESS TESTS

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

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

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

### Choosing an agent:

- **Adenosine/Regadenoson:** detects ischemia by coronary steal (vasodilation via cAMP). Stenosed coronary arteries are unable to further dilate to adenosine → limited flow reserve to distal areas and relative perfusion deficit
  - Side effects: **wheezing, bradycardia, HoTN.** Caution if ACTIVE bronchospasm, high grade AVB, SSS, severe AS
  - **Regadenoson:** decreased respiratory/conduction side effects, more cost-effective in obese pts. Caution if seizure hx (reversal agent aminophylline ↑seizure risk)
  - False negative can occur in 3VD: no relative perfusion deficit when all 3 vessels affected equally ("balanced ischemia")
- **Dobutamine:** workload induced by positive inotropy and chronotropy via β-1 receptor agonism
  - Extremely high dose of dobutamine is given, dose titrated up to 40mcg/kg/min
  - Side effects: tachyarrhythmias. Caution if MI <48h, hx of malignant arrhythmia, severe AS, HOCM, severe HTN, severe PAH, aortic dissection

### Choosing an imaging modality:

- **TTE:** preferred if primary objective is to exclude CAD (76% Sn, 88% Sp). Can give info regarding hemodynamics/valve disorders
  - *Do not use* in pts with LBBB, V-pacing or extensive wall motion abnormalities at rest
- **Nuclear imaging:** utilizes a radioactive tracer to detect areas of ↓ perfusion between rest and stress states. More expensive than TTE & high amount of radiation (SPECT > PET)
  - **PET** is more Sn & Sp than SPECT with faster image acquisition, quantitative. Less widely available & most expensive.  
Additional uses for imaging in rheumatologic (i.e. cardiac sarcoid) and oncologic contexts (i.e. cardiac myxoma, metastases)

## VIABILITY TESTING

- Indication: determine viability of ischemic myocardial tissue ("hibernating myocardium")

- Imaging modalities: SPECT (thallium or sestamibi), PET, TTE, MRI
  - SPECT is performed using exercise or pharmacologic stress. PET/TTE/MI performed using pharmacologic stress only

## REST IMAGING

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

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

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

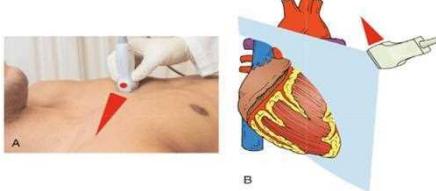
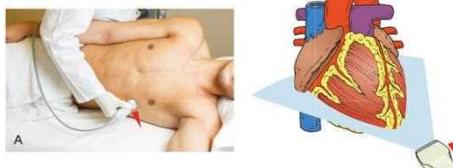
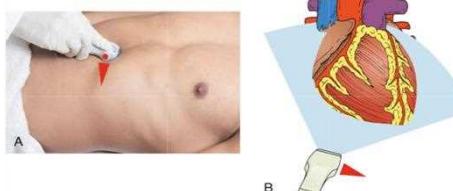
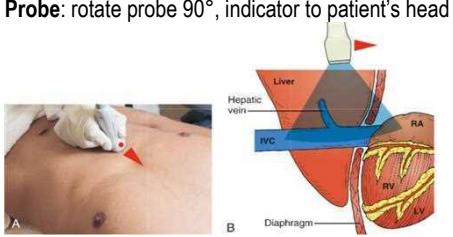
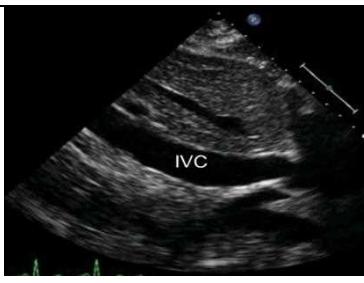
- Indications: to guide decision making for primary prevention for asymptomatic adults ≥40y at intermediate risk (7.5-19.9% 10y ASCVD risk) if statin therapy decision remains uncertain. Do NOT use as a stand-alone test in evaluation of symptoms of myocardial ischemia. Do NOT use in high risk patients, including those with familial hypercholesterolemia
- Findings:
  - If CAC (Agatston) scores ≥100 or >75 %ile for age & gender independent of ASCVD risk, recommend aggressive therapeutic lifestyle changes, ASCVD RF modification (BP, smoking cessation, diabetes treatment), & statin therapy ([JACC 2019;73:285](#))
  - For those with calcium score of 0 without significant risk factors, reasonable to defer statin therapy for up to 5 years ([Circ 2019;140:496](#))
  - MESA score accounts for CAC score and is able to refine 10 year risk estimates

## Cardiac MRI:

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

# Cardiology

# Echocardiography

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

\*Images from: Soni, N. J., Arntfield, R., & Kory, P. (2020). Point of care ultrasound. Elsevier.

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

- Valvulopathy: stenosis/regurgitation (valve area, gradients, severity), leaflets, vegetations
- Structure/chamber dimensions: aorta, LVIDd & LVIDs (LV internal diameter in diastole, range: 42 – 58mm & systole, range: 25 – 40mm), IVS (septum, 6-10mm), PWT (posterior wall thickness, 6-10mm, ↑ in LHV, diastolic dysfunction), LV volume (ULN: 74ml/m<sup>2</sup> in men 61 in women, <40 suggest restrictive), LA volume (ULN: 34ml/m<sup>2</sup>, ↑ in MR/MS, diastolic dysfunction, AF)
- EF: “preserved” EF ≥50%, “borderline” EF 40-50%, “reduced” EF <40%
- WMA: territory correlates w/ coronary vessels (anterior + septal = LAD, inferior = RCA, lateral = LCx). If global WMA, r/o diffuse ischemia vs non-ischemic insult (sepsis, stress)
- RVSP: RVSP=4v<sup>2</sup> + RAP. **RAP assumed to be 10 mmHg** and v = TR jet velocity

#### Indications for STAT TTE:

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

#### CLINICAL QUESTIONS AND ASSOCIATED TTE FINDINGS

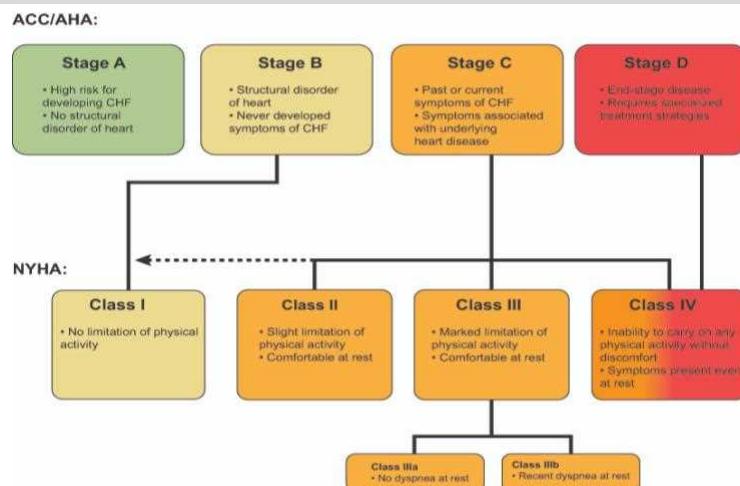
- Right heart strain in acute PE: RV WMA or hypokinesis, RV dilation (RV:LV ratio >1), interventricular septal bowing, IVC collapse, “D-sign”: septal flattening, “McConnell’s sign”: RV free wall akinesia w/ normal RV apex motion (77% Sn, 94% Sp for acute PE)
- Tamponade: large effusion, swinging heart, R-sided chamber collapse, interventricular septal bowing, dilated IVC (no ↓ w/ inspiration)
- ACS/mechanical complications of ACS: regional WMA, septal/free wall rupture, acute MR, LV thrombus
- Stress (Takotsubo) cardiomyopathy: LV apical ballooning and akinesis/hypokinesis; Heart failure: depressed EF, RV/LV hypertrophy and/or dilation
- Diastolic dysfunction: LA enlargement, E/e' >14, LVH (note: diastolic dysfunction not typically called on MGH TTE reports)
- Constrictive pericarditis: thickened or hyperechoic pericardium, abnormal septal motion, respiratory variation in ventricular size, dilated IVC

# Cardiology

# Heart Failure

## INITIAL WORKUP - NEW HEART FAILURE DIAGNOSIS

- Clinical syndrome with signs/symptoms consistent with impaired cardiac function ± cardiomyopathy
- Echocardiography: TTE for all new presentations; obtain thereafter only if concern for clinical/functional change
  - HF<sub>r</sub>EF** (EF ≤40%), **HF<sub>m</sub>EF** ("mid-range" EF 41-49%), **HF<sub>p</sub>EF** (EF ≥50%)
- Ischemic workup: FHx, ECG, TnT, noninvasive or invasive cardiac testing
- Non-ischemic workup: FHx, genetic testing, med hx, alcohol use history, lipid panel, TSH, A1c, urine hCG, iron studies, HIV, SPEP/SFLC w/ UFC
  - Consider: cardiac MRI, ANA, *T. cruzi* serologies, viral panel, antimyosin Ab, tox screen, thiamine/carnitine/selenium, genetic testing, ARVC, sarcoid, PYP scan, cardiac masses; endomyocardial bx (if serologic testing neg, new onset <6mo unexplained HF, unexplained HF <2wks and HDUS, major arrhythmias) to r/o myocarditis
- Consider high-output etiologies: anemia, thyroid dysfxn, liver failure, Paget's, systemic infection, AV shunts



## Dilated Cardiomyopathy

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

Condition	Etiology and Management
<b>Alcohol-induced</b>	Mechanism: >80g/d EtOH over >5y (toxic to myocytes via O <sub>2</sub> free radicals + defects in protein synthesis) Tx: abstinence + HF therapy Prognosis: better/equivalent to idiopathic CM if <20g/d (<2 drinks) or abstinence, worse w/ continued EtOH use
<b>Stress-induced (Takotsubo)</b> <i>(JACC. 2018;72:1955)</i>	Mechanisms: catecholamine surge from physical/emotional stress, coronary artery spasm, microvascular ACS Presentation: may present like ACS with CP (most common), SOB, shock, syncope. If in shock, urgent TTE to assess for LVOT obstruction Dx (need all 4): <b>1</b> ) transient dysfxn of LV mid-segments, WMAs extending beyond a single coronary distribution; <b>2</b> ) rule out ACS/obstructive CAD (via cath); <b>3</b> ) new ECG Δ (STE or TWI) OR ↑TnT; <b>4</b> ) absence of pheno or myocarditis Tx/Prognosis: remove stressor, ACEi (may improve survival), BB; most recover LV function in 1-4w

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

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

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

Dx: **ECG** (prominent voltages w/ depolarization abnormalities, large abnormal Q waves in inferior/lateral leads, LAD, giant negative T waves in V2-V4 (apical HCM variant aka "Yamaguchi syndrome")), **TTE** (unexplained LVH >15mm, SAM of MV, outflow tract gradient +/- provocative testing), **cMRI** (late gadolinium enhancement [LGE] = fibrosis)

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

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

Risk factors for **SCD/VT**: prior VT/SCD/unexplained syncope; FHx of SCD in 1° relative; massive LVH (>30mm); NSVT on Holter; abnormal BP response to exercise; burden of LGE on cMRI; h/o suspected cardiac syncope; EF<50%

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

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

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

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

# Cardiology

# Heart Failure

## INPATIENT ACUTE DECOMPENSATED HEART FAILURE (ADHF)

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

## ADHF MANAGEMENT – FLOOR/SDU

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

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

- History
  - Identify precipitants:** dietary/med non-adherence (~40%), **new ischemia/infarction**, uncontrolled HTN, arrhythmia, inadequate diuretic dose, meds (NSAIDs, steroids, CCB, TZDs, anthracyclines), acute infection (URI, PNA, UTI), AKI, PE, toxins (EtOH, cocaine), new/worsening valve disease, myocarditis
  - Cardiac/HF history** (last EF, dry weight, prior ischemic w/u, prior TTE, cardiologist); accurate PAML; social history

- Early/Acute Management:
  - Diuresis:** ↓CVP, PCWP to optimize Starling curve mechanics & relieve sx ([NEJM 2017;377:1964](#); [JACC 2020;75:1178](#))
    - Initial tx:** IV loop diuretics (furosemide, torsemide, bumetanide), start with 2-2.5x home dose (IV/PO). No difference between continuous gtt vs bolus dosing ([NEJM 2011;364:797](#)); furosemide & torsemide have equivalent outcomes ([JAMA 2023;329:214-223](#)). See *Advanced Diuresis* for conversions
    - Refractory diuresis:** metolazone 2.5-5mg (or chlorothiazide 500mg IV) administered 30min before loop diuretic. May need RHC to clarify hemodynamics or inotropes to augment diuresis. Acetazolamide (500mg daily) may also augment successful decongestion ([NEJM 2022;387:1185](#)). Step-up pharmacologic therapy superior to RRT in the setting of cardiorenal syndrome ([NEJM 2012;367:2296](#))
    - Worsening renal function:** occurs in ~23% of pts treated for ADHF. Mild-mod “Cr bumps” are likely benign hemodynamic changes, should not necessarily preclude further diuresis if pt still congested ([Circ 2018;137:2016](#))
    - Endpoints:** target resolution of signs/symptoms of congestion. Daily weights & hemoconcentration are useful adjuncts
  - If acute pulmonary edema, **NIPPV** may improve mortality and reduce need for intubation ([Annals 2010;152:590](#))
  - Vasodilators:** arterial/venous dilation can relieve symptoms by ↓afterload, ↓PCWP and ↑SV. Can accelerate early sx relief. Consider esp. in severe HTN, acute MR, acute AR
    - Floor:** isosorbide dinitrate, hydralazine, nitropaste, captopril; **SDU/CCU:** TNG, nitroprusside
  - Guideline-Directed Medical Therapy (GDMT):** if not in cardiogenic shock or new AKI, continue ACEi/ARB/ARNi and βB during ADHF (but do not newly initiate βB) ([EHJ 2009;30:2186](#))

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

- HFrEF (EF ≤40%) GDMT, including HFrecEF (recovered EF):**

- Beta blockers:** initiate, uptitrate evidence-based βB (carvedilol, metoprolol succ., bisoprolol) ([COPERNICUS](#); [MERIT-HF](#)). Caution if recently weaned from inotropes
- RAAS inhibitors:** if renal fxn stable, initiate/titrate ARNI (sacubitril/valsartan) ([PARADIGM-HF](#); [PIONEER-HF](#)), second line ACEi/ARB ([CONSENSUS](#); [CHARM](#)). Switch to ARNI from ACEi/ARB if no contraindications/cost concerns, 36h washout period for ACEi prior to starting ARNI.
  - Guidance for GDMT in advanced CKD: [JACC HF 2019;7:371](#)
- Mineralocorticoid receptor antagonist:** initiate spironolactone or eplerenone if CrCl >30 ([EMPHASIS-HF](#); [RALES](#)). Watch for rebound hyperK after de-escalation of diuretics (check K, Cr within 72h of discharge)
- SGLT2i (dapagliflozin, empagliflozin):** further reduce CV mortality & HF admissions regardless of DM ([DAPA-HF](#); [EMPEROR-Reduced](#); [Lancet 2020;396:819](#)) (see *Outpatient Type 2 Diabetes*)
- GDMT dosing - AHA/ACC/HFSA 2022 Guidelines** ([Circ 2022;145:895](#))

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

# Cardiology

# Heart Failure

- **Diuretic plan:** determine maintenance diuretic dose and provide specific instructions for taking additional rescue doses. Observe on maintenance dose and decide if needs K replacement
- **HFmrEF** (EF 40-49%): treat with diuretics & consider adding GDMT agents for HFrEF ([Curr Heart Fail Rep 2020;17:1](#))
- **HFpEF** (EF ≥50%): prevent volume overload, treat with diuretics, treat comorbidities (DM, HTN, AF)
  - **SGLT2i** only agent found to ↓CV death/hospitalizations in pt with EF ≥40% ([EMPEROR-Preserved](#))
  - Consider **spironolactone** if normal renal fxn/K, ↓CV death/admits in N/S Am. sites in TOPCAT ([Circ 2015;131:34](#))
  - No proven benefit to BB ([EHJ 2018;39:26](#)), ACEi ([PEP-CHF](#)), ARNi ([PARAGON-HF](#)), ARB ([CHARM-Preserved](#))
- **ICD indicated if:** ischemic CM w/ EF ≤30 or ≤35% w/ NYHA II-III; CRT if: EF ≤35% & prolonged QRS ± LBBB & some w/ EF ≤50% (see *Cardiac Devices: PPM/ICD* & guidelines for specifics: [JACC 2013;61:e6](#); [EHJ 2016;37:2129](#))

## OUTPATIENT HEART FAILURE ([JACC 2021;77:772](#), [Circ 2022;145:895](#))

Not comprehensive; assumes EF ≤ 40% (HFrEF), co-management by cardiology and/or heart failure specialist.

- At each visit: assess med/dietary/lifestyle compliance, document weight, detailed volume exam, assess symptoms and classify ACC Stage/NYHA Class, review current GDMT, review ambulatory BP / HR measurements for GDMT titration targets
- **Lab monitoring:** BMP/Mg and 1-2 weeks following uptitration of ACE-i/ARB/ARNi; spironolactone requires close monitoring
- **Goal:** toleration of target doses of ACE/ARB/ARNi, β-blocker, aldosterone antagonist, and SGLT-2 inhibitor without symptomatic hypotension or metabolic disarray. For β blockade, target resting HR < 70 without postural hypotension or unacceptable SE.
- **Principles:** start GDMT immediately on dx, often “quad therapy” at lower than target dosing is preferred over maxing out a single agent
- **Diuretic:** see *Advanced Diuresis*. Diuretic needs may change when SGLT-2i is added due to mild diuretic effect.
- **Avoid:** NSAIDs, CCBs, flecainide, steroids, OTC decongestants (e.g. Sudafed), Bactrim
- **Special considerations/scenarios:**
  - Ivabradine: add if sinus rhythm & resting HR > 70 on max β blockade. Start at 2.5 mg – 5 mg qd
  - Hydralazine/isosorbide dinitrate: add if SBP persistently > 130 on target GDMT; especially beneficial in AA patients
  - Symptomatic hypotension on GDMT: consider over-diuresis or other offending prior to reducing GDMT
- **Adjuvant care/ambulatory referrals to consider:** cardiac rehab (often under-prescribed); nutrition consultation for assistance with dietary adherence; patient-centered education is critical to enhance adherence

## CARDIOGENIC SHOCK – CCU

- **Definition:** HoTN (**SBP<90** for 30min or pressor req) + **hypoperfusion** (cold extremities, oliguria, lactate) + hemodynamics (**CI <2.2, PCWP >15**) ([EHJ 2019;40:2671](#))
- **Etiology:** acute MI ± mechanical complications, end-stage heart failure, acute myocarditis, acute MR/AR, myocardial contusion
- **Evaluation:** ECG, troponin to r/o acute MI. TTE to exclude tamponade/mechanical lesions/contraindications to MCS
- **Monitoring:** A-line, consider **PA catheter** for inotropes/pressors and MVO<sub>2</sub> monitoring

### Immediate Management:

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

### Tailored Therapy: uses invasive hemodynamic monitoring (i.e., PAC) to guide medical therapy

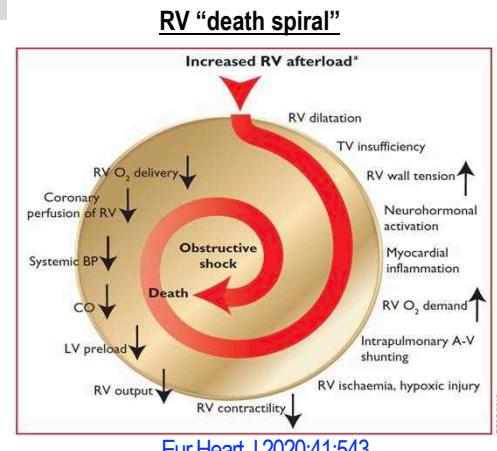
- **Goals:** tissue perfusion (↑CO, MAP), decongestion (↓CVP, PCWP), ventricular unloading (minimize myocardial O<sub>2</sub> demand)
  - **Preload:** LVEDV ∝ LVEDP ≈ PCWP; goal **PCWP 14-18, PAD 16-20, CVP 8-12** → diuresis, UF with RRT, TNG
  - **Afterload:** wall stress ∝ MAP (Laplace's law); SVR = (MAP - CVP)/CO; goal **MAP >60, SVR <800-1200**
    - **Vasodilators:** captopril, hydralazine, nitroprusside, TNG
    - **Vasopressors:** ↑afterload, sometimes needed to ↑MAP in mixed shock or to counteract vasodilatory effect of inodilators
    - **IABP:** see *Mechanical Circulatory Support*
  - **Contractility:** ∝ CO for given preload/afterload; goal **CO>4, CI >2.0-2.2, MVO<sub>2</sub> >65**
    - **Dobutamine (inodilator):** β1>β2 agonist (↑production of cAMP); initial dose 0.5-1 mcg/kg/min
      - Watch for tachycardia, ↑ventricular response to AF, arrhythmias, ischemia, HoTN, tachyphylaxis in infusions >24-48h
    - **Milrinone (inodilator):** PDE-3 inhibitor (↓breakdown of cAMP); initial dose 0.125 mcg/kg/min
      - Watch for tachycardia, arrhythmias, ischemia, HoTN. Compared to dobutamine, milrinone has longer half-life, greater pulmonary vasodilatation, slightly less chronotropic, fewer arrhythmic events
      - Preferred in patients on βB and w/ RV failure. Renally cleared. Often choice for home inotrope for palliative therapy
      - **Epinephrine, norepinephrine, dopamine (inopressors):** use if severe HoTN often in combination with inodilators
        - Watch for tachycardia, arrhythmias, end-organ hypoperfusion
  - **Advanced:** consideration of need for mechanical circulatory support or transplant
    - Goal of mechanical circulatory support: improve systemic perfusion while reducing myocardial oxygen demand (in contrast to inotropes which ↑CO at the expense of increased oxygen demand); see *MCS*
- **Limitations:**
  - **CO approximated via thermodilution or Fick equation:** CO = VO<sub>2</sub>/(13.4 x Hgb x [SpO<sub>2</sub>-MVO<sub>2</sub>]); CI = CO/BSA; VO<sub>2</sub> = 125 x BSA
    - **Thermodilution:** uses temp gradient between two points on PAC. Less reliable if shunt/valvular insufficiency (e.g., TR)
    - **Fick equation:** assumes a VO<sub>2</sub> (oxygen consumption) that in reality varies depending on physiologic state (e.g., infxn)

# Cardiology

# Right Ventricular Failure

## PATHOPHYSIOLOGY

- Normal RV function: governed by systemic venous return, PA pressure, pericardial compliance, and native contractility of the RV free wall and interventricular septum (where RV and LV are “tethered”).
  - The RV is coupled to the high-compliance, low-resistance pulm circulation → RV ejects blood at lower pressure compared to LV → RV is more afterload sensitive than LV. RV can adapt to changes in volume > pressure.
- Acute RV Failure: RV & LV interdependent → failure of RV → failure of LV via: (1) decreased LV preload, as RV output = LV preload & (2) septal bowing into LV, causing diastolic impairment (“Diastolic Ventricular Interaction”)
  - ↑RV afterload (e.g. PE, hypoxia, acidemia), ↑RV preload (e.g. L→R shunt or TV disease), or ↓RV contractility (e.g. MI, myocarditis) all lead to increased RV wall stress & resultant ischemia
- Chronic RV Failure: gradual ↑RV afterload (from Pulmonary Hypertension / Pulmonic Stenosis / Tricuspid Regurgitation) → **RV “death spiral”**



Eur Heart J 2020;41:543

## CLINICAL FEATURES AND WORKUP ([Circ 2018;137:e578-e622](#))

- Exam: ↑JVP, peripheral edema, RV heave, pulsatile liver, split S2, new TR (holosystolic murmur at LLSB with radiation to RLSB)
- Imaging: PA/lateral CXR; CT → RV/LV ratio >0.9 suggests RV strain
- Echo: measure RV size/function to elucidate underlying etiology. RVEF based on displacement of base towards apex; TAPSE = tricuspid annular plane systolic excursion (normal ≥ 17 mm; reflects RV apex-to-base shortening, correlates with RVEF)
  - RVSP: correlates w/ RHC but can vary up to 10mmHg (esp w/ chronic lung disease, PPV)
- RHC w/ placement of PA line: gold standard for measurement of ventricular filling pressures, CO, PA pressures
  - RV function: CVP/PCWP ratio: normal = 0.5; ↑ is sign of RV failure; PAPI: (PAs – PAd)/CVP <0.9 = RV failure, for pts w/ VAD < 1.85 = RV failure; RV stroke work index: (mPAP – CVP) x (CI/HR) x 0.0136 (normal 8-12 g/m/beat/m<sup>2</sup>)
- Labs: ↑NT-proBNP, troponin, also ↑Cr and LFTs secondary to venous congestion

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

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

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

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

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

- EKG: check R-sided ECG leads in pts with inferior STEMI (10-15% have RV involvement)
  - 1mm STE in V4R → 88% Sn, 78% Sp in inferior STEMI; STE III>II suggests RCA > LCx and RVMI
  - High-grade AV block seen in ~50% of pts with RVMI
- Management: pts with RVMI may initially benefit from fluid bolus; **caution w/ TNG** (↓preload) & **BB**

# Cardiology

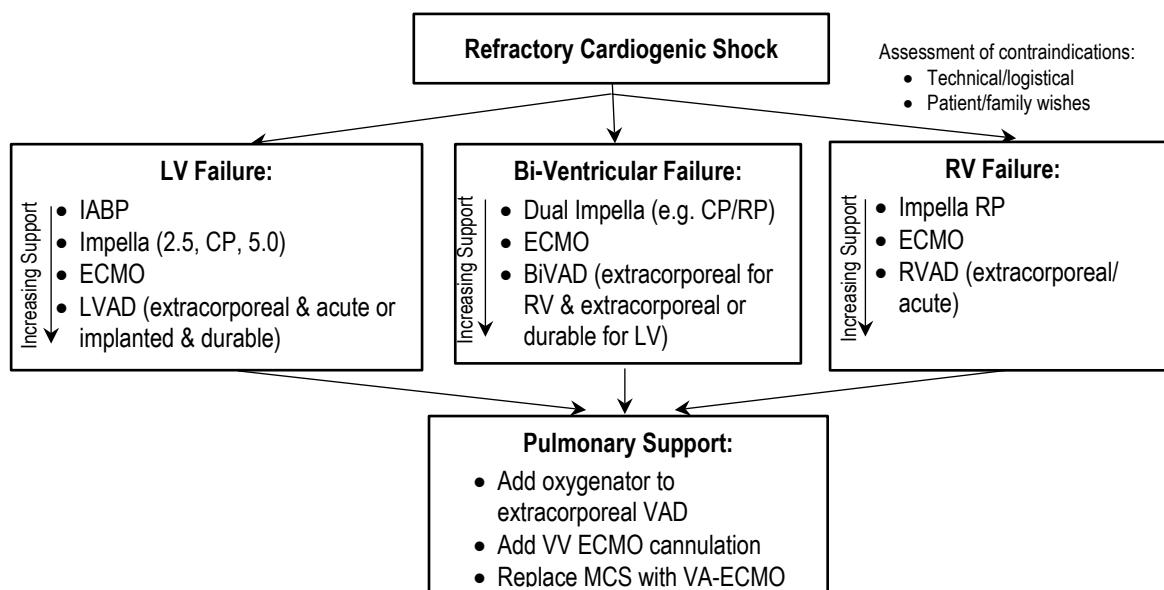
# Mechanical Circulatory Support

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

**Note:** if inotrope-refractory cardiogenic shock, call SHOCK team (p11511) and/or HCICU attending (p29151)

## Selected MCS Modalities

Device	Indications	Support Provided	Considerations	Management	Complications
IABP (intra-aortic balloon pump)	<ul style="list-style-type: none"> <li>- Refractory heart failure (<b>bridge to</b> durable MCS or transplant)</li> <li>- Refractory ischemia</li> <li>- <b>Cardiogenic shock/massive PE</b></li> </ul>	<p>Mechanism: balloon inflation/deflation; <b>LV support</b> Minimal hemodynamic support (<b>0.5 L/min</b>), greater in ADHF than acute MI shock (<a href="#">Am J Card 2019;124:1947</a>)</p> <ul style="list-style-type: none"> <li>- <b>↓LV afterload (deflation)</b>- improves forward flow in MR/VSD</li> <li>- <b>↑Coronary perfusion (inflation)</b></li> <li>- Requires native contractility &amp; stable rhythm</li> </ul>	<ul style="list-style-type: none"> <li>- Bedside insertion (quick)</li> <li>- Does not always require AC (when at 1:1)</li> <li>- No ↓ mortality in cardiogenic shock (IABP-SHOCK II, <a href="#">NEJM 2012;367:1287</a>)</li> <li>- Prevents mobility (if femoral placement)</li> <li>- Least costly</li> </ul>	<ul style="list-style-type: none"> <li>- Check <b>CXR</b> daily (tip 1-4cm below aortic knob)</li> <li>- Check <b>waveform</b> twice daily</li> <li>- Wean by ↓ ratio (then return to 1:1, stop AC, pull)</li> <li>- Pulse checks</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Limb ischemia</b></li> <li>- Vascular injury</li> <li>- Thromboembolism</li> <li>- Bleeding</li> <li>- Infection</li> <li>- Balloon leak/rupture (STAT c/s to attending and vascular surg c/s)</li> </ul>
Impella	<ul style="list-style-type: none"> <li>- Refractory malignant arrhythmias</li> <li>- Support during <b>high-risk procedures</b>: <ul style="list-style-type: none"> <li>o Complex PCI</li> <li>o Ablation of ventricular arrhythmias</li> <li>o Percutaneous valve repair</li> </ul> </li> <li>- Acute allograft failure</li> </ul>	<p>Mechanism: axial flow continuous pump</p> <p><b>Partial LV support</b></p> <ul style="list-style-type: none"> <li>- <u>Cath lab placement</u>: Impella 2.5 (<b>2.5 L/min</b>), Impella CP (<b>3.5 L/min</b>)</li> <li>- <u>OR placement</u>: Impella 5.0 (<b>5 L/min</b>) or 5.5 (<b>6.5 L/min</b>)</li> </ul> <p><b>Partial RV support</b></p> <ul style="list-style-type: none"> <li>- Impella RP (<b>4 L/min</b>)</li> </ul>	<ul style="list-style-type: none"> <li>- Ventricular unloading</li> <li>- <b>Requires AC</b> (purge ± systemic)</li> <li>- Allows pt <b>mobilization</b> (if axillary placement)</li> <li>- Longer-term support (days to weeks)</li> <li>- ↑ complications compared to IABP</li> </ul>	<ul style="list-style-type: none"> <li>- P1 (lowest) to P9 (highest support)</li> <li>- Check urine color (<b>hemolysis</b>), LDH</li> <li>- Check <b>suction events</b> (↑preload, RV failure, position)</li> <li>- Check ventricular arrhythmias (device migration)</li> </ul>	<ul style="list-style-type: none"> <li>- Infection</li> <li>- Bleeding</li> <li>- Limb ischemia</li> <li>- Thromboembolism</li> <li>- Thrombocytopenia</li> <li>- Vascular injury</li> <li>- <b>Position alarm</b> (reposition under fluoro/echo)</li> </ul>
VA-ECMO	<ul style="list-style-type: none"> <li>- Bridge to transplant</li> <li>- Bridge to candidacy</li> <li>- Destination therapy</li> <li>- Bridge to <b>recovery</b> (LV unloading can be therapeutic)</li> </ul>	<p><b>Full bi-ventricular support</b> (<b>4-10 L/min</b>) + oxygenation &amp; CO<sub>2</sub> clearance</p>	<ul style="list-style-type: none"> <li>- Bedside and urgent insertion possible</li> <li>- Short-term support (days/weeks)</li> <li>- Often requires Impella for LV venting (prevent complications such as pulmonary edema)</li> </ul>	See ECMO	
Durable VAD	<ul style="list-style-type: none"> <li>- Bridge to transplant</li> <li>- Bridge to candidacy</li> <li>- Destination therapy</li> <li>- Bridge to <b>recovery</b> (LV unloading can be therapeutic)</li> </ul>	<p><b>Full LV support (10 L/min)</b></p> <ul style="list-style-type: none"> <li>- HeartMate II</li> <li>- HeartMate 3</li> <li>- HeartWare HVAD</li> </ul> <p>48% reduction in all cause mortality with LVAD as compared to optimal GDMT in Class IV HF (<a href="#">REMATCH</a>)</p> <p>Off-label for RV support (RVAD) or both (BiVAD)</p>	<ul style="list-style-type: none"> <li>- <b>Mobility</b></li> <li>- <b>Long-term support</b> (years)</li> <li>- <b>Require lifelong anticoagulation</b></li> </ul>	<ul style="list-style-type: none"> <li>- BP via <b>manual cuff w/ doppler</b> (goal MAP 70-80); continuous flow device does not generate pulse</li> <li>- If hypotensive, place A-line</li> <li>- If unconscious, w/o hum and unable to troubleshoot OR MAP&lt;50: chest compressions</li> <li>- TTE if any concern</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Acquired vWF deficiency</b></li> <li>- <b>Hemolysis</b> (possible pump thrombosis)</li> <li>- Ventricular arrhythmias</li> <li>- Thromboembolism</li> <li>- RV failure</li> <li>- AR</li> <li>- <b>Driveline infections</b></li> </ul>



# Cardiology

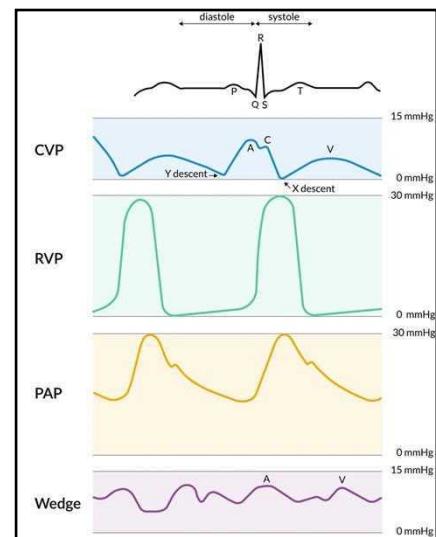
# Pulmonary Artery Catheterization

## OVERVIEW

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

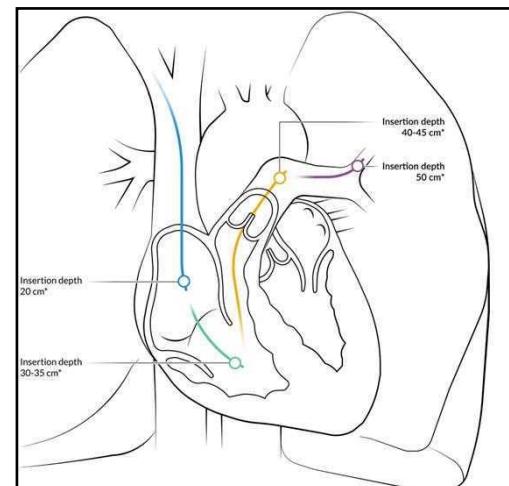
## VENOUS WAVEFORMS (CVP/PCWP)

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



## OBTAINING PA LINE NUMBERS ON AM ROUNDS

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



## CALCULATING HEMODYNAMIC PARAMETERS

- Normal:** "rule of 5s" → RA 5, RV 25/5, PA 25/10, PCWP 10, LV 125/10
- Cardiac output:** TD better predicts mortality ([JAMA Cardiol 2017;10:10](#))
  - Fick** =  $\dot{V}O_2 / (13.4 * \text{Hgb} * [\text{SpO}_2 - \text{MV}_O_2])$  [nmol: 4-7 L/min]
    - $\dot{V}O_2 \approx 250 \text{ ml/min OR } 3^* \text{wt(kg)} \text{ OR } 125^*\text{BSA}$
  - Thermodilution (TD):** temp change (measured by thermistor in PA) is proportional to LV CO (inaccurate w/ TR/PR, intracardiac shunt)
- Cardiac index** = CO/BSA [normal: 2.6-4.2 L/min/m<sup>2</sup>]
- SVR** =  $(\text{MAP}-\text{CVP}) / \text{CO} \times 80$  [normal: 700-1200 dynes\*s\*cm<sup>5</sup>]
- PVR** =  $(\text{mPAP}-\text{PCWP}) / \text{CO} \times 80$  [normal: <2 Woods units]

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

## HEMODYNAMIC CONSIDERATIONS

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

## CLINICAL CONSIDERATIONS

- Placement:** usually through RIJ Cordis. Advance ONLY with balloon inflated. **Deflate balloon when withdrawing and at ALL other times.** Must have cardiology or pulmonary fellow present to place/advance at MGH
  - Cath lab if: severe PH (>70mmHg), large RV/RA, LBBB, PPM/ICD <6mo, temp wire, severe TR, prosthetic TV/PV, femoral access
- Contraindications:** absolute – insertion site infection, RVAD; RA/RV mass/thrombosis, mechanical TV/PV, endocarditis (TV/PV)
- Position:** on CXR: should be in middle 1/3 of the chest bilaterally. Ability to wedge more important than CXR position
- Complications:** infection, bleeding, PTX, VT, RBBB, CHB, PA rupture (place patient on side with the catheter "bleeding side down", order STAT CXR, CBC, coags, CT surgery consult), pulm infarct, PE, catheter knotting (difficult removal)

# Cardiology

# Cardiac Devices: PPM, ICD, & CRT

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

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

## HARDWARE OVERVIEW

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

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

### Sinus Node Dysfunction:

- Symptomatic sinus brady (± sinus pauses) or chronotropic incompetence (after tx reversible causes, ensure symptoms temporally correlated)
  - Recommend DDD for symptomatic SND with extension of AV interval to minimize V-pacing; prefer physiologic pacing
- Symptomatic medication-induced bradycardia if there is no accepted alternative medication
- Permanent AF and symptomatic bradycardia

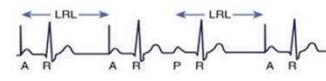
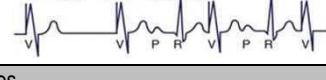
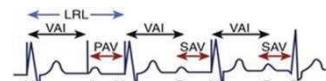
### AV Block (AVB)/Conduction Disease:

- 3°AVB with or without symptoms
- Symptomatic 2° AVB Mobitz I or II (conduction disease must correlate temporally w/ symptoms)
- Permanent 2° AVB Mobitz II or intermittent 3° AVB (regardless of symptoms)
- Alternating bundle branch block

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

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

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

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

## ICD INDICATIONS (CLASS I) ([JACC 2018;72:e91](#))

- 1° prevention indicated for pts with HF only if already on optimized medical therapy. All pts must have a reasonable expectation of 1-year survival.

Primary Prevention	Secondary Prevention
Ischemic CM: NYHA Class I: EF ≤30% at least 40d s/p MI & 90d s/p revascularization NYHA Class II/III: EF ≤35% at least 40d s/p MI & 90d s/p revascularization Other: EF ≤40% at least 40d s/p MI + NSVT + inducible VT/VF	- Prior episode of cardiac arrest (VF/pulseless VT), unstable VT, or sustained stable VT if no reversible cause found - Cardiac syncope w/ LVEF <35% OR cardiac syncope w/ inducible VT/VF on EP study
Non-ischemic CM*: EF ≤35% + NYHA Class II/III Other: cardiac sarcoidosis w/ LVEF ≤35%, LQTS refractory to βB. ARVC w/ LV or RV EF ≤35%, NICM + Lamin A/C and 2+ RF	

\*DANISH ([NEJM 2016;375:1221](#)): in pts with NICM, ICD ↓ risk of SCD, but no mortality benefit; long-term outcomes in SCD-HeFT ([JACC 2020;76\(4\):405](#)) did not show benefit from ICD in the NICM subgroup

## CRT INDICATIONS (CLASS I) ([JACC 2013;61:e6](#))

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

# Cardiology

# Valvular Heart Disease

## AORTIC STENOSIS

- **Etiology:** senile calcific (most common cause >70yo; a/w metabolic syndrome, CAD, CKD), bicuspid valve (most common cause <70yo), rheumatic heart disease (leaflets fuse, often with concurrent MV disease), radiation-induced
- **Clinical Manifestations:** most important determinant of prognosis → 50% mortality at 5y for angina, 3y for syncope, 2y for HF
  - Angina: ↑afterload → ↑LV pressures → LVH → ↑O<sub>2</sub> demand → supply-demand mismatch w/ exertion or tachycardia
  - Syncope: exercise-induced vasodilation → inability to augment CO due to obstruction → hypotension
  - Heart failure (dyspnea): LVH → diastolic dysfunction (*systolic dysfunction is a late finding*)
  - Acquired vWF def: 20% of severe AS, can worsen bleeding from GI AVMs "Heyde syndrome" ([NEJM 2012;367:1954](#))
- **Diagnosis:**
  - Physical exam: harsh, mid-systolic crescendo-decrescendo murmur at RUSB radiating to carotids. **If more severe:** murmur late-peaking, delayed carotid upstroke (pulsus parvus et tardus), soft S2 ([Am Heart J 1999;137:298](#))
  - TTE: measure mean (not peak) gradient, valve area, & jet velocity; also, important to assess EF (gradient can be underestimated with **reduced EF → low flow, low gradient AS**)
- **Severe AS:** peak AV velocity ≥4m/s, **mean AV pressure grad ≥40mmHg**, or **AV area (AVA) ≤1cm<sup>2</sup>** (ACC/AHA: [Circ 2021;143:e35](#))
  - ECG: LVH, LAE, LAFB, LBBB
  - Exercise stress testing: recommended in asymptomatic severe AS to assess for symptoms; do **not** perform in pts w/ sx
- **Natural History:** highly variable, but on average, AVA ↓ ~0.1 cm<sup>2</sup>/y & mean gradient ↑8mmHg/y ([JACC 1989;13:545](#)). Patients with bicuspid valves, advanced age, & those with severe leaflet calcification are at risk for more rapid progression
- **Aortic Valve Replacement (AVR)** ([J Am Soc Echo 2018;31:117](#)): determining indication for valve replacement is based on evaluating: (1) presence of **symptoms**, (2) **severity** by TTE criteria, (3) LV function (**EF**)
  - Symptomatic, severe AS (Stage D): AVR indicated
  - Asymptomatic, severe AS (Stage C): AVR appropriate if LVEF<50% or undergoing other cardiac surgery; for patients with asymptomatic very severe AS (AVA ≤0.75cm<sup>2</sup>) early surgery may have mortality benefit ([NEJM 2020;382:111](#))
  - If suspect low-flow (LVEF <50%) & low-gradient (<40mmHg w/ AVA <1cm<sup>2</sup>): **dobutamine stress TTE (DSE)** to distinguish between low-flow, low-gradient AS versus "pseudosevere AS" ([Circ 2011;124:739](#))
    - Low-flow, low-gradient severe AS: if DSE results in V<sub>max</sub>>4m/s or mean gradient>40mmHg while AVA remains <1cm<sup>2</sup>, AVR is indicated
    - Pseudosevere AS: if DSE results in AVA >1cm<sup>2</sup>, AVR not indicated
  - **Bioprosthetic vs Mechanical:** if contraindications to AC with VKA, must offer bioprosthetic; if pt <50 years of age without contraindications to AC, SAVR w/ mechanical valve recommended (COR 1; [Circulation 2021; 143:35](#)); if >65 yrs of age, bioprosthetic recommended (COR 2a); 50-65 years of age require shared decision making
  - **SAVR vs TAVI for bioprosthetic:** pts <65y, SAVR recommended d/t increased durability; >80y TAVI recommended
    - 65-80 yrs of age: depends on surgical risk ([STS-PROM score](#)), concomitant heart/vascular disease, valvular/vascular anatomy that is amenable to TAVI ([Circulation 2021; 143:35](#))
    - TAVI is recommended for those at extreme surgical risk (compared to medical therapy, [PARTNER](#)); noninferior to SAVR in those at high ([NEJM 2011;364:2187](#)), intermediate ([PARTNER 2](#)), & low surgical risk ([PARTNER 3](#)). Valve-in-valve TAVI may additionally be beneficial in pts with surgical bioprosthetic AV failure ([JACC 2017;69:2253](#))
  - **TAVI Evaluation:** c/s **structural cardiology, cardiac surgery.** Obtain TTE, TAVI-protocol CT, **dental clearance** (Panorex)
  - **TAVI Complications:** Valve: embolization, paravalvular leak; Stroke: embolic (first 48h), ischemic/hemorrhagic; Conduction: HGBVB requiring PPM (Major RF: baseline RBBB, need for pacing or HGBVB s/p TAVI; Minor: h/o AF, valve oversized >15%; [Card Fail Rev 2021; 7:e12](#)); Bleeding: Access site complication; Hemodynamics: dynamic LVOT obstruction due to LVH ("suicide LV"), HTN (sudden ↓ in obstruction after TAVI), hypotension (d/t ↓preload), tamponade (perforation, usually immediate); AKI
  - **Medical Management:** AS is a surgical disease & medical management is only utilized for treatment of sx
    - Treat HTN: reduce the "double load" on the ventricle. In theory, ACE-I may have beneficial effect on LV fibrosis. However, no optimal regimen exists because anti-hypertensives can lead to hemodynamic issues. Bottom line: **start low and go slow**
    - Control volume status: operate within a narrow preload range, prone to underfilling (low preload) & overfilling (volume overload)
  - **Anticoagulation after Valve Replacement:**
    - Bridging UFH or LMWH if AC interrupted only in mechanical MV or mechanical AV with RFs (Class I),
    - RFs: AF, LV dysfxn, prior VTE, hypercoag, older gen mech AVR ([Circ 2021;143:e35](#))
    - Bleeding risk: mechanical > bioprosthetic (likely AC related). Reoperation risk: bioprosthetic > mechanical
    - TAVI: ASA monotherapy non-inferior to DAPT for thrombotic events & associated with less bleeding ([NEJM 2020;383:1447](#))
    - If need AC for AF, DOACs similar outcome after TAVI, not approved for valvular MS (moderate+) ([JAHA 2021;11:e023561](#))

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

# Cardiology

# Valvular Heart Disease

## AORTIC REGURGITATION (AKA INSUFFICIENCY)

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

## MITRAL STENOSIS

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

## MITRAL REGURGITATION

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

## TRICUSPID REGURGITATION

- **Etiology:** Primary: RHD, IE, iatrogenic (device leads, etc), congenital, trauma, carcinoid, drugs; Secondary: pulmonary HTN w/ RV remodeling ("functional"), dilated annulus (associated with AF), dilated CM, RV volume overload/ischemic papillary muscle dysfunction
- **Pathophysiology:** similar to mitral regurgitation, but involving RA/RV and tricuspid annulus
- **Clinical:** Right-sided heart failure: hepatosplenomegaly, ascites, peripheral edema, large V in JVP, pulsatile liver, substernal pulsation
  - Auscultation: holosystolic murmur at left mid- or lower- sternal border that increases with inspiration, S3
- **Treatment:** Medical: Diuresis (COR 2a), management of underlying cause
  - **Tricuspid valve replacement**: Consider if primary severe TR OR secondary severe TR with RV dilation/dysfx
    - Primary severe TR: if: 1) at time of LV valve surgery, 2) R heart failure, 3) moderate TR with progressive RV dilation/dysfx
    - Secondary severe TR if: 1) R heart failure poorly responsive to GDMT without ↑PAP or left HF ([Circ 2021;143:e35](#)).
    - Progressive TR (Stage B): consider if undergoing L valve surgery OR tricuspid annular dilation >4 cm w/ R heart failure
    - Transcatheter therapies are potential options but lack longterm outcomes and performance data ([JACC 2018;71:2935](#))

## GENERAL PRINCIPLES

- **Rheumatic Disease:** secondary ppx against streptococcus recommended for 10y or until 40 yrs old (whichever longer, COR I)
- **AF and Valvular disease:** w/o mechanical valve, DOAC reasonable VKA except in rheumatic MS, practice variable for nonrheum MS
- **IE Prophylaxis:** Reasonable in pts undergoing dental manipulation with 1) prosthetic heart valves, 2) prosthetic material used in valve repair, 3) prior IE, 4) Unrepaired cyanotic CHD, or 5) s/p cardiac transplant with valve abnormality (COR 2a; [Circulation 2021; 143:35](#))

# Cardiology

# Pericardial Disease

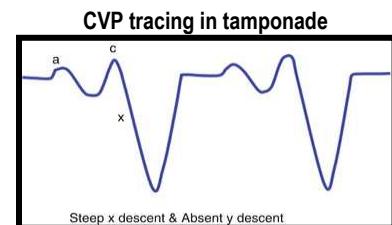
## CARDIAC TAMPONADE

- **Definition:** hemodynamic insufficiency caused by impaired cardiac filling due to ↑ pericardial pressure due to effusion, leading to ↑ intracardiac chamber pressures & eventually equalization of diastolic pressure in all 4 heart chambers
- **Etiologies of pericardial effusion:** idiopathic (20%), iatrogenic (16%), malignant (13%), uremic, HF, autoimmune ([Am J Med 2000;109:95](#)). Tamponade more likely in malignant, post-viral (including SARS-CoV-2), uremic, iatrogenic (i.e. post-cath) etiologies. Also seen with prox. aortic dissection & myocardial wall rupture

## Clinical Manifestation and Diagnosis:

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

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

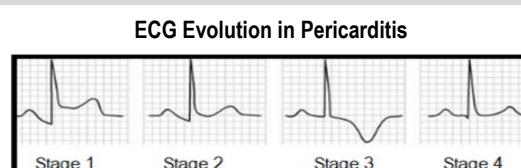


## Treatment:

- **Fluid resuscitation:** administer volume urgently to increase intracardiac pressures (monitor closely as overfilling can worsen tamponade), starting w/ 250-500cc bolus; greatest benefit for SBP  $< 100\text{ mmHg}$  ([Circ 2008;117:1545](#))
- **Inotropes:** administer if IVF insufficient. Unclear benefit b/c endogenous catecholamines already at max level. Avoid BB
- **PPV:** avoid if possible as ↑ positive intrathoracic pressure will further impede ventricular filling
- **Pericardial effusion removal:** catheter **pericardiocentesis**, surgical pericardectomy (if aortic/myocardial rupture), or HD (if uremic)
  - Analysis of pericardial fluid: cell count, total protein, LDH, gram stain/cx, viral markers/cx (Coxsackie, HSV, CMV, EBV, HIV), AFB smear/cx, ADA/IFN-gamma/lysozyme (if concerned for TB pericarditis), cytology/tumor markers
  - Removal of drain: when output  $< 50\text{ cc/d}$ , otherwise consider **pericardial window** (pleural>abdominal). See *Pericardial Drain*

## PERICARDITIS

- **Classification:** acute (<6w), subacute (6w to 6mo), chronic (>6mo)
- **Epidemiology:** 5% of pts in ED w/ CP and no MI, M  $> F$
- **Etiology:** 80-90% idiopathic (usually viral/post-viral), bacterial, fungal, post-MI, uremic, mycobacterial (TB), autoimmune (CTD, vasculitis), malignancy (e.g. lung, breast), XRT, drugs (procainamide, hydral, INH) ([NEJM 2014;371:2410](#))



## Clinical Manifestations and Diagnosis:

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

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

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

# Cardiology

# Aortic Disease

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

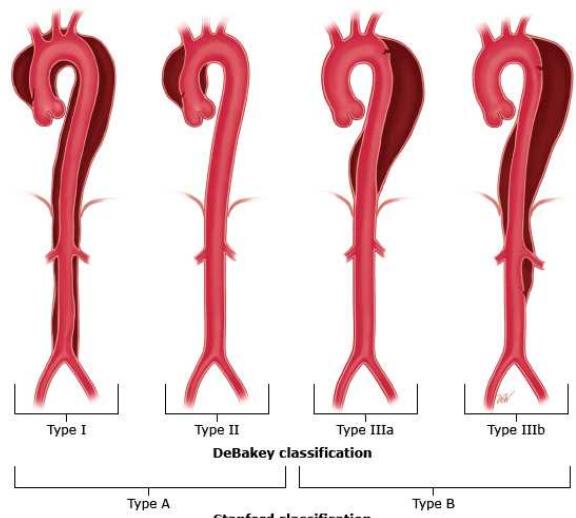
**Definitions:** three distinct processes with risk of rupture

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



### Classification:

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



Source: [UpToDate 2023](#)

### Epidemiology:

- Prevalence: aortic dissection most common (62-88%), followed by IMH (10-30%) & PAU (2-8%)
- Risk factors: male, HTN, age 60-70 (if <40yo, think Marfan syndrome, Ehlers-Danlos Syndrome type IV, CTD, bicuspid valve), atherosclerosis, prior cardiac surgery, aortic aneurysm, FHx of AAS, aortitis, trauma, pregnancy
- Aortic dissection prognosis:
  - Type A: mortality at 3y among patients discharged alive: *Medical*: 31%, *Surgical*: 10% ([Circ 2006;114:1350](#))
  - Type B: *Medical*: 8% in-hospital mortality, 15% 1y, 24% 3y, 57% 10y ([J Vasc Surg 2021;73:48](#))
- IMH will progress to complete dissection in 28-47%. PAU will progress to aortic rupture in 42%

### Diagnosis:

- Clinical features: AD, IMH, & PAU cannot be distinguished by presentation alone
  - Signs: AI murmur, pulse deficit, upper extremity BP differential (>20mmHg), CHF
  - Sx: chest or back pain (radiates to neck/jaw if ascending; back/abdomen if descending; may be migratory pain as dissection propagates)
- Complications: syncope, shock, branch artery occlusion (MI, CVA, paraplegia, cold extremity, renal failure); aortic valve regurgitation, cardiac tamponade, stroke
- Labs: rule out if D-dimer <500ng/mL (96% NPV), **troponin** (can be + if dissection extends into coronaries), ↑MMP-9
- Imaging:

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

### Management:

- Goal: “impulse control” → minimize aortic wall stress by ↓LV ejection force (dP/dT): goal HR <60, SBP 100-120mmHg
- Agents:
  - **IV beta blockade** (esmolol, labetalol); **except** if acute severe AI.
  - If additional BP control required, consider IV nitroprusside, TNG, nicardipine. If refractory HTN, consider renal artery involvement.
    - **NEVER** use vasodilators for AA without AI without concomitant beta blockade → will increase wall stress via reflex tachycardia, thereby increasing dP/dT. **Opiate analgesia** attenuates release of catecholamines ([Lancet 2015;385:800](#))
- Urgent surgical consultation (CT surgery)
- Aortic Dissection:
  - **Type A**: immediate open surgical repair 26% mortality vs >50% with medical management ([JAMA 2000;283:897](#))
  - **Type B**: *uncomplicated*: medical therapy (80% survival at 5y); *complicated* (compromise of renal/mesenteric vessels): TEVAR. However, **INSTEAD-XL** showed improved outcomes with low-risk preemptive TEVAR in all Type B dissections
- IMH & PAU:
  - **Type A**: urgent (i.e., within days) open surgical repair
  - **Type B**: medical management or TEVAR

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

	<b>Abdominal Aortic Aneurysm (AAA)</b>	<b>Thoracic Aortic Aneurysm (TAA)</b>
<b>Epidemiology</b>	<ul style="list-style-type: none"> <li>M&gt;F; &gt;65yo, mostly infrarenal</li> </ul>	<ul style="list-style-type: none"> <li>M&gt;F, mostly 50-70yo, 50% ascending Ao, 40% descending Ao, 10% arch</li> </ul>
<b>Etiology</b>	<ul style="list-style-type: none"> <li>Usually due to <b>atherosclerotic disease</b></li> <li><b>RFs:</b> <b>smoking, male sex, age, pre-existing atherosclerosis, obesity, HLD, HTN, FHx</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Atherosclerotic:</b> majority of cases, especially descending Ao. <b>RFs:</b> <b>smoking, HLD, HTN</b></li> <li><b>Structural/genetic:</b> mostly root &amp; ascending aorta. Causes: CTD (Marfan, Ehlers-Danlos, Loeys-Dietz), Turner, bicuspid AoV, trauma</li> <li><b>Infectious:</b> 3° syphilis, mycotic aneurysm (most common org: <i>Staph</i> spp., <i>Salmonella</i> spp.)</li> <li><b>Inflammatory:</b> GCA (~10% have TAA), Takayasu, RA, psoriasis, Behcet's, Wegener's, IgG4</li> </ul>
<b>Screening / Surveillance</b>	<ul style="list-style-type: none"> <li><b>ACC/AHA:</b> one-time abdominal US in all men &gt;60 w/ FHx of AAA &amp; all men 65-75 who have ever smoked</li> <li><b>Surveillance</b> (<a href="#">JVasc Surg 2018;67:2</a>): interval depends on size <ul style="list-style-type: none"> <li>3.0-3.9cm: q2-3y; 4.0-4.9cm: q12 months;</li> <li>5.0-5.4cm: q6 months</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li><b>General population:</b> not recommended</li> <li><b>Indications:</b> at time of dx of Marfan, Turner, Loeys-Dietz, Takayasu or GCA. 1° relatives of pt w/ TAA, dissection, bicuspid valve</li> <li><b>Surveillance</b> (<a href="#">JACC 2010;55:e27</a>): interval depends on presence of aneurysm vs dissection &amp; size by CT/MRI; ranging from q6-12months</li> </ul>
<b>Imaging Modalities</b>	<ul style="list-style-type: none"> <li><b>Abdominal US:</b> screening and surveillance of infrarenal AAAs. High Sn/Sp (&gt;90%), operator-dependent</li> <li><b>CT w/ contrast:</b> high Sn/Sp, better than US for suprarenal AAAs</li> <li><b>MRI/MRA:</b> good Sn/Sp, preferred for aortic root imaging &amp; for imaging tortuous aortas</li> <li><b>CXR:</b> "enlarged aorta" nonspecific (tortuous aorta vs aneurysm)</li> <li><b>TTE:</b> useful for root &amp; proximal thoracic aorta; <b>TEE:</b> will visualize entire thoracic aorta but rarely used</li> </ul>	
<b>Treatment</b>	<p><b>Medical</b></p> <ul style="list-style-type: none"> <li><b>Smoking cessation</b> (slows growth) (<a href="#">J Vasc Surg 2010;52:539</a>)</li> <li><b>Reduce BP</b> per ACC/AHA guidelines</li> <li><b>Meds:</b> statins (reduce all-cause mortality in pts s/p surgery) (<a href="#">JAHA 2018;7:19</a>) ; BBs (have not been clearly shown to slow expansion) (<a href="#">J Vasc Surg 2002;35:72</a>) ; ACEi (controversial); low dose ASA (may slow growth); avoid fluoroquinolones</li> </ul> <p><b>Surgical</b></p> <ul style="list-style-type: none"> <li>Men: <b>&gt;5.5cm OR growing &gt;0.5cm/6mo or &gt;1.0cm/y OR symptomatic</b> Women: <b>&gt;4.5-5cm</b> (controversial)</li> <li>Open repair vs EVAR</li> </ul>	<p><b>Medical</b></p> <ul style="list-style-type: none"> <li><b>Reduce BP</b> (&lt;140/90 or &lt;130/80 if DM or CKD)</li> <li><b>Meds:</b> BBs (decrease TAA growth in Marfan pts), ARBs (slows expansion in Marfan pts) (<a href="#">JACC 2014;64:1725</a>), statins (goal LDL&lt;70)</li> <li>Smoking cessation, avoid straining</li> <li>Stress test used to guide BP management</li> </ul> <p><b>Surgical</b></p> <ul style="list-style-type: none"> <li>Root/ascending TAAs: ± concomitant AVR</li> <li>Arch/descending TAAs: mostly open graft (EVAR)</li> </ul>
<b>Complications</b>	<ul style="list-style-type: none"> <li><b>Rupture:</b> devastating mortality. <b>Risk factors:</b> size, rate of expansion, female gender. <b>Sx:</b> triad of <b>abd/back pain + pulsatile abd mass + HoTN</b> → immediate OR</li> <li><b>Dissection:</b> pain (chest/abdomen/back), <b>occlusion of aortic vessels, thromboembolism</b></li> <li><b>Post-repair:</b> <b>EVAR:</b> endoleak, graft failure, thrombosis. <b>Open:</b> MI, embolization, AKI, ischemic colitis</li> </ul>	

# Cardiology

# Syncope

## OVERVIEW

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

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

Etiology	Historical Features	Diagnosis	Treatment
<b>Reflex (60%)</b> <ul style="list-style-type: none"> <li>• Vasovagal</li> <li>• Situational</li> <li>• Carotid sinus syncope</li> </ul>	<u>Vasovagal</u> : prodrome of dizziness, nausea, warmth, diaphoresis, pallor; a/w intense emotion, pain, or stress <u>Situational</u> : cough, sneeze, laugh, micturition, defecation <u>CSS</u> : neck turning/surgery/irradiation	<ul style="list-style-type: none"> <li>• <u>Vasovagal</u>: can dx w/ tilt table test, not necessary if clear dx by history (<a href="#">JACC 1996;28:263</a>)</li> <li>• <u>Carotid sinus syncope</u>: diagnose via carotid sinus massage (if no underlying bruits or CVA history)</li> </ul>	<ul style="list-style-type: none"> <li>• Avoid provocative stimuli</li> <li>• Isometric counterpressure maneuvers of the limbs (e.g. leg crossing, hand grip, arm tensing, Valsalva, squatting)</li> <li>• Meds for select cases (i.e. midodrine, fludrocortisone, βB) (<a href="#">NEJM 2005;352:1004</a>)</li> </ul>
<b>Orthostasis (15%)</b> <ul style="list-style-type: none"> <li>• Autonomic failure (1° or 2°)</li> <li>• Drug-induced</li> <li>• Volume depletion</li> </ul>	Prodrome of dizziness, nausea, warmth, diaphoresis, pallor <u>Risk factors for autonomic failure</u> : <ul style="list-style-type: none"> <li>- 1°: PD, Lewy body, MSA (formerly known as Shy-Drager)</li> <li>- 2°: DM, amyloid, spinal cord injury, chronic EtOH, Lyme, syphilis, B12 deficiency, meds (vasodilators, diuretics, BB, TCAs, PD meds, opiates, α-blockers)</li> </ul>	<ul style="list-style-type: none"> <li>• <u>Orthostatic vital signs</u> (systolic ↓20mmHg or diastolic ↓10mmHg w/in 3min of standing) <ul style="list-style-type: none"> <li>- ↑HR is <b>NOT</b> part of definition</li> </ul> </li> <li>• <u>Consider</u>: Hct, A1C, SPEP if c/f amyloid, RPR, B12</li> </ul>	<ul style="list-style-type: none"> <li>• <u>Primary</u>: <b>fludrocortisone</b> (0.1-0.2mg qd), <b>midodrine</b> (5-20mg tid), pyridostigmine, droxidopa (for PD-associated orthostasis)</li> <li>• <u>Secondary</u>: treat underlying etiology, replete volume, d/c culprit meds</li> </ul>
<b>Cardiac (15%)</b> <ul style="list-style-type: none"> <li>• Arrhythmia</li> <li>• Structural (AS, LVOT obs.)</li> <li>• Obstruction (e.g., PE, tamponade)</li> <li>• Dissection</li> </ul>	<u>No prodrome</u> , syncope while in sitting or supine position, palpitations, FHx or personal history of heart disease	<ul style="list-style-type: none"> <li>• Causes of cardiac syncope in young people (+ ECG signs): <ul style="list-style-type: none"> <li>1. WPW (delta wave)</li> <li>2. HOCM (LVH, apical TWI)</li> <li>3. Brugada (pseudo-RBBB with coved/saddleback pattern in V1-V2)</li> <li>4. Long QTc syndrome (QTc &gt;500ms)</li> <li>5. ARVC (Epsilon wave)</li> </ul> </li> <li>• <b>Consider cardiac monitoring</b> on basis of frequency and nature of syncope events (inpatient telemetry, Holter, Zio patch, implantable cardiac monitor)</li> <li>• <b>TTE only if H&amp;P suggestive</b> of cardiac cause (<u>&lt;1% yield if no underlying heart disease and normal ECG</u>) <ul style="list-style-type: none"> <li>○ ROMEO criteria: Sn 99.5%, Sp 15.4% (<a href="#">JHM 2018;13:823</a>)</li> </ul> </li> <li>• <b>Consider PE</b> if no other apparent cause → identified in 17.3% hospitalized w/ 1<sup>st</sup> syncope (&amp; 25.4% w/ no other apparent cause for syncope) (<a href="#">NEJM 2016;375:1524</a>)</li> </ul>	<ul style="list-style-type: none"> <li>• VT- Therapy with ablation and/or an implantable cardioverter-defibrillator (ICD) is indicated in most patients (<a href="#">JACC 2017;70:e39</a>)</li> <li>• SVT (Less common)- If evidence of accessory pathway is found, should be treated with catheter ablation.</li> <li>• Bradyarrhythmias- Depending on etiology of bradycardia, pacemaker therapy could be indicated</li> <li>• AS- If all other sources of syncope are ruled out, AVR may be indicated if patient is a surgical candidate</li> </ul>
<b>Neurologic (&lt;10%)</b> <ul style="list-style-type: none"> <li>• Seizure</li> <li>• Stroke/TIA</li> <li>• Subclavian steal</li> </ul>	<u>Seizure</u> : lateral tongue biting (Sn 20-33%, Sp 96-100%), urinary/fecal incontinence (Sn 38%, Sp 57%), aura, postictal confusion <u>Focal deficits</u> : stroke, TIA <u>Steal</u> : syncope after arm exercise	<ul style="list-style-type: none"> <li>• <u>Seizure</u>: EEG</li> <li>• <u>Stroke</u>: CT, MRI/MRA</li> <li>• <u>Steal</u>: UENI w/ Dopplers (specify for subclavian steal)</li> <li>• Carotid dopplers are of <u>low clinical utility</u> (changes management in &lt;2% of patients) (<a href="#">JAHA 2014;3:e001063</a>)</li> </ul>	<ul style="list-style-type: none"> <li>• Based on etiology, consider neurology consult and follow guideline-directed management &amp; therapy</li> </ul>

# Cardiology

# Severe Asymptomatic HTN & Emergency

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

- **Severe asymptomatic HTN** (formerly HTN urgency): BP  $\geq 180/120$  w/o evidence of end-organ damage (may have **mild headache**)
  - **Assess adherence** to prior rx before aggressively up-titrating regimen to avoid overcorrection of BPs & hypotension
  - **Assess cause** before tx; commonly due to pain, anxiety, urine retention, meds (e.g. steroids), OSA, nausea, withdrawal, etc.
- **Hypertensive emergency:** BP  $\geq 180/120$  w/ evidence of acute end-organ damage (rate of rise may be more impt. than actual BP)
  - **End-organ damage:** Neuro: HTN encephalopathy (severe HA, seizure, AMS), PRES, TIA, CVA (SAH, ICH); **Retinopathy:** papilledema, hemorrhage; **Resp/CV:** pulm edema, MI, angina, Ao dissection; **Heme:** MAHA; **Renal:** AKI, hematuria

	Severe Asymp. HTN ( <a href="#">JHM 2018;13:860</a> )	Hypertensive Emergency
Triage location	Floor vs outpatient mgmt (with close follow up) ( <a href="#">JAMA IM 2016;176:981</a> )	Floor vs ICU (ICU if needs arterial line, antihypertensive gtt, or if severe end-organ damage)
Correction time course	$\downarrow$ BP no more than 25-30% over hrs-days; then to goal as output. If hospitalized for non-cardiac reason, <b>worse outcomes w/ intensifying anti-HTN during admission</b> ( <a href="#">JAMA IM 2021;181:345-352</a> )	Reduce by max 25% within first hour, and to no lower than 160/100 within 2-6h; reduce to normal range over 24-48h
Route of medication administration	PO meds; avoid IV or high-dose meds (risk for AKI, stroke, MI d/t hypoperfusion)	Start with short-acting, titratable IV agents; transition to PO agents for floor/discharge
Suggested meds (see below for dosing)	PO: start captopril, labetalol >> hydralazine (unpredict., reflex tachy) & convert to long-acting before discharge OR start long-acting agents	IV: labetalol >> hydralazine Topical: nitro paste (may be used on the floor) Drips: see below

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

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

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

# Cardiology

# Peripheral Artery Disease

## OVERVIEW

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

## CLINICAL PRESENTATION AND DIAGNOSIS

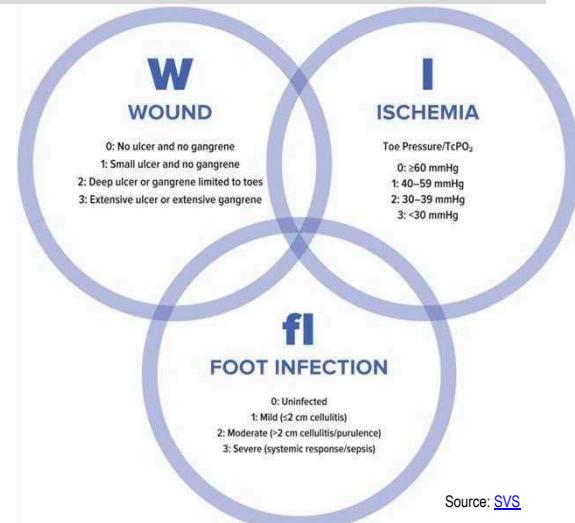
- Symptoms: ([Circ 2006;113:e463](#))
  - **Classic claudication** (10-35%) - reproducible exertional pain distal to occlusion, relieved by rest (differentiate from pseudo-claudication from spinal stenosis); **atypical leg pain** (most common, 40-50%); asymptomatic (20-50%).
  - **Threatened limb** (1-2%):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

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

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

## TREATMENT

- Optimize CV risk factors (e.g., HTN, DM, HLD, weight loss), formal exercise program, high-intensity statin, smoking cessation
  - CLEVER-RCT: supervised exercise therapy is at least as effective as stenting ([JACC 2015;12:2055](#))
  - ERASE-RCT: supervised exercise therapy + revascularization > exercise alone ([JAMA 2015;314:1936](#))
- Ischemic ulcers: wound care, may also need revascularization for appropriate healing depending on ABI
- Anti-platelets: if symptomatic, **ASA** 81-325mg qd or **clopidogrel** 75mg qd: ↓MI, CVA, vascular death ([NEJM 2017;376:32](#)). If asymptomatic, consider ASA 81mg. **Avoid DAPT** ([NEJM 2006;354:1706](#)) unless clinically indicated, usually post-revascularization. Review w/ clinical decision making algorithm ([JACC 2018;71:2450](#)).
- Anti-coagulation: rivaroxaban 2.5mg BID + ASA: ↓major adverse cardiac & limb events vs ASA alone ([Lancet 2018;391:219](#)). Caution as ↑major bleeding, but no ↑fatal bleeding in pts w/ stable PAD in study
- Cilostazol: Start 100mg BID. PDE3 inhibitor w/ vasodilatory and anti-platelet effects. Adjunct for symptom relief refractory to exercise therapy/smoking cessation. Use in combination with ASA or anti platelet ([Chest 2012; 142:1608](#)). Only AHA/ACC recommended med to ↑exercise capacity ([Circ 2017;135:e686](#)). Contraindicated in HF
- Endovascular repair (angioplasty vs stent) if threatened limb and/or severe symptoms refractory to medical management. Assess benefit of revascularization vs amputation with SVS Wifl score, above ([JVS 2014; 59:P220-234](#))



## ACUTE LIMB ISCHEMIA ([BMJ 2000;320:764](#))

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

## OVERVIEW ([JACC 2017;70:2536](#); [JACC 2017;70:2552](#))

Cardiotoxicities have been noted throughout the cardiovascular system including HF, ischemia, atherosclerosis, HTN, myocarditis, pericardial diseases, thromboembolism, QT prolongation, and arrhythmias.

**Risk factors:** pre-existing CV disease or known cardiovascular risk factors (DM, HLD), extremes of age, female

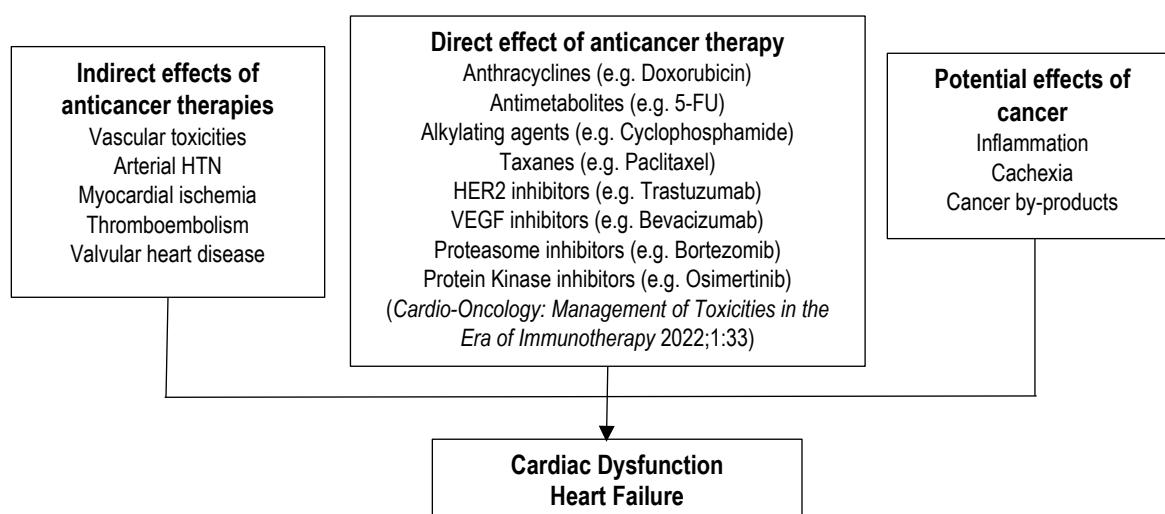
**Diagnosis:** TTE (compared to baseline), ECG, TnT ( $\uparrow$  correlates to adverse cardiac events post-chemo), MRI/PET/biopsy if suspect ICI myocarditis ([Lancet Onc 2018;19:e447](#))

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

### Screening/monitoring:

- TTE surveillance schedule depends on therapy & baseline cardiac risk; ranges from q3-6mo with long-term risk >10y. Must be completed baseline prior to anthracyclines.
- Monitor weekly BP in first cycle, then q2-3 weeks on therapy, initiate therapy when DBP > 20mmHg
- Certain therapies with well-studied CV risk (i.e., anthracyclines, Trastuzumab, radiation) have guidelines to direct CV monitoring, however, most do not and proper CV monitoring is an ongoing area of investigation. Pragmatic surveillance strategies have been proposed and may be useful managing a cancer patient with a new cardiac symptom/condition ([JAHA 2020;9:e018403](#))

**Treatment:** optimize preventative CV health (e.g., lipids, DM, blood pressure, etc.) and standard HF and ischemic work up/management(generally, ASA if plt>10k, DAPT if plt>30k). Cessation of chemotherapy often last-resort (multi-disciplinary conversation)



## IMMUNE CHECKPOINT INHIBITORS AND RADIATION

Examples: Ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab

- ICI Cardiac Toxicity (see ICI):** Myocarditis (best studied), also been associated with Takotsubo syndrome, ACS, arrhythmias and pericardial diseases (pericarditis), Fulminant myocarditis (RF = combo therapy)
  - Dx: troponins, EKG, TTE, cMRI (Sn 50%), endomyocardial bx (lymphohistiocytic infiltrate, T cells in HPF)
  - Tx: stop ICI; pulse-dose steroids (e.g., 1g IV methylprednisolone x 3-5d) → steroid taper; with cardiology/oncology team can consider further immunosuppressive agents
- Radiation:** Can cause CAD (up to 85%), pericardial disease (6-30%), CM (up to 10%), valvular abnormalities, PVD, arrhythmias, autonomic dysfunction, can occur 10-15 years later, many RF including dosage, metabolic RF
  - Screening:** recommend stress testing within 5-10 years after chest radiation

## ADDITIONAL COMMON CARDIOTOXIC THERAPIES

- Anthracyclines** (Doxorubicin, idarubicin, epirubicin, daunorubicin): Best characterized cardiotoxicity; HF in dose-dependent manner; LV dysfunction (5-23%), irreversible damage; should perform baseline cardiac imaging (TTE) prior to tx
- Taxanes** (paclitaxel, docetaxel): Conduction abnormalities (bradycardia, heart block); potentiate toxicity of anthracyclines
- Alkylating agents:**
  - Cyclophosphamide:** Cardiomyopathy associated with high-dose protocols (not cumulative dose); hemorrhagic myocarditis
  - Ifosfamide:** Arrhythmias, ST-T changes, HF (dose-related)
  - Cisplatin:** SVT, bradycardia, ST-T changes, LBBB, ACS, iCM. Peripheral vascular: Raynaud, HTN, CVAs
- Etoposide:** Myocardial infarction, vasospastic angina
- Monoclonal Abs:**
  - Trastuzumab (HER2):** 2.1% risk of  $\downarrow$ LV dysfunction, resolves once stopped; TTE q3months
  - Bevacizumab (VEGF):** HTN, 3-fold increase in arterial thromboembolic events
- Protein kinase inhibitors:**
  - Osimertinib, mobocertinib (EGFRi):** CMP, QTc prolongation
  - Sorafenib, sunitinib (multi TKI):** HTN, HF, conduction abnormalities
  - Ibrutinib, zanubrutinib (Bruton TKI):** SVT, VT, HF, HTN
- Proteasome inhibitors** (carfilzomib, bortezomib): HF, pHTN, MI

# Cardiology

# Outpatient CV Health

## EPIDEMILOGY OF CARDIOVASCULAR DISEASE

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

### Risk Factors:

- **Non-modifiable:** Age (each decade confers 2x ↑ risk from prior), Sex (F with ~20% ↓ risk than M, though risk ↑ 3x in F post-menopause), FHx premature ASCVD (1<sup>st</sup> degree relative w/ ASCVD before 55y M or 65y F)
- **Modifiable:** HTN, HLD (↑ Total, LDL-C, ApoB, Non-HDL, Lp(a), or TG; ↓ HDL), DM, CKD, obesity, smoking (esp. current), exercise, alcohol, diet, psychosocial stress (chronic + acute), chronic inflammation (CRP best biomarker), mediastinal radiation, HIV

## ASPIRIN FOR CVD PREVENTION

### Primary prevention:

- **2019 ACC/AHA 1° prevention guidelines:** No routine rx; might consider low-dose ASA for 1° prevention in select pts 40-70y at ↑ ASCVD risk & not at ↑ bleeding risk; avoid ASA for 1° prevention in pts >70y ([Circ 2019;140:e596](#))
- **Key trials:** ASCEND ([NEJM 2018;379:1529](#), pts >40y w/ DM), ARRIVE ([Lancet 2018;392:1036](#), pts w/ multiple non-DM CVD RFs), & ASPREE ([NEJM 2018;379:1519](#), pts >70y [>65y if Black/Hispanic]): low-dose ASA either w/out sig CV benefit or w/ CV benefit counterbalanced by ↑ risk of major bleeding

**Secondary prevention:** In pts w/ stable CVD, low-dose ASA ↓ incidence of adverse CV events and all-cause mortality ([Am J Med 2008;121:43](#))

## OUTPATIENT BLOOD PRESSURE SCREENING AND MANAGEMENT

**2017 ACC/AHA guidelines** ([HTN 2018;71:1261](#)):

- **Definition:** HTN = SBP >129 or DBP >79 independent of kidney function or age; US prevalence 46%
- **Method:** 2 checks >1w apart, sitting 5min with arm at heart level, cuff bladder 80% length & 40% width of arm circumference
  - 24h ambulatory SBPs show greater association w/ all-cause mortality than clinic BPs. Patient log [here](#).
- **Categories:** Normal: <120/(and)<80; Elevated: 120-129/(and)<80; Stage 1 HTN: 130-139/(or)80-89; Stage 2 HTN: >140/(or)>90

**Initial Workup:** BMP, UA, Ualb/Cr ratio, CBC, fasting glucose, TSH, lipids, baseline ECG, 10-yr ASCVD risk, consider TTE (eval for LVH)

**2° HTN: targeted approach to workup**, consider the following indications ([HTN 2018;72:e53](#)):

- Resistant HTN (not controlled on 3+ agents [at least one diuretic]) OR Severe HTN (controlled on 4+ agents [at least one diuretic])
- Acute rise in blood pressure in a previously well-controlled patient, esp. DBP
- Age <30y w/o risk factors (e.g. obesity, FHx)
- HTN with suggestive electrolyte disorders (hypoK, metabolic acidosis)
- Malignant OR Accelerated HTN (severe HTN presenting with clinical or laboratory signs of end-organ damage)

Secondary Causes of HTN		
Cause	Clinical Clues	Work-up
Medications/Drugs (use or withdrawal)	NSAIDs, OTC decongestants, OCPs, anti-depressants, corticosteroids, sudden d/c of anti-HTN meds (i.e., clonidine)	Thorough history
OSA	Obesity, snoring, smoking	Sleep study
Renal disease	Elevated Cr, protein/blood on UA	See AKI and CKD
Primary aldosteronism	Hypokalemia, hypernatremia, adrenal incidentaloma, FHx	Plasma aldo:renin activity; measure together in morning (~8AM), after pt awake for >2h, seated for >5 minutes; <b>high rates of underdiagnosis and undertreatment</b>
Renal artery stenosis	>50% rise in Cr after ACE/ARB initiation; lateralizing abdominal bruit; severe HTN in s/o atrophic/asymmetric kidneys, or diffuse atherosclerosis/FMD	If intervention likely to be pursued, begin with Duplex Doppler US (Sn 85%, Sp 92%) → if stenosis (ARAS>50%) or ambiguous results, consider angio

**Rare:** pheochromocytoma, Cushing's disease, hyper/hypothyroidism, hyperparathyroidism, aortic coarctation, ADPKD

Lifestyle Counseling ( <a href="#">HTN 2018;71:1261</a> )		
Intervention	Approach	SBP impact in pts w/ HTN
Exercise	Aerobic: 90–150 min/wk at 65–75% HR reserve	↓5–8mmHg
Exercise	Dynamic resistance (see guidelines for program specs)	↓4mmHg
Exercise	Isometric resistance (see guidelines for program specs)	↓5mmHg
Weight loss	Weight reduction in overweight/obese adults	↓1mmHg for every 1kg of weight lost
Diet (DASH)	↑veg, fruit, whole grain, lean meat; ↓sweets, red meat	↓11mmHg
Sodium	Consume <1.5g/day	↓5–6mmHg
Potassium	Consume 3.5–5g/day	↓4–5mmHg
Alcohol	Limit consumption to <1/2 standard drink/d in F/M	↓4mmHg

## Medical Management ([HTN 2018;71:1261](#))

When to Treat	Stage II HTN or Stage I if: clinical CVD, DM2, CKD, or ASCVD ≥10%
Target BP	<130/80

# Cardiology

# Outpatient CV Health

Choice of Agent	First-line: thiazides (chlorthalidone may not be > HCTZ, ↑SEs ( <a href="#">JAMA IM 2020;180:542</a> )), ACEi/ARB, CCB Other: βB, hydralazine, isosorbide, clonidine, α-blockers (e.g. doxazosin), minoxidil (rare)
Compelling Indications	DM2: ACEi/ARB (if proteinuria)      HF: βB, ACEi/ARB, diuretic, spiro      CKD: ACEi/ARB CAD: βB Pregnancy: labetalol, CCB
Monitoring	Follow-up eval for BP response/adherence at monthly intervals until BP controlled Labs: check BMP/Mg if starting ACEi/ARB or diuretic, 2-4w after initiation, then yearly or w/ Δdose
Important Trials Re: BP goals	SPRINT ( <a href="#">NEJM 2015;373:2103</a> ): SBP goal <120 vs 135-139 ↓CVD events & all-cause mortality in high-risk pts, but ↑ non-orthostatic hypotension, syncope, electrolyte abnormalities, & AKI ACCORD BP ( <a href="#">NEJM 2010;362:1575</a> ): in pts w/ DM, no CV mortality benefit a/w SBP goal <120 vs <140

## OUTPATIENT CHOLESTEROL SCREENING AND MANAGEMENT

2018 ACC/AHA guidelines ([Circ 2018;139:e1082](#)):

- Screening:
  - Check a lipid panel in adults ≥20y to establish baseline LDL-C and estimate ASCVD risk
  - Measurement of apoB and Lp(a) may confer nuance to risk estimation; approaches are evolving ([JAMA Cardiol 2019;4\(12\):1287](#); [JAMA 2021;326\(4\):352](#))
- Methods:
  - Fasting: *not routinely recommended*; consider if non-fasting TG >400 or pt has FHx premature ASCVD or genetic hyperlipidemia
  - Low LDL-C: If LDL-C <70 and precise measurement warranted, measure direct/modified LDL-C (Friedewald formula less accurate with decreasing LDL-C)
- Familial hypercholesterolemia (FH): Heterogeneous diagnostic criteria, typically combo of suggestive clinical (premature CVD, tendon xanthomas), lab (LDL-C ↑↑), genetic (LDLR, APOB, PCSK9), and FHx (strong FHx premature CVD) findings
- Common 2° causes of dyslipidemia: Diet (weight gain, anorexia, alcohol, diet rich in trans/sat fats or refined carbs), drugs (orals estrogens, glucocorticoids, diuretics, anabolic steroids, amiodarone, tamoxifen, raloxifene), diseases (nephrotic syndrome, chronic renal failure, biliary obstruction), disordered metabolism (hypothyroid, obesity, pregnancy, poorly-controlled DM)
- See indications for/approaches to rx below; statin therapy is the cornerstone of med rx, should be added to maximally tolerated effect before reaching for secondary meds
- Lipid monitoring:
  - Yearly if pt at goal & compliant
  - Assess 4-12w after statin initiation or dose change, repeat q3-12mo as needed

Lifestyle Counseling ( <a href="#">Circ 2018;139:e1082</a> )	
Intervention	Approach
Diet	<u>Emphasize</u> : veg, fruit, whole grain, legume, healthy protein sources (low-fat dairy/poultry, fish, nuts), non-tropical veg oils, unsat fats <u>Limit</u> : sweets, refined carbs, processed/red meats, trans/sat fats
Weight control	Weight loss in overweight/obese pts; reasonable to track risk with BMI, waist circumference measurement
Exercise	<u>Target</u> : aerobic, 3-4 sessions/wk, ~ 40min/session, moderate-to-vigorous intensity Decrease sedentary behavior

Indications for Statin Therapy	
ASCVD Risk Score	
Clinical ASCVD, <75y	Maximally-tolerated statin to reduce LDL-C by ≥50%
LDL-C ≥190, 20-75y	Maximally-tolerated statin to reduce LDL-C by ≥50%
Diabetes (age 40-75)	Moderate-intensity statin; consider high-intensity statin for ASCVD risk >20%, multiple ASCVD RFs to reduce LDL-C by ≥50%
Age 40-75 w/o above	(10 yr ASCVD) <u>Low risk &lt;5%</u> : lifestyle changes <u>Borderline risk 5-7.5%</u> : consider mod-intensity statin based on risk-enhancers* <u>Intermediate risk 7.5-20%</u> : statin to ↓ LDL-C ≥30-49%, CAC may help decision <u>High risk &gt;20%</u> : statin to ↓ LDL-C ≥50%

\*ASCVD risk enhancers: FHx premature ASCVD, LDL-C ≥160, CKD, premature menopause (age <40), pre-eclampsia, metabolic syndrome, inflammatory dz (RA, HIV, SLE, psoriasis), ethnicity (South Asian), TG ≥175, hs-CRP ≥2, Lp(a) ≥50, apoB ≥130, ABI <0.9

\*Coronary artery calcium (CAC) score: 0 favors no statin in intermediate risk in absence of DM, active smoking, or early FHx; 1-99 favors statin therapy; CAC 100+, initiate statin

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

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

Statin Potency	
<b>High-intensity</b> (≥50% ↓ LDL-C)	atorvastatin 40-80mg rosuvastatin 20-40mg
<b>Mod-intensity</b> (30-49% ↓ LDL-C)	atorvastatin 10-20mg, rosuvastatin 5-10mg, simvastatin 20-40mg, pravastatin 40-80mg, lovastatin 40-80mg
<b>Low-intensity</b> (<30% ↓ LDL-C)	simvastatin 10mg, pravastatin 10-20mg, lovastatin 20mg

#### \*Statin Properties:

Biggest change in LDL: rosuvastatin > atorvastatin > simvastatin

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

Safest in cirrhosis: pravastatin

Lowest rate of myopathy: pravastatin, fluvastatin

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

Lower overall side effects: pravastatin, rosuvastatin (hydrophilic)

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

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

**Definition:** Overweight: BMI 25.0-29.9kg/m<sup>2</sup>; Obesity: BMI ≥30kg/m<sup>2</sup>; Severe Obesity: BMI ≥40kg/m<sup>2</sup>

### Management:

- Goals:** Comprehensive lifestyle approach; sustained weight loss of just 3-5% body weight = clinically meaningful health benefits (↓ TG, A1c); ↑ benefits with ↑ sustained weight loss (↓ TG, A1c, BP, LDL-C) (Circ 2014;129:S102)
- Diet:**
  - Compliance: ↓ calories ↑ imp than macronutrient composition. No data to guide specific diet ([JAMA 2014;312:923](#))
  - Mediterranean: high in monounsaturated fats, fruits, vegetables, legumes, grains; moderate dairy & EtOH; low meat (↓ overall & CV mortality; may ↓ DM incidence independent of wt loss) ([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:**
  - >30min, 5-7 days/w; combine aerobic + resistance training for optimal health gains ([Arch Intern Med 2009;169:122](#))
  - Not sufficient for wt loss; improves glycemic control, BP, & functioning; ↓ CVD risk, predicts long-term weight mgmt
- Medications:**
  - Consider pharmacotherapy if BMI ≥30 or BMI ≥27 with ≥1 comorbidity and not meeting weight loss goals
  - First line: GLP-1 agonist, sustained & clinically relevant weight loss when combined with exercise; tirzepatide > semaglutide, though both effective options ([NEJM 2021;385:503](#))
  - Other options: Orlistat, phentermine/topiramate, naltrexone/bupropion, lorcaserin, metformin (if pre-diabetic)
  - All have significant short-term weight loss (~5-15lbs), but weight is typically gained back when medication stopped
- Bariatric surgery:** recommended for: BMI ≥40 OR BMI ≥35 with comorbid conditions; BMI <35 has insufficient evidence

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

#### To lose 1-2 pounds per week:

- Total daily caloric intake should = daily caloric requirement – 500
- Daily caloric requirement = basal metabolic rate (BMR) + daily activity level + thermic effect of food

# Cardiology

# Anti-Arrhythmic Medications

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

\*Renal dosing required

†Green = @MGH commonly used drugs in each class

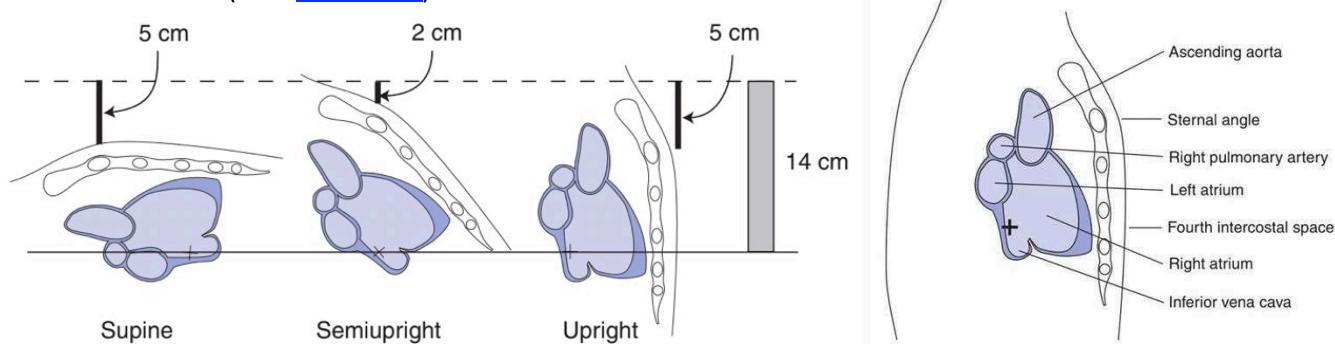
# Cardiology

# Telemetry & Physical Exam

## BRIEF PHYSICAL EXAM TIPS (McGEE 2021)

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

## Measurement of JVP (From McGee 2021)



## CARDIAC TELEMETRY: RUNNING THE "TELE"

Step 1: Locate the name of the desired patient on the telemetry monitor and select their telemetry strip.

Step 2: Once on patient's telemetry strip, select "Patient Data."

Step 3: Click "Event Review" which will show you any abnormal events the patient had since being placed on telemetry. From this list, click the desired episode of choice.

Step 4: After clicking on the desired event, you will have multiple options to choose from:

- Events: events sorted in reverse chronological order (e.g. runs of NSVT, bradycardia)
- FD Strip: telemetry strip for a specific moment in time
- FD Page: global view useful in identifying abrupt changes that can be zoomed in on using the FD Strip view
- Graphic Trends: graphic view of HR trends over time
- Calipers: interactive calipers used to calculate intervals on telemetry strip

While a patient is on telemetry, review indication daily and discontinue if not using monitoring for clinical decision-making (refer to [AHA Guidelines](#) for appropriate use of hospital telemetry)

# Pulmonary & Critical Care

**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  $\geq 20$ )
- Cyanosis (typically SpO<sub>2</sub>  $<80\%$ )
- ↑WOB (nose flaring, retractions, grunting, tripod-ing, diaphoresis)
- Obstruction (wheezing, stridor)

## APPROACH

- 1) **Confirm code status**
- 2) **Low threshold to call Rapid Response for assistance**
- 3) **Assess airway, breathing, circulation & confirm access**
  - **Place on supplemental O<sub>2</sub>**: NRB to start, can always wean later
  - **Red flags (RICU STAT)**: GCS  $<8$  (hard criteria for intubation), pooling secretions, hemoptysis, life-threatening hypoxemia despite supplemental O<sub>2</sub> (SpO<sub>2</sub>  $<80\%$ , PaO<sub>2</sub>  $<55\text{ mmHg}$ ), severe hypercapnia despite BiPAP, tiring out ( $\uparrow$ WOB, progressive hypercapnia), RR  $>35$
  - **Temporize**: suction, head-tilt chin lift (preferred if no concern for C-spine injury) vs jaw-thrust to open airway, bag-mask ventilation (enough volume to see chest rise, no more than 8-10cc/kg or 5-6cc/kg during CPR; 8-10 breaths/min). If use of bag-mask will not be brief & pt unresponsive, consider OP airway prior to intubation
- 4) **Initial workup**:
  - **CXR** (order STAT, must call **x6-3050**): look for new infiltrate (aspiration, PNA), pulmonary edema, lobar collapse (mucus plug), PTX. For read, call **x4-1533**. If nl, consider ischemia, PE, acidosis
  - **ABG**: worrisome if PaCO<sub>2</sub>  $>45\text{ mmHg}$  (poor ventilation) or falling (tachypnea), PaO<sub>2</sub>  $<60\text{ mmHg}$  (poor oxygenation), pH  $<7.25$
  - **Labs**: VBG (& ABG if possible, correlate to VBG. Widened A-a gradient  $>20$  = abnormal gas exchange vs nl  $<20$  = global hypoventilation), hs-Trop, NT-proBNP, lactate, BMP, CBC
  - **Additional studies based on clinical suspicion**: CT-PA (if stable to travel), Stat TTE (acute valvular dz, RV strain), NCHCT vs stat CTA head/neck with code stroke if suspected and suspicion high

## TREATMENT

- **Supplemental oxygen therapy** (see *Oxygen Delivery Therapies* for more detail):
  - **NC**: for every liter increase in O<sub>2</sub>, approx.  $\uparrow$ FiO<sub>2</sub> 0.03/L (max: 6L = 0.40 FiO<sub>2</sub>, dependent on V<sub>e</sub>/entrainment)
  - **NRB**: can give FiO<sub>2</sub>  $\sim 0.90$ , but in tachypneic patient, FiO<sub>2</sub>  $\sim 0.60$  (due to entrainment of room air)
  - **HFNC**: FiO<sub>2</sub> 0.6 to 1.0 at 10-60 L/min (humidified air);  $\downarrow$ 90d mortality vs BiPAP for pts with hypoxic respiratory failure secondary to PNA ; benefit not seen in pulmonary edema or obstructive lung disease ([NEJM 2015;372:2185](#))
- **NIPPV** (BiPAP for COPD; CPAP for CHF): RR  $>25-30$ , accessory muscle use, pH  $<7.35$ , PaCO<sub>2</sub>  $>45\text{ mmHg}$
- **Intubation**: see **red flags** above

## DISEASE SPECIFIC TREATMENT

- **CHF**: CPAP, IV diuresis, nitrates (*paste or drip*, if BP room)
- **Asthma**: nebulizers (albuterol 2.5-5mg q20min or stacked DuoNeb), steroids (IV methylpred 125mg q6h), IV Mg (2g/20 min). Trial BiPAP; however, if RR remains  $>25$ , VBG w/ nl or rising CO<sub>2</sub>, AMS, or bradycardia, discuss intubation.
- **COPD**: BiPAP, nebulizers (stacked DuoNebs), steroids (IV methylpred 60-125mg); IV Mg (2g/20 min), abx if 2/3:  $\uparrow$ sputum volume, purulence, dyspnea
- **Hemoptysis (massive)**: place pt in lateral decubitus, **bleeding lung side down**; volume resuscitate, reverse coagulopathies
- **Mucus plugging**: airway suctioning, chest PT, guaifenesin, place pt in lateral decubitus, **good lung side down**
- **PE**: if high suspicion and no contraindication, start **empiric AC** (LMWH therapeutic faster vs UFH gtt). **Consult PERT x4-7378**
- **PTX**: if unstable, bedside needle thoracostomy (**STAT page Thoracic Surgery**, 14-16G angiocath, 5<sup>th</sup> ICS at mid-axillary line or 2<sup>nd</sup> ICS at mid-clavicular line); page Thoracic Surgery or IP for chest tube
- **Pleural effusion**: Therapeutic thoracentesis (see *Thoracentesis*; done by Pulm, IP, or supervised by pulm attending)
- **Opioid overdose**: Narcan 0.4mg starting dose up to 2mg IV/IM q2min, observe response, uptitrate to adequate RR. Given short half-life, consider gtt if responsive to bolus at 2/3 of bolus dose per hour (ex: 0.2–0.6 mg/h)
- **Anaphylaxis**: Initial: epi (1:1000) 0.3mL = 0.3mg IM, q5-15min PRN. Other agents may follow: diphenhydramine 25-50mg IV, nebulized albuterol, methylprednisolone 125 mg IV
- **ACS** (see ACS): ASA 325mg, atorvastatin 80mg, nitrates (SL/nitropaste → gtt), heparin, diuresis, O<sub>2</sub>, Pain cntrl, consult Cards

# Respiratory Distress

## DYSPNEA DDx

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

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

## DECISION TO INTUBATE

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

**RICU Communication Guide**: have following information ready prior to intubation

- **Code status & urgency/acute of decline**
- **Hemodynamics**: LV, RV, valves, volume status, access
- **Aspiration risk**: NPO, last meal, NGT?, RFs
- **Difficult airway** (from prior intubation notes)
- **Allergies**

**Have ready**: sedation (propofol, fentanyl, midaz), pressor (Neo vs Epi if RV failure  $>$  Levo), IVF w/ push line; RICU brings paralytic

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

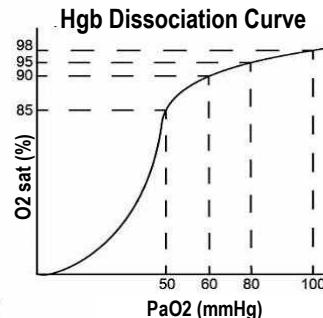
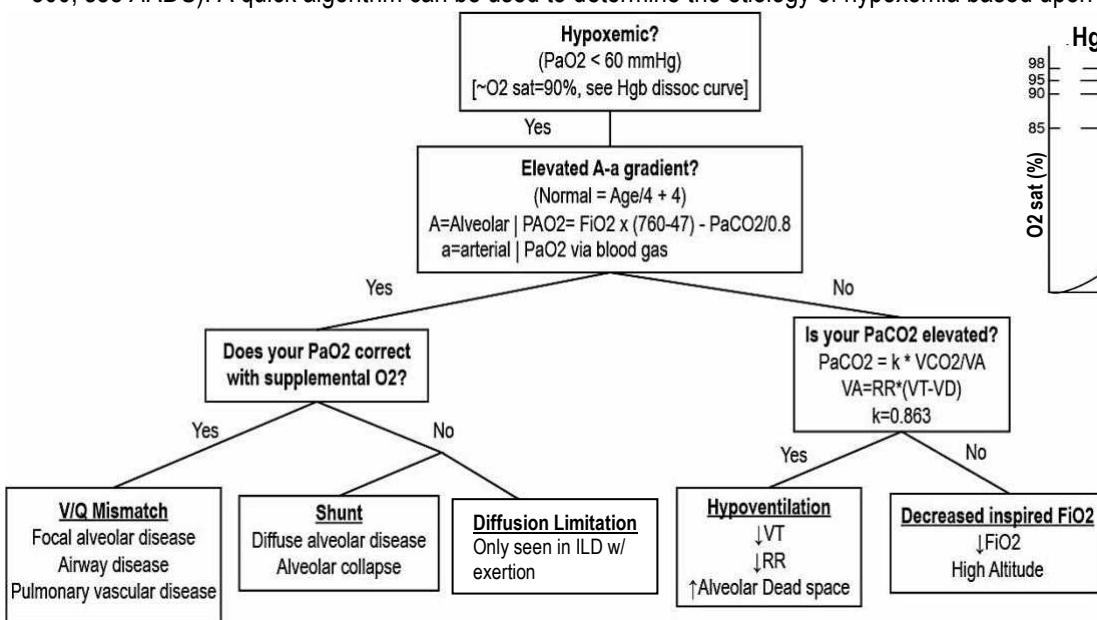
## INTUBATION IS NOT AN ACT OF

**WEAKNESS** Do not delay intubation in patients with impending respiratory failure

# Pulmonary & Critical Care

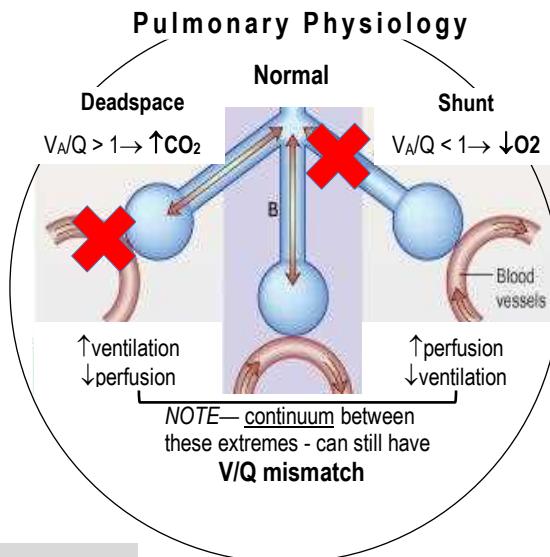
# Hypoxemia & Hypercapnia

**Respiratory Failure:** inability to oxygenate (deliver O<sub>2</sub>) or ventilate (blow off CO<sub>2</sub>). Can be **hypoxicemic** (PaO<sub>2</sub> < 60 mmHg), **hypercapnic** (PaCO<sub>2</sub> > 45 mmHg), or both. **P:F Ratio** (P=PaO<sub>2</sub>/F=FiO<sub>2</sub>) quick surrogate for A-a gradient (consider ARDS if P:F < 300; see ARDS). A quick algorithm can be used to determine the etiology of hypoxemia based upon ABG results.



## HYPOXEMIC RESPIRATORY FAILURE

- **Hypoventilation & low FiO<sub>2</sub>:** decreased O<sub>2</sub> delivery to lungs
- **V/Q mismatch:** imbalance in delivery of oxygenated air & blood flow
  1. **FOCAL** alveolar infiltrates: **pus (PNA), edema, hemorrhage (DAH), cells (cancer), aspiration**
  2. Airway: **asthma, COPD, bronchiectasis**
  3. Vascular: **pHTN, PE**
- **Shunt:** flow of blood through lung without encountering oxygenated air, “perfusion without ventilation” (severe V/Q mismatch). Will not improve with supplemental oxygen (refractory hypoxemia)
  1. **DIFFUSE** alveolar infiltrates: **above + ARDS**
  2. Alveolar collapse: **PTX, atelectasis, mucus plug**
  3. Intra-cardiac/pulm shunts: **PFO/ASD/VSD** ( $\uparrow$ PEEP worsens this by  $\uparrow$ west zones 1&2 =  $\uparrow$ RV afterload), **AVM** (e.g., hepatopulm.)
- **Impaired diffusion (↓DLCO):** hypoxemia worse w/ exertion
  - o ILD (correlates with severity on CT), pHTN, advanced COPD



## HYPERCAPNIC RESPIRATORY FAILURE

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

## ACID-BASE INTERPRETATION

**Hypercapnia** → Resp acidosis ( $\uparrow$ pCO<sub>2</sub>)

- Acute: HCO<sub>3</sub> ↓ by 1 (per pCO<sub>2</sub> ↑ 10)
- Chronic: HCO<sub>3</sub> ↓ by 3-4 (per pCO<sub>2</sub> ↑ 10)

**Hypocapnia** → Resp alkalosis ( $\downarrow$ pCO<sub>2</sub>)

- Acute: HCO<sub>3</sub> ↓ by 2 (per pCO<sub>2</sub> ↓ 10)
- Chronic: HCO<sub>3</sub> ↓ by 5 (per pCO<sub>2</sub> ↓ 10)

## CONVENTIONAL OXYGEN DELIVERY DEVICES

### Recommendations for Supplemental Oxygen Therapy ([BMJ 2018](#))

- Target SpO<sub>2</sub> 90-94%: Most acutely ill patients (↑SpO<sub>2</sub> >94-96% in acutely ill adults a/w ↑mortality ([Lancet 2018;391:1693](#)))
- Lower target (SpO<sub>2</sub> 88-92%): At risk for hypercapnic respiratory failure (COPD, OHS, OSA, decreased central respiratory drive, neuromuscular respiratory disease)
- Higher Target (~SpO<sub>2</sub> ~100%): CO poisoning, cluster headaches, sickle cell crisis, pneumothorax

Mask Type	Flow (LPM)	FiO <sub>2</sub> (%)	Notes	Aerosol?
Nasal Cannula	1 - 6	24 - 40	FiO <sub>2</sub> ↑ by 0.04 per L Allows patient to eat/speak. Consider humidification if >4LPM	N
Oxymizer	1 - 15	24 - 45	20mL reservoir allows for higher FiO <sub>2</sub> compared to NC	N
Simple Facemask	6 - 10	30 - 60	Flow rates < 6LPM lead to re-breathing of CO <sub>2</sub>	N
Face Tent (Shovel mask)	5 - 10	24 - 50	Less claustrophobic, FiO <sub>2</sub> variable (lots of leakage). Use if stable O <sub>2</sub> needs Offers humidification without a mask	Y, if humidified
Non-Rebreather	10 - 15	60 - 100	Consider first for acute hypoxemia (easily accessible) ↑FiO <sub>2</sub> with tachypnea and ↑Vt due to entrainment Titrate flow rate to avoid reservoir bag collapse (<1/3) on inspiration	N
Venturi	Var. color	24 - 50	Color-coded adapters determine flow and FiO <sub>2</sub> independent of ventilatory demand. Useful for set SpO <sub>2</sub> goals (e.g., COPD) <b>NOT</b> for acute respiratory distress	Y, if >15 LPM or humidified

Racial disparities in pulse oximeter measurement: ↓accuracy in Black patients w/ ↑occult hypoxemia ([NEJM 2020](#), [Annals of ATS 2022](#))

## HIGH FLOW NASAL CANNULA (HFNC) & NONINVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)

[NEJM 2022;387:1688-98](#)

	HFNC	NIPPV (CPAP + BiPAP)
Parameters	Flow: 10-60 LPM (up to 80 at some institutions) FiO <sub>2</sub> (%): 21-100 ~0.7-4.2cm H <sub>2</sub> O of PEEP w/ mouth closed (~0.7cm H <sub>2</sub> O/ 10LPM)	CPAP: constant level of pos. pressure; targets oxygenation BLPAP (or BiPAP™): provides positive inspiratory pressure (IPAP) above PEEP with each pt-triggered breath; targets ventilation and oxygenation
Physiologic Effects	Oxygenation: ↑delivery of O <sub>2</sub> , some PEEP Ventilation: ↑ventilation (↓dead space during expiration) Other: Humidification ↑mucociliary clearance of secretions	Oxygenation: ↓atelectasis, ↓upper airway obstruction, ↓WOB (& O <sub>2</sub> consumption) Ventilation: ↑tidal volume and minute ventilation (via IPAP) Other: ↓venous return (↓LV & RV preload), ↓LV afterload
Clinical Scenarios		
Acute COPD exacerbation w resp. acidosis	<b>Strong indication for BiPAP</b> (ERS/ATS: <a href="#">ERJ 2017;50</a> ) BiPAP: off-load respiratory muscles, counter-act dynamic hyperinflation, ↑ventilation ⇌ ↓mortality, ↓intubation, & ↓ LOS ( <a href="#">Cochrane Rev 2017</a> ). Asthma can be treated similarly but there is less evidence to support.	
Acute cardiogenic pulmonary edema	NIPPV (BiPAP / CPAP) ↓intubation, ↓in-hospital mortality by ↓ WOB, ↑FRC, ↓LV / RV preload, ↓LV afterload ( <a href="#">NEJM 2008;359:142</a> ; <a href="#">Cochrane Rev 2013</a> )	
Acute hypoxic respiratory failure (AHRF)	Mixed evidence for NON-hypercapnic resp. failure May ↓intubation, but no Δ in mortality or LOS vs standard O <sub>2</sub> tx ( <a href="#">Cochrane 2020</a> ). Consider 1 <sup>st</sup> if ILD, ARDS physio. May be non-inf to BiPAP in PNA. Can be used as rescue in asthma or in pts that can't tolerate bipap to help w/ dead space wash out along w/ ongoing eval. for intub.	NIPPV may ↓mortality & ↓intubation ( <a href="#">JAMA 2020;324:57</a> ). Consider if also significant hypercapnia eg OHS, neuromuscular failure (e.g. ALS, MG). <u>Caveats:</u> ( <a href="#">AJRCCM 2017;195:67-77</a> ) <ul style="list-style-type: none"><li>• P:F &lt; 150: ↑ death vs. up-front intubation</li><li>• TV &gt; 9-9.5 cc/kg IDW: ↑death, ↑intubation</li></ul>
Post-extubation	Extub. to NIPPV or HFNC ↓ reintub. and post-extub. resp. failure in ↑risk pts: COPD, obesity ( <a href="#">JAMA 2016;316:1565</a> )	

### Contraindications to NIPPV:

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

### Monitoring for and Preventing Failure

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

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

## CHEST X-RAY

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

#### 1. (A)sess technical quality and (A)irways:

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

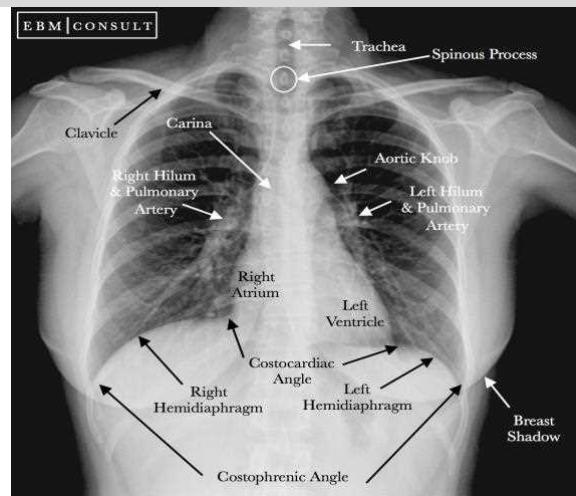
#### 2. (B)ones/soft tissue: subQ air, rib fractures, cervical ribs

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

4. (D)iaphragm (gastric bubble): left hemidiaphragm usually < than the right. Flattening of diaphragm sensitive for emphysema. ↑distance from gastric bubble and LLL air can indicate early pleural eff, before blunting of CP angle

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

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



## CT CHEST

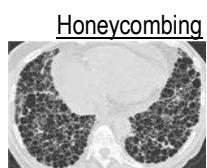
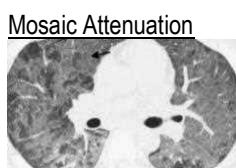
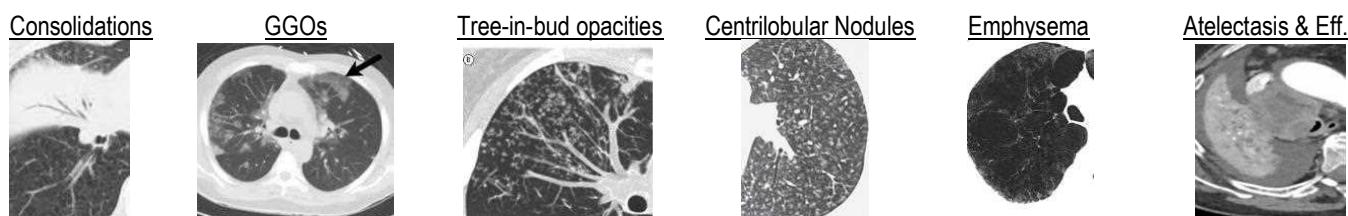
- To characterize abnormal CXR w/ cross-section or w/ suspicion for pathology despite unrevealing CXR
- HRCT (thin-section CT, <2mm): for diagnosing diffuse lung path (ILD, sarcoid, PJP, emphys, bronchiectasis, bronchiolitis). Must be non-con

### Approach to interpretation:

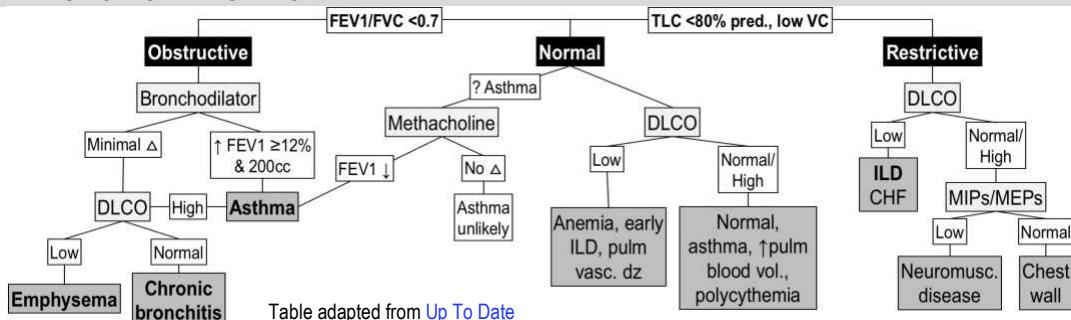
- Review scout imaging: gives anatomic overview.
- Review lines/tubes, extra-thoracic abnormalities.
- Mediastinum/Heart/Vessels: axial soft tissue window: LV>RV normally. Look for IVS bowing to L (RV strain). Can see coronary calcification on non-con. Diameter of main PA should be < ascending aorta (PA 29 mm or more has PPV 97% for pHTN, [Pulm HTN radiology](#))
- Airways: review in soft tissue and lung windows. *Inspiratory HRCT*= round trachea; *Expiratory HRCT*= "D-shaped" trachea.



Common Findings	Definition	Associated Etiologies
Consolidations	Complete filling of alveoli, dense ↑ attenuation obscuring underlying lung architecture and can be seen with air bronchograms	PNA > Malignancy
GGO's	Partial filling of alveoli +/- interstitium, appears as hazy ↑ lung attenuation (light gray) that does NOT obscure underlying architecture	Infxn, edema, blood, fibrosis, malig
Tree-in-Bud (AJR 2009;193:472)	Branching linear opacities & nodules that represent dz'd lobular bronchioles or bronchiolitis & filling with fluid, pus, mucus, or pulmonary tumoral emboli	Infxn (incl. tb), CTD, ABPA, carc. Endarteritis, CF
Emphysema	Airspace enlargement > 1-2 cm in diameter. "Bleb"= similar, but < 1-2 cm	COPD, congenital, spont
Mosaic Attenuation	Patchy low and high atten. areas due to air trapping (w/ ↓ blood flow leading to low atten w/ increased flow in others), decreased perfusion, diffuse GGOs	HP, OLD, CTEPH, Infxn, Edema/hemorrhage
Honeycombing	Clustering of cystic airspace disease. Microcystic <4mm, macrocystic >4mm	ILD: NSIP <4mm; IPF>4mm
Subpleural Retic	Linear opacification of the inter/intralobar septae around 1 cm from pleura.	UIP>NSIP, NL w/ aging
Atelectasis & Effus	Atelectasis will enhance on CT chest w/ con. Effusion more homogenous	



## PULMONARY FUNCTION TESTING



## ASTHMA - DIAGNOSIS (GINA 2022)

**DEFINITION:** chronic airway inflammation w/ resp sx (wheeze, SOB, chest tightness, cough) w variable airflow limitation (GINA 2022)

<b>Symptoms</b>	Resp sx (wheeze, SOB, cough, chest tightness) that vary over time & intensity, worse @ night/early AM
<b>Spirometry</b>	<b>Obstructive</b> (FEV1/FVC < LLN or 0.7), <b>reverses w/ bronchodilator</b> ( $\uparrow$ 0.12 or $>$ 200mL), worsens w/ methacholine (can be nl before provocation, FEV1 $\downarrow$ 0.2)
<b>Allergy testing</b>	If allergic suspected (e.g., atopy): check IgE, CBC/diff (Eos), refer to Allergy for skin testing
<b>New-onset adult cases differential includes:</b>	systemic disease (ABPA, EGPA, systemic mastocytosis), occupational asthma (10-25%; NEJM 2014;370:640), ASA-exacerbated resp. disease (esp. if nasal polyps; <a href="#">J Allergy Clin Immunol 2015;135:676</a> )

## OUTPATIENT CARE (GINA 2022; ERJ 2019;53:1901046)

- Controller + reliever:** stepwise based on severity (below); **step up** if not controlled; **step down** if well controlled 2-3mo
  - Note: new GINA guidelines rec ICS-containing controller; no longer rec. tx w/ SABA only as a/w  $\uparrow$ allergic responses & airway inflammation,  $\downarrow$ response, & overuse a/w  $\uparrow$ severe exacerbations, though NAEPP still recs SABA PRN
  - Mild asthma: PRN ICS-LABA > PRN SABA (NEJM 2019;238:2020; NEJM 2018;378:1865) & non-inferior to maintenance ICS for  $\downarrow$  exacerbations (though  $\uparrow$ sx: NEJM 2018;378:1877)
  - Mild/mod: maintenance ICS-LABA + PRN ICS-LABA also > + PRN SABA (AJRCCM 2005;171:129; Chest 2006;129:246). PRN ICS w/ SABA > PRN SABA alone (Lancet 2011;377:650)
  - May be some phenotypes w/ low eos. inflamm. (<2% in sputum) in whom ICS  $\downarrow$ effective (NEJM 2019;380:2009)
- Trigger avoidance:** e.g., exercise, cold air, irritants (smoke, perfume), allergens, infection, drugs (ASA, NSAIDs,  $\beta$ -blockers)
- Non-pharm interventions:** smoking cessation, regular physical activity, breathing exercises, weight loss if obese

	Mild intermittent Step 1	Mild persistent Step 2	Moderate persistent Step 3	Severe persistent Step 4	Severe Step 5
<b>Daytime sx</b>	< 2 / week	2-7 days / week	Daily	All day	All day
<b>PM awakenings</b>	< 2 / month	3-4 nights/month	> 1/week	Nightly	Nightly
<b>FEV1</b>	Normal	Normal	60-80% predicted	< 60%	< 60%
<b>Exacerbations</b>	0-1/year	> 2/year	> 2/year	> 2/year	> 2/year
<b>Preferred Controller (GINA 2022)</b>	PRN low dose ICS-LABA	PRN low-dose ICS-LABA	Daily and PRN low-dose ICS-LABA	Daily + PRN med-dose ICS-LABA	Daily + PRN med-dose ICS-LABA + daily LAMA Assess phenotype + Eval for asthma biologics
<b>Other Options</b>	<ul style="list-style-type: none"> <li>Low-dose ICS taken w/ SABA</li> <li>Daily ICS + SABA PRN</li> <li>LTRA + SABA</li> </ul>	<ul style="list-style-type: none"> <li>Daily ICS + SABA PRN</li> <li>Med-dose ICS</li> <li>Low-dose ICS + LTRA + SABA PRN</li> </ul>	<ul style="list-style-type: none"> <li>Low-dose LABA daily + SABA PRN</li> <li>Med-dose ICS</li> <li>Low-dose ICS + LTRA + SABA PRN</li> </ul>	<ul style="list-style-type: none"> <li>High-dose ICS-LABA</li> <li>Add-on LAMA</li> <li>Add-on LTRA</li> <li>ICS-LAMA-LABA</li> </ul>	<ul style="list-style-type: none"> <li>Med-dose ICS-LABA + LAMA + PRN SABA</li> <li>High-dose ICS-LABA</li> <li>Add LTRA or azithro</li> <li>PO steroids</li> </ul>
<b>Preferred Reliever</b>	PRN low-dose ICS-LABA		PRN low-dose ICS-LABA. NOTE: pt must also be ICS on maintenance		
<b>Other Options</b>			PRN SABA		

**LTRA:** leukotriene receptor antagonist **Biologics:** anti-IL4 (dupilumab), anti-IgE (omalizumab), anti-IL5 (mepo-, res-, benra- lizumab, tezepelumab)  
**Contraindicated to use LABA w/out ICS** (CHEST 2006;129:15; NEJM 2010;362:1169). Figure adapted from [GINA 2022](#).

## ASTHMA EXACERBATIONS (GINA 2022)

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

**INPATIENT:** assess severity of exacerbation (VS, mental status, SpO<sub>2</sub>, WOB, PEF < 50% severe), consider VBG/ABG, CXR

**Severe:**  $\uparrow$ resp drive  $\rightarrow$   $\uparrow$ RR  $\rightarrow$   $\downarrow$ pCO<sub>2</sub>, nl/ $\downarrow$ pH suggest resp. failure. If sig hypoxemia, consider resp failure vs PTX, PNA, PE, plug, etc.

Floor Patient	ICU Patient (Thorax 2003;58:81)
<ul style="list-style-type: none"> <li><b>Bronchodilators:</b> albuterol (2.5-5g) <math>\pm</math> ipratropium (0.5-1.5mg) q20m x3           <ul style="list-style-type: none"> <li>DuoNeb in ED a/w <math>\downarrow</math>admit (Cochrane Rev 2017)</li> <li>SABA mono-tx unless severe/worsening (GINA 2022, NAEPP 2020)</li> </ul> </li> <li><b>Steroids:</b> pred 40-60mg total x5-7d (Cochrane Rev 2016)</li> <li>O<sub>2</sub> &gt;92% (93-95% in severe; &gt;95% increases pCO<sub>2</sub>; Thorax 2011;66:937)</li> <li>If impending respiratory failure: stacked DuoNeb (x3/h), methylpred IV 60-125mg q6h, Mg IV 2g/20min, transfer to ICU</li> </ul>	<ul style="list-style-type: none"> <li><b>Bronchodilators:</b> albuterol + ipratropium, Methylpred 125mg IV q6h</li> <li><b>NIV:</b> BIPAP <math>\rightarrow</math> BIPAP w/ sedation <math>\rightarrow</math> HFNC</li> <li><b>Rescue therapies:</b> Mg IV 2g, continuous albuterol nebs (CAB). Less data: IV epi, ketamine, inhaled anesthetic, Heliox. ECMO=last resort</li> <li><b>Mechanical ventilation:</b> large ETT (8+), <math>\uparrow</math>insp flow rate (80-100L/min), <math>\downarrow</math>V<sub>T</sub> (6-8cc/kg), <math>\downarrow</math>RR (10-14), <math>\downarrow</math>PEEP, paralysis; <b>Goal:</b> max exp. phase, minimize hyperinflation, permissive hypercapnia</li> </ul>

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

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

# Pulmonary & Critical Care

## COPD

**DEFINITION:** persistent respiratory symptoms (dyspnea, cough, sputum production, recurrent wheezing, exacerbations) d/t abnormalities of airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that lead to persistent airflow limitation ([GOLD 2023](#))

### DIAGNOSIS AND STAGING (GOLD 2023; AJRCCM 2017;195:557)

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

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

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

### DIFFERENTIAL

**Pre-COPD:** respiratory symptoms with structural lung lesions (emphysema) and/or physiological abnormalities w/o airflow obstruction

**Preserved Ratio Impaired Spirometry (PRISM):** resp sx w/ nl ratio (FEV1/FVC > 0.7) but impaired FEV1 (< 80) after bronchodilation

**Chronic bronchitis:** overlapping condition; chronic cough + sputum > 3 months / yr for 2+ years. **Asthma:** see "PFTs and Asthma"

**Bronchiectasis:** large volumes of purulent sputum, a/w bacterial ifxn, bronchial dilat on CXR/HRCT. **Obliterative bronchiolitis:** lung/BM txp, HRCT: hypodense areas on exp. **Diffuse panbronchiolitis:** Asian pts, chronic sinusitis, CXR/HRCT: diffuse small centrilob nodular opac & hyperinflation

### MANAGEMENT OF STABLE COPD (GOLD 2023; NEJM 2019;381:1257)

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

	GOLD A	GOLD B	GOLD E
Starting tx:	Bronchodilator (LABA or LAMA)	LABA+LAMA	LABA+LAMA Eos>300/asthma component: LABA+LAMA+ICS
Rescue therapy:	Short-acting bronchodilator		
Escalate to:	Dyspnea: LAMA + LABA Exacerbation: LAMA + LABA		
Notes	<ul style="list-style-type: none"> <li>Long-acting&gt;short-acting unless occ. dyspnea</li> <li>Tiotrop may slow decline in FEV1 in early COPD (<a href="#">NEJM 2017;377:923</a>)</li> </ul>	<ul style="list-style-type: none"> <li>LABA+LAMA &gt; mono-therapy (<a href="#">Chest 2014;145:981</a>; <a href="#">Cochrane Rev 2015</a>)</li> </ul>	<ul style="list-style-type: none"> <li>Include ICS if features of asthma</li> <li>LAMA+LABA+ICS &gt; LAMA+LABA to ↓exacerbations, but may ↑PNA (<a href="#">Lancet 2018;391:1076</a>; <a href="#">NEJM 2018;378:1671</a>). Consider d/c ICS if persist. exacerb, PNA (if eos &gt;300, high risk ↑exacerb. w/ d/c)</li> </ul>

**Non-Rx interventions:** **Smoking cessation:** ↓mortality; [Annals 2005;142:233](#), **Vax:** Flu, COVID, PCV20, Tdap, Zoster

**Lung CA screening:** annual low-dose CT (age 50-80 & ≥ 20 pack-years & has smoked in last 15y) ([USPSTF 2021](#))

**Pulmonary rehab (GOLD B/E):** ↑QoL, ↑exercise capacity ([Cochrane Rev 2015](#)), possibly ↓mortality ([JAMA 2020;323:1813](#))

**Home O<sub>2</sub>:** if PaO<sub>2</sub> ≤55 or SpO<sub>2</sub> ≤88% (PaO<sub>2</sub> ≤59 or SpO<sub>2</sub> ≤89 if pulmonary HTN or Hct >55% or CHF) for goal SpO<sub>2</sub> >90%

**Nocturnal NIPPV:** if daytime pCO<sub>2</sub> ≥52 & nocturnal SpO<sub>2</sub> ≤88% (despite 2L O<sub>2</sub>) or recent exacerb. & persistent PaCO<sub>2</sub> >53 (↓risk of readmit & mortality: [JAMA 2017;317:2177](#)) **Interventional therapies:** bronchoscopic lung reduction (emphysema + hyperinflation), bullectomy, lung txp

### COPD EXACERBATION (AECOPD) (ERS/ATS: ERJ 2017;49, GOLD 2023)

- **Hx:** ↑dyspnea, ↑Δ sputum, and/or ↑cough < 14d; ask re: URI sx, CHF sx, VTE risk fx, prior exacerbations/steroids/intubations/abx
- **W-up:** CXR, ABG/VBG ± ECG, trop, NT-proBNP. Flu, COVID, PE (PE in 25% severe exacerb w/o clear trigger: [Annals 2006;144:390](#))

#### Management:

- **SpO<sub>2</sub> 88-92%:** hyperoxia → ↓vent. via Haldane effect & hypoxic vasoconstrict, ↑V/Q mismatch; ↑mortality ([BMJ 2010;341:c5462](#))
- **Bronchodilators:** albuterol, ipratropium, DuoNeb (combo)
  - "Stacked" DuoNeb (x3 in 1h) initially → space to standing DuoNeb q4 w/ albuterol PRN q2 → space further as able
- **Steroids:** pred 40mg x5d. PO ~ IV ([Chest 2007;132:1741](#)) & 5d ~ 14d ([REDUCE JAMA 2013;309:2223](#); [Cochrane Rev 2018](#)); some may need higher dose/longer course if severe, but ↑PNA risk
  - **If severe:** IV methylpred 60-125mg q6-q12x72h, budesonide neb.
- **NIPPV:** if resp acidosis (pH < 7.35 & PaCO<sub>2</sub> > 45), severe dyspnea, ↑WOB, pers hypoxemia. ↓mortality, intub., LOS ([Cochrane Rev 2004](#)).
- **Intubation:** NIV failure, s/p arrest, aspiration/vomiting, HDUS

- **Antibiotics:** controversial; ↓mortality but challenging to identify who will benefit ([Chest 2008;133:756](#); [Cochrane Rev 2012](#))
  - **Indicated if:** ↑all 3 cardinal sx, 2/3 w/ ↑sputum purulence, or require NIPPV/mechanical ventilation
    - CRP may be useful ([NEJM 2019;381:111](#)). PCT may be useful but ↑mortality when used in ICU ([Eur Resp Rev 2017;26](#); [ICM 2018;44:428](#))
  - **Choice:** based on PsA risk, prior SCx, resist. ⊖ PsA RFs: FQ, CTX; amox/clav, azithro, doxy. ⊕ PsA RFs: FQ, cefe, pip/tazo **Duration:** 5-7d inpt; 3-5 outpt (vary by drug)
    - Concurrent CAP: treat by CAP guidelines
- **Antivirals:** oseltamivir if influenza+, even if ≥48-72h
- **VTE ppx**

### INHALED THERAPIES FOR ASTHMA & COPD

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

# Pulmonary & Critical Care

# Bronchiectasis & Hemoptysis

## BRONCHIECTASIS

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

<b>Symptoms</b>	Chronic productive cough, recurrent bronchitis/pneumonia, wheezing, dyspnea, hemoptysis, recurrent pleurisy	
<b>Etiology</b>	<b>Recurrent insult:</b> infection (PNA, MAC, TB, PsA, childhood infections, ABPA), inhalation, GERD/aspiration <b>Impaired immunity:</b> ↓ mucus clearance (CF, 1° ciliary dyskinesia [PCD]), immunodeficiency (e.g., HIV, CVID, ↓ IgG) <b>Obstruction:</b> foreign body, tumor, COPD, tracheomalacia/tracheobronchomegaly, CTD (Marfan's), radiation <b>Systemic disease:</b> RA, Sjogren's, SLE, IBD, A1AT; <b>Idiopathic</b> = ~50%	
<b>Workup</b>	Initial: MDCT or DLDCT, PFTs, CBC/diff, Ig levels, sputum Cx (bacterial, mycobacterial, fungal) - <u>CT: bronchial diameter &gt; adj artery</u> (signet-ring sign), thickened bronchi w/ lack of tapering (tram track sign)	<b>As indicated:</b> exclude CF (gene/sweat Cl- testing), Aspergillus Ab, ANA, RF/CCP, SSA/SSB, A1AT, HIV; consider nasal NO (PCD), pneumococcal vaccine titers (often low), bronch w/ BAL, GI eval
<b>Natural Hx</b>	Exacerbations (avg 1.5/y), progressive ↓ in FEV <sub>1</sub> , PsA colonization → worsening disease	
<b>Chronic Management</b>		<b>Acute Exacerbation</b>
CF: <a href="#">AJRCCM 2013;187:680</a> , <a href="#">AJRCCM 2009;180:802</a> ; non-CF: <a href="#">AJRCCM 2013;188:647</a> , ERS: <a href="#">Eur Resp J 2017;50</a> , BTS: <a href="#">Thorax 2019;74</a>		
<ul style="list-style-type: none"> <li><b>Airway clearance:</b> nebs (albuterol, 3% NaCl) + chest PT (acapella, vest)           <ul style="list-style-type: none"> <li>CF: add DNase to neb bundle; not effective in non-CF</li> </ul> </li> <li><b>Antimicrobials/anti-inflammatories:</b> <ul style="list-style-type: none"> <li>Non-CF: Long-term azithro ↓ exacerb. but c/f ↑ abx resistance (<a href="#">Lancet 2012;380:9842</a>; <a href="#">JAMA 2013;309:1251</a>; <a href="#">Coch Rev 2018</a>; <a href="#">Lancet RM 2019;7:845</a>). Ensure no NTM first               <ul style="list-style-type: none"> <li>Intermittent abx (FLQ, β-lactam, tobra) in pts w/ ≥3 exacerb/y ↓ exacerb but ↑ abx resistance (<a href="#">Coch Rev 2022</a>)</li> <li>Trial inhaled abx if PsA colonization &amp; ≥3 exacerb/y, consider eradication of new PsA isolate</li> </ul> </li> <li>CF: azithro + inhaled tobramycin (for PsA; alt: aztreonam, colistin)</li> </ul> </li> <li><b>Disease specific treatment:</b> <ul style="list-style-type: none"> <li>Non-CF: treat underlying cause if found; consider PPI/H<sub>2</sub> blocker</li> <li>CF: <i>CFTR mut</i> → defective Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> transport on airway surface               <ul style="list-style-type: none"> <li><u>Potentiators</u> open CFTR channel (<b>ivacaftor</b>); <u>correctors</u> bring CFTR to surface (<b>lumacaftor, tezacaftor, elexacaftor</b>)</li> <li>Dual/triple tx → long-term FEV1 benefits (<a href="#">NEJM 2015;373:220</a>; <a href="#">NEJM 2017;377:2013</a>; <a href="#">NEJM 2018;379:1599</a>; <a href="#">NEJM 2019;381:1809</a>)</li> <li><b>Pancreatic enzyme supplementation</b>, vitamins ADEK</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li><b>Sx:</b> ↑ cough/sputum/dyspnea; usually ⊖ fever</li> <li><b>Obtain resp cx prior to abx, CXR</b></li> <li><b>Micro:</b> PsA + <i>S. aureus</i> &gt; <i>H. flu</i>, <i>Moraxella</i>, <i>Burkholderia</i>; treat <i>Stenotrophomonas</i> and <i>Achromobacter</i> as pathogenic; <i>Aspergillus</i> in CF not treated</li> <li><b>Abx:</b> use previous Cx data; <b>tx 14d</b> <ul style="list-style-type: none"> <li><u>No prior cx data:</u> empiric FLQ (for PsA)</li> <li><u>If prior R-PsA:</u> IV abx; 2 agents – β-lactam &amp; either FLQ or IV tobra (dosed qd)               <ul style="list-style-type: none"> <li><i>No great evidence for double coverage of PsA though is standard of care in CF</i></li> </ul> </li> <li>If β-lactamase+ <i>H. flu</i> or <i>Moraxella</i>: amox/clav, CTX, doxy, macrolide, or FQ</li> <li><u>Home abx:</u> continue azithro ± inh tobra (practice varies)</li> </ul> </li> <li>Steroids only w/ concom. asthma, COPD, ABPA</li> <li>Continue chronic treatment (airway clearance)</li> </ul>	

## HEMOPTYSIS (expectoration of blood from lower respiratory tract)

<b>Etiology</b>	<ul style="list-style-type: none"> <li><b>Airway:</b> bronchitis, bronchiectasis (incl. CF), CA (usually primary lung CA), trauma (incl. foreign body)</li> <li><b>Pulmonary parenchyma:</b> infection (PNA, abscess, TB, aspergilloma), vasculitis (ANCA, anti-GBM, immune-complex, drug-induced; see <i>Vasculitis</i> and <i>Autoantibodies</i>), coagulopathy, endometriosis, inhalation injury, sarcoid, pulmonary hemosiderosis</li> <li><b>Pulmonary vascular:</b> PE, CHF (esp if on AC), mitral valve dz, bronchovascular fistula, aneurysm, AVM</li> </ul>
<b>Work-up</b>	<ol style="list-style-type: none"> <li>Consider other sources (GI or nasopharyngeal)</li> <li><b>CXR (most important)</b>, CBC, coags, U/A (vasculitis, anti-GBM), sputum Cx, CTA chest (if stable), bronch</li> <li>Consider NT-proBNP, D-dimer, ESR/CRP, C3/C4, ANA, ANCA, anti-GBM, APLAS, IGRA/AFB, RVP</li> </ol>

**Non-massive:** if minimal (<30mL) & likely benign (ex: infxn/bronchiectasis): observe. If active, recurrent, >1w: CT → bronch

**MASSIVE HEMOPTYSIS** (>500mL/d or >100mL/h) = **life-threatening emergency** with mortality 50-80%. **Asphyxiation**, NOT exsanguination, is mechanism of death (maximum pulmonary blood volume ~500mL, [CCM 2000;28:1684](#))

- LIE PATIENT WITH SIDE OF SUSPECTED BLEED DOWN** (preserve gas exchange in unaffected lung)
- Ensure hemodynamic stability, active T&S, correct coagulopathy. Inhaled TXA may be beneficial ([Chest 2018;154:1379](#))
- STAT RICU** (x6-3333) → control airway if dyspneic, rapid bleed, largest possible ETT (8mm+), suction as blood can fill ETT
- Call IP → bronch to localize; temporize w/ balloon tamponade, bronchial blockade, electrocautery, topical vasoconstriction  
Call IR → if stable, can CTA to localize; otherwise, bronchial angiography to embolize site. *If refractory*, call thoracic surgery
- Can consider pulse dose methylprednisolone if vasculitis suspected

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

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

**Etiology:** capillaritis (rheum, drugs), bland hemorrhage (AC, low plt, CHF), diffuse alveolar damage (ARDS, infxn, PE, drugs)

**Workup:** CXR, CT (diffuse GGO central > peripheral), BAL (progressively more hemorrhagic serially), labs guided by clinical picture

**Management:** Primarily supportive. If hypoxemic, may require supplemental O<sub>2</sub>, intubation; treatment of underlying dz.

Capillaritis/AI syndromes: Systemic glucocorticoids (pulse dose IV methylpred 500-1000mg/day up to 5 doses, w/ taper), cyclophosphamide, ritux. Excess AC/bleeding disorder: reversal of AC. Infection: antimicrobial/antiviral therapy ([Int J Mol Sci. 2021;22\(2\):793](#))

## OVERVIEW

Heterogeneous group of lung diseases involving the replacement of normal lung parenchyma with varying degrees of inflammation and fibrosis (scarring), can involve any part of the lung parenchyma

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

**History:** tempo, hx CTD/IBD/malig/thoracic XRT, rheum ROS, meds, exposures (chemicals, dust, humidity, pets, barns), smoking, FHx

**Exam:** "velcro-like" crackles, clubbing, e/o CTD (heliotrope rash, Gottron's papules, mechanic's hands, synovitis, foot/wrist drop, sclerodactyly, sicca), vasculitic rash, extrapulmonary manifestations of other systemic diseases

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

Idiopathic Interstitial PNAs (IIPs)	Connective Tissue Disease <sup>7</sup>	Exposure-Related	Granulomatous
<b>Idiopathic Pulmonary Fibrosis (IPF)<sup>1</sup></b>	Scleroderma	<u>Organic:</u> grain, mold, birds, hay (cause <u>Hypersensitivity Pneumonitis</u> ) <sup>8</sup>	Sarcoidosis <sup>9</sup>
<b>Idiopathic Non-Specific Interstitial PNA (NSIP)<sup>2</sup></b>	Sjogren's Syndrome	<u>Inorganic:</u> silica, asbestos, coal (cause <u>pneumoconiosis</u> )	Hypersensitivity pneumonitis <sup>8</sup>
<b>Acute Interstitial PNA (AIP)<sup>3</sup></b>	MCTD	<u>Drugs:</u> nitrofurantoin, MTX, amiodarone, pembro/nivo (see: <a href="#">PneumoTox</a> )	Mycobacterial disease
<b>Cryptogenic Organizing PNA (COP)<sup>4</sup></b>	Polymyositis		Fungal disease
<b>Respiratory Bronchiolitis-ILD (RB-ILD)<sup>5</sup></b>	Dermatomyositis		Langerhans cell histiocytosis <sup>10</sup>
<b>Desquamative Interstitial PNA (DIP)<sup>6</sup></b>	Rheumatoid arthritis		
	Lupus	<u>Other:</u> radiation	

## Radiographic Associations:

<sup>1</sup> *Usual interstitial pneumonia (UIP)* pattern: heterogenous subpleural/basal predominant, honeycombing, traction bronchiectasis

<sup>2</sup> *Non-specific interstitial pneumonia (NSIP)* pattern: upper/mid-lung predominant, ground glass opacities, micronodules

<sup>3</sup> *Diffuse alveolar damage (DAD)* pattern: diffuse, bilateral, central>peripheral ground glass or consolidative opacities

<sup>4</sup> *Organizing PNA (OP)* pattern: bilateral peripheral, peribulbar consolidations with subpleural sparing

<sup>5</sup> *Respiratory-bronchiolitis (RB)* pattern: centrilobular nodules, GGOs, interlobular septal thickening

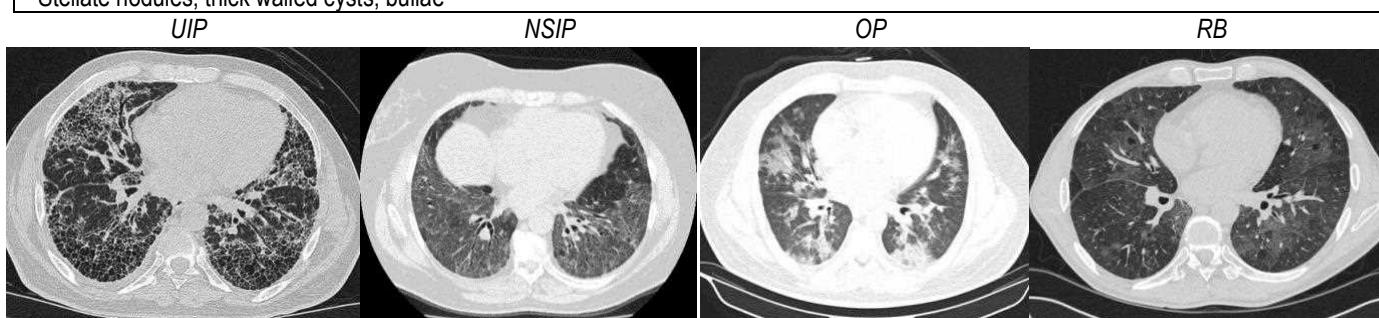
<sup>6</sup> *Desquamative interstitial pneumonia* pattern: homogenous or patchy GGOs in mid/lower lung zones

<sup>7</sup> May be associated with **any** pattern (UIP, NSIP, etc)

<sup>8</sup> May be associated with RB pattern (see <sup>5</sup>), with progression to traction bronchiectasis, honeycombing, centrilobular nodules

<sup>9</sup> Peribronchovascular, hilar, subpleural nodules (granulomas)

<sup>10</sup> Stellate nodules, thick walled cysts, bullae



## DIAGNOSTIC EVALUATION

- Exclude chronic infxn as cause, especially in immunocompromised pts; consider sputum bacterial/fungal culture, HIV/hepatitis testing
- General Approach:** remove potential environmental causes. If improves no further w/u. If not assess for systemic dz. If unlikely systemic dz, HRCT (see Radiographic Associations above) consider bronch and/or biopsy based on findings
- Labs: CBC/diff, CMP, UA, ESR/CRP, CPK/aldolase, C3/C4, autoantibodies (ANA, RF/CCP, RNP, Ro/La, Scl-70, ANCA, hypersensitivity panel, myositis panel, anti-GBM Ab)
- PFTs:** restrictive ( $\downarrow$ TLC,  $\downarrow$ FRC,  $\downarrow$ RV; FEV1/FVC normal to  $\uparrow$ );  $\downarrow$ DLCO can be early sign
- Lung biopsy:** if dx unclear & will  $\Delta$ tx. Rec against if definite UIP secondary to high morbidity/ $\uparrow$ exacerbations ([AJRCCM 2018;198:e44](#))

## TREATMENT

- IPF:** ([AJRCCM 2015;192:e3](#))
  - Acute exacerbations: ddx includes infxn PE, HF; send BNP, trop, procalcitonin, d-dimer, blood cultures, *s. pneumo* & *legionella* urinary antigens, extended RVP. Treat with **pred** ~1mg/kg/d & broad-spectrum **abx** (vanc/cefe/azithro) X 7d generally given
  - Chronic therapy: consider **pirfenidone** (antifibrotic; SE: nausea, fatigue; [NEJM 2014;370:2083](#)), or **nintedanib** (TKI; SE: diarrhea; [NEJM 2014;370:2071](#)). Promising data for new PDE4 inhibitors ([NEJM 2022; 386:2178](#)). All  $\downarrow$ FVC decline, may not  $\Delta$  overall survival. Consider lung transplant eval. AZA, pred, NAC tx  $\uparrow$ mortality ([NEJM 2012;366:1968](#)). GERD tx (PPIs) & aspiration precautions may be beneficial ([Lancet RM 2013;1:369](#))
- NSIP:** remove inciting exposures, tx underlying condition; can be **steroid-responsive** (pred 0.5-1mg/kg/d or pulse methylpred if requiring hospitalization); **2nd agent** (AZA, MMF, ritux, CYC) pending response. **Nintedanib** may benefit non-IPF progressive fibrotic disease irrespective of underlying ILD diagnosis ([NEJM 2019;381:1718](#); [Lancet RM 2020;8:453](#))
- COP:** monitor; if sx persist/progress **pred** ~0.75-1mg/kg/d (pulse if fulminant)
- AIP:** idiopathic ARDS; usually not steroid-responsive, but often trial steroids & abx as in-hospital mortality is >50%

# Pulmonary & Critical Care

# VTE Diagnostics

## CLINICAL MANIFESTATIONS

### Signs/Symptoms

#### Deep Vein Thrombosis (DVT)

- S/Sx: pain, warmth, erythema or cyanosis, edema (esp. asymm.), palpable cord, venous distention, Homan's sign (sudden dorsiflexion of ankle w/ knee flexed to 30° → pain in upper calf); **none Sn/Sp** ([JAMA 1998;279:1094](#)) & can be axillary
- Types:** **proximal** = iliac, femoral, popliteal veins; **distal** = calf veins below knee (ant./post. tibial, peroneal, soleal, gastrocnemius)
  - Massive iliofemoral DVT: *phlegmasia alba dolens* (edema, pain) → *phlegmasia cerulea dolens* (cyanosis, venous gangrene)
  - May-Thurner syndrome: anatomic variant → compression of L common iliac vein by R iliac artery → LLE DVT and/or swelling
- DVT of CVC: MC site is Internal Jugular. In PICCs, brachial, axillary, and subclavian. Originates as fibrin sheath at catheter tip. Generally, first p/w inability to draw back, then inability to infuse.
- Ddx:** superficial thrombophlebitis, cellulitis, arthritis, arterial occlusion, varicose veins, lymphedema, ruptured Baker cyst, chronic venous insufficiency ([Arch IM 1998;158:2315](#))

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

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

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

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

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

- Pre-test prob:** [Wells' for LE DVT](#), [Constans'](#) for UE ([Thromb Haemost 2008;99:202](#)), [Wells' for PE](#) ([Annals 2001;135:98](#))
  - If **low** (or mod. DVT), can r/o w/ D-dimer (see below) or [PERC score for PE](#); if D-dimer  $\oplus$  need further eval. If **high** (or mod. PE) → imaging
- DVT diagnosis:** venous Doppler US ("LENIs" = Lower Extremity Non-Invasives; "UENI" = Upper Extremity Non-Invasives)
- PE diagnosis:**
  - PE-CT:** study of choice; may also detect alternate dx ([NEJM 2006;354:2317](#))
  - V/Q scan:** validated ([JAMA 1990;263:2753](#)). Performed if c/i to CT I+. **Need nl CXR** (minimize other causes of V/Q mismatch)
  - LENIs:** if suspect PE, unable to CT or V/Q, &  $\oplus$ , can treat; if  $\ominus$ , however, does not exclude PE (clot may have migrated or be from another source)
  - Echo:** most useful for risk stratification (not dx), though demonstration of clot or new RV strain can provide presumptive diagnosis if needed rapidly
  - ABG:** hypoxemia ( $\uparrow A-a$  gradient, normal in ~20%), respiratory alkalosis
- PE risk stratification:**
  - PESI** (PE Severity Index): **prediction of morbidity/mortality in patients w/ newly diagnosed PE** using 11 clinical criteria, including PMH (cancer, HF, lung dz) & abnormal vital signs (e.g. HR>110, RR>30,  $\text{SpO}_2 < 90\%$ )
  - "Massive" = High Risk; "Submassive" = Intermediate-High or Intermediate-Low Risk; "Nonmassive" = Low Risk

INTERPRETING D-DIMER (nl <500)
- <b>DVT/PE:</b> if nl + low pretest prob, excludes DVT/PE ( <a href="#">NEJM 2003;349:1227</a> ; <a href="#">JAMA 2006;295:199</a> ; <a href="#">Thromb Haemost 2009; 101:886</a> )
- <b>Adjusted D-dimer:</b> → ↓imaging w/o ↑ in PE
<ul style="list-style-type: none"> <li><b>Age-adjusted:</b> if &gt;50, use age <math>\times 10</math> as cut off (<a href="#">JAMA 2014;311:1117</a>)</li> <li><b>Prob.-adjusted:</b> use of &lt;1000 cutoff w/ low prob. (<a href="#">NEJM 2019;381:2125</a>)</li> </ul>
- <b>Ddx for ↑D-dimer:</b> arterial thrombus (MI, stroke, AF/intracardiac, acute limb ischemia), DIC, CA, inflammation/infection, ESLD, CHF, renal disease, ↑age, aortic dissection, trauma, surgery

Risk	HDIS: Cardiac arrest, pressors, SBP <90	PESI Class III-V and/or sPESI ≥1	Imaging Evidence of RV Dysfunction <sup>a</sup>	Elevated Cardiac Biomarkers <sup>b</sup>
High (Massive)	+	+ <sup>c</sup>	+	+ <sup>c</sup>
Intermediate-High (Submassive)	-	+	+	+
Intermediate-Low (Submassive)	-	+	One (or none) of these positive	
Low (Nonmassive)	-	-	-	-

<sup>a</sup> Imaging Evidence: **CT:** RV/LV diameter ratio >0.9 ([EHJ 2011;32:1657](#)); **TTE:** RV Overload/Dysfunction - enlarged RV, flattened IVS, mod/severe TR, McConnell's Sign (RV free wall akinesis sparing apex; [Circ 2008;118:517](#)), ↓TAPSE ([JEM 2020;58:449](#)).

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

<sup>c</sup> Hemodynamic instability w/ confirmed PE on CTPA and/or RV dysfunction on TTE classifies as high-risk PE. Calculation of PESI classes or investigation for elevated cardiac biomarkers are unnecessary.

# Pulmonary & Critical Care

# VTE Management

MANAGEMENT OF VTE (CHEST: [Chest 2021;160:545](#)); ESC: [EHJ 2020;41:543](#))

Proximal DVT (popliteal, femoral, iliac vv.)	Distal DVT (calf: ant./post. tibial, peroneal vv.)
<p><b>Anti-coagulate</b> (unless contraindications), regardless of sx  <b>Agent:</b> DOAC &gt; VKA or LMWH; if malig.: DOAC or LMWH &gt; VKA (for dosing &amp; info on choosing agent, see AC and AC Mgmt sections)  <b>Duration:</b> at least 3mo for all. Extend &gt;3mo if:</p> <ul style="list-style-type: none"> <li>• 1<sup>st</sup> or 2<sup>nd</sup> <b>unprovoked</b> prox. DVT &amp; <b>low/mod. bleeding risk</b>. If high bleeding risk (see below), stop at 3mo. Unprovoked have ↑recurrence rate (10% &lt;1y off AC, 5% each subsequent yr)</li> <li>• If stop AC after 1<sup>st</sup> VTE, D-dimer at 1mo may help decide whether to resume, esp. in ♀ (<a href="#">NEJM 2006;355:1780</a>; <a href="#">Blood 2014;124:196</a>; <a href="#">Annals 2015;162:27</a>)</li> <li>• If stop AC, ASA 100mg if no CI (<a href="#">NEJM 2012;367:1979</a>; <a href="#">NEJM 2012;366:1959</a>; <a href="#">Circ 2014;130:1062</a>)</li> </ul> <p>If contraindications to AC (active bleeding, recent/planned high bleeding-risk procedure, major trauma, acute ICH) → <b>IVC filter w/ IR</b></p> <ul style="list-style-type: none"> <li>• Remove once no longer needed (typical implantation time ~1-2mo; <a href="#">JVIR 2011;22:1522</a>). Complications incl. IVC thrombosis, acute/recurrent DVT or PE, filter migration/erosion/fracture</li> </ul>	<p><b>Serial imaging vs. anticoagulation</b></p> <p><b>Serial imaging:</b> if asx, low risk for extension, or high risk for bleeding</p> <ul style="list-style-type: none"> <li>• Repeat US at 1-2w (1/3 will extend; ↓risk in muscular veins: soleal, gastrocnemius)</li> </ul> <p><b>Anticoagulate if:</b></p> <ul style="list-style-type: none"> <li>• <b>Severe symptoms</b></li> <li>• <b>RFs for extension:</b> ⊕ D-dimer, extensive (&gt;5cm, mult. veins, &gt;7mm in diam.), close to prox. veins, no reversible provoking factor, active CA, h/o VTE, inpt</li> <li>• On serial imaging, <b>extends</b> into proximal veins. AC also suggested if extends but remains in distal vein</li> </ul>
<p><b>UE DVT</b> (<a href="#">NEJM 2011;364:861</a>): brachial, axillary, subclav. vv.; ↓ complications vs. LE DVT. Tx same as LE DVT. If PICC/CVC, no need for catheter removal if needed/functional/∅ infected. AC continued while catheter in place (esp. if CA), data extrapolated from LE DVT.</p>	
<p><b>Bleeding risk:</b> <u>low</u> = 0 RFs (1.6%/3mo; 0.8%/y after 3mo); <u>mod</u> = 1 (3.2%/3mo; 1.6%/y); <u>high</u> = ≥2 (12.8%/3mo; ≥6.5%/y)  <b>RFs:</b> age &gt;65-75, previous bleeding, CA, renal failure, liver failure, thrombocytopenia, prior CVA, DM, anemia, anti-platelet tx, poor AC control, ↓functional capacity, recent surgery, frequent falls, AUD, NSAID use</p>	
<p><b>Testing in unprovoked VTE:</b> age-appropriate cancer screening (found in 1/20 within 1y; <a href="#">Annals 2017;167:410</a>) &amp; symptom-directed studies. Hypercoagulability workup limited at time of acute VTE while on AC (see <i>Coagulation Disorders</i> for details)</p>	

High Risk PE	Intermediate Risk PE	Low Risk PE
PERT consult (x47378): for High or Intermediate-High Risk PE		
<p><b>Resuscitation:</b></p> <ul style="list-style-type: none"> <li>• <u>Limit IVF</u>: can try 500cc if CVP low, but ↑RV distention → RV ischemia + septal bowing → ↓LV SV → ↓CO</li> <li>• <u>Inotropes</u>: if low CO, consider dobutamine</li> <li>• <u>Vasopressors</u>: NE generally preferred</li> <li>• <u>O<sub>2</sub></u>: HFNC pref. for severe hypoxemia. Mech vent. ↑↑↑ risk: HoTN from induction &amp; PPV → ↓venous return → ↓RV CO, ↑RV failure</li> <li>• <u>Circulatory collapse/arrest</u>: VA ECMO</li> </ul> <p><b>Anticoagulation:</b> UFH (w/ bolus)  <b>Thrombolysis:</b> systemic unless contraindicated  <b>Embolectomy:</b> if thrombolysis contraind/fails; can be catheter-directed; surgery if all options contraind/fail or if clot in transit in RA/RV, PFO</p>	<p><b>Anticoagulation:</b> LMWH preferred &gt; UFH (faster time to therapeutic range) unless impending hemodynamic collapse, thrombolysis (or CrCl &lt;30 or severe obesity).  <b>Thrombolytic therapy (catheter-directed preferred over systemic) in select pts:</b> (<a href="#">Circ 2011;123:1788</a>)</p> <ul style="list-style-type: none"> <li>• May be observed x24h on AC first, pending trajectory</li> <li>• No strict guidelines, indications include: developing shock, resp failure, mod/severe RV dysfunction on TTE (RV hypokinesis, RVSP &gt;40) w/ ↑↑ hs-TnT/NT-proBNP (&gt;900)</li> <li>• Routine tPA in int. risk PE → ↓hemodynamic decomp., no clear long-term Δ in mortality; ↑major bleeding &amp; hemorrhagic CVA (<a href="#">NEJM 2014;370:1402</a>; <a href="#">JACC 2017;69:1536</a>)</li> </ul> <p>Intermediate-high risk: transition to long-term AC agent after 48-72h of stability. Intermediate-low risk: transition after 24h.</p>	<p><b>Anticoagulation:</b> See above (DVT) and AC, AC Mgmt sections</p> <p><b>Discharge:</b> if no other reasons for hospitalization, can d/c; can use <a href="#">Hestia score</a> to help determine safety for outpatient treatment</p> <p><b>Isolated Subsegmental PE (w/ no DVT):</b> Rule out proximal DVT. If low risk of recurrent VTE, can consider surveillance with repeat imaging. If higher risk, anticoagulate (<a href="#">Chest 2021;160:e545</a>)</p>
<p><b>Thrombolysis:</b> → ↓mortality (<a href="#">Am J Card 2019;123:684</a>; <a href="#">JAMA 2014;311:2414</a>; <a href="#">CDSR 2021;4:CD00437</a>)  <u>Systemic</u>: alteplase 100mg/2h (bolus 50mg/2min if cardiac arrest). Hold AC during infusion (but do not delay if got LMWH). No convincing evidence to support <u>routine</u> use of lower dose tPA (<a href="#">Am J Card 2013;111:273</a>)</p> <ul style="list-style-type: none"> <li>• <u>Absolute contraindications</u>: intracranial neoplasm, CNS surgery/trauma &lt;2-3mo, h/o ICH, active bleeding, non-ICH stroke &lt;3mo</li> </ul> <p><u>Catheter-directed</u>: infused into pulmonary artery via PA catheter, significantly less lytic agent given than in systemic lysis. May be preferred if high-risk for bleeding, failed systemic thrombolysis, or otherwise selected pts; can couple w/ US-assisted thrombolysis (EKOS) to enhance mechanical breakdown of thrombus or suction thrombectomy. ↓ in RVSP, ↓RV/LV ratio, no data for mortality benefit (<a href="#">Circ 2014;129:479</a>; <a href="#">JACC Card Interv 2015;8:1382</a>; <a href="#">Am J Med 2019;132:240</a>; <a href="#">Am J Card 2019;124:1470</a>)</p>		
<p><b>PERT (x47378):</b> call if large PE w/ abnormal VS (tachycardia, hypotension), evidence of RH strain (TTE, EKG, biomarkers), saddle PE. Order: CBC/diff, BMP, LFTs, lactate, D-dimer, ABG, PT/INR, PTT, T&amp;S, NT-proBNP, hs-TnT, EKG, CT-PE, LENLs, TTE</p>		

# Pulmonary & Critical Care

<b>Pulmonary Hypertension = mean PA pressure (mPAP) <math>\geq 20</math> mmHg</b> $PVR = (mPAP - PCWP) / CO$ ; rearranged: $mPAP = (PVR \times CO) + PCWP$ $\therefore \uparrow$ in PVR or PCWP can $\rightarrow$ pulmonary hypertension (PH)
<ul style="list-style-type: none"> <li>▪ <b>Pre-capillary PH:</b> PVR <math>\geq 3</math>, PCWP <math>\leq 15</math>, <math>\uparrow</math> DPG &amp; TPG</li> <li>▪ <b>Post-capillary PH:</b> PVR <math>&lt; 3</math>, PCWP <math>&gt; 15</math>, nl DPG &amp; TPG</li> <li>▪ <b>Mixed PH:</b> PVR <math>\geq 3</math>, PCWP <math>&gt; 15</math>, <math>\uparrow</math> DPG &amp; TPG</li> </ul>
Transpulmonary gradient (TPG) = mPAP – PCWP; nl $< 12$
Diastolic pulmonary gradient (DPG) = PA diastolic (PAD) – PCWP; nl $< 7$

## DIAGNOSIS (ERJ 2019;53:1801904)

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

## WHO CLASSIFICATION (6<sup>th</sup> World Symposium on PH: ERJ 2019;53:1801913; JACC 2013;62:D34)

Pre-Capillary			
Group 1: Pulmonary Arterial Hypertension (PAH)	Group 3: Lung disease and/or hypoxemia	Group 4: Pulmonary artery obstructions	Group 2: Left heart disease
<ul style="list-style-type: none"> <li>- <b>Idiopathic</b> (<math>\text{♀} &gt; \text{♂}</math>)</li> <li>- <b>Heritable</b> (e.g. BMPR2)</li> <li>- <b>Drug/toxin-induced:</b> cocaine, anorexigens, etc</li> <li>- <b>Associated with:</b> CTD (MCTD, SSc, SLE), HIV, portal HTN, congenital heart disease, schisto</li> <li>- PAH long-term responders to CCBs</li> <li>- PVOD and/or pulmonary capillary hemangiomatosis</li> <li>- Persistent PH of newborn</li> </ul>	<ul style="list-style-type: none"> <li>Obstructive: COPD</li> <li>Restrictive: ILD</li> <li>Mixed</li> <li>obstructive/restrictive</li> <li>Chronic hypoxia w/o lung disease: <b>OSA, OHS</b></li> <li>Developmental lung dz (ERJ 2019;53:1801914)</li> </ul>	<ul style="list-style-type: none"> <li><b>Chronic thromboembolic disease</b> (ERJ 2019;53:1801915)</li> <li>NB: only ~33-75% had known prior VTE. Occurs after ~4% of PEs (NEJM 2004;350:2257)</li> <li>Other PA obstructions: malig., arteritis w/out CTD, parasites, congenital PA stenosis</li> </ul>	<ul style="list-style-type: none"> <li><b>HFpEF</b></li> <li><b>HFrEF</b></li> <li><b>Valvular disease</b></li> <li>Congenital/acquired conditions (ERJ 2019;53:1801897)</li> </ul>
<b>Group 5: Misc.</b> chronic hemolytic anemia (e.g., sickle cell), MPN, sarcoid, metabolic d/o, complex congenital heart disease			

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

## MANAGEMENT

Treat underlying etiology: CTD, CHF, hypoxemia, VTE, etc. Advanced therapies (below): guided by WHO functional class (reserved for II-IV). **Most evidence in Group 1.** Surgery: pulmonary thromboendarterectomy (CTEPH), atrial septostomy (R  $\rightarrow$  L shunt), lung txp in select pts. General: exercise/pulm rehab, O<sub>2</sub>, diuresis (in RHF), contraception required in ♀ (2 forms vs permanent form), vaccines

Mechanism	Medication	Indication	Side effects	
Endothelin receptor antagonists	Bosentan, ambrisentan, macitentan	Blocks pulmonary vasoconstriction & proliferation	<p>Group 1: <math>\downarrow</math> sx, <math>\uparrow</math> 6MWT (NEJM 2002;346:896; Circ 2008;117:3010)</p> <p>Macitentan: <math>\downarrow</math> morbid/mortality (NEJM 2013;369:809)</p>	Anemia, PNA, edema, hepatotoxic. Macitentan: also flu, HA, UTI, bronchitis
(NO)-cGMP enhancers	PDE5 inhibitors: sildenafil, tadalafil, vardenafil (not FDA approved for PAH)	Increases cGMP $\rightarrow$ vasodilation, blocks proliferation	Group 1 (sildenafil studied in some etiologies of Group 2 and 5): $\downarrow$ sx, $\uparrow$ 6MWT (NEJM 2005;353:2148; NEJM 2009;361:1864)	Erythema, flushing, indigestion, HA, insomnia, epistaxis, rhinitis, retinal hemorrhage, *contraindicated if using nitrates
	sGC stimulator: riociguat		Group 1 & Group 4: $\downarrow$ sx, $\uparrow$ 6MWT (NEJM 2013;369:330)	$\downarrow$ BP, n/v/d/const., GERD, anemia, dizziness, HA, hemorrhage
Prostacyclin pathway agonists (PPA)	Analogues: epoprostenol, treprostinil, iloprost	Increase cAMP $\rightarrow$ vasodilation, blocks proliferation	Group 1: $\uparrow$ 6MWT, $\uparrow$ QOL; reserved for sickest patients (NEJM 1996;334:296)	CP, $\downarrow$ BP, $\uparrow$ HR, flushing, abd pain, anorexia, n/v/d, MSK & jaw pain, dizziness, HA, hemorrhage
	Receptor agonist: selexipag		Group 1: $\downarrow$ hospitalization; no $\Delta$ mortality (NEJM 2015;373:2522)	Diarrhea, nausea, jaw pain, HA, anemia
CCB (trial)	Nifedipine, diltiazem	Vasodilation	$\oplus$ iNO vasoreactivity test. $\ominus$ RV failure	$\downarrow$ BP, LE edema

Initiating Therapy based on ERS/ESC risk stratification guidelines (ERJ 2015;46:903): refer to Pulm HTN clinic

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

**Goal of therapy is to attain  $\geq 3$  low risk criteria:** CI  $\geq 2.5$ , RAP  $< 8$ , WHO/NYHA class I or II, 6MWT  $> 440$ m. May add IV/SQ prostacyclin if low risk criteria are not met 3-6mo after initiation of oral agents (ERJ 2017;50:1700889)

# Pulmonary Hypertension

## CLINICAL MANIFESTATIONS

**S/Sx:** nonspecific; 2y delay to dx in 20% (Chest 2011;140:19)

- **Early:** DOE, lethargy, **fatigue** (2/2 inadequate CO w/ activity)
- **Late:** exertional CP, **syncope**, edema, anorexia, abdominal distention (secondary to progressive RV failure)
- **Rare:** cough, hemoptysis, hoarseness (Ortner's syndrome)

**Exam:** loud P2;  $\uparrow$  JVP, edema, ascites, TR murmur, R-sided gallop, parasternal heave (LSB), PA tap (L 2<sup>nd</sup> ICS), edema, hepatomegaly, ascites

**Imaging:** CXR w/ enlarged PA, RA, RV ( $\downarrow$  retrosternal space on lat.), pruning of peripheral vessels; CT w/ PA/Ao diameter  $\geq 1$

**ECG:** normal vs signs of RV hypertrophy/strain: RAD, R/S  $> 1$  in V1, RBBB, P pulmonale in II (RAE)

**TTE:** TR peak velocity  $\geq 3.4$  = high prob for PH, or  $> 2.8$  with RVSP  $> 35$  mmHg, PA diameter  $> 25$  mm; RVOT acceleration time  $< 105$  ms, RV dilation/hypokinesis, RV/LV  $> 1$ , IVC  $> 21$  mm

# Pulmonary & Critical Care

# Mechanical Ventilation

## INDICATIONS FOR INTUBATION

- Failure of NIPPV:** unable to tolerate, progressive hypoxemia/capnia, high pressures, ↓ mental status, ↑ fatigue/WOB
- Poor ventilation:**  $\text{PaCO}_2 > 60$  with severe acidemia (COPD/asthma, sedation, neuromuscular disease, resp. muscle fatigue, trauma)
- Poor oxygenation:** worsening P:F ratio (PNA, pulmonary edema, ARDS, PE)
- Airway protection/instability:** ↓ consciousness (GCS < 8), shock, facial/head trauma, n/v/UGIB, severe secretions, severe bronchospasm/anaphylaxis
- Persistent increased work of breathing:** severe bronchospasm, airway obstruction, inability to compensate for severe acidemia
- Hemodynamic instability:** unstable arrhythmia, severe shock

Call RICU for intubation: x6-3333

RICU will ask: AMPLE

A = allergies

M = medications (current)

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

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

E = events (prompting intubation)

During intubation, have at bedside:

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

## HEMODYNAMIC CONSEQUENCES OF INTUBATION

- PPV # intrathoracic pressure → ↓ LV & RV preload, # PVR/RV afterload & LV afterload. Can precipitate RV failure in pHTN and RV dysfx
- In acidosis such as DKA, can be difficult to match RR to physiologic needs
- Vasoplegia from sedatives and ↓ sympathetic tone = ↓ BPs; have appropriate pressors ready

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

Five main variables: (1) RR, (2) tidal volume ( $V_T$ ), (3)  $\text{FiO}_2$ , (4) positive end-expiratory pressure (PEEP), (5) mode of ventilation

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

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

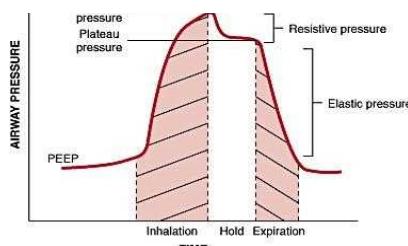
MODE	SET Indep. Var.	MEASURED Dep. Var.	PROS/CONS	HOW TO READ	WHEN TO USE
<b>AC/VC</b> <i>Assist</i> <u>Control/Volume Control:</u> delivers a breath until set tidal volume is reached	$V_T$ PEEP RR $\text{FiO}_2$ I:E or flow	PIP & $P_{plat}$ I:E or flow	⊕: ↑ control (fixed $V_T$ prevents barotrauma or atelectrauma) ⊖: fixed insp. flow regardless of effort, ↑ dyssynchrony	"Pt is on Volume Control w/ $V_T$ of 400 (4cc/kg), set at a rate of 16 breaths/min, PEEP of 8, and $\text{FiO}_2$ 0.6; breathing at set rate of 16 (or over) with $V_T$ ~400 for MV of 6.4L"	- Acute resp failure - ARDS - Airflow limitation (e.g. COPD, asthma)
<b>AC/PC</b> <i>Assist</i> <u>Control/Pressure Control:</u> delivers a breath until set pressure is reached	$P_{insp}$ PEEP RR $\text{FiO}_2$ I:E	Flow $V_T$	⊕: variable flow (& $V_T$ ) during inspiration to satisfy pt demand, ↓ dyssynchrony ⊖: can cause volutrauma as compliance or pt effort changes	"Pt is on Pressure Control of 18 ( $P_{insp}$ ) over 5 (PEEP), set at a rate of 16 breaths/min, and $\text{FiO}_2$ 0.3; breathing $V_T$ ~400, at set rate of 16 (or over) for a MV of 6.4L."	- Air leak (e.g. PTX) - May trial in situations of vent dyssynchrony
<b>PSV</b> <i>Pressure Support Ventilation:</i> delivers set pressure triggered by patient's spont breaths	$P_{insp}$ PEEP $\text{FiO}_2$ RR (backup)	I:E Flow $V_T$ RR	⊕: better tolerated, less sedation, trial pre-extubation (e.g. SBT on 0/0 or 5/5) ⊖: ↓ control over parameters, volutrauma possible, no fixed RR (only backup)	"Pt is on Pressure Support of 10 ( $P_{insp}$ ) over 5 (PEEP) with an $\text{FiO}_2$ 0.3; breathing $V_T$ of ~500 at 20 breaths/min. for a MV of 10L."	- Intubated for non-cardiac or lung failure (e.g. AMS) - Weaning vent - Severe met acidosis

## MONITORING MECHANICS

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

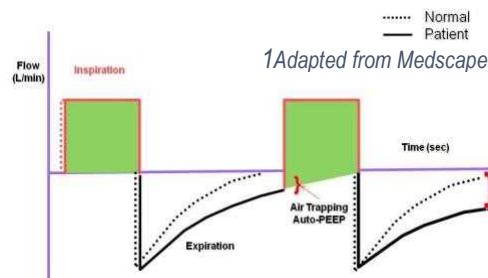
## VENTILATOR MANEUVERS FOR MONITORING MECHANICS

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



## VENTILATOR COMPLICATIONS

- Dynamic hyperinflation (auto-PEEP):** measured by end expiratory hold. Auto PEEP = end exp pressure – set PEEP
  - Diagnosis: end-expiratory flow  $>0$  due to incomplete alveolar emptying
  - RFs: vent strategy causing hyperinflation (high RR,  $\uparrow I:E$  ratio) or obstructive disease (asthma, COPD, CF)
  - Consequences: adverse hemodynamic effects (HoTN secondary to ↓ venous return), alveolar over-distention ( $\rightarrow$  volu-/barotrauma); ↑ effort to trigger breath
  - Tx: longer exhalation ( $\downarrow I:E$  ratio,  $\downarrow RR$ ), set exogenous PEEP to 2/3 auto-PEEP, bronchodilators for obstruction
  - If severe hemodynamic or resp. compromise, transiently disconnect pt from ventilator and manually bag ventilate to allow deflation
- Ventilator-induced lung injury (VILI):** alveolar injury  $\rightarrow$  ↑ alveolar permeability, interstitial & alveolar edema, alveolar hemorrhage, hyaline membranes, & alveolar collapse (similar to ARDS) ([NEJM 2013;369:2126](#)). Avoid w/ lung protective ventilation (see ARDS).
  - Volutrauma:** over-distension of alveoli due to high  $V_T$ ; or, if there is heterogenous consolidation or atelectasis, a disproportionate volume from each breath is delivered to open alveoli
  - Atelectrauma:** shear forces from cyclic alveolar recruitment and de-recruitment injure adj alveoli/airways
  - Biotrauma:** cytokine release from lung epithelium  $\rightarrow$  multi-organ dysfunction
  - Oxytrauma:**  $\uparrow \text{FiO}_2 \rightarrow$  free radical production, lung injury
  - Barotrauma:** injury from high  $P_{\text{plat}}$  (highest risk  $>35$ )  $\rightarrow$  PTX, subcutaneous emphysema, pneumomediastinum
- ↑ Peak inspiratory pressure (PIP) = airway resistance + elastic resistance ( $P_{\text{plat}}$ ):** To troubleshoot, determine  $P_{\text{plat}}$  with insp. hold
  - If normal  $P_{\text{plat}} (<30)$ : ↑ airway resistance: bronchospasm, secretions/mucus plug, ET malposition/kink/biting, airway edema
  - If elevated  $P_{\text{plat}} (>30)$ : ↑ elastic pressure = ↓ compliance
    - Decreased functional lung size/overdistention: auto-peep, atelectasis, R main stem, ARDS, PNA, DAH, pulm edema
    - Increased thoracic pressure: obesity, kyphosis, burns, abdominal compartment/ascites, effusions, PTX, Tberg position
    - Parenchymal disease: ILD, post radiation
  - Low PIP? leak in the system: bronchopleural fistula, ET cuff rupture/dislodge, tubing damage
- Other complications:** VAP, laryngeal edema, tracheal stenosis, PTX



## ALGORITHM FOR RESPIRATORY PLAN (REMIX)

R	Reason for intubation	ARDS, PNA, COPD, pulmonary edema, aspiration, hypoventilation, altered mental status, etc
E	Exchange (gas exchange)	Recent ABG; how to improve $\text{PaO}_2$ (i.e. diuresis, pulmonary vasodilators) and/or $\text{PCO}_2$ (i.e. #RR)
M	Mechanics	$P_{\text{plat}}$ , PIP, resistance pressure, elastic pressures; chest wall/respiratory muscle strength
I	ID/infection	Sputum cx data, abx day #, source control, need for bronchoscopy; assess for VAP
X	eXtubation barriers	Daily SAT/SBT, secretion clearance, mental status, planned procedures
(S)	Sedation	Current sedation, whether $\Delta$ needed e.g. start dexmedetomidine/quetiapine as bridge peri-extubation

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

- Requirements for extubation:**
  - adequately treated underlying disease and hemodynamic stability
  - adequate oxygenation and ventilation:  $\text{PaO}_2/\text{FiO}_2 \geq 150-200$ ,  $\text{PEEP} \leq 5-8$ ,  $\text{FiO}_2 \leq 0.4-0.5$ ,  $\text{pH} > 7.25$ 
    - Rapid Shallow Breathing Index (RSBI) =  $\text{RR}/V_T$ :** RSBI  $>105$  predicts extubation failure ( $\text{Sn}>\text{Sp}$ ) ([NEJM 1991;324:1445](#))
  - ability to cough/manage secretions (ideally alert/following commands, but if protecting airway, AMS does not preclude extubation)
  - +cuff leak. Absence of cuff leak is concerning for laryngeal edema  $\rightarrow$  consider methylpred 20mg IV q4h 12hrs prior to extubation or IV methylpred 40mg x1 4hrs prior or IV dexamethasone 5mg q6h ([Eur J Anaesthesiol 2010;27:534](#)).
- Liberation protocol:** daily Spontaneous Awakening Trial (SAT) + Spontaneous Breathing Trial (SBT)
  - SAT:** ↓ ventilator time, ICU LOS, & mortality if paired with SBT ([NEJM 2000;342:1471](#); [Lancet 2008;371:126](#))
  - SBT:** ~30-120min daily trials w min support ( $\text{PEEP} \leq 5$  on PSV)=↓ vent time ([NEJM 1996;335:1864](#); [NEJM 1995;332:345](#))
    - Ways to fail: hypoxemia ( $\text{SaO}_2 < 90\%$ ,  $\text{PaO}_2 < 60$ ), hypercarbia ( $\text{PaCO}_2 \uparrow$  by  $>10$ ), low  $V_T$ , respiratory distress ( $\uparrow \text{HR}$ ,  $\uparrow \text{RR}$ , HTN, accessory muscle use, diaphoresis), arrhythmia, hemodynamic instability, anxiety/agitation, somnolence
    - Causes of SBT failure: underlying etiology not corrected, volume overload, cardiac dysfunction, neuromuscular weakness, delirium, anxiety, metabolic abnormalities
- Extubation strategies:**
  - Extubation to NIPPV or HFNC in patients with hypercarbia / risk factors for reintubation, not done routinely  $\rightarrow$  ↓ post-extubation respiratory failure ([Lancet 2009;374:1082](#); [JAMA 2016;316:1565](#)). HFNC w/ intermittent NIV post-extubation  $\rightarrow$  ↓ reintubation compared to HFNC alone ([JAMA 2019;322:1465](#)).
  - If agitation is limiting ability to extubate, consider dexmedetomidine  $\rightarrow$  may improve odds of extubation ([JAMA 2009;301:489](#))
- Post-extubation respiratory failure:** due to poor secretion clearance, CHF, aspiration, bronchospasm, laryngeal edema
  - NB:** no benefit to NIPPV as rescue therapy during post-extubation respiratory failure and may be associated w/ worse outcomes ([NEJM 2004;350:2454](#)). Not recommended per ERS/ATS guidelines ([ERJ 2017;50](#)).
- Tracheostomy:** usually performed once intubated for 14-21 days. Early tracheostomy (7 days) if expect intubation  $>14$  days  $\rightarrow$  ↑ comfort, allows ↓ sedation, ↓ risk of tracheal stenosis, ↓ vent-free and ↓ ICU days, though no change in VAP rate ([JAMA 2010;303:1483](#); [Crit Care 2015;19:424](#); [Br J Anaesth 2015;114:396](#))

# Pulmonary & Critical Care

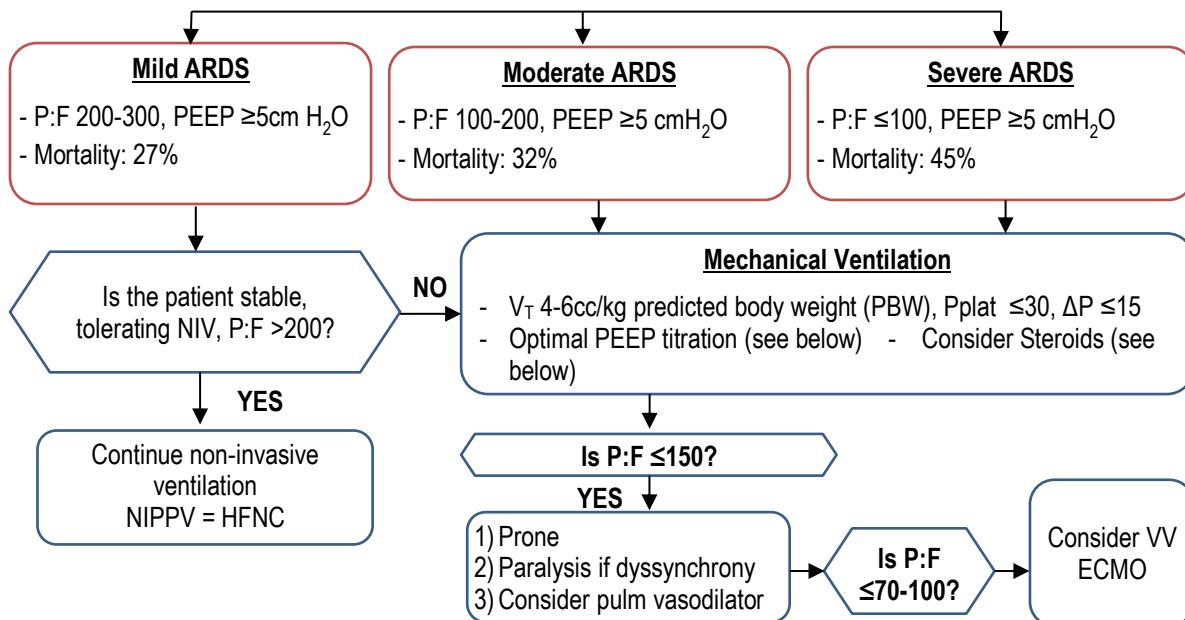
ARDS

## PATHOPHYSIOLOGY AND BERLIN DEFINITION OF ARDS

- Direct lung injury:** pneumonia, aspiration, inhalational injury, near drowning, pulmonary contusion; **indirect lung injury:** sepsis, trauma, pancreatitis, drugs, burns, cardiopulmonary bypass/pump, transfusion-related acute lung injury (TRALI)
- Ddx (ARDS Mimics):** Eosinophilic PNA (AEP), acute interstitial PNA (AIP), organizing PNA
- Pathway:** diffuse, immune-mediated lung injury causing pulmonary capillary and alveolar epithelial damage leading to increased vascular permeability, impaired gas exchange, and decreased lung compliance ([NEJM 2017;377:562](#))

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

- 1) Onset within 1 week of insult (usually 72h)
- 2) Not primarily due to hydrostatic/cardogenic pulmonary edema
- 3) Imaging showing bilateral opacities on CXR
- 4)  $\text{PaO}_2:\text{FiO}_2 \text{ (P:F) ratio} \leq 300$  with  $\text{PEEP/CPAP} \geq 5 \text{ cm H}_2\text{O}$



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

Strategies including the 6P's (in order of ↓ LOE): if refractory hypoxemia see "ECMO page" the 6 <sup>th</sup> P	Effects
<b>Low Tidal Volume Ventilation (LTVV)</b> ( <a href="#">NEJM 2007;357:1113</a> ) ( <a href="#">NEJM 2000;342:1301</a> )	<ul style="list-style-type: none"> <li>Maintain oxygenation while preventing ventilator-induced lung injury (VILI)</li> <li><math>V_T</math> 4-6 cc/kg PBW w/ goal <math>P_{plat} \leq 30</math>, driving pressure (<math>P_{plat}-PEEP</math>) ≤ 15           <ul style="list-style-type: none"> <li>May allow ↑ <math>P_{plat}</math> if ascites, obesity, etc. as may not accurately reflect Transpulm. Pressures (see "esophageal balloon catheter" on next page)</li> </ul> </li> <li>Permissive hypercapnia: pH goal ≥ 7.20-7.25 allows for lower <math>V_T</math> to ↓ VILI           <ul style="list-style-type: none"> <li>Contraind: ↑ ICP, RV fail./PH (↑ pulm. vasoconst.), TCA/ASA o/d, pregnant</li> </ul> </li> </ul>
<b>Prone Positioning</b> ( <a href="#">PROSEVA NEJM 2013;368:2159</a> )	<ul style="list-style-type: none"> <li>↓ V/Q mismatch by ↓ compressive atelectasis from heart &amp; diaphragm → ↑ alveolar recruit. → ↓ regional volutrauma &amp; ↑ compliance</li> <li>Initiate early (w/in 12-24h) in mod-sev. ARDS after initial stab. period while supine if P:F &lt; 150 (or 200) despite optimal PEEP titration</li> <li>Maintain prone ≥ 16h. If supinate and P:F remains &gt; 150 (or 200) and ΔP ≤ 15 after 2h, can remain supine</li> <li>C/I: HDUS, ↑ ICP, fixed/unstable C-spine/neck, 2/3<sup>rd</sup> tri. Preg., recent sternotomy</li> </ul>
<b>Conservative Fluid Management (Pee)</b> ( <a href="#">NEJM 2006;354:2564</a> )	<ul style="list-style-type: none"> <li>FACTT Trial: CVP &lt; 4 (conservative) &gt; CVP ≤ 10-14 (liberal)</li> <li>Diurese prn to minimize pulmonary edema after resolution of shock</li> </ul>
<b>PEEP</b> ( <a href="#">NEJM 2004;351:327</a> ) ( <a href="#">JAMA 2010;303:865</a> )	<ul style="list-style-type: none"> <li>↑ recruitment, ↓ trauma from cyclic atelectasis</li> <li>↑ PEEP distributes <math>V_T</math> over ↑ alveoli → ↓ over-distention → improves oxygenation (via ↓ V/Q mismatch and ↓ shunt fraction) &amp; compliance</li> <li>CV effects of PEEP: ↓ preload/SV, ↑ RV afterload, ↓ LV "afterload", ↓ BP</li> <li>Harms of PEEP: barotrauma, ↑ dead space, hemodynamic effects</li> </ul>
<b>NMB (Paralysis)</b> ( <a href="#">ROSE NEJM 2019;380:1997</a> )	<ul style="list-style-type: none"> <li>↑ oxygenation by ↓ vent dyssynchrony if present and chest wall compliance</li> <li>Start w/ intermittent boluses &amp; transition to infusion if persistent dyssynchrony &gt; 3 boluses/2h (cisatracurium 0.1-0.2mg/kg q30min PRN → 0-5mcg/kg/min; rocuronium 0.6-1.2mg/kg q30-60min PRN → 0-20mcg/kg/min)</li> </ul>

# Pulmonary & Critical Care

ARDS

Strategies including the 6P's (in order of ↓ LOE): if refractory hypoxemia see "ECMO page" the 6 <sup>th</sup> P		Effects
<b>Pulmonary Vasodilators</b> (Cochrane Rev 2016; Crit Care 2012;16:R36)	<ul style="list-style-type: none"> <li>Start w/ iNO trial (40ppm - 80ppm) → inhaled Veletri or just start w/ Veletri</li> <li>Should see at least 20% ↑PaO<sub>2</sub>, otherwise do not continue therapy due to cost and risks, including hypotension</li> <li>↓V/Q mismatch by selectively dilating vessels that perfuse well-ventilated lung; also ↓PVR and ↓RV afterload</li> <li>risk of methemoglobinemia w/ iNO</li> </ul>	No mortality benefit and ↑ risk of renal failure, but may improve oxygenation in first 24h and TLC at 6mo (Cochrane Rev 2016; Crit Care 2012;16:R36).
<b>Steroids</b> (Lancet RM 2020;8:267; Chest 2007;131:954; Chest 2020;107:059; NEJM 2006;354:1671)	<ul style="list-style-type: none"> <li>Covid-19: dexamethasone use is associated with ↑ventilator-free-days &amp; ↓mortality as seen in the RECOVERY trial (NEJM 2021;384:693).</li> <li>Non-Covid-19 ARDS: consider on case by case basis in those with moderate-severe ARDS, onset 14 days or less, esp. when ARDS is due to severe bacterial or PJP PNA, organizing PNA, or eosinophilic PNA.</li> </ul>	a/w ↑vent. free-days & ↓mort., esp. in COVID-19. Still controversial in non-Covid-19 ARDS

**Summary of the 6 Ps of refractory hypoxemia:** 1. Prone 2. Pee (fluid management) 3. PEEP 4. Paralysis 5. Pulmonary vasodilators 6. Perfusion (ECMO)

## LUNG PROTECTIVE (ARDSNET) VENTILATION

- Initial ventilator set-up:  $V_T = 6 \text{ cc/kg PBW}$ , RR to approximate baseline MV (RR <35), moderate PEEP (8-10)
- Adjustments:** (also see *Mechanical Ventilation*)
  - Oxygenation:** goal  $\text{PaO}_2 55-80 \text{ mmHg}$  or  $\text{SaO}_2 88-94\%$ 
    - $\text{SpO}_2 <94\%$  a/w ↓mortality; hyperoxia leads to ↑mortality (JAMA 2016;316:1583; Crit Care 2014;18:711)
    - If persistent hypoxemia requiring  $\text{FiO}_2 >\sim 0.6$ , optimize PEEP (see below)
  - Mechanics:** goal **plateau pressure ( $P_{plat}$ ) ≤30 & driving pressure ( $\Delta P$ ) ≤15** (obtain with inspiratory hold)
    - If  $P_{plat} >30$  and/or  $\Delta P >15$ : ↓ $V_T$  by 1 cc/kg PBW (minimum  $V_T$  4 cc/kg PBW); limit on ability to ↓ is ↓MV → ↑ $\text{pCO}_2$  & ↓pH
    - If  $P_{plat} <25$  and  $V_T <6 \text{ cc/kg PBW}$ : can ↑ $V_T$  by 1 cc/kg until  $P_{plat} >25$  or  $V_T$  6 cc/kg PBW
  - pH:** goal **7.20-7.25 to 7.45** ("permissive hypercapnia" unless contraindicated, lower boundary context dependent)
    - pH below goal: ↑RR (up to 35/min) until pH at goal or  $\text{PaCO}_2 <25$ ; watch for auto-PEEP development at high RR
    - If RR = 30-35/min & pH goals not met: can ↑ $V_T$  (may cause ↑ $P_{plat} >30$ )

### Mechanical Ventilation Goals in ARDS

Measure	Goal
Oxygenation	$\text{PaO}_2 55-80 \text{ mmHg}$ $\text{SaO}_2 88-94\%$
Mechanics	Plateau pressure ( $P_{plat}$ ) ≤30 Driving pressure ( $\Delta P$ ) ≤15
pH	7.20-7.25 to 7.45

## OPTIMIZING PEEP FOR ARDS

- ARDSNet FiO<sub>2</sub>/PEEP scale:**
  - If P:F <150 @ PEEP 5, attempt to recruit lung by inc. PEEP from 5 → 15
  - If improvement, use high PEEP/low FiO<sub>2</sub> scale; if not, use low PEEP/high FiO<sub>2</sub> scale (see right)
- Best PEEP trial:** select the PEEP corresponding to best global recruitment with lowest risk for overdistention based on **resp system compliance ( $C_{RS} = V_T / [P_{plat} - P_{PEEP_{Total}}]$ )**
  - Keep  $V_T$  constant and use **decremental titration of PEEP**; choose best PEEP based on balance of highest compliance, lowest driving pressure (<15), acceptable oxygenation, and stable hemodynamics
- Driving pressure:**  $\Delta P = P_{plat} - P_{PEEP}$  (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,  $P_{plat}$ ) (NEJM 2015;372:747)
- Recruitment maneuvers** (if hemodynamically stable): opens collapsed alveoli to ↑participation in gas exchange
  - Begin with **high PEEP** to open up alveoli, then decremental PEEP titration to optimize mechanics (JAMA 2008;299:637)
  - Outcomes are mixed w/ ↑ (JAMA 2017;318:1335) and ↓mortality (low quality, Cochrane Rev 2016); avoid ↑↑PIP (>50)
- Esophageal balloon catheter:** estimates intrapleural pressure; used to calculate **transpulmonary pressure ( $P_{tp}$ )** = alveolar pressure [ $P_{plat}$ ] - intrapleural pressure). PEEP then titrated to maintain optimal  $P_{tp}$  (<25 at end-inspiration to prevent VILI, 1-2 at end-expiration to prevent atelectrauma) (NEJM 2008;359:2095). Consider in pts with high intra-abd. pressure (obesity, ascites, abd. comp. syn.)
  - No Δ on mort., vent or ICU free days, despite ↑O<sub>2</sub> and lung compliance. ↓risk of needing adv. rescue tx (JAMA 2019;321:846)

### NIH NHLBI ARDS Clinical Network Mechanical

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

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

# Pulmonary & Critical Care

ECMO

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

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

## To call ECMO consult:

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

## Indications:

- Reversible acute resp failure (VV): e.g. ARDS, bridge to transplant or recovery  
PaO<sub>2</sub>/FiO<sub>2</sub> <80 despite optimization, unable to achieve safe inflation pressures (Pplat <30), CO<sub>2</sub> retention (pH<7.25) with inability to mechanically ventilate. See [ELSO](#).
- Reversible cardiogenic shock (VA): e.g. PE, cardiac arrest. Refractory low cardiac index (<2L/min/m<sup>2</sup>) & HoTN despite adequate volume, inotropes, & IABP. ECPR.
- Bridge to definitive therapy (transplantation, VAD, recovery)

## Contraindications:

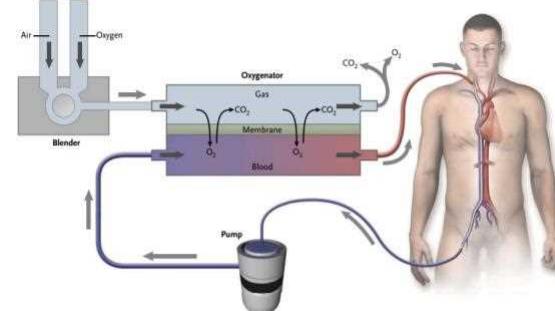
- Absolute (VA or VV): non-recoverable multi-organ failure/neurological disease; unwitnessed arrest/CPR >30min w/o ROSC; active severe bleeding; contraindication to AC, recent NSGY procedure/active intracranial bleed (<10d)
- Absolute VA: BMI>40; AoD; severe AI; ESLD/ESRD
- Absolute VV: severe right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

## ECMO VARIABLES

### Drainage Cannula in large central veins (IVC, SVC, or RA)

### Return Cannula in RA or Ao (depending on configuration)

- **Sweep** (aka fresh gas flow, replaces ventilation (L/min)): ↑sweep → ↓PaCO<sub>2</sub> in blood returning to pt therefore ↑sweep requirements = worsening ventilation vs ↑ CO<sub>2</sub> production (fever, infxn, renal failure). Controls O<sub>2</sub> delivery if any. When sweep is weaned off or "capped" in VV-ECMO, ECMO support for ventilation / oxygenation is also off.
- **FdO<sub>2</sub>** (fraction of delivered O<sub>2</sub> in sweep gas flow): Generally set at 1.0
- **RPM:** RPM is predominant determinant of **blood flow** (2-5L/min; >7LPM limited by membrane lung efficiency also affected by cannula size & native CO). VV ECMO – based on BSA to estimate O<sub>2</sub> consumption (BMI may limit candidacy), partially weaned. VA ECMO – indicates % of CO support from ECMO, main weaning variable.
- **Transmembrane Pressure** (dP or ΔP = P<sub>pre</sub> - P<sub>post</sub>): reflects oxygenator function (membrane acts as oxygenator) and flow
  - o ↑ ΔP: check membrane for clots and ABG to assess impact on gas exchange. Check RPM (ΔP = BF × R so may reflect ↑ flow).
  - o ↓ ΔP: check ECMO circuit for kinks either at the inflow or outflow sites
- **Baseline lab goals:** Hgb >7.5g/dL; plt >75K; fibrinogen >150; active T&S. Maintain SpO<sub>2</sub> > 85% and PaO<sub>2</sub> > 55.
- **AC:** UFH, follow PTT, Xa, AT-III. Goals: d/w attending/pharmacist



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

- **ECMO:** clots (oxygenator, pump, tubing, hemofilter; 0.13-22%); **cannula displacement** (0.8-8%); **air embolism, oxygenator failure, pump failure.** [For emergencies, STAT page ECMO team.](#)
- **Patient:** bleeds (access sites, ENT/Pulm/GI/GU, intracranial, hemolysis, DIC; 5.3-79%); **neuro** (ICH, stroke, seizure, encephalopathy; 10-33%); **limb ischemia** (13-25%); **infxn** (17-49%); **AKI** (30-58%); **multi-organ failure** (10%); **cannular** (4.8%)

## TROUBLESHOOTING THE CIRCUIT

- **Chatter:** shaking & sound caused by ↑ ⊖ pressure in tubing; can be due to **hypovolemia, vasodilation, thrombosis, tamponade, or other cause of ↓CO, straining:** Tx w/ volume resuscitation (usually albumin), ↓ RPMs, cannula and/or patient repositioning
- **Hypoxemia** (as measured on **patient ABG or sats**):
  - a) Recirculation: blood travels from the outflow (return) catheter back into the inflow (drainage) catheter, bypassing body. Can be NL if <25 % recirculation. If >25% or ↑ consider catheter malposition. Dx: unexplained ↑inflow O<sub>2</sub> sat, BRB in drainage catheter Tx: reposition cannula (10 cm apart) or switch to dual lumen cannula, ↓RPM
  - b) Membrane failure: often due to excessive and/or abnormal clots/fibrin Dx: visual inspection of circuit with worsening hypoxemia on outflow sat/ABG (PaO<sub>2</sub><200 on 100% F<sub>d</sub>O<sub>2</sub>) or ↑ΔP by 20 in 4hrs Tx: replace membrane
  - c) Shunt: occurs if native CO >> ECMO flow or w/ improving native CO (larger % of blood never travels through ECMO circuit and is poorly oxygenated) Dx: hypoxemia on pt ABG/sats. Tx: 1RPM to ↑flow. To ↑ CO: ↓fever, ↓inotropes, βB, CCB, phenylephrine
- **Harlequin (North-South) syndrome (VA only):** **hypoxia of upper extremities R worse than L, heart, brain** – can occur only when fem. artery cannulated. Cardiac recovery, but poor lung fx → native CO (deoxygenated) pushes against oxygenated ECMO blood in aortic arch leading to hypoxia of UE, brain, heart. Dx: low sats on R arm but normal sats on L (need R radial art line in VA ECMO) Tx: add a venous return cannula/transition to V-AV ECMO ([HeartLung Ves 2015;7:320](#))

## OUTCOMES

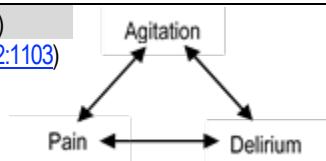
- **Acute respiratory failure:** 2 major studies show ↓mortality, but unclear if from referral to ECMO center or ECMO itself: [CESAR](#): ([Lancet 2009;374:135](#)) & [EOLIA](#): ([NEJM 2018;378:1965](#)) with similar mortality in COVID-19 ARDS ([Lancet 2020;396:1071](#))
- **Refractory cardiogenic shock:** ~40% discharge survival; CPR→ECMO = best death predictor ([CCM 2008;36:1404](#); [ASAIO 2017;63:60](#))
- **ECPR:** ECMO as extension of CPR in cardiac arrest. In-hospital cardiac arrest: ↑survival (OR: 0.17) compared to CPR ([CCM 2011;39:1](#)); OHCA: 22% w/ meaningful neurologic recovery ([Resuscitation 2016;101:12](#)); overall: 29% survive to discharge ([ASAIO 2017;63:60](#)). Consider calling ECMO team if 10 minutes w/o ROSC to discuss VA ECMO

# Pulmonary & Critical Care

# Sedation

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

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



ABCDE Bundle (CCM 2014;42:1024)		
A/w ↑vent-free days, ↓delirium ( <a href="#">CCM 2014;42:1024</a> )		
A Spontaneous Awakening Trial (SAT)	Daily sedation interruption; a/w ↓ICU LOS, ↓vent days ( <a href="#">NEJM 2000;342:1471</a> ), ↓PTSD sx ( <a href="#">AJRCCM 2003;168:1457</a> )	
B Spontaneous Breathing Trial (SBT)	If SAT passed, assess readiness for extubation ( <a href="#">Lancet 2008;371:126</a> ).	
C Choice of Sedation	See agents below	
D Delirium	Assess CAM-ICU daily	
E Early Mobility	↑functional status, ↓pressure inj., ↓delirium, & ↓vent days ( <a href="#">Lancet 2009;373:1874</a> )	

RASS (Richmond Agitation Sedation Scale) (AJRCCM 2002;166:1338)		
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube/catheters; aggressive
+2	Agitated	Frequent, non-purposeful mvmt; fights ventilator
+1	Restless	Anxious, but mvmt not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Sustained awakening to voice (≥10sec)
-2	Light sedation	Briefly awakens w/ eye contact to voice
-3	Mod. sedation	Mvmt or eye opening to voice but no eye contact
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
-5	Cannot be aroused	No response to voice or physical stimulation

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

Usual Initial Agents		For pain control, add:
Non-BZD Sedatives (targeting agitation/delirium)		
Propofol 5-50mcg/kg/min (max 83) <i>GABA modulator</i>	<b>1st line sedative.</b> Immediate onset/rapid awakening. ↓ICP & controls seizures → use in status epilepticus & EtOH w/d. Earlier extubation, ↓ICU LOS, mortality vs BZDs ( <a href="#">AJRCCM 2014;189:1383</a> ) <ul style="list-style-type: none"> <li>• Requires monitoring TGs (&gt;500 = pancreatitis risk, PRIS)</li> <li>• SEs: HoTN, bradycardia, <b>hypertriglyceridemia</b>, <b>propofol infusion syndrome (PRIS)</b> (&gt;48h): acidosis, bradycardia, renal/liver failure, rhabdo, HLD, HSM</li> <li>• No Δ w/ renal/liver failure; accumulates in adipose</li> </ul>	<b>Opioids</b> (targeting analgesia) <ul style="list-style-type: none"> <li>• Start w/ <b>bolus</b>, gtt for more sedation (ECMO, chronic pain)</li> <li>• SEs: <b>resp depression, tolerance, constipation/ileus</b></li> </ul>
Dexmedetomidine (Precedex) 0.2-1.5mcg/kg/h <i>Central α2 agonist</i>	Sympathomolytic, <b>anxiolysis w/o resp. depression</b> or amnesia. Can use w/o ETT (EtOH w/d, post-extubation). A/w ↓delirium & earlier extubation ( <a href="#">JAMA 2016;315:1460</a> ); ↓vent days vs midaz ( <a href="#">JAMA 2012;307:1151</a> ; <a href="#">JAMA 2009;301:489</a> ), ↓delirium vs loraz ( <a href="#">JAMA 2007;298:2644</a> ) & propofol ( <a href="#">Eur J Anaesthesiol 2020;37:121</a> ); nightly admin. may prevent delirium ( <a href="#">AJRCCM 2018;197:1147</a> ). No Δ in mortality ( <a href="#">NEJM 2019;380:2506</a> ) <ul style="list-style-type: none"> <li>• SEs: <b>bradycardia, HoTN</b>, tolerance, withdrawal syndrome (if used for &gt;3-5 days)</li> <li>• Dose-reduce in <b>renal, liver failure</b></li> </ul>	<b>Hydromorphone</b> bolus 0.25-1mg q1h, gtt 0.5-5mg/h ↑potency (compared to morphine), • Accumulate in <b>liver/renal failure</b>
		<b>Fentanyl</b> bolus 25-50mcg q30m, gtt 50-200mcg/h Bolus t <sub>1/2</sub> 30-60m; gtt t <sub>1/2</sub> 9-16h • SE: chest wall rigidity • Accumulates in adipose tissue • No renal metabolites
		<b>Morphine</b> bolus 2-4mg q1h, gtt 2-30mg/h Inexpensive, generally tolerated • SEs: pruritus, bradycardia, HoTN • Accumulates in <b>renal failure</b>
<b>Strategies for weaning sedation:</b> Assess daily for improving resp failure (↓FiO <sub>2</sub> , PEEP, no NMB); MGH criteria for extended taper: sedation > 7 days with P:F > 200 & transition to PS in 24-48h - ↓benzos ~20-25% per day → <b>phenobarb</b> or <b>lorazepam</b> - ↓dexmed. ~20-25% q6h → <b>clonidine</b> q8-12h or patch - ↓opioids ~20-25% per day (taper last) → PO opioid ( <b>methadone</b> )		

If deeper sedation is required/propofol contraindicated:		
<b>Benzodiazepines</b> (targeting amnesia, anxiolysis)		
GABA agonist: ↑mortality, time to light sedation & extubation, & delirium --> avoid whenever possible		
• SEs: <b>resp depression, agitation, withdrawal/tolerance</b>		
Midazolam bolus 0.5-4mg q2h, gtt 2-8mg/h	Shorter t <sub>1/2</sub> vs lorazepam (~2-6h vs 14h), fast onset (2-5min); only IV BZD not in propylene glycol <ul style="list-style-type: none"> <li>• Note CYP3A4 metab med interactions (fluconazole, azithro, flagyl, amio)</li> <li>• Metabolites <b>accumulate in liver/renal failure</b>; accumulate in adipose</li> </ul>	
Lorazepam bolus 1-2mg	Preferred > midaz in renal, liver failure <b>but caution in severe liver dz</b> <ul style="list-style-type: none"> <li>• Propylene glycol (solvent) toxicity w/ ↑dose (lactic acid, HoTN, arrhythmia)</li> <li>• Risk of oversedation 2/2 delayed response/accumulation</li> </ul>	
<b>AND/OR</b>		
Ketamine 5-30mcg/kg/min <i>NMDA antagonist</i>	"Dissociated amnesia" & <b>analgesia w/o resp depression</b> ; some bronchodilation <ul style="list-style-type: none"> <li>• SEs: <b>hallucinations, sympathetic stimulation</b> (HTN, bronchodilation, hypersalivation), delirium upon withdrawal, <b>false #BIS activity</b></li> </ul> Metabolites accumulate in <b>renal/liver failure</b> . Monitor LFTs	
Adjunct Agents	quetiapine (50mg q6-12h, max 400mg/d), haloperidol (2.5-5mg IV q4-8h), olanzapine (2.5-5mg), valproate (10-15 mg/kg, max 60mg/kg/day), phenobarbital (consult pharmacy)	

Cher Huang

# Pulmonary & Critical Care

# Shock

## OVERVIEW (NEJM 2013;369:1726)

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

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

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

(2/3) DBP + (1/3) SBP
HR × SV

SVR determined by vessel diameter/length and blood viscosity
SV determined by preload, afterload, & contractility

## Lactic Acidosis (NEJM 2014;371:2309)

**Type A:** tissue hypoperfusion, typical in shock; can be profound iso bowel ischemia, necrosis

**Type B:** NOT marked tissue hypoperfusion. Metformin, cancer (e.g. Warburg), EtOH, ↓ thiamine, albuterol, D-lactate, mitochondrion dysfunc., liver dz

## ETIOLOGIES OF SHOCK

Signs of ↑CO:		SHOCK	Signs of ↓CO:	
- Widened pulse pressure		↑CO		↓CO
- Low diastolic BP				
- Warm extremities				
- Normal cap refill				
<b>Distributive (66%)</b>		<b>Hypovolemic (16%)</b>	<b>Cardiogenic (16%)</b>	<b>Obstructive (2%)</b>
Pathophys.	↓SVR & altered oxygen extraction	↓ cardiac output → inadequate oxygen delivery		
Examples	Sepsis/SIRS, anaphyl., adrenal insuff., liver fail., tox/med, neurogenic (NEJM 2013; 369:840; NEJM 2001;345:588)	Hemorrhagic, GI losses, 3rd spacing (pancreatitis) (NEJM 2018;378:370)	MI, HF, myocarditis, severe valve disease, arrhythmias	Extra-cardiac causes: PE, tension PTX, tamponade
Extremities	Warm and dry	Cold and dry	Cold and wet	Cold and dry
CVP/PCWP (Preload)	↓/normal	↓↓ (< 5 mmHg)	↑↑ (> 7 mmHg)	↑/normal
CO or CVO <sub>2</sub>	↑/normal (Can be low pre-resuscitation)	↓ (<70%)	↓ (<70%)	↓ (<70%)
SVR (Afterload)	↓↓	↑	↑	↑
TTE Findings	Normal chamber size, normal/↑ contractility	Small chambers, normal/↑ contractility	Large chambers, poor contractility	Tamponade: pericardial effusion PE/PTX: dilated RV

## GENERAL CONSIDERATIONS (ANY ETIOLOGY)

- Vasoactive agents (Vasopressors):** titrate **MAP >65 mmHg** (cardiogenic MAP >60 mmHg); acidosis = ↓ vascular response to pressors
- Ventilatory support:** intubate if necessary (concomitant respiratory failure, unable to compensate for metabolic acidosis, marked hemodynamic instability) with pressors available; SpO<sub>2</sub> may be unreliable due to peripheral vasoconstriction, use ABG
- PA catheter:** no mortality/LOS/cost benefit in unselected ICU or CHF pts (Cochrane Rev 2013; JAMA 2005;294:1625; Lancet 2005;366:472)
- Steroids:** known adrenal insufficiency / chronic steroids, stress-dose steroids (hydrocortisone 50mg q6h / 100mg q8h x5-7d)
- Bicarbonate:** if pH <7.1 or <7.2 w/ severe AKI, can use bicarb amps or bicarb gtt. No mortality benefit except in AKI (Lancet 2018;392:31)
- Refractory Shock:** Consider: dynamic LVOT obstruction (due ↑inotropy), anaphylaxis, abdominal compartment syndrome, abdominal catastrophe (can be masked by steroids), new obstructive shock (HOCM/PE), and refractory vasodilation
- Rescue therapies:** hydroxocobalamin (NO scavenger), methylene blue (reverse NO mediated vasodilation), thiamine, ECMO

## DISTRIBUTIVE SHOCK

**Septic Shock** (see Sepsis); **Anaphylactic Shock** (see Anaphylaxis); **Neurogenic Shock:** Suspect if hypotension is in the context of TBI or SCI. Fluid resuscitation, watch for signs of increased ICP

## HYPOVOLEMIC SHOCK

- Access:** obtain 3 IVs (16G or less) if possible. Consider Cordis for rapid infusion; TLC, PICC cannot resus. as quickly
  - Fluid resuscitation:** crystalloid bolus (not infusion). **Use caution w/ fluids if c/f cardiogenic shock** (NEJM 2013;369:1243)
- Management of Major Bleeding:** obtain STAT coags, CBC, fibrinogen, iCa<sup>2+</sup>. Ensure access. **Hold pressure**, correct coagulopathies. PCC for warfarin reversal, DDAVP for antiplatelet reversal. If INR >2, use FFP; Plt <50, transfuse plts, fibrinogen <100, use cryoprecipitate. If iCal < 1.10, give IV Ca, consider TXA (1g IV over 10 min, then 1g over 8h), aminocaproic acid (5g IV over 1h, then 1g per hr X 8hr)
  - If suspect bleed secondary to variceal bleeding, administer octreotide for splanchnic vasoconstriction.
  - If hypotensive/unstable, consider TXA (1g IV over 10 min, then 1g over 8h), aminocaproic acid (5g IV over 1h, then 1g per hr X 8hr)
- Fluid resus.:** **Blood >> 5% albumin > LR > NS.** Transfuse pRBCs if Hgb < 7.0 or if active bleeding – transfuse to hemodynamics.
  - Obtain source control: call proceduralists, obtain STAT CTA if stable.

## CARDIOGENIC SHOCK

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

## OBSTRUCTIVE SHOCK

Relief of obstruction is primary management strategy (see Tamponade) (see PE)

- PTX:** O<sub>2</sub>, needle decompression or chest tube placement); Avoid mechanical ventilation or BIPVV

# Pulmonary & Critical Care

# Sepsis

## OVERVIEW

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

<b>qSOFA</b>
1. RR $> 22$
2. AMS
3. SBP $\leq 100$

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

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

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

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

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

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

- Delay →  $\uparrow$ mortality by 7.6%/h ([CCM 2006;34:1589](#); [CCM 2010;38:1045](#)). More rapid abx → decr. mortality ([NEJM 2017;376:2235](#))
- Abx selection:** guided by site of infection, prior pathogens, exposures (SNF, lines, recent abx, etc), immunocompromise, etc.
  - Consider **double coverage** of PsA if known/suspected PsA infection w/ severe sepsis/septic shock, bacteremia in neutropenic pt, burn pt, or otherwise high incidence of resistance to chosen class (10-15%). Usually  $\beta$ -lactam + (FLQ or aminoglycoside)
  - For ESBL organisms in non-GU infections, carbapenems are preferred to pip-tazo despite micro sensitivity ([JAMA 2018;320:984](#))
  - If there is suspicion of **toxic shock syndrome**, add **clindamycin** for anti-toxin effects (& additional staph/strep coverage)
  - If RFs for **invasive Candida infection** (neutropenia, chemotherapy, transplant, indwelling catheters, TPN, recent major surgery [esp. abdominal], prolonged admission/abx), consider empiric antifungals (typically **micafungin**). In non-neutropenic pts w/ *Candida* colonization, empiric AFs not a/w  $\uparrow$ fungal infection-free survival but decr. invasive fungal infxn ([JAMA 2016;316:1555](#))
- De-escalation:** once causative organism identified,  $\Delta$  to narrowest effective agent, w/ duration individualized to pt/etiology/trajectory
  - Procyclitomin may be useful in guiding cessation ([Lancet 2010;375:463](#); [Lancet ID 2016;16:819](#); [CCM 2018;46:684](#))

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

- Balanced crystalloids** (e.g. LR) with decr. **mortality** & **renal impairment** in critically ill adults compared to NS ([NEJM 2018;378:829](#)); no mortality benefit to colloids ([NEJM 2004;350:2247](#); [JAMA 2013;310:1809](#); [NEJM 2014;370:1412](#))
- Targets of resuscitation:** **lactate clearance** (normalization or  $> 20\%$ /2h) ([JAMA 2010;303:739](#)); **cap. refill** (<30s) ([JAMA 2019;321:654](#))
- In patients w/ CHF** less restrictive fluid resuscitation ( $\geq 30$  mL/kg) had decr. **mortality** w/o  $\uparrow$ mechanical ventilation ([PLoS 2021;16:8](#))
- After the initial resuscitation effort, further fluid administration should be guided by dynamic measures of fluid responsiveness (see table below). Lack of volume responsiveness → use/increase **vasopressors** instead
- No mortality benefit in restrictive fluid resuscitation strategies ([NEJM 2022;386:2459](#))

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

Method	Fluid responsive if:
<b>Pulse pressure variation:</b> validated in mechanically ventilated w/ $V_T \geq 8$ cc/kg, not spontaneously triggering ventilator, & in NSR ( <a href="#">Crit Care 2014;18:650</a> )  <b>Mech ventilation</b> = pos. pressure during inspiration → decr. venous return/RV preload → $\uparrow$ LV filling/output → PPmax in inspiration, PPmin in expiration $PPV = (PP_{max} - PP_{min})/PP_{mean}$	PPV $\geq 13\%$ If on ascending portion of Starling curve, sensitive to $\Delta s$ in preload. Volume responsive pts will show larger variations in PP or SV during resp cycle
<b>Passive leg raise:</b> raise legs to 45° w/ torso horizontal x1min in any mech. ventilated pt → "autotransfusion" of ~250-350cc; assess $\Delta$ in hemodynamics	$\uparrow$ PP $\geq 10\%$ (surrogate for $\uparrow$ SV if no invasive measure of CO)
<b>Fluid challenge:</b> bolus 250-500cc fluids; check CVP before & immediately after, if $\uparrow \geq 2$ , adequate volume challenge	Improved hemodynamics, UOP, lactate; $\uparrow$ PP $\geq 10\%$

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

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

- Norepinephrine (NE, Levophed): **first choice vasopressor**
- Vasopressin: add when NE at 5-15mcg/min to 1 kidney function. Not usually titrated, on or off at 0.04U/min ([NEJM 2008;358:877](#))
- Epinephrine: recommended when 2<sup>nd</sup> or 3<sup>rd</sup> agent is needed; consider trial when NE escalating  $>25\text{mcg/min}$
- Phenylephrine (Neo): recommended primarily when (a) NE is associated with serious arrhythmias, (b) CO is high & BP persistently low, (c) NE + vaso have failed to achieve MAP target at  $>25\text{mcg/min}$  and pt is tachycardic (d) hypotension a/w AFRVR
- Dopamine: reserved for highly selective patient population with bradycardia and low risk of tachyarrhythmia; a/w ↑ risk of arrhythmias/mortality in all-comers ([CCM 2012;40:725](#); [NEJM 2010;362:779](#))
- Methylene blue: uncommonly used, pressor of last resort when NO-mediated vasoplegia is suspected
- Angiotensin II: not currently avail at MGH; ATHOS-3 trial ([NEJM 2019;377:419](#))

## 4) Source Identification and Control

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

### Where to draw blood cultures?

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

## OTHER ASPECTS OF MANAGEMENT

### AKI

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

### Metabolic Acidosis/Lactic Acidosis

- Ultimately, **need to correct underlying etiology**. Can temporize with bicarbonate if:
  - Severe acidemia w/ pH <7.1: used as cutoff as evidence in animal/tissue studies of myocardial depression, ↓ catecholamine efficacy, arrhythmias, though generally not replicated in human studies & pts w/ DKA can have pH <7 w/o these effects
  - Less severe acidemia (pH <7.2) w/ AKI: BICAR-ICU → NaHCO<sub>3</sub> gtt to keep pH >7.3 ( $\leq 1\text{L}/24\text{h}$ ) ↓ mortality ([Lancet 2018;392:31](#))
- Bicarbonate administration: **1 amp** = 50mEq/50mL (or 8.4%); or **infusion** of solution of 150mEq (3 amps) in 1L of D5W
  - **Caution**: HCO<sub>3</sub> → pCO<sub>2</sub> that must be ventilated off, so must have sufficient resp. drive/be intubated. Also → ↓iCa

### Transfusions

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

## CONTROVERSIAL MANAGEMENT STRATEGIES

### Corticosteroids

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

### Vitamin C

- Rationale: Vitamin C is an antioxidant; may also act synergistically with hydrocortisone to ↓ inflammation
- Controversy: Small, 1-center cohort ([Chest 2017;151:1229](#)) ↓ mortality w/ high dose **Vit C, hydrocort, & IV thiamine**, not validated. No benefit to Vit C alone ([CCM 2019;47:774](#); [JAMA 2019;322:1261](#)) or w/ thiamine + hydrocort ([JAMA 2020; 323:423](#)). Placebo-controlled RCT ([NEJM 2022;386:2387](#)) w/ ↑ mortality and organ dysfunction in Vitamin C group.
- Conclusion: **No proven benefit** to Vitamin C, either alone or in combination w/ thiamine & hydrocortisone, **evidence of ↑ mortality**

### Esmolol

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

# Pulmonary & Critical Care

# Vasopressors

Category	Name	$\alpha$	$\beta_1$	$\beta_2$	D	PVR	SVR	CO
Vasoconstrictors	Phenylephrine	5+	0	0	0	2+	↑	↓
	Vasopressin			V1		±	↑	-/↓
Inoconstrictors	Norepinephrine	4+	2+	(+)	0	1+	↑	↑
	Dopamine (low)	0	1+	0	2+	±	-/↑	↑
	Dopamine (med)	1+	2+	0	2+	±	↑	↑
	Dopamine (high)	2+	2+	0	2+	±	↑	↑
Inodilators	Epinephrine	4+	3+	2+	0	1-	-/↑	↑
	Dobutamine	(+)	3+	2+	0	1-	↓	↑
	Milrinone			PDE inhibitor		2-	↓	↑
Chronotrope	Isoproterenol	0	3+	3+	0	0	↓	↑
<b>Pressor Initiation/titration:</b> Start when SBP drops by >30 or MAP <65 WITH end-organ dysfunction despite optimization of volume status. Monitor MAP, UOP, mentation to titrate pressor dose. Responsiveness may decrease over time. *Subcutaneous medications may ↓ effectiveness due to ↑ vasoconstriction.								
<b>Access: Ideal access is central (CVC, IO)</b> Temporize w/ peripheral levo (<10 mcg/min) or neo (<150 mcg/min) for <72 hrs. Requires PIVx2, <20G w/ blood return in upper extremity AC or more prox. Check q1h given risk of extravasation. If extravasation, draw back any infusing medication, give <b>phentolamine</b> 5-10mg in 10cc NS directly into area of extravasation, apply dry warm compress.								

VASOPRESSORS & INOTROPES (Circulation 2008;118:1047)						
	Name	Mechanism	Uses	Side effects	Dosing	
VASOPRESSORS	Norepinephrine (NE) Levophed "Levo"	$\alpha_1 > \beta_1$ agonist: <b>↑↑SVR, ↑CO</b> Reflex brady from vasodilation can negate ↑HR from chronotropy	Septic shock (1 <sup>st</sup> ) Cardiogenic shock (1 <sup>st</sup> ) Hypovolemic shock (1 <sup>st</sup> )	Arrhythmia Digital ischemia ↑FSBG	Initial: 2-12mcg/min (0.1-0.15mcg/kg/min) PIV: <10mcg/min Max: 35-100mcg/min (0.75mcg/kg/min)	
	Phenylephrine Neosynephrine "Neo"	Pure vasopressor $\alpha_1$ agonist: <b>↑↑ SVR</b>	Septic shock if <b>↑↑HR</b> from NE or <b>↑ CO</b> w/ <b>↓↓BP</b> or <b>3<sup>rd</sup> agent needed AFRVR, HOCM, AS, RV failure</b>	<b>Reflex bradycardia</b> ↓CO, ↑PAP, ↑SVR Digital ischemia	Initial: 50-180mcg/min (0.5-2mcg/kg/min) PIV: <150mcg/min Max: 360-1000mcg/min (6mcg/kg/min)	
	Vasopressin Pitressin "Vaso"	V <sub>1</sub> agonist: <b>↑SVR</b> V <sub>2</sub> agonist: <b>↑ renal H<sub>2</sub>O reabsorption</b>	Septic shock (2 <sup>nd</sup> ), add when NE 5-15 mcg/min (↓ mortality vs. NE alone) ( <a href="#">NEJM 2008;358:877</a> ) Anaphylaxis (2 <sup>nd</sup> ) Pulmonary HTN/RV failure, HRS	Coronary ischemia Mesenteric ischemia (especially high dose) ↓Na	Usual: 0.04U/min Consider when NE 5-15 Max: 0.08U/min (only as salvage therapy)	
	Epinephrine Adrenalin "Epi"	<u>Low:</u> $\beta_1 > \beta_2 > \alpha_1$ : <b>↑CO</b> , neutral <b>SVR</b> <u>High:</u> $\alpha_1 > \beta_1 > \beta_2$ : <b>↑CO</b> , <b>↑SVR</b>	<b>ACLS</b> (1 <sup>st</sup> ) <b>Anaphylaxis</b> (1 <sup>st</sup> ) <b>Symptomatic bradycardia</b> (2 <sup>nd</sup> ) Septic shock Bronchospasm	↑HR, arrhythmias Myocardial ischemia ↑lactate ↑splanchnic SVR ↑FSBG	<u>Low:</u> 1-4mcg/min <u>High:</u> 5-35mcg/min	
	Dopamine Intropin "Dopa"	<u>Low:</u> D <sub>1</sub> > $\beta_1$ : <b>↑CO</b> , <b>↑UOP</b> <u>Med:</u> $\beta_1$ >D <sub>1</sub> : <b>↑CO</b> , <b>↑SVR</b> <u>High:</u> $\alpha_1 > \beta_1 > D_1$ : <b>↑SVR</b>	Symptomatic bradycardia Septic shock w/ bradycardia  <u>↑mortality vs. NE in septic</u> ( <a href="#">CCM 2017;45:486</a> ) & cardiogenic shock ( <a href="#">NEJM 2010;362:779</a> )	Tachyarrhythmia Myocardial ischemia ↓BP (low dose) ↑PCWP, pulm shunt ↑FSBG	<u>Low:</u> 1-2mcg/kg/min <u>Med:</u> 5-10mcg/kg/min <u>High:</u> 10-50mcg/kg/min	
	Methylene blue	↓NO and cGMP, ↑smooth muscle tone: <b>↑SVR</b>	Refractory vasoplegia due to sepsis/anaphylaxis Post-cardiopulm bypass Amlodipine overdose Metformin overdose Methemoglobinemia	Falsey ↓SpO <sub>2</sub> Arrhythmias ↑PVR Rash, hemolysis, serotonin syndrome ○○○ in G6PD	<u>Initial:</u> 1-2mg/kg <u>Max:</u> 5mg/kg	
	Angiotensin II	ANG-II agonist: <b>↑SVR</b>	Refractory septic shock (NB: not available at MGH)	Peripheral ischemia	10-20ng/kg/min; max 40	
	Hydroxocobalamin	IV Vitamin B12, NO synthase inhibition Modifies H <sub>2</sub> S (NO and smooth muscle activity)	Tx of vasoplegia refractory to methylene blue treatment (or if methylene blue contraindicated)		<u>Initial:</u> 5g over 15 minutes <u>Max:</u> 30g in 24 hrs	
INODILATORS	Dobutamine Dobutrex "Dobuta"	$\beta_1, \beta_2 > \alpha_1$ agonist: <b>↑CO</b> , <b>↓SVR</b>	Cardiogenic shock Sepsis + ↓LV EF (add to NE/vaso)	↓BP, ↑HR, Arrhythmias Myocardial ischemia Tachyphylaxis	<u>Initial:</u> 0.5-1mcg/kg/min (2.5 if more severe) <u>Max:</u> 20-40mcg/kg/min	
	Milrinone Primacor	PDE inhibitor ( <b>↑cAMP</b> ), <b>↑inotropy</b> , <b>vasodilation</b> : <b>↑CO</b> , <b>↓PVR/SVR</b>	Cardiogenic shock RV failure (↓PVR, ↓LVEDV)	<b>Hypotension</b> Arrhythmias Myocardial ischemia	<u>Initial:</u> 0.125mcg/kg/min <u>Max:</u> 0.75mcg/kg/min	
	Isoproterenol Isuprel	$\beta_1 = \beta_2$ agonist: <b>↑HR</b> , <b>↓SVR</b>	Symptomatic bradycardia Mg-refractory torsades de pointes	↓BP, ↑HR, Arrhythmias Myocardial ischemia Flushing, anxiety	<u>Initial:</u> 2-10mcg/min (can bolus 2-6mcg first) <u>Max:</u> 30mcg/min	

# Pulmonary & Critical Care

# Toxicology & Lung Transplant

Tox resident pager 21827 • Poison Control 1-800-222-1222 • MGH Lab Tox Screen Guru: Dr. Jim Flood

	Drug/Toxin	Presenting Symptoms	Diagnostic Workup	Management
Toxidromes	<b>Anticholinergic</b> Atropine, Benztropine, Scopolamine, Diphenhydramine	Mydriasis, hyperthermia, ↓ sweating, flushing, delirium, urinary retention, ileus, tachycardia, HTN	Hx, EKG, CPK	Supportive, cooling for hyperthermia; charcoal (1g/kg, max 50g) if <1h, BZDs for agitation & seizure, physostigmine if severe (ICU, atropine at bedside; not for TCA ODs)
	<b>Cholinergics</b> Organophosphates, carbamate insecticides, nicotine	"DUMBBELLS": Diaphoresis/Diarrhea, Urination, Miosis/Muscle spasm, Bronchoconstriction/Bronchorrhea, Bradycardia, Emesis, Lacrimation, Lethargy, Salivation/Seizure	ABG, EKG, BMP, CPK, lactate. Can monitor RBC AChE inhibitor if available	100% O <sub>2</sub> , atropine (2-5mg, redose to effect q3-5min, no effect on muscular symptoms); pralidoxime (30mg/kg over 30min → 8-20mg/kg/h. Only for organophosphate toxicity), avoid succinylcholine for intubation
	<b>Sympathomimetics</b> Amphetamines, MDMA, cathinones "bath salts"	Agitation, mydriasis, hallucinations, paranoia, tachycardia, HTN, diaphoresis, hyperthermia, piloerection, seizure	EKG, BMP, lactate, CPK, LFTs, coags	IV BZDs, atypical antipsych. if refractory agitation, avoid succinylcholine and ketamine
	<b>Neuroleptic Malignant Syndrome (NMS)</b> Dopamine blockade, dopaminergic w/d	AMS, "lead pipe" rigidity, sialorrhea, hyperthermia, dysautonomia, diaphoresis <u>Typically no N/V/D or hyperreflexia</u>	Search for causative agent. CPK (↑↑), CBC (↑WBC), LDH, LFTs, BMP, serum Fe (often ↓); consider brain imaging, LP, EEG	D/c causative agent (restart dopamine if DCd), IVF, cooling blanket, nitroprusside for HTN, BZD for agitation. Dantrolene, bromocriptine, amantadine
	<b>Serotonin Syndrome</b> Antidepressants, Linezolid, Tramadol	AMS, hyperreflexia (LE predominant), hyperthermia, mydriasis, ↑HR, HTN, diarrhea, diaphoresis, clonus, rigidity	Search for causative agent. CBC, CPK, BMP, coags, LFTs, UA, CXR	BZDs for agitation (avoid antipsychotics); supportive care for altered VS (esmolol, nitroprusside for ↑HR & HTN, cooling). If all else fails, consider cyproheptadine
Psychiatric Medications	<b>Benzodiazepines</b>	Depressed MS, ataxia, slurred speech, hyporeflexia, ↓RR, coma	Hx, urine tox can give qualitative result	Supportive; avoid flumazenil as it precipitates withdrawal + seizure
	<b>Antipsychotics</b>	Physiologic depression, miosis, anticholinergic effects, extrapyramidal reactions/NMS, tachycardia	CMP, CBC, CPK, LDH, LFTs, serum iron, EKG, EEG	NaHCO <sub>3</sub> for QTc prolong.; Mg, isoprot., overdrive pacing if torsades. Avoid class IA, IC, and III antiarrhythmics
	<b>TCAs</b>	Prolonged QRS, arrhythmia, hypotension, anticholinergic toxicity, myoclonus, hyperthermia, AMS, coma, szr	CPK, tox screen, EKG: ↑QRS duration (>100ms, 26% szr risk; >160, 50% risk), terminal R wave >3mm in aVR. Watch for ventricular arrhythmia	NaHCO <sub>3</sub> (for the Na) if QRS >100ms or HoTN. BZDs for szr. Salvage: 3% NaCl, lipid emulsion, avoid physostigmine
	<b>Lithium</b>	N/V/D, tremor, hyperreflexia, clonus, ataxia, AMS, szr, AV block, sinus brady, long QT, hyper/hypothyroid, nephrogenic DI if chronic	BUN/Cr, Li levels (nl 0.5-1.5mmol/L), EKG. Toxicity common w/ AKI from NSAIDs, ACEi, diuretics	Frequent neuro checks; IVF (NS preferred), maintain UOP, HD if encephalopathy, renal dysfunction
Pain Medications	<b>Acetaminophen</b>	Malaise, vomiting, sweating, RUQ pain, DILI/ALF	See Acute Liver Injury & Failure	
	<b>Opioids</b>	↓RR & VT, CNS depression, ↓ bowel sounds, miosis	EKG, core temp, FSBG, CPK	IV or intranasal naloxone (0.4-2mg). See Opioid Use Disorder & Withdrawal
	<b>Salicylates</b>	Tinnitus, fever, vertigo, N/V/D, ↑RR, pulmonary edema, AMS (can have neuroglycopenia w/ nl FSBG)	ABG (mixed resp alkalosis/met acidosis), BMP, CXR, salicylate level (>30-50mg/dL). Trend levels & ABG q2h	Avoid intubation (if required, hyperventilate to avoid acidemia), IVF, charcoal (1g/kg), glucose (100mL D50), NaHCO <sub>3</sub> , alkalinize urine to pH 7.5-8, avoid acetazolamide. Consider HD
Cardiac medication	<b>CCBs</b>	N/V, HoTN, CHF, ↓HR, AV block, stupor, cardiac arrest, ↑FSBG	Hx, EKG (↓HR, long PR), blood levels (slow, correlate poorly). Extended release more dangerous. High FSBG = poor prognosis	Calcium, pressors, glucagon, HIGH DOSE-insulin (1U/kg bolus, then 0.5-1U/kg/h gtt, adjust to cardiac response), IVF; consider pacing, atropine, ECMO
	<b>B-Blockers</b>	HoTN, ↓HR, AV block, long QTc (sotalol), CHF, bronchospasm, ↓FSBG, stupor, ↑K, szr (propranolol), miosis	Hx, EKG, blood levels (slow, correlate poorly); propranolol highest mortality	Pressors, calcium, glucagon (5 mg bolus, if no improvement of HR or BP repeat in 10-15 min), high-dose insulin (see above), IVF; atropine, pacing, ECMO
	<b>Digoxin</b>	↓HR, AV block, N/V/abd pain, ↑K, AMS, xanthopsia (yellow-green halo), bidirectional VT, "regularization of AF"	EKG, BMP, UOP, dig level (nl 0.9-2ng/mL; may not be accurate if drawn w/in 6h of last dose, as includes bound Fab fragments)	Digoxin-specific Fab fragments (if K>5.5, severe end-organ dysfxn, or life-threatening arrhythmia), Mg, <u>AVOID</u> hypokalemia
Other	<b>Cocaine</b>	Agitation, psychosis, seizure, HTN, ↑HR, vasospasm/MI, arrhythmia, stroke, vasculitis, lung injury, rhabdo	Serum/urine tox (metabolites detectable for 2-5d), EKG, cardiac biomarkers if chest pain, CPK, UA	Hyperthermia treatment (cooling, BZDs), treat chest pain with ASA, CCB, nitrates, labetalol (no pure βB)

# Pulmonary & Critical Care

# Toxicology & Lung Transplant

	Drug/Toxin	Presenting Symptoms	Diagnostic Workup	Management
Other Exposure	<b>Carbon Monoxide</b>	<u>Minor sx:</u> headache, N/V <u>Major sx:</u> confusion, LOC, seizure, coma, cardiac ischemia, arrhythmias	Hx (house fire, winter w/ space heaters), cyanide & carboxyhemoglobin levels, co-oximetry (SpO2 invalid), AG acidosis, EKG, TnT	100% O <sub>2</sub> (t <sub>1/2</sub> 250-320 mins → 75-90 min); hyperbaric O <sub>2</sub> (t <sub>1/2</sub> 250-320 mins → 30 min); watch for delayed neuropsychiatric sequelae
	<b>Cyanide</b>	HA, nausea, AMS, seizure, coma, shock. Suspect in structural fires, prolonged nitroprusside infusion	Lactate, AGMA, cyanide & carboxyhemoglobin levels	Hydroxocobalamin (5g over 15min, use amyl nitrate if unavailable) & sodium thiosulfate
	<b>Gamma-hydroxybutarate (GHB)</b>	Agitation, ↓HR, ↓RR, ↓BP, coma (sudden onset/resolution), co-intoxicants common	Not detected on routine tox screen, need 100mL urine & 10-30mL blood for send-out. EKG, r/o other causes, βhCG	Supportive; BZDs for withdrawal. <u>Note:</u> OD at low dose if on protease inhibitors
	<b>Synthetic Cannabinoids</b> "Spice" or "K2"	Anxiety, paranoia, sedation, memory impairment, hallucinations, psychosis, szr, tachycardia, HTN, N/V, AKI	Not detected on routine tox screen, can send blood & urine for send-out	Supportive care. BZDs for agitation and szr. Antipsychotics for agitation

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

## DECONTAMINATION THERAPIES

- Activated Charcoal**
  - Most effective if given when substance is **still in stomach** (usually considered to be **within 1h of ingestion**, but data is lacking)
  - Not useful for: cyanide, lithium, ethanol/methanol, glycols, mineral acids (e.g. sulfuric acid, nitric acid), alkali metals (potassium, magnesium, sodium, including sodium hydroxide [Drano]); iron; ammonia
  - Other therapies not routinely used: whole bowel irrigation (with polyethylene glycol), gastric lavage, Ipecac
- Dialysis and Acid/Alkaline Diuresis** (consult Nephrology):
  - Dialyzable toxins: methanol, isopropyl alcohol, glycol, acetone, lithium, salicylates, barbituates, INH, atenolol/sotalol, rarely EtOH
    - Acid diuresis (give vitamin C): quinine, PCP; Alkaline diuresis (give NaHCO<sub>3</sub>): phenobarbital, salicylates, MTX, TCAs

## LUNG TRANSPLANT OVERVIEW

- Bilateral vs. single LT: BLT in younger patients, severe pHTN and suppurative LD; ↑ op morbidity/mortality; SLT for COPD & ILD ↓ LTS but better utilization of resource and ↓ periop morbidity/mortality
- Lung allocation score:** diagnosis, age, BMI, PFTs, NYHA FS, CVP, PCO<sub>2</sub>, O<sub>2</sub> cap, renal & liver fxn ([JHLT 2015;34:1](#))

## LUNG TRANSPLANT EVALUATION

**As a medicine provider:** HCM, tx comorbidities, ⊖ substance use, optimize weight, limit blood product, refer for txp early  
**Pre-op assessments:** Medical: cardiac, pulm, ID, GI, renal, HCM; Surgical/anesthesia: Functional: 6MWT, pulm rehab, nutrition;  
Psychosocial: SW, psych, financial services, caregiver eval

**Contraindications to transplant** ([JHLT 2021;40\(1350\)](#))

- Absolute:** acute medical instability, significant multiorgan dysfunction, severe coagulopathy, recent malignancy, active TB, BMI >35, hx of non-adherence to medical therapies, active substance use
- Relative:** age >65, BMI 30-34.9, HIV, active hepatitis, MDRO colonization/infection, hx chest surg, severe malnutrition, severe osteoporosis, mech ventilation

## POST-TRANSPLANT COMPLICATIONS

**Early:** surgical (post-op hemorrhage), airway (stenosis, necrosis, bronchomalacia), ifxn, graft (ischemic-reperfusion injury)

### Late Complications

	Complication	Diagnostics	Treatment
Immunologic	<b>Acute Cellular Rejection (ACR)</b> T-cell mediated; perivascular (A-grade) or lymphocytic bronchiolitis (B-grade).	Clinically, highest risk in first year Graded on scale of 0-4 histology, degree of perivascular, interstitial, & air-space inflammation	<b>Initial therapy:</b> Pulse dose steroids <b>Refractory or persistent:</b> Longer steroid course, changing maintenance regimen, augmentation with ATG, anti-IL-2R, anti-CD3
	<b>Antibody-Mediated Rejection (AMR)</b>	Clinical diagnosis, detection of donor-specific abs, histology, lung bx C4d ( <a href="#">JHLT 2016;35:397</a> )	<b>Treatment:</b> Plasmapheresis, IVIG, rituximab ATG, photopheresis <b>Ppx:</b> antivirals, azithro
	<b>Chronic Lung Allograft Dysfunction (CLAD): Bronchiolitis Obliterans Syndrome (BOS) &amp; Restrictive Allograft Syndrome (RAS)</b>	Diagnose based on PFTs – CLAD staged 0-4 depending on FEV1 compared to baseline. BOS is obstructive; RAS is restrictive. RAS mortality > BOS ( <a href="#">JHLT 2011;30:735</a> )	<b>BOS:</b> change CNI (tacrolimus > cyclosporine), azithro, consider fundoplication if +GERD, DO NOT use high dose steroids ( <a href="#">ERJ 2014;44:1479</a> ) <b>RAS:</b> no effective treatments; ?anti-fibrotics

- Infectious complications:** typically donor-derived pathogens in immediate post-op period; bacterial (esp. *P. aeruginosa*, *S. aureus*, *B. cepaci*, *E. faecalis*), viral (esp. CMV, HHV), fungal (esp. *Aspergillus*) ([ATS 2009;6\(94\)](#))
- Malignancy:** esp. dermatologic, SCC #1, PTLD

## IMMUNOSUPPRESSION ([JTD 2014;6\(1039\)](#))

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

# Gastroenterology

# Upper GI Bleeding

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

- **Definition:** bleeding proximal to ligament of Treitz
- **S/Sx:** hematemesis, melena (on exam: +LR 25; [JAMA 2012;307:1072](#)), hematochezia if brisk, BUN/Cr >30 (+LR 7.5; [JAMA 2012;307:1072](#)), especially >35 (100% Sp; [J Clin Gastro 1990;12:500](#))
- **Risk Stratification and Triage:**
  - High-Risk Features in UGIB: hypotension, tachycardia, coagulopathy (INR > 1.5), AMS, syncope, age > 65, liver dx, CHF
  - Risk scores: [Glasgow-Blatchford Score](#) and [ABC score](#) recommended over [AIMS65 \(Annals 2019;171:805; BMJ 2017;356:e432; Gut 2021;70:707\)](#)
  - **Triage:** Call Med Sr for MICU bed if BP <90 and HR >100 x2 30min apart; Hct <20/Hgb <7 regardless of vital signs with evidence of active significant bleed in past 12hrs; require >2L IVF or 2u pRBCs to prevent instability/keep Hct >25; ATLS hemorrhagic shock class III; clinical judgment
- **Assessment/Management:** Stabilize → Intervene
  - **Initial Workup:** CBC (q2-8hr), CMP, coags, type & screen, rectal exam
  - **Stabilization:** NPO; supplemental O<sub>2</sub> as needed, intubation if high-risk for aspiration (large volume hematemesis, AMS); ensure ≥2 PIV (18G or larger: green = 18, pink = 20, blue = 22; rarely done by IV nurse)
    - **Resuscitation/Transfusion:** IVF (isotonic crystalloid) for hypotension. Do not delay transfusion if actively hemorrhaging, otherwise transfuse pRBCs for Hgb >7 ([NEJM 2013;368:11; Lancet 2017;2:354](#)) or Hgb >8 if CAD ([Annals 2019;171:805](#)). Note: Hct drop lags 24-72h from onset of bleeding. For severe/ongoing bleeding (generally after 4u pRBCs), activate massive transfusion protocol (see *Transfusion Medicine*). Avoid overtransfusion if possible EVs (can ↑ portal pressures and worsen bleeding).
    - **Correct coagulopathy:** Tranfuse plts for plt >50k. Consider prothrombin complex concentrate (PCC) (preferred over FFP for lower volume, faster onset). If uremic, consider ddAVP (0.3 mcg/kg). If ESLD, INR inaccurate - avoid FFP volume → ↑ portal pressure).
    - **Consults:** GI for EGD and/or colonoscopy, surgery/IR if hemodynamic instability or if endoscopy not preferred
      - **EGD generally within 24hrs** (debated), but no Δ in outcomes if between 0-6hrs vs. 6-24hrs for non-variceal or non-HDUS bleeds ([NEJM 2020;382:1299](#))
  - **Pre-EGD Pharmacotherapy:**
    - **IV PPI:** pantoprazole 40mg BID (neutralizing acid stabilizes clots); ↓ high-risk lesions requiring endoscopic therapy but unclear clinical impact pre-EGD ([Cochrane Rev. 2010](#))
    - **IV prokinetics:** erythromycin 250mg 30m prior to EGD ↑ gut motility & visualization ([Ann Gastroenterol 2016;29:312](#))
    - **For cirrhosis:** **IV octreotide** 50 mcg bolus (may repeat bolus in first hour if bleeding uncontrolled) followed by octreotide gtt at 50 mcg/hr for 3-5 days. **IV CTX** 1g q24hr x7 days for ppx against bacterial infections and mortality benefit ([Gastro 2006;131:1049; APT 2011;34:509](#)). Stop β-blockers.
  - **Anticoagulation/Antiplatelet Management:** ([Gastrointest Endosc 2016;83:3; Am J Gastroenterol 2022;117:542](#))
    - **Warfarin:** Hold during bleed. For reversal, can consider PCC, but FFP or vit K NOT recommended. Resume after hemostasis (w/ UFH bridge for ~48hrs if indicated; see *Hematology* section). ↓ risk of thrombosis/death in AF if resumed within 7d ([Am J Cardiol 2014;113:662](#)).
    - **DOAC:** Hold during bleed. Reversal with idarucizumab, andexanet alfa, or PCC NOT recommended. Resume within 72hrs in high thrombotic risk pts, within 7d for low thrombotic risk pts.
    - **ASA:** Continue during bleed if low-moderate risk, hold if high risk (unless recent PCI/ACS – see below). Resume ASA for 2° prevention after hemostasis endoscopically confirmed ([Gastrointest Endosc 2016;83:3](#)) ↑ risk of 30d mortality if not resumed ([Annals 2010;152:1](#)); if PUD, add PPI to ↓ risk of re-bleeding.
    - **DAPT for PCI/ACS:** Discuss with cardiologist. Generally if very recent (<30d PCI, <90d ACS), continue both unless life-threatening; if more distant, continue ASA but less risk with holding P2Y12i. Resume within 1-5d pending course
    - Overall, restarting AC/AP sooner → ↓ risk of vascular events, though ↑ risk of bleeding ([APT 2019;50:8](#)).
  - **Post-EGD Pharmacotherapy/Management:** Review GI procedure note for specific diet, PPI, etc. recommendations.
    - For high-risk PUD: **IV pantoprazole** 40mg BID x 72hrs (intermittent dose non-inferior to bolus+gtt [[JAMA IM 2014;174:1755](#)]) → ↓ re-bleeds and need for repeat EGD. Switch to PO PPI after 72hrs, d/c with BID dosing x 2-8wks. **Treat H. pylori** if positive (see *GERD and Peptic Ulcer Disease*).
    - For variceal bleed: consider **octreotide** x 2-5d, continue **IV CTX** 1g q24hr x7 days
    - For angiomyolipoma: consider long-term **octreotide** ([APT 2012;36:587](#)), **bevacizumab**, or **thalidone** w/ GI help.
    - If re-bleed: consider repeat EGD, angiography, surgical/IR consult. If variceal bleeding, consider balloon tamponade, TIPS, or BRTO.
  - **Prognosis:**
    - **PUD rebleeding w/o med management:** 90% if active bleed, 50% if visible vessel, 30% if clot, 20% if oozing, else < 10%.
    - **EV bleed:** 40-50% resolve spontaneously; 30% mortality → 70% if continued bleeding; 60% risk re-bleeding overall.

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

# Gastroenterology

# Lower GI Bleeding

## ACUTE LOWER GI BLEED (NEJM 2017;376:1054; Gut 2019;68:776)

- **Definition:** distal to ligament of Treitz
- **S/Sx:** hematochezia (maroon or bright red blood, blood clots; Note: BRBPR can be seen in brisk UGIB); rarely melena (requires blood spend 14hr in GI tract); BUN/Cr typically <20
- **Risk stratification and Triage:**
  - Risk scores: [ABC score](#) to predict 30d mortality ([Gut 2021; 70:707](#)); [Oakland Score](#) to predict safe discharge ([JAMA 2020;3:e209630](#), [Lancet 2017;2:635](#))
  - Triage: Call Med Sr for MICU bed if hemodynamic instability, persistent bleeding, significant comorbidities
- **Assessment/Management:** See Figure 1 in [ACG Guidelines](#) for flow chart.

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

- Initial Workup: CBC (q2-12hr depending on severity of bleed), CMP, coags, type & screen. Consider:
  - CT angiography: 1st line imaging for lower GI bleeding in both hemodynamically stable and hemodynamically unstable patients ([ACR Approp. Criteria](#)). Detects bleeding at a rate of 0.3-0.5mL/min. Consider if shock index (HR/SBP) >1. Non-therapeutic, requiring subsequent intervention (ie, angiography).
  - NGT if moderate suspicion for UGIB (contraind. with hx of varices)
    - Coffee-ground material, bright red blood → EGD; No blood or bile seen: indicates indeterminate source → consider EGD before colonoscopy; Bilious fluid: no active UGIB source → colonoscopy
- Stabilization: NPO; supplemental O2 as needed; ensure ≥2 PIV (18G or larger: green = 18, pink = 20, blue = 22)
- Resuscitation/Transfusion: IVF (isotonic crystalloid) for hypotension. Do not delay transfusion if actively hemorrhaging, otherwise transfuse pRBCs for Hgb >7 ([NEJM 2013;368:11](#); [Lancet 2017;2:354](#)) or Hgb >8 if CAD ([Annals 2019;171:805](#); [JAMA 2021;325:552](#)). Note: Hct drop lags 24-72h from onset of bleeding. For severe/ongoing bleeding (generally after 4u pRBCs), activate massive transfusion protocol (see *Transfusion Medicine*). Tranfuse plt for plt >50k.
- Anticoagulation/Antiplatelet Management
  - Most data extrapolated from UGIB, see AC/AP Management section in Upper GI Bleeding
  - Lower GI bleeding data suggests ASA for 1° prevention should be stopped and generally not resumed. ASA for 2° prevention should not be held; if it is, should be resumed soon after bleed resolves ([Gastro 2016;151:271](#)).
- Approach to intervention:
  - **If hemodynamically UNSTABLE:** Consult GI, IR, and consider surgery.
    - GI: Exonerate UGIB first with EGD (10-15% of patients with severe hematochezia)
    - IR angiography: Employed when patients are too hemodynamically unstable for endoscopy. Detects bleeding at a rate of 0.5-1.0 mL/min. Therapeutic if embolization done, but risk of bowel ischemia and vascular injury
    - Surgical consult for subtotal colectomy if cannot locate colonic bleed
  - **If hemodynamically STABLE:** Consult GI for discussion of colonoscopy vs flexible sigmoidoscopy.
  - Colonoscopy: should generally be performed as soon as possible after adequate bowel preparation
    - Timing: Colonoscopy at 24-36hrs may be a safe approach in most stable patients ([Gastro 2020;158:1](#)). Remains controversial, studies show delay has no impact vs ↓ identification of stigmata of hemorrhage, ↓ LOS ([Gastroenterology 2020;158:168](#); [J Clin Gastroenterol 2019;53:591](#); Am J Gastroenterol 2005;100:2395).
    - Bowel preparation: No solid food for 8 hours prior, use order set "Gastroenterology Bowel Prep" → "Suprep" ([Am J Gastro 2019;114:305](#)).

## UNIDENTIFIED SOURCE AFTER EGD/COLOSCOPY (ACG: AJG 2015;110:1265)

- **Source:** ~75% small bowel, 25% UGIB/LGIB
- **Small Bowel Causes:** Common: angioectasia (20-30%), IBD (esp. <40), Dieulafoy's lesion, neoplasm, Meckel's diverticulum (esp. <40), polyposis syndrome (esp. <40), NSAID ulcers; Rare: varices, portal hypertensive enteropathy, amyloid, HHT, Kaposi, inherited connective tissue disorders, congenital vascular abnormalities. Consider Heyde syndrome (triad of AS, GI bleeding, and acquired von Willebrand syndrome).
- **Assessment/Management:** ([ASGE 2017;85:22](#), see Figure 1 for flow chart)
  - Video capsule (VCE): 1<sup>st</sup> line but Cl if strictures (retention). Consider post- placement IV erythromycin 250mg IV to promote passage
  - 2<sup>nd</sup> look EGD ± push enteroscopy: (prox 60cm jejunum) if recurrent UGI sx; 2<sup>nd</sup> look colo: if recurrent hematochezia
  - CT enterography: if ⊖ VCE or if risk of strictures (IBD, XRT, prior SB surgery, suspected stenosis); CTE>MRE
  - Balloon enteroscopy (single vs double): if strong suspicion of SB lesion and therapy required; often after ⊕VCE
  - If brisk bleed: CTA if stable then angio. If unstable, can intervene with embolization, enteroscopy, or surgery
  - If no source found: iron repletion; consider octreotide, anti-angiogenic tx; replace aortic valve if Heyde & ongoing bleeding

# Gastroenterology

# Abdominal Pain

Abdominal Pain History and Physical – Key Elements		Initial Tests to Consider BMP, Ca, Mg, CBC w/ diff, LFTs, lipase, lactate, ESR/CRP, UA, b-hCG, troponin, coags, T&S Infectious studies as appropriate including COVID-19 ( <a href="#">Gastro 2020;159:320</a> )
<b>History:</b> fever, pain Δ w/ eating or BMs, Δ in BMs (caliber, color, diarrhea, constipation), jaundice, recent medications (NSAID, abx, steroids), surgeries <b>Exam:</b> distention, abdominal veins, caput medusa, rigidity, guarding, rebound pain, percussion pain, Carnett's sign ( <a href="#">AJG 2017;112:760</a> ), Castell's sign, McBurney's point, Rovsing's sign, obturator sign, HSM, flank/shifting dullness, DRE <b>Special populations:</b> immunosuppressed, sexually active, elderly ( <a href="#">Am Fam Physician 2006;74:1537</a> )	<b>RED FLAGS of Acute Abdominal Pain</b> • HDUS, rigidity, guarding, or rebound    • "Pain out of proportion"    • "Tinkling" or absent bowel sounds • Gross distention + cannot tolerate PO    • Bilious emesis, hematemesis, hematochezia <b>"Can't miss" Dx:</b> vascular infarct, perforation, extra-intestinal hemorrhage, obstruction, ectopic preg	

Acute Abdominal Pain – Anatomic Approach		
Adapted from ( <a href="#">Am Fam Physician 2008;77:971</a> )		
<b>Right Upper Quadrant</b> • Liver pathologies (hepatitis, abscess, Budd-Chiari, portal vein thrombus, Fitz-Hugh-Curtis) • Biliary pathologies (cholelithiasis/biliary colic, cholecystitis, cholangitis, Sphincter of Oddi dysfunction) • Extra-abdominal: PE, PNA, CHF	<b>Epigastric</b> • Pancreatitis • Gastric pathologies (GERD, PUD, gastritis/gastropathy, functional dyspepsia, gastroparesis) • Mesenteric ischemia • Esophagitis • Extra-abdominal: MI, Aortic dissection	<b>Left Upper Quadrant</b> • Splenic pathologies (splenomegaly, abscess, infarction, rupture, trauma) • Gastritis, PUD • Sub-diaphragm or abdominal abscess (either side)
<b>Right Lower Quadrant</b> • Appendicitis    • Lymphadenitis    • Ileal Crohn's	<b>Perumbilical</b> • Early appendicitis • PUD • Bowel obstruction (SBO >LBO) • Umbilical hernia	<b>Left or Right Lower Quadrants</b> • Intestinal pathologies (diverticulitis, colitis, constipation, IBD, IBS, volvulus, lymphadenitis) • Renal pathologies (nephrolithiasis, pyelonephritis) • Pelvic pathologies (ectopic preg, fibroids, ruptured cyst, endometriosis, torsion, PID, abscess, epididymitis) • Hernia • Hematoma
<b>Diffuse</b> Obstruction/SBO/LBO, ischemia, AAA, perforation, peritonitis, gastroenteritis, IBD, dietary, SBP, toxin, meds (iron), cancer, ketoacidosis, adrenal insufficiency, celiac, Familial Mediterranean Fever, hereditary angioedema, Acute Intermittent Porphyria	<b>Suprapubic</b> • Cystitis    • Prostatitis • Urinary retention	

Imaging/Testing ( <a href="#">ACR Appropriateness Criteria</a> )	IMAGING NEGATIVE ABDOMINAL PAIN
• Acute, nonlocalized with fever: CT AP I+ • Suspect bowel obstruction: CT AP I+ over plain film (no need for PO contrast) • Suspect mesenteric ischemia: CTA AP • AAA suspected: HDS stable → CTA AP; HDUS→STAT surgery consult • Epigastric pain, suspected PUD: H. pylori stool antigen, EGD • Epigastric, suspect pancreatitis: CT AP I+ • RUQ, suspect biliary: RUQUS followed by MRCP w/ clinical suspicion • RLQ, suspect appendicitis: CT AP I+ vs ultrasound • Lower quadrant, suspect diverticulitis: CT AP I+ • Lower quadrant/flank, suspect kidney stone: CT AP I- • Lower quadrant/pelvic, b-hCG+: pelvic and transvaginal US	<b>Metabolic:</b> DKA, Ca, uremia, heavy metals, Al, Acute Intermittent Porphyria <b>Meds/Toxins:</b> EtOH, opioids/opioid withdrawal, cocaine, anticholinergics, lead/heavy metal <b>Functional:</b> IBS, abdominal migraine, functional dyspepsia <b>Episodic:</b> passed kidney stone, sphincter of Oddi dysfunction <b>Other:</b> angioedema, VZV, eosinophilic gastroenteritis, gastritis, polyradiculopathy, abdominal epilepsy

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

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

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

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

# Gastroenterology

# GERD & Peptic Ulcer Disease

## GASTROESOPHAGEAL REFLUX DISEASE (GERD) (ACG: AJG 2022;117:1 ; AGA: Gastro 2008;135:4)

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

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

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

**Evaluation:** No alarm sxs → trial of 8-wk normal dose or short (1-2 wk) high-dose PPI BID (metanalysis: Sn 79% / Sp 45%; NEJM 2022; 387:1207). If alarm symptoms or no/incomplete response to PPI → EGD w/ biopsy: look for tissue damage and/or complications, alt. ddx

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

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

- Lifestyle Δs: wt loss (goal BMI <25), tobacco cessation, drinking <2 cups of coffee/tea/soda, "prudent" diet (i.e., high intake of fruits, vegetables and whole grains); ≥30 min exercise daily, no eating 2-3 hours before bed (JAMA IM 2021;e207238)
- PPIs > than antacids/H2RAs for sx relief in empiric tx and optimal for erosive esophagitis (Cochrane Rev 2013)
  - Start low-dose PPI (e.g. 20mg omeprazole) 30min before AM meal. Reassess 4-8wk, uptitrate to high-dose (e.g. 40mg omeprazole), then BID if no relief. Assess at 8w if able to d/c
  - Maintenance PPI: if continue to have sx after PPI discontinued or if severe complications (erosive esophagitis, Barrett's)
  - Discontinuing PPI: if on PPI >6mo., taper by 50% per wk to prevent rebound hypersecretion
  - PPI risks: probable association: Mg wasting (↑QTc), AIN, iron deficiency; possible association (controversial): C.diff/other enteric infxn, ↑risk of osteoporosis, CKD (Gastro 2017;152:706); no association: no demonstrated risk of dementia (Gastro 2020;115:671)
- H2RAs (ranitidine 150mg daily-BID, famotidine 10-20mg BID): can also use nightly PRN w/ PPI, tachyphylaxis common after wks
- Others: PRN antacids, sodium alginate (APT 2013;38:1059; APT 2014;39:595), baclofen (as adjunct)

**Severe/Refractory Symptoms:** If no relief after 8w on high-dose PPI BID, refer for EGD/impedance testing & consider ddx e.g. functional dyspepsia (symptoms >3mo; Gastro 2020;158:2286), nonerosive reflux disease, reflux hypersensitivity, EoE, rumination, hiatal hernia

- EoE: dysphagia, GERD sx, food impaction; a/w allergic conditions. Eos on bx. PPI, topical steroids (Gastro 2020;158:1776), dupilumab (IL4,13 antibody) (JACI 2022;149:AB312)
- Hiatal hernia: Type I (sliding)– asx; Type 2-4 (paraesophageal hernias) – refractory GERD; surgery controversial
- Reflux hypersensitivity: dx w/ pH impedance w/ acid exposure time <4% + reflux symptom association (normal manometry)

- Gastric fundoplication may be superior to medical tx for refractory heartburn (NEJM 2019;381:1513)

### Complications:

- **Barrett's Esophagus (BE)**: squamous epithelium → intestinal metaplasia (IM). **AdenoCA** risk 0.38% (IM) vs 0.07% (no IM)/yr. Screen w/ EGD in: chronic GERD sx + ≥3 RFs (>50, white, male, central obesity, tobacco hx, FH of BE or adenoCA) (AJD 2022;117:559). Mgmt: indefinite PPI; limited evidence for NSAIDs/ASA ↓ risk of CA (Lancet 2018;392:400)
- **Esophageal stricture**: p/w progressive solid food dysphagia. Endoscopy w/ biopsy can differentiate stricture from cancer

## PEPTIC ULCER DISEASE (PUD) (BMJ 2019;367:I5495; Lancet 2017;390:613)

**Signs & Sx:** dyspepsia - intermittent gnawing, dull, aching, or "hunger-like" epigastric pain relieved w/ antacids though 70% are asx (often in elderly and NSAID use); **Associated sx**: early satiety, bloating, n/v

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

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

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

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

**Management:** PPI (duration depends on etiology); if need to continue ASA, continue w/ PPI (NEJM 2005;352:238; Gastro 2010;138:82). F/u EGD after 8-12w if refractory sx (see below) or most gastric ulcers to exclude malignant etiology (Gastrointest Endosc 2010;71:663)

### Treatment for H. pylori (AJG 2017;112:2)(Gastro 2016;151:51)

- First line = quadruple therapy: PPI BID, bismuth 300mg QID, tetracycline 500mg QID (alternative: doxy 100mg BID), metronidazole 500 QID x 14d. Combo pill (Pylera) available; note ~35% resistance rate in US to metro, clari, levo
  - Recently FDA approved treatment: \$\$ rifabutin, amoxicillin, PPI (combo pill Talcia). Associated with higher eradication rate, but has not yet incorporated into clinical guidelines (AGA Expert Review; 2021;160:5)
- Salvage therapy: Avoid antibiotics used previously. Trial clarithromycin, levofloxacin, or amoxicillin-based regimens (AJG 2017;112:2).
- Confirmation of eradication: confirm for all pts w/ stool Ag, urea breath test, or EGD >4 wks after completion of abx and off PPI for 2w

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

- Ensure H. pylori eradicated, NSAIDs & other contributing meds discontinued. Test for ZES w/ fasting serum gastrin (if on PPI, recheck 1 week s/p cessation); secretin stimulation test if non-diagnostic. Search for rare causes.
- Continue PPI x additional 12w and then repeat EGD. **Surgical tx**: rarely required; resection, vagotomy, partial gastrectomy

**Complications and Management:** ulcer considered complicated if any of the following are present: Bleeding: see *Upper GI bleeding*;

- Perforation: IVF, IV PPI, abx ± surgery; Gastric outlet obstruction: pyloric channel/duodenal ulceration → spasm, edema, inflammation, dysmotility → fibrosis/scarring; Tx: IVF, correct electrolytes, NGT; may need endoscopic dilatation or surgical tx if persists w/ medical mgmt. If gastric outlet obstruction sxs - be certain to exclude malignancy

# Gastroenterology

# Nausea & Vomiting

## APPROACH TO PATIENT WITH ACUTE (<1 MO.) NAUSEA/VOMITING ([Gastro 2001;120:1](#), [AFP 2007;76:1](#))

- 1) Initial assessment
  - a. Rule out life-threatening causes: bowel obstruction, perforation, mesenteric ischemia, acute pancreatitis, MI, DKA, ↑ ICP
  - b. History: onset, frequency, & severity, hematemesis, feculent vomit. Last BM, LMP  
Triggers: relation to POs, relation to time of day, recent foods/meds, sick contacts, drug use (opioids, marijuana)  
Other symptoms: abd pain (see *Abdominal Pain*), fever, wt loss, diarrhea, melena, heartburn, vertigo, headache, CP, SOB  
PMH: head trauma, prior abd surgery, uncontrolled DM, migraines
  - c. Exam: dehydration, orthostatics, jaundice, abdominal tenderness, masses, lymphadenopathy, CN exam/nystagmus, gait
- 2) Labs to consider: BMP (and blood glucose), LFTs, lipase, B-hCG, UTox, VPAIN, UA, ABG, lactate, cort stim, TSH, Troponin
- 3) Studies to consider: KUB, EKG, CT abdomen (I+/O+), Barium swallow or EGD, Gastric emptying study, CT head
- 4) Manage complications: IVF to correct hypovolemia. Address electrolyte abnormalities (hyperchloremic metabolic alkalosis, HypoK)
- 5) Address underlying cause while treating sxs (see table)
  - Chemo PPX: dex ± lorazepam ± ondansetron ± aprepitant ± olanzapine ([NEJM 2016;375:134](#))
  - Adhesive SBO (prior GI surg, hernias, neoplasms, Crohn's disease): conserv. mgmt x 48h (NGT with suction, NPO) → gastrografin per NGT ↓ surgery by 74% ([BJS 2010;97:470](#))
- 6) Practical approach to empiric inpatient nausea treatment (see table with meds and doses below):

Normal QTc → Start with ondansetron; add prochlorperazine if persistent. Prolonged QTc → Lorazepam if able. If cannot use lorazepam/benzos, try dexamethasone, scopolamine, or diphenhydramine. If persistent, further w/u and targeted treatment.  
Non-pharm options: acupuncture, meditation, ginger root, inhaled alcohol ([AEM 2018;72:2](#))

Etiologies (VVOOMMIITING)		Receptor	Targeted treatment
Vestibular & Vertigo	Acute/gait instability; labyrinthitis, BPPV, vestibular neuritis, Meniere's disease	Ach, H <sub>1</sub>	Scopolamine, dimenhydrinate, diphenhydramine, meclizine, Dix-Hallpike → <u>Epley maneuver</u>
Obstruction	Adhesions, hernia, volvulus, constipation, gastric outlet obstruction	Multiple	NGT, bowel rest, IVF, surgery consult, serial exams Meds: Prochlorperazine, ondansetron, NO metoclopramide (risk of perf)
Operative	Post-op n/v (risk factors: F > M, nonsmoker, post-op opioids, hx of condition, type of surgery), 1/3 cases	Multiple	Ondansetron, aprepitant, dexamethasone (use 2 in combo as ppx if 3+ RFs), gabapentin
Motility	Gastroparesis (common in uncontrolled DM), autonomic dysfunction, cyclic vomiting syndrome, chronic idiopathic nausea (see <i>Motility Disorders</i> )	D <sub>2</sub> (periph)	Low fat & insoluble fiber diet, metoclopramide, erythromycin (tachyphylaxis after 4 wks; motilin agonist), diphenhydramine, cannabis abstinence, TCAs, olanzapine, benzos, SSRI/SNRI
Meds	Antibiotics, AEDs, chemo, opioids, cannabis hyperemesis, anti-arrhythmics	D <sub>2</sub> (central)	Stop offending med if possible, prochlorperazine, haloperidol
Inflammation/ Infection/ Ischemia	Chemo, XRT, bowel ischemia, gastroenteritis, PUD, hepatitis, pancreatitis, cholecystitis, pyelonephritis	5-HT <sub>3</sub> , NK1	Ondansetron, prochlorperazine, dexamethasone, olanzapine & aprepitant (chemo), treat underlying disorder (antibiotics, surgery, etc.)
Toxins	Uremia, ketoacidosis, hypercalcemia, food poisoning, hypo/hyperglycemia	D <sub>2</sub> (central)	Prochlorperazine, haloperidol, treat underlying disorder
Intracranial	Elevated ICP, migraine, meningeal irritation, acute glaucoma	Ach, H <sub>1</sub> , 5-HT <sub>3</sub>	Dexamethasone (if ↑ICP), treat underlying disorder
Nerves	Anxiety, depression, anticipatory nausea, pain	Multiple	Lorazepam (anticipatory N/V), dexamethasone, pain control
Gums/mouth	Mucositis thrush, oral HSV	Multiple	Treat cause; magic mouthwash

Recep.	Med	Dose	QTc	Other side effects
5HT <sub>3</sub>	Ondansetron (Zofran)	4-8 mg PO/IV q8h	↑	constipation, HA
	Palonosetron (Aloxi)	0.075-0.25mg IV x1	-	more potent
D <sub>2</sub>	Metoclopramide (Reglan)	10-20 mg PO/IV q6-8h	↑	EPS (black box), dystonia (peripheral), promotility agent
	Prochlorperazine (Compazine)	5-10 mg PO/IV/PR q6h	↑	EPS, <b>sedation</b>
	Haloperidol (Haldol)	0.5-4 mg PO/IV q6h	↑	EPS, <b>sedation</b>
Cortical	Dexamethasone (Decadron)	4-8mg PO q4-6h	-	<b>psychosis</b> , CHF, ↑appetite
	Lorazepam (Ativan)	0.5-2 mg PO/IV q6h	-	<b>delirium</b> , sedation
NK <sub>1</sub>	Aprepitant (Emend)	125mg day 1, 80mg days 2-3	-	CYP3A4 inhib, GI upset
CB <sub>1</sub>	Dronabinol (Marinol)	2.5-10 mg q4-6h	-	dysphoria, asthenia, ↑appetite
5HT <sub>2A</sub> , D <sub>2</sub>	Olanzapine (Zyprexa)	5-10mg PO QD	↑	metabolic (wt gain, ↑lipids); ↑ mortality in dementia (black box)
H <sub>1</sub> , ACh, D <sub>2</sub>	Promethazine (Phenergan)	12.5-25 mg PO/IV/PR q4-6h	↑	EPS, <b>sedation</b> , tissue injury (black box)
ACh, H <sub>1</sub>	Scopolamine	0.3-0.6 mg q24h	-	<b>delirium</b> , <b>sedation</b> , dry mouth, urinary retention, ileus, blurry vision
	Hyoscyamine	0.125-0.25 mg SL/PO/IV q4h	-	
	Diphenhydramine (Benadryl)	25-50 mg PO/IV q6h	-	

# Gastroenterology

# Diarrhea

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

- Evaluation:** small bowel (absorbs ~10L) = watery, large vol., +cramping/bloating; large bowel (absorbs 1L) = freq., small vol., painful, ± fever, blood, mucus  
Exposure hx: travel, abx, hospitalization, food, sick contact, daycare  
“High Risk”: immunocomp/HIV, IBD, age >70, CAD, pregnant  
“Severe”: >6 BMs/24hr, severe pain, profuse watery, hypovolemia
- Workup:** BMP (hypovolemia), BCx (fever/immunocomp), stool Cx if severe/persistent (salmonella, campylobacter, shigella), fecal elastase; fecal electrolytes (Na, K); if >2w, celiac panel, CBC, ESR/CRP, TSH, LFTs, FOBT; O&P (3 samples q24hr) if immunocomp, MSM, travel; *C. diff* if abx. If confirmed infxn, no re-test
- Common pathogens:** See table. Immunocomp: CMV, *C. diff*, Cryptospor., Isospor., Microspor., MAC, TB, Histopl., Cryptococcus
- Treatment:** volume & electrolyte repletion critical. Empiric abx: controversial; if febrile, septic, inflammatory diarrhea: FQ or azithro. Consider in age ≥70, hospitalized, serious comorbidities. **Avoid abx if suspect EHEC** as can ↑ risk of HUS. Probiotics controversial: not recommended by ACG except for post-abx diarrhea.
- Anti-diarrheals:** Only if NO fever/blood/c diff. Options include: loperamide 4 mg x1 then 2mg after BM, max 16 mg/d; diphenoxylate; tincture of opium; soluble fiber (i.e. Benefiber)
- Diet:** potatoes, noodles, rice, oats, bananas, soup, broiled veggies

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

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

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

- Hx: freq., stool vol., tenesmus, abd pain, fever, bloating, wt loss, nocturnal sx, postprandial sx, steatorrhea, past surgical hx, travel, immunocompromised, meds, radiation
- Labs: CBC, BMP, ESR/CRP, LFTs, TSH; stool lytes (Na, K, pH), fecal calprotectin (marker of neutrophil activity)/lactoferrin (marker for fecal leukocytes), fecal fat (24-48h collection), FOBT, celiac panel ([Gastroenterology 2019;157\(3\):851](#))
  - Negative fecal calprotectin/lactoferrin rules out IBD;  $\oplus$  FOBT w/ diarrhea suggests chronic infection or IBD (poor sensitivity for colorectal cancer)
  - Other tests to consider: total stool bile acid, *C. diff* (recent antibiotics), *Giardia* (common in MA)/*Cryptosporidium/Cyclospora* (travel; exposure to infants in daycares), *Microsporidium* (immunocompromised), KUB (overflow incontinence)
- Stool osmotic gap for watery diarrhea:**  $290 - 2^*(\text{stool } [\text{Na}] + [\text{K}])$ ; normal 50-100mOsm/kg

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

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

## CONSTIPATION

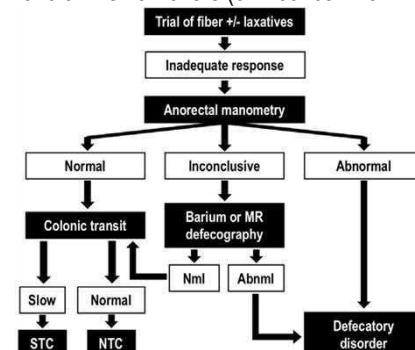
**Definition:** dissatisfaction with defecation; at least 2 of: straining during defecation, lumpy/hard stool, sensation of incomplete defecation/blockage, manual facilitation of BM, <3 BMs per week

### Etiologies:

- **1° constipation:**
  - Slow-transit constipation (STC): sitz-marker study shows delay in colonic transit; associated with bloating & pain
  - Normal-transit constipation (NTC): normal testing, does not meet criteria for IBS-C, but has constipation sx
  - Dyssynergic defecation (e.g. pelvic floor dysfunction): impaired rectal evacuation w/ normal or delayed colonic transit; inadequate rectal propulsive forces or increased resistance to evacuation (e.g. failure to relax or inappropriate contraction)
  - IBS-C: see below; recurrent abd. pain or discomfort a/w hard or infrequent stools or relieved by defecation
- **2° constipation:**
  - **Lifestyle:** low fiber, dehydration, sedentary
  - **Medications:** analgesics, opioids, anticholinergics (antihistamines, antidepressants, antipsychotics), iron, aluminum (antacids, sucralfate), diuretics, clonidine, amiodarone, CCB, ondansetron
  - **CTD:** amyloidosis, sarcoidosis
  - **Metabolic:** ↑Ca, hypothyroid, ↓Mg, ↓K, uremia, heavy metal poisoning, pregnancy
  - **Neuro:** autonomic neuropathy, DM, Hirschsprung's, multiple sclerosis, anorexia nervosa, spinal cord injury, PD, stroke
  - **Obstruction:** anal stenosis, colon ca, stricture, rectocele, compression

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

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

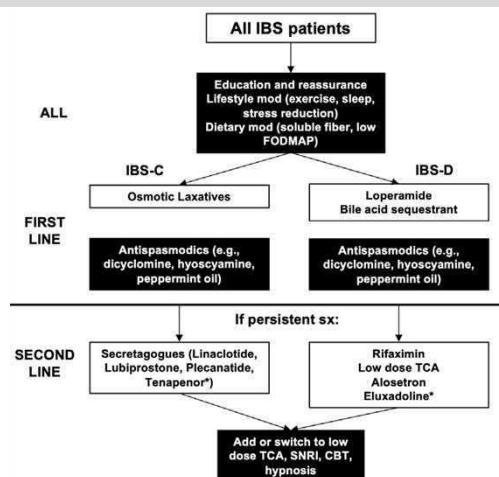


### Hospital Constipation Prophylaxis and Bowel Regimens

- **Risk factors:** >60 yo, prolonged immobility, decreased fluid intake, preexisting constipation, meds (see above)
- Docusate (Colace) lacks evidence in hospitalized pts ([J Pain Symp 2000;2:130](#)) & increases cost & pill burden ([JAMA Int Med 2016;178:1216](#)); senna 2 tabs QHS > senna + colace ([J Pall Med 2008;11:575](#))
- **General ppx for at-risk patients:** senna 2 tabs QHS or BID standing + Miralax 17 gm daily prn
- **High-risk ppx for patients on opioids:** senna 2 tabs BID standing + Miralax 17 gm daily standing
- **Stepwise approach:** senna + Miralax → ↑Miralax to 34g → mag citrate/lactulose → bisacodyl PR → enemas → disimpaction → **1-2L GoLYTELY** (Note: disimpaction can cause vasovagal; all rectal procedures are contraindicated in neutropenia)
  - Types of enemas (stepwise): tap water → soap suds/mineral oil → milk and molasses (MGH specific) → Fleet's
- **Avoid Mg and Phos containing products in renal insufficiency (MOM, Mg citrate, Fleet's enema)** → can cause nephrocalcinosis

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

- **Definition (Rome IV Criteria):** recurrent abd discomfort ≥ 1x/wk for 3 months a/w 2+ of: (1) related to defecation, (2) Δ in stool frequency, (3) Δ in stool form. No alarm symptoms (sudden change in BMs in >50 y/o, blood, weight loss, FH of CRC or IBD, nocturnal diarrhea or ↑ calprotectin/lactoferrin)
- **Epidemiology:** 10-15% of US adults; younger age pop, ♀ > ♂, psychosocial stressors, low QoL, hypochondriasis; prior gastroenteritis
- **Types:** IBS-C (constipation-predominant), IBS-D (diarrhea-predominant), IBS-M (mixed), IBS-U (unclassified), by [Bristol Stool Scale](#)
- **Initial workup:** phys exam as per above; if IBS-D, send calprotectin/lactoferrin, Giardia, celiac serologies
- **Treatment:** all - exercise, diet Δ (low FODMAP), soluble fiber (psyllium preferred, particularly for IBS-M as helps normalize stool)
  - Mild: IBS-C - osmotic lax (e.g. PEG) +/- antispasmodics (dicyclomine, hyoscyamine, peppermint oil); IBS-D – loperamide (45 min before meal, sched), bile acid sequestrant (cholestyramine)
  - Moderate/Severe: IBS-C – secretagogues; IBS-D – rifaximin (2 week trial, can retreat if good resp), TCAs (start at 10mg), alosetron (♀), eluxadoline (↑ risk of pancreatitis, Ø patie nts w/o gallbladder or + biliary hx, + signif alc use)



# Gastroenterology

# Constipation, IBS, & Colonic Disorders

## COLONOSCOPY PREP

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

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

Type	Agent	Dose	Notes
Bulk agents	Psyllium (Metamucil), Methylcellulose (Citrucel)	1 tsp up to TID (for psyllium: up to 30g/d)	In some (esp. STC), can $\uparrow$ bloating in large amounts. Start low & $\uparrow$
Surfactants	Docusate (Colace)	50-360mg QD	Less effective than other laxatives; may be inferior to psyllium, not recommended ( <a href="#">JHM 2019;14:110</a> )
Stimulants	Senna	1-4 tabs QHS or BID	$\uparrow$ colon secretions, motility. Can cause cramping
	Bisacodyl (Dulcolax)	5-15 mg up to 3x/w	$\uparrow$ colon motility, can cause cramping. PO QHS or PR AM
Non-absorbed substances (osmotic)	Polyethylene glycol Miralax (PEG alone) GoLyteLy/NuLyteLy (PEG+salts)	17 g QD; max 34g/d	Modestly more effective and better tolerated (less bloating) than lactulose ( <a href="#">Cochrane Rev 2010</a> ). Dose daily. If 17g does not work, increase to 34g
	Lactulose, sorbitol	15-30 ml QD or BID	$\uparrow$ flatulence/bloating. Less effective than PEG
	Milk of magnesia (MOM)	15-30 mL QD or BID	Benefit of simultaneous neutralization of gastric acidity and water retention in stool. Avoid if renal failure
	Magnesium citrate	150-300 mL QD	Exact mechanism unknown. Can be used as a lower-volume alternative to PEG bowel prep (2+ bottles + Dulcolax PR). Avoid if renal failure
Enemas	Tap water, soapsuds mineral oil, Fleet's (sodium phos.), milk & molasses	Varies	All work via lubrication. Soapsuds also stimulates peristalsis. Fleet's is hypertonic and also has osmotic effect. <u>Avoid Fleet's in elderly or renal failure (phos.)</u>
Secretagogue	Lubiprostone (Amitiza)	24 $\mu$ g BID for STC/NTC; 8 $\mu$ g BID for IBS-C	Binds Cl- channel & increases secretion, $\uparrow$ small bowel & colon transit. Most common side-effect is nausea
	Linaclootide (Linzess) Plecanatide (Trulance)	145-290 $\mu$ g QD 3g QD	Guanylate cyclase-C agonists; $\uparrow$ Cl/HCO3 secretion & colonic transit; Most common side effect is diarrhea
Pro-kinetic drugs	Prucalopride (Motegrity)	2mg daily	5-HT4 selective receptor agonist; $\uparrow$ cholinergic and noradrenergic neurotransmission to promote motility
Peripheral opioid receptor antagonists	Methylnaltrexone, Naloxegol (pegylated naloxone), Alvimopan	Methylnaltrexone: 1 dose SQ QOD PRN - 38-62kg: 8mg - 62-114kg: 12 mg - CrCl <30: 1/2 dose	At MGH, methylnaltrexone approved only if on stable dose of opioids $\geq$ 2 weeks x3d w/o BM AND failed multiple other laxatives. Contraindicated in obstruction, small risk of perforation (AGA guidelines for OIC: <a href="#">Gastro 2019;156:218</a> ; <a href="#">Gastro 2019;156:229</a> )

## COLONIC DISORDERS

### Stercoral Colitis

- Definition: inflammation of colonic wall 2/2 pressure from impacted feces  $\rightarrow$   $\uparrow$  intraluminal pressures  $\rightarrow$  ischemic pressure necrosis
- Epidemiology: nursing home residents; bedridden; hypothyroidism; diabetic enteropathy; opioids; clozapine; other constipating meds
- Treatment: fecal disimpaction if no defects in colonic wall on CT; consider CTX flagged; consider as cause of sepsis or hemorrhage

### Diverticulosis

- Definition: herniation of colonic mucosa into muscularis propria, where vasa recta penetrate
- Risk factors: low fiber diet  $\pm$  chronic constipation, obesity, physical inactivity,  $\uparrow$  age (present in 50% of patients  $>60$ yo; common incidental finding), smoking, NSAIDs, red meat consumption, ♀ = ♂. Nuts, seeds, popcorn consumption is **not** associated
- Location: 90% L-sided (primarily sigmoid) in "Western" populations; 75-85% R-sided in Asia
- Bleeding: **painless** bleeding of *vasa recta* within the diverticuli. 75% are self-limited & resolve with bowel rest. Recurrence is common. Tx if bleeding does not stop: 1) colonoscopy, 2) angio (IR embolization), 3) surgery. See *Lower GI Bleed*
- Diverticulitis develops in 4% of pts with diverticulosis ([Clin Gastroenterol Hepatol 2013;12:1609](#)).

### Diverticulitis

- Definition: infection of diverticuli: micro-perforation secondary to erosion of the diverticular wall by increased intraluminal pressure
  - Uncomplicated** (75%): abdominal pain (LLQ), fever, leukocytosis, anorexia,  $\Delta$  in BMs (diarrhea or constipation)
  - Complicated** (25%): bowel obstruction, abscess, fistula (potentially with bladder, vagina, skin, or peritoneum), or perforation
- Diagnosis: characteristic s/sx & CT A/P (I+, O+) (findings: diverticula, bowel wall  $>4$ mm, inflammation w/ pericolic fat  $\pm$  abscess/fistula)
- Management (AGA: [Gastro 2015;149:1944](#)):
  - Uncomplicated (medical):** PO abx x7d (cipro/flagyl, bactrim/flagyl, or augmentin), bowel rest. No abx is noninferior to abx if uncomplicated ([Clin Gastroenterol Hepatol 2021;19:503](#); [Br J Surg. 2019;106:1542](#))—use selectively (IC, pregnant, comorbidities, sepsis)
  - Complicated:** IV abx (GNR + anaerobe coverage), bowel rest, and IR/surgical evaluation (peritonitis typically present; evaluation for abscess drainage or colonic resection)
- To prevent recurrence: rec high fiber diet for pts w/ hx acute diverticulitis ([Gastro 2015;149:1950](#)), avoid NSAID, exercise, d/c smoking
- Follow-up: consider colonoscopy 6-8w after to evaluate for malignancy; advised in patients with complicated diverticulitis, first episode of diverticulitis, or alarm symptoms; can be deferred if recent colonoscopy (w/i 1 year) ([Gastroenterology 2021; 160\(3\):906](#))

# Gastroenterology

# Esophageal & Upper GI Disorders

		OROPHARYNGEAL DYSPHAGIA	ESOPHAGEAL DYSPHAGIA
Symptoms		Difficulty initiating swallowing; drooling, coughing, aspir.	Difficulty seconds after initiation, food stuck in esophagus
Etiologies	<b>Neuro-muscular</b> (solids + liq.) <u>Central</u> : tumor, stroke, PD, ALS, MS, polio <u>Peripheral</u> : neuropathy, myasthenia gravis <u>Muscular</u> : polymyositis, muscular dystrophy	<u>1°</u> : achalasia, esophageal motility disorders (e.g. distal esophageal spasm, hypercontractile "Jackhammer" esoph.) <u>2°</u> : diabetes, scleroderma, CTD, amyloid, Chagas, MG (Chicago classification: <a href="#">Neurogastro Motil 2015;27:160</a> )	<u>Intrinsic</u> : tumor, stricture, infection, EoE, rings, webs (e.g., Plummer-Vinson), pills (NSAIDs, doxy, tetracyc., bisphosph) <u>Extrinsic</u> : vascular rings (e.g. dysphagia lusoria), Ao. enlarge., LA compression, mediastinal, substernal thyroid, LAD
	<b>Structural</b> (solids > liquids) <u>Intrinsic</u> : tumor, XRT, trauma/surgery/infection, Zenker's <u>Extrinsic</u> : anterior mediastinal mass, goiter, cervical spondylosis		
<b>Work-up</b>		History: onset & duration, solid/liquid & localization, +/- odynophagia, underlying conditions (e.g., CNS, malignancy, thyroid, DM, scleroderma), <b>offending meds</b> (pill esophagitis), immunocompromise (Candida, CMV, HSV esophagitis or lymphoma in HIV), radiation. Dysphagia in older adults is <b>not</b> normal aging PE: appearance (systemic disease or CNS issue), HEENT exam (evidence of LAD, tumor, asymmetry), FOB Labs (consider): CBC, TFTs, ANA, $\alpha$ -Scl-70, $\alpha$ -centromere, $\alpha$ -RNP, $\alpha$ -Jo, HgbA1C, iron studies, HIV, AChR-Ab	
<b>Diagnostics</b>		1) Bedside swallow, SLP consult, VSS 2) Modified barium swallow; ENT, neuro evals, +/- EGD to identify obstructive structural problem 3) Consider chest/neck CT to dx extrinsic compression	1) EGD is the most useful test +/- barium swallow (mucosal pathology or structural abnormality) 2) if normal $\rightarrow$ <u>esoph. manometry</u> to diagnose motility d/o 3) Consider chest/neck CT to dx extrinsic compression
<b>Selected Conditions</b>		<u>Zenker's diverticulum</u> : p/w halitosis, regurgitation of food/aspiration, cough. Tx: endoscopic surgery (rigid vs. flexible) <u>Strictures &amp; rings</u> : if lumen <13mm, dysphagia common. Tx: PPI, dilation, intralesional steroid injection, stent <u>Distal esophageal spasm</u> : uncoordinated peristalsis a/w intermittent chest pain & regurgitation; barium swallow: corkscrew (vs. nml). <u>Hypercontractile esophagus</u> : similar sx; nml barium swall. Tx (both): PPI, nitrates/CCB/PDEi, TCA <u>Achalasia</u> : progressive dysphagia solids/liquids + <b>regurgitation</b> ; <b>barium swallow</b> : bird's beak distal esophagus; <b>manometry</b> : absent distal peristalsis, incomplete LES relaxation; EGD/CT r/o pseudo-achalasia (2/2 CA), +EndoFLIP for LES relaxation. <b>Tx</b> : pneumatic dilation, Heller myotomy, POEM, botox, CCB, esophagectomy (AGA: <a href="#">AJG 2013; JAMA 2015</a> ) <u>Infectious esophagitis</u> : odynophagia; often immunosuppressed – Candida, HSV, CMV <u>Eosinophilic esophagitis (EoE)</u> : dysphagia, refractory GERD sx. EGD w/ stacked rings, strict. Bx: >15 eos/hpf. Tx: PPI, diet $\Delta$ s (dairy, wheat > soy, eggs, nuts, fish), topical steroids (MDI/neb/liq.); consider dilation (AGA: <a href="#">Gastro 2020;158:1776</a> )	

## GASTRO PARESIS (ACG: [AJG 2022;117:1197](#))

Definition: delayed gastric emptying w/o mechanical obstruction

Sx: **nausea, vomiting of undigested food, early satiety**, postprandial fullness, bloating  $\pm$  abd pain

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

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

Dx: EGD to exclude obstruction, gastric emptying tests (hold motility meds, opiates 48h prior)

- Gastric emptying tests: gastric scintigraphy (egg > liquid)  $\oplus$  if retained solids @ 4h  $\gg$  wireless capsule motility test,  $^{13}\text{C}$  breath test
  - **Indications**: post-prandial n/v, abd pain, early satiety; reflux unresponsive to therapy; patients with DM w/ poor glycemic control; evaluate for rapid gastric emptying; w/u of cyclic vomiting syndrome
  - **Contraindications**: hyperglycemia at time of test > 275 mg/dL, motility agents or opiates within 48-72 hours ([JNMT 2008](#))

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

Treatment: optimize glucose control, small meals with low fat & low non-digestible fiber, prokinetic agents before meals (metoclopramide, domperidone, erythromycin; give drug holidays due to tachyphylaxis/to assess benefit), 5-HT4 agonists (prucalopride); venting G-tube if refractory, J-tube for nutrition if wt loss

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

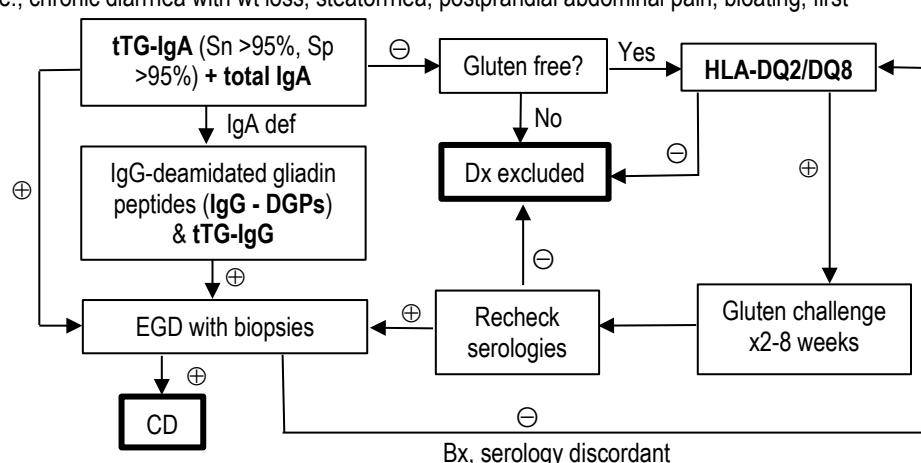
Pathophysiology: abnormal immune response to gluten  $\rightarrow$  diarrhea, wt loss, abd pain, IDA, vit D def, dermatitis herpetiformis

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

Diagnosis: see flow diagram

Biopsy: 1 intraepithelial lymphocytes, crypt elongation/hyperplasia, villous atrophy – Marsh Score ([AJG 2013](#))

Treatment: strict gluten-free diet; IgA anti-TTG titer should return to normal over time. Replete vitamin deficiencies (A, D, E, B12), Cu, Zn, carotene, folic acid, Fe +/- thiamine, vit B6, Mg, and selenium



# Gastroenterology

# Inflammatory Bowel Disease

## CLINICAL PRESENTATION

**Epidemiology:** ~1.3% USA prevalence, onset 15-30y, bimodal w/ 2nd peak 50-80y. Genetic predisposition ( $\uparrow$  risk: +FamHx, other autoimmune dz; female (Crohn's);  $\uparrow$  incidence in Jewish, white, however increasing dx rate in non-white) + environment ( $\uparrow$  risk: Western diet, abx, NSAIDs, sleep deprivation, OCPs; smoking  $\uparrow$  risk for CD &  $\downarrow$  risk for UC)

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

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

## INPATIENT WORK-UP AND MANAGEMENT

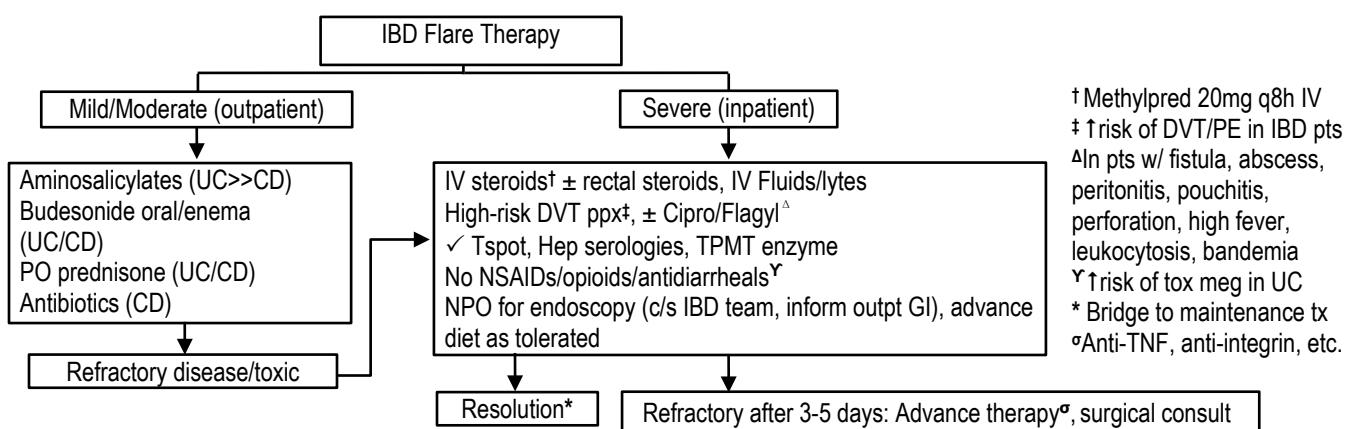
**Labs:** CBC, BMP, LFTs ( $\uparrow$ ALP→?PSC), ESR/CRP, Mg, fecal calprotectin, C. diff, Stool Cx, O&P, Fe/TIBC/B12 (if anemic). *Prior to medication initiation:* Hep serologies and TSpot (immunomodulators), TPMT enzyme (metabolizes AZA toxic metabolites) for AZA

**Imaging:** if concern for peritonitis/obstruction/mass (abscess) → KUB, CT A/P. Consider CT/MRI enterography to eval small intestine. Consider pelvic MRI to eval perianal dz

**Procedures:** Colonoscopy with biopsy (+/- EGD) necessary to confirm dx

**Ddx:** infectious colitis, celiac disease, lactose intolerance, IBS, diverticular colitis, microscopic colitis, lymphocytic colitis, collagenous colitis, appendicitis, functional abdominal pain

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



# Gastroenterology

# Inflammatory Bowel Disease

## General Step-Up Treatment for IBD (subject to practice variation):

1. 5-ASA (mesalamine, sulfasalazine) – generally for mild UC and CD limited to terminal colon/rectum.
2. Rectal steroids
3. PO Steroids (prednisone, budesonide) and PO 5-ASA – PO budesonide 1<sup>st</sup> line in mild CD (Systemic steroids usually used for acute flare mgmt and weaned within 6 weeks after starting steroid sparing agent)
4. Immunomodulators (azathioprine, mercaptopurine, methotrexate)
5. Biologics (infliximab, adalimumab, vedolizumab, ustekinumab) (biologics often started when ≥2 flares/year requiring systemic steroids)
6. Surgery

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

**Management Guidelines:** NEJM: [NEJM 2021:385:1302](#)

- CD: ACG: [AJG 2018;113:481](#), AGA: [Gastro 2021;160:2496](#)
- UC: ACG: [AJG 2019;114:384](#), AGA: [Gastro 2020;158:1450](#)

## IBD THERAPEUTICS

Class	Drug	Use	Notes & Adverse Effects (AE)
Steroids	Budesonide (PO/PR), Pred (PO), Methylpred (IV)	Induction	<b>PO budesonide</b> 1 <sup>st</sup> -line in mild CD, 2nd-line to ASA for mild UC, but can be 1 <sup>st</sup> -line for mod. <b>AE</b> : osteoporosis, infection, AVN, AI, delirium
Amino-salicylates (UC>>CD)	Sulfasalazine Mesalamine (PO: Pentasa, Ascol, Lialda, Apriso. PR: Canasa, Rowasa)	Induction + Maintenance for moderate disease	<b>Sulfasalazine</b> : pro-drug with more AEs, also systemic effects <b>Mesalamine</b> forms differ in gut penetration: Pentasa (ileum, R>L colon), Ascol (R>L colon), Lialda & Apriso (pancolon), Canasa & Rowasa (distal). <b>AE</b> : HA, fever, rash, diarrhea, pancreatitis, ↓sperm count, AKI
Thiopurines	Azathioprine (pro-drug) 6-MP	Induction + Maintenance	Typically as combination therapy for induction; can be monotherapy for maintenance. Test Thiopurine methyltransferase (TPMT) prior to use. 6-TGN for monitoring. <b>AE</b> : n/v, hepatitis, BM suppression, malignancy (non-melanoma skin cancer, lymphomas)
Antimetabolites	Methotrexate	Induction + Maintenance	For pts unable to tolerate thiopurines. Typically as combination therapy. Give with folic acid. <b>AE</b> : n/v, hepatotoxicity, BM suppression, lung injury
Anti-TNF	Infliximab (Remicade) (IV) Adalimumab (Humira) (SQ) Certolizumab (Cimzia)-CD Golimumab (Simponi)-UC	Induction + Maintenance for mod-severe	<b>Infliximab</b> for induction in pts naïve to biologics. Contraindicated if toxic megacolon, pyogenic infxns. Typically in combination with immunomodulator. Preferred agent with concomitant IBD-associated arthritis. <b>If flare during maintenance</b> : measure trough (24hrs prior to dose) and antidrug Ab. If non-responsive despite adequate levels -> another class. <b>AE</b> : infxn, TB/HBV reactiv., malignancy
Anti-integrin	Vedolizumab (Entyvio) (IV) ( <a href="#">NEJM 2013;369:699</a> ; <a href="#">NEJM 2013;369:711</a> ) Natalizumab (Tysabri)	Induction + Maintenance for mod-severe	Induction in pts naïve to biologics. VARSITY ( <a href="#">NEJM 2019;381:1215</a> ): in mod-severe UC, achieved ↑clinical remission at 52wks vs. Humira, but w/ greater steroid use. <b>AE</b> : infusion reactions, nasopharyngitis ACG recommends against natalizumab due to risk for JC-virus associated PML, can consider if pt adheres to JC virus monitoring
IL-12, -23 inhibitor	Ustekinumab (Stelara) ( <a href="#">NEJM 2019;381:1201</a> ) Risankizumab (Skyrizi, IL-23 only) ( <a href="#">Lancet 2022;399:2031</a> )	Induction + Maintenance	Ustekinumab shown to have no differences in outcomes compared to adalimumab in Crohn's patients ( <a href="#">Lancet 2022;399:2200</a> ). Sometimes preferred for less frequent ~q8week dosing. <b>AE</b> : infection, HA, nasopharyngitis, nausea, abdominal pain, arthralgias
JAK inhibitor	Tofacitinib (Xeljanz) ( <a href="#">NEJM 2017;376:1723</a> ) Upadacitinib ( <a href="#">Lancet 2022;399:2113</a> )	Induction + Maintenance	Consider if previously failed anti-TNFs <b>AE</b> : infection, herpes zoster, HA, nasopharyngitis, arthralgias, CPK elevation, acne
Calcineurin inhib (IV)	Cyclosporine	Induction only for severe UC	C/i in s/o toxic megacolon. Labs: troughs (q2-3d) Cr, Mg, lipids, LFTs <b>AE</b> : renal injury, ↑K, infxn, neurotox/seizures (esp. if ↓Mg or cholesterol)
Sphingosine-1-phosphate receptor	Ozanimod	Induction + remission moderate to severe UC	Prior to initiation: CBC, LFTs, EKG, VZV Ab (vaccinate if neg), ophthalmic exam (uveitis, macular edema). <b>AE</b> : anemia, nasopharyngitis

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

# Gastroenterology

# Intestinal Disorders

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

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

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

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

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

# Gastroenterology

# Nutrition & Feeding

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

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

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

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

- **Oral:** assess aspiration risk, dysphagia, odynophagia. Consider SLP c/s for dietary modifications (e.g. pureed, thick liquids etc.)
- **Enteral (EN):** if pt unable to tolerate oral diet safely or meet caloric needs through oral diet alone, may need enteral nutrition. Place tube **post-pyloric (JG/PEG-J)** if gastroparesis, obstruction, n/v, or high aspiration risk. **Gastric residuals not recommended** ([NEJM 2014;370:1227](#)). Consider PEG if neck/throat cancer, dysphagia, prolonged recovery (in discussion with family)
- **Parenteral:** TPN (central access) or PPN (peripheral). Used when GI tract non-functional or no reliable enteral access anticipated.

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

## ARTIFICIAL NUTRITION

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

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

### TPN: "TPN (Nutritional Support Team)" in PPD (p22445)

Consider if NPO ≥7d. Need central access w/ clean dedicated lumen (PICC Preferred). Order by 1PM to start same day. Page about new orders if close to 1 PM.

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

## REFEEDING SYNDROME

Electrolyte/fluid shifts caused by initiation of nutrition in severely malnourished patient (d/t insulin surge and increased Na/K pump activity), can be fatal; most likely to occur within 72h of starting nutritional therapy ([Nutrition 2018;47:13; Front Gastro 2019;11:404](#))

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

## SPECIAL CONSIDERATIONS

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

## TIPS FOR ORDERING INPATIENT DIETS

- **Diabetes:** Consistent carbohydrate (no calorie/carb restrictions, just consistent amount- can add restriction within order)
- **Cardiac:** no added salt (4g) vs 2g Na (renal/liver/cardiac). Consider fluid restriction (usually 2L) for HF/SIADH/cirrhosis
- **GI:** low fat (GI) for gallbladder dz/fat malabsorption/pancreatitis, **red dye restricted** for pre-EGD/colo
- **Renal:** low K (2 g), **low protein** in some CKD (NOT dialysis), **low phos** for ESRD
- **Onc:** Neutropenic/BMT (no garnishes), **PET scan** is carbohydrate restricted (will NOT restrict glucose or make patient NPO)

# Gastroenterology

# Weight & Weight Loss

## OBESITY

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

- Increased waist circumference: >40 inches men, >35 inches women
- \*Caveat: studies suggest using a lower BMI criterion for people of Asian descent ([AADI BMI calculator](#))

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

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

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

## Treatment:

- Diet:** 1200-1500 kcal/d for women; 1500-1800 kcal/d for men; a diet that is 500-750 kcal/day less than usual. Variety of diets – all achieve calorie deficit: balanced low calorie, higher protein, low carbohydrate, low-fat vegan, vegetarian, macronutrient targeted, Mediterranean style, intermittent fasting ([Circ 2014;129:S102](#)). Patient choice based on highest likelihood to adhere, comorbidities.
- Lifestyle:** comprehensive program – dieting, exercise (effective for weight loss but much more important for weight maintenance), behavioral techniques (Weight Watchers, outpatient programs)
- Meds:** see table. Indication: wt loss & mgmt. + diet for adults w/ initial BMI ≥30 or BMI ≥27 + wt-related comorbidities (DM, HTN, HLD)

## MEDICATIONS FOR WEIGHT LOSS ([APJ 2016;43](#); [JAMA 2016;315:2424](#); [DMJ 2020;44](#); [NEJM 2022; 387:205](#))

Agent	Mechanism of Action	Dose	Side effects	Notes
Semaglutide (weekly, preferred) Liraglutide (daily) Tirzepatide (weekly)	GLP-1 receptor agonist; injectable (Tirzepatide GLP-1/GIP) ( <a href="#">NEJM 2021;384:989</a> ) ( <a href="#">JAMA 2021;325:1414</a> ) ( <a href="#">JAMA 2022; 327:138</a> )	Sema: 0.25 mg → <b>2.4mg weekly</b> Lira: 0.6mg → <b>full dose 3mg daily</b> Tirz: 2.5 mg → <b>15 mg weekly</b>	N/V/D (typically resolve w/ time); delay in GE; thyroid C cell tumors in rodents (must ask if hx of thyroid cancer)	Benefit to DM, CAD, NAFLD; <b>insurance limitations</b>
Orlistat (Xenical, Alli OTC)	Inhibit GI lipases that hydrolyze TGs into FFA; increases fecal excretion of TG	60-120mg TID AC	GI - fecal incontinence (>10%); reduced vitamin absorption; drug interactions; rare liver/ kidney injury	Reduced BG, lipids, BP; <b>no longer first-line due to GI effects</b>
Phentermine/topiramate (Qsymia)	Phentermine = stimulant, anorectic, increases satiety by action at the hypothalamus Topiramate = mechanism for weight loss unknown	3.75/23mg x14d → 7.5/46mg x12w; can increase to max 15/92mg	<b>Teratogenic.</b> Interacts with metformin. Activating/ insomnia. Paresthesia, constipation, dry mouth, URI, dysgeusia	Should not be used w/ HTN or CAD, caution in anxiety
Naltrexone/bupropion (Contrave)	Works at hypothalamus to increase satiety + inhibition of mesolimbic dopamine (reward) circuit	8/90mg daily 16/180mg BID	Nausea, constipation, HA, vomiting; lower seizure threshold; increase BP; cannot be taken with opioids	Not first line due to side effects, helpful in patients w/ AUD

**Choice of agent:** Semaglutide first line for convenience and tolerability; but recent trial showed greater reduction in weight with tirzepatide (GLP-1/GIP) vs semaglutide ([NEJM 2022; 387:205](#)); current data: tirz> sema > lira. Metformin can produce modest weight loss in overweight patients (<5% weight loss) but not FDA approved for weight loss. Consider patient characteristics and comorbidities.

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

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

## WEIGHT LOSS SURGERY ([NEJM 2007;356:2176](#); [Lancet 2022;400:441](#))

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

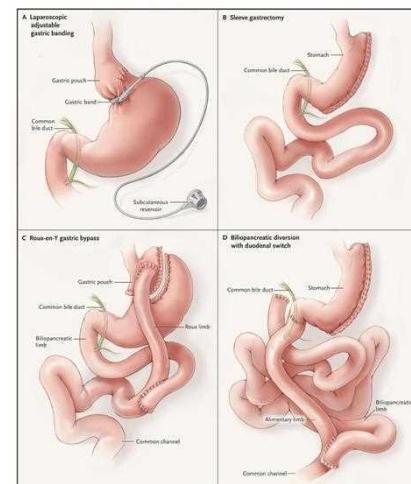
**Mechanism of weight loss:** restriction (reduced stomach capacity) ± malabsorption (↓ nutrient absorption by shortening the absorption length of SI)

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

**Benefits:** 49% (endo sleeve) excess wt lost at 1y vs 3.2% (control) ([Lancet 2022;400:441](#)); remission of DM, HTN, HLD, OSA; ↓ CV & cancer mortality (30-50%), extended life expectancy by 3 years ([NEJM 2020;383:1535](#); [Annals 2020;173:694](#)), improvements in NASH ([JAMA 2021;326:2031](#))

### Complications:

- <30d: anastomotic leak, MI, and PE (total 0-1.55%) ([Obes Rev 2018;19:529](#))
- Long term:** food aversions/intolerances, **vitamin deficiencies** (absorbed in SI: fat soluble vit **ADEK; thiamine, B12, folate; iron, zinc, selenium, copper, Ca**), psychosocial impairment, **dumping syndrome** (rapid transit of hyperosmolar simple carbs cause fluid shifts/hypotension/sympathetic surge), **osteoporosis**, weight re-gain, increased sensitivity to EtOH



# Gastroenterology

## Etiology (NEJM 2014;317:1983)

- **Gallstones/sludge** (40-75%): #1 in female sex
- **Alcohol** (30%): #1 in male sex
- **Hypertriglyceridemia** (10%): #3; suspect if TG>1000
- **Anatomic**: ampullary diverticula/stenosis, duodenal stricture, tumor, divisum, parasites, foreign body
- **Post-ERCP**: 4.5% of ERCP; **rectal NSAIDs** ↓ risk ([Endoscopy 2020](#); [Endosc Int Open 2019;7:477](#))
- **Autoimmune**: ↑IgG4, +ANA ([Am J Gastro 2018;113:1301](#))
- **Acute hypercalcemia**: Ca activates pancreatic enzymes
- **Genetic**: often CFTR, CTRC, PRSS1 or SPINK1

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

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

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

## MANAGEMENT (AGA: [Gastro 2018;154:1096](#); WATERFALL trial NEJM 2022; 389:989)

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

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

	Local		Vascular	Systemic
	<4 weeks	>4 weeks		
Interstitial edematous pancreatitis	Acute peripancreatic fluid collection: w/o features of pseudocyst; resolve spontaneously w/o drainage	Pancreatic pseudocyst: fluid collection w/ well-defined wall. If dx unclear, EUS w/ FNA (↑amylase). Drain if sx, rapidly ↑, infxn (endo vs. perc/surg)	<b>Thromboses</b> : splenic, portal, SMV; AC if portal vein or bowel ischemia <b>Pseudoaneurysm</b> : erosion of GDA/splenic artery → bleeding into pseudocyst. Suspect if ↓Hgb, expansion of fluid collection, unexplained GIB. <b>Dx</b> : arterial phase CT <b>Tx</b> : IR embo. prior to drainage of fluid collection	<b>Abd. compartment syndrome</b> : intra-abd pressure >20 w/ new organ failure. ✓ bladder pressure if in ICU <b>ARDS</b> : via phospholipase degradation of surfactant <b>Metabolic</b> : ↓Ca, ↑Glc, ↑TG <b>GIB</b> : via pseudoaneurysm <b>AKI</b> <b>DIC</b>
Necrotizing pancreatitis	Acute necrotic fluid collection: intra- or extra-pancreatic Infected necrosis: 1/3 become infected, usually later in course; early enteral feeding decreases risk of infection. <b>Abx</b> : (cefepime or cipro) + flagyl vs. pip/tazo vs. carbapenem in critically ill. Necrosectomy – can delay 4w if stable	Walled off necrosis: encapsulated necrotic collection. <b>Drain</b> at >2-4 wks if sx or infxn (endo vs. perc)		

## CHRONIC PANCREATITIS (ACG: [AJG 2020;115:322](#))

Repeat acute attacks (esp. EtOH & smoking) → fibrosis & loss of glandular tissue → chronic abd pain, exocrine insufficiency (steatorrhea, wt loss, vitamin deficiencies), endocrine insufficiency (brittle DM). Lipase/amylase may be ↑ early but nml/low as more tissue lost. ⊕ Fecal fat, ↓stool elastase. CT/MRI with calcifications, ductal dilation, parenchymal atrophy. ↑risk of pancreatic CA. Consider genetic testing. Tx: pancreatic enzyme replacement (Creon), ensure vit ADEK replete, pain control. Refer to MGH Pancreas Center: 617-726-5523

## PANCREATIC MASSES (Cur Gastro Rep 2013;15:347)

- **Solid**: adenoCA (85-90%), autoimmune panc, neuroendocrine (1-5%), 1<sup>o</sup> lymphoma (<1%), mets (melanoma, RCC, etc.)
- **Cystic**: inflammatory (pseudocyst, paraduodenal wall cyst), neoplastic (malignant potential: main duct IPMN >> side branch IPMN > mucinous cystic = solid pseudopapillary > serous cystadenoma) ([AJG 2018;113:464](#); [Gastro 2015;148:819](#))
- **Imaging**: **CT abd pancreatic mass protocol**: EUS with FNA for lesions >2-3cm (87% Sn, 96% Sp); MRI useful in <2 cm lesions or when vascular involvement needs to be delineated better; consider PET-CT, MRCP for malignancy in IPMN (70% Sn, 92% Sp)
- **Labs**: CA 19-9 (⊕ in 80% of panc CA, 86% Sn, 87% Sp), CEA (mucinous), ANA, IgG4 (if autoimmune suspected)

# Pancreatitis & Pancreatic Masses

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

**1) Identify pattern of liver test abnormality.** R-factor =  $(\text{ALT} / \text{ULN}) / (\text{Alk-P} / \text{ULN})$

- Hepatocellular: R factor >5, ↑ ALT
- Mixed: R factor 2-5, ↑ ALT, ↑ Alk-P
- Cholestatic: R factor <2, ↑↑ Alk-P, ↑↑ GGT, ↑ ALT

**2) Identify chronicity**

- Acute: < 6 months
- Chronic: > 6 months

**Hepatocellular markers:** Released from hepatocytes in response to injury  
**ALT:** Expressed primarily in liver, typically more specific marker of hepatocellular injury  
**AST:** Present in liver as well as cardiac muscle, skeletal muscle, kidney, brain, and RBCs

*Magnitude of ALT and AST elevation:*

- **Extreme elevation (>1,000 U/L):** Most consistent with acute liver injury, including acute ischemic liver injury, severe drug-induced liver injury, or acute viral hepatitis
- **Borderline to mild elevation (<5x ULN):** Broad differential including med/Toxins (see below), acute liver injury, chronic liver disease (e.g., NAFLD, Alcohol related liver disease, viral hepatitis, AI hepatitis), biliary obstruction (mixed markers)

**AST/ALT ratio:** Usually ALT>AST (AST has shorter serum half-life, 18h vs 36h). Ratio can vary widely, especially in acute liver injury

- Mild AST/ALT elevation with ratio ~2:1 suggestive of alcohol related liver dz
- Typical AST/ALT ratio in hepatocytes

Is 2.5:1, so ratio >2.5:1 think non-hepatic source of AST ([Clin. Bio. Rev.: 2013; 34\(3\):117](#))

For more info and work-up, see [Acute Liver Injury & Failure](#), [Non-Alcoholic Fatty Liver Disease](#), [Viral Hepatitis](#), and [Alcohol Related Liver Disease](#)

**Cholestatic markers:** Released from cells lining bile canaliculi/ducts in response to injury

**Alk-P:** Expressed in bile duct, liver, kidney, bone, intestinal mucosa, and placenta (fractionated assay available, slow to result). If accompanied by other LFT abnormalities (e.g. elevated bili), do not need to confirm source

**GGT:** Expressed in bile duct, liver, pancreas, and kidney. Often measured to support biliary/hepatic source of Alk-P. Non-specific marker of alcohol ingestion

*Magnitude of Alk-P elevation:*

- **1-1.5x ULN:** Common in adults over age 60
- **1-3x ULN:** Any liver disease
- **>4x ULN:** Cholestatic liver dz, infiltrative liver dz such as cancer and amyloidosis, bone conditions characterized by rapid bone turnover. In absence of ↑ bili or ALT/AST, elevated liver Alk-P suggests early cholestasis or hepatic infiltration by tumor or granulomatous dz

For more info and work-up, see [Biliary Disease](#)

**Markers of impaired liver function:**

**Bilirubinemia:** Heme breakdown product conjugated in the liver and excreted in bile

- **Conjugated (direct) hyperbilirubinemia:** Elevated **total and direct bilirubin**. Caused by hepatocellular disease, impaired excretion or biliary obstruction. Likely liver or biliary tract disease. Only conjugated bilirubin excreted in urine, so bilirubinuria also implies liver disease
- **Unconjugated (indirect) hyperbilirubinemia:** Elevated **indirect bilirubin**. Caused by ↑ production, impaired uptake by the liver, or ↓ conjugation. Consider hemolytic disorders, resorption of hematoma, and genetic conditions (Gilbert syndrome,Rotor syndrome, and Dubin-Johnson syndrome)

**Hypoalbuminemia:** Seen in chronic liver disorders such as cirrhosis. Not specific to hepatic dysfunction; can also occur in systemic inflammation, nephrotic syndrome, malnutrition, ascites (due to marked increase in plasma volume)

**Clotting factors deficiency (elevated PT-INR):** Poor utilization of Vit K due to parenchymal liver disease (Vit K supplementation does NOT improve INR). First, consider consumption of clotting factors (e.g., DIC, severe GI bleeding) and medications. If not, Vit K challenge can differentiate from deficiency of Vit K (e.g., inadequate dietary intake, prolonged obstructive jaundice [adequate bile salts needed for Vit K uptake], administration of antibiotics that alter gut flora)

**Thrombocytopenia:** Decreased platelets associated with decreased synthesis (liver produces thrombopoietin), splenic sequestration

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

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

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

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

# Gastroenterology

# Biliary Disease

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

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

## AUTOIMMUNE BILIARY DISEASES

Primary Biliary Cholangitis (PBC) (AASLD: <a href="#">Hepatology 2019;69:394</a> )	Primary Sclerosing Cholangitis (PSC) (AASLD: <a href="#">Hepatology 2022</a> )
<p>Autoimmune destruction of <i>intrahepatic</i> bile ducts</p> <ul style="list-style-type: none"> <li>Clinical manifestations: F&gt;M; asx (50-60%), pruritus, fatigue, sicca symptoms, cirrhosis (late)</li> <li><b>Dx:</b> ≥2 of the following: <b>ALP</b> ≥1.5x ULN; <b>Antimitochondrial Ab</b>&gt;1:40 titer (95% pts); biopsy findings; can have AMA (-) PBC</li> <li>SPATA31A3 and GARP new biomarkers for diagnosis (<a href="#">Liver International 2019;39:2124</a>)</li> <li><b>Associated with:</b> <b>hypothyroidism</b> (20% pts), anemia, metabolic bone disease, Sjogren's, autoimmune hepatitis (overlap)</li> <li><b>Tx:</b> <b>ursodiol</b>: first line, ↓progression &amp; ↑survival (<a href="#">NEJM 1994;330:1342</a>); <b>obeticholic acid</b> (FXR agonist) 2<sup>nd</sup> line after ursodiol; <b>fibrates</b>: off label altern.; <b>cholestyramine</b> for pruritus; <b>modafinil</b> for fatigue; <b>liver transplant</b>: 22% recurrence in 5yrs</li> </ul>	<p>Affects <i>intra- + extrahepatic</i> bile ducts</p> <ul style="list-style-type: none"> <li>Clinical manifestations: M&gt;F; asx (50%), pruritus and fatigue (most common), cirrhosis (late); cholangitis due to strictures</li> <li><b>Dx:</b> ↑ALP ± bili; may have +auto-Abs but of unclear significance; MRCP (segmental strictures), ± biopsy if suspect small duct PSC (otherwise not required); check AMA/IgG4 to exclude alt. dx</li> <li><b>Associated with:</b> <b>IBD</b> (60-80%; UC&gt;Crohn's), <b>cholangioCA</b> (10-15% pts), metabolic bone disease, AIH (overlap), HLA-83</li> <li><b>Tx:</b> <b>supportive</b>; ursodiol may improve sx, ERCP for stricture, <b>liver transplant definitive tx</b> (MELD exceptions for recurrent cholangitis, intractable pruritus): 20% recurrence 5 years post-LT</li> <li>Hepatobiliary CA surveillance q6-12 month (imaging, CA 19-9, AFP) improves survival (<a href="#">Hepatology 2018;67:2338</a>)</li> </ul>

## MALIGNANT DISEASE OF THE BILIARY TRACT

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

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

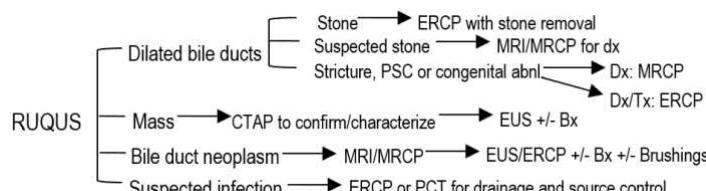
**Cholangiocarcinoma:** may be extrahepatic (90%) or intrahepatic (10%); risk factors: PSC, liver flukes, intrahepatic gallstones

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

## SPHINCTER OF ODDI DYSFUNCTION

F>M; Often occurs post-CCY, provoked by opioids (due to spasm of sphincter) and associated with idiopathic recurrent pancreatitis, Rome IV criteria ([MD Calc](#)). **Diagnosis:** ERCP/manometry. **Treatment:** surgical/endoscopic sphincter ablation ([Curr Gastro Rep 2015;17:31](#))

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



**Acute Liver Injury (ALI):** acute liver injury <26w with coagulopathy but NOT encephalopathy

**Acute Liver Failure (ALF):** encephalopathy & coagulopathy (INR >1.5) of <26w in pts without cirrhosis or known liver disease

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

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

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

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

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

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

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

## ETIOLOGY-SPECIFIC MANAGEMENT

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

**King's College Criteria** – list for OLT if:

### Acetaminophen-induced ALF:

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

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

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

# Gastroenterology

# Viral Hepatitis

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

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

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

<b>Screening</b>	<u>HBsAg</u> . Pts from area w/ prev. $\geq$ 2%, parents from high prev. area $\geq$ 8%, HIV+, PWID, MSM, close contact of HBV+ person, unexplained elevated LFTs, those requiring immunosuppressive therapy (e.g. done before chemo)		
<b>Risk Factors</b>	Vertical transmission (SE Asia), sexual contact, PWID, needlestick, unvaccinated (US before 1994), immunosuppress.		
<b>Clinical Pres.</b>	<b>Acute:</b> 70% subclinical, 30% w/ jaundice, <1% ALF. S/S: anorexia, nausea, fatigue, RUQ discomfort. ALT>AST in 1000s, +/- $\uparrow$ Bili. <b>Chronic:</b> $\oplus$ HBsAg >6mo. (often w/ persistent $\uparrow$ ALT), occurs <5% adults. 40% $\rightarrow$ cirrhosis		
<b>Extrahepatic</b>	Polyarteritis Nodosa, membranous nephropathy/MPGN, aplastic anemia, arthritis		
<b>Diagnosis</b>	HBsAg, anti-HBs, anti-HBc total (identifies all infected). Interpretation below		
<b>Treatment</b>	First line: tenofovir or entecavir ( <a href="#">Hepatology 2018;67:1560</a> ) PegIFN option for young w/o cirrhosis for a finite treatment course. <b>Goal:</b> suppress HBV DNA, lose HBsAg & HBeAg		
<b>HCC Screen.</b>	<b>Indications:</b> all HBsAg+ w/ cirrhosis, HBsAg+ & high-risk (Asian/Black M >40; Asian F >50; +HDV; +FH HCC)		

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

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

Management: **Acute:** unless severe, supportive. **Chronic:** tx if decompensated cirrhosis or if compensated w/ DNA >2k (& consider if <2k) regardless of ALT to  $\downarrow$  risk of decompensation. If no cirrhosis, depends on eAg/ALT/DNA level (see p.1571 [Hepatology 2018;67:1560](#))

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

<b>Screening</b>	<u>HCV Ab</u> . If positive, order RNA Viral Load (PCR). MGH does not have reflex testing. <b>Everyone: universal one-time screening</b> (CDC: <a href="#">MMWR Rec Rep 2020;69:1</a> ; USPSTF: <a href="#">JAMA 2020;323:970</a> ). IVDU or MSM w/ HIV: annual		
<b>Risk Factors</b>	IVDU, blood products before 1992 or from infected individual, MSM, HIV, chronic HD, incarceration, immigration from high prevalence area, birth to HCV infected mother, sex with HCV partner		
<b>Diagnosis</b>	$\oplus$ Ab, $\oplus$ RNA = current infection. $\ominus$ Ab, $\ominus$ RNA = cleared or treated (can still get reinfected)		
<b>Natural History</b>	<b>Acute HCV:</b> 75% subclinical. If sx, develop 2-26w after exposure, last 2-12w. Fulminant rare (<1%) <b>Chronic HCV:</b> 80% $\rightarrow$ chronic; if younger, female sex, genotype 1, IL28B, jaundice, $\uparrow$ ALT more likely to clear spontaneously 20% $\rightarrow$ cirrhosis ( $\uparrow$ risk if male sex, EtOH, obesity, HIV, immunosupp.). HCC risk 1-13%/yr		
<b>Extrahepatic</b>	Mixed cryo., porphyria cutanea tarda, lichen planus, LCV, thyroiditis, Sjogren's, renal dz (e.g., MPGN), NHL		
<b>Treatment</b>	1) Assess advanced fibrosis with <a href="#">FIB-4 score</a> (Age, AST/ALT/plt), U/S Elastography (FibroScan), FibroSure 2) Confirm HIV (-) (if +, initiate ART 1 <sup>st</sup> ), HBsAg (tx if applicable), and Upreg neg. Get CBC, LFTs, GFR baseline 3) Confirm pt <b>eligible for simplified tx</b> . Eligible if: no cirrhosis, no prior HCV tx; NOT eligible if eGFR <30, HIV (+), HBV (+), pregnant, prior liver transplant, known/suspected HCV. Consider GI (if cirrhosis) or ID referral if not eligible 4) If eligible for simplified tx: <b>Start pan-genotypic Rx:</b> Mavyret (Gle/Pib) x8wks or Epclusa (Sof/Vel) x12wks. <b>HCV genotype DOES NOT guide initial therapy.</b> If on coumadin, monitor for subtherapeutic INR. No other monitoring needed. <b>Note: patients DO NOT need to be abstinent from drugs or EtOH.</b> ( <a href="#">AASLD, IDSA 2020</a> ).		
<b>Follow-up</b>	HCV RNA >12 wk after Tx to assess SVR. If advanced fibrosis, need ongoing HCC surveillance (q6mo U/S) and variceal screening (q6mo EGD) EVEN after SVR. If no SVR at 12 wk, consider getting HCV genotype, ID/GI referral		

## HEPATITIS D (Gastro 2019;156:461)

Can have coinfection or superinfection with HBV. **Coinfection** similar to HBV but more severe,  $\uparrow$  risk ALF; often biphasic ALT course. Superinfection most severe, highest risk ALF & chronic infxn (90%)  $\rightarrow$  cirrhosis in 80% in 5-10y. 3x  $\uparrow$  risk HCC vs. HBV mono-infection. Check total anti-HDV once in all HBV infected patients. If suspect false negative Ab, confirm with HDV RNA PCR

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

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

# Gastroenterology

# Alcohol-Related Liver Disease

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

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

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

### Disease spectrum:

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

**Alcohol Liver Evaluation Team (ALiVE, p26299):** eval. inpts w/ ALD or AUD w/o known ALD admitted for non-liver related complaints. Goal earlier identification of subclinical advanced fibrosis and connection to hepatology team for treatment.

## ALCOHOL-RELATED HEPATITIS

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

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

**Dx:** jaundice w/in prior 8w, ongoing heavy EtOH (F >3 std. drinks/d, M >4 std. drinks/d for >6mo). <60d abstinence before onset of jaundice, AST moderate  $\uparrow$  (50-300) w/ AST/ALT >2, Tbil >3 ([Gastro 2016;150:785](#)). Often  $\uparrow$  WBC (<20k,  $\uparrow$  PMNs),  $\uparrow$  INR

- Ddx: other etiologies of acute hepatitis/jaundice (viral, meds/herbs, ischemia, AIH, Budd-Chiari, biliary obstruct.), decompensated cirrhosis; can be superimposed in 10-20% ([Alcohol CER 2004;28:31](#)). Check HAV/HBV/HCV, APAP level, US w/ Doppler,  $\pm$  others. Assess for signs of cirrhosis

- Transjugular Bx: consider if atypical presentation and/or labs (e.g., AST or ALT >300), uncertain alcohol intake hx, confounding factors such as use of hepatotoxic meds w/in last 30 days, possible ischemic insult (e.g., HoTN, cocaine use) or other etiology

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

### Prognostic tools:

Tool	Use	Components	Stratification
<u>Maddrey Discriminant Function (MDF)</u>	Identify who will benefit from steroid therapy (consult hepatology)	PT, PT control (14.5 at MGH), Tbil	$\geq 32$ = severe $\rightarrow$ 1mo. mortality 30-50%; GI consult re: steroids ( <a href="#">Gastro 1978;75:193</a> )
<u>MELD</u>		Tbil, INR, Cr, Na	$>20$ = 3mo. mortality 20%; GI re: steroids ( <a href="#">Hepatology 2005;41:353</a> )
<u>Lille</u>	Perform on day 7 to assess steroid response	Day 0: Age, Albumin, PT, Cr Day 0 & Day 7: Tbil	$\geq 0.45$ : Nonresponse $\rightarrow$ stop steroids $<0.45$ : Response $\rightarrow$ continue steroids ( <a href="#">Hepatology 2007;45:1348</a> )

## TREATMENT OF ALCOHOL-RELATED HEPATITIS

### Corticosteroids: see algorithm

- Prednisolone used as not metabolized by liver (methylpred 32mg is IV alternative): 40mg x 28d w/ 2-4w taper. Lille score at 1 week to assess steroid response.
- No mortality difference at 28d or 90d,  $\uparrow$  infxn ([NEJM 2015;372:1619](#)).

**NAC:** may benefit, no harm (though is large volume load) x5d

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

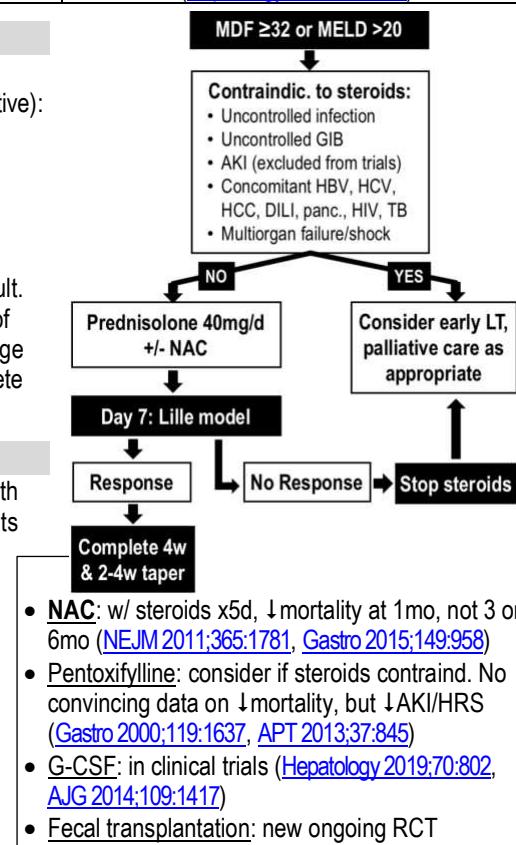
**Nutrition:** ensure adequate kcal, protein; supplement w/ MVI, thiamine, folate, B6, consider Zn. Low kcal in severe AH a/w  $\uparrow$  infxn ([Gastro 2016;150:903](#)). Nutrition consult.

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

## LIVER TRANSPLANTATION:

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

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



# Gastroenterology

## NAFLD

### DEFINITIONS

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

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

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

### EPIDEMIOLOGY ([Gut 2018;67:963](#); [CLD 2016;8:100](#); [J. Hepatol 2022;77:1237](#))

- **Prevalence:** 10-46% in US; >95% in pts w/ obesity undergoing bariatric surg, 33-66% in pts w/ T2DM, and 50% in pts w/ dyslipidemia, ↑ with ↑TC:HDL & TG:HDL (but growing number of lean NAFLD)
- **Risk factors for progression:** insulin resistance, DM, weight gain, HTN, AST/ALT >1 ([JAMA 2015;313:2263](#))
- Progression rates: NAFLD -> cirrhosis: 3% in 15 yrs, compensated cirrhosis to first decompensation: 33% in 4 yrs.

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

- **Presentation:** mild ↑AST, ALT (2-4x ULN with AST:ALT ratio <1) or imaging w/ hepatic steatosis (~70% w/ nl LFTs)
  - No indication for routine screening in high-risk pts due to limited tx options. However, maintain high index of suspicion in those with RFs ([CLD 2021;17.1:23](#))
- **History & Physical:**
  - **DDx:** EtOH use, viral hepatitis, parenteral nutrition, Wilson's disease, malnutrition, hemochromatosis, autoimmune liver disease, α-1 AT deficiency, DILI, celiac disease, thyroid disease
  - Screen for significant EtOH consumption (>21 standard drinks/wk in men, >14 in women)
  - Evaluate for associated comorbidities (T2DM, obesity, central adiposity, dyslipidemia, hypothyroidism, PCOS, OSA)
  - Assess for signs of cirrhosis and insulin resistance (e.g., acanthosis nigricans)
- **Labs:** LFTs, CBC, PT/INR, HCV Ab, lipid panel, HgbA1c, celiac serologies, TSH
  - If elevated LFTs: consider iron studies, α-1AT, ANA, ASMA, SPEP, HBV
    - Ferritin may be ↑ in hemochromatosis and NAFLD, so if iron sat also elevated, consider HFE testing
- **Imaging:** ultrasound to confirm hepatic steatosis, rule out other pathology
  - Non-invasive evaluation for advanced fibrosis (F3-4); assess q3y – if indeterminate, consider 2<sup>nd</sup> test including liver biopsy ([J Hepatol 2015;63:237](#); [Hepatology 2019;70:1521](#); [DDS 2016;61:1356](#); [Hepatology 2018;67:260](#))

Diagnostic	Considerations	Rule Out	Rule In
<a href="#">NAFLD fibrosis score (NFS)</a>	Use to triage pts 35-65yo w/ ↓ risk of advanced fibrosis & monitor progression; quick but not liver-specific	< -1.455 (Sn 90%, Sp 60%)	≥ 0.676 (Sn 67%, Sp 97%)
<a href="#">FIB-4</a>		< 1.3 (Sn 82%, Sp 57%)	> 2.67 (Sn 36%, Sp 93%)
<a href="#">VCTE (FibroScan)</a>	Most used/validated; high user variability, limited in pts w/ severe obesity and ascites	< 9.9 kPa (Sn 83%, Sp 61%)	≥ 11.4 kPa (Sn 75%, Sp 71%)
Ultrasound elastography	Similar to FibroScan, also provides imaging; obtain if need for ultrasound	< 7.1 kPa (Sn 94%, Sp 52%)	> 9.2 kPa (Sn 93%, Sp 81%)

- **Referral to Hepatology:** persistent/significant transaminase elevation, advanced fibrosis, need for liver bx
- **Biopsy:** for pts with F3 or > on non-invasive imaging, at high risk of advanced fibrosis/NASH or competing etiologies of liver disease ([CLD 2021;17.1:23](#))

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

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

# Gastroenterology

# End Stage Liver Disease

## DEFINITIONS

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

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

- **Symptoms:** fatigue/weakness, jaundice, pruritus, nausea, anorexia, abdominal distention, GIB, confusion, muscle cramps
- **Exam:** ↓BP, splenomegaly, caput medusae, ascites (+LR 7.3), jaundice, spider angiomas (+LR 4.3), gynecomastia, testicular atrophy, palmar erythema, asterixis, white nails, Dupuytren's contracture
- **Labs:** ↑TBili, ↑INR, ↓alb, ↓Na, ↓PLT (<160, +LR 6.3), ± ↓Hgb/Hct, ↓WBC; AST, ALT, alk phos, and GGT may be ↑ or normal
- **Diagnostics:** viral hepatitis panel, iron studies, ANA, ASMA, AMA, α1AT, ceruloplasmin
- **Imaging:** RUQUS (with Doppler) to assess echogenicity/morphology of liver, ascites, vascular patency, biliary tree, HCC; US elastography measures liver stiffness by applying mechanical waves and measuring propagation speed through tissue
- **Biopsy:** gold standard but performed less often. Main indications are dx uncertainty or indeterminate fibrosis severity ([NEJM 2017;377:756](#)). Perc. (cannot do through ascites, massive obesity) or transjugular (allows HVPG measurement; pref. if coagulopathy)

## ETIOLOGIES

- **Most common:** non-alcoholic fatty liver disease (NAFLD), alcohol, viral (HCV, HBV). Global epi: NAFLD (54%), HBV (29%), HCV (9%), ALD (2%) ([CLD 2021; 17:365](#)): in the US, ALD a much higher proportion.
- **Genetic disorders:** hemochromatosis, Wilson's, α1AT deficiency, CF, inherited disorders of glucose metabolism
- **Immune-related:** autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), celiac disease
- **Vascular:** post-hepatic portal HTN (right heart failure, Budd-Chiari syndrome, veno-occlusive disease)
- **Other:** infection (i.e., schistosomiasis), meds (e.g., MTX, isoniazid, amiodarone; see [LiverTox](#)), cryptogenic/idiopathic

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

- **MELD Na score:** predicts 90d mortality, used for transplant allocation using Na, Tbili, INR, Cr,
- New MELD 3.0 added: 1) female sex and albumin to correct transplant disparities for women, 2) interaction btwn Tbili & Na and albumin &Cr, 3) upper bound of Cr of 3 ([Gastro 2021;161:1887](#))
- **Child-Pugh class:** assesses cirrhosis severity, predicts 1-2y mortality using Tbili, INR, albumin, presence of ascites encephalopathy
  - Compensated: Child-Pugh Class A; median survival 12y, 1y survival >95%. 5-10% risk of decompensation per year
  - Decompensated: Child-Pugh Class B/C; median survival 2y, 1y survival 40-80%

## COMPLICATIONS OF CIRRHOSIS

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

## VIBES: a systematic approach to the management of cirrhosis

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

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

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

### Infection

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

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

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

### Encephalopathy

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

### Screening/Surgery (transplant)

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

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

- Most common cirrhosis complication (50% in 10 years); development of ascites → 15% 1y mortality, 44% 5y mortality
- Pathophysiology: portal hypertension → ↑NO, prostaglandins → splanchnic vasodilation → ↓intravascular volume → ↑RAAS, ADH → Na & water retention. Severity of hypoNa (from ADH secretion) correlates with worsening survival
- Diagnosis: dx para indicated for ALL patients with cirrhosis and ascites presenting to the hospital. No role for routine use of ppx FFP or platelets ([Hepatology 2021;73:366](#)). EARLY paracentesis (within 24 hours of admission) is associated with reduced inpatient mortality and 30 day readmissions ([AJG 2019; 114:1863](#))
  - Studies: cell count w/ diff, albumin, total protein, GS/Cx ± glucose, LDH, amylase, cytology (malignancy), AFB Cx/ADA (TB)
  - DDx: portal HTN vs. non-portal HTN. SAAG differentiates 97% of time ([Annals 1992;117:215](#))

SAAG ≥1.1 g/dL: related to portal HTN		SAAG <1.1 g/dL: NOT related to portal HTN
Etiology related to portal hypertension	Etiology not related to portal hypertension	
<ul style="list-style-type: none"> <li>Cirrhosis (ascites fluid total protein [AFTP] &lt;2.5)</li> <li>CHF, constrictive pericarditis (AFTP &gt;2.5)</li> <li>Acute hepatitis (including EtOH)</li> <li>Acute liver failure</li> <li>Massive liver metastases</li> <li>Hepatocellular carcinoma</li> <li>Budd-Chiari syndrome (AFTP &gt;2.5)</li> <li>Portal vein thrombosis</li> </ul>	<ul style="list-style-type: none"> <li>Secondary bacterial peritonitis</li> <li>Peritoneal TB (+AFB culture)</li> <li>Peritoneal carcinomatosis (+cytology)</li> <li>Chylous ascites (triglycerides &gt;200)</li> <li>Hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy; AFTP &lt;2.5)</li> <li>Serositis (e.g., SLE)</li> <li>Pancreaticobiliary (i.e., bile leak, can check ascitic fluid bilirubin)</li> </ul>	

- Management of ascites:
  - 1<sup>st</sup> line: <2g Na, ○EtOH, ○NSAIDs, diuretics (see below), avoid ACEi/ARB; fluid restrict 1.5L if Na <125
    - Initiating therapy: 100mg/d spironolactone + 40mg/d furosemide usual starting dose (5:2 ratio)*. Ratio maintains eukalemia & mobilizes fluid faster. Consider spironolactone alone for mild first ascites if output (lasix is added for normokalemia, never add it alone for managing ascites)
    - Ongoing therapy: ↑dose q3-5 days if inadequate diuresis (5:2 ratio, though can adjust PRN if abnormal K). Max doses: 400mg spironolactone and 160mg furosemide. Δ to eplerenone or amiloride if painful gynecomastia w/ spironolactone*
    - Check U<sub>Na</sub>/U<sub>K</sub> ratio if pt gaining weight/requiring LVPs on diuretics; U<sub>Na</sub>/U<sub>K</sub> <1 suggests ineffective diuretic dose or resistance; U<sub>Na</sub>/U<sub>K</sub> >1 suggests >2g Na dietary intake*
  - Weight loss goals: 0.5 kg/d** (TBB -500) if no peripheral edema (AKI risk if too fast); if edema, 1kg/d or -1L. **Avoid IV diuretics** (azotemia risk ↑). Ascites mobilizes fluid slower than other compartments at a rate of 0.5L/day ([Gastro 1986;90:1827](#))
  - Therapeutic LVP**: indicated for tense or refractory ascites or inability to use diuretics; **if >5L removed, give 6-8g albumin for every 1L ascites removed** to reduce risk of post-paracentesis circulatory dysfunction (PPCD)
  - Albumin: long-term administration in pts with cirrhosis and uncomplicated ascites may offer survival benefit ([Lancet 2018;391:2417](#)); in hospitalized pts with acute decompensated cirrhosis, no benefit (and potential harm) targeting albumin > 3 g/dl ([NEJM 2021; 384:808](#)); expensive to administer
- Refractory ascites:
  - Defined as: 1) unresponsive to Na-restriction & high-dose diuretics (or unable to tolerate) or 2) rapid reaccumulation after LVP
  - Management: Discontinue diuretics if urine Na<30mEq/day, discontinue βBs (↑mortality in refractory ascites [[Hepatology 2010;52:1017](#)]), avoid ACEi/ARB (↓renal perfusion), midodrine TID ([J Hepatol 2012;56:348](#)), serial LVPs (usually ~q2w), TIPS as bridge to OLT (poor TIPS candidate if: MELD>18, Child-Pugh class C cirrhosis, heart failure, severe HE).

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

- Must r/o SBP in all inpatients w/ cirrhosis & ascites w/ dx para and blood Cx**; 10-30% hospitalized pts w/ cirrhosis have SBP
- Diagnosis: >250 PMN/L w/ positive GS/Cx (SBP) or negative GS/Cx (CNNA = similar mortality to those w/ +Cx; treat similarly)
  - RBC >50,000/mm<sup>3</sup>, often due to traumatic tap → correct PMN count by subtracting 1 PMN for every 250 RBCs
- Usually monomicrobial; GNR 70% (*E. coli*, *Klebsiella*), GPC 25% (*S. pneumoniae*), anaerobes 5%
- If polymicrobial, consider secondary bacterial peritonitis 2/2 perforation vs. loculated abscesses
- Bowel perf. suggested if ≥2 of the following: TP >1, LDH >ULN, or Glc <50; also CEA >5 & ALP >240 (Runyon's criteria)
- Treatment:
  - 1) Abx: Community acquired: CTX 2g q24h x 5d; IV cipro (400mg q12) if allergy to cephalosporin (unless taking cipro for ppx)
    - Tx should be broader in those with higher risk of MDRO infxn** (recent hospitalization, nosocomial infection, or critically ill pts in the ICU). Pip-Tazo AND Daptomycin (if known VRE in past or evidence of GI colonization) OR Meropenem if known to harbor MDR gram negative organisms or recent Pip-Tazo exposure
  - 2) 25% albumin: 1.5g/kg day 1, then 1.0g/kg on day 3, max 100g (given risk of AKI in SBP); (NB) Recommended for all pts by AASLD, some groups only recommend for those meeting study pop. criteria: Cr >1, BUN >30, or TBili >4 ([NEJM 1999;341:403](#)).
  - Discontinue βBs while hospitalized given increased risk of AKI & HRS once SBP is diagnosed ([Gastro 2014;146:1680](#)).
  - Given increasing failure rates of initial abx tx, AASLD recommends diagnostic para be performed 48 hours after starting abx to assess response. A negative response is defined by a ↓ in PMN count <25% from baseline and should lead to broadening abx and investigating secondary peritonitis w/ CTAP and GI consult. Repeat para may be unnecessary if an organism is isolated, it is susceptible to the abx used, and pt is improving clinically. This has not yet widely come in to practice at MGH.
- Prophylaxis:
  - IV CTX 1g q24 x7 days if GIB
  - All patients w/ prior SBP should receive 2° PPX (after full tx above) w/ PO cipro 500 qd (at MGH) or PO Bactrim DS qd
  - Consider 1° prophylaxis if ascitic TP <1.5 AND impaired renal function (creatinine ≥1.2, BUN ≥25 or serum Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3) ([Hepatology 2021;74\(2\):1014](#))

# Gastroenterology

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

- **Pathophysiology:** ↑NH<sub>3</sub> → neurotoxic effects, abnl neurotransmission, ↑GABA- & BDZ-like neurotransmitters & altered glutaminergic inputs → ↓excitatory transmission. In ALF, acute ↑NH<sub>3</sub> → cerebral edema
- **Diagnosis:** clinical. Serum NH<sub>3</sub> should not be used to screen for HE. ↑NH<sub>3</sub> **does not add diagnostic, staging, or prognostic value** in CLD ([JHM 2017;12:659](#)). Only helpful in ALF (predicts mortality). Trend via **exam findings** (see grades)
- **Asterixis:** “flapping tremor” is **negative myoclonus** w/ loss of postural tone
- **Precipitants:** infection, dehydration/overdiuresis, GIB, ↓K or alkalosis (↑renal NH<sub>3</sub>), constipation, sedatives/BZD/opioids, new HCC, new clot, TIPS
- **Treatment:** ↓GI NH<sub>3</sub> absorption, avoid/correct precipitating factors
  - **Lactulose:** Δs gut microbiome, has laxative effect; 30mL q2h until BM → titrate to 3-4 soft BM/day (PO, NGT, or enema)
  - **Lactulose + rifaximin 550mg BID > lactulose alone** for HE reversal. Add rifaximin if refractory or 2<sup>nd</sup> admission
  - If refractory, consider non-standard therapies: oral branched-chain AAs ([Cochrane Reviews 2017;5](#)), IV L-ornithine L-aspartate ([Hepatology 2018;67:700](#)), probiotics ([Cochrane Rev 2017;2](#)), PEG ([JAMA Int Med 2014;174:1727](#)); FMT may have role ([Hepatology 2017;66:1727](#); [Gastro 2019;156:1921](#))
  - Maintain K >4 to improve ammonia clearance via kidneys ([Mineral electrolyte metab. 1993;19:362](#))

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

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

- **Screening:** esophageal varices most common (50% of patients). Baseline EGD at cirrhosis diagnosis unless liver stiffness <20kPa (by transient elastography) & platelets >150k (very low probability)
  - **Screening intervals:** q1yr if known EV and active liver dz, q2yr if known EV but injury quiescent OR no EV but ongoing liver dz, q3yr if no EV and injury quiescent

1° PPX	EVs identified → <b>ppx if high risk of bleeding:</b> (1) medium/large size (>5mm) (2) small (<5mm) w/ red wale signs (3) decompensated cirrhosis w/ small varices	- <b>Medium/large:</b> non-sel. βB (see below), carvedilol (6.25mg qd x3d → ↑ to 6.25mg BID), OR serial endoscopic variceal ligation (EVL) q2-8w until eradication - <b>Small EV or decompensated cirrhosis:</b> non-selective βB
2° PPX	Episode of variceal bleeding → <b>ppx to prevent recurrence</b> w/ combination of non-selective βB + EVL	- <b>Non-selective βB:</b> nadolol 20-40mg qd or propranolol 20-40mg BID; adjust every 2-3d to goal HR 55-60, SBP>90; max daily dose in patients with without ascites: propranolol 160 320mg/d or nadolol 80 160mg/d - <b>Serial EVL:</b> q1-4w until obliteration; repeat EGD 3-6mo after & then q6-12mo

- **Acute bleeding:** IV access, IVF, pRBC, PPI, octreotide, CTX, EGD. May need intubation for EVL, Blakemore as a bridge (GI), urgent TIPS (IR) if cannot band. **Conservative transfusion:** goal Hgb 7-9 ([NEJM 2013;368:11](#)). See *Upper GI Bleeding*
- **Indications for TIPS:** early “preemptive” TIPS (<72h) in pts with high risk of treatment failure or rebleeding ([NEJM 2010;362:2370](#); [Hepatology 2019;69:282](#)); “rescue” TIPS if uncontrolled bleeding or if recurs despite max medical & endoscopic therapy
- **Gastric varices:** similar mgmt. of acute bleed. Can consider TIPS, BRTO, or endoscopic glue or coil injection. TIPS favored if also EV
- **Stop βB if:** active SBP, refractory ascites, HRS, SBP<90, sepsis; “window hypothesis” (βB have no effect on survival or prevention in early cirrhosis, have survival benefit in middle stages, & ↓ survival in advanced cirrhosis) ([J Hepatol 2014;60:643](#); [Gastro 2014;146:1597](#))

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

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

# Gastroenterology

# End Stage Liver Disease

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

- 2-4% risk per year. May be asx, lead to decompensation, and/or have sx related to mass effect (pain, early satiety, palpable mass)
- Screening indicated in:
  - **Cirrhosis due to any etiology**, except in Child-Pugh Class C pts not on transplant list (due to low survival time)
  - HBV carriers without cirrhosis if: active hepatitis, high viral load ( $>100k$  copies/mL), Asian M  $>40$ , Asian F  $>50$ , African/African-American, or FHx HCC
- Screen with: RUQUS ± AFP q6mo; if U/S inadequate, can use multiphase CT or MRI
  - If nodule  $<1$ cm, repeat US in 3-6mo
  - If nodule  $\geq 1$ cm or AFP  $\geq 20$ ng/mL, obtain multiphase CT or MRI & proceed according to [LI-RADS class](#)
- Staging:
  - [AJCC TNM system](#) (for patients getting surgical resection or transplant)
  - [Barcelona system](#) (medical mgmt): size, # of nodules, LN & portal vein involvement, mets, Child-Pugh score, performance status
- Management:
  - **Curative:** surgical resection (1<sup>st</sup> line if Child-Pugh A & T1-T2 nodule), OLT (if non-resectable but within [Milan criteria](#))
  - **Noncurative:** ablation, chemoembolization (TACE), radioembolization (TARE), radiation, chemo (sorafenib), immunotherapy
  - Within Milan criteria → locoregional tx (LRT) as bridge to OLT. Outside Milan → LRT to downstage to w/in Milan → OLT
  - Not OLT candidate (and non-resectable) → LRT and/or systemic chemotherapy
- Prognosis: survival by Barcelona stage: A (early):  $>5$ y, B (intermediate): 2-5y, C (advanced):  $>1$ y, D (terminal): 3mo

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

- Transudative effusion due to **shift of ascites into pleural space** (due to neg. intrathoracic pressure) via small diaphragmatic defects. Can be seen w/o significant ascites. Usually **unilateral**: R- ( $-75\%$ )  $>$  L-sided ( $\sim 15\%$ )  $>$  bilateral ( $\sim 10\%$ ) ([Medicine 2014;93:135](#))
- Diagnosis: exclude other causes of transudative effusion; can visualize w/ radioisotope injection into ascites if dx unclear
- Treatment: first line: **diuretics, 2g Na restriction**. Therapeutic thora for dyspnea. TIPS or OLT if refractory. **Chest tube not recommended due to infection risk, massive protein and electrolyte depletion, renal failure, and increased mortality 2.5%** ([Chest 2019;155:546](#))
- Spontaneous bacterial empyema: can become infected ( $\sim 15\%$ ) due to translocation of bacteria from abd. cavity.  $\sim 40\%$  occur in absence of SBP ([Hepatology 1996;23:719](#)). Dx:  $>250$  PMNs w/ +Cx or  $>500$  PMNs w/o +Cx. Tx: same as for SBP

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

- Syndrome of **shunting through intrapulmonary vascular dilatations**; mechanism unclear, **possibly due to ↑ circulating NO**
- Presentation: shunting tends to occur at bases → **platypnea** (dyspnea when upright, relieved when supine) & **orthodeoxia** (upright hypoxemia,  $\text{PaO}_2 \downarrow$  by 4 mmHg or  $\geq 5\%$ ), clubbing, cyanosis, diffuse telangiectasias, hypoxemia ( $\text{PaO}_2 <70-80$ )
- Diagnosis: **TTE with late bubbles** (3-6 cardiac cycles after RA vs early bubbles in PFO), **↑A-a gradient  $\geq 15$ mmHg** (or  $\geq 20$ mmHg if age  $>64$ )
  - $^{99m}\text{Tc}$  MAA scan is alternative to TTE but more invasive, less sensitive. May be useful in quantifying shunting if severe hypoxemia and coexisting intrinsic lung disease
  - Pulmonary angiography performed if severe hypoxemia poorly responsive to 100% O<sub>2</sub> & areas amenable to embolization
  - PFTs can be performed to evaluate for intrinsic lung disease;  $\downarrow$ DLCO in HPS
- Management: no effective medical therapies. OLT can significantly improve (and reverse) HPS – MELD exception points given for severe HPS

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

- Rare cause of **group 1 pulmonary hypertension** in setting of portal HTN
- Pathogenesis:  $\downarrow$ blood flow to pulm. arterial bed. Mechanisms unclear but include vasoconstrictors normally cleared by liver (e.g., endothelin-1, estradiol) reaching pulmonary circulation,  $\downarrow$ prostacyclin synthase, endothelial proliferation and PLT aggregation; 3x higher risk in women than men; more common in autoimmune liver disease
- Diagnosis: euvolemic RHC w/ PAH (mPAP  $\geq 20$ mmHg, PCWP  $<15$  mmHg, PVR  $>3$ ) in pt with portal HTN in absence of other etiology
- Risk stratification: mild: mPAP  $<35$ , moderate: mPAP 35-44, severe: mPAP  $\geq 45$
- Management: may benefit from advanced therapies (epoprostenol, bosentan, sildenafil, iloprost); OLT can improve PAH (MELD exception points given for moderate PPH);  $\beta$ -blockers and TIPS may be harmful and should be avoided
- Transplant: increased risk of morbidity/mortality with mPAP  $\geq 35$ ; mPAP  $\geq 50$  is an absolute contraindication to transplant

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

- Chronic cardiac dysfunction in cirrhotic pts w/o known cardiac disease; characterized by 1) impaired cardiac contractility in response to stress, 2) altered diastolic relaxation, 3) electrophysiological abnormalities such as prolonged QTc
- Pathophysiology: myocardial dysfunction 2/2 systemic inflammation; shear stress from portal hypertension → mechanical force on myocardial fibers; other possible mechanisms involve collagen configuration, sodium retention, activation of RAAS,  $\uparrow$  bile acids ([Biochim. Biophys. 2018; 1864:1345](#))
- Prevalence: up to 50% of pts undergoing liver transplantation have signs of cardiac dysfunction
- Diagnosis: echocardiography with dynamic stress testing
- Treatment: same as HF management in pts w/o cirrhosis
- Prognosis: largely subclinical; poses risk with stressors (infection, TIPS, OLT); detailed cardiac assessment prior to interventions

# Gastroenterology

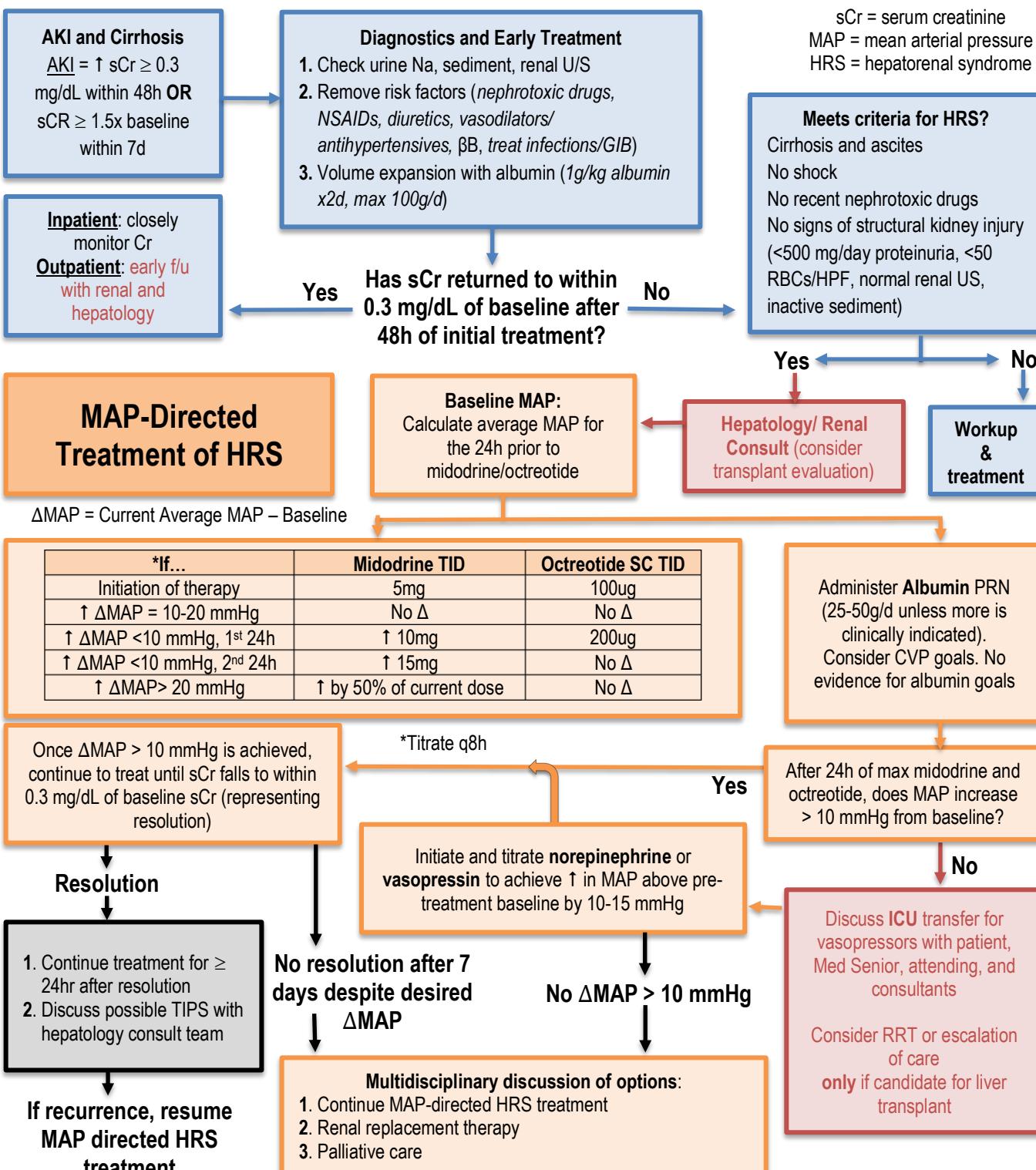
# Hepatorenal Syndrome

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

- Pathophysiology: portal HTN → ↑NO, prostaglandins → splanchnic vasodil. → ↓EABV → ↑RAAS, ADH, SNS → renal vasoconstr.
- Diagnosis: **dx of exclusion**; need: (1) chronic or acute hepatic disease w/ portal HTN, (2) ↑Cr >0.3/48hrs or >50%/7d, (3) absence of shock, (4) no parenchymal disease, (5) no current/recent nephrotoxins, (6) no improvement after 2d cessation of diuretics + **albumin challenge** (1g/kg of 25% albumin x2d, max 100g/d; goal is a volume challenge to rule out pre-renal etiology)
- Type I (AKI-HRS): ↑Cr 2x b/l and >2.5 mg/dL in <2w + multiorgan dysfxn; Type II (CKD-HRS): slower ↓, often have refractory ascites
- Precipitants: infection (SBP > other), GI bleed, fluid shifts after LVP, alcohol-related hepatitis
- Management: see below. Use combination of albumin and 1) octreotide + midodrine, 2) terlipressin (FDA approved, awaiting MGH protocol), or 3) norepinephrine to increase MAP & albumin levels. No diuretics, βB, or other vasodilators or nephrotoxins. Poor prognosis, RRT does not improve survival. Consider only if management ineffective and a candidate for OLT. OLT is definitive treatment. CONFIRM trial: Terlipressin was more effective than placebo in improving renal function but associated with more pulmonary edema (NEJM 2021;384: 818). Relative contraindications to terlipressin: hypoxemia, sCr>5, ACLF grade 3

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

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



# Gastroenterology

# Liver Transplant

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

- Acute liver failure: see *Acute Liver Injury & Failure*
- Cirrhosis with MELD  $\geq 15$  or complication (e.g., ascites, HE, EV bleed, HRS, chronic gastropathy bleed). Survival benefit of OLT  $>$  risk at MELD  $\geq 15$  ([AJT 2005;5:307](#))
- HCC: *first-line option* within Milan criteria but unsuitable for resection ([NEJM 1996;334:693](#); [Hepatology 2018;69:182](#)) assigned score of 22; can be “down-staged” to within Milan with treatment; composite criteria (surrogates of tumor biology such as AFP, treatment response, tumor size, number of nodules) may replace conventional criteria. See *ESLD: HCC*
- Liver-based metabolic disorders w/ systemic manifestations: A1AT deficiency, familial amyloidosis, Wilson’s disease (won’t resolve neurologic issues), hemochromatosis, glycogen storage disease, primary oxaluria
- Decompensated biliary disorders: PBC (intractable pruritus), PSC (recurrent cholangitis and sepsis)
- Systemic complications of chronic liver disease: hepatopulmonary syndrome, portopulmonary HTN
- Conditions qualifying for Exception Points (see below under “Prioritization for Liver Transplant”)

### Milan Criteria:

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

## CONTRAINDICATIONS TO LIVER TRANSPLANT

- Absolute: severe cardiac or pulmonary disease, AIDS, HCC w/ metastatic spread, ongoing EtOH/illicit substance use within 6mo (changing for EtOH in select cases; see *Alcohol-Related Liver Disease*), uncontrolled sepsis, anatomic abnormality that precludes LT, intrahepatic cholangiocarcinoma, extrahepatic malignancy (not meeting criteria for cure), mPAP  $>35$  or PVR  $>400$ , fulminant hepatic failure with sustained ICP  $>50$ mmHg or CPP  $<40$ mmHg, hemangiosarcoma, persistent nonadherence to medical care, lack of adequate social support system
- Relative: BMI  $\geq 40$ , HIV (all center-specific); age  $>70$  is not a contraindication ([Mayo Clinic Proceedings 2009; 84](#))

## PRIORITIZATION FOR LIVER TRANSPLANT

- Prioritized based on MELD Score ([AJT 2015;15:2552](#)) & stratified by blood type
- Certain conditions result in impaired survival but are not directly accounted for in the MELD score  $\rightarrow$  specific disease-related criteria for MELD exceptions that upgrade MELD score w/ subsequent automatic upgrade q6mo
- Standard MELD exceptions: HCC (w/in Milan criteria, AFP  $<1000$ ), hepatopulmonary syndrome (RA PaO<sub>2</sub>  $<60$ mmHg), portopulmonary HTN (mPAP  $<35$ ), familial amyloid polyneuropathy (TTR mutation), primary hyperoxaluria, CF (FEV1  $<40\%$ ), hilar/early-stage cholangiocarcinoma, hepatic artery thrombosis (w/in 14d of LT but not meeting status 1A criteria)
- Can also petition review board for non-standard exceptions (e.g., refractory complications)

## TRANSPLANT EVALUATION PROCESS

- Laboratory testing: order set in EPIC; BMP, Ca, Mg, Phos, LFTs, GGT, CBC w/ diff, PT/PTT, T&S, Fe/TIBC, ferritin, ceruloplasmin, A1AT level, autoimmune (ANA, ASMA, AMA, SPEP), viral hepatitis (HAV IgG, HBsAg, HBsAb, HBcAb [total], HBeAb, HBV DNA, HCV Ab & PCR, HDV Ab), HIV, EBV, CMV, VZV, HSV, RPR, toxo, measles/mumps/rubella titers, IGRA, AFP, PSA, amylase, uric acid, total cholesterol, U/A, UCx
- Additional tests: ABG (on RA), EKG, CXR, U/S w/ Doppler, abdominal CT or MRI (eval for HCC), age-appropriate cancer screening (colonoscopy annual for PSC w/ IBD, mammogram, pap smear), bone density, cardiopulmonary eval as below
- Immunizations: HAV, HBV, pneumococcus, influenza, Tdap, MMR, varicella, COVID19
- Consults: transplant surgery, psychiatry, social work (address psychosocial issues, adequacy of support, financial screening, insurance counseling), nutrition
- Cardiopulmonary eval: TTE w/ bubble  $\pm$  PFTs. Dobutamine stress echo may be indicated (typically if  $>40$  or CAD RFs). Optimal strategy debated – AASLD: stress testing in all candidates; AHA/ACC: if multiple CAD RFs ([JACC 2012;60:434](#)); may consider PCI prior to LT if significant stenosis; if concerned for HPS can get Tc99 shunt scan
- ID eval: eval for LTBI as above and tx pre-LT if able. Coccidiomycosis, strongyloides testing if from endemic area. Dental extractions pre-LT. HIV not a contraindication if immune function adequate. HBV tx pre-LT. HCV can be tx pre- or post-LT (timing depends on if LT imminent, access to HCV+ donor, comorbidities). Transplant ID consult
- Combined kidney transplant: eligible if CKD w/ GFR  $\leq 30$  or ESRD on HD; sustained AKI w/ dialysis  $\geq 6$ wk or GFR  $\leq 25$  for  $\geq 6$ wk; or metabolic disease (e.g. hyperoxaluria) (UNOS/OPTN: [AJT 2016;16:758](#))
- Living Donor Transplant (LDLT): recipients should fulfill same minimal listing criteria as for deceased donor. Recipients of LDLT have reduced wait list mortality compared to potential recipients of deceased donor organs.

# Nephrology

# Acute Kidney Injury

## DEFINING AKI (KDIGO 2012 Guidelines)

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

## Diagnostic Tips

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

## STEPWISE WORKUP

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

**2) Urinalysis (UA):** see *Urinalysis*. If AKI and UA demonstrates unexplained heme and protein, need to consider GN, consider renal c/s.

**3) Urine chemistries:**

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

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

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

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

**7) Monitor Cr, UOP, BP, and electrolytes:** assess response to empiric treatment of presumed cause

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

## DIFFERENTIAL DIAGNOSIS OF AKI

PRE-RENAL (FENa <1% or FEUrea <35%)	INTRINSIC (FENa >2%)	POST-RENAL (Hx and RBUS)			
<b>↓ Absolute volume</b> <ul style="list-style-type: none"> <li>Bleeding</li> <li>GI or skin loss</li> <li>Diuretics</li> <li>Osmotic diuresis</li> <li>Cerebral salt wasting</li> </ul> <b>↓ Effective volume</b> <ul style="list-style-type: none"> <li>CHF/cardiorenal</li> <li>Cirrhosis/hepatorenal</li> <li>Nephrotic syndrome</li> <li>Sepsis/third-spacing</li> </ul> <b>Δ renal dynamics</b> <ul style="list-style-type: none"> <li>NSAIDs/COX-2s</li> <li>ACEi/ARBs</li> <li>Abd compart. syndr.</li> </ul> <b>Relative hypotension</b>	<b>GLOMERULAR</b> <ul style="list-style-type: none"> <li><b>Anti-GBM</b></li> <li><b>ANCA +</b> <ul style="list-style-type: none"> <li>Microscopic polyangiitis</li> <li>Granulomatosis with polyangiitis (GPA)</li> <li>Eosinophilic GPA</li> <li>Drug-induced ANCA</li> </ul> </li> <li><b>Immune complex</b> <ul style="list-style-type: none"> <li><b>Low complement:</b> <ul style="list-style-type: none"> <li>PSGN, SLE, cryo, MPGN, MGRS</li> </ul> </li> <li><b>Normal complement:</b> <ul style="list-style-type: none"> <li>IgA nephropathy/HSP</li> <li>Fibrillary/immunotactoid</li> </ul> </li> </ul> </li> </ul>	<b>TUBULO-INTERSTITIAL</b> <ul style="list-style-type: none"> <li><b>ATN</b> <ul style="list-style-type: none"> <li>Ischemia, sepsis, toxic</li> <li>Contrast, rhabdo, aminoglycosides</li> </ul> </li> <li><b>AIN</b> <ul style="list-style-type: none"> <li>Meds (see below)</li> <li>Infectious: CMV, leptospirosis, legionella</li> <li>Autoimmune/infiltrative: TINU, IgG4 disease, sarcoid, Sjogren</li> </ul> </li> <li><b>Crystals</b> <ul style="list-style-type: none"> <li>TLS, acyclovir, ethylene glycol</li> </ul> </li> <li><b>Proteins</b> <ul style="list-style-type: none"> <li>MM, amyloid, Ig deposition</li> </ul> </li> </ul>	<b>VASCULAR</b> <ul style="list-style-type: none"> <li><b>Microvascular</b> <ul style="list-style-type: none"> <li>TTP/HUS</li> <li>APLAS</li> <li>HELLP/eclampsia</li> <li>Scleroderma</li> <li>Meds (calcineurin inhibitor/CIN, gemcitabine)</li> </ul> </li> <li><b>Macrovascular</b> <ul style="list-style-type: none"> <li>RAS (athero, FMD)</li> <li>Dissection</li> <li>Renal artery/vein thrombosis</li> <li>Polyarteritis nodosa</li> </ul> </li> </ul>	<b>Urinary retention</b> <ul style="list-style-type: none"> <li>BPH, meds, neurogenic</li> <li>Foley dysfunction</li> </ul>	<b>Urinary obstruction (bilateral)</b> <ul style="list-style-type: none"> <li>Stones (single kidney/transplant)</li> <li>Malignancy</li> <li>Retroperitoneal fibrosis (Radiation)</li> <li>-IgG4 disease w/ retroperitoneal fibrosis</li> <li>-Congenital anomalies</li> </ul>

**Common nephrotoxins (not comprehensive):** see [AAFP review \(Am Fam Phy 2008; 78\(6\): 743\)](#) for list common nephrotoxins

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

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

## MANAGEMENT

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

- Optimize hemodynamics, avoid nephrotoxins:** correct volume status - IVF if hypovolemic, diuretics if hypervolemic. Stop NSAIDs/ACEi/ARBs, spironolactone, diuretics (if hypovolemic prerenal). Avoid ↑glucose and contrast. No evidence of benefit for

# Nephrology

# Acute Kidney Injury

- empiric diuretics in oliguria ([JAMA 2002;288:2547](#)). If fluids needed in critically ill adults, generally LR > NS ([NEJM 2018;378:819](#); [NEJM 2018;378:829](#))
2. **Renally dose meds:** use Lexicomp for guidance on dosing by GFR, run patient's med list with pharmacy as additional resource.
  3. **Manage complications:**
    - **HyperK:** check EKG, monitor on telemetry until improved. Can stabilize with calcium gluconate, shift K+ with insulin/dextrose, IVF/Lasix → Remove K from body with patiromer/sodium zirconium cyclosilicate, bowel reg, furosemide. Start low K diet.
    - **HyperPhos:** start phosphorus binder such as sevelamer (start >5.5 mg/dl) vs. calcium acetate depending on calcium level. **Avoid** IV calcium if Ca/Phos product > 70 as can precipitate. Low phos diet.
    - **Metabolic acidosis:** sodium bicarb PO/IV (see Acid-Base Disorders)
    - Bleeding with concern for uremic platelets: DDAVP 0.3 mcg/kg IV, onset 1h, lasts 4-8h
  4. **Indications for HD (AEIOU):** Acidosis (esp. pH <7.0, refractory to bicarb), Electrolytes (refractory hyperK<sup>+</sup>), Intoxication (lithium, ethylene glycol, metformin, salicylates, theophylline), refractory Volume Overload, Uremia (encephalopathy, neuropathy, pericarditis)

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

- **Acidosis:** severe metabolic acidosis, unstable patient, usually in the ICU with pH <7.1. Temporize with bicarb pushes and isotonic bicarb gtt, intubation and hyperventilation if unable to compensate by breathing off CO<sub>2</sub>. May need RRT particularly if other indications. **CVVH does not remove lactic acid and is similar in correction rate to bicarbonate infusion.**
- **Hyperkalemia:** marked hyperkalemia leading to ECG changes or arrhythmia (K >6.5). Temporize with Ca gluconate, furosemide, insulin/D50, albuterol, etc. Note iHD much faster at clearing K than CVVH so would be preferred in a stable pt who can tolerate iHD.
- **Hyponatremia:** call if severely symptomatic (AMS with low GCS, seizures, etc.) requiring bolus hypertonic saline +/- DDAVP clamp.
- **Anuria w/ ADHF:** place Foley, monitor UOP/MvO<sub>2</sub>/signs of shock (LFTs, Cr, Lactate, Cl). Improving cardiac output (volume optimization with diuretics or HD, ± inotropes) will raise GFR.
- **Ingestions:** ethylene glycol, methanol (elevated osmolar gap -> elevated anion gap), metformin with end organ damage (i.e. renal failure, vision loss), see "Indications for HD (AEIOU)" above.
- **RPGN:** when suspected, urgent renal consultation to consider pulse dose steroids ± plasmapheresis. See *Glomerular Disease*.
- **Scleroderma renal crisis:** ACEi (captopril) at maximum tolerated dose (starting at 6.25 or 12.5mg, titrating up q4h). Avoid steroids.

## SPECIFIC MANAGEMENT BY CAUSE

- **Acute interstitial nephritis (AIN):** stop offending agent, consider prednisone 40-60mg qd for 1-2w if biopsy-confirmed or high pre-test probability though not great evidence ([CJASN 2018;13:1851](#))
- **Cardiorenal syndrome (type 1):** ([Nat Rev Neph 2013;9:99](#); [Circ 2019;139:e840](#))
  - **Definition:** 5 phenotypes that impact the heart and kidneys with various causal relationships. Type 1 is HF resulting in AKI.
  - **Pathophysiology:** decreased renal perfusion from ↑ venous congestion ± ↓CO lead to a low trans-renal perfusion pressure. More of a problem with "under-draining" (congestion) than "under-filling" (perfusion)
  - **Treatment:** relief of renal venous congestion. Trend Cr against TBB and daily weights to test hypothesis, expect a lag effect
    - Loop diuretics are first line for type 1 ± addition of thiazide (metolazone/chlorothiazide), see *Advanced Diuresis*
    - No benefit of low dose dopamine or nesiritide to improve forward flow ([JAMA 2013;310:2533](#))
  - Ultrafiltration showed similar outcomes re: weight loss and CHF sx, but worsened renal function compared to pharmacologic therapy with loop/thiazide diuretics ([NEJM 2012;367:2296](#))
- **Contrast-Induced AKI (CI-AKI, formerly "contrast-induced nephropathy")** ([Nat Rev Nephrol 2017;13:169](#))
  - **Definition:** ↑Cr ≥0.5 or 25% within 48-72h of contrast without other causes
  - **Clinical syndrome:** starts 24-48h, peaks 3-5d, resolves 10d; usually non-oliguric. Recent studies: unclear risk of AKI following contrast, likely lower than previously estimated ([Ann Em Med 2017;69:577](#)). In recent regression discontinuity analysis, no difference in kidney function at 6 months after contrast administration for CTPE in ED setting ([JAMA Intern Med 2021;181:767](#))
  - **Pathophysiology:** vasospasm vs acute tubular injury due to osmotic injury.
  - **Risk factors:** higher contrast load, hyperosmolar contrast, intra-arterial injection (cardiac cath), DM, proteinuria, concomitant AKI
  - **Prophylaxis:** for high-risk pts (GFR <30 or 30-45 + DM) receiving arterial/IV contrast, consider IV NS per MGH protocol (see *Contrast*). If treating volume overload, hold diuretics day of contrast with no additional IVF. No added benefit for IV bicarb or NAC ([NEJM 2018;378:603](#)) or pre/post/intra HD for anuric patient ([Am J Med 2012;125:66](#)).
  - Rule of thumb: balance risk as detailed above with potential harm of delayed diagnosis that guides treatment on individual basis.
- **Crystalline nephropathy:** discontinue drug; fomepizole/HD if ethylene glycol toxicity; rasburicase/HD if TLS (see *Tumor Lysis Syndrome*); IVF and diuresis if Acyclovir toxicity (goal UOP >150 cc/h)
- **HRS:** see *Hepatorenal Syndrome*
- **Myeloma kidney (Cast Nephropathy):**
  - **Dx:** TP/Cr, SPEP/UPEP, SFLC, kidney bx if dx unclear
  - **Tx:** IV hydration to target UOP >3L/d to minimize precipitation (volume overload can be treated with diuretics), chemotherapy to decrease production of SFLC per oncology. Unclear benefit of plasmapheresis given rebound of light chain production.
- **Post-renal:** Foley, α-antagonists; 5α-reductase inhibitor (effect not immediate); urology/IR if percutaneous nephrostomy tube needed
- **Rhabdomyolysis:** AKI unlikely unless CK >2k-5k; aggressive IVF for UOP >250cc/h with NS. Consider isotonic sodium bicarb if marked acidosis ([NEJM 2009;361:62](#)) and no hypocalcemia, but no convincing evidence that HCO<sub>3</sub> is superior to NS. Monitor for electrolyte abnormalities: hyperK, hypoCa. Continue aggressive IVF until CK <5000; if overloaded, continue IVF with close monitoring and add diuresis

# Nephrology

# Glomerular Disease

## NEPHROTIC SYNDROME (NS)

**Etiology:** ↓ podocyte integrity (foot process effacement) → **Triad:** proteinuria >3.5g/day (albuminuria), sAlb <3.0g/dL, edema

**S/Sx & sequelae:** constitutional sx (fatigue, anorexia), HLD + premature atherosclerosis, foamy urine, hypercoagulability (10-40% VTE risk 2/2 loss of antithrombin & plasminogen), Vit D deficiency (loss of binding protein), infectious risk (↓ IgG/opsonins), protein malnutrition

**Workup:** Basic: UA/sed, HgbA1c (most proteinuria secondary to DM), spot urine labs [P/C ratio, total protein, microalbumin, & creatinine (assess for tubular protein)], consider 24h urine protein if P/C ratio abnl

Advanced: ANA, anti-dsDNA, anti-PLA2R, SPEP, SFLC, HBV, HCV, HIV, C3/C4, nephrology c/s for possible renal biopsy

**Labs:** 3+ protein (dip detects albumin), 24h UPr >3.5 g/d or spot urine P/C ratio > 4.9, fatty casts or oval fat bodies = epithelial cells w/ engulfed lipid (Maltese crosses under polarizer), Cr normal or ↑, may have mild nephritic features (hematuria, HTN)

**Treatment:** edema: diuretics + low Na diet; HLD: statin; VTE risk: consider ppx AC; ACE/ARB (↓ glom pressure). May consider steroids.

Disease	Associations	Biopsy Findings
Diabetes	T1DM and T2DM, retinopathy/neuropathy. <b>Most common cause of NS</b>	Nodular glomerulosclerosis
FSGS	1°: toxin → podocyte effacement in patients with APOL1 polymorphism 2°: viral (HIV, parvo, EBV, CMV), drugs (NSAIDs, pamidronate, INF, rapamycin, heroin), adaptive (2/2 nephrectomy, CKD, obesity, reflux, HTN), chronic hypoxemia (OSA, sickle cell)	Mesangial collapse & sclerosis. Collapsing variant (a/w HIV & SLE) rapidly progresses to ESRD
Membranous	1°: Abs to podocyte PLA2R (75%) ( <a href="#">NEJM 2009;361:11</a> ) or THSD7A 2°: SLE, HBV, syphilis, drugs (NSAIDs, penicillamine, gold), solid tumors	Thick BM w/dense subepithelial deposits & no cellular infiltrates
Minimal Change	Idiopathic, a/w NSAIDs, lymphoma (HL most commonly), children>adults	Podocyte effacement (EM)
MPGN	Mixed nephritic/nephrotic. <u>Immune complex mediated:</u> chronic infxn (HBV, HCV+cryos), SLE, lymphoma, MM. <u>Complement-mediated:</u> dense deposit disease or C3/C4-glomerulonephritis	Thick BM, mesangial proliferation, subendothelial ± subepithelial deposits
Amyloidosis	AL (myeloma) and AA (systemic inflammation, e.g. RA, IBD)	Diffuse amorphous hyaline glomerular deposits; +Congo red. IF κ/λ, LC if AL

## GLOMERULONEPHRITIS (GN)

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

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

- 1) Asymptomatic urinary abnormalities: subnephrotic proteinuria +/- microscopic hematuria; no renal impairment, edema, or HTN
- 2) Rapidly progressive GN (RPGN): ↓ GFR >50% in ~3 mo, glomerular crescents on bx, 0.5-2.5 g/d proteinuria, dysmorphic RBC. Consult Renal ASAP, consider methylpred (0.5-1g IV QD x3d). Per etiology/biopsy: cyclophosphamide (CYC) or mycophenolate ± rituximab (RTX). For **RPGN from ANCA vasculitis:** induction w/ steroids + RTX or CYC ([NEJM 2010;363:221](#)); maintenance w/ RTX > AZA ([NEJM 2014;371:1771](#)). Induction w/o PLEX and w/ ↓-dose steroids appears non-inferior and ↓ infx risk ([NEJM 2020;382:622](#))
- 3) Chronic GN: persistent proteinuria, +/- hematuria, slow progression

**Workup:** See above under NS, also consider ESR/CRP, anti-GBM, RF/cryos, anti-DNAse, ASO

Disease	Associations	Labs
<b>Renal-Limited Immune Complex Deposition</b>		
Post-strep GN	~1-2w post-pharyngitis, 3-6w post-cellulitis	⊕ASO, ↓C3
Fibrillary GN	Idiopathic; cancer; autoimm (Crohn's, SLE, Graves', ITP)	Normal C3 (bx IF +DNAJB9)
IgA nephropathy	1°: ~1-2d post-viral URI or GI infx. 2°: liver dx, Celiac, HIV	+/- ↑ IgA, nl C3
<b>Systemic Immune Complex Deposition</b>		
SLE (Classes 3, 4)	Photosensitivity, malar rash, sicca, pleuritis, cytopenias, arthralgias	⊕ANA, ⊕anti-dsDNA, ⊕anti-Sm, ↓C3, ↓C4
Cryoglobulinemia (Type 2)	HCV > HBV, ESLD, MM	⊕Cryos (↑↑RF), ⊕HCV, ↓C3, ↓C4
Endocarditis	Fever, valve dx, emboli	⊕BCx, ↓C3, ANCA (⊕can be induced)
IgA Vasculitis (HSP)	Post-URI, malignancy, nephropathy, purpura, arthritis, GIB	⊕IgA, nl C3 (IgA does not fix complement)
<b>Pauci-Immune Glomerulonephritis</b>		
Granulomatosis with polyangiitis (GPA)	Multi-system, granulomatous sinusitis/otitis, other ENT sx, pulmonary sx (DAH, granuloma), arthritis, palpable purpura, RPGN	c-ANCA/anti-PR3 (80%), p-ANCA/anti-MPO (10%)
Eosinophilic granulomatosis w/ polyangiitis (EGPA)	Multi-system, new-onset asthma, allergic rhinitis/sinusitis, mononeuritis multiplex	p-ANCA/anti-MPO (50%), eos ≥1500
Microscopic polyangiitis (MPA)	Multi-system, non-granulomatous	Anti-MPO (60-70%)
Drug-induced vasculitis	Hydralazine, PTU, allopurinol, adulterated cocaine (levamisole → ear necrosis)	↑-titer p-ANCA (95% drug-ind; MPO, HNE); c-ANCA (50%; anti-histone)
<b>GBM Diseases</b>		
Anti-GBM/Goodpasture	RPGN (crescentic), DAH (Goodpasture)	Linear IgG along BM, ⊕anti-GBM IgG
Alport	Mutant COL4A (renal, hearing, eye dx), familial	EM w/ split GBM, ⊕COL4A3-5 testing

# Nephrology

# Chronic Kidney Disease

## OVERVIEW

- CKD definition: GFR <60mL/min OR presence of kidney damage (typically albuminuria  $\geq 30\text{mg/d}$ ) for  $\geq 3\text{mo}$  (JAMA 2015;313:837).
- Estimating GFR: 2021 CKD-EPI (NEJM 2021;385:1737) (race omitted). Race in eGFR calc can lead to undertreatment and transplant for Black pts (NEJM 2020;383:874).
- Role for Cystatin C: protein excreted by cells, less affected than Cr by gender, age, body size, nutritional status (Expert Rev Mol Diagn. 2020; 20(10): 1019.)
- Etiology: **DM (47%), HTN (28%), GN (7%),** cystic kidney (3%), other (15%) (USRDS 2018)
- Epidemiology: 15% US adults; ESRD prevalence 4-fold higher in Black pts than White pts (USRDS 2021). 13% of Black individuals have a high-risk **apolipoprotein-1 (Apol1)** genotype, which confers  $\uparrow$ CKD risk.
- Disease Monitoring: G1-G3a: risk factor reduction. G3a-G3b: evaluate & treat complications. G4 (or A3): nephrology referral, prep for RRT/transplant. G5: RRT (if indicated), transplant eval.

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

Persistent albuminuria categories Description and range			
A1	A2	A3	
Normal to mildly increased	Moderately increased	Severely increased	
<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol	
G1	Normal or high	$\geq 90$	55.6 1.9 0.4 57.9
G2	Mildly decreased	60-89	32.9 2.2 0.3 35.4
G3a	Mildly to moderately decreased	45-59	3.6 0.8 0.2 4.6
G3b	Moderately to severely decreased	30-44	1.0 0.4 0.2 1.6
G4	Severely decreased	15-29	0.2 0.1 0.1 0.4
G5	Kidney failure	<15	0.0 0.0 0.1 0.1
			93.2 5.4 1.3 100.0

## MANAGEMENT

- BP control: goal <120/80 ([KDIGO 2021 Guideline](#)). Mortality benefit w/ intensive BP mgmt (SBP <120 mmHg) (NEJM 2021;384(20)).
  - If proteinuria: ACEi; if edema: loop diuretic if eGFR <30, thiazide if >30 (emerging evidence for considering chlorothalidone in advanced CKD in select pts) ([NEJM 2021;385:2507](#)); if resistant HTN or HFpEF: spironolactone.
- Proteinuria: Albuminuria independently predicts mortality and CKD progression. Goal <300mg/d with RAAS blockade (ACEi or ARB) ([NEJM 2013;369:1892](#)). If albuminuria >300 mg/d or proteinuria >500 mg/d, add SGLT2-i if eGFR>20,  $\downarrow$  CKD progression (NEJM 2022;388:117)
- DM: goal HgbA1c <7%. SGLT2i (if eGFR >20) indicated in pts with T2DM and DKD ([BMJ 2021;372:4573](#)), other agents include metformin (eGFR >45), GLP-1r agonists (eGFR >30). Insulin safe at any eGFR, though may have to be dose adjusted as insulin clearance  $\downarrow$  w/  $\downarrow$ GFR.  $\downarrow$ Rate of CKD progression with SGLT2i ([NEJM 2019;380:2295](#)) & GLP-1r agonists ([NEJM 2017;377:839](#)).
- CVD: risk 2-4x general population. Statin if >50 y/o and no ESRD/tx ([Kidney Int 2014;85:1303](#)). SGLT2 inhibitors  $\downarrow$ CKD progression/mortality/CVD outcomes. ([NEJM 2020;383:1436](#)). No benefit seen in initial invasive vs. conservative strategy in stable CAD + advanced CKD, and mod/sev ischemia ([NEJM 2020;382:1608](#)).
- Avoid nephrotoxins (see list), renally dose meds (Lexicomp has renal dosing for each med), treat HCV ([Kidney Int 2020;97:193](#)).
- Nutrition: nephrocaps (B-complex + C), Na <2 g/d, K/phos/FR as needed (don't over-restrict). Mixed evidence for  $\downarrow$ protein.
- Monitoring: q4-12mo Cr & electrolytes, PTH, CBC, Fe studies. Annual UAlb/Cr & UProt/Cr ratios, 25-vitD. Renal U/S at time of dx.
- Nephrology referral: GFR  $\downarrow$  30, sudden  $\downarrow$  in GFR, severe proteinuria (Alb:Cr >300), UA w/ +blood/protein with  $\downarrow$ GFR, resistant HTN
- Prognosis: based on 1) cause of CKD, 2) GFR category, 3) albuminuria, 4) other risks  $\rightarrow$  [Tangri risk score](#) (JAMA 2016;315:164)

## COMPLICATIONS

Hyperparathyroidism					
Type	Ca	PO <sub>4</sub>	PTH	VitD	Pathophysiology
1° HyperPTH	↑	↓	↑	nl	Excess PTH production by parathyroid gland
2° HyperPTH (2/2 ↓VitD)	↓	↓	↑	↓	Decreased Ca absorption stimulates PTH secretion
2° HyperPTH (2/2 CKD)	nl/↓	↑	↑	nl/ ↓	↓ PO <sub>4</sub> excretion increases PTH secretion
3° HyperPTH	↑	↑	↑↑	nl/ ↓	Longstanding 2° hyperPTH leads to PTH gland hyperplasia

- Mineral and bone disorder: check Ca, PO<sub>4</sub>, ALP, 25-OH vit D (1,25-OH vit D level will fluctuate) ([Annals 2018;168:422](#)).
  - PTH rising or persistently above goal (2-9x ULN, based on CKD stage): restrict dietary phos, non-Ca phos binders (sevelamer preferred, w/ meals & snacks) ([CJASN 2016;11:232](#)), calcium/Vit D supplements not recommended unless on HD
  - Severe/refractory PTH > 1000: calcitriol vs calcimimetic vs parathyroidectomy if non-responsive to medical therapy
- Anemia: Hgb < 13 (M), < 12 (F). **Screening:** annual if eGFR >45, q6m if <45, q3-6m if anemic. Goal Hb 10-11.5 ([Kidney Int 2012](#))
  - Iron repletion (PO or IV) when Tsat <30% and ferritin <500ng/mL. Check q3m if on ESA. IV > PO ([Cochrane 2019;2:7857](#))
  - If Fe replete and Hgb <10, consider erythropoiesis stimulating agents (ESA) consider ESA, which  $\downarrow$  transfusions, Fe overload, Ab formation. Contraindicated in cancer, SBP>160, HF, stroke. Hb >13 with ESA increases risk of CVA ([NEJM 2009;361:2019](#))
- Metabolic acidosis: NaHCO<sub>3</sub> starting at 650 mg 2-3x/day titrating up to 1300 mg up to TID for goal HCO<sub>3</sub> in normal range (23-29 mEq/L; avoid >29 mEq/L bc  $\uparrow$  mortality). Slows progression of CKD, improves bone health ([CJASN 2019;14:1011](#))
- Uremic bleeding: no need to treat unless unable to achieve hemostasis or pre-procedure; can use DDAVP
- Preparation for HD access: avoid BP measurements and venipuncture in non-dominant arm, avoid subclavian/PICC lines due to risk of central stenosis (precludes future AVF placement)  $\rightarrow$  prefer IR small bore tunneled IJ. Prefer L IJ CVC in case need for HD.

## OTHER RESOURCES

Podcasts:

- CurbSiders:** [Chronic Kidney Disease Pearls](#), [CKD: Prescribing Do's and Don'ts](#), [Iron Deficiency and Anemia of CKD](#), [Pain Meds in CKD](#)
- MedScape In Discussion:** [Primary Care Screening and Treatment of Chronic Kidney Disease](#)

# Nephrology

# Dialysis & Transplant

## OVERVIEW (NEJM 2012;367:2505)

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

## IMPORTANT CONSIDERATIONS

- Timing: controversial, most recent studies suggest no benefit to early RRT
  - ELAIN ([JAMA 2016;315:2190](#)): early RRT → ↓ duration RRT, LOS/mortality
  - IDEAL-ICU ([NEJM 2018;379:1431](#)): no Δmortality w/ early RRT (pt w/ sepsis, AKI)
  - STAR-T-AKI ([NEJM 2020;383:240](#)): early RRT did not reduce 90d mortality vs. standard RRT (clinical indication).

## Emergent Indications for RRT (AEIOU)

- Acidosis: pH <7.1, refractory to bicarb
- Electrolytes: refractory/rapidly rising K
- Ingestions: dialyzable toxins (eg: Li, ASA, methanol, ethylene glycol, metformin)
- Overload: diuretic-refractory volume
- Uremia: encephalopathy, pericarditis, coagulopathy with uremic bleeding

## ACCESS FOR HEMODIALYSIS

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

Types of access for HD	Duration of use	Benefits	Risks/Downsides
Non-tunneled double lumen central line, femoral or R IJ	Days-weeks	Can be placed and used immediately.	Infection. Cannot use outside hospital. ONLY to be used for RRT. Can clot or kink.
Tunneled central line	Weeks-mos, can be yrs	Can be placed by IR within hrs	Infection, ONLY to be used for RRT.
AV fistula (pt A-V) or AV graft (synthetic graft connects A-V)	Yrs	Lowest risk infection and complication risk once mature.	Needs ~3-6 mos. Failure risk ~40% for AVF, ~20% for AVG. Risk of stenosis/thrombosis.

## INTERMITTENT HEMODIALYSIS (IHD) ([NEJM 2010;363:1833](#)); consider in critically ill pts ([Lancet 2006;368:379](#))

- Mechanism: Cr, urea, K<sup>+</sup> move from blood to dialysate; Ca<sup>2+</sup> and HCO<sub>3</sub><sup>-</sup> move from dialysate to blood (down concentration gradients). Volume removal occurs via UF. Blood flow rate ~200-500mL/min. Usually three 4h sessions/wk.
- Intradialytic medications: erythropoietin, iron, vitamin D analogues, antibiotics, heparin (to prevent clotting of HD circuit)
- Complications: HoTN, arrhythmia/cardiac events, cramps, disequilibrium syndrome, dialyzer reaction, HIT, hemolysis, EtOH w/d

## PERITONEAL DIALYSIS (PD) ([NEJM 2021;385:1786](#)) call PD RN on call 24/7 for any inpatient on PD

- Mechanism: infusion of fluid rich in osmotic agent (e.g. dextrose) → use peritoneum as membrane → solute removal via diffusion
- Benefits: preserves residual GFR longer than IHD, better middle molecule clearance, can be done at home.
- Modalities: (1) continuous ambulatory PD (**CAPD**): manual exchanges occurring both day and night, all inpatients receive CAPD; (2) Automated PD (**APD**): multiple automated exchanges overnight with long dwell during day
- Complications: **peritonitis** (dx in PD if ascitic fluid WBC count as low as 100/ $\mu$ L if >50% neutrophils) → catheter removal if fails to resolve w/in >5d of tx w/ intraperitoneal abx or if fungal infxn; encapsulating peritoneal sclerosis; hernia; pleural effusion; leaking.

## CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

- Principles: continuous slow clearance, replacement fluid must be added back to restore volume, A/B balance + electrolytes. Less effective in toxin removal/volume overload compared w/ IHD. Not ideal for hyperK/toxins. Blood flow rate ~100-200mL/min.
  - CVVH: continuous veno-venous HF, removes solute via convection; **AVVH**: intermediate CVVH circuit setting w/ ↑ flow rates/12h
  - CVVHD**: continuous veno-venous HD, removes solute by diffusion; **CVVHDF**: combines convection + diffusion to remove solute
- Indications: (1) **HD instability/inability to tolerate iHD** (2) persistent acidemia despite iHD (3) risk of cerebral edema w/ IHD.
- Volume management: run negative, even, or slightly positive. Replacement fluid w/ dextrose, bicarb, lactate, acetate or citrate.
- Anticoagulation: used to ↓ risk of circuit clotting, use heparin OR citrate, citrate achieves regional AC by Ca chelation → follow iCa levels (will see ↑ total Ca but ↓ iCa), metabolized in liver → if ↑ AG with met alk=possible citrate toxicity (avoid in liver failure).
- Complications: HoTN, arrhythmias, hypothermia, ↓ iCa/K/PO<sub>4</sub>, bleeding, thrombocytopenia (mechanical destruction in circuit), HIT
- Drug dosing: drugs can bind to circuit resulting in ↑ V<sub>D</sub> → work with pharmacy to re-dose all meds based on flow rate

## RENAL TRANSPLANT

- Basics: mortality & QOL benefit, more cost-effective than HD; LDKT > DDKT; racial disparities exist in transplant access
- Listing: refer EARLY (GFR <30), pts can be listed when GFR <20; pt & graft survival are improved if transplant occurs PRIOR to HD
- Contraindications: short life expectancy, active malignancy, SUD, nonadherence; age/HIV/psych comorbidities NOT contraindications
- Allograft dysfunction: **delayed graft function**: <1w (prerenal, ATN, thrombus, obstruction), **early**: 1-12w (prerenal, CNI tox, infxn [BK virus, CMV], acute rejection), **late acute**: >3mo (prerenal, CNI tox, noncompliance), **late chronic**: yrs (HTN, CNI tox, BK virus, recurrence of original renal pathology, chronic allograft nephropathy)

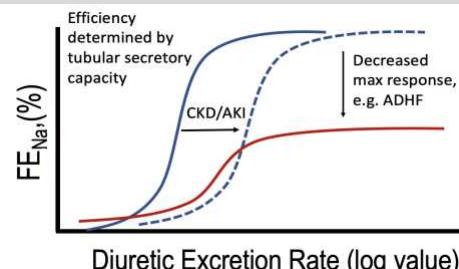
IMMUNOSUPPRESSION			
Class	Examples	Mechanism of Action	Adverse Events
Calcineurin inhibitor (CNI)	Cyclosporine Tacrolimus (FK506)	Inhibits calcineurin-mediated activation of NFAT → blocks T-cell cytokine production	Nephrotoxicity (long-term fibrosis), HTN, tremor, insomnia, hirsutism (CsA only)
mTOR inhibitor	Sirolimus (Rapamycin)	Inhibits mTOR → blocks IL-2 production	Pulm edema, poor healing, ↑TG, oral ulcer
Antimetabolite	Mycophenolate Azathioprine	Inhibits de-novo purine synthesis Purine analogue	N/V/D, cytopenias BM suppression, N/V/D, hepatitis

# Nephrology

# Advanced Diuresis

## GENERAL PRINCIPLES

- Obtain daily standing weights,  $\text{Na}^+$  restriction 2g/day, consider fluid restriction
- Loop diuretics have a sigmoidal dose-response curve (i.e. diuretic threshold effect), so double dose until adequate response is achieved; natriuresis determined by total time above the natriuretic threshold.
- Transient ↑ in serum Cr are common in diuresis, can be tolerated if effective decongestion. No assoc. between ↓ renal function during diuresis and biomarkers of tubular injury; ↑ survival in HF ([Circ 2018;137:2016](#))
- Tailor diuresis to intravascular volume in CKD. Neurohormonal modulation in over-diuresis can negatively impact already tenuous patients ([Crit Care 2015;19](#))



	Loop Diuretics (Loop of Henle)			Thiazide Diuretics (DCT)
	Furosemide	Torsemide	Bumetanide	Chlorthalidone, HCTZ, metolazone, chlorothiazide (IV/PO)
Mechanism of Action	Inhibit Na-K-2Cl transporter in ascending limb of loop of Henle to ↓Na reabsorption and "break" medullary concentrating gradient (unable to concentrate urine)			Inhibit NaCl channel in DCT to ↓Na reabsorption and prevent urinary dilution (avoid if SIADH); no effect on medullary concentrating gradient
PO Bioavailability	20-50%	80-90%	80%	Variable
Duration of action	~6 hours	6-8 hours	4-6 hours	HCTZ: 6-12h; chlorthalidone: 24-48h; metolazone: 24h; chlorothiazide (IV): 2h
Dosing considerations	1mg Bumetanide IV/PO = 20mg Torsemide PO = 20mg Furosemide IV = 40mg Furosemide PO. Consider dosing BID-QID to avoid anti-natriuresis seen in QD dosing			Administer 30 min before loop diuretic to "disable" Na reabsorption in DCT ( <b>sequential nephron blockade</b> ). Metolazone 2.5-10mg PO > chlorothiazide 500-1000mg IV (↑half-life, \$\$\$)
Side effects	↓K, ↓Mg, ↓Ca, ↑urate, ↑HCO <sub>3</sub> , ototox, allergy			↓Na, ↓K, ↓Mg, ↑Ca, ↑urate, ↑glucose, HLD, pancreatitis, MBD

## OTHER DIURETICS

- Carbonic anhydrase inhibitors:** PCT blockade. Acetazolamide 250-1000mg PO QD, can do TID x1d vs QD x3d for metabolic alkalosis limiting diuresis. (↑HCO<sub>3</sub>, pH > 7.5). ADVOR ([NEJM 2022;387:1185](#)) better decongestion in ADHF. Be careful in COPD, acidosis, hypoglycemia (SGLT2i), and sulfa allergies.
- SGLT2-i:** Increasing role in ADHF → [EMPA-HF](#) (Circ 2022; 146(4): 289). Addition of early empagliflozin daily to standard medical treatment of acute decompensated heart failure resulted in a 25% increase in UOP and lower NTproBNP at d/c.
- Aldosterone antagonists:** spironolactone 25-200mg QD-BID/eplerenone 25-50mg QD-BID. Role in ADHF, cirrhosis. Causes ↑K, gynecomastia (10% pts, only spironolactone); eplerenone has ↑aldosterone receptor selectivity but more \$.

## DISEASE-SPECIFIC CONSIDERATIONS

Condition	Mechanism	Treatment
CKD/AKI	• ↓GFR → ↓delivery of diuretic to nephron → <b>higher</b> doses needed for effective diuresis • Organic acids accumulate and compete with diuretics	• High-dose loop ± thiazide augmentation ( <i>prefer Furosemide in CKD given renal excretion, longer ½ life</i> )
Chronic Diuretic Use	• "Braking phenomenon" of compensatory DCT hypertrophy leads to ↑ distal Na reabsorption	• Add metolazone or chlorothiazide
CHF	• GI edema leads to ↓ absorption of PO furosemide (consider torsemide/bumex given ↑ bioavailability) • ↓High sympathetic tone → ↑RAAS, Na reabsorption	• DOSE ( <a href="#">NEJM 2011;364:797</a> ): in ADHF, no Δ sx or renal function for pts receiving low vs high dose diuretics and drip vs bolus dosing • No benefit of RRT over stepwise diuresis • Consider sequential nephron blockade
↓ Albumin, nephrotic syndrome	• Loop diuretic (needs to bind to albumin) leaks out of vasculature (↑V <sub>D</sub> ) resulting in ↓ delivery to nephron	• Consider bumetanide (lower albumin-binding need) • No evidence for benefit of albumin + loop diuretic • Usually need ↑ doses diuretics
Cirrhosis	• Decreased delivery to nephron in setting of ↓ albumin • Splanchnic vasodilation → ↓EABV → renal hypoperfusion • SNS and RAAS → ↑Na reabsorption	• Avoid IV diuretics unless respiratory distress or significant peripheral edema • See ESLD: Ascites

## STEPWISE APPROACH IN HEART FAILURE ([NEJM 2017;377:1964](#))

- IV loop diuretic. Starting dose: 2.5x home dose as IV furosemide (CHF) (e.g. if home 80mg PO, give ~80-120mg IV) or Cr×40 as IV furosemide (e.g. if Cr 3, use lasix 120mg IV); if unknown, start with furosemide 40mg IV.
- Reassess in 1-2 hrs and double dose Q1H until response achieved. Adequate dose causes brisk diuresis (Goal >100-150 cc/hr). Consider loop diuretic gtt (bolus when initiating gtt and re-bolus every time gtt increased), though evidence suggests not more effective in ADHF ([NEJM 2011;364:797](#)):
- If refractory edema, can add a thiazide to achieve sequential nephron blockade. Consider SGLT-I addition.
- Nephrology consult for consideration of short term UF/RRT as a bridge to advanced therapies

# Nephrology

# Acid-Base Disorders

## OVERVIEW

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

## STEP-WISE APPROACH (NEJM 1998;338:26; NEJM 2014;371:1434)

- Is there **acidemia** (pH <7.36) or **alkalemia** (pH >7.44)?
- Is 1° disorder **metabolic** (parallels pH Δ) or **resp** (opposite pH Δ)?
- Is pt compensating? (respiratory takes min-hrs, renal 3-5d)
- Is there an **anion gap**? Calculate regardless of pH or HCO<sub>3</sub>.  
**AG = Na - (Cl + HCO<sub>3</sub>)** = unmeasured anions – unmeasured cations  
Correct AG for albumin: AG<sub>c</sub> = AG + 2.5(4 - albumin)  
Negative AG: ↑↑Na, lipids (interfere with chloride), bromide intox
- If there is ↑AG metabolic acidosis (AGMA), calculate “**delta-gap**Delta gap = (Albumin corrected AG-12) + HCO<sub>3</sub>**. If <18 additional NAGMA, 18-30 no additional disorder, >30 additional met alk**
- Consider Osm gap = [2(Na + K) + Urea/2.8 + glucose/18 + EtOH/4.6 – serum Osm] to screen for exogenous osmoles (e.g. toxic alcohols), also seen in pseudohyponatremia

## Expected Compensation (JASN 2010;21:920)

Metabolic acidosis: 2-24h

Winter's formula: pCO<sub>2</sub> = (1.5 x HCO<sub>3</sub>) + 8 ± 2

Metabolic alkalosis: start 30min, complete 24h

PaCO<sub>2</sub> = 0.7 x (HCO<sub>3</sub>-24) + 40 ± 2 = HCO<sub>3</sub> + 15

Δ HCO<sub>3</sub> ↑ 1 → expect Δ pCO<sub>2</sub> ↑ 0.7

Respiratory acidosis:

Acute: Δ pCO<sub>2</sub> ↑ 10 → Δ HCO<sub>3</sub> ↑ 1 or ↓ pH 0.08

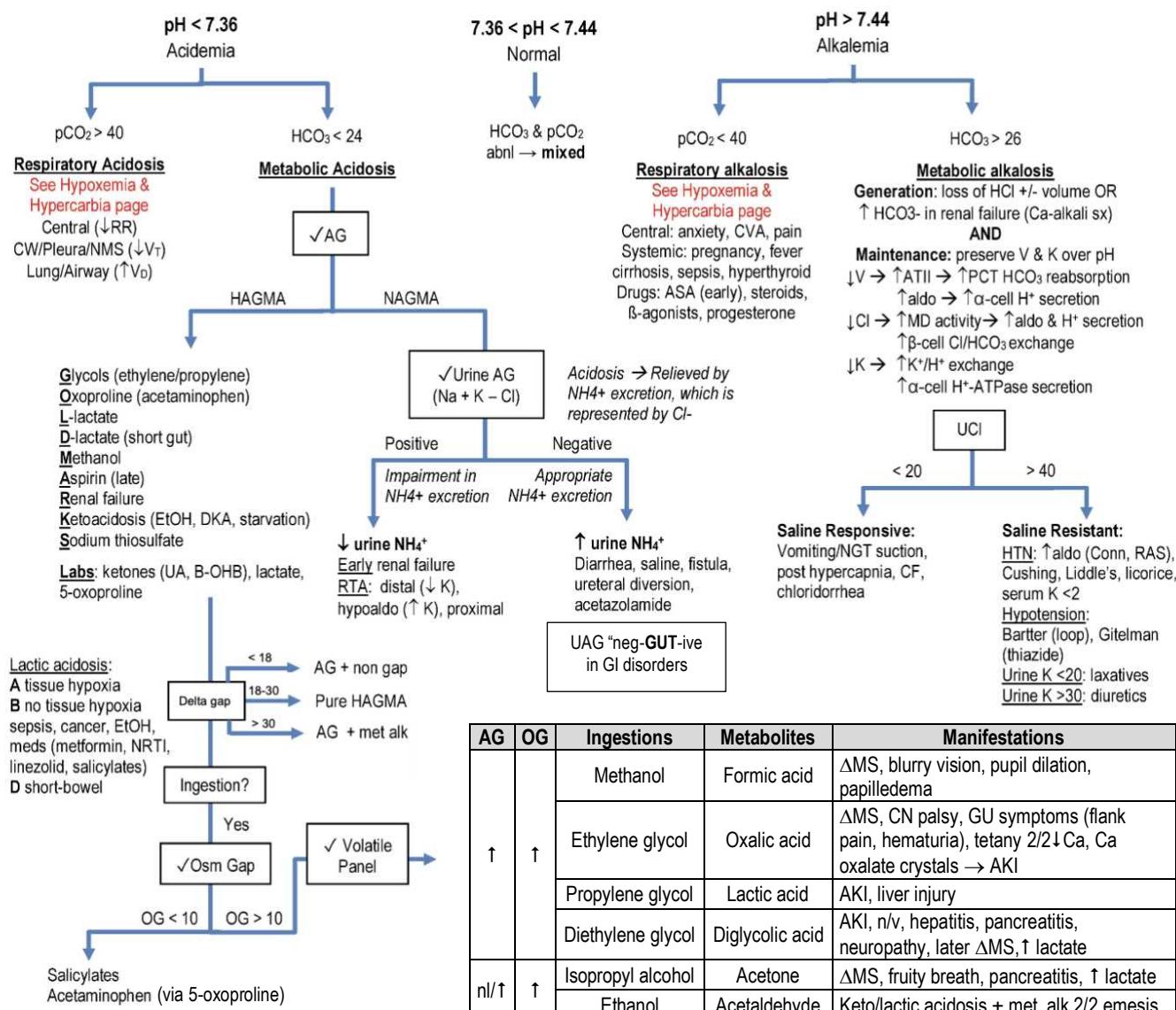
Chronic: Δ pCO<sub>2</sub> ↑ 10 → Δ HCO<sub>3</sub> ↑ 4 or ↓ pH 0.03

Respiratory alkalosis:

Acute: Δ pCO<sub>2</sub> ↓ 10 → Δ HCO<sub>3</sub> ↓ 2 or ↑pH 0.08

Chronic: Δ pCO<sub>2</sub> ↓ 10 → Δ HCO<sub>3</sub> ↓ 4 or ↑pH 0.03

## ALGORITHMIC APPROACH



## MANAGEMENT OF ACID-BASE DISORDERS: treat the underlying cause!

- **Metabolic acidosis:**
  - **Acute:**
    - In BICAR-ICU ([Lancet 2018;392:31](#)), pts with metabolic acidosis (pH <7.2) tx w/ IV HCO<sub>3</sub> for goal pH >7.3 had no Δ in overall mortality but ↓RRT initiation. A subset of pts w/ AKIN stages 2-3 had improved mortality at 28d
    - For pH <7.1 or HCO<sub>3</sub> <6: if HDS, can start **isotonic HCO<sub>3</sub> gtt.** Monitor VBG/ABG q1h. Bolus admin is controversial due to c/f CO<sub>2</sub> accumulation → hypercapnia (acidosis), hypernatremia, hypocalcemia, hypertonicity, hypervolemia, overshoot alkalosis
    - For bicarb to have full effect on serum pH, pt must be able to increase minute ventilation to ventilate off CO<sub>2</sub>
  - **Special considerations:**
    - **Toxic alcohols:** call poison control, NaHCO<sub>3</sub>, **fomepizole**, or HD (if vision Δ, AKI, HAGMA, methanol >50mg/dL, ethylene glycol >300mg/dL)
    - **Salicylate poisoning:** NaHCO<sub>3</sub> to goal urine pH >6.5 and serum salicylate level <40 or HD (if level >80mg/dL, coma, AKI, hypervolemia, AMS), dextrose containing fluids if AMS. **Acetazolamide is contraindicated**
    - NAGMA and uremic acidosis are more responsive to HCO<sub>3</sub> than lactic and ketoacidosis
  - Chronic: in CKD, replete with PO NaHCO<sub>3</sub> for goal HCO<sub>3</sub> >22. See CKD
- **Metabolic alkalosis:** replete volume, K, & Cl
  - Treat both (1) underlying cause of metabolic alkalosis and (2) cause of renal retention of HCO<sub>3</sub>
  - **If saline responsive:** NS w/ KCl until urine pH >7. For pts w/ CHF/cirrhosis & alkalosis 2/2 diuresis, consider Acetazolamide and/or K<sup>+</sup> sparing diuretic. See *Advanced Diuresis*
  - **If saline resistant:** for mineralocorticoid excess → use K<sup>+</sup>-sparing diuretic (**prefer amiloride, faster than spironolactone**) & consider surgical removal of adenoma
  - If pH >7.6 & persistently volume overloaded, give **acetazolamide** + loop diuretic with close K<sup>+</sup> monitoring. May need KCl
- **Respiratory acidosis:** treat underlying process; adjust vent settings if intubated. NaHCO<sub>3</sub> unlikely to be helpful, theoretically harmful if unable to ventilate subsequent CO<sub>2</sub> produced. For every 100mEq HCO<sub>3</sub> administered, 2.2L CO<sub>2</sub> must be exhaled.
- **Respiratory alkalosis:** address underlying cause (correct hypoxemia, treat pain/anxiety/fever); adjust vent settings if intubated

## RENAL TUBULAR ACIDOSIS (RTA) ([Int J Clin Pract 2011;65:350](#))

Consider in select pts w/ Hyperchloremic NAGMA or hyperK (Type IV). R/o GI losses & ↑IV NS use before ordering UAG!

**Pathophysiology:** inappropriate net retention of acid or inadequate reabsorption of bicarb

- In acidemia, kidney should ↑NH<sub>4</sub><sup>+</sup>+Cl<sup>-</sup> excretion and urine pH should be <5.3; this process is defective in RTAs.
- **Caveat:** CKD of any etiology is associated with ↓NH<sub>4</sub><sup>+</sup> production & acidosis

**Etiologies:**

- **Proximal RTA (Type II):** decreased threshold for proximal tubule HCO<sub>3</sub><sup>-</sup> reabsorption → more HCO<sub>3</sub> spills into urine
  - Primary (rare): Na-HCO<sub>3</sub> cotransporter defect
  - Acquired: **amyloidosis**, MM, post-renal transplant, bladder outlet obstruction, heavy metals, ↓Vit D, Wilson's disease, PNH
  - Meds: acetazolamide, cisplatin, tenofovir, aminoglycosides, topiramate
  - Often a/w Fanconi Syndrome: glucosuria (w/ serum gluc <180), hypouricemia, aminoaciduria
- **Distal RTA (Type I):** inability to secrete H<sup>+</sup> in distal tubule. Various subtypes of distal RTA related to affected transporter/tight junction
  - Primary: genetic loss of H<sup>+</sup> or HCO<sub>3</sub> transporters in intercalated cells
  - Acquired: **autoimmune disease** (RA, SLE, SS); **hypercalciuria** (any cause); obstructive nephropathy; SCD, MM, amyloid, cryoglobulinemia, tubulointerstitial injury, renal transplant rejection, cirrhosis, glue sniffing (toluene)
  - Meds: amphotericin B, Li<sup>+</sup>, ifosfamide, ibuprofen, codeine
- **Type IV:** effective hypoaldosteronism: ↓aldo secretion OR tubular resistance → ↑K → ↓NH<sub>3</sub> synthesis → ↓NH<sub>4</sub><sup>+</sup> excretion
  - Hyperkalemia inhibits glutaminase enzyme, which generates NH<sub>3</sub> ("ammoniogenesis"). Acidosis ensues as unable to fix and excrete H<sup>+</sup> as ammonium.
  - **Hyporeninemic hypoaldosteronism** (most common): diabetic nephropathy, CIN, NSAIDs, calcineurin inhibitor, HIV
  - ↓ Aldo production: ACEi/ARB > **heparin** > adrenal insufficiency, severe illness
  - **Aldosterone resistance:** (ENaC inhibition) K-sparing diuretic, trimethoprim, pentamidine

**Workup:** clinical history (PMH – autoimmune or malignancy, med review, stones), response to HCO<sub>3</sub> supplementation

- VBG, BMP (AG, HCO<sub>3</sub>, K, UA (pH), urine lytes. Consider urine Ca/Cr to differentiate proximal vs distal RTA
- Estimate of Urine NH<sub>4</sub><sup>+</sup>: UAG = Na + K - Cl (less useful when ↑urine pH >6.5 or UNa < 25, high aldo state)

	PROXIMAL RTA (TYPE II)	DISTAL RTA (TYPE I)	TYPE IV RTA
Defect	Proximal HCO <sub>3</sub> <sup>-</sup> resorption	Distal H <sup>+</sup> secretion	Hyperkalemia
Serum HCO <sub>3</sub> <sup>-</sup>	12 – 20	<10	>17
Serum K	↓ or normal	↓ or normal	↑
Urine pH during acidemia	Varies, but >5.5 after HCO <sub>3</sub> <sup>-</sup>	>5.5	<5.5, but cannot buffer w/ NH <sub>4</sub> <sup>+</sup>
Urine AG = Na + K – Cl	⊖	⊕	⊕
Additional dx testing	Urine Ca/Cr nml, give bicarbonate and check urine pH	Urine Ca/Cr elevated	Renin, aldosterone, cortisol
Complications	Rickets, osteomalacia	CaPO <sub>4</sub> urinary stones	Hyperkalemia
Tx (Goal HCO <sub>3</sub> 22-24)	Challenging. NaHCO <sub>3</sub> (10-20 mEq/kg) or KCitrate.	NaHCO <sub>3</sub> (1-4mEq/kg)	Treat hyperK: loop, low K diet If hypoaldo, can give fludrocort

# Nephrology

# Sodium Disorders

**HYPONATREMIA**: free water excess relative to serum sodium ([NEJM 2015;372:55](#))

**S/Sx**: often asymptomatic; can present with AMS, HA, N/V, weakness, seizures, signs of increased ICP

**Workup**: H&P focused on symptoms, etiology, chronicity, new meds, endocrine ROS, volume status

- **Studies**: Obtain prior to treatment **Serum**: BMP, Osm. Consider uric acid, TSH, AM cortisol. **Urine**: UA, Osm, Na, uric acid.
- Determine if ADH is present (**UOsm >100**). Can approx UOsm from UA: last 2 digits of SG x 30 (e.g., SG 1.010 ≈ UOsm 300)
- Other diagnostic clues ([Eur J Inter Med 2016;29:22](#); [JCEM 2008;93:2991](#); [Ann Intern Med 1980;93:716](#); [Cureus 2020;12:e7762](#)):
  - Other solutes: SIADH: often serum uric acid (sUA) <4, BUN <5, fractional excretion of uric acid (FEUA) ≥10-12% (small studies: 100% PPV for SIADH/thiazide hypoNa; FEUA ≤8% = 100% NPV for SIADH). ↓EABV: often sUA >5, BUN↑, FEUA <4%
  - IVF: SIADH: NS initially ↑SNa but then will ↓SNa (Na is excreted while H<sub>2</sub>O retained). Hypovolemia: NS will ↑SNa

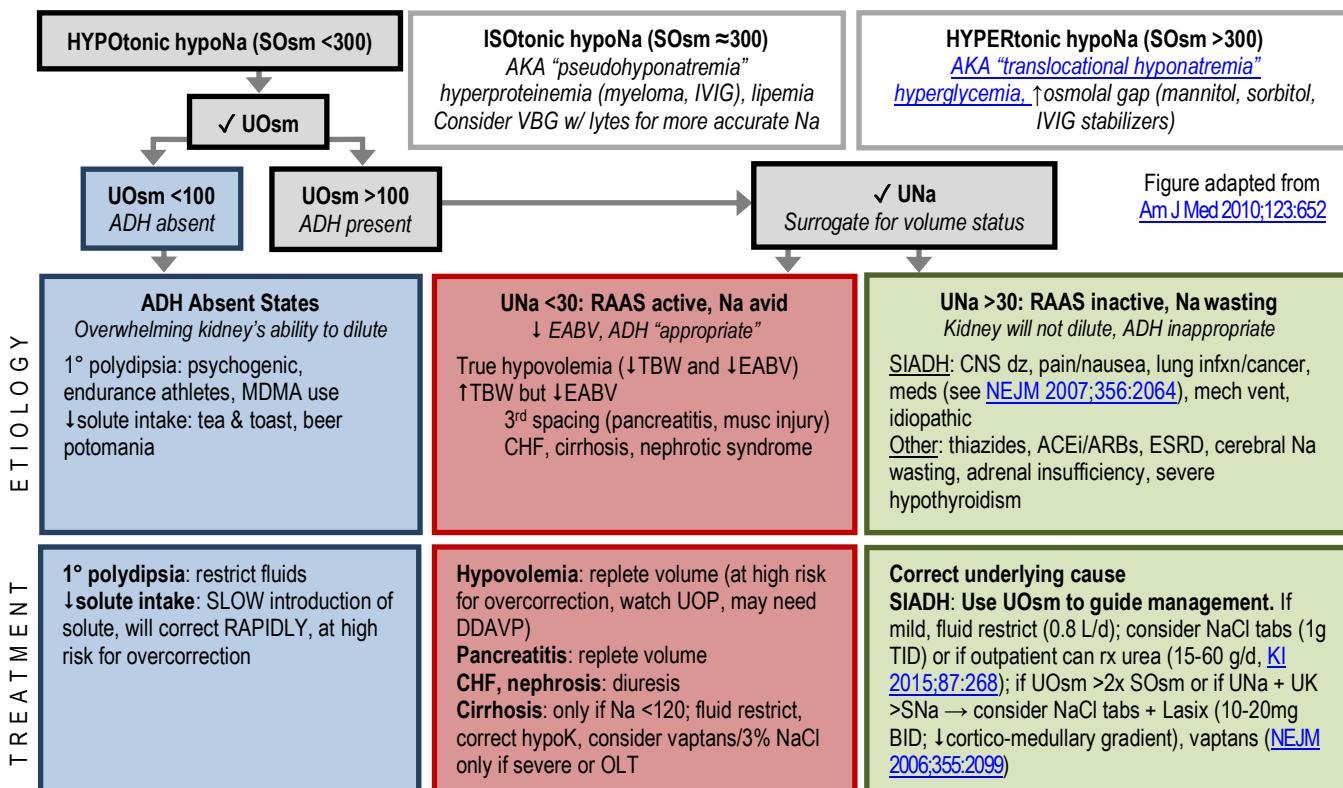


Figure adapted from [Am J Med 2010;123:652](#)

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

- **Rate/goal**: ↑Na 4-6 mEq/L per 24h, to short-term goal ≥125; typically, ↑Na 4-6 will alleviate sx
- **Severe symptomatic** (sz, AMS): 3% NaCl via 100mL bolus over 10-60 min (↑Na 1.5-3); up to 3X until sx resolve or Na 15
- **Severe asymptomatic** (Na <120): 3% NaCl at [Na Correction Rate](#), usually 15-30mL/h, until Na ≥125; Na <120 a/w 6-10% in-hospital mortality ([Clin J Am Soc Nephrol 2018;13:641](#))
- **Mild/mod** (Na 130-134/Na 120-129): etiology-specific treatment (e.g., fluid repletion, fluid restriction, diuresis, hold diuresis)
- **Overcorrection**: Na ↑ >8 in 24h or >18 in 48h
  - Osmotic demyelination syndrome (ODS): delayed onset (2-6d) dysarthria/dysphagia, paresis, AMS, locked-in syndrome
    - Dx with MRI ~4w after sx onset
    - RFs: starting Na ≤105 (ODS unlikely if starting Na >120, [Hosp Pract 1995;37:128](#)), malnutrition, EtOH use, cirrhosis, ↓K
    - Be mindful of rapid correction in hypovolemic hyponatremia and low solute hyponatremia
  - If Na trajectory predicts overcorrection, consider **DDAVP clamp** ([Am J Kidney Dis 2013;61:571](#)):
    - DDAVP 2-4mcg IV/SC q6-8h with Na measured q4-6h, until Na ≥125. If needed, add 3% NaCl at [Na Correction Rate](#)
  - If already overcorrected, urgently reduce Na to within bounds of previous goal correction (i.e., ΔNa < 8 mEq/L/24h):
    - D5W 6mL/kg IBW over 2h (↓Na by 2) and continue with q2h Na measurements until at goal level, PLUS
    - DDAVP 2-4mcg IV/SC q6h for 24-48h even after relowering goal initially achieved
- **Concurrent hypokalemia**: K and Na freely exchanged, giving 1mEq of K = giving 1mEq of Na; can overcorrect w/ K supplementation

**HYPERNATREMIA**: free water loss in excess of NaCl loss ([Crit Care 2013;17:206](#), [NEJM 2015;372:55](#))

**Etiologies**: ↓access to free water or ↓thirst, DI

- **Renal losses**: UOsm <800; ↓ADH release or kidney response: post-ATN, osmotic, DI, loop diuretic, hyperCa, elderly
- **Extrarenal losses**: UOsm >800; GI loss from NGT, vomiting, diarrhea, insensible losses, hypodipsia

**Treatment**: BMP q12-24h, strict I/O. Aim to ↓SNa by 12 mEq/L per 24h (accidental overcorrection unlikely to be dangerous, complications of more rapid correction (e.g. cerebral edema) are rare in adults, [CJASN 2019;14:656](#))

1. [Calculate current free water deficit](#). Shortcut FWD (L) = (Current Na – Goal Na)/3. Target Na should be 24h goal
2. Account for ongoing losses:
  - Insensible losses: 700-900 mL/d typically but ↑ if burns, fever, diarrhea (cannot measure, so ↑replenishment if inadequate)
  - Urine: 24h UOP x (1- (UNa+UK)/SNa)); alternative = (0 x 1<sup>st</sup> L) + (0.5 x 2<sup>nd</sup> & 3<sup>rd</sup> L) + (1 x urine beyond 3L)
3. FW to give today = current FWD + ongoing losses. Give via PO, TF (FWB), or IV (D5W). If DI see *Pituitary Disorders* for DDAVP

# Nephrology

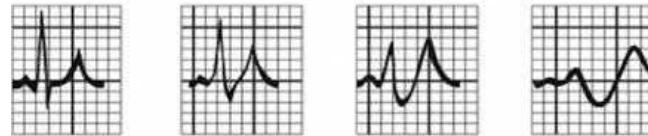
# Potassium Disorders

## NORMAL POTASSIUM HANDLING/HOMEOSTASIS (NEJM 2015;373:60)

- Ingested K<sup>+</sup> absorbed in intestines → taken up and sequestered by liver/muscle cells via insulin & β2 receptors → ↑Na-K ATPase
- 98% of K<sup>+</sup> is intracellular; remaining extracellular levels trigger aldosterone secretion → principal cell K<sup>+</sup> secretion → excretion in urine
- Excretion also driven by Na<sup>+</sup> delivery to distal nephron (macula densa). ↑Na<sup>+</sup> delivery → K<sup>+</sup> excretion; ↓Na<sup>+</sup> delivery → K<sup>+</sup> retention

## HYPERKALEMIA

- S/S:** Muscle cramps, weakness (ascending), paralysis, conduction delay (e.g. CHB, BBB, sinus arrest), arrhythmia (VT/VF, asystole, idioventricular rhythms) ([CCM 2008;36:3246](#))
- Dx:** confirm K<sup>+</sup> not d/t hemolyzed sample, plt>500K, WBC>120, or infusion of K<sup>+</sup>-containing IVF; consider blood gas K<sup>+</sup>
- ECG:** peaked T waves → ↓QT → ↑PR interval ± AVB, flat p → wide QRS ± BBB → sine wave pattern → PEA/asystole/VF
  - ECG does not correlate w/[K<sup>+</sup>] ([Clin J Am Soc Neph 2008;3:324](#))
- Etiologies:** Acidosis, ↓Aldosterone; B-blocker, Blood; Cell lysis/turnover; Drugs, DM, Decreased GFR
  - Redistribution:** cell lysis (hemolysis, rhabdo, TLS), acidosis, ↓insulin, hyperosm, meds (digoxin, β-blockers, minoxidil), hyperK periodic paralysis, post-hypothermia
    - Usually transient unless impaired renal K<sup>+</sup> excretion
  - ↓ Renal K<sup>+</sup> excretion: required for persistent hyperK<sup>+</sup>
    - ↓ Aldo production/action: ACEi/ARBs, NSAIDs, K<sup>+</sup>-sparing diuretics, calcineurin inhib, pentamidine, TMP, type IV RTA
    - Impaired Na<sup>+</sup> delivery to distal nephron: hypovolemia, CHF, cirrhosis
    - AKI/CKD (esp. if oliguric): usually GFR<15
    - Other: ureterojejunostomy – urine K<sup>+</sup> reabsorbed
- Management:** acute changes are most dangerous → **STAT ECG**. Treat if ECG changes, K<sup>+</sup>>6, rapid rise, or sx
  - Elimination is key, other measures are temporizing. Address reversible factors (optimize volume status, low K<sup>+</sup> diet, meds). Of note, hyperK-related sine waves can be misinterpreted as VT. Do NOT use amiodarone if suspected hyperkalemia (deadly)



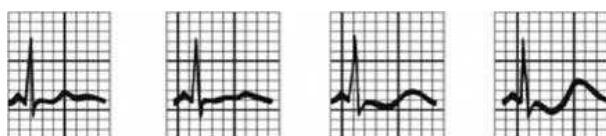
## HYPERKALEMIA TREATMENT

Strategy	Treatment	Onset	Duration	Notes
Stabilize	<b>Calcium:</b> calcium gluconate or CaCl <sub>2</sub> (central line) 1-2g IV, can repeat q5 min PRN	1-3m	30-60m	1 <sup>st</sup> line if any ECG Δs. Stabilizes cardiac membrane. Avoid if on dig
Redistribute	<b>Bicarb</b> (sodium bicarbonate 1-2 amps IV vs gtt)	5-10m	1-2h	Drives K <sup>+</sup> into cells. Consider only if ↓↓ pH
	<b>Insulin</b> (10U IV; 5U if ESRD) + D50 25g (if BS<250)	10-30m	4-6h	Drives K <sup>+</sup> into cells.
	<b>Albuterol</b> (10-20mg neb)	15-30m	15-90m	↓K <sup>+</sup> 0.5-1.5mEq/L
Eliminate	<b>Furosemide</b> ≥40mg IV; can approx. as 40xCr if K>6.	30m	Variable	Urinary K <sup>+</sup> excretion
	<b>Patiromer</b> (8.4g/d PO) or <b>Lokelma*</b> (10g TID initially) > <b>Kayexalate**</b> (15-30g PO/PR)	*1h 7h	24h	Swaps K <sup>+</sup> for Ca <sup>++</sup> or Na <sup>+</sup> in gut
	<b>HD</b> lowers K immediately	N/A	3h	Removes K <sup>+</sup> , may rebound d/t shifts

\*\*GI ischemia/necrosis reported w/ Kayexalate, contraindicated post-op, ileus, bowel obstruction, colitis ([JAMA Intern Med 2019; 179:1023](#))

## HYPOKALEMIA

- Signs and symptoms:** usually with K<sup>+</sup><3 → cramps, ileus, weakness (ascending, can involve respiratory muscles), rhabdo, paralysis, worsened HE in cirrhosis ([Nat Rev Neph 2010;7:75](#))
- ECG:** flat T waves, ST dep, U waves, ↑QT, atrial or ventricular ectopy → VT, VF (esp if K<sup>+</sup><2.5, susceptible pts, or on digoxin)
- Etiologies:**
  - Lab artifact** (pseudo-hypokalemia): WBC >100 absorb K<sup>+</sup> if sample sits out (check K<sup>+</sup> on blood gas)
  - Inadequate intake:** unlikely to be 1° cause, usually combined with another etiology
  - Redistribution:** ↑pH, ↑insulin, refeeding syndrome, ↑β-adrenergic activity (e.g. albuterol, epi), ↑blood cell prod (e.g. s/p G-CSF), hypothermia, toxins (cesium, barium, chloroquine), antipsychotics, hypoK/thyroxine periodic paralysis
  - Extrarenal losses:** diarrhea (esp. if chronic, VIPoma, villous adenoma, laxatives), vomiting/NGT
  - Renal losses (w/o HTN):** ↑urine flow (1° polydipsia, excess IVF), ↓Mg, meds (ampho B, ifosfamide, cisplatin, gent)
    - Acidemia: DKA, RTA (proximal [Type II] and some distal [Type I])
    - Alkalemia: diuretics, UGI losses (2° hyperaldo), Bartter's (~loop diuretic), Gitelman's (~thiazide)
    - Other: ↑urine excretion of anions (β-OH-butyrate in DKA, bicarb [e.g. UGI losses], toluene + PCN metabolites)
  - Renal losses (with HTN):**
    - 1° hyperaldo: ↑aldo, ↓renin (e.g. adrenal adenoma); 2°: ↑aldo, ↑renin (e.g. renal artery stenosis, renin-secreting tumor)
    - Other: ↑glucocorticoid or ↑EnaC activity (e.g. Cushing's, Liddle's syndrome, black licorice)
- Management:** 10mEq raises K<sup>+</sup> by 0.1mmol/L; caution if ↑Cr or if due to transcellular shifts (e.g. periodic paralysis)
  - Oral KCl (ER = pill, IR = powder) preferred for tx as safer, quick acting, and many pts are Cl<sup>-</sup> depleted
  - IV formulation KCl if unable to take PO or if severe/high-risk/symptomatic → max 10mEq/h (floor), 20mEq/h (ICU)
  - Always replete Mg, otherwise K<sup>+</sup> repletion ineffective due to K<sup>+</sup> wasting via ROMK ([JASN 2007;18:2649](#))
  - Avoid dextrose-containing solutions → can acutely worsen hypokalemia (dextrose ↑insulin secretion → K<sup>+</sup> shifts into cell)



## HYPOMAGNESEMIA ([Med Sci \(Basel\) 2019;7:56](#))

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

## HYPERMAGNESEMIA (rarely pathologic w/o renal insufficiency)

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

## HYPOPHOSPHATEMIA

- S/Sx: (typically if phos <1.0 mg/dL, esp. if acute):  $\downarrow$  intracellular ATP → global cellular dysfunction → AMS/encephalopathy, paresthesias, seizures, CHF, resp depression, proximal myopathy, rhabdo, dysphagia/ileus, hemolysis, mineral Δ (bone pain, hypercalciuria, rickets/osteomalacia) ([JASN 2007;18:1999](#))
- Etiologies:
  - **Redistribution (into cells):**  $\uparrow$  insulin (DKA, HNK, **refeeding**), **acute resp alkalosis** ( $\uparrow pH \rightarrow \uparrow$  glycolysis), hungry bone syndrome (deposition of Ca and phos in bone immediately following parathyroidectomy)
  - **$\downarrow$  GI absorption:** poor PO, chronic diarrhea,  $\downarrow$  vit D, antacids or phos binders (e.g. aluminum, Mg, sevelamer)
  - **$\uparrow$  Renal excretion:**  $\uparrow$  PTH (1° or 2° hyperPTH), Fanconi syndrome (multiple myeloma, tenofovir),  $\uparrow$  FGF-23 (genetic/paraneoplastic), meds (acetazolamide, metolazone, IV iron) ([QJM 2010;103:449](#)), osmotic diuresis (glycosuria), CVVH (esp at high bicarb dose)
  - Use **FEPO<sub>4</sub>** to distinguish GI/redistribution vs renal (>5% suggests renal wasting)
- Treatment:
  - **Severe** (<1 mg/dL or 1-2 mg/dL and at high risk of becoming severe e.g. refeeding) **or symptomatic**
    - **IV Na or K phos 30mmol q4-6h** with frequent levels (can give 15, 30, or 45mmol doses at MGH). Change to PO once >1.5mg/dL. Give ½ dose in CKD/ESRD.
    - Aggressive IV tx can cause Ca precipitation, hypotension (often due to hypocalcemia), AKI, arrhythmia
  - **Asymptomatic** (<2 mg/dL and not at high risk): Na or K phos 1mmol/kg/d PO in 3-4 divided doses (max 80mmol/d)
    - NeutraPhos: 1 packet = 250mg phos (8mmol); 7.1mEq K, 6.9mEq Na; *preferred if need K or want lower Na*
    - K-Phos Neutral: 1 tab = 250mg phos (8mmol); 1.1mEq K, 13 mEq Na
    - If poorly tolerated (can cause diarrhea), can give scheduled skim milk (8oz = 8mmol phos)

## ACUTE HYPERPHOSPHATEMIA (for chronic hyperphosphatemia, see CKD)

- S/Sx: results from Ca precipitation → hypocalcemia (muscle cramps, tetany, tingling, perioral numbness)
- Etiologies:
  - **Acute phos load** (TLS, rhabdo, exogenous/phosphate-containing laxatives)
  - **Acute extracellular shift** (DKA, lactic acidosis, severe hyperglycemia)
  - **Acute kidney injury or CKD** due to decreased clearance (including acute phosphate nephropathy)
  - **Increased tubular reabsorption** (vit D toxicity)
  - **Pseudohyperphosphatemia** (hyperglobulinemia, hyperlipidemia, hyperbilirubinemia, hemolysis)
- Treatment: normal saline (though can worsen hypocalcemia), HD. Consider low phos diet, phos binders (sevelamer), renal consult if refractory/profound

# Nephrology

# IV Fluids & Electrolyte Repletion

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

- Types:** **crystalloid** (e.g. NS or LR), **free water** (e.g. D5W), and **colloid** (e.g. albumin, blood products)
  - Fluids can be isotonic (NS more isotonic than LR), hypotonic (D5W, 1/2 NS, 1/4 NS), or hypertonic (3% saline)
- Bolus fluids** = volume expansion in shock, GI losses, burns
  - Rate: 1L over 30min-2h. If concerned about volume overload, start w/ smaller volume (250-500cc).
  - NS in large volumes can cause hyperchloremic non-AG metabolic acidosis (NAGMA) and ↑ need for RRT ([NEJM 2018;378:829](#); [NEJM 2018;378:718](#)) however no differences in mortality when compared to LR ([JAMA 2021;326:818](#))
  - LR has **minor** quantities of K & lactate. ↑K & lactate ([JEM 2018;55:313](#)) are **NOT** contraindications to LR.
  - Colloid is NOT superior to crystalloid for volume resuscitation in shock ([JAMA 2013;310:1809](#))
- Maintenance fluids** = goal to replace daily losses (~1.6L/d in adults w/ normal renal function) while preserving electrolyte balance
  - D5NS or LR are typical maintenance fluid. Rate 60 – 100 mL/h (guided by comorbidities, insensible losses, presence of oliguria or ADH excess) **Always order with time limit.** ([NEJM 2015;373:1350](#))
  - Consider NS in oliguric AKI with ↑K (maximize distal Na delivery and K excretion), cerebral edema, and cirrhosis ([Clin J Am Soc Nephrol 2022;17:588](#))

Fluid	pH	Osm	[Na <sup>+</sup> ]	[Cl <sup>-</sup> ]	[K <sup>+</sup> ]	[Ca <sup>2+</sup> ]	Dextrose	Other/Notes
Human plasma	7.35-7.45	275-295 mOsm/L	135-145 mEq/L	94-111 mEq/L	3.5-5.0 mEq/L	2.2-2.6 mg/dL	60-100 mg/dL	1-2 mEq/L lactate
Normal Saline (NS)	4.5-7	308	154	154				
Lactated Ringers	6-7.5	281	130	109	4	1.35		29 mEq/L lactate
D5-LR	4-6.5	525	130	109	4	1.35	5 g/dL	29 mEq/L lactate
D5-NS	3.2-6.5	560	154	154			5 g/dL	
1/2 NS	5	154	77	77				
3% NS	5	1026	513	513				See Hyponatremia
D5-1/2 NS	3.5-6.5	406	77	77			5 g/dL	
D5-1/2 NS w/ 20-40KCL	3.5-6.5	426-446	77	97-117	20-40		5 g/dL	
Isotonic NaHCO <sub>3</sub>	~8	552	150				5 g/dL	=3 amps 50mEq NaHCO <sub>3</sub> in 1L D5W
D5W	3.5-6.5	252					5 g/dL	use to correct ↑Na
D10W	3.2-6.5	505					10 g/dL	use w/ insulin gtt
D20W	3.2-6.5	1010					20 g/dL	use w/ insulin gtt

**Albumin:** [MGH Albumin Policy](#) put in place to prevent non-evidence-based overuse ([ASA Choosing Wisely](#))

Albumin 25% = 12.5g albumin in 50mL solution; Albumin 5% = 12.5g albumin in 250mL solution

Indications: use to replace serum oncotic pressure, not typically for volume resuscitation

- SBP:** improves renal outcomes. Dosing: 1<sup>st</sup> dose albumin 25% at 1.5g/kg w/in 6h (max 100g), 2<sup>nd</sup> dose 1g/kg on Day 3
- Large volume paracentesis in cirrhosis:** only if >5L removed. Dosing: Albumin 25% at 6-8g/L ascites removed
- Augmenting diuresis in ARDS:** already on high dose loop diuretic AND albumin <2.5 or Total Prot <6  
Dosing: Albumin 25% at 25g q8h for 3 doses (requires attending approval; stop once alb >2.5. Max 3 days)
- Hepatorenal syndrome:** see *Hepatorenal Syndrome*
- Other:** ECMO chatter, mechanical circulatory support, burns, nephrotic syndrome, acute hemorrhagic shock, intra-dialysis
- NOT helpful in decompensated cirrhosis unless for the above indications ([NEJM 2021;384:808](#))

## ELECTROLYTE REPLETION

	Potassium	Magnesium	Phosphorus	Calcium
<b>Goal</b>	- CAD/arrhythmia: ≥4 - Everyone else: ≥3.5 - Do not replete if on HD unless <3.0	- CAD/arrhythmia: ≥2 - Everyone else ≥1.7	- Replete if severe (phos <1), symptomatic, or if phos 1-2 and at risk for refeeding	- Replete if sx, long QTc, Ca <7.5, iCal <1.15mmol/L
<b>PO or IV?</b>	PO > IV	IV > PO	PO > IV	IV if severe,
<b>PO repletion</b>	- KCl IR (powder): q4-6h - KCl ER (pills): giant pills - If K <3.5, ≥20 mEq KCl IR - see <a href="#">Lexicomp</a> for dosing	- Mg oxide 400mg (240mg elemental Mg) TID x1d	- K-Phos: 1 packet QID - Neutra-Phos: 1 packet QID	- Ca carbonate 1250mg PO BID
<b>IV repletion</b>	- Peripheral: 10mEq/h - Central: 20mEq/h w/ telemetry monitoring	- Mg sulfate 2g IV	- Give 15-45mmol Phos at a time - K-Phos (1.5mEq K/mmol Phos) - Na-Phos (1.3mEq Na/mmol Phos)	- Ca gluconate 1-2g IV; - CaCl <sub>2</sub> used in codes, 0.5-1g q2-5min
<b>Comments</b>	- 10mEq K ↑serum K by 0.1 (in normal kidney function) - re-check K every 40-80mEq unless on stable daily dose - Correct hypoMg	- 2g ↑serum Mg by 0.5 - ↓Mg can cause ↓K/Ca	- IV Phosphate can precipitate Ca → causing hypocalcemia	- Correct for low Alb & hyperphos first - 1g Ca gluconate ↑serum Ca by 0.5

# Nephrology

# Urinalysis & Nephrolithiasis

## URINALYSIS

**URINE DIPSTICK** – urine should be analyzed within 2-4h

<b>Specific Gravity</b>	Can help approximate urine osm: decimal of SG x 30 (e.g. SG 1.020 → 20 x 30 → ~ 600mosms) <b>SG &lt;1.010:</b> post-ATN (concentrating defect), diuretics, DI, polydipsia, hypovolemic hypoNa after resuscitation <b>SG 1.010 – 1.025:</b> normal; <b>SG &gt;1.025:</b> prerenal, contrast (esp >1.030), ↓EABV, glycosuria (DM), proteinuria, SIADH
<b>pH</b>	Normal 4.5 - 8, but strongly depends on serum pH and dietary intake If normal urine pH + metabolic acidosis, suspect type I RTA (kidney not secreting H <sup>+</sup> ions) If pH ≥7, suspect urease-producing organisms (Proteus, PsA), strict vegetarians (low protein diet), type I RTA
<b>LE</b>	Released from lysed PMNs; <b>FP:</b> ↓pH or ↓SG (lyses WBCs); <b>FN:</b> proteinuria, glycosuria. For UTI, <b>Sn 80%, Sp low</b>
<b>Nitrite</b>	Indicates nitrate-reducing GNR (E. coli, Klebsiella, Proteus, PsA – NOT Enterococcus). For UTI, <b>Sn 60%, Sp&gt;90%</b>
<b>WBC</b>	UTI; if sterile pyuria, consider AIN, GN, chlamydia, ureaplasma, urethritis, TB, foreign body, exercise, steroids
<b>Blood</b>	Detects heme (glomerular, renal, or urologic); <b>FP:</b> hemoglobinuria (hemolysis), myoglobinuria (rhabdo), semen, drugs (rifampin, chloroquine, iodine), peroxidase producing bacteria
<b>Protein</b>	Only detects albumin, not LMW proteins or light chains. + Protein when excretion >300mg/d. Falsey elevated by high SG, heavy hematuria (heme protein), and iodinated contrast (w/in 24h)
<b>Ketones</b>	Detects only acetoacetate, NOT β-hydroxybutyrate; yield decreases as collected urine sits
<b>Glucose</b>	Reflects glomerular overflow (serum glucose >180mg/dL or SGLT-inhibitor/mutation) OR PCT failure (glycosuria w/ normal serum glucose → consider Fanconi's syndrome 2/2 MM, heavy metal, drugs, etc.)

## URINE SEDIMENT (MICROSCOPY)

- Urine microscopy room:** to the left of Harris room, outside White 10
- Nephrology fellow/attending (day) or Security (night) can let you in
  - Obtain 10cc of **fresh urine**
  - Centrifuge** using a balance @ 3000 RPM x3-5min
  - Invert/drain supernatant** and **resuspend** sediment in the few drops of urine that remain in the tube. Place one drop of sample on slide and place coverslip.
  - Bright Field Microscopy: keep light source subdued, lower condenser to maximize contrast, start at **low power** (10x) to obtain a general impression. Pay attention to **coverslip edge** where casts tend to migrate.
  - Phase contrast microscopy:** maximizes contrast and definition, allows better visualization of casts and cells. Raise condenser up high and turn light source to maximum brightness. Objective and condenser annulus should always match.

Findings	Description
<b>RBCs</b>	Glomerular (dysmorphic RBCs “mickey mouse ears”) vs non-glomerular (normal)
<b>WBCs</b>	UTI/cystitis (>10/microL expected for true infxn), pyelonephritis, AIN, atheroembolic, glomerular injury, renal/bladder TB, stones
<b>Epithelial Cells</b>	Tubular (ATN), transitional (proximal urethra to renal pelvis), squamous (contamination by genital secretions)
<b>Casts</b>	Viewed best w phase contrast: Hyaline, RBC, WBC, Muddy brown, Granular, Waxy, Fatty
<b>Crystals</b>	Viewed best w phase contrast: Acyclovir (“needles”), Tenofovir, Struvite (NH4·Mg·PO4), ethylene glycol (oxalate)

CONDITION	UA	CELLS	CASTS/CRYSTALS	COMMENTS
<b>Pre-renal azotemia</b>	SG >1.010		Hyaline, granular	↓FENa (if oliguric), ↓FEUrea
<b>Nephrotic syndrome</b>	3+ protein		Oval fat bodies, hyaline	
<b>Glomerulonephritis</b>	+ heme, +protein	Dysmorphic RBCs	RBC casts, WBC, granular	
<b>ATN</b>	SG ~ 1.010 (“isosthenuria”)		Hallmarks: renal tubular epithelial cells (RTECs) and muddy casts ( <a href="#">CJASN 2008;3:1615</a> ) PPV for ATN ~100% if ↑pre-test prob and any RTECs and/or muddy casts present.	
<b>Rhabdomyolysis, hemolysis</b>	3+ heme w/o RBCs on sediment	NO cells	Acellular hyaline casts with red or brown pigmentation	↓FENa, red/brown urine
<b>AIN</b>	Sterile pyuria	WBCs	WBC casts, granular	Urine eos NOT sens or spec
<b>Renal infarct</b>	Sterile pyuria	+ RBCs, WBCs		↑urine LDH (↑serum LDH)
<b>Cholesterol emboli</b>	Sterile pyuria		Cholesterol	
<b>Myeloma kidney</b>		Bland	Bland	Proteinuria NOT detected by UA
<b>CKD</b>			Waxy	± impaired ability to concentrate

## NEPHROLITHIASIS

**Composition and prevalence:** CaOxylate > CaPhosphate > Urate = Struvite > Cysteine

**Risk factors:** male, obesity, DM, white, southeastern US, oral antibiotics, CKD, ESRD, family history (2% attributed to inherited disease)

**Workup:** CT (I-) > US (urological procedures require CT for planning). Can strain urine to type stone. Can also get 24h urine (“[Litholink](#)”) at home both before and after interventions (usually dietary) are made

**Precipitating factors:** low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, hypomagnesuria, hypercystinuria, urea splitting bacteria, high sodium intake, acidic urine (urate, cysteine), or basic urine (calcium phosphate, struvite), drug-induced (guaiifenesin, triamterene, sulfa drugs, protease inhibitors), toxic ingestion (ethylene glycol → Ca oxalate stones)

**Acute management:** IVF, pain management (ketorolac preferred to opioids) alpha blockers (>5 mm); urologic intervention if >10mm, concern for infected stone, AKI, unremitting pain/n/v, or anuria. See: *Ureteral obstruction*. See AAFP algorithm ([Am Fam Phy 2019;99:490](#))

**Chronic management:** fluid intake >2.5L/d, low Na diet, high K diet, low oxalate diet (no nuts, chocolate, green leafy veggies, etc.), increase Ca intake, avoid excess vitamin D, thiazide diuretics if calcium stones, allopurinol if hyperuricosuria

**Citrate supplementation:** used for inhibition of Ca and uric acid stone formation. Leads to metabolic alkalosis. ↓new stones, stone size

# Infectious Disease

# Empiric Antibiotics

## PRINCIPLES OF ANTIBIOTIC SELECTION ([IDSA Guidelines](#), [Sanford Guide](#), [Johns Hopkins Abx Guide](#))

Consider the *substrate*:

- Is the patient **immunocompromised**? Think about age, DM, medications ( $\geq 20$  mg prednisone QD x 2 weeks), HIV, neutropenia, ESLD, ESRD.
- Is the patient **at risk** for any particular kind of infection? Think about prostheses, lines, altered anatomy, behaviors, and recent hospitalizations.

Consider the *tempo/severity*:

- Is the patient **unstable**? If so, start broad spectrum antibiotics quickly; *time to antibiotics correlates with mortality in septic shock*.

Consider the *syndrome*:

- What **evidence** is there of infection? e.g., fever, localizing symptoms, leukocytosis, hypotension, inflammatory markers
- What is the likely **source**? e.g., PNA, UTI, SSTI, bone & joint infection, CLABSI, GI
- If a source is evident, what are the **most common pathogens**?
- Might there be **metastatic disease**? e.g., blood, CSF, valves, bones, joints

Other considerations:

- If safe, **cultures before antibiotics** to improve diagnostic yield.
- Review the patient's **prior microbiology** to assess for history of resistant bugs
- **Broader ≠ better**. We routinely overcover for MRSA, *Pseudomonas*, and anaerobes.
- **Longer ≠ better**. Emerging studies show shorter duration is noninferior in a number of infections.
- **Fever ≠ infection**. Don't forget to consider inflammation, thrombus, medications, etc.
- **Narrow and convert to PO** when able (if indicated). Use the *MGH antibiogram* and, eventually, the *susceptibility report*.
- **Inadequate source control** is a common cause of treatment failure. Remove the line, drain the abscess, etc.

Antibiotic pharmacokinetic properties:

- High **CNS penetration** (*not exhaustive*): PCN, ampicillin, nafcillin, CTX, imipenem, mero, metronidazole, doxy (Lyme only), linezolid. Vanc is moderate but improves with severe meningeal inflammation. MGH [Antibiotic penetration tip-sheet](#)
- High **oral bioavailability** (i.e., PO=IV) (*not exhaustive*): metronidazole, linezolid, doxy, FQs, azithro, clindamycin
- High **urinary accumulation** (*not exhaustive*): PCN, amoxicillin, cefazolin, cipro, aminoglycosides, vancomycin

Additional resources:

- For up to date MGH Antibiogram & Guidelines for Empiric Therapy for Inpatients: [click](#) & scroll down
- Surviving Sepsis Campaign – [2021 Adult Guidelines](#)

General spectrum of coverage for common IV β-lactams

Gram positives	Gram negatives	Anaerobes	Pseudomonas
penicillin / cefazolin			
ampicillin			
ceftriaxone / cefotaxime			
cefpime			
ampicillin-sulbactam			
piperacillin-tazobactam / meropenem			

Commonly encountered Bugs & Drugs

Microbe	Antibiotics	Notes
<i>Staphylococcus aureus</i>	MSSA: IV nafcillin, cefazolin, oxacillin PO cephalixin, cefadroxil	-Cefadroxil is BID, cephalexin is QID -β-lactam >>> vancomycin
	MRSA: IV vancomycin, daptomycin, ceftaroline PO doxy, TMP-SMX, LZD, clinda Long-acting dalbavancin, oritavancin	-Dapo is inactivated in lung by surfactant -LZD highly bioavailable if PO and well tolerated for short course (<2wk)
Group A streptococci	-penicillins	-Add clinda if concern for TSS
Enterococci	-ampicillin, vancomycin, daptomycin, linezolid -fosfomycin, nitrofurantoin (UTI only)	-MGH antibiogram shows good <i>E. faecalis</i> susceptibility to ampicillin -If <i>E faecium</i> , more likely to harbor resistance
<i>Pseudomonas aeruginosa</i>	-IV cefepime, ceftazidime, piperacillin-tazobactam, imipenem, meropenem, aminoglycosides -PO ciprofloxacin, levofloxacin	-Ertapenem does not cover PsA -MGH defines resistant PsA as R to ceftaz and may need ID guidance for abx choice
MDR GNRs (AmpC inducers and ESBL producers)	-IV cefepime, carbapenems, aminoglycosides -PO fluoroquinolone, TMP-SMX	-AmpC: <i>Enterobacter</i> , <i>Serratia</i> , <i>Providencia</i> , <i>Proteus</i> (indole+), <i>Morganella</i> , <i>Citrobacter</i> -Cefepime success highly-dependent on MIC
Cell wall-deficient ("atypicals")	-doxycycline, azithromycin, levofloxacin	- <i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Legionella</i>
Anaerobes	-IV pip-tazo, unasyn, carbapenems -PO metronidazole, clinda, amox-clav	-Think twice if anaerobic coverage needed -Vanc+cefe does NOT cover anaerobes

# Infectious Disease

# Empiric Antibiotics

Suspected Process	Microbiology	Empiric Antimicrobial Therapy	Notes
Meningitis <a href="#">(CID 2004;39:e1267; CID 2017;64:e34)</a>	-Generally: <i>S. pneumoniae</i> , HSV, other viral > <i>N. meningitidis</i> -If >50 y, immunocompromised, EtOH: <i>Listeria monocytogenes</i> -If hardware or nosocomial: Staph, PsA; <i>C. acnes</i> if VP shunt	-vancomycin+ CTX 2g Q12 -Listeria: ampicillin -HSV: acyclovir -Healthcare-assoc, hardware, VP shunt, PWID: vancomycin + cefepime or meropenem	-If <i>S. pneumoniae</i> , add dexamethasone (reduces neurologic sequelae) -Remove hardware if possible (e.g., place external ventricular catheter in place of shunt)
Community Acquired Pneumonia (CAP) <a href="#">(AJRCCM 2019;200:e45)</a>	-viral > bacterial -Legionella, Mycoplasma, Chlamydia ("atypical") - <i>S. pneumoniae</i> (classic lobar PNA), <i>H. influenzae</i> , <i>Moraxella catarrhalis</i> - <i>S. aureus</i> (usually very sick) - <i>Klebsiella</i> (EtOH)	-Healthy outpt: amox > azithromycin or doxy -Outpt with comorbidities: Amox-clav+azithro or doxy, cefpodoxime+azithro or doxy, or levoflox alone -Most inpatients: CTX+azithro, or levo alone -Prior MRSA/PsA OR IV abx in past 90 d: vancomycin+cefepime+azithromycin	-Consider flu testing ± oseltamivir -Consider local azithromycin resistance -Can substitute doxycycline for azithro -Levofloxacin preferred for structural lung disease outpatient -If postviral, consider <i>S. aureus</i> -If empyema, <b>needs drainage</b>
Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP) <a href="#">(CID 2016;63:e61)</a>	-CAP organisms, <i>S. aureus</i> , GNRs including PsA, <i>Stenotrophomonas</i>	-vancomycin+cefepime	-Consider local MDRO prevalence
Endocarditis <a href="#">(Circ 2015;132:1435)</a>	-Native: <i>S. aureus</i> , strep, enterococci, few GNRs, HACEK -Prosthetic: <i>S. aureus</i> , <i>S. epidermidis</i> most likely; others above rarely	-Native: vancomycin+ceftriaxone -Prosthetic: vancomycin+gentamicin+rifampin, but ask ID	-Early ID consult improves mortality and can help guide empiric therapy early based on patient characteristics!! -MSSA: β-lactam >> vancomycin
Cholecystitis/ Cholangitis <a href="#">(CID 2010;50:133)</a>	- <i>E. coli</i> , <i>Klebsiella</i> , enterococci, anaerobes -Often polymicrobial	-CTX+MNZ, cipro+MNZ -Nosocomial/severe: cefepime+MNZ, piperacillin-tazobactam, imipenem, meropenem	-Source control: CCY, ERCP, or perc choly -Consider vancomycin if c/f enterococci -Often polymicrobial → broad abx for 48 h even if BCx growing only 1 organism
Other Intra-abdominal <a href="#">(CID 2010;50:133)</a>	-Abscess: GNRs, anaerobes, enterococci, <i>Candida</i> , polymicrobial -Diverticulitis: GNRs, anaerobes, rarely enterococci, polymicrobial	-CTX+MNZ, ciprofloxacin+MNZ -Nosocomial/severe: cefepime+MNZ, piperacillin-tazobactam, imipenem, meropenem	-Drain if abscess -Surgical evaluation if peritonitis, perforation, fistula, recurrent diverticulitis
Spontaneous Bacterial Peritonitis (SBP) <a href="#">(Hep 2021;74:1014)</a>	-Enteric GNR, streptococci, enterococci; rarely anaerobes	-ceftriaxone, cefotaxime	-Ciprofloxacin reserved for patients w/ β-lactam allergies and used for ppx -Initiate ppx after first episode of SBP
UTI (non-pregnant) <a href="#">(CID 2011;52:e103; CID 2010;50:625)</a>	-Uncomplicated: <i>E. coli</i> , <i>Klebsiella</i> , <i>S. saprophyticus</i> , <i>Proteus</i> -Complicated (i.e. systemic infxn, pyelo): above + enterococci, PsA, <i>Serratia</i> , <i>Providentia</i> -CAUTI: above + other GNRs	-Uncomp: nitrofurantoin, TMP-SMX, fosfomycin -Complicated: CTX, ciprofloxacin/levofloxacin -CAUTI: vancomycin+ceftriaxone -Cefepime if c/f PsA, carbapenem if c/f ESBL	-Do not treat asymptomatic bacteruria in nonpregnant immunocompetent patients -Exchange Foley, consider repeat UA/UCx 48 h later if CAUTI
Osteomyelitis <a href="#">(CID 2012;54:e132; CID 2015;61:e26)</a>	-Hematogenous source: <i>S. aureus</i> -Direct inoculation/vascular: <i>S. aureus</i> > strep, PsA, GNR, enterococci, <i>Escherichia</i> (human bite), <i>Pasteurella</i> (animal bite)	-No abx if HDS, no signs c/f cord compression, and awaiting bone biopsy -Vanc+CTX; cefepime if DM/PAD ulcer or direct inoculation	-Dx: CRP, ESR, MRI, bone biopsy -Debride (ortho/vasc surg/plastics) w/ bone bx+cx -Use unasyn if originated from bite
Septic Arthritis <a href="#">(Infect Dis Clin North Am 2017;31:203)</a>	-staph, strep, <i>N. gonorrhoeae</i> , PsA (PWID), Lyme	-vancomycin+ceftriaxone (consider cefepime if PWID or other risk factor for PsA) -Definitive rx is a joint wash out	-Dx: fluid aspirate with >50k WBC -Consult ortho for joint washout asap -Blood+joint fluid cx prior to abx
Skin/Soft Tissue (SSTI) <a href="#">(CID 2014;59:e10)</a>	-Impetigo: <i>S. aureus</i> > strep -Cellulitis/Erysipelas: strep > staph -Nec fasc: strep, <i>C. perfringens</i> , MRSA	-Purulent: vancomycin -Non-purulent: cefazolin -Bite: ampicillin-sulbactam -Nec fasc: vanc+ [pip-tazo or mero] ± clinda -DM/PAD ulcer: vanc + [CTX or cefe]	-If abscess, drain -If nec fasc (rapid spread, crepitus, pain out of proportion), URGENT SURGICAL EVAL -If nec fasc, clinda meant to inhibit exotoxin production
Septic shock, no source <a href="#">(Intensive Care Med 2017;43:304)</a>	-GNRs, <i>S. aureus</i> , streptococci, PsA, anaerobes -Consider TSS	-vanc+cefe±MNZ, vanc+pip-tazo -Concern for MDRO: carbapenem -Critical illness: consider 1 dose aminoglycoside -TSS: add clindamycin	-Start antibiotics within 1 h of recognition -Amikacin generally the aminoglycoside of choice for critical illness
Febrile Neutropenia (T≥100.4F & ANC<500) <a href="#">(CID 2011;52:e56)</a>	-Source not identified ~70% of time -When source is identified, 60% GPCs (CoNS > <i>S. aureus</i> , streptococci, enterococci), 40% GNRs ( <i>E. coli</i> , <i>Klebsiella</i> > PsA)	-cefepime -Suspect CLABSI, SSTI, PNA, mucositis: add vancomycin -HDUS, GPCs on BCx: add vancomycin -Persistent fevers > 4-7 d: consider micafungin	-Start antibiotics within 1 h of fever -If afebrile x 72 h or ANC > 500, consider de-escalation -Oral ppx: consider levo or amox-clav + cipro for prolonged neutropenia

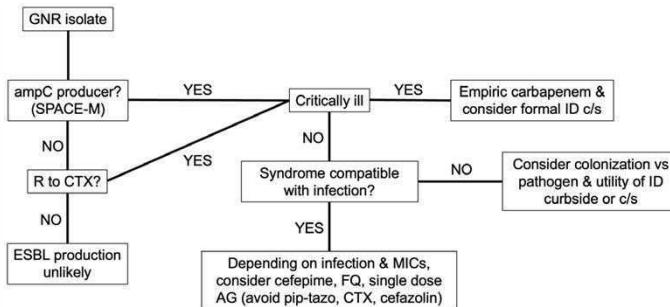
# Infectious Disease

# Multidrug Resistant Organisms

MDR GNRs ([CID 2021;72:169](#))

## AmpC $\beta$ -Lactamase (cephalosporinase)

- Mechanism: Inactivate 3<sup>rd</sup> gen cephalosporins & piperacillin-tazo. Constitutive (plasmid-mediated) or inducible (chromosomal). Inducible form is turned on by accumulation of cell wall fragments due to  $\beta$ -lactam inhibition of penicillin-binding proteins.
- Pathogens: Inducible AmpC producers include MISPACE (aka SPICE, SPACE-M) organisms: *Morganella spp.*, Indole-positive *Proteus spp.* (non-*mirabilis*), *Serratia spp.*, *Providencia spp.*, *Acinetobacter spp.*, *Citrobacter spp.*, *Enterobacter spp.*
  - MISPACE organisms don't equally produce AmpC; *E. cloacae*, *K. aerogenes* (formerly *E. aerogenes*), & *C. freundii* are highest risk ([CID 2021;74:2089](#)).
- Treatment: Do not treat these organisms with 3<sup>rd</sup> gen ceph (e.g., CTX), even if the micro lab report says "susceptible."
  - If critically ill, treat with meropenem or **cefpime** if MIC  $\leq 2 \mu\text{g/mL}$ . Generally, cefepime noninferior to meropenem ([CID 2013;57:781](#)).
  - If not critically ill, can de-escalate to alternatives (e.g., FQ, TMP-SMX, or nitrofurantoin [only cystitis]) if susceptible.



## Extended-Spectrum Beta Lactamases (ESBL)

- Mechanism: Plasmid-mediated, inactivate most  $\beta$ -lactams (penicillins, cephalosporins, aztreonam).
- Pathogens: *Klebsiella spp.* (#1), *E. coli* (#2), *Proteus mirabilis* (#3), other GNR
- Risk Factors: Abx w/in past 6 mo, long hospitalization, nursing home occupancy, >65 yo, lines/catheter/tubes/ventilator, TPN, HD
- Laboratory detection: MGH infection control defines potential ESBL as a GNR resistant to ceftriaxone.
- Treatment: Avoid penicillins and cephalosporins (including piperacillin-tazobactam) even if "susceptible" ([JAMA 2018;320:984](#))
  - If not critically ill, possibly use **cefpime** if MIC  $\leq 2 \mu\text{g/mL}$  ([CID 2014;58:1554](#)) or  $\beta$ -lactam alternatives if susceptible ([CID 2017;64:972](#)). TMP-SMX, nitrofurantoin, fosfomycin, or single-dose aminoglycoside preferred for simple cystitis.
  - If critically ill or prior ESBL-positive BCx, empiric treatment with **imipenem-cilastatin** or **meropenem**

## Carbapenem Resistant Enterobacteriaceae (CRE)

- Mechanisms: Inactivating carbapenemase, porin loss (limits penem entry), efflux pump extrusion, or combination of factors
- Risk Factors: Cephalosporin or carbapenem use in past 3mo (\*\*penem exposure not required\*\*), medical care in India/Pakistan
- Laboratory detection: Suspicious when MIC  $> 2 \mu\text{g/mL}$  for imipenem, meropenem, or ertapenem
- Treatment: Preferred option is usually **ceftazidime-avibactam** (+aztreonam if care in India/Pakistan); **C/s ID**
  - Meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also active
  - Alternatives may include extended-infusion meropenem (if MIC  $\leq 1 \mu\text{g/mL}$ ), aminoglycoside, polymyxins, or tigecycline.
  - If uncomplicated UTI – FQ, TMP-SMX, nitrofurantoin, fosfomycin, or single-dose aminoglycoside if susceptible.

## Difficult-to-Treat Resistance *Pseudomonas aeruginosa* (DTR-PsA)

- Definition: Non-susceptible to pip-tazo, ceftazidime, cefepime, aztreonam, fluoroquinolone, meropenem, AND imipenem-cilastatin
- Treatment: **Ceftolozane-tazobactam** usually preferred but other options (e.g. ceftazidime-avibactam, cefiderocol, etc.); **C/s ID**

## METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

**Community-associated MRSA:** no healthcare exposure, SSTI in young & healthy patient

- Risk Factors: HIV, PWID, prior antibiotic use; outbreaks: incarceration, military, sports, sharing needles/razors

**Healthcare-associated MRSA:** occurs >48h following hospitalization or w/in 12mo of healthcare exposure

- Risk Factors: recent hospitalization/surgery, HD, LTC facility residence
- Nasal swab: NPV in CAP = 96.5% ([CID 2018;18:1](#)) if  $\ominus$  consider d/c MRSA coverage. MGH use [Antimicrobial De-escalation Guidelines](#) in HAP/VAP; emerging evidence that NPV for Staph infection at other sites is also high ([CID 2020;71:1142](#)).

## Treatment

- Check the vanc MIC: Vanc susceptible if MIC  $\leq 2 \mu\text{g/mL}$  (though ↑ tx failure and mortality when MIC = 2  $\mu\text{g/mL}$ ), Vanc-intermediate (VISA) if 4  $\mu\text{g/mL} \leq \text{MIC} \leq 8 \mu\text{g/mL}$ , Vanc-resistant (VRSA) if MIC  $\geq 16 \mu\text{g/mL}$
- Serious infections (i.e. bacteremia): **vancomycin** (consider [AUC dosing](#), trough ~15-20) and **ID consult** ([J Infect. 2016;72:19](#)). If persistent bacteremia or MIC  $\geq 2 \mu\text{g/mL}$ , consider switching to **daptomycin** (not in PNA or meningitis), adding ceftaroline ([Antimicrob Agents Chemother. 2018;62:01554](#)), or both ([Open Forum Infect Dis 2019;7:538](#)).
- Mild infections (e.g., SSTI): TMP-SMX, doxycycline >> clindamycin (increased resistance at MGH); linezolid

## VANCOMYCIN RESISTANT ENTEROCOCCI (VRE)

- E. faecium*: often resistant & generally less virulent. *E. faecalis*: more virulent but highly Amp<sup>S</sup> at MGH.
- RFs: prior abx, Foley, indwelling lines; proximity to other VRE pts; long hospitalization/SNF; immunocompromised
- Clinical sites of infection: UTI (often an **asymptomatic colonizer**); bacteremia (2<sup>nd</sup> most common CLABSI); intra-abdominal and pelvic infections; endocarditis (esp. if prosthetic valve); meningitis (immunocompromised or VP shunt)
- Treatment:
  - Invasive infection (e.g., bacteremia, endocarditis): daptomycin (+ amp or CTX or ceftaroline), linezolid; **ID c/s**
  - Uncomplicated UTI: fosfomycin x1 (consider repeat dose on days 4 and 7) or nitrofurantoin

# Infectious Disease

# Community Acquired Pneumonia

## COMMUNITY ACQUIRED PNEUMONIA (CAP) ([AJRCCM 2019;200:45](#))

- **Definition:** PNA acquired in the community, including patients from nursing homes, dialysis, or with outpatient clinic exposure
- **Diagnosis:** new CXR opacity AND s/sx (e.g. fever, cough, leukocytosis, purulent sputum, hypoxemia)
  - Elderly at ↑ risk of blunted s/sx but also ↑ prevalence of atelectasis/aspiration
  - Radiographic consolidation NOT specific for bacterial vs viral PNA
  - If CXR ⊖ but high clinical suspicion → tx and repeat CXR in 24h (PNA may "blossom" after fluid resuscitation and/or time); if still ⊖ → consider chest CT or other dx
- **Triage:** CURB-65 (Confusion, BUN>20, RR>30, BP<90/60, age>65) → outpatient if score 0-1, inpatient if 2, consider ICU if 3-5. Pneumonia Severity Index (PSI) more comprehensive → outpatient if <70, inpatient if >90
- **Severe CAP (ATS/IDSA Criteria): 1 Major:** pressors or mech vent, OR **3 Minor:** RR>30, P:F<250, multilobar infiltrates, confusion, BUN>20, WBC<4K (not due to chemo), plt<100K, T<36C, HoTN requiring aggressive fluid resuscitation
- **Micro:** S. pneumoniae (most common in inpts, ICU), H. influenzae, GNRs, S. aureus, Legionella. Most common pathogens identified are viruses – rhinovirus, influenza, others ([NEJM 2015;358:415](#))
- **Work-up (inpatient):**
  - **Sputum culture and gram stain** (ET aspirate if intubated): adequate sample if >25 PMN/lpf and <10 SEC/lpf. NOTE: "abundant squamous cells" or more squamous cells than polys suggests the sample is saliva
  - **Blood cultures:** controversial benefit, positive <20% of inpt PNA, 2/3<sup>rd</sup> of positive Cx are S. pneumoniae
    - Obtain Scx and Bcx if: severe CAP, empiric treatment for MRSA/PsA, prev. MRSA/PsA, or hosp. w/ IV abx ≤90d
  - **Procalcitonin (PCT):** ↑ in acute resp. infxn from bacterial causes. No validated threshold to distinguish bacterial vs. viral infxn. ([ATS 2019;200:45](#)). Can be helpful when deciding to dc abx; dc if <0.25 or >80% drop from peak. ([JAMA 2009;302:1059](#))
  - **Legionella urine Ag** (Sn 70%, Sp 99%); detects only serogroup 1 (80-90% in US). Check if severe CAP or recent exposure/travel. Clinical predictors include hypoNa, fever, diarrhea, and recent travel ([CID 2019;68:2026](#))
  - **MRSA nasal swab:** high NPV (~98%). ⊖ test → consider d/c MRSA coverage ([CID 2018;67:1](#))
  - **Influenza:** test seasonally. **Tx:** oseltamivir (see URI page for tx indications)
- **IDSA/ATS CAP Empiric Treatment** (NOTE: additional considerations for travelers, immunocompromised) ([ATS 2019; 200:45](#))
 

Outpatient	Preferred	Alternative/Other info
No Comorbidities or MRSA/PsA RFs	Amox 1g TID OR doxy 100mg BID OR macrolide (azithro OR clarithro) ( <u>if local resistance &lt;25%</u> )	<u>NOTE: U.S. has high rates of macrolide- and doxy-resistant S. pneumo</u>
Comorbidities°	[Amox-clav 2g BID <u>AND</u> azithro] <u>OR</u> levofloxacin 750mg QD monotherapy	Cefpodox or cefurox. can replace amox-clav, doxy can replace azithro
Inpatient	Preferred	Alternative/Other info
Non-Severe	(β-lactam [CTX] <u>AND</u> macrolide [azithro]) <u>OR</u> levofloxacin monotherapy	Amp/sulb can replace CTX, clarithro can replace azithro
Severe/ICU	β-lactam (CTX 1-2g QD) <u>AND</u> (azithro OR levofloxacin)	<b>In ICU, azithro &gt;&gt; levofloxacin (anti-inflamm. effect);</b> consider add'l agents for drug-resistance (see below)
MRSA/PsA RFs*	Vancomycin <u>AND</u> ceftazidime	Obtain Cx and nasal MRSA swab to inform de-escalation. Do not use daptomycin (poor lung penetration)

°Chronic heart, lung, liver, or renal disease; DM; AUD; malignancy; or asplenia.

\*Prior resp. isolation of MRSA/PsA, hospitalization w/ IV abx ≤90d.

- **Risk factors for drug-resistant pathogens in CAP:**
  - General: hospitalization & IV abx in past 90d; prior respiratory isolation of MRSA, PsA or other resistant organisms
  - PsA: GNR on gram stain, h/o PsA, bronchiectasis, COPD w/ freq exacerbations req abx/steroids. **Tx:** (for normal renal function) ceftazidime 2g q8h, ceftazidime 2g q8h, pip-tazo 4.5g q6h, mero/imipenem; double coverage usually not necessary
  - MRSA: GPC clusters on gram stain, recent flu-like illness, necrotizing/cavitation/empyema, ⊕ nasal swab, risk factors for colonization (ESRD, IVDU, prior abx [esp. fluoroquinolones]). **Tx:** vancomycin or linezolid
- **Anaerobic coverage:** only if suspicion for empyema or lung abscess, (see HAP/VAP & Aspiration Pneumonia)
- **Steroids:** some data for benefit in severe CAP but not routinely used, not rec. by IDSA/ATS unless o/w indicated for refractory septic shock or COPD/other comorbidity ([Cochrane Rev 2017](#)). **AVOID** in INFLUENZA as might ↑ mortality ([Cochrane Rev 2016](#))
- **Duration:** usually **5d; 7d** in suspected or proven MRSA or PsA CAP, assuming clinical stability (afebrile x48h + ≤1 sign of CAP instability: HR >100, RR >24, O2<90%, AMS, no PO intake). MRSA should be treated longer if not improving within 72h (e.g. 10-14d in critically ill, 2-6w with ID consult if c/b bacteremia or necrotizing PNA)
  - If have not achieved clinical stability, extend course & eval. for resist. pathogen, complication (empyema, abscess), alt. source
  - Convert IV → PO when clinically improving; **no need to observe x24h on PO**
- **Response to therapy:** tachycardia resolves by 2-3d; fever resolves by 2-4d; hypoxemia resolves by 3-6d.
  - CXR clears by 1mo in 50% (up to 12wks in elderly, lung disease); **do not** need repeat CXR if clinical improvement
  - If no response to therapy after 72h: consider chest CT (± BAL) to evaluate for empyema, abscess, fungal infxn.
- **Parapneumonic effusion:** exudative, develops adjacent to a pneumonia, 20-57% of PNA hospitalizations ([CID 2007;45:1480](#)). Appropriately sized effusions need diagnostic thora for evaluation esp if concern for infxn.
  - **Definitions:** Uncomplicated (~pH >7.2/glucose >60, ⊖ GS/Cx) → complicated (requires drainage, pH <7.2/glucose ↓, still ⊖ GS/Cx) → empyema (requires drainage, frank pus, + GS/Cx).
  - **Management:** Uncomp. effusions ok for abx alone if <1/2 hemithorax & free flowing; consider therap. thora if symptoms. Chest tube after diag. thora if: empyema, loculation, >1/2 hemithorax, thickened parietal pleura, sepsis w/ suspected pleural source ([Chest 2000;118:1158](#); [Ann Thor Surg 2018;105:1589](#))
  - Duration of abx, utility of surgery, timing of repeat imaging: guided by severity and clinical/radiographic progression

# Infectious Disease

# HAP/VAP & Aspiration Pneumonia

HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA (IDSA/ATS: [CID 2016;63:e61](#))

## Definitions:

<b>Hospital-acquired pneumonia (HAP)</b>	Pneumonia that develops $\geq 48\text{h}$ after admission
<b>Ventilator-associated pneumonia (VAP)***</b>	Pneumonia that develops $\geq 48\text{h}$ after endotracheal intubation
<b>Dx criteria:</b> new/progressive infiltrates on CXR + 2/3 of fever, leukocytosis, purulent tracheal secretions	

\*\*\*Ddx also includes non-infectious ventilator-associated events (VAEs) such as atelectasis, ARDS, pulmonary edema, and pulmonary embolism ([Ann Transl Med. 2018; 6: 425](#); [Infect Control Hosp Epidemiol. 2017; 38:867](#))

**Common microbiology:** enteric GNRs (*Klebsiella*, *E. coli*), MRSA/MSSA, *PsA*, *Acinetobacter*

**Workup:** CXR, SpCx, BCx, MRSA swab; consider induced sputum, bronch with BAL

**MDRO RFs:** IV abx use w/in 90 days preceding onset (most important); high local prevalence (>10%) of MDR GNRs & MRSA; structural lung disease (CF, bronchiectasis); prior hx of MDRO infection

- **MDR VAP RFs:** septic shock/ICU, ARDS, onset  $\geq 5\text{d}$  in hospital, or RRT preceding onset

**Empiric Tx of HAP/VAP w/ MDRO risk:** 1 anti-PsA ( $\beta$ -lactam pref.) AND 1 anti-MRSA agent (typically **vancomycin**)

- Consider double PsA coverage if: septic shock, rapid progression of PNA requiring mech. ventilation, hx of MDR PsA
- Pulmonary toilet (oral hygiene, oral and subglottic suctioning, mucolytics, etc.) ([Crit Care. 2008;12:209](#))

Antipseudomonal $\beta$ -lactams	Antipseudomonal non- $\beta$ -lactams	Anti-MRSA agents
<ul style="list-style-type: none"><li>- Cefepime 2g IV q8h</li><li>- Ceftazidime 2g IV q8h</li><li>- Pip/Tazo 4.5g IV q6h</li><li>- Meropenem 1g IV q8h</li><li>- Aztreonam 2g IV q8h (only if severe PCN allergy: <a href="#">Ellucid</a>)</li></ul>	<ul style="list-style-type: none"><li>- Levofloxacin 750mg IV qd (*PsA susceptibility only 70% at MGH)</li><li>- Ciprofloxacin 400mg IV q8h</li><li>- Tobramycin 5-7mg/kg IV x1, then dose by level</li><li>- Polymyxin B (call ID)</li></ul>	<ul style="list-style-type: none"><li>- <a href="#">Vancomycin IV</a></li><li>- Linezolid 600mg q12h</li></ul>

*Always adjust dosing for renal function. When in doubt, call Pharmacy!*

## • Tailoring therapy:

- Improvement after 48h or pathogen ID'd: narrow abx and d/c MRSA+PsA coverage if possible. ⊖ MRSA swab w/ 96% NPV for MRSA infection, most evidence comes from swab on admission and not further into course ([CID 2018;18:67](#); [CID 2020;71:1142](#)). VAP: ⊖ tracheal aspirate NPV 94%, consider d/c abx after 72h ([IJD 2010;14:18](#))
- No improvement after 48h: broaden to cover MDROs (if not already), consider other sites of infection/abscess, non-infectious causes of clinical syndrome
- [MGH Ellucid Policy: HAP/VAP De-escalation Algorithm](#)

- **Duration:** 7d. Consider serial procalcitonin → d/c abx when <0.25ng/mL ([ERJ 2009;34:1364](#))

## ASPIRATION PNEUMONIA ([NEJM 2019;380:651](#))

- **Definition:** pneumonia secondary to excessive secretions, particulate matter, or fluid into airways. Micro-aspirations are common and the definition of aspiration pneumonia as a distinct clinical entity remains unclear. Aspiration PNA/pneumonitis are often result of larger volume/frank aspiration events
- **Predisposing factors:** AMS/dementia, esophageal dysmotility, post-bronchial obstruction, post extubation, gum disease/poor dentition, seizure, tube feeding
- **Microbiology:** most common organisms are GNRs and standard CAP/HAP organisms ([AJRCCM 2003;167:1650](#)). Role of anaerobes is likely overstated ([Chest 1999;115:178](#))
- **Characteristics:** indolent, putrid sputum, pulmonary necrosis w/ cavitation/abscess/empyema
- **Workup:** CXR, SpCx (anaerobic respiratory culture not performed at MGH due to low utility)
- **Empiric treatment:** same as CAP/HAP empiric treatment ([AJRCCM 2019;200:e45](#); [JHM 2020;15:754](#))
  - **Anaerobic coverage:** only recommended in pts w/ **suspected lung abscess** or **empyema**. First line: ampicillin-sulbactam if not severely ill, pip-tazo if severely ill, amox-clav if outpatient; alternative: (CTX+MNZ) OR clindamycin
  - **Duration:** 7d unless complicated by cavitation/abscess/empyema
- No clear clinical benefit for abx for ppx for aspiration unless pt symptomatic ([CID 2018;67:513](#))

## ASPIRATION PNEUMONITIS

- **Definition:** aspiration of chemical substances into the airways without bacterial infection
- **Clinical manifestations:** abrupt onset (2h), low-grade fever, ↑WBC, hypoxemia, CXR consolidation (RML/RLL upright, RUL supine) → often indistinguishable from pneumonia in the acute setting
- **Treatment:** no mortality benefit in initiating antibiotics in a patient with aspiration pneumonitis, however since it is clinically difficult to distinguish from PNA in the acute setting generally initiate empiric abx and reassess q24h → d/c if culture data remains negative AND if signs/sx/consolidation resolve rapidly

# Infectious Disease

# Viral Respiratory & Head & Neck Infections

## VIRAL RESPIRATORY INFECTIONS (for COVID-19; for bacterial pharyngitis see HEENT Concerns)

- **Epidemiology**
  - >200 viral pathogens may cause VRIs, most common include rhinovirus, influenza, coronavirus, parainfluenza
  - LRTI (bronchitis, bronchiolitis, PNA): coronavirus, influenza, RSV, parainfluenza, adenovirus ([Lancet 2011;377:1264](#))
  - In immunocompromised hosts, consider reactivation of latent viruses (HSV, CMV, adenovirus)
- **Presentation**
  - Transmission: hand contact, small droplets that become airborne, large droplet, peak viral shedding at 2-3d of illness
  - Symptoms: nasal congestion, rhinorrhea, dry/sore throat, cough, fever, conjunctivitis, myalgias w/ sx peaking at 3-5d and lasting 10-14d (if significant systemic illness consider influenza, COVID19 >> measles, SARS, Hantavirus)
  - Complications: bacterial PNA (occurs in 1/800 w/ initial improvement → worsening after ~7d, micro: S. pneumo, S. aureus), asthma/COPD exacerbation, secondary bacterial sinusitis (occurs 2/100), otitis media, ARDS
- **Diagnosis**
  - Clinical diagnosis that generally does not require microbiological testing except for influenza and COVID-19
  - Resp. viral panel: at MGH NP swab PCR (PRO) for COVID19, Flu A/B, RSV; can help avoid unnecessary abx; collect w/in 5d of sx onset. Consider extended PRO for immunosupp or initial PRO negative w/ high clinical suspicion for viral URI
  - Influenza testing: (IDSA: [CID 2019;68:895](#))
    - RT PCR most sensitive and specific; can differentiate A, B and subtypes (1-8h)
    - Rapid molecular assay 92% Sn, 96% Sp, can differentiate A, B (15-30min)
    - Rapid Ag test 62% Sn, 98% Sp (<15min); during season ⊖ test does not exclude, not sufficient to stop tx
- **General Viral URI Treatment**
  - Sx management with decongestants, nasal sprays, anti-inflammatory agents, humidified air. No role for ppx abx
  - COVID-19 specific treatments: dexamethasone ([NEJM 2021;384:693](#)), remdesivir ([NEJM 2020;383:1813](#)) in select patients. See [Handbook](#) for most up to date guidance.
- **Influenza Treatment and Post-Exposure Prophylaxis**
  - Treatment: oseltamivir 75mg BID x5d (can extend in severely ill or immunocompromised)
    - Indications: hospitalized pts. and outpts. w/ severe or progressive dz regardless of illness duration, ↑ risk (age >65, long-term care facility resident, pregnant, <2 wks post-partum, immunosuppressed, cirrhosis, DM, CHF/CAD, CKD, COPD, SCD, asthma, BMI >40, neuro dz) also regardless of illness duration
    - Consider: outpts with sx <48h or those with high-risk household members
  - Prophylaxis: oseltamivir 75mg qd x7d if ≤48h post-exposure (x14d ± additional 7d after last case if outbreak at long-term care facility); switch ppx → treatment dosing (IDSA: [CID 2019;68:895](#))

## HEAD AND NECK INFECTIONS (Principles of Crit Care. Chow AW. 4th edition. McGraw-Hill, NY 2015)

- Epidemiology: often from odontogenic, otogenic or sinogenic infection with contiguous spread
- Organisms: Streptococci, H flu, oral anaerobes. PsA in otogenic source. MRSA in sinogenic source and PWID
- Diagnostics: blood cultures, **CT Neck**, MRI (consider to evaluate for osteo), IR or ENT for tissue or abscess culture
- Empiric Treatment: varies based on likely source; odontogenic – amp-sulbactam or CTX+MNZ, otogenic - cefepime+MNZ, sinogenic - vancomycin+CTX+MNZ. **Involve ENT early** for drainage and airway monitoring
  - **Submandibular space** (Ludwig angina): sources- periodontal infection, peritonsillar abscess, parotitis; p/w mouth pain, "double tongue," drooling, dysphagia can rapidly progress to airway compromise; polymicrobial esp viridans Strep
  - **Internal jugular septic thrombophlebitis** (Lemierre syndrome): pharyngitis and septic emboli (esp lungs). Most commonly *Fusobacterium necrophorum* or viridans Strep. Treat with abx ± anticoagulation
  - **Deep neck space**: involving retropharyngeal, "danger," or paravertebral spaces. Presents with neck pain and systemic toxicity. Can progress to carotid sheath abscess, mediastinitis, vertebral osteo, paravertebral abscess

## ORBITAL AND PRESEPTAL CELLULITIS ([Surv Ophthalmol 2018;63:505](#))

	Preseptal/Periorbital	Orbital
<b>Definition</b>	Infxn anterior eyelid (not orbit or ocular structures)	Infxn of orbit contents (fat, ocular muscles) but not the globe
<b>Pathogenesis</b>	Local trauma	Rhinosinusitis, oral abscess, dacryocystitis, local trauma, direct inoculation, ophthalmic surgery
<b>Organism</b>	Staph aureus, Strep spp.	Staph aureus, Strep spp; in immunosupp. consider Mucor and Aspergillus
<b>Symptoms</b>	Eyelid pain, edema, erythema ± chemosis & fever	Preseptal sx + pain with eye movement, proptosis, ophthalmoplegia w/ diplopia, fever & chemosis common
<b>Diagnosis</b>	Clinical; CT orbit and sinus to r/o orbital	Clinical + CT orbit & sinus, blood cx; LP if c/f CNS extension, MRI if c/f cavernous sinus thrombophlebitis
<b>Empiric Treatment</b>	Augmentin 875mg q12h ± Bactrim 1-2 DS q12h OR Clindamycin 600mg q8h	Vancomycin + CTX; add MNZ if c/f CNS involvement or odontogenic/sinogenic spread, involve ophtho early
<b>Complications</b>	Rare: eyelid necrosis, amblyopia	Vision loss, orbital/subperiosteal abscess, CNS spread

# Infectious Disease

# Urinary Tract Infections

## ASYMPTOMATIC BACTERIURIA

**Definition:** bacteriuria ( $\geq 10^5$  CFU/mL) w/o sx referable to a UTI, irrespective of pyuria

- **Treatment:** asymptomatic bacteriuria or pyuria should NOT be treated (*exceptions*: pregnant woman, s/p renal transplant in past 1mo, treatment prior to invasive urologic procedures) (IDSA: [CID 2019;68:1611](#))

## UTI

**Clinical features:** frequency, urgency, dysuria (premenopausal), incontinence, nocturia, suprapubic tenderness in otherwise healthy nonpregnant women. In men w/ UTI sx, consider a dx of prostatitis, evaluate the prostate w/ DRE.



**Complicated UTI?** Acute UTI + any of: fever, chills/rigors/sx of systemic illness, CVA tenderness/flank pain, pelvic or perineal pain in men, pregnant, renal transplant

No ↓

↓ Yes

### Uncomplicated UTI (Cystitis) ([JAMA 2014; 312:1677](#))

- **Diagnosis:** clinical; U/A can be used to confirm; pyuria ( $>10$  WBC); nitrite and LE both  $\oplus$  on dipstick  $\rightarrow$  Sn 68-88%
  - **Women:** dysuria + ↑frequency w/o vaginal discharge/irritation  $\rightarrow$  >90% likelihood of UTI. Outpatient, U/A unnecessary unless immunocompromised or RFs for complicated UTI
  - Absence of pyuria *strongly suggests against cystitis*
  - **Nitrite:**  $\oplus$  w/ Enterobacteriales (convert nitrate  $\rightarrow$  nitrite)
  - Outpatient, get UCx if: male, atypical sx, persist 48-72h after abx initiated, or recur w/in 3 mo of tx
- **Differential diagnosis:** vaginitis, urethritis, structural abnormality, PID, nephrolithiasis
- **Microbiology:** *E. coli*, *Klebs*, *Proteus*, *S. Saproxyticus*, ***Enterococcus rarely causes true infection***
- **Treatment:** NFT 100mg BID x5d OR T/S DS BID x3d OR **fosfomycin** 3g x1; alternatives: oral  $\beta$ -lactam (e.g. Augmentin 500mg BID, Cefpodoxime 200mg BID) x7d, single dose aminoglycoside if c/f MDRO ([Antimicrob 2019;63:e02165](#); [MGH Policy Ellucid](#))
  - Avoid NFT if CrCl <40
  - Avoid empiric T/S if resistance >20% (*E. Coli* resistance 27% at MGH)

### Complicated UTI

- 30% w/ UTI **and** fever are bacteremic (usually older, flank / suprapubic pain, ↑CRP, ↓BP) ([JAMA 2018;378:48](#))
- **Pyelonephritis is a complicated UTI** & may itself be complicated by perinephric or renal abscess
  - WBC casts on U/A are suggestive of pyelo
- **Microbiology:** same as uncomp. UTI plus *Serratia*, *Morganella*, *Providencia*, *Pseudomonas*, *Citrobacter*. Gram-positives rare. If *S. aureus*, think bacteremia. Increasingly resistant organisms (especially to FQ, TMP/SMX)
- **Dx:** UCx in all; imaging if ill, suspect obstruction, persistent sx
- **Treatment:** Outpt: CPO 500mg BID OR LVO 750mg x5-7d OR T/S DS BID x7-10d. Can give 1x IV CTX prior to oral tx. Inpt: CTX OR CEFE OR P/T; CBPN if c/f ESBL. Narrow to oral if improving. Duration for inpt: depends on clinical course & oral agent chosen (5-7d for FQ; 7-10d for T/S; 10-14d for  $\beta$ -lactam), consult ID and IR for associated abscesses
  - Avoid **NFT & fosfomycin** (poor for upper GU track)
  - Remove/replace coated urologic devices
  - **Prostatitis:** FQN preferred for better penetration (can also consider TMP-SMX); tx duration up to **6w**

## CATHETER-ASSOCIATED UTI (CAUTI) (IDSA: [CID 2010; 50:625](#))

- **Definition:** leading healthcare-assoc. infection; requires: (1) s/sx with no other identified source of infection; **AND** (2) UCx with one uropathogenic species  $>10^3$  CFU/ml from single catheterized urine specimen (catheter in place  $>2$ d) **OR** midstream voided specimen from pt whose catheter was removed w/in previous 48h
  - In pts w/ neurogenic bladder and ↓ sensation, other signs of UTI include new onset incontinence, autonomic hyperreflexia, malaise, lethargy, bladder pain ([Urology 2015;6:321](#))
- **Prevention:** restrict catheters to pts w/ appropriate indications; remove catheters ASAP; consider short-term straight cath
- **Dx:** do not screen asx patients; pyuria, turbidity, odor cannot differentiate asymptomatic bacteriuria from CAUTI
  - **Remove/Replace** catheter ASAP, obtain repeat UA/UCx from new catheter PRIOR to abx. Catheters may become coated with a biofilm that acts as a reservoir for microorganisms and can compromise the action of antibiotics and host defenses
  - Purple urine bag syndrome: occurs due to byproducts from bacterial enzymes in urine; benign and  $\neq$  UTI
- **Micro:** same as complicated UTI, with addition of *Candida* (see below); can be polymicrobial
- **Treatment:** same abx as complicated UTI, use Cx to narrow. If recent catheterization/instrumentation, h/o MRSA in urine, add vanc, then narrow pending culture results. Duration: 7d if improving; 10-14d otherwise

## FUNGURIA (IDSA: [CID 2016;62:e1](#))

- Asymptomatic colonization common; only treat if symptoms present OR neutropenic OR before urologic procedure
- Tx: Fluc 200-400mg (pyelo) PO qd x14d OR for resistant *C. glabrata* or krusei, Amphotericin 0.3-0.6 mg/kg qd x1-7d

## RECURRENT UTI

- Behavior Δs: 2-3L water intake daily, post-coital voiding, avoid spermicide use, wiping front to back for pt. w/ female anatomy
- Abx ppx (usually ↓dose T/S or NFT) may be used in some ♀ w/ recurrent simple cystitis ( $\geq 2$  UTI/6mo) if behavior Δs ineffective. Either post-coital or continuous if no temporal relation to sexual activity ([Cochrane Rev 2004](#)).
- Other inventions include: Vaginal estrogen for post-menopausal women ([Cochrane Rev 2008](#)), possible benefit from D-mannose 2g daily, methenamine hippurate 1g BID ([BMJ 2022, 68229](#)), cranberry products, and *Lactobacillus* probiotics.
- Pts w/ recurrent admission for complicated UTI, review prior micro & consider resistant orgs. Consider ID +/- urology involvement. Abx ppx is not indicated for recurrent complicated UTI with resistant organisms due to risk of ↑ resistance

# Infectious Disease

# Skin & Soft Tissue Infections

## CELLULITIS (IDSA: [CID 2014;59:147](#); [JAMA 2016;316:325](#))

- **Clinical features:** erythema, warmth, tenderness, edema, induration ± purulence; smooth, often poorly demarcated. May have lymphangitis, LAD, vesicles/bullae, fever (20-77%), leukocytosis (34-50%)
- **Risk Factors:** trauma, venous stasis, chronic edema (esp. lymphedema), immunosuppression (DM, HIV), obesity, PWID, neutropenia, inflammation (eczema, psoriasis, radiation therapy), prior surgery/biopsy, toe web abnormalities
- **Diagnosis: CLINICAL.** Can use [ALT-70 score](#) to avoid unnecessary abx (data req to calc: location, age, WBC, HR) ([J Am Acad Derm 2017;76:618](#); [JAMA Derm 2018;154:529](#)). Consider US to assess for presence of drainable abscess.
  - BCx & wound Cx NOT recommended (low yield, pos in <10%). Obtain if: systemic tox, extensive involvement, immunosuppression, surgical wounds, special exposures (bites, water), recurrent/persistent cellulitis, extremes of age. 20-30% skin bx return pathogen.
- **Differential diagnosis:** (if "bilateral cellulitis," strongly consider alternative diagnosis)
  - Non-infectious: inflammatory (contact dermatitis, drug rxn, Sweet syndrome, gout, bursitis, EN, pyoderma gangrenosum, GVHD); vascular (stasis dermatitis, DVT, superficial thrombophlebitis, calciphylaxis), neoplastic (leukemia cutis, lymphoma)
  - Unilateral: contact dermatitis, gout, drug rxn, vasculitis, insect bite, DVT, vaccine site rxn, erythema ab igne
  - Bilateral: stasis dermatitis, lipodermatosclerosis (often heavily pigmented, thickened subq tissue), lymphedema
  - Infectious: abscess, erysipelas (well demarcated, superficial cellulitis involving upper dermis & superficial lymphatics), nec fasc, septic joint/bursa, osteomyelitis, herpes zoster, HSV, Orf virus, erythema migrans, toxic shock syndrome, mycotic aneurysm
  - If abscess present, ddx includes: folliculitis, cyst, hydrantitis suppurativa (often intertriginous skin), lymphangitis
- **Treatment:** based on 1) **purulence** and 2) **severity**. Elevate affected limb. Duration: 5d; up to 14d if delayed signs of improvement

Severity	Purulent (abscess or fluctuance)	Non-purulent°
Mild	MRSA >> MSSA > Strep I&D only	Strep >> <i>S. aureus</i> > aerobic GNRs PO: cephalexin, cefadroxil, dicloxacillin, pen VK, amox-clav
<b>Moderate:</b> systemic signs of infxn‡ <u>OR</u> abscess >2cm	I&D+Cx. <u>Empiric:</u> TMP-SMX <u>OR</u> doxy MSSA: dicloxacillin <u>OR</u> cephalexin. <u>MRSA:</u> TMP-SMX	IV: cefazolin, CTX, pen G <u>Severe β-lactam allergy:</u> vanc, telavancin
<b>Severe:</b> systemic signs of infxn‡ <u>AND</u> HoTN, immunocomp., rapid evolution, deeper infection, or failed PO tx	I&D+Cx. <u>Empiric:</u> vanc <u>OR</u> LZD <u>OR</u> daptomycin <u>OR</u> ceftaroline. <u>MSSA:</u> naftcilin <u>OR</u> cefazolin	Vanc+(pip-tazo <u>OR</u> cefepime+MNZ). <u>Nec fasc or TSS:</u> add clinda for toxin inhibition

°Non-purulent w/ **MRSA risk factors\*** (prev. MRSA infxn/colonization, hosp./surgery/abx in prev 8wks, PWID, penetrating trauma, hemodialysis, HIV, athletes, prisoners, military, LTC facility residents): add empiric PO/IV MRSA coverage (TMP-SMX or doxy)

\*MRSA incidence increasing and many patients with MRSA infection do not have any risk factors ([Med. Clin 2021;4:723-725](#))

‡Systemic signs of infection include: T >38°C or <36°C, HR >90, tachypnea (RR >20), WBC >12 or <4

NB: erythema may worsen initially; should improve w/ 72h of abx. Document daily photos & draw margin lines.

- **Additional coverage:** anaerobes (if necrosis, crepitus, certain diabetic infxns [see below], animal bite); GNRs (cirrhosis w/ severe infection, immunocompromise, certain diabetic infxns [as below]); PsA (neutropenic, trauma, burns, post-op)
- **Specific associations:** gas gangrene → *C. perfringens*; dog/cat bite → *Capnocytophaga*, *Pasteurella*; animals NOS → *Erysipelothrix*; human bite/PWID → *Eikenella*; freshwater → *Aeromonas*; saltwater → *Vibrio vulnificus* (esp. cirrhosis)
- **Sporotrichoid spread ddx:** sporotrichosis, Nocardia, NTM (e.g. *M. marinum*), Bartonella, tularemia
- **PWID:** infxn sources (H<sub>2</sub>O, syringe, cotton filter, skin flora), share safe injection practices/PrEP (resources: [CDC 1](#); [CDC 2](#))
- **Prevention:** Compression therapy: ↓ recurrence of cellulitis (v conservative therapy (education) alone). Patients should be advised to wear compression stockings daily to shift fluid away from the lower leg ([NEJM 2020;383:630](#))
- PCN ppx effective for reducing recurrent cellulitis over 6 & 12 month periods, but not once ppx stopped ([PATCH, NEJM 2013;368](#))

## NECROTIZING SOFT TISSUE INFECTIONS ([NEJM 2017;377:2253](#))

- **Micro:** Type I: polymicrobial (mixed aerobes/anaerobes); Type II: monomicrobial (usually GAS > Strep, Staph, Vibrio, Aeromonas), associated with TSS; myonecrosis (i.e., gas gangrene): caused by *C. perfringens*, p/w tissue gas, severe pain, toxin-mediated shock
- **Risk Factors:** immunosup., DM (e.g. Fournier gangrene – perineal nec fasc), cirrhosis, neutropenia, EtOH, trauma (even minor), skin/mucosal breach, PAD
- **Clinical manifestations:** pain out of proportion to exam, bullae, induration (risk of compartment syndrome), tissue anesthesia, rapid skin changes (purple-red → blue-grey), crepitus (suggestive of myonecrosis); systemic toxicity, TCK, lactate, Cr, WBC
- **Diagnosis:** early suspicion and involvement of a **surgeon for surgical exploration** and ID is critical
  - [LRINEC score](#) ≥6 high suspicion for nec fasc (uses CRP, WBC, Hgb, Na, Cr, glucose); 90% Sn, 95% Sp ([CCM 2004;32:1535](#))
- **Treatment:** urgent surgical debridement + abx: vanc + mero or cefepime/MNZ or pip-tazo + clinda (NB: LZD also inhibits toxin production). Adjunctive clindamycin may improve outcomes ([Lancet Infect Dis. 2021;21:697](#))

## DIABETIC FOOT INFECTIONS (IDSA: [CID 2012;54:e132](#))

- **Severity:** mild (superficial ulcer, no involvement of deeper structures, erythema <2cm); moderate (ulcer with involvement of deeper structures or erythema >2cm); severe (moderate + systemic signs of infxn)
- **Initial evaluation:** cleanse, debride, probe, culture. Check pulses/sensation, ABIs (40% have PAD), consider XR/MRI
- **Diagnosis:** Wound Cx. Most polymicrobial w/ GPCs>GNRs, anaerobes. Mod/severe: blood Cx + ESR/CRP
- **Treatment:** definitive tx based on deep Cx obtained **PRIOR** to abx initiation. If c/f **osteomyelitis** (see osteo), MRI ± surgery ± ID c/s
  - Mild (rx 1-2wk): oral → target GPCs (cephalexin, cefadroxil, amox-clav, dicloxacillin, levofloxacin); TMP-SMX or doxy for MRSA
  - Moderate/severe (rx 2-3wk): IV → target GPCs, GNRs ± anaerobes: (CTX or FQ) + MNZ; or amp-sulb. MRSA coverage w/vanc, LZD, or daptomycin if: severe infxn, prior MRSA infxn/colonization, other RFs (see above). PsA coverage w/ cefepime or pip/tazo if: severe infxn, immunocompromised, neutropenic, water exposure, burn/puncture, nosocomial
  - If improving, may de-escalate IV to highly bioavailable PO regimen to complete course

# Infectious Disease

## Osteomyelitis

### CLINICAL MANIFESTATIONS

- **Acute:** <2wk of sx & absence of necrotic bone or sequestrum. Sx: localized pain & diminished function, evidence of inflammation (fever/chills/night sweats/erythema). Patients can be afebrile
- **Chronic:** previously failed tx, >3wk sx, presence of bony sequestrum, persistent drainage or sinus tract. Sx: pain (absent if neuropathy), erythema, swelling, poorly healing ulcers; *hallmark is necrotic bone*
- **Etiologies:** hematogenous seeding (usually monomicrobial) from bacteremia ( $\uparrow$  risk if endocarditis or indwelling device) or contiguous spread (polymicrobial) via direct inoculation after surgery/trauma
  - Hip, vertebra, pelvis: often have fewer symptoms, can present as septic arthritis
  - Vertebral: point tenderness, unremitting, >50yo (except PWID),  $\pm$  fever ([NEJM 2010;362:1022](#); IDSA: [CID 2015;61:e26](#))
  - Pelvic: a/w bacteremia, sacral pressure ulcers, trauma (esp. athletes), urogyn/pelvic surgery, femoral access site; many present subacutely, may have localized pain or poorly localized, may not have fever
  - Sternoclavicular: ant. chest wall swelling, pain, tenderness; may be mistaken for abscess or atypical cellulitis; can occur via hematog. spread or post-CT surgery  $\pm$  mediastinitis
  - Mandibular: usually contiguous spread of oral flora/odontogenic infection; often w/ anaerobes
  - Foot: toe osteomyelitis or osteo a/w ulcer common in DM (IDSA: [CID 2012;54:e132](#)); PAD also risk factor

### DIAGNOSTIC APPROACH ([JAMA 2008;299:806](#))

- **Exam:** probing to bone sufficient for dx in patients w/ DM (83% Sp, 87% Sn) w/o need for further imaging ([CID 2016;63:944](#))
- **Blood Cx:** often  $\oplus$  with hematogenous infxn involving vertebra, clavicle, pelvis (**always obtain BCx x2 before starting antibiotics**)
- **Labs:** ESR/CRP (if high can use for monitoring response)  $\pm$  leukocytosis
- **Imaging:**
  - **>2wk of sx:** obtain plain XR 1<sup>st</sup>. XR non-diagnostic and concerning story: obtain advanced imaging (MRI)
  - **<2wk of sx, suspected vertebral OM or DM:** start w/ advanced imaging (MRI), contrast preferred for vertebral OM
  - MRI: study of choice for further assessment after plain films; Sn 90%, Sp 82%, high NPV in foot osteo ([Arch Intern Med 2007;167:125](#)); best in DM or if c/f vertebral osteo ([CID 2015;61:e26](#))
  - CT: if MRI not available; can demonstrate periosteal reaction & cortical/medullary destruction
  - Radionuclide bone scan: very sens, but non-spec (false  $\oplus$  if soft tissue inflamm.); option if hardware precludes MRI
- **Bone biopsy: gold standard diagnostic test**
  - C/s ortho vs. MSK IR; Surg > IR if concern for overlying cellulitis to mitigate risk of seeding. Open Bx preferred to percutaneous ([CID 2009;48:888](#)). If perc. Bx  $\ominus$  and suspicion high, repeat vs. obtain open biopsy
  - Bone Cx may be  $\oplus$  even on abx; need 2 specimens: GS/Cx (aerobic, anaerobic, mycobacterial, fungal) + histopath
  - If evidence of OM on imaging or  $\oplus$  probe to bone, bone biopsy  $\oplus$  up to 86% of cases ([CID 2006;42:57](#)). Biopsy not required if  $\oplus$  blood Cx and clinical/radiographic findings of OM

Risk Factors	Likelihood Ratio
Ulcer area >2cm	7.2 (1.1-49)
Probe-to-bone	6.4 (3.6-11)
ESR >70mm/h	11 (1.6-79)
Abnormal XR	2.3 (1.6-3.3)
MRI c/w OM	3.8 (2.5-5.8)
Normal MRI	0.14 (0.08-0.26)

### TREATMENT

- **Antibiotics** (tx based on culture data, see table)
  - **Delay empiric tx until biopsy** if pt HD stable, has no neurologic compromise or e/o epidural abscess
  - **Common organisms:** **MSSA/MRSA**, CoNS, Strep, Enterococci, aerobic GNRs > Brucella, mycobacteria, fungi
  - Can consider adding rifampin if Staph + hardware (for biofilm) ([Antimicrob Agents Chemother 2019;63:e01746](#))
  - **Duration:** ~6w, PO may be adequate after sufficient response to IV but d/w ID (OVIVA, [NEJM 2019;380:425](#)). If PO, FQ+RIF most common (RIF monotherapy not rec'd due to low barrier to resistance)
  - Longer durations likely needed if prosthetic joint infection ([NEJM 2021;384:1991](#); [NEJM 2023;388:251](#)) and ID should be involved
  - No residual infected bone (i.e. amputation): abx 2-5d  $\rightarrow$  up to 10-14 if associated SSTI
  - Consider rechecking ESR/CRP; if elevated at end of abx, consider further w/u (*NB: NO routine repeat MRI, findings take weeks to months to resolve*)
- **Surgical debridement:** indicated if failure to respond to medical therapies, chronic OM, complications of pyogenic vertebral OM (e.g., early signs of cord compression, spinal instability, epidural abscess), or infected prosthesis

Empiric Tx	
Vancomycin + GNR coverage (typically CTX 2g q24h). Include PsA coverage (cefepime) for PWID	
Organism-Specific Tx	
MSSA	Nafcillin 2g IV q4h; cefazolin 2g IV q8h (not if CNS infxn)
MRSA or CoNS	Vanc; dapto
PCN-S Strep	Pen G 4 mill U IV q4h; amp 2g q6h; CTX 2g q24h; vanc
Enterococci	Pen G 4 mill U IV q4h; amp 2g q6h +/- CTX 2g q24h; vanc; dapto
GNR	CTX 2g q24h; cipro 750mg PO BID; levoflox 750mg PO/IV q24h; cefepime 2g q12h (q8h if PsA)

# Infectious Disease

# Bloodstream Infections & Endocarditis

## BLOODSTREAM INFECTIONS (BSI)

Evaluation ([JAMA 2012;308:502](#))

- Sources: lines, procedures, meningitis, endocarditis, osteomyelitis (OM), septic arthritis, PNA, UTI, SSTI, abscesses
- When should I/should I not send blood cultures? ([JHM 2017;12:510](#); [JHM 2016;11:336](#))

Predictive signs/symptoms	Predictive clinical scenario	Other Considerations
Fever+chills (+LR 1.1-6.1); <b>rigors</b> (+LR 4.7, <a href="#">Amer J Med 2005;118:1417</a> ); SIRS (-LR 0.09), normal food intake (-LR 0.18)	<b>High risk:</b> septic shock (38-69% $\oplus$ BCx), meningitis (53%) <b>Medium risk:</b> pyelonephritis (19-25%) <b>Low risk:</b> cellulitis (2%), CAP (7%), other community-onset fever (13%)	Immunocompromised (neutropenia, HIV); hard-to-isolate source (OM, septic arthritis)

- How should I send blood cultures?

- PRIOR to abx, 2 sets minimum, ideally 3 peripheral venipunctures over 1h; draw from central line only if c/f catheter-related infxn (criteria: catheter CFUs 3x peripheral blood OR cath. growth 2h before peripheral) (IDSA: [CID 2009;49:1](#))
- Signs of contaminant: only 1 bottle growing, certain organisms (e.g. CoNS, GPRs), no systemic sx, time to positivity >3-5d

- Further testing:

- Staph aureus** and **Staph lugdunensis**: very sticky and never contaminants. **Daily surveillance cultures** (not necessary for GNRs) ([CID 2017;65:1776](#)), **remove lines/hardware**, TTE/TEE to r/o endocarditis, consider back imaging for discitis/OM if having back pain or imaging for pain at other joints and arthrocentesis for swollen joints
- Consider TTE for high grade Strep spp. No routine TTE for GNRs
- Yeast**: TTE, ophthalmology c/s to r/o fungal endophthalmitis, **remove lines**

## Antimicrobial selection:

Gram stain	Empiric abx	Other considerations
GPCs	Vanc+CTX	<b>S. aureus:</b> ID c/s $\downarrow$ mortality. Adding $\beta$ -lactam (cefazolin/nafcillin) <i>may</i> improve outcomes ( <a href="#">CID 2013;57:1760</a> ) <b>MSSA:</b> $\beta$ -lactam >>> vanc ( <a href="#">CID 2015;61:361</a> )
GPRs	Call ID	More likely true infection in immunocomp hosts, multiple bottles, hardware, or known GPR infection
GNRs	See MDRO	Can de-escalate to oral options. 7d for TMP-SMX or FQN ( <a href="#">JAMA IM 2019;179:3</a> ; <a href="#">CID 2019;69:7</a> )
Candida	Micafungin	ID c/s $\downarrow$ mortality ( <a href="#">Lancet ID 2019;19:1336</a> ); ALWAYS treat as true infection in blood

## ENDOCARDITIS (AHA/IDSA: [Circ 2015;132:1435](#); ESC: [EHJ 2015;36:3075](#))

- Etiology:** cutaneous (40%), oral (29%), GI (23%) – source often unknown
- Clinical manifestations:** BSI s/sx; valvular complications  $\rightarrow$  acute HF, AV block; septic emboli (CVA/CNS, pulm/PE, MI, kidneys, spleen, joints), immune-complex deposition (arthritis, GN)
- Exam:** new murmur, arthritis, embolic phenom. (petechiae, splinter hemorrhage)
- Diagnosis:** **Duke criteria**  $\rightarrow$  2 major OR 1 major + 3 minor OR 5 minor
  - TTE in all; TEE if:  $\ominus$  TTE w/ high susp; PVE; intracardiac device; suspected complications (AHA/ACC: [JACC 2014;63:e57](#)); consult ID
  - May be role for PET in PVE (less so in NVE) ([CID 2020;70:583](#))
- Monitoring:** repeat BCx q24h until sterile x48h & serial ECGs for: new AV block (prolonging PR most common); p mitrale; low QRS voltage
- Microbiology:** Native Valve: Strep, Staph, CoNS/Enterococcus, HACEK; PV (<12mo): CoNS, Staph, Enterococc./GNR/fungus; PV (>12mo): similar to NVE (w/ more CoNS)
- Indications for surgical consult:** **emergent:** new-onset HF (acute valvulopathy), annular/aortic abscess (new AV block on ECG); **other:** L-sided S. aureus/fungus/MDRO, persistent infxn after 5-7d abx, PVE w/ recurrent infxn, large vegetation (>10mm on L, >20mm on R), embolic phenomena despite abx (AATS: [JTCVS 2017;153:1241](#)); **can c/s surgery for all PVE** ( $\pm$  streptococcal)
- AC/antiplatelet:** generally ok to continue but no indication to initiate; if CVA/ICH, hold x2w
- IVDU-assoc IE:** refer to MGH Drug Use Endocarditis Team (DUET, Epic phrase: .MGHDEUT). Includes CT surgery, ID, ACT
- IV  $\rightarrow$  PO may be non-inferior to IV in **carefully selected** L-sided IE pts ([POET, NEJM 2019;380:415](#))
- Ppx:** if prior IE, prosthetic valve, unrepairable cyanotic CHD, or w/in 6mo of CHD repair, give amox. 2g or clinda. 600mg x1 (if PCN allergy) w/in 30-60 min pre-dental procedure; not recommended for GI/GU procedures unless ongoing GI/GU infxn ([Circ 2007;116:15](#))

Modified Duke Criteria for Infective Endocarditis	
MAJOR CRITERIA	
$\oplus$ BCx (likely org.* in 2 Cx 12h apart or 3 Cx 1h apart) or <i>C. burnetii</i> IgG titer 1:800	
Endocardial involvement on imaging: vegetation, abscess, dehiscence, or new regurgitation	
MINOR CRITERIA	
RFs: valve dz, IVDU, prior infxn, indwelling line, prosthetic	
Temperature $>38$ or $100.4$ F	
Vascular phenomena: septic arterial/pulm emboli, mycotic aneurysm, ICH, conjunctival hemorrhages, Janeway lesions	
Immunologic phenomena: GN, Osler, Roth spots, $\oplus$ RF	
$\oplus$ BCx not meeting major criteria	

\*S. aureus, Viridans strep, strep gallolyticus, HACEK, community-acquired enterococci in absence of 1° focus

Organism	Therapy	Notes
<b>Streptococci</b> (VGS [ <i>mitis</i> , <i>mutans</i> , <i>anginosus</i> , etc.]; <i>gallolyticus</i> [a/w colon cancer]; <i>Gemella</i> spp.; <i>Abiotrophia</i> [treat as ↑MIC])	- PCN OR CTX x4w (some infxns may have 2w options) - may add gent based on PCN MIC and severity of infection - PVE: generally requires gent	- Dosing: PCN varies; CTX 2g q24; amp 2g q4; gent 1mg/kg q8, peak 3-4, trough <1 - Vanc inferior to beta-lactams
<b>Staphylococci</b> ( <i>aureus</i> ; <i>lugdunensis</i> [virulent, treat like SA]; CoNS [often methicillin-resistant])	- MSSA: oxacillin (better for CNS penetration), nafcillin (some risk for nephrotoxicity), cefazolin (good for kidneys) x6w - MRSA: vanc OR dapt x6w - PVE: may add gent for first 2w and rifampin for 6w	- Dosing: ox and naf 2g q4; cefazolin 2g q8; dapt 8-12mg/kg q24; gent as above - Vanc inferior to beta lactams for MSSA
<b>Enterococci</b> ( <i>faecalis</i> , <i>faecium</i> )	- Amp AND CTX x6w, may add gent or streptomycin - Vanc if amp-resistant. VRE: dapt + amp OR linezolid	- Dosing: as above - 4w amp+gent sufficient if NVE and <3mo sx; 6w if >3mo or PVE
Gram $\ominus$ (HACEKs mostly, PsA, other GNRs possible)	- HACEK: CTX OR amp OR cipro x4w (6w for PVE) - GNRs: $\beta$ -lactam + (AG or FQ) x6w	- Rare etiology, minimal data to firmly direct treatment modalities
<b>Fungi</b> ( <i>Candida</i> , <i>Aspergillus</i> )	- Candida: amphi B 3-5 mg/kg/d ( $\pm$ flucytosine 25mg/kg q6h) OR Micafungin 150mg q24. <b>C/s surgery</b> ( <a href="#">CID 2016;62:4</a> ) - Aspergillus: vori (6mg/kg q12h x2 dose load then 4mg/kg q12h) or amphi B ( <a href="#">CID 2016;63:4</a> )	- RFs: TPN, lines, PPM/ICD, prosthesis, IVDU

# Infectious Disease

# Meningitis & Encephalitis

## BACTERIAL MENINGITIS

### Clinical Features

- History: 95% have ≥2 of: fever, neck stiffness, AMS, HA ([NEJM 2004;351:1849](#)). Lethargy, hypothermia may be common in elderly. Abd pain, peritonitis can be seen w/ VP shunts. Can also cause seizures, stroke (infectious vasculitis), hydrocephalus, CN deficits (esp TB and fungal) ([Continuum 2021;27:836](#)).
- Exam: most findings more Sp than Sn. Nuchal rigidity 30% Sn, 68% Sp. Kernig's 5% Sn, 95% Sp. Brudzinski's 5% Sn, 95% Sp ([CID 2002;35:46](#)). Jolt sign (worsening HA with horizontal rotation of the head) 64% Sn, 43% Sp ([Am JEM 2013;31:1601](#)). May be absent if >65 yo, immunocompromised, taking analgesics ([Continuum 2021;27:836-854](#)). Meningococcemia with petechial rash, palpable purpura

### Diagnosis ([CID 2004;39:1267](#))

- Blood cultures **STAT – BEFORE** antibiotics (positive in 70% patients); **DO NOT** delay antibiotics for LP or imaging
- Lumbar puncture **ASAP**
  - Head CT prior to LP only indicated if: immunocompromised, known CNS disease (mass lesion, CVA, focal infection), new seizure, papilledema, ↓ level of consciousness, focal neurologic deficit
  - Obtain opening pressure with simple column manometer (nml 200mm H<sub>2</sub>O; mean 350mm H<sub>2</sub>O in bacterial meningitis)
  - For a list of studies to send and CSF analysis/interpretation, see *Procedures: Fluid Analysis*
  - Repeat LP if no clinical improvement after 48h of appropriate antibiotics

### Microbiology ([NEJM 2011;364:2016](#); [NEJM 2010;362:146](#); [Cochrane 2015;9:CD004405](#))

Community			Nosocomial (intracranial procedure, >48h in hospital, head trauma)
Adults 18-34	Adults 35-49	Adults >50	
S. pneumoniae (50%) N. meningitidis (35%) H. influenzae (7%) GBS (6%) Listeria (2%)	S. pneumoniae (75%) N. meningitidis (10%) GBS (7%) H. influenzae (5%) Listeria (3%)	S. pneumoniae (76%) GBS (8%), Listeria (7%) H. influenzae (6%) N. meningitidis (5%) Aerobic gram neg bacilli	Gram neg bacilli (40%) S. aureus (10%) Coag neg Staph (10%) C. acnes (takes 10 days to grow!)

### Empiric Treatment ([Lancet 2021;398:1171](#))

Adults < 50	Adults > 50	Immunocompromised	Nosocomial	SEVERE β-lactam allergy
Vanc + CTX 2g q12h	Vanc + CTX 2g q12h + ampicillin 2g q4h	Vanc + [cefepime 2g q8h OR meropenem 2g q8h] + ampicillin 2g q4h (not needed if on mero) (consider fungal & viral)	Vanc + [cefepime 2g q8h OR ceftazidime 2g q8h OR meropenem 2g q8h]	Vanc + meropenem 2g q8h OR moxifloxacin 400mg qd [if >50 or immunocomp., for Listeria: Bactrim 5mg/kg IV qd div q6-12h] if not on mero

Note: vancomycin is added empirically to cover PCN-resistant *S. pneumo*, not MRSA

- Duration: N. meningitidis/H. flu (7d); S. pneumo (14d); Listeria (2-4w if immunocompetent; 4-8w if immunocompromised)
- Dexamethasone**: greatest benefit in suspected/confirmed *S. pneumococcal* meningitis w/ GCS 8-11 (↓ mortality/hearing loss, & short-term neuro sequelae in high-income countries) **0.15 mg/kg q6h x 4d**; start prior to or with 1<sup>st</sup> dose of abx, but **do not delay abx**
- CSF shunts**: consult Neurosurgery for assistance with mgmt and/or shunt removal (IDSA: [CID 2017;64:701](#))
- BBB penetration**: meningeal inflammation ↑ BBB permeability esp when severe. Abx with poor penetration into CSF in cases of mildly-inflamed meninges include β-lactams (overcome by ↑ dosage), aminoglycosides, tetracyclines, daptomycin
- Prevention: MenACWY/MenB, Hib, pneumococcal vaccines. **PPx**: All close contacts of patients w/ **suspected** *N. meningitidis* or close contacts (w/ increased risk factors) of patients w/ Hib.

## ASEPTIC MENINGITIS

: meningeal inflammation with negative bacterial cultures

### Clinical Features

: similar to bacterial, usually less toxic. **LP: lymphocytic pleocytosis**

**Etiology**: Infectious: enteroviruses (most common), HSV2>1 ([Neurology 2006;66:75-80](#)), VZV, partially tx'd bacterial meningitis (usually days-wks), any stage of syphilis, Lyme, leptospira, mumps, Nocardia, TB, HIV (primary infxn), LCMV, fungal (see below), brain/parameningeal abscess; Non-infectious: autoimmune (Behcet's, sarcoid, SLE, SJS), neoplastic (leukemia, lymphoma), drugs (NSAIDs, antimicrobials, IVIG)

**Treatment**: tx underlying cause (if possible) & supportive care. If suspect TB, c/s ID re: tx, addition of steroids; see *Tuberculosis*

## FUNGAL MENINGITIS

: see *Invasive Fungal Infections*

**Causes**: Primary (immunocompetent): Cryptococcus, Blastomyces, Histoplasma, Coccidioides, other dimorphic fungi; Secondary (immunocompromised): Cryptococcus, Candida, Aspergillus, other molds

**Diagnosis**: CSF CRAG, (1,3)-B-D-glucan, fungal wet prep, fungal culture, large volume (40-50mL) for Cx ([J Clin Microbiol 2013;51:1285](#))

**Treatment**: ID to guide. See *Invasive Fungal Infections*.

## ENCEPHALITIS

(IDSA: [CID 2008;47:303](#))

**Presentation**: abnormal brain function (vs. normal cerebral function in meningitis): AMS, focal neuro deficits

**Etiology**: Infectious: HSV1>>2, VZV, arbo (**West Nile**, WEE/EEE, St Louis, Japanese), enteroviruses (Coxsackie viruses, echoviruses, polioviruses), HIV, CMV (extremely rare), JC, adeno, influenza, Powassan virus, Zika; Non-infectious: post-infectious demyelination (ADEM), autoimmune, paraneoplastic (anti-Hu [SCLC], anti-Ma2 [testicular], anti-CRMP5 [SCLC/thymoma], anti-NMDA receptor [ovarian teratoma, idiopathic])

**Diagnosis**: send CSF for HSV, VZV PCR; other viruses less common. If clinical suspicion ↑ (West Nile IgM, JC, CMV/EBV [extremely rare]); autoimmunity-Mayo ab panel; consider MRI (HSV→temporal lobe enhancement, W. Nile→basal ganglia/thalamic foci); EEG

**Treatment**: HSV, VZV → acyclovir 10 mg/kg IV q8h; otherwise supportive care ([Neurol Clinic 2021;39:197](#)). If sx recur s/p tx, consider viral relapse vs. autoimmune encephalitis – high rates of autoimm. dz wks later ([Lancet Neurol 2018;17:760](#))

# Infectious Disease

## C. Difficile Infection

### OVERVIEW (IDSA 2021 update: [CID 2021;73:1029](#); [CID 2018;66:987](#))

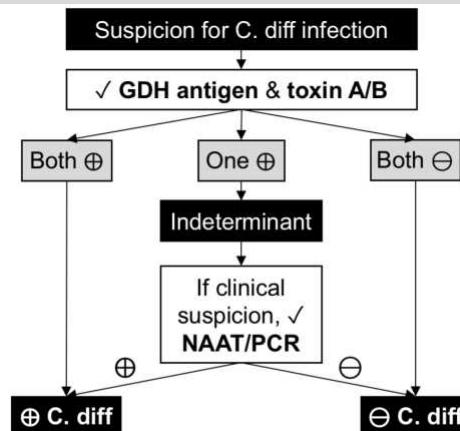
- Definition: C. difficile infection (CDI): acute-onset sx (usually ≥3 episodes/d of watery diarrhea) + e/o toxin-producing C. difficile or histopathology c/w pseudomembranous colitis
- RFs: abx w/in 3mo (particularly associated with penicillins, 2<sup>nd</sup>/3<sup>rd</sup>/4<sup>th</sup> gen ceph, FQ, carbapenems, clinda), ↑age (≥65yo), recent hosp or ↑LOS, severe comorbid illness, IBD, chemo/immunocompromise, GI surgery, tube feeding, PPI/H2RA
- Pathogenesis: fecal-oral via spores, colonized host; most often infection requires both acquisition of C. diff plus loss of gut microbial abundance/diversity (e.g. due to abx). Symptoms are toxin-mediated: toxin A (enterotoxic) & toxin B (cytotoxic)
- Community-acquired CDI: ~1/3 new cases; p/w diarrhea in pt w/o hospitalization in last 12 wks. Potential sources: contam. food/H<sub>2</sub>O, pets, asx colonization in family, babies, outpt visits ([AJG 2012;107:89](#); [JAMA IM 2013;173:1359](#))

### CLINICAL MANIFESTATIONS

- Features: **watery diarrhea** (≥3 loose stools in 24h) +/- mucus/occult blood; ileus, fever, abd pain, nausea, ↑WBC
- Ddx: non-C. diff abx-associated diarrhea, infectious diarrhea, post-infectious IBS, IBD, microscopic colitis, Celiac disease
- Severity: see table below; severe colitis may be c/b hypovolemia, AKI, marked leukocytosis, lactic acidosis, protein-losing enteropathy; fulminant colitis characterized by hypotension/shock, ileus, toxic megacolon w/ ↑mortality

### DIAGNOSIS

- **MGH protocol:** see algorithm to right; indeterminant results can be 2/2 asymptomatic (non-toxin-producing) colonization
  - GDH: enzyme produced by all C. diff strains; assay sensitive but cannot distinguish toxigenic & non-toxigenic strains
  - Toxin A/B: assay detects toxin production; high Sp but poor Sn
  - NAAT/PCR toxin gene: high Sn but can be  $\oplus$  even in the absence of active infection (strain may have toxin gene but not produce it)
- **DO NOT** retest within 7d w/o significant clinical change
- **DO NOT** test for “cure” (may remain  $\oplus$  for up to 6w despite resolved sx)
- CT A/P: if severe illness or fulminant colitis to assess for complications warranting surgical intervention (e.g. toxic megacolon, bowel perf)
- Flex sig: in rare cases when alt dx suspected and need visualization/bx



### TREATMENT (IDSA 2021 update: [CID 2021;73:1029](#); [CID 2018;66:987](#))

Category	Criteria	Treatment
Non-severe	WBC <15 AND Cr <1.5	- <b>Fidaxomicin*</b> 200mg PO BID x10d OR Vanc 125mg PO q6h x10d - Alternative: metronidazole 500mg PO q8h 10-14d (if Fidax & Vanc not avail) - D/c antimotility agents, non-essential abx, cholestyramine (binds vanc)
Severe	WBC >15 OR Cr >1.5	- <b>Fidaxomicin*</b> 200mg PO BID x10d OR Vanc 125mg PO q6h x10d
Fulminant	Hypotension/shock, ileus, megacolon	- Vanc 500mg PO q6h AND metronidazole 500mg IV q8h - If ileus: can add vanc PR 500mg in 100cc NS as retention enema Q6H - <b>Surgery c/s:</b> consider FMT if ileus, tx nonresponsive, or recurrent dz

**Duration:** 10d for non-fatal; if receiving concurrent abx duration may be **extended** 7d after completion of other abx

\*Fidaxomicin: 1<sup>st</sup> line, ↓ recurrence vs vanc; currently cost prohibitive at MGH ([CID 2021;73:1029](#); [Cochrane Rev 2017](#))

### RECURRENCE

- Recurrent CDI: resolution of sx w/ tx, reappearance of sx w/in 2-8 wks after abx completed. Often due to relapse as opposed to reinfection vs. refractory disease (no resolution on therapy → consider alt diagnosis and ID or GI c/s)
- **1<sup>st</sup> recurrence:** Fidax\* 200mg PO BID x10d OR 200mg PO BID x5d then qod x20d OR Pulse-tapered PO vanc 125mg x6-8w AND IV **Bezlotoxumab 10mg/kg x1 w/ fidax or vanc reg. if w/in 6 mos of prior episode** ([CID 2021;73:1029](#))  
**2<sup>nd</sup> recurrence:** Fidax\* regimen (same as 1<sup>st</sup> recurrence) OR pulse-tapered vanc 125mg x6-8w OR vanc 125mg q6 x10d followed by rifaximin 400mg TID x20d) AND IV **Bezlotoxumab as above**. IDSA recommends evaluation for **fecal microbiota transplant (FMT)** after 2<sup>nd</sup> recurrence; more effective than vanc or fidax alone ([NEJM 2013;368:407](#); [CID 2019;68:1351](#); [Gastro 2019;156:1324](#)). Consult ID for FMT evaluation.

### OTHER CONSIDERATIONS

- **Infxn ctrl:** Contact precautions, wash hands with soap & water after contact (alcohol-based rubs won't eliminate spores)
- **Prophylaxis:** vanc 125mg PO qd for abx duration + additional 7d may ↓recurrence in pts w/ prior CDI receiving systemic abx ([AJG 2016;111:1834](#); [CID 2016;63:651](#); [ICHE 2019;40:662](#)). May also be effective as primary ppx in high-risk patients (≥60yo, current or recent <30d systemic abx) w/ 125mg daily dosing ([CID 2020;71:1133](#))
- **Probiotics:** Not recommended for prevention of CDI by society guidelines ([CID 2018;66:987](#)). Some evidence supports use w/ abx to reduce abx-associated diarrhea ([JAMA 2012;307:1959](#)).

# Infectious Disease

## RISK FACTORS

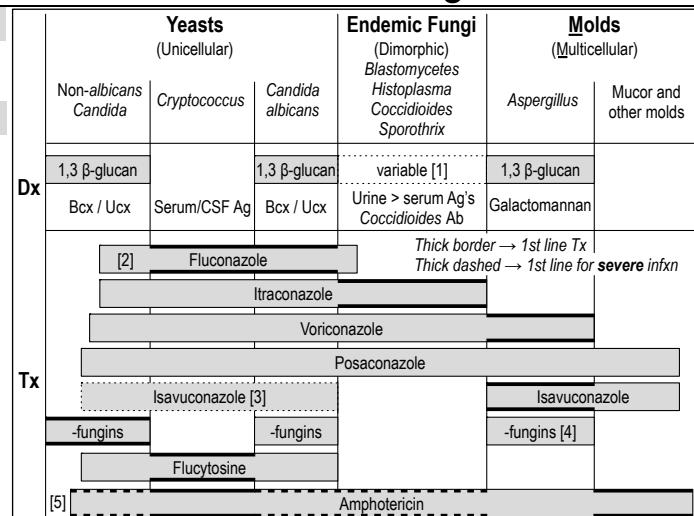
Heme malignancy, HSCT > SOT > biologic Tx, HIV/AIDS, prolonged neutropenia, prolonged glucocorticoids

## DIAGNOSTIC TESTING

Fungal markers:

- 1,3-β-D Glucan (BDG)** ([CID 2011;52:750](#)): cell wall polysaccharide, detects *Candida*, *Aspergillus*, PJP, *Fusarium*, *Trichosporon*, *Histo*, *Coccidioides* with Sn 77%, Sp 86% (cutoff 80). **CANNOT** dx Mucor, Rhizopus, Blasto, Crypto
  - False  $\oplus$  w/ IVIG, albumin, HD, pip-tazo, unasyn, Strep, Pseudomonas ([J Clin Microbiol 2013;51:3478](#))
  - False  $\ominus$  possible w/ candidemia ([CID 2020;70:1925](#))
- Galactomannan (GM)** ([Cochrane Rev 2015](#)): detects *Aspergillus* cell wall component; Sn (serum 65-80%, BAL 90-95%), Sp 88%
  - False  $\oplus$  w/ some TPN formulations, IVIG, blood products
- Histo Ag**: UAg Sn 90% if disseminated (vs. sAg 80%); Sp limited by cross-reactivity (esp. with blasto)
- Crypto Ag (CrAg)**: serum Sn&Sp >90% if disseminated, ↓ w/ pulm dz only, ↑Sn for pulm if HIV
- Blastomycoses**: uAg > sAg; ↑Sn, modest Sp d/t cross-reactivity

# Invasive Fungal Infections



Adapted from JA Freed and AJ Hale, [IDModules.com](#)

## Invasive Opportunistic Fungi \*\*ID consultation is advised for these diagnoses\*\*

YEAST	<b>Candida</b> <a href="#">CID 2016;62:e1</a>	RFs: neutropenia, immunocompromised (heme malignancy, transplant, HIV/AIDS), TPN, PWID, CVC, prior abdominal surgery, ICU Spectrum of illness: sepsis (25% mortality), macronodular skin lesions (10%), endophthalmitis, endocarditis, osteomyelitis, UTI Dx: BCx (never contaminant, grows slowly [ <a href="#">BMC Infect Dis. 2013;13:486</a> ]), c/s ophtho & ID, TTE, repeat Cx daily. ↓Sn if deep tissue/hepatosplenic infxn; $\oplus$ RCx usually colonization not infxn. Ophtho c/s for dilated eye exam in non-neutropenic patients (if neutropenic, perform within first week of ANC recovery) ( <a href="#">CID 2016;62:e1</a> ). Skin biopsy with cx if suspicious lesion. <b>Candida score</b> Tx: BSI → echinocandins → azole (amphotericin for resistant strains); remove CVCs. <b>Endophthalmitis</b> : may need intravitreal amphotericin/vori. <b>UTI</b> : see <a href="#">UTI</a> . Duration: BSI: 2w after 1 <sup>st</sup> $\ominus$ Cx w/ no dissemination, deep-seated infxn: longer, see <a href="#">BSI</a>
	<b>Cryptococcus</b> <a href="#">CID 2010;50:291</a>	RFs: immunocompromised (HIV/AIDS), liver disease, can occur in immunocompetent (esp. <i>C. gattii</i> > <i>C. neoformans</i> ) Spectrum of illness: asymptomatic → meningoencephalitis, (pulmonary [acute resp failure], cutaneous nodules, liver abscesses) Dx: serum/CSF CrAg ( $\oplus$ serum w/ $\ominus$ CSF = cryptococcal antigenemia), LP/CSF: OP>20, ↓gluc, ↑TP, lymphs, cryptococcomas on imaging, skin lesions can umbilicate. Screen for serum CrAg in HIV/AIDS CD4<100 → LP if positive. Tx: CM: amphotericin B + flucytosine (x2w) → fluc (≥8w), serial LPs if OP≥25 or symptoms of T1CP, fluc for mild pulm dz/antigenemia Ppx: fluc for HIV/AIDS (CD4<100) in high-risk, low-resource settings (in US not recommended unless positive serum antigen)
	<b>Pneumocystis</b> <a href="#">HIV.gov</a>	RFs: immunocompromised (HIV/AIDS, heme malignancy, transplant), steroids equiv. to pred 20mg/day x4w Spectrum of illness: pulm sx onset over days/weeks, PTX, hypoxemia out of proportion to CXR (diffuse GGO on CT) Dx: LDH >500 (Sn not Sp), BAL > induced sputum for silver stain/DFA 1,3-BDG ( <a href="#">Eur J Clin Microbiol 2014;33:1173</a> ) Tx: T/S (PO/IV8-12mg/kg/d, adjust PRN renal fxn). Consider pred 40mg BID if severe hypoxemia; Alternatives: TMP+dapsone, clinda+primaquine, atovaquone or pentamidine; Duration: 21d Ppx: T/S (1 DS qD > SS qD, 1 DS MWF), atovaquone, dapsone (check G6PD), pentamidine
MOLD	<b>Aspergillus</b> <a href="#">CID 2016;63:e1</a>	RFs: neutropenia, steroids, transplant, COPD w/ prolonged ICU stay, anti-TNF, cannabis use, <a href="#">COVID19 with ARDS/ICU stay</a> Spectrum of illness: invasive pulm (IPA), aspergilloma, sinus, tracheobronchitis, CNS, endophthalmitis, disseminated, necrotic skin Dx: CT w/ halo sign, BAL/sputum wet prep/fungal cx ± biopsy, serum 1,3-BDG (not Sp), GM (Sp; trend serum in tx, BAL > serum) Tx: vori (monitor trough, drug-drug int), posa or isa; debridement if necrotic. Duration: >6-12w for pulm dz Ppx: vori or posa (prolonged neutropenia, GVHD [ <a href="#">NEJM 2007;356:348</a> ]), vori/itra/inhaled amphotericin (lung transplant ± h/o IPA)
	<b>Mucor</b>	RFs: DKA, iron overload, heme malignancy, prolonged neutropenia, immunocompromised ( <a href="#">Semin Respir Crit Care Med 2015;36:692</a> ) Spectrum of illness: rhino/orbital/cerebral invasion, pulmonary, GI, renal; black eschars over ulcers, rapidly progressive Dx: biopsy, fungal wet prep/culture (broad non-septate hyphae), inform lab concerned for mucor, CT w/ reverse halo sign Tx: DEBRIDEMENT, amphotericin, consider posaconazole or isavuconazole (for salvage therapy or if renal dz)

## Endemic Mycoses\* (maps)

<b>Histoplasmosis</b> <a href="#">CID 2007;45:807</a>	Endemic areas: Central/eastern US (OH/MS River valleys), Central America, Asia, Africa Spectrum of illness: PNA, meningitis, mediastinal disease, disseminated disease, pericarditis, arthritis Dx: urine + serum Ag (improves sensitivity for detecting pulmonary infxn), histology, Cx; NB: chest imaging similar to sarcoid Tx: itra or fluc or no tx (mild-mod), amphotericin B → itra (severe); NSAID for extrapulm; Duration: 6-12w Ppx: for both Histo and Blasto (below), consider itraconazole for HIV (CD4 <150) in hyperendemic areas
<b>Blastomycosis</b> <a href="#">CID 2008;46:1801</a>	Endemic areas: Midwest, south-central, SE US (OH/MS River valleys & Great Lakes), Canada Spectrum of illness: fever, PNA (acute or chronic), ARDS, ulcerated skin lesions, osteomyelitis, prostatitis, CNS Dx: wet prep (broad-based, budding yeast), Cx, uAg > sAg, never a colonizer Tx: itra (mild-mod), amphotericin B → itra (severe); Duration: 6-12mo
<b>Coccidioidomycosis</b> <a href="#">CID 2016;63:e112</a>	Endemic areas: Desert regions: SW and S US, Mexico, Central & South America Spectrum of illness: PNA (+/- nodules), fever, rash (erythema nodosum), HA, eosinophilia, meningitis, osteomyelitis Dx: serologies, Cx (if high concern, alert lab for biohazard), spherules on bx/aspirate, Ag for extrapulm (urine, blood, CSF) Tx: no tx (mild-mod, immunocompetent); fluc or itra, consider amphotericin B (severe); Duration: 3-12mo Ppx: fluc for 1 <sup>st</sup> ppx for transplant in endemic areas; fluc ppx for HIV in endemic areas if CD4 <250, newly (+) serology w/o evidence of active disease; fluc for 2 <sup>nd</sup> ppx

\*Other endemic mycoses include: Paracoccidioidomycosis, Sporotrichosis, Talaromycosis, Emergomycosis ([PLoS Pathog. 2019;15:9](#)), etc.

# Infectious Disease

# Tuberculosis

## EPIDEMILOGY AND RFs

- World: 1/4 infected; US: incidence 2.4/100,000, w/ ~4% HIV coinfection and ~1% MDR ([CDC MMWR TB US 2022](#))
- Acquisition: travel hx (if high-prevalence area), homelessness, incarceration, PWID, healthcare work, racial/ethnic minority
- Reactivation: risk 5% first 2y, 5-10% lifetime, higher if ≥1 RF: HIV, immunosupp, CKD (esp. RRT), DM, CA, transplant, TNFα inhib., silicosis, malabsorption/malnutrition, tobacco, EtOH ([NEJM 2011;364:1441](#)); untreated HIV has 7-10% **yearly** risk

## SCREENING FOR LATENT TB

Test based on likelihood of exposure & progression to active disease. **IGRA preferred** (TSPOT test of choice at MGH); **TST acceptable** (NB: use [TST/IGRA interpreter](#) if BCG vaccinated). Both IGRA and TST are 80-90% Sn and >95% Sp in immunocompetent, ↓Sn in immunocomprom. Neither rules in/out active TB, can be **discordant ~30%** of the time. If ⊕ test w/ no RFs, repeat either IGRA or TST prior to tx. If ⊕ test in ↑risk pt, proceed to tx (\*\*[TST/IGRA Interpreter](#)\*\*; ATS/CDC/IDSA: [CID 2017;64:111](#))

TST at 48-72h	Patient Population
≥5mm	HIV, prior TB hx, CXR c/w prior TB, silicosis, immunosuppression
≥10mm	Diabetes, CKD, PWID
≥15mm	No risk factors

NB: size reflects skin *induration*, NOT erythema

## CLINICAL MANIFESTATIONS

- Primary TB: fever, chest pain, cough, arthralgia. CXR often normal or ⊕ hilar LAD
- Reactivation TB: fever, cough, hemoptysis, night sweats, wt loss; CXR often w/ posterior/apical involvement or cavitation (seen in 1/3 of pts, a/w ↑org. burden → ↑infectious, AFB⊕) ([J Clin Microbiol 2007;45:4064](#)); more common than primary TB
- Extrapulmonary TB: meningitis with basilar predominance, Pott disease, GU involvement, intestinal TB, pericarditis, scrofula

## DIAGNOSTICS: ACTIVE PULMONARY/EXTRAPULMONARY TB (ATS/CDC/IDSA: [CID 2017;64:111](#); [Lancet 2007;369:9578](#))

Site of Infection		Diagnostic Tests
Lung	Sputum	Expectorated or induced, AFB smear/Cx x3 ≥8h apart (with one AM sample), add NAAT/PCR (Xpert) to one of the specimens; smear may be ⊖ if low burden (~20% if HIV-, ~60% if HIV+)
	Bronch	AFB smear, NAAT/PCR (Xpert), and Cx; +/- transbronch bx, post-bronch induced sputum ↑yield
Ascites or pleural fluid	Adenosine deaminase (ADA) >39 units/L → high Sn/Sp; free IFN-γ elevated → high Sn/Sp; AFB smear, NAAT/PCR (Xpert), & Cx (poor Sn but helpful if positive)	
Pericardial fluid	AFB, Cx, cell counts (typically exudative, ↑prot, lymphocytes), ADA. No evidence for free IFN-γ	
CSF	At least 3 large volume (10-15cc) serial LPs if possible (↑yield). ↓glucose, ↑protein, lymphocyte predominance; ↑ADA useful adjunct. AFB smear, Cx, and NAAT/PCR (Xpert)	
Wound/Tissue	AFB-positive staining and caseating granulomas; cytopenias → consider bone marrow bx	
Urine	UA w/ "sterile" pyuria; send first AM void (large vol ~50cc) Cx x3d. Urine LAM not available at MGH	
Blood	Can send mycobacterial cultures (isolators) for AFB	

## PATIENT ISOLATION: clinical decision based on likelihood of active TB

- When: cough, dyspnea, or hemoptysis + ≥1 RF (HIV+, foreign born, substance use disorder, homelessness, recent incarceration, prior TB/exposure). First obtain CXR; if CXR normal (and HIV- or CD4>200), TB less likely. If CXR abnormal/equivocal (or HIV+ and CD4<200), maintain isolation & obtain sputum x3 as above. Consider ID c/s
- Discontinue: if alt dx **OR** AFB smear ⊖ x3 w/ very low suspicion **OR** on TB tx x2w + AFB smear ⊖ x3 + clinical improv

## APPROACH TO TREATMENT (ATS/CDC/IDSA: [CID 2016;63:e147](#); [NEJM 2015;373:2149](#))

- **Prior to starting treatment:**
  - Check baseline LFTs/Cr, visual acuity/color discrimination, screen for HIV, Hep A/B/C, DM, EtOH use, pregnancy
  - Before treating latent TB: rule out active TB (obtain relevant history and CXR. Sputum AFB if ↑clinical suspicion)
  - Before treating active TB: **c/s ID**, send TB for drug sensitivity testing
- **Treatment regimens:**
  - Active TB: isoniazid (INH) + rifampin (RIF) + pyrazinamide (PZA) + ethambutol (EMB) x2mo, followed by INH+RIF x4mo
    - In 2022, [CDC](#) added 4mo rifapentine-moxifloxacin based regimen as option for drug-susceptible pulm TB
    - Obtain monthly sputum AFB smear/cx until ⊖ x2 consecutive months to assess tx response
  - Latent TB: INH+rifapentine (RPT) qw x12 (3HP) **OR** RIF x4mo (4R) **OR** INH+RIF x3mo (3HR) **OR** INH+B6 x6-9mo (6H, 9H, less preferred) ([CDC Tx Table: Rand R 2020:69:1](#))
  - Quinolones: 1<sup>st</sup> line w/ MDR-TB, **avoid in bacterial PNA** if suspicious for active TB (↓dx yield & ↑risk of resistance)
- **Drug-resistant TB**: **suspect if previously treated**, treatment failure, from prevalent area (India, China, Russia, S. Africa), or known exposure. Treatment regimen depends on drug susceptibility profile; usually 12-24mo course. High mortality
  - ATS/CDC/ERS/IDSA 2019 Guidelines for Drug-resistant TB ([Am J Respir Crit Care Med 2019;200:e93](#))
- HIV co-infection: discuss timing of ART initiation w/ ID due to risk for IRIS
- Extrapulmonary TB: highly variable presentation/therapy, duration depends on site of infection & response. For CNS TB: 12mo tx, glucocorticoids confer 25% short term reduction in mortality ([Cochrane Rev 2016](#))
- Medication side effects: hepatotoxicity (INH, RIF, PZA), optic neuritis (EMB), peripheral neuropathy (INH → add pyridoxine [B6] with initiation of treatment), orange bodily fluids (RIF), numerous drug-drug interactions (especially RIF)
- RIF/RPT remain widely used despite 2020 FDA announcement of nitrosamine impurities as perceived risk TB > cancer risk

# Infectious Disease

# HIV/AIDS & Opportunistic Infections

## DEFINITION AND CLINICAL MANIFESTATIONS

- Acute HIV: mono-like syndrome w/ rash, LAD, fever, oral ulcers, pharyngitis, myalgias, diarrhea; **presents 3-6w after infection**
- AIDS: HIV w/ CD4 count <200 or CD4 T-cell <14% of total lymphs or AIDS-defining illness

## HIV SCREENING AND DIAGNOSTICS

- Screen all 13-64yrs **once**, every pregnancy, dx of another STI, PWID annually, commercial sex (CS), MSM >1 partner since last test, partners of all ↑risk pts. MA: verbal informed consent req. HCP can consent for incapacitated pt (e.g. ICU)
- Preferred: 4<sup>th</sup> gen HIV 1/2 Ab/p24 Ag assay: mean detection limit 18d ([STD 2017;44:739](#)). If +, f/u w/ HIV 1/2 Ab differentiation assay
- HIV RNA PCR (viral load, VL): mean 12d, high Sn/Sp but slow, expensive; used for: 1) concern for acute HIV (Ab/Ag testing are negative early in disease course); 2) confirmation of HIV diagnosis; 3) treatment efficacy in known HIV

## PROPHYLAXIS

- PrEP (Pre-Exp): offer to any pt w/ ↑ risk of acquiring HIV: **serodiscordant couple**, STI last 6mo, inconsistent condom use, PWID, ↑risk sex ([JAMA 2019;321:2203](#)). Transmission risk near zero if HIV+ partner has undetectable VL ([JAMA 2016;316:171](#))
  - Prior to initiation: negative HIV test, screen for HBV/HCV, other STIs, Cr, pregnancy test
  - Daily\* regimen: **TDF/FTC (Truvada)** qd ↓risk (40-75%, >95% w/ excellent adherence), d/c when risk is no longer present. **TAF/FTC (Descovy)** also FDA-approved (except for pts w/ receptive vaginal intercourse) → ↑cost, wt gain, ↓renal/bone issues
    - \*Injectable form (cabotegravir extended-release) also recently FDA approved (q2month) ([NEJM 2021;385:595](#))
  - Event-driven PrEP: Truvada “2-1-1”: double dose 2-24h before sex, then 1 dose daily x 2d (not FDA-approved). If discrete exposure (e.g. vacation), start Truvada qd 1w prior and for 1mo after (MSM only) ([Lancet HIV 2019;7:113](#))
  - Monitoring: HIV q3mo, Cr q3-6mo (stop Truvada if eGFR <60, consider Descovy eGFR 30-60), STIs q3mo, pregnancy q3mo
- Non-Occupational Post-Exp: pts ≤72h after non-occupational ↑risk exposure to HIV; case-by-case decision if HIV status of source unknown; check HIV Ab/Ag, HBV, HCV, STIs. **Truvada + raltegravir or dolutegravir x28d**; if ≥1 nPEP in last year, consider PrEP

## BASIC EVALUATION FOR NEWLY DIAGNOSED HIV \*\*ID consultation is advised\*\*

- CD4 count w/ %, quantitative HIV RNA (VL), genotype/resistance, CBC/diff, BMP, UA, lipids, 3-site GC/CT, syphilis Ab, TST/IGRA if no prior TB hx, Hep A/B/C, MMR w/ vax PRN, VZV if nonimmune, hCG, cervical and/or anal Pap, ± HLA B\*5701 (IDSA: [CID 2020](#))
- Initiate ART early through referral at all CD4 levels to ↓ mortality ([NEJM 2015;373:795](#)); exceptions: crypto meningitis & therapy for HIV/TB co-infection ([NEJM 2014;370:2487](#)). ART can often be initiated prior to genotype, even in ↑risk pts ([AIDS 2018;32:17](#))
- Recheck VL after 2-4w, then q4-8w until suppression achieved → monitor VL q3-4mo

**TREATMENT:** choose based on individual pt factors, drug-drug interactions, resistance, HLA B\*5701 (abacavir hypersens.)

- ART naive: 2 NRTI (typically TAF/FTC or TDF/FTC) + 1 of another class (often integrase inhibitor e.g. dolutegravir or bictegravir)
- Pregnancy: if new dx, 1<sup>st</sup> line TDF/FTC or abacavir-lamivudine (ABC/3TC) + dolutegravir; if prev well treated, cont existing regimen

## HOSPITAL MANAGEMENT OF PEOPLE WITH HIV

- Patient on ART: determine regimen & adherence; typically **continue ARVs** (interruptions can ↑ disease progression)
  - If ARVs must be held, hold **all** ARVs and **c/s ID**. Beware drug-drug interactions esp ritonavir boosted PIs (check [DDI database](#))
  - ARVs historically a/w with lactic acidosis (AZT, ddI, d4T) rarely used nowadays. If pt. has elevated lactate look for other causes.
- Patient not yet on ART: prioritize OI tx, ppx, **c/s ID** re: early inpt vs outpt initiation of ART
- IRIS: worsening sx of underlying infxn (TB, CM, MAC, CMV, others) 1-3mo post-ART initiation, ↑risk if ↓CD4 count
  - Early ART initiation safe after OI dx ([PLoS ONE 2009;4:e5575](#)) (except in CNS TB or crypto meningitis, or TB pericarditis)

## Opportunistic Infections Prophylaxis Summary Recommendations for HIV in the US (HIV.gov 2020: [Full, Tables](#))

CD4	Opportunistic Infection	Prophylaxis	Criteria for D/C
All	Influenza, HAV, HBV, HPV, VZV, S. pneumonia (most common OI), TB	Vax: Flu; HAV, HBV, HPV, PCV15 or 20, PPSV23 after 8w; no live vax w/ CD4<200; LTBI: see <i>Tuberculosis</i>	None
<200	<i>Pneumocystis jirovecii</i> (or hx of thrush)	TMP-SMX DS qd (preferred) or 1 SS qd or dapsone 100mg qd or atovaquone 1500mg qd	CD4 >200 x 3mo
<150	<i>Histo</i> (hyperendemic or exposure; not in MA)	Itraconazole 200mg PO qd	CD4 >150 x 6mo
<100	<i>Toxoplasma</i>	TMP-SMX DS qd or dapsone 50mg qd + pyrimethamine 50mg qw + leucovorin 25 qw	CD4 >200 x 3mo
<50	<i>Mycobacterium avium</i> complex (MAC)	Azithro 1200mg q1wk if not on ART, d/c once on ART	CD4 >100 x3mo

## Treatment of Specific OIs in Adults with HIV (\*review renal dosing for reduced GFR)

Pathogen	Diagnosis	1st Line Treatment
See <i>Invasive Fungal Infections</i> for diagnostics and therapeutics for PJP and <i>Cryptococcus</i> , <i>Tuberculosis</i> for TB		
Herpes Simplex Virus (HSV)	Oral/genital: DFA, PCR, viral Cx CNS: LP + CSF PCR	Orolabial: acycl 400mg PO q8h/valacycl 1g PO q12h x5-10d; Genital: tx x5-14d; CNS: acycl 10mg/kg IV q8h x3w
Cytomegalovirus (CMV)	Retinitis: ophtho exam; Colitis/esophagitis: bx; PNA: bronch w/ cytopath; Neuro: CSF PCR, brain Bx, Blood: PCR	Gancicl IV → valgan PO w/ improvement. Consider foscarnet for resistant dz
Toxoplasma gondii	CT/MRI: ring-enhancing; most pts IgG+ but not IgM+, brain Bx if tx fails (to r/o CNS lymphoma)	Pyrimeth 200mg x1; then by wt + sulfadiazine + leucovorin qd x6w
PML	MRI: non-enhancing lesions; LP: JCV PCR	Only disease-modifying tx is ART
Mucocutaneous candidiasis (esophageal/oral)	Clinical dx: white plaque removed w/ tongue depressor, +KOH; EGD + Bx	Oral: fluc 100mg PO x7-14d; Eso: fluc 100-400mg PO/IV or itra oral soln 200mg PO qd x14-21d
MAC	Cx (blood/sputum/bronch/marrow/tissue), AFB stain	(Clarithro 500mg BID > azithro 600mg qd) + ethambutol 15mg/kg qd

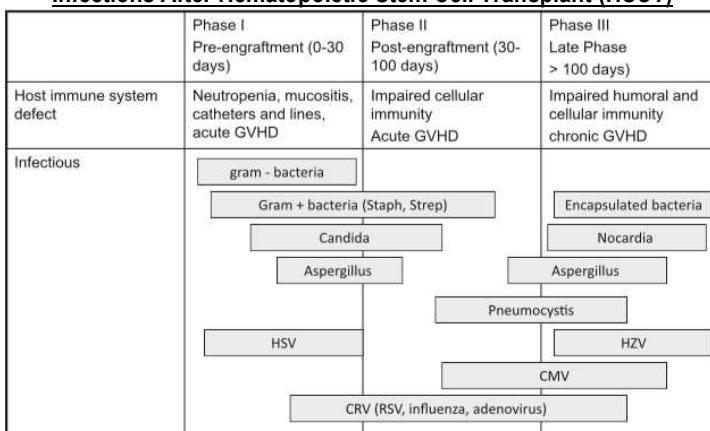
# Infectious Disease

# Transplant ID

## GENERAL PRINCIPLES (AJT 2017;17:856)

- Early infections:** donor-derived, nosocomial/reactivation early, followed by OIs as immune suppression peaks
- Late infections:** community-acquired infections, fungal infections
- Pre-transplant evaluation:** check mumps/measles/rubella/VZV/CMV/EBV/HAV IgG, HBV (sAb, sAg, cAb), HCV, HIV, syphilis, Toxoplasma, TST/IGRA. Consider: endemic fungi (esp. Coccidioides), T. cruzi, Strongy. Goal: immunize or treat prior to txp
  - Serologic tests are helpful to identify latent infection pre-transplantation, but less useful after transplant for acute disease

## Infections After Hematopoietic Stem Cell Transplant (HSCT)



Adapted from AJT 2017;17:856

## Infections After Solid Organ Transplant (SOT)

	<4wk.	1-12mo.	>12mo.
<b>Donor-derived</b>		Adeno, BK	
		EBV, HCV, HBV	
		HSV	
	HHV 6,7	HPV, JC/PML, PTLD	
		VZV	
<b>Fungus</b>		CMV, community-acquired	
	Aspergillus		Aspergillus
	Candida	Endemic fungi	Crypto
<b>Bact.</b>	Mucor	PJP	Mucor
		Listeria, Nocardia	
<b>Para.</b>		TB, non-TB mycobacteria	
		Toxo, leishmaniasis	
		Strongy, T. cruzi	

## HSCT PROPHYLAXIS (JNCCN 2016;14:882)

- Candida:** fluconazole 400mg daily (d0-365 at MGH)
- HSV/VZV:** famciclovir 250mg BID, acyclovir 400mg q8-12h or valacyclovir 500mg BID (d0-365)
- PJP:** T/S (1 DS > SS qD, 1 DS MWF); also covers *Toxo*, *Nocardia*, *Listeria*; alternatives: atovaquone, dapsone (d0-180 or 365)
- High-risk HBV reactivation:** entecavir, tenofovir, or lamivudine (duration varies)
- CMV:** pre-emptive monitoring of VL in high-risk pts & initiate tx (valganciclovir or ganciclovir) when ↑ in VL vs. ppx in high-risk pts. Letermovir (CMV-specific; no activity against HSV) can be considered for ppx in select cases (NEJM 2017;377:2433)

Select Transplant-Associated Infections (ID c/s is advised)			
Pathogen	Clinical Syndrome	Diagnosis/Treatment	Additional comments
<b>CMV</b>	Fever, malaise, leukopenia, +/- hepatitis, colitis/esophagitis, pneumonitis, retinitis	<b>Dx:</b> serum PCR (may be ⊖ in colitis, 15%) ± bx involved organ (GI, BAL w/ cytopath) <b>Tx:</b> PO valganciclovir vs. IV ganciclovir. Consider resistance testing if not improving (UL97, UL57). <u>Alt Tx:</u> foscarnet or maribavir (CID 2021;75:690)	Most common infxn s/p SOT. Highest risk: D+/R- in SOT and D-/R+ in HSCT. May ↑ rejection and susceptibility to OIs. Repeat VL at least 7d apart ( $t_{1/2}$ of CMV), not comparable between labs
<b>PJP</b>	Subacute dyspnea, hypoxemia, fever	See <i>Invasive Fungal Infections</i>	In contrast to HIV, there is limited data to support the use of steroids
<b>BK Virus</b>	Nephritis w/ AKI, ureteral stenosis, hemorrhagic cystitis	<b>Dx:</b> BK PCR +/- bx <b>Tx:</b> ↓ immunosuppression	Mainly in renal txp (nephritis) and HSCT (hemorrhagic cystitis) pts
<b>JC Virus</b>	Progressive multifocal leukoencephalopathy (ataxia, hemiparesis, VF deficits, cognitive Δ)	<b>Dx:</b> MRI brain w/ contrast, LP w/ JC PCR <b>Tx:</b> ↓ immunosuppr, optimize ART	Mainly in pts with HIV, but also w/ heme malignancies, organ tx, and pts receiving lymphocyte-targeted agents
<b>Strongyloides</b>	<i>Hyperinfection syndrome:</i> fever, n/v/d, cough/wheeze, hemoptysis, ⊖ eos; 2° polymicrob. bacteremia (GNRs)	Ivermectin 200mcg/kg/d until stool ⊖ x2w	Identify at-risk individuals and tx pre-txp

## Symptom-Driven Diagnostics

<b>SOB</b>	CXR, CT chest, induced sputum (GS/Cx, consider AFB stain, MB Cx, PJP exam), Legionella urine Ag (Sn 70-90%, Sp 100%), viral resp panel. <b>If cavitating or nodular lesions:</b> 1,3-β-D-glucan/galactomannan, sCrAg, urine/serum histo Ag, early bronch w/ BAL. <u>NB:</u> engraftment syndrome, cryptogenic organizing PNA also on DDx
<b>Diarrhea</b>	Stool Cx, O+P (consider micro add-on for: <i>Cryptosporidium</i> , <i>Cystoisopora</i> , <i>Cyclospora</i> , <i>Microsporidia</i> ), C. diff, CMV PCR. If high suspicion for viral colitis (e.g., CMV, adeno), c/s GI re: colo w/ Bx. In HSCT, consider <i>typhlitis</i> (NEC) and GVHD
<b>AMS/HA</b>	CT head, LP (OP, GS/Cx, glucose, TP, HSV PCR, CrAg, save for more tests). <u>NB:</u> fludarabine, cytarabine, calcineurin inhibitors also a/w encephalopathy
<b>Rash</b>	Outline, photos, may require skin biopsy. GVHD, medication allergy, HSV, cellulitis, local vs disseminated fungal infection
<b>Leukopenia</b>	CMV PCR, EBV PCR, consider tickborne illnesses during the correct season or if frequent blood transfusions
<b>Hepatitis</b>	If post-HSCT, consider viral (HAV, HBV, HCV, EBV, CMV, HSV, adenovirus & more rarely enterovirus and HHV6), <i>Candida</i> , and non-infectious (GVHD, iron toxicity, DILI, hepatic sinusoidal obstruction syndrome)
<b>AKI</b>	UA/UCx, renal U/S, BK PCR if renal tx. Consider med toxicity and check levels (esp tacrol, cyclosporine)

# Infectious Disease

# STIs & Travel Medicine

## SEXUALLY TRANSMITTED INFECTIONS; Routine STI testing in asymptomatic adults ([CDC 2021](#))

	Lesions	Symptoms	Diagnosis	Treatment
Painless	Syphilis* <i>(T pallidum)</i> <a href="#">(CDC Pocket Guide; PCOI)</a>	1°: painless, firm, round ulcer 2°: fever, condyloma lata of skin/mucus membranes, rash, LAD, uveitis 3°: aortitis/aneurysm, disseminated gummas, CN palsies, tabes dorsalis (impaired gait, sensation, reflexes) <b>Latent</b> = by definition, <u>asx</u> (early <1y; late >1y or unknown). Highly infectious in 1°, 2° <i>Neurosyphilis can occur at any stage</i>	1 <sup>st</sup> : anti-treponemal CMIA (Sn & Sp >98%); generally, remains + for life <b>If CMIA+</b> , lab reflexes to RPR. RPR titer gives info on disease staging. Pregnancy & anti-cardiolipin can cause false +. CSF VDRL if c/f neurosyphilis ( <a href="#">JSTD AIDS 2006;17:768</a> ) <b>If CMIA+, RPR-</b> : send out test to state for 2 <sup>nd</sup> treponemal test (TPPA) to confirm CMIA+	1°/2°/early latent: benzathine PCN G 2.4milliU IM x1 3°/late latent: benzathine PCN G 2.4milliU IM qw x3 <b>Neuro:</b> IV PCN G 3-4milliU q4h or infusion x10-14d ( <a href="#">CDC 2021</a> ) <b>PCN allergy:</b> try to desensitize Serologic cure = RPR falls by factor ≥4
	LGV* <i>(C trachomatis</i> serovars L1-3)	1°: transient, painless anogenital lesion 2°: 2-6w later, painful inguinal LAD 3°: pelvic/abd LAD, inflamn diarrhea, abscess ("genitoanorectal syndrome")	Chlamydia NAAT detects LGV serovars LGV-specific PCR available as sendout test	Doxy 100mg BID x21d + aspiration of buboes ( <a href="#">CDC 2021</a> )
	GI/Donovanosis <i>(K granulomatis)</i>	Painless progressive beefy red ulcerative genital lesions	Presence of Donovan bodies in phagocytes on bx specimen	Azithro 1g qw/500mg qd x3w until healed ( <a href="#">CDC 2021</a> ). Relapses can occur 6-18 mo s/p tx
Painful	Genital herpes <i>(HSV2&gt;1)</i>	Prodrome → painful vesicles → ulcers 1° infection: systemic sx ± LAD	Confirm clinical dx with PCR of vesicular fluid from unroofed lesion	Acyclovir/valacyclovir. Consider episodic vs. chronic suppressive tx based on frequency, severity, & risk of spread ( <a href="#">CDC 2021</a> )
	Chancroid* <i>(H ducreyi)</i>	Painful genital/perianal ulcer 5-7d post-exposure w/ inguinal LAD ± drainage	Usually clinical with negative syphilis/HSV; GS/Cx, PCR in some labs	Azithro 1g or CTX 250mg IV ( <a href="#">CDC 2021</a> ); often empiric PCN for syph; eval partners

\*[Reportable](#) to public health department ^expedited partner therapy: offer treatment for any partner w/i 60d without exam ([Instructions](#))

Discharge	Symptoms	Diagnosis	Treatment
Gonorrhea <i>(N gonorrhoeae)</i> , Chlamydia <i>(C trachomatis)</i>	Vaginal/cervical: frequently asx, mucopurulent cervicitis, urethritis, PID Penile: dysuria, purulent discharge, epididymitis Pharyngitis or anorectal infxn possible	Vaginal/cervical: can self-swab, vaginal > urine NAAT (Sn >65%, >57%) Penile: first-catch urine NAAT > urethra Pharyngeal/anal swab based on hx (can self-swab) ( <a href="#">BMJ Open 2019;9</a> ) NB: Cx if c/f resistance	Gonorrhea: CTX 500mg IM x1, 1g if ≥ 150kg ( <a href="#">CDC 2021</a> ); Chlamydia: doxy 100mg BID PO x7d > azithro 1g PO x1 ( <a href="#">CDC 2021</a> ) <u>Concurrent infxn/empiric tx for both:</u> CTX + doxy (azithro-R gonorrhea) ( <a href="#">MMWR 2020;69:1911</a> ). Eval partners
Mycoplasma genitalium (Suspect in pts who fail tx for GC/CT)	Vaginal/cervical: cervicitis, PID, often asymptomatic Penile: dysuria, purulent discharge Anorectal: proctalgia, dyschezia	Vaginal/cervical: vaginal swab PCR Penile: urine or urethral swab PCR (send out test)	If failed tx GC/CT (e.g. with doxycycline): moxifloxacin 400mg qd x7-14d (esp. if macrolide-R) ( <a href="#">CID 2015;60:1228</a> )
Trichomoniasis <i>(T vaginalis)</i>	Vaginal/cervical: purulent malodorous discharge, pruritus, dysuria, dyspareunia Penile: usually asymptomatic	Wet mount → vaginal swab NAAT	Metronidazole or tinidazole 2g PO ±GC/CT tx; tx partner Retest after 3 months
Virus	Risk factors	Screening	Prevention
HIV	Bacterial STI, inconsistent condom use, HIV+ partner, persons who inject drugs	See HIV/AIDS & OI section	PrEP (see HIV); condom use
HPV	Rectal HPV: receptive anal intercourse Cervical HPV: vaginal intercourse	Rectal: anal Pap, anoscopy Cervical: Pap per USPSTF	HPV vaccine series per USPSTF
Hepatitis B	MSM, PWID, >1 partner in 6 m, HBV+ partner, HCV, HIV, other STIs	HBs Ag (can have false + if recent HBV vaccine), HBs AB, HBc Ab	HBV vaccination series
Hepatitis C	MSM, HIV+, group / chem-sex, persons who inject drugs, intranasal cocaine, non-professional tattoo parlor	HCV Ab (remain + after tx), HCV VL if Ab+	Condom use, needle exchange, professional tattoos

## TRAVEL MEDICINE

### Pre-Travel Counseling

- Patient: medical conditions, med supply, dosing schedule changes for travel (e.g. insulin), supplemental O2 needs, allergies (epi pen), pregnancy, immunization history, prior malaria exposure
- Trip: duration, season, purpose of trip, exposures based on itinerary (urban v rural, cruise ship, animals, cave or water exposure)
- General Counseling: sunscreen (SPF 50+), seatbelt/helmet, safe sex, hand hygiene, animal avoidance, considerations re: tap water & raw foods, considerations re: travel & evacuation insurance, contingency planning if ill. Provide patient with [CDC Travel Tips](#)
- Arthropod bite avoidance: ↓ exposed skin, insect repellant (DEET, picaridin, Metofluthrin, IR3535), treated clothing, mosquito nets

**Immunizations:** Ensure routine vaccinations are UTD, then use "[Pre Travel PREP](#)" or [CDC site](#) for country-specific recs; common travel vaccines: Influenza, Yellow Fever, Meningococcal, Typhoid, HAV, HBV, Japanese encephalitis, pre-exposure rabies, cholera

**Malaria Prophylaxis** (typically S/SE Asia, Africa, Central/S America): [CDC tool](#): Rx options based on resistance. ~1w pre-travel, up to 4w after.

Daily: atovaquone-proguanil (Malarone), doxy, primaquine Weekly: mefloquine (a/w bad dreams; avoid if psych hx), chloroquine

**Traveler's Diarrhea** ([CDC Yellow Book](#)). Pathogens: ETEC, C. Jejuni, Shigella spp, Salmonella spp, Vibrio spp, norovirus, rotavirus, Giardia, etc. Tx: *mild*: loperamide; *severe* (fever, dysentery, travel interference): azithro 500mg x3 > FQ or rifaximin, avoid loperamide

**Infections in a Returning Traveler:** Broad ddx, consider geography, exposure risk, pt vulnerability, incubation periods. Common culprits: Malaria, dengue, EBV/CMV, tick-borne, typhoid fever, respiratory viruses, TB, STIs, typical infections (CAP/UTI etc) ([NEJM 2017;376:548](#))

# Infectious Disease

# Tick-Borne Diseases

## TICKBORNE DISEASES ([CDC Guide](#))

### Approach to tick bites and prevention:

Physical prevention: daily tick check, shower after outdoors, check pets, clothing and gear, walk in center of trails ([CDC handout](#))

Chemical prevention: DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-diol, 2-undecanone; 0.5% permethrin for fabrics

Removal: ASAP, pull straight out w/o twisting or jerking w/ clean tweezers, then wash area w/ soap/water or rubbing alcohol

### Approach to tickborne illness:

Hx: hiking/outdoor activity, late spring-early autumn. **Most (50-80%) will NOT recall tick bite** ([Tick Borne Dis 2019;10:694](#))

Sx/signs/labs: fever, myalgias, arthralgias, rash; ↓WBC & PLT, ↑AST & ALT. **Coinfection is common**

Empiric tx: if high suspicion, send all dx incl. babesia smear (not tx by doxycycline), **start empiric doxycycline 100mg PO BID**

Other similar zoonoses to consider: tularemia (rabbits), leptospirosis (rats), brucella/coxiella (cows/sheep), though less common

### Tick identity and geography:

Amblyomma americanum (lone star/turkey tick, **Ehrlichia**): widely found in eastern US, more common in the south

Dermacentor variabilis (American dog/wood tick, **RMSF**): East of Rocky Mtns., limited areas of Pacific Coast

Ixodes scapularis (deer/bear/black-legged tick, **all others below**): Northeast, Mid-Atlantic, and central Midwest

Disease	Presentation	Diagnosis	Treatment
Lyme Disease (IDSA: <a href="#">CID 2021;72:e1</a> ; <a href="#">Lancet 2012;379:461</a> ; <a href="#">NEJM 2014;370:1724</a> )	<p><u>Early localized</u> (days to 1 month): erythema migrans (w/in 3-30 d of bite, red ovoid lesion ± central clearing, 80% of pts), ± fever, fatigue, anorexia, myalgia, arthralgia, HA, neck stiffness, regional LAD. Asx in 30% cases</p> <p><u>Early disseminated</u> (wks-mos): multiple EM lesions, sx above ± migratory arthralgias 60%; neuro 15%: CN palsies, meningitis, mononeuritis, radiculopathy; cardiac 1%: heart block, myopericarditis, CM; LAD; Eye; conjunctivitis, keratitis, retinal vasculitis</p> <p><u>Late disseminated</u> (mos- yrs): <b>arthritis</b> 60% (mono- or polyarthritides of large joints, esp. knee), <b>neuro</b> (mild encephalopathy, peripheral neuropathy)</p> <p><u>Post-treatment syndromes</u> (yrs): nonspecific sx; fatigue, MSK pain, cognitive difficulties; NOT a "chronic infection" so no role for abx (<a href="#">NEJM 2007;357:1422</a>)</p>	<p><b>Avoid serologic testing w/o objective s/sx</b></p> <p>Early: can dx w/ clinical suspicion only (seronegative early on)</p> <p><b>Early &amp; Late disseminated</b></p> <ol style="list-style-type: none"> <li>Screening ELISA IgM/IgG</li> <li>Western blot (WB) if screen ⊕ or <b>equivocal</b></li> </ol> <p>IgM⊕ = 2 of 3 bands detected</p> <p>IgG⊕ = 5 of 10 bands detected</p> <p>IgG⊕ at 6-8w; if ELISA/WB IgM⊕ IgG⊖ at 6-8w: <b>false ⊕</b></p>	<p>Early: doxy 100mg PO BID x10d OR Amox 500mg TID x14d OR Cefuroxime 500mg BID x14d</p> <p><b>Disseminated</b> (neuro, cardiac involvement, arthritis): CTX 2g q24h x14-28d based on severity; check <a href="#">IDSA</a> for specific recs on regimen</p> <p>Ppx: doxy 200mg PO x1 IF tick attached &amp; engorged ≥36h in endemic area <b>AND</b> ≤72h after tick removed</p>
Babesiosis (IDSA: <a href="#">CID 2021;72:e49</a> ; <a href="#">NEJM 2012;366:2397</a> )	<p><u>Asymptomatic:</u> 20% adults; no tx unless smear ⊕ &gt; 1 mo.</p> <p><u>Mild-to-moderate:</u> 1-4 wks after bite or 1-6 mos. from blood transfusion; <b>fever</b>, fatigue, chills, sweats, myalgias, anorexia, HA, n/v, cough – can be subacute (up to 6mo)</p> <p><u>Severe</u> (usually immunosupp, malignancy, HIV, <u>asplenic</u>, &gt;50yo): sx above w/ pronounced n/v, diarrhea, Complications: <b>severe hemolysis</b>, DIC, ARDS, multiorgan failure, CHF</p>	<p><b>Labs:</b> DAT⊖ <b>hemolytic anemia</b>, ↓PLT, ↑ALT/AST</p> <p><b>Blood smear:</b> ring forms in RBC (Maltese cross rare); parasitemia = %infected RBCs; monitor in immunosupp pts until neg smear</p> <p><b>PCR:</b> very Sn &amp; Sp, not widely available</p>	<p><b>Mild-mod:</b> 7-10 d of atovaquone 750mg q12h + azithro 500mg x1 -&gt; 250mg qd</p> <p><b>Severe:</b> c/s ID; Azithro 500mg IV qd + atovaquone 750mg q12h; consider exchange transfusion if parasitemia &gt; 0% or severe hemolysis or organ failure</p>
<i>Borrelia miyamotoi</i> ( <a href="#">NEJM 2013;368:2910</a> )	<u>Relapsing fever</u> (e.g. qOD), HA, AMS, photophobia, chills; ↓WBC/PLT, ↑ALT/AST (mimics anaplasmosis); rash usually absent (this is mostly seen in western US)	<p><b>PCR &gt; serology</b></p> <p><b>NB:</b> EIA cross-reacts w/ Lyme</p>	<p><b>Mild:</b> Doxy 100mg BID x14d</p> <p><b>Hospitalized:</b> CTX 2g qd x 14-28d</p>
Powassan virus ( <a href="#">CID 2016;62:707</a> )	Fever, chills, malaise, somnolence, n/v, <b>encephalopathy</b> <b>MRI:</b> T2/FLAIR hyperintensities (esp. basal ganglia) <b>CSF:</b> lymphocytic pleocytosis (can also be neutrophilic)	Serum/CSF serology (send-out to state lab): IgM ELISA if + then neutralizing antibody testing	Supportive care, no antivirals known to be effective
Anaplasmosis	<u>Common:</u> fever, malaise, myalgias, HA, n/v, arthralgias, cough; rash is less common (<30%)	<b>PCR:</b> morulae in neutrophils on smear in 20-80% of pts	Doxy 100mg BID x 7-10d
Ehrlichiosis	<u>Labs:</u> ↓WBC/PLT, ↑ALT/AST, ↑LDH, ↑ALP, ↑TCK	<b>PCR:</b> morulae in mononuclear on smear in 0-20% of pts	<a href="#">IDCNA 2015;29:341</a>
Rocky Mountain Spotted Fever ( <a href="#">MMWR Recomm Rep. 2016;13:1</a> )	<p>3-5d prodrome (fever, malaise, myalgias, HA, n/v) → progressive macular rash → petechial rash (limbs → trunk, spares face, end stage on palms and soles characteristic)</p> <p><u>Severe:</u> meningoencephalitis, shock, ARDS, DIC, organ failure</p> <p><u>Labs:</u> WBC variable, ↓PLT, ↓Na, AKI, ↑LFTs, ↑ INR</p>	<p><b>Clinical dx:</b> start empiric tx</p> <p><b>Serology:</b> undetectable until 7-10d after sx onset; repeat 14-21d after sx onset to confirm</p> <p><b>PCR:</b> special sendout</p> <p><b>Skin biopsy:</b> 70-90% Sn</p>	<p>Doxy 100mg BID x5-7d minimum + ≥3d after afebrile (tx for all ages)</p> <p>Can consider load 200mg x1 if critically ill</p>

# Infectious Disease

# Mpox & Ectoparasites

## VIROLOGY AND EPIDEMIOLOGY

Caused by **monkeypox virus**, an orthopoxvirus closely related to smallpox. **Three clades**: Clade I (Central Africa, ~10% mortality rate); Clade II (Western Africa, 0.1% mortality rate); Clade III (2022 global outbreak, related to clade II, low mortality). ([NEJM 2022;387:1783](#)).

**Animal-to-human transmission**: bites, infected animal fluids, preparation of bush meat. Rodents are likely reservoir.

**Human-to-human transmission**: direct contact with infectious lesions; respiratory secretions; transplacental; viral DNA found on fomites and bodily fluids (semen, feces, urine, saliva), but unknown if these are mechanisms of transmission

**2022 global outbreak**: 98% cases in MSM and close sexual contacts. 40% pts HIV+ (conflicting data on severity vs HIV- pts, likely more severe in uncontrolled HIV but confounded by delays in tx), 40% on HIV PrEP. Up to 30% associated with concomitant STIs. ([HIV Med 2022;BMJ 2022;378:72410;Lancet 2022;400:661;MMWR Morb Mortal Wkly Rep 2022;71:1412](#)).

## CLINICAL MANIFESTATIONS

**Incubation period**: mean 13 d, range 3-34 d

**Prodromal phase**: associated with viremia; 1-4 days with high fever, headache, fatigue, **lymphadenopathy**

**Eruptive phase**: 14-28 days with **mucocutaneous lesions** (including **palmoplantar**), progress from macules → papules/vesicles → pseudopustules (filled with debris rather than pus) → crusting and desquamation, may result in scarring. Lesions **well circumscribed**, **umbilicated** with associated pain and pruritus. 2022 outbreak commonly with **anogenital lesions** ([NEJM 2022;387:679](#)).

**Complications**:

- **Proctitis**: anorectal pain, bleeding, tenesmus, purulent discharge. Associated with receptive anal sex. Anoscopy not routinely performed due to severe pain. Risk of bowel obstruction, perforation.
- **Pharyngitis/tonsillitis**: pain may limit PO intake.
- **Ocular**: conjunctivitis, blepharitis, keratitis, blindness.
- **CNS disease**: demyelinating encephalitis/encephalomyelitis/transverse myelitis. LP consistent with viral meningitis but may be negative for mpox via PCR. ([MMWR Morb Mortal Wkly Rep 2022;71:1212](#)).
- **Superimposed cellulitis**: most common complication, in anogenital region may progress to Fournier's.

## DIAGNOSTICS

Consider testing in patients with consistent rash and epidemiological risk factors → **c/s infection control/ID**; co-test for STIs, HIV.

**Orthopoxvirus PCR**: vigorously swab lesions to collect cells (do not attempt to unroof), collect 2 swabs/lesion and can swab multiple lesions. PCR of throat swabs and blood used for epidemiological, but not clinical testing.

**Serologic testing**: CDC IgM and IgG test → positive 5 and 8 days after rash onset

**Lumbar puncture**: if c/f encephalitis/myelitis → cell count, glucose, protein, orthopoxvirus PCR, IgM

**Biopsy**: may be helpful if multiple concomitant infections present (e.g. in immunocompromised patients). Lesions are positive for orthopoxvirus and histologically distinct from herpesvirus lesions.

## THERAPEUTICS

Most patients have mild disease, supportive care only. Hospitalization for complications and/or severe pain.

**Tecovirimat (TPOXX)**: high preclinical efficacy but limited human data. Indicated for hospitalized pts, high risk pts (immunocompromised, pregnant, skin disease), or oropharyngeal/anogenital/ocular/CNS involvement. Most common side effects: fatigue, nausea, HA. Tx 14d. ([JAMA 2022;328:134;Open Forum Infect Dis 2022;9:377;NEJM 2022;387:579;NEJM 2022](#)).

- PO: take within 30 mins of fatty meal. 40-119 kg: 600 mg q12h; ≥120 kg: 600 mg q8h
- IV: contraindicated CrCl<30 mL/min. 35-119 kg: 200 mg q12h; ≥120 kg: 300 mg q12h

**Cidofovir/brincidofovir**: limited data suggests less efficacious than tecovirimat. Renal & hepatic toxicity. ([Lancet Infect Dis 2022;22:1153](#)).

**Trifluridine/vidarabine eye drops**: use w/ tecovirimat for ophthalmic infections, q4h 7-10 d, c/s ophtho. ([Arch Ophthalmol 2003;121:715](#)).

**CNS involvement**: c/s neurology, high dose corticosteroids for demyelinating encephalitis/myelitis ([JAMA Neurol 2022;79:1180](#))

## PROPHYLAXIS

**Vaccination**: JYNNEOS → attenuated nonreplicating vaccinia virus, also confers smallpox immunity. Safe in immunocompromised patients. **Post-exposure prophylaxis**: Vaccination within 14 d of close/sexual contact with infected patient or presumed exposure (MSM who have had sex in areas where mpox is spreading). **Pre-exposure prophylaxis**: Offer vaccination for MSM/trans/nonbinary patients who have had at least one STI or >1 sex partners in last 6 mo, or any patient who has had sex at a commercial/public sex venue in last 6 mo. Limited data suggests breakthrough infections rare and mild ([NEJM 2019;381:1897;NEJM 2022;387:2477](#)).

## COMMON ECTOPARASITES ([Am Fam Physician 2019;99:635; NEJM 2020;382:2230](#))

- **Scabies**: Initial infxn w/o sx then intense pruritis ~6wk after inoculation 2/2 hypersensitivity rxn. Sx classically worsen at night. Exam w/ excoriated papulovesicles +/- burrows in interdigital spaces, intertriginous skin, wrist, inguinal region
  - **Rx**: 5% permethrin cream applied jawline downwards after bathing w/ removal after 8-14hr (reapply 7d later)
  - Clothing/bedding needs hot water (>130°F) + high heat drying **OR** 1wk isolation in sealed plastic bag
- **Lice**: Pruritis from saliva of lice. Live lice should be visualized. Nits ≠ infestation. W/o human blood meal, lice die ≤2d
  - **Rx**: head lice - 1% permethrin shampoo (re-apply 7-10d later since not ovicidal); pubic lice - 1% permethrin cream (reapply 9-10d later if persist + test for STIs + rx partners); body lice - laundry and hygiene +/- permethrin
  - Use high-heat (>130°F) laundering/drying exposed items + vacuuming **OR** 2wk isolation in sealed plastic bag
- **Bedbugs**: Suspect if recent travel. Crops of bites on exposed skin not covered by sheets or clothing. "Breakfast, lunch, and dinner" sign. Feces leave black debris on bedding + furniture. W/o blood meal, bedbugs can still live **70d**
  - **Rx**: Resistant to insecticides. Use mechanical methods. Clothing/bedding needs washed at high heat (>140°F). Can expose items to -4°F for 2hr. Physical removal via vacuum. Isolate items in plastic bags for prolonged periods

# Infectious Disease

# Fever of Unknown Origin

## DEFINITION ([CCM 2008;36:1330](#); [Medicine 1961;60:1](#))

- Classically T>38.3C on multiple occasions for ≥3w, persisting w/o diagnosis despite ≥3d of inpatient investigation or 3 ambulatory visits ([Curr Clin Top Infect Dis 1991;11:35](#); [Br J Hosp Med 1996;56:21](#))
  - Special subpopulations:* nosocomial (first fever after 24h of hospitalization), neutropenic (current ANC<500 or expected in 1-2d), HIV-associated – def: fever persisting without diagnosis despite ≥3d of inpatient investigation
- Far more often an atypical presentation of a more common dz than very rare dz

## WORKUP ([AJM 2015;128:1138e1](#))

- Ddx: most commonly **rheumatologic > infectious > malignant > other**
  - 25-50% of cases, no source is identified ([Medicine 2007;86:26](#))
- History:** review fever pattern, B symptoms, PMH (incl. dental hx, immunocompromise), valvular dz, exposures including travel, birthplace, animal, arthropod, food, blood products, sick contacts, sexual contact, drugs, occupation, TB RFs, meds (antimicrobials, vaccines), procedure/hospitalization, family history
- Exam:** dental caries/thrush, sinus and temporal artery tenderness, thyromegaly, murmur, abd tenderness, HSM, eyes, fundi, lymph nodes, joints, skin/nails, rectal, urogenital
- Initial:** CBC, BMP, LFTs, ESR/CRP, UA/UCx, BCx x3 (diff. sites), CXR, HIV
  - ESR: measure of chronic inflammation. Falsely elevated in ESRD, paraproteinemia, anemia, obesity, advanced age
    - Correction for age → ♂: age/2, ♀: (age/2)+10**
  - CRP: rises more acutely than ESR; may be falsely low in cirrhosis
- Other labs to consider:** IGRA, syphilis Ab, LDH, TFTs, SPEP/SFLC, ANA, ANCA, RF/CCP, cryo, CK/aldolase, EBV serologies, CMV PCR, ferritin, blood smear, HBV/HCV
- Imaging** ([Arch Intern Med 2003;163:545](#)): CT C/A/P (71% Sn, 71% Sp), LENIs, TTE/TEE, FDG-PET/CT (Sn 86%, Sp 52%, 58% yield, [J Nucl Med 2016;57:1913](#)), tagged WBC scan (Sn 45-60%, Sp 78-86%), maxillofacial CT
- Tissue diagnosis:** LN, liver bx (14-17% yield), BM (low yield at 0-2%), temporal artery biopsy (GCA), kidney (RPGN), consider LP if CNS findings

## TREATMENT

- Try to avoid empiric antibiotics** and observe (unless hemodynamic instability or immunocompromised)
- D/C possible offending meds
- If ↑ suspicion for GCA/vasculitis, strongly consider empiric steroids (prior to bx) to prevent vision loss/end-organ damage
- If extensive workup ⊖, prognosis usually good, most cases defervesce ([AJM 2015;128:1138e1](#))

## ETOIOLOGIES BY PATIENT POPULATION

Patient Population	Etiologies
General ( <a href="#">Am J Med Sci 2012;344:307</a> )	Infection 14-59%, rheumatic 2-36%, malignancy 3-28%, miscellaneous 0-18%, undiagnosed 7-51%
Elderly patients ( <a href="#">Am Geriatr Soc 1993;41:1187</a> )	Infx 25% (abscess 4%), rheum 31% (most common GCA/PMR), malignancy 12%
Uncontrolled HIV* ( <a href="#">CID 1999;28:341</a> )	Inf 88% (dMAC 31%, PJP 13%, CMV 11%, histo 7%, other viral 7%), malignancy 8% (lymphoma 7%) *Mean CD4 count 58/mm <sup>3</sup>
Neutropenic (refractory to abx) ( <a href="#">NEJM 2002;346:222</a> )	Fungal infx 45%, bacterial infx 10-15% (resistant, biofilms), GVHD 10%, viral infx 5%, misc 25%
Returned traveler* ( <a href="#">AJTMH 2013;88:397</a> )	Falciparum malaria (77%), typhoid fever (12%), paratyphoid fever (6%), leptospirosis (2%), rickettsiosis (2%), dengue (1%)

\*Only considers infectious etiologies, returned from Central or South America, Africa, Oceania, tropical and subtropical parts of Asia

## SELECT CAUSES OF FUO

- Drug fever:** dx of exclusion, broadly refers to any febrile response to medication. Can occur at any time while taking drug, with resolution post-cessation (resolution can take up to 1w)
  - Fevers can be in excess of >102F. Rarely, ⊕ accompanying signs (e.g., morbilliform rash, LFT elevations, eosinophilia)
  - Mechanisms include: hypersensitivity rxn (incl. SJS/TEN), dysfunctional thermoregulation, aseptic meningitis, Jarisch-Herxheimer reaction, NMS/serotonin syndrome, G6PD deficiency
  - Medications commonly associated: antimicrobials (β-lactams, sulfa, macrolides), AEDs, dexmedetomidine, chemo
- VTE:** DVT, PE, thrombophlebitis may cause fever. Usually low grade (6% w/ fever >101F and 1.4% >102F) ([Chest 2000;117:39](#))
- Central fever:** most commonly associated with SAH, intraventricular bleed, brain tumors ([JAMA Neurol 2013;70:1499](#))

Etiologies of FUO	
<b>*bold = common causes (<a href="#">OFID 2020;7:ofaa132</a>)</b>	
<b>Infectious</b>	Abscess (perianal, brain, dental), HIV, <b>EBV, CMV, HHV6-8, HBV, HCV, endocarditis</b> (fastidious/HACEK, nutritionally variant <i>Strep</i> ), nosocomial infection, hardware/graft infection, <b>osteomyelitis</b> , septic arthritis, sinusitis, complicated UTIs, <b>TB (extrapulmonary)</b> , tick-borne infections, endemic fungi (e.g. cocci/histo/paracocci), malaria (#1 cause in returned traveler), cat-scratch disease, toxoplasmosis, Q fever, brucellosis, bartonellosis, salmonella, typhus, melioidosis, schistosomiasis, visceral leishmaniasis, Whipple's disease, lymphogranuloma venereum
<b>Malig.</b>	<b>Lymphoma, leukemia, MM, myeloproliferative disorders, RCC, HCC, CRC, melanoma, pancreatic, cervical, gastric, Castleman's</b>
<b>Rheum.</b>	Cryo, <b>PMR, GCA, RA, Adult Still's, (JRA)/MAS, SLE</b> , dermatopolymyositis, sarcoid, HSP, PAN, Kikuchi's, Takayasu's, Behcet's, GPA/MPA/EGPA
<b>Other</b>	<b>Drug fever</b> , serotonin syndrome, NMS, <b>DVT/PE/hematoma</b> , hypothalamic dysfunction, pheo, <b>hyperthyroidism</b> , alcoholic hepatitis, <b>cirrhosis, IBD</b> , factitious, HLH, familial periodic fever syndromes (FMF, Hyper-IgD Syndrome, Schnitzler's, TRAPS)

# Infectious Disease

# Rare Diseases at MGH

Epi & Transmission		Symptoms	Labs	Diagnostic Tests	Treatment (c/s ID)
Malaria ( <i>Plasmodium</i> spp)	Africa, Latin Am, Asia, Mid East, Eastern Europe	12-35d incub (up to yrs if <i>P. vivax</i> ); fever, HSM, AMS, jaundice, petechiae	Anemia, ↓PLT, AKI, ↑LFTs, ↓glucose, acidemia	<b>BinaxNOW (RDT) + thick/thin blood smear w/ Giemsa</b>	c/s ID; Variable (see travel medicine) Promising RTS,S vaccine
	<i>Anopheles</i> spp.				
<b>Mosquito-borne viruses:</b> Dengue, Chikungunya, and Zika are often indistinguishable clinically/epidemiologically; consider testing for all 3 if concerned					
Dengue fever (DENV serotypes 1-4; Flavivirus)	India, Asia/Pac, Africa, Lat Am	Fever, retro-orbital HA, arthralgia "break bone fever", petechiae, shock	Lymphopenia, thrombocytopenia, ↑Hct	IgG/IgM (cross-rxn w/ Zika); tourniquet test	Rest, fluid; avoid NSAIDs due to ↑ hemorrhagic sx
	<i>A. aegypti</i> & <i>A. albopictus</i>				
Chikungunya fever (Alphavirus)	Africa, Asia/Pac, Caribbean, Lat Am, S USA	Fever (>102 in chik), HA, rash, polyarthralgia, conjunctivitis; Guillain-Barré syndrome + fetal microcephaly (Zika)	Chik: lymphopenia, thrombocytopenia, ↑LFTs, AKI	Chik: PCR if <7d sx; serology if ≥7d Zika: serology/plaque reduct; PCR if <7d of sx, serology if ≥7d	Rest, fluid; avoid NSAIDs unless definitely not dengue. Chik: Rheum referral if pain >3 mo
	<i>A aegypti</i> & <i>A albopictus</i> (diurnal feeders); STI (Zika)				
West Nile virus (Flavivirus)	Africa/MEast, Europe, Americas	Ax; fever, HA, myalgia, 1% meningitis	CSF pleocytosis (lymphs)	<b>Serum + CSF Abs &gt; CSF PCR only for immunocomp. (c/s ID)</b>	Rest, fluid
	<i>Culex</i> spp. (nocturnal)				
Leishmaniasis, cutaneous/visceral ( <i>Leishmania</i> spp)	C/S America, S Europe, Mid East, E Africa, S Asia	CL: painless ulcer(s), regional LAD	VL: cytopenias, ↑LFTs	Clinical dx, skin bx PCR/smear/cx; rarely Ab	Variable, c/s ID; abx if superinfected lesions
	<i>Lutzomyia/Phlebotomus</i>				
<b>Bacterial Zoonoses:</b> <i>Coxiella</i> , <i>Bartonella quintana</i> , and <i>Brucella</i> are important causes of culture-negative endocarditis					
Cat scratch disease ( <i>Bartonella henslae</i> )	Worldwide	Fever, LAD 1-3w, neuro, ocular	↑ESR/CRP, ↑LFT	Ab 1-2w; histology	Variable, c/s ID
	Cat bite/scratch, fleas				
Leptospirosis ( <i>Leptospira</i> spp.)	Worldwide; tropics > temp.	Fever, HA, myalgia, jaundice, conjuc. suffusion	AKI, ALF, rhabdo, anemia, hypoNa	Serology if 3-5d sx	Outpt: doxy 100mg BID x7d; inpt: PCN G, doxy, or CTX
	Water contaminated by animal urine/sewage				
Q fever ( <i>Coxiella burnetii</i> )	Worldwide (except N.Z.)	Fever, HA, myalgia, PNA, <b>endocarditis</b>	↑AST/ALT, ↑Bili, ↓PLT, ↑CK	Serology ≥7d	Doxy 100mg BID x14d
	Aerosolized ungulate fluid				
Brucellosis ( <i>Brucella</i> spp)	Worldwide	Fever, arthritis (SI/spine), endocarditis	↑AST/ALT, ↓WBC w/ relative ↑lymph	Serology if 7-10d sx	Doxy 100mg BID x6w + gent/streptomycin or rifampin
	Dairy products, ungulate contact, lab exposure				
Tularemia ( <i>Francisella tularensis</i> )	N America, Europe > Asia	<b>Regional LAD:</b> 6 syndromes: ulceroglandular, glandular, oculoglandular, pharyngeal, PNA, & typhoidal	Nonspecific; ↑ESR/CRP; ↓PLT	Serology if sx ≥2w; GS, Cx (cysteine + media)	Streptomycin or gent 7-10d; cipro or doxy 10-21d if mild dz
	Arthropod bite, animal contact (rabbit), food/water, airborne				
<b>Rickettsia:</b> in general, rickettsial diseases with eschars are scrub typhus, African tick-bite fever, RMSF, Mediterranean spotted fever, and rickettsialpox					
Murine typhus ( <i>Rickettsia typhi</i> )	SE Asia, N Africa, N America	Fever, <b>centrifugal rash</b> , HA, myalgia	↓Plt, ↑AST/ALT	Serology 2w apart	Doxy 100mg BID x7d
	Feces of infected rat fleas				
Scrub typhus ( <i>Orientia tsutsugamushi</i> )	India → E Asia; Pacific, Chile	Eschar, fever, lymphadenopathy, centrifugal rash, HA	↓Plt, ↑AST/ALT, ↑Bili, AKI, WBC usually wnl	Serology 2w apart; consider eschar bx	Doxy 100mg BID x7d; azithromycin if tetracycline-R
	Bites from infected mite larvae (AKA chiggers)				
<b>Helminths:</b> if concerned about intestinal worms, albendazole is an effective and safe medication to give empirically while awaiting lab results					
Schistosomiasis ( <i>Schistosoma</i> spp)	Africa, Brazil, MidEast, Asia	Acute (3-8w): fever, urticaria, HA, swimmer's itch. Chronic: HSM, portal HTN, GN, hematuria, neuroschisto	↑Eos (30-60%) in acute, ↓Plt; LFTs usually wnl	Serology 6-12w; stool/urine microscopy for speciation	Acute: pred 20-40mg x5d + praziquantel Chronic: 40-60 x1 of praziquantel
	Fresh water with free cercariae from infected snails				
Trichinellosis ( <i>Trichinella</i> spp)	Worldwide, esp. Europe	Abd pain, n/v, diarrhea → myalgia, weakness, ± fever	↑Eos, ↑WBC, ↑CK, ↑LDH	Serology 2-8d; muscle biopsy	Albendazole 400mg BID + pred 30-60mg qd x8-14d
	Undercooked meat, esp. pork				
Strongyloidiasis ( <i>Strongyloides stercoralis</i> )	Rural tropics/subtropics; Appalachia, SE USA	Skin rxn, epigastric pain, diarrhea, resp. sx; fever, n/v, sepsis/shock if hyperinfection	↑Eos, ↑WBC; hyperinfection & disseminated dz (in immunosupp.) w/ normal eos	Serology Sn > stool, but ↓ Sp. ✓ BCx, may have GN bacteremia (gut translocation)	Ivermectin 200 mcg/kg/day x2d; for 5-7d if disseminated (if from endemic region, scr. for loiasis prior to tx)
	Skin contact w/ soil w/ human feces, fecal-oral, autoinfection				
<b>Other Infections</b>					
Typhoid fever ( <i>Salmonella enterica</i> serotype Typhi)	India, SE Asia, Africa	Fever, lethargy, abd pain, 'rose spots', diarrhea (>50%), constip. (30%), HSM	↓HR, ↑LFTs, ↓WBC (↑WBC sign of intest. perf.), anemia, abnl coags	Stool/blood Cx. BMBx 90% Sn. Serology effective in non-endemic regions	Azithro/ciprofloxacin Severe: CTX (meropenem if Pakistan or Iraq)
	Fecal oral; asymptomatic carriers				
Melioidosis ( <i>Burkholderia pseudomallei</i> )	SE Asia, Aus, US Gulf Coast	Fever, PNA, skin abscess, community-acquired sepsis, GU	↑WBC; other nonspecific values c/w organ failure	Blood Cx on Ashdown's agar, GS	Abscess I&D + IV mero/ceftaz x2w → T/S x3mo
Hantaviruses	SW US, Lat Am, Eur., Asia	Hemorrhagic fever, renal failure, ARDS	↑PTT, ↓Plt, AKI, proteinuria	Serology via state department of health	Supportive care
Toxoplasmosis ( <i>Toxoplasma gondii</i> )	Worldwide				
	Cats; cont. meat/water	Mono-like symptoms	Atypical lymphs, ↑AST/ALT	Serology 1-7d; CSF 2-5d	Tx if CNS, chorioraditis, or preg (consult MFM)

Multiple: NEJM2017376548, NEJM2018392557, NEJM2017357108, NEJM2015372954, JAMA2002287291; Malaria: JAMA2010304208, J Clin Invest 2022;132; Dengue: NEJM20123651423, Zika: NEJM20163741552, Chikungunya: NEJM2015372123; West Nile: JAMA2013310308; Cat scratch disease: Am Fam Physician. 2011;83; Brucellosis: NEJM20053522205; Schistosomiasis: NEJM20023461212; Typhoid: NEJM20023471770; Melioidosis: NEJM20123671036

# Infectious Disease

# Infection Control

Resources: [Infection Control Website](#) on Ellucid for the most up-to-date MGH policies and list of diseases/conditions requiring isolation. For additional support, work with unit-specific nursing leadership and contact Infection Control (x62036)

**Standard Precautions:** apply to *all* patients. Hand hygiene (HH) is the most important action to stop the spread of infection. Please stay up-to-date re: source control for masking/hospital-approved eyewear.

- Disinfect hands with an alcohol-based hand rub (ABHR)
  - Before entering and upon exiting the patient room
  - After contact with the patient or items in the patient environment
  - When glove use is indicated, HH is performed **before** donning AND **after** doffing gloves
  - Hands are visibly soiled: wash hands with soap/water, **dry** hands, then apply ABHR
- **Gloves/gowns** for contact w/ blood, bodily fluids (e.g., wound), secretions, excretions, mucous membranes, broken skin
- **Mask + eye** protection for procedures that can **splash** blood, bodily fluids, or secretions (e.g., ABGs, paracenteses)
- **Dispose** of materials **heavily soiled** with blood or bodily fluids into biohazardous waste (**red bag**)
- **Disinfect** reusable patient equipment (e.g., personal stethoscope, U/S) with hospital-approved disinfectant **wipes** according to instructions on label after patient contact/use

Transmission-Based Precautions (follow links in isolation column for additional details)

Isolation	Risk & Transmission	Description	Examples
Contact	Direct or indirect contact w/ pt or his/her environment	<ul style="list-style-type: none"><li>◦ Hand hygiene + nonsterile gloves + isolation gowns</li><li>◦ <b>Do not touch</b> phones, beepers, notes while in room</li><li>◦ Remove gown and gloves <i>together</i> only touching <i>inside</i> of PPE with bare hands, dispose of PPE inside or immediately outside the room</li><li>◦ Dedicate the use of equipment (stethoscope, BP cuff) to avoid sharing w/ other pts. All equipment w/in the room is presumed contaminated</li><li>◦ Disinfect reusable non-critical equipment (stethoscope) using hospital-approved disinfectant wipes for pathogen of concern</li></ul>	MRSA VRE MDROs CRE Disseminated HSV
Contact PLUS	Spore forming & alcohol-resistant orgs transmitted by indirect/direct contact	<ul style="list-style-type: none"><li>◦ Contact precautions + hand wash soap/water + ABHR + private room</li><li>◦ After doffing PPE; wash hands with soap/water x15-20sec, dry, then apply ABHR; use bleach wipes for equipment</li><li>◦ Isolate pt empirically while awaiting results</li></ul>	C. diff Norovirus C. auris Cutaneous anthrax
Enhanced	Cystic Fibrosis (bidirection protection)	<ul style="list-style-type: none"><li>◦ Contact precautions + private room and limitations on use of shared spaces</li></ul>	
Droplet	Large respiratory droplets (coughing, sneezing, talking)	<ul style="list-style-type: none"><li>◦ Surgical mask + eye protection + private room</li><li>◦ Isolate pt empirically while awaiting results</li></ul>	N. meningitidis Influenza Rhinovirus Adenovirus Pertussis Mumps
Enhanced Respiratory	COVID-19	<ul style="list-style-type: none"><li>◦ Contact precautions + N95/PAPR + eye protection + private room (may cohort known with known COVID-19)</li><li>◦ Airborne Infection Isolation Room (AIIR, "negative pressure") preferred when aerosol-generating procedures anticipated</li></ul>	COVID-19
Airborne	Small droplet nuclei that remain suspended in air & disperse widely	<ul style="list-style-type: none"><li>◦ Standard precautions + N95/PAPR + AIIR</li></ul>	Tuberculosis Varicella Disseminated VZV
Strict	Highly pathogenic organisms	<ul style="list-style-type: none"><li>◦ Contact precautions + N95/PAPR + eye protection + AIIR. If suspected, isolate, contact Biothreats (Non-COVID) Pager #26876</li></ul>	SARS/MERS Avian Influenza Variola Mpox

## Immunocompromised Hosts:

- BMT, lung txp, neutropenic patients: standard precautions + positive pressure room + N95 for pt during travel + dietary precautions
  - BMT: gloves and surgical mask for healthcare workers
  - Lung transplant: gown, gloves, and surgical mask for healthcare workers
  - Note: Plants and flowers should not be allowed in immunocompromised host rooms due to risk of fungal infection

## How Infection Statuses are Resolved and Transmission-Based Precautions Discontinued:

Use .Resolve (previously CORAL/NEMO) for all COVID-related infxn statuses. For screening for resolution of prior MRSA, VRE, MDRO status, please review [MGH Resolution Policy](#) and use .Resolve. Discuss resolving any other infection status w/ Infection Control

**Bloodborne Pathogen Exposure:** (needlestick, splash to eyes, mouth, nose, open cut), see *Exposures & Needle Sticks*

1. Immediately wash affected area
2. Normal business hours: call MGH OHS (6-2217). Outside business hours: page on-call OHS clinician, pager #21272. Can also page MGH needlestick consultant, pager #36222.
3. Notify supervisor. Floor charge nurse can help with paperwork and expediting any necessary patient labs

## Pregnant Health Care Workers and Infectious Disease

# Infectious Disease

# Antimicrobial Dosing

General guidance: if questions re: dosing should confirm with pharmacist. See [MGH/Partners antimicrobial dosing guidelines](#)

Drug (By Class)	Usual Dosage	CrCl 50-25	CrCl 25-10	CrCl<10	HD
<b>PENICILLINS</b>					
Ampicillin IV (bacteremia)	2g q6h	CrCl 10-50: 2g q8-12h	CrCl <10: 2g q12h	2g q8-12h*	
Ampicillin IV (endocarditis, meningitis, Listeria)	2g q4h	CrCl 10-50: 2g q6-8h	CrCl <10: 2g q12h	2g q8-12h*	
Ampicillin-sulbactam IV (SSTI, intra-abd, PID)	3g q6h	CrCl 15-30: 3g q8-12h	CrCl <15: 3g q12h	3g q12h*	
Piperacillin-tazobactam IV (non-Pseudomonas)	3.375g q6h	CrCl 20-40: 2.25g q6h	CrCl <20: 2.25g q8h	2.25g q8h	
Piperacillin-tazobactam IV (Pseudomonas)	4.5g q6h	CrCl 20-40: 3.375g q6h	CrCl <20: 2.25g q6h	2.25g q8h	
<b>CEPHALOSPORINS</b>					
Cefazolin IV	2g q8h	CrCl 10-50: 2g q12h	CrCl <10: 2g q24h	1g q24h* OR 2-3g post-HD	
Ceftriaxone IV (bloodstream, bone, PNA, intra-abd, Lyme)	2g q24h	No change with renal function; meningitis/Enterococcal endocarditis dosing is 2g q12h to max 4g/day; on HD days, give post-HD			
Ceftriaxone IV (UTI, SSTI, PNA, intra-abd, SBP ppx)	1g q24h	No change with renal function; on HD days, give post-HD			
Ceftazidime IV (most indications; UTI can use lower doses)	2g q8h	CrCl 31-50: 2g q12h	CrCl 16-30: 2g q24h	CrCl 5-15: 2g x1 → 1g q24h; CrCl <5: 2g x1 → 1g q48h	2g x1 → 1g q24h* OR 2g post-HD
Cefepime IV (febrile neutropenia, PNA, CF, CNS)	2g q8h	CrCl 30-59: 2g q12h	CrCl 10-29: 2g q24h	CrCl <10: 1g q24h	1g q24h* OR 2g post-HD
Cefepime IV (others)	1-2g q8-12h	CrCl 30-59: 1-2g q12-24h	CrCl 10-29: 1g q24h	CrCl <10: 1g q24h	1g q24h* OR 2g post-HD
<b>FLUOROQUINOLONES</b>					
Ciprofloxacin IV (for systemic Pseudomonas, q8h dosing)	400mg q8-12h	CrCl <30: 400mg q24h			400mg q24h*
Levofloxacin IV/PO (CAP, complicated SSTI, MDR TB)	750mg q24h	CrCl 20-49: 750mg q48h	CrCl <20: 750mg x1 → 500mg q48h	750mg x1 → 500mg q48h*	
<b>CARBAPENEMS</b>					
Meropenem IV (most except meningitis, CF, obesity in which case double dose)	1g q8h	CrCl 26-50: 1g q12h	CrCl 10-25: 500mg q12h	CrCl <10: 500mg q24h	500mg q24h*
<b>OTHER ANTI-INFECTIVES</b>					
Acyclovir IV (higher dose for CNS/VZV, adjusted wt if obese; recommend confirming dosing)	5-10mg/kg q8h	CrCl 26-49: 5-10mg/kg q12h	CrCl 10-25: 5-10mg/kg q24h	CrCl <10: 2.5-5mg/kg q24h	2.5-5mg/kg q24h*
Clindamycin IV	600-900mg q8h	Usual dose since clindamycin not renally eliminated; max 2,700mg/day			
Fluconazole IV/PO (invasive candidiasis, weight-based dosing if obese)	12mg/kg x1 → 6mg/kg q24h OR 800mg x1 → 400mg q24h	CrCl <50: 6mg/kg x1 → 3mg/kg q24h OR 400mg x1 → 200mg q24h			6mg/kg x1 → 3mg/kg q24h* OR 400-800mg x1 → 200mg q24h* (or 400mg post-HD)
Metronidazole IV/PO	500mg q8h	Usual dose. Can use q6h dosing interval for CNS infection			

\*Dialysis dosing: if drug dosed multiple times/day, administer 1 of the doses after HD. If drug dosed qd, administer after HD on HD days

Adapted from [MGH/Partners antimicrobial dosing guidelines](#) (contains more info on renal dosing for other antimicrobials, including **CVVH dosing**). To access, sign into VPN or Epic Resources → Handbook → Entity Resources → Guidelines → Infectious Disease → Antimicrobial Renal Dosing Guideline (3a)

## VANCOMYCIN DOSING including HD/CVVH/PD dosing:

Typical dosing regimen (if **stable renal fxn**): **20-25mg/kg** LOAD (can choose **higher dose for obesity or critical illness, max 2g** regardless of wt) → **10-15mg/kg q8-12h** (using adjusted body wt if obese) maintenance; adjustments for renal function (page 2 of empiric dosing guideline above). Dose by level for unstable renal function including AKI

- **Monitoring:** Trough versus area under the curve (AUC) depending on indication - see table below. Check trough **1h prior to 4<sup>th</sup> dose** (or 3<sup>rd</sup>/5<sup>th</sup> to avoid overnight levels). AUC monitoring: PK calculation assistance from pharmacist, requires peak 1-2h after completion of (typically) 4<sup>th</sup> dose (usual infusion 60min/g) and trough 30-60min prior to next dose

SUMMARY OF THERAPEUTIC VANCOMYCIN GOALS	
Confirmed or high suspicion for serious MRSA infection (bacteremia, bone & joint, endocarditis/vascular, intra-abdominal, pneumonia, necrotizing infxns)	AUC <sub>24h</sub> 400-600mg-h/L as determined by peak and trough, followed by patient-specific trough (pharmacist will place note in chart)
Serious non-MRSA infection or <b>empiric</b> use	Trough 10-20mcg/ml
Skin/soft tissue & urinary tract infections	Trough 10-15mcg/ml
Central nervous system	Trough 15-20mcg/ml
Unstable renal function (dose by level)	10-20mcg/ml

- **Subtherapeutic level:** first trough ≤1mcg from target (e.g. 9.3, w/ goal 10-15): continue same dose; first trough >1 to <5mcg lower than target (e.g. 11 w/ goal 13-18): ↑dose by 250mg (e.g. 1000mg → 1250mg); first trough >5mcg lower than target: shorten dosing interval (e.g. q12 → q8h)
- **Supratherapeutic level:** ≤2mcg from target: delay next dose by ~½ dosing interval (e.g. 4h for q8h dosing), reinitiate at 250mg less (e.g. 1250mg → 1000mg); 3-5mcg from target, delay next dose by ½ dosing interval, adjust dosing to next longer interval (e.g. q8 → q12); >5mcg from target: hold, repeat level in 12-24h or discuss with pharmacist

# Hematology

# Pancytopenia & Anemia

## PANCYTOPENIA

Etiologies	
Infection	viral (HIV, HBV/HCV, CMV/EBV, parvo), bacterial (Brucella, TB), fungal (Histo), parasitic (leish, malaria, schisto)
BM infiltration	Malignant: leukemia, MPN, MDS, MM, metastasis. Non-malignant: MF, infection, storage diseases
BM failure	Nutrition: ↓B12/folate/Cu/Zn, EtOH. Marrow suppression from viral (HIV, hep, EBV, CMV, parvo). Immune destruction/suppression: AA, PNH, drugs, LGLL, SLE/RA, sepsis, HLH. Ineffective hematopoiesis: MDS
Destruction / sequestration	Consumption: autoimmune, DIC/TMA. Splenomegaly: portal HTN/cirrhosis, infection, autoimmune (SLE/RA), others
Congenital	Wiskott-Aldrich, Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, GATA2 deficiency, HLH
Work-up	
Initial labs	Check meds, CBC/diff, retic, DAT (Coombs), special slide, LFT, TSH, B12, folate, ESR/CRP, INR/PTT/fibrinogen Also consider: Cu, Zn, LDH, haptoglobin, SPEP/SFLC, uric acid, ANA, HIV/HBV/HCV/CMV/EBV/Parvo
Review meds	NSAIDs, PPIs, sulfas, antihistamine, chemo, anticonvulsants, antiprotozoals, heavy metals, many others
Hematology	Consult if concerned for: unexplained significant neutropenia/thrombocytopenia, DIC/TMA, HLH, heme malig.

Always consider the possibility of multiple independent cytopenias in addition to a unifying diagnosis

## ANEMIA ([Williams Hematology 2021](#))

S/Sx: ↓O2 delivery → fatigue, lightheaded, DOE, pallor, angina (if CAD), claudication, cramps, abd pain, N/V; compensatory mechanisms, incl ↑RR, ↑CO (↑HR, palpitations, flow murmur, later: high-output HF), ↑erythropoiesis (bone pain)

Other findings: jaundice (hemolysis), glossitis (folate/B12/Fe def), motor/sensory deficits (B12 def), pica/koilonychias/angular cheilitis (Fe def), splenomegaly (cirrhosis, infxn, thalassemia, malignancy, chronic hemolysis), constipation/bone pain (myeloma), melena (GIB), thal/SS, unusual thromboses (PNH), petechiae/purpura (coagulopathy, pancytopenia)

Initial labs (draw/add on prior to transfusion): CBC/diff (Δs in other cell lines, MCV, RDW), retic, special slide, T&S

- Calculate **reticulocyte index** (RI) = [% retic x (Hct/nl Hct)] / maturation factor, adjusts for Hct/early release of retics. Determines if adequate BM response: hypo- (<2%) vs hyper-proliferative (>2%); RI <0.1% indicative of aplastic anemia or red cell aplasia

Additional labs depend on RI and clinical history:

- RI <2% → "Anemia labs": Fe/TIBC/ferritin, folate/B12 (in last 6mo), BMP, LFTs, TSH, CRP, review prior CBC
  - If unrevealing/otherwise indicated by history: ± SPEP/SFLC, Hgb electrophoresis, AM testosterone, Epo, BMBx
- RI >2% → "Hemolysis labs" vs recent bleeding: LDH, bilirubin, haptoglobin, DAT (Coombs), coags, UA

## CLASSIFICATION OF ANEMIA ([NEJM 2014;371:1324; Lancet 2018;391:155; JACC: Heart Failure 2019;7:36; Williams Hematology 2021](#))

UNDERPRODUCTION (RI < 2%)		
Microcytic (MCV <80 $\mu\text{m}^3$ )	Normocytic (MCV 80-99 $\mu\text{m}^3$ )	Macrocytic (MCV $\geq 100 \mu\text{m}^3$ )
<b>Iron deficiency anemia (IDA)</b> <ul style="list-style-type: none"> <li>↓Fe, ↑TIBC, ↓ferritin (&lt;30 high Sp; &lt;15=○Fe in BM), Fe/TIBC &lt;16%, &lt;20% with inflammation, ↑RDW</li> </ul>	<b>Inflammation &amp; variant:</b> <ul style="list-style-type: none"> <li>Early IDA or early ACI</li> <li>Mixed IDA &amp; ↓folate/B12 (dimorphic: nml MCV w/ ↑RDW)</li> </ul> <b>Organ-specific:</b> <ul style="list-style-type: none"> <li>Renal (CKD/ESRD): ↓Epo (should ↑10x per 10% Hct drop)</li> <li>Endocrine (thyroid, pituitary, adrenal, parathyroid, testosterone; ↓metab. Rate→ ↓O2 demand): ↓Epo</li> <li>Marrow (red cell aplasia, aplastic anemia, MDS, myelofibrosis, myelophthisis, PNH, MM): check SPEP, serum FLC, BMBx</li> </ul>	<b>Megaloblastic:</b> smear shows hyper-seg PMNs and macro-ovalocytes <ul style="list-style-type: none"> <li>↓Folate: ↑homocysteine, nl MMA</li> <li>↓B12: ↑homocysteine, ↑MMA (↑anti-IF Ab, ↑gastrin if pernicious anemia; falsely nml B12 possible)</li> <li>Early myeloproliferative d/o</li> </ul> <b>Non-megaloblastic:</b> MCV usually <110 <ul style="list-style-type: none"> <li>Cirrhosis, EtOH</li> <li>Reticulocytosis: lysis or bleed</li> <li>Hypothyroidism</li> <li>MDS (refractory anemia) &amp; MM</li> </ul> <b>Meds:</b> antifolates, pur/pyr analogs, AEDs, HAART, AraC, Hydrea
<b>Anemia of inflammation/chronic dz (ACI/ACD)</b> <ul style="list-style-type: none"> <li>↓Fe, ↓nl TIBC, ↑ferritin (&lt;100 if ACI+IDA or &lt;200 in ESRD), Fe/TIBC ↓/nl (&gt;18%)</li> <li>In CHF (concomitant IDA/ACI), ferritin &lt;100 (or &lt;300, if Tsat &lt;20)</li> </ul>		
<b>Thalassemias</b> <ul style="list-style-type: none"> <li>Fe studies nml, MCV ↓↓ (often &lt;70), Mentzer index (MCV/RBC &lt;13; high Sp); Hb electrophoresis</li> </ul>		
<b>Sideroblastic anemia</b> <ul style="list-style-type: none"> <li>↑ferritin, Fe/TIBC nml; smear: basophilic stippling (Pb); BMBx: ringed sideroblasts</li> </ul>		

## DESTRUCTION/LOSS (RI > 2%)

Extrinsic (to RBC)	Intrinsic (to RBC)
<b>MAHA (-DAT, +schisto):</b> see <i>Thrombocytopenia</i> <ul style="list-style-type: none"> <li>Smear (<math>\geq 2</math> schisto/HPF), plt ~25K, ↑LDH, ↑indirect bili, ↓hapt</li> </ul>	<b>Hereditary:</b> <ul style="list-style-type: none"> <li>Hb disease (SS, HbC, thal): <u>Hb electrophoresis</u></li> <li>Enzyme deficiency (G6PD, PK): <u>G6PD levels often nml in attack</u>; check 4w later &amp; repeat in 3mo if ○</li> <li>Membrane defect: spherocytosis, elliptocytosis</li> </ul>
<b>Immune (+DAT, +spherocytosis):</b> Ab- and/or complement-mediated <ul style="list-style-type: none"> <li>Warm autoimmune (CLL, HIV, lymphoma, SLE): +DAT anti-IgG/C3</li> <li>Cold autoimmune (EBV, lymphoid malig., Mycoplasma): +DAT anti-C3</li> <li>Drugs (PCN, cephalosporins), alloimmune (hemolytic transfusion rxn)</li> </ul>	<b>Acquired (new onset):</b> <ul style="list-style-type: none"> <li>PNH (paroxysmal nocturnal hemoglobinuria): <u>flow cytometry</u> ± FLAER for GPI anchor, smear nml, UA (Hgb/hemosiderin), thrombosis (intra-abd/cerebral)</li> </ul>
<b>Non-immune (-DAT):</b> <ul style="list-style-type: none"> <li>Infection: Babesia, Malaria, Bartonella, C. perfringens, H. flu (type B)</li> <li>Toxin: lead, copper, insect/spider/snake bites, hypotonic infusion</li> <li>Hypersplenism: many; massive SM usually secondary to heme malignancy or infection</li> <li>Supine-related pseudoanemia in early hospitalization (<a href="#">J Hosp Med 2021;16:219</a>)</li> </ul>	<b>Acute blood loss:</b> GI blood loss, hematoma

Intravascular: ↑↑LDH, ↓hapt, hemoglobinemia & -uria; Extravascular: ↑indirect bili ± ↑LDH ± ↓hapt (if free Hb escapes spleen), SM

# Hematology

# Pancytopenia & Anemia

## IRON DEFICIENCY ANEMIA ([NEJM 2015;372:1832](#); [Blood 2019;133:30](#))

- Etiology:** ↑loss due to chronic bleeding (PUD/UGIB [ $\uparrow$ BUN w/o  $\uparrow$ Cr], LGIB/CRC, menses, parasites, intravascular hemolysis), ↑demand (Epo, pregnancy, blood donation), ↓intake (malnutrition) or ↓absorption (Crohn's,  $\uparrow$ pH [e.g. PPI], post-gastrectomy, Celiac)
- Evaluation:** GI bleed eval, H. pylori; consider Celiac disease (esp. if not responsive to PO iron)
- Treatment:** PO 325mg FeSO<sub>4</sub>QOD (QOD  $\uparrow$  absorb: [Lancet Haematology 2017;4:e524](#)). ~6w to correct anemia, ~3-6mo to replete stores. ↑absorb. on empty stomach, w/ VitC, ↓w/ Ca foods, antacids. GI SE: constipation, epigastric pain, N/V
  - IV iron if excessive SEs, CKD, malabsorption, IBD, intolerant to PO, or chronic CHF ([NEJM 2009;361:2436](#)). IV Iron at d/c following ADHF ↓risk of future HF hospitalizations ([Lancet 2020;396:1895](#)). Calculate Fe deficit with [Ganzoni equation](#). Typical dose: iron sucrose 200mg QOD x5 or 300mg QOD x3. SE: n/v, pruritus, flushing, myalgia/arthritis, CP; ⊖ by 48h. Anaphylaxis rare

## ANEMIA OF INFLAMMATION/CHRONIC DISEASE ([NEJM 2019;381:1148](#); [Blood 2019;133:40](#))

- Etiology:** autoimmune, infection, malignancy, CHF, CKD; inflammatory cytokines (IL-1, IL-6 & TNF $\alpha$ ) →  $\uparrow$ hepcidin →  $\uparrow$ ferroportin internalized / degraded → ↓intestinal Fe absorption, ↓Fe & hepatic Fe mobilization
- Time course:** usually 1-2mo to develop, but can ↓Hgb 2-3g/dL in 1-2d in acute illness
- Treatment:** tx underlying disease. Fe if concomitant Fe deficiency: Tsat <15-20%, or no response to EPO.
  - Erythropoiesis stimulating agents (ESA):** FDA-approved for anemia a/w CKD & HIV on HAART. Controversial in cancer pts ([JCO 2019;37:1336](#)). Evidence against use in CHF ([NEJM 2013;368:1210](#)). Maintain Tsat ≥20%, ferritin ≥100 for EPO therapy

## MACROCYTIC / MEGLOBLASTIC ANEMIA (MCV ≥100 $\mu$ m<sup>3</sup>)

- Macrocytosis without megaloblastic changes (hyperseg PMN): consider thyroid, liver, nutritional causes (incl B-vit d/t EtOH), MDS
- ↓Folate ("foliage"), **3mo** stores; ↓intake (EtOH, elderly), ↓absorption (Celiac, jejunum), ↑demand (pregnancy, hemolysis, malignancy), meds (MTX, TMP, AEDs). When severe a/w hemolysis & pancytopenia; ↑homocysteine, MMA nmL
  - Tx: 1-5mg PO qd (can worsen B12 deficiency and associated neurologic complications if not replete)
- ↓B12 ("beef"), **3y** stores; ↓intake (EtOH, vegan), **pernicious anemia** (Ab to intrinsic factor (IF), gastric parietal cells), ↓absorption (gastrectomy, Celiac, Crohn's, PPI, chronic pancreatitis), ↑competition (SIBO, tapeworm); when severe a/w pancytopenia & subacute combined degeneration (dorsal columns, corticospinal tract) w/ dementia, ataxia, paresthesia
  - Labs: check homocysteine/MMA if B12 borderline (200-350). Consider anti-IF Ab if homocysteine/MMA ↑ or if B12 <200
  - Tx: 1-2mg PO B12 qd (= IM if not secondary to malabsorption, IM for pernicious anemia) ([Blood 1998;92:1191](#)). Post-tx, neuro sx start to improve 3mo-1y ([NEJM 2013;368:149](#))

## AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) ([NEJM 2019;381:647](#); [Blood 2017;129:2971](#))

- Warm AIHA:**
  - Etiology: antibody-mediated, often **idiopathic**, less common CLL/lymphoma, SLE, HIV, Babesia, meds. Extravascular > intravascular hemolysis. Rule out other causes of hemolytic anemia
  - Dx: +DAT anti-IgG and/or C3d (typically IgG and panagglutinin). ↓haptoglobin, ↑LDH, ↑indirect bili, ↑reticulocytes.
  - Tx: transfusion for symptomatic anemia or Hgb <7, steroids, d/w blood bank. 2<sup>nd</sup> line: rituximab, splenectomy, mycophenolate
- Cold agglutinin disease:**
  - Etiology: Often associated with lymphoproliferative process, EBV, mycoplasma, autoimmune. Hemolysis mediated by complement.
  - Dx: +DAT anti-C3d only and cold agglutinin titer
  - Tx: Tx underlying process, workup clonal lymphoproliferative disorder. If symptomatic, warm transfusions, plasmapheresis, rituximab, sutimlimab. Steroids/splenectomy not indicated.
- Drugs:** both Ab & non-Ab-mediated; abx (PCN, cephalosporins, sulfa); NSAIDs; CV (methyldopa, procainamide); rasburicase (G6PD)
  - If +DAT but no hemolysis, think **drugs**, ↑IgG (IVIG/Rhlg/myeloma), CTD (e.g., controlled SLE)
- Other etiologies:** paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria (PCH; anti-C3).

## HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

- Excessive inflammation/tissue destruction secondary to abnormal macrophage immune activation & lymphocyte phagocytosis of host blood cells & cytokine storm
- Workup:** dx with 5/8 of **fever**, **↑spleen**, **2/3 cytopenias**, **↑TG /↓fibrinog**, ferritin ≥500 (usually >7-10k), **↑sIL-2R**, hemophagocytosis in BM, low/no NK activity. Also **↑LFTs**, hepatomegaly, **↑LDH**, **↑D-dimer**, **↓fibrinogen**, **↓ESR**. **H-score** for probability.
- Consider evaluating for associated/underlying illness:** infection (pan-culture, viral titer/PCR [EBV, CMV, hepatitis, HSV, VZV, HIV, HHV-8, parvo]), malignancy, CAR-T, rheum, neuro (brain MRI, LP), genetic
- Tx:** depends on etiology. Consider etoposide-based regimen or allogeneic SCT (ASH: [Blood 2019;133:2465](#))

# Hematology

# Sickle Cell Disease

## OVERVIEW ([NEJM 2017;376:1561](#))

- **Definitions:**
  - Sickle Cell allele: autosomal recessive  $\beta$ globin gene A->T (Glu6Val) missense mutation
  - **Sickle Cell Trait (SCT):** heterozygous for HbS w/o aberrancy in partnered  $\beta$ globin gene
  - **Sickle Cell Anemia (SCA):** homozygous for HbS
  - **Sickle Cell Disease (SCD):** any variant of an inherited hemoglobinopathy with formation of Hemoglobin S (HbS) leading to sickle shape of red blood cells
  - **HbSC disease:** Equal amounts of HbS & HbC (greater loss of K<sup>+</sup> dehydrating RBCs & promoting sickling). Freq dehydration, relative to SCD retain splenic function & less hemolysis. Smear: target cell, HbC crystals, some sickled cells.
- **Epidemiology:** ~300K born with SCA per year worldwide. ~100K w/ SCD in U.S., 1.2K families in Boston area. ~2-3mil worldwide
- **Pathophysiology:** deoxygenated HbS polymerization → sickle shaped RBCs, impacts RBC membrane integrity, adherence to vascular endothelium → vaso-occlusive events (**VOE**) can affect **any organ**
- **Diagnostics:** baseline Hb electrophoresis and HPLC: tests to separate HbS from other variants (HbA, HbF, HbC)

## CLINICAL MANIFESTATIONS

Most severe in SCA, intermediate for SC, or S/Thal disease

- **Acute Pain Episodes** ([Complement Ther Med 2020; 49:102327](#)):
  - Complication for which patients most commonly seek medical attention; frequency peaks between ages 19-39
  - **Sx:** swelling, tenderness, HTN, N/V. Frequency peaks age 19-39. ↑ risk when Hb >8.5 and ↓ HbF.
  - **Triggers:** dehydration, infection, changes in the weather, stress, menses, EtOH. Over 50% w/o clear etiology.
  - **Dx:** patient description of symptoms is gold standard; cannot diagnose with a lab test
- **Acute Chest Syndrome:** #2 cause of hospitalization. Pulmonary arterial circ ↓O<sub>2</sub> tension → ↑ risk VOE. Complications including PNA, thromboses, fat embolism. **NB:** 50% preceded by or a/w acute pain episodes
  - **Definition:** new imaging infiltrate + pulmonary symptoms in a patient with SCD, freq. with fever, chest pain, cough
  - **Dx:** CXR, ↑WBC, r/o PE & MI
  - **Tx:** antibiotics (CTX+azithro or FQ), **transfusions** (simple vs exchange), **bronchodilator**
- **Other organ systems:**
  - 1) **Splenic sequestration:** 20% pts; acute 2g/dL ↓Hb
  - 2) **Infection:** given functional asplenia and hypoplasplenism, ↑ risk of encapsulated org, defects in alternative complement pathway. If febrile, send BCx and cover empirically w/ CTX (+azithro if c/f acute chest; +vanc if HDUS or c/f meningitis)
  - 3) **CV:** major cause of death, CM (secondary to chronic anemia, hemosiderosis), ↑MI risk (even in absence of atherosclerosis)
  - 4) **Neurologic:** stroke (~1/4 of pts with SCA with experience a stroke by age 45) → neurocog impairment, epilepsy
  - 5) **Hepatobiliary:** acute hepatic ischemia, iron overload from frequent transfusions, pigmented gallstones
  - 6) **Bone:** ↑ rate Vit D def & osteoporosis, osteonecrosis
  - 7) **Heme:** chronic compensated anemia (Hg 8-10), aplastic crisis, & **hyper-hemolytic episode:** rare; pain, fever, ↓Hb w/in 7-15d of transfusion; Tx: notify blood bank, hydration ± steroids, IVIG, rituximab, eculizumab
  - 8) **Vascular/cutaneous:** priapism, leg ulcers, pulmonary HTN, renal insufficiency, proliferative retinopathy

## MANAGEMENT

**Sickle Cell Pager (p28439) and consult Hematology for every admission!**

- **Workup:** CBC/diff, BMP, LFTs, coags, hemolysis labs, BCx, UA/UCx; CXR; special slide (polychromasia, sickle cells, Howell-Jolly)
- **All inpatients:** VTE ppx, pain control, O<sub>2</sub> (SpO<sub>2</sub> <92%), often IVF for acute pain episodes. **See Acute Care Plan.** Utilize **Epic Order Set ("General Adult Sickle Cell Crisis")**.
  - **Pain control:** **opioids** ± NSAIDs (5-7 days; ketorolac ≤ 5 days; [Blood Adv 2020;4:2656](#)); if unknown prior dose: IV morphine 0.1-0.15mg/kg ≤10mg or Dilaudid 0.02-0.05mg/kg (max 1.5mg) → PCA. Avoid steroids (↑ rebound pain). **Give aggressive bowel regimen** ± methylnaltrexone.
  - **Pruritis:** chronic (non-sedating antihistamine or 5-HT<sub>3</sub>RA), inpatient consider continuous infusion ↓dose naloxone gtt (0.25 mcg/kg/hr), compatible for simultaneous admin w/morphine
  - **For patients with vaso-occlusive pain crisis in Adult ED, follow MGH protocol** ([Ellucid](#))
- **Neutral language:** misperceptions interfere with management, biased language a/w poor pain control and ⊖ attitude to pt ([JGIM 2018;33:685](#)). **Avoid stigmatizing terms**, including: "sickler, freq. flyer, pain seeking"
- **Transfusions:** mechanisms of benefit include: dilute HbS, ↓Epo reducing production of new HbS cells, ↑SpO<sub>2</sub>. Indicated in stroke, multiorgan failure, acute chest, sequestration, peri-op. symptomatic or severe anemia. **No e/o benefit in acute pain episode** ([Br J Haematol 2015;171:288](#)). Exchange > simple (risk of hyperviscosity). **Judicious w/ transfusion** (risk of clinically significant iron overload if >15-20 RBC units) ([Blood Adv 2020;4:327](#))
  - Iron chelators: deferoxamine (subcutaneous and IV), deferiprone and deferasirox (PO, poorly tolerated, toxic). Initiated ~1-2 years of chronic transfusions or ferritin >1000-1500 ng/mL.
- **Outpatient:** hydroxyurea (↑HbF; continue inpatient), folate/MVI, L-glutamine (↓ RBC oxidative stress; [NEJM 2018;379:226](#)), voxelotor (inhibits HbS polymerization; no improvement in VOEs or mortality; [NEJM 2019;381:509](#)), crizanlizumab (P-selectin antag, ↓RBC adhesion; approved for prevention of VOCs; [NEJM 2017;376:429](#)). Vaccines for encapsulated bacteria (Mening, HiB, Pneumo), HBV, flu, CoV-19. Consider prophylactic transfusions in patients with multiple episodes of acute chest despite maximal therapy. SNRIs for chronic pain from avascular necrosis ([Blood Adv 2020;4:2656](#)).
- **Other therapies:** **allogeneic BMT** only curative option. **Gene therapy** evolving (incl. CRISPR use) ([NEJM 2021;384:205](#))

# Hematology

# Thrombocytopenia

## THROMBOCYTOPENIA ([Hematology 2012;2012:191](#))

**Definitions:** 100-150k mild, 50-99k mod, <50k severe. **Bleed risk:** <50k w/ surgery/active bleed, <30k w/ mild trauma, <10k spontaneous

↓Production	↑Destruction	Sequestration/Dilution
- <u>Infection</u> : sepsis, HIV/HCV, VZV/CMV/EBV, parvo, tickborne	- <u>Immune</u> : ITP, SLE/APLS, RA, lymphoma, post-transfusion	- Hypersplenism (cirrhosis, portal HTN)
- <u>Nutrition</u> : EtOH, ↓B12, ↓folate	- <u>Drugs</u> : heparin, MTX, abx, anti-GPIIb/IIIa, quinine	- Massive transfusion
- <u>Drugs</u> : abx, chemo ( <a href="#">ASH Edu 2018:2018:576</a> )	- <u>MAHA</u> : DIC, TTP, HUS, mHTN, preeclampsia/HELLP	- Hypothermia
- <u>Neoplasm</u> : MDS, BM infiltration, 1° heme	- <u>Shearing</u> : CVVH, bypass, IABP, vasculitis, hemangioma	- Gestational
- <u>Other</u> : cirrhosis (↓TPO), aplastic anemia, some vWD		

### Workup:

- H&P focused on bleeding (GI, GU, epistaxis, HA, mucocutaneous), etiology, timing of plt ↓. If new HA: consider CTH
- R/o alarming causes: HIT, TMA, catastrophic APLS. Identify common causes: infxn, drug, immune, nutrition, hypersplenism, MDS
- Initial labs: CBC, BMP, LFTs, coags, special slide, T+S, HIV, HCV, pregnancy test, citrated plt count (r/o pseudo-thrombocytopenia)
- If asymptomatic, mild (100-150k): history of risk factors (i.e. alcohol use), routine exam, CBC for other cytopenias, special slide, HIV/HCV testing (common cause of over-testing)
- If c/f MAHA (e.g. schistocytes on slide): add LDH, haptoglobin, DAT, retics, D-dimer, fibrinogen
- If c/f SLE/APLS: add ANA, lupus anticoagulant, anti-cardiolipin, anti-β2GP1
- If c/f BM disease: consult Hematology, consider BM biopsy

## IMMUNE THROMBOCYTOPENIA (ITP) ([Blood Adv 2019;3:3829](#); [Blood 2017;129:2829](#); [NEJM 2019;381:945](#))

Pathologic antiplatelet antibodies cause plt clearance and bind to megakaryocytes/progenitors, resulting in apoptosis and near-normal rate of platelet production. Defined by isolated plt <100k, **dx of exclusion – must exonerate other causes of thrombocytopenia**

**Presentation:** asx or mucocutaneous bleeding; 10% of ITP has AIHA = Evan's syndrome. Screen for H. pylori, HCV, HIV. Consider thrombopoietin level (may predict likelihood/magnitude of response to TPO receptor agonists ([Am J Hematol 2018;93:1501-1508](#))).

**Prognosis:** <10% spontaneous resolution, up to 50% recover with 1<sup>st</sup> line tx. 1.4% risk of ICH, 9.5% risk of severe bleeding

**Management:** “response” = plt ↑2X to ≥30k within 3mo

- Plt ≥30k & asx/minor bleed: observe; consider steroids if elderly, comorbidities, on AC/anti-plts, upcoming procedures, & plt near 30k
- Plt 10k-29k: steroids ± IVIG, RhoGAM if RhD+; if not bleeding, DO NOT give plts (destroyed & ↓Plt further) ([Blood 2015;125:1470](#))
  - Steroids (takes 4-14d to work): dexamethasone 40mg/d x4d, methylpred 1g/d x3d, or prednisone 60mg/d x3w w/ taper
- Plt <10k: steroids + IVIG, consider romiplostim, do not give plts unless c/f bleeding
- Severe bleeding: Plt, IVIG, steroids (pulse-dose methylpred & dex), Amicar (0.1g/kg/30min→gtt 0.5-1g/h)/TXA, romiplostim
- Refractory/recurrent: ↑ romiplostim dose, ritux, fostamatinib; last resort (>12m after dx) splenectomy (>50% effective, risk of relapse)

## HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) ([Blood Adv 2018;2:3360](#); [Blood 2017;129:2864](#); [NEJM 2015;373:252](#))

IgG anti-PF4-heparin complex binds & activates plts, hypercoagulable state. Can occur with any heparin (UFH, LMWH, heparin flushes)

**Types:** HIT Type 1 (mild platelet drop no lower than 100k 1-2d from heparin exposure, not clinically significant) vs. HIT Type 2 (see below)

**Presentation:** 5-10d after exposure, ↓plt >50%, nadir 40-80k, thrombosis in 30-50% (skin necrosis, DVT/PE, arterial), GIB (~3%)

- Consider rapid-onset HIT if <24h with prior exposure within 100d; delayed-onset can present up to 3w after last heparin

**Diagnosis/Management:** Calculate 4Ts Score. (If incomplete information, may be prudent to err on side of higher 4T score. Recalculate for change in clinical picture). If 0-3: HIT unlikely (NPV 99%), OK to continue heparin. **If ≥4:**

- 1) Stop heparin, reverse warfarin (prevent skin necrosis), and start non-heparin AC. No plt transfusion unless severe hemorrhage
  - 2) Send **anti-PF4**. Send **serotonin release assay (SRA)** (gold standard). Do not wait for results to do Step 1
    - PF4 neg: HIT unlikely; OK to resume heparin. PF4 OD ≥2, or OD ≥1.5 with 4Ts ≥6: HIT likely. Otherwise: decide based on SRA
  - 3) Screen for DVT with upper/lower extremity ultrasound
- Duration of AC: if no thrombosis, until plt >150k (at least 4 weeks); if thrombosis, at least 3mo. Non-heparin AC options:
    - Fondaparinux (IV or SQ): for stable non-surgical patients, contraindicated if GFR <30, irreversible
    - Argatroban (IV): preferred in renal failure & surgical pts, monitor w/ chromogenic Xa (goal 20-40%)
    - Bivalirudin (IV): only approved for HIT undergoing PCI, preferred in liver failure
    - PO Options: DOACs for non-urgent AC, **warfarin** not until plt >150K for 2 consecutive days
  - Add heparin to allergies, avoid in future & use other VTE ppx. If strong indication (e.g., bypass) small studies suggest no ↑ risk of HIT in pts with h/o HIT >100d prior if anti-PF4 now neg ([NEJM 2001;344:1286](#); [NEJM 2000;343:515](#)). **Resolution of ↓Plt expected in ~7d**

## THROMBOTIC MICROANGIOPATHY (TMA) ([NEJM 2014;371:654](#))

Microthrombi → **MAHA** (↓Hb, ↑LDH, ↓haptoglobin, +schistos, -DAT), ↓↓plt (consumption), **end-organ injury** (vascular occlusion)

- **Drug-induced (DITMA):** gemcitabine, oxaliplatin, quetiapine, quinine, tacrolimus, cyclosporine, bevacizumab, opioids
- **TTP (Plt <30K):** inherited/acq. ADAMTS13 def. →vWF multimers →formation of plt microthrombi. **S/Sx:** purpura, GI sx, neuro sx; fever, AKI. **Dx:** PLASMIC score mod/high, lab testing of ADAMTS13 activity. **Tx:** plasma exchange/FFP, steroids, ritux. DO NOT transfuse to correct Plt unless severe bleed, though transfusion not a/w ↑ risk of mortality/CNS comp ([Transfusion 2009;49:873](#)).
- **HUS (plt >30K):**
  - **Shiga-toxin-mediated** O157:H7 *E. coli*, *Shigella* (“ST-HUS”). **S/Sx:** bloody diarrhea, severe AKI; severe neuro sx rare. **Dx:** stool ⊕ for organism or toxin (at MGH need to request this with micro add-on); **Tx:** supportive (IVF, HD) ([Blood 2017;129:2847](#))
  - **Complement-mediated** (“atypical HUS”): **S/Sx:** severe AKI + 20% w/ extra-renal sx (CNS, cardiac, pulm hemorrhage, panc.); **Dx:** complement genotyping, anti-complement Ab. **Tx:** plasma exchange; eculizumab ([NEJM 2013;368:2169](#))
- **2° Etiologies:** DIC, infxn, malignancy, SLE/APLS, scleroderma, malignant HTN, HELLP, post-HSCT
- **Immediate Management:** if DITMA, d/c drug. Special slide (+schistos), c/s Heme if concerned and/or severe anemia/↓Plt, monitor UOP (for renal impairment), consider complement (C3/C4) testing. 1<sup>st</sup> line: therapeutic plasma exchange, transfuse RBCs if symptomatic anemia, transfuse platelets for <20k or <50k with bleeding/pre-procedure.

# Hematology

# Eosinophilia

## OVERVIEW ([Am J Hematol 2017;92:1243](#); [Hematology 2015;2015:92](#))

- **Eosinophilia:** AEC >500. **Hypereosinophilia:** AEC >1500. **Hypereosinophilic syndromes (HES):** AEC >1500 + organ dysfunction
  - Eosinophils are quickly eliminated by steroids → eosinophilia may be unmasked as pts taper off chronic glucocorticoids
- Primary = due to clonal expansion (HES/leukemia). Secondary (reactive) = due to infection, atopy, meds, rheum dz, etc

Infections	<b>Helminthic:</b> strongyloides, toxocariasis, schistosomiasis, ascaris, filariasis, trichinellosis, hookworm, fascioliasis. <b>Fungal:</b> aspergillus (ABPA), coccidiomycosis, histoplasmosis. <b>Protozoal:</b> isospora. <b>Viral:</b> HIV, HTLV1/2
Malignancy	Primary HES (PDGFRA-assoc.), eosinophilic leukemia, CML, NHL, HL, mastocytosis; less common with solid tumors
Autoimmune	EGPA (see <a href="#">Vasculitis</a> ), PAN, eosinophilic fasciitis, RA, IBD, EoE, IgG4, sarcoidosis, GVHD, blistering disease
Allergic	Drugs (i.e. penicillins, cephalosporins, NSAIDs, ranitidine, aspirin, allopurinol, phenytoin, tetracyclines), DRESS, asthma/atopy, ABPA, hyper IgE syndrome, AIN, episodic angioedema (Gleich syndrome)
Misc	Adrenal insufficiency, cholesterol emboli syndrome, acute arterial thrombosis, radiation exposure

## WORKUP ([Br J Haematol 2017;176:553](#); [J Allergy Clin Immunol Pract 2018;6:1446](#); [Hematology 2015;2015:92](#))

- **Hx:** meds/supplements (<6w), diet, travel, occupational exposures, atopy, infxn, malignancy, rheumatic dz, full ROS, Δ in sx
- **Exam:** assess for rashes, cardiac/pulmonary abnormalities, nasal/sinus involvement, LAD, hepatosplenomegaly, neuropathy
- **Initial diagnostics:** CBC/diff (repeat), special slide, BMP, LFTs, LDH, ESR/CRP
  - If AEC 500-1500: check troponin, B12/tryptase, CXR if clinically indicated
  - If AEC >1500, assess for HES: check U/A, CK, troponin, EKG, CXR, PFTs, CT C/A/P (for adenopathy, organomegaly, masses, organ infiltration), tissue biopsy of affected organs; also B12, tryptase, serum Ig levels
- **Additional diagnostics** (as clinically indicated): Strongyloides serology, stool O&P, other serologies if potential exposure; ANCA if c/f EGPA; ANA, RF, CCP if c/f rheum dz; IgE levels, allergy testing if c/f allergy; imaging/bronch, serologies (e.g. aspergillus IgE) if c/f pulm dz; endoscopy if c/f EoE/EGE; TTE/CMR if c/f cardiac dz; periph. flow ± BMBx if c/f MPD or >1500 & no obvious 2° cause
- **When to suspect drug reaction:** isolated ↑Eos or w/ systemic illness (e.g. DRESS, hepatitis, AIN). PCN/cephalosporins common culprits. Suspect DRESS if new drug 2-8w prior, fever, rash, facial edema, LAD, ↑ LFTs, ± organ involvement, atyp. lymphs.

## TREATMENT ([Hematology 2015;2015:92](#))

- Urgent Tx: if cardiac, neuro, or thromboembolic complications, AEC >100,000/rapidly rising, or s/sx of leukostasis → 1mg/kg to 1g methylpred (+empiric ivermectin 200mcg/kg if potential Strongyloides exposure); obtain HES diagnostics above prior to initiating
- Non-urgent Tx: symptomatic or evidence of end-organ damage but does not need urgent Tx; see below for Tx by condition
- No Tx: if asymptomatic, no organ involvement, & no identified cause to treat, can monitor for resolution & organ damage

## ORGAN-SPECIFIC PATHOLOGY

### Cardiac: ([Immunol Allergy Clin North Am 2007;27:457](#); [JACC 2017;70:2363](#))

- Eosinophilic endomyocarditis: necrosis → thrombus formation (→ embolic events) → fibrosis → restrictive CM, valve involvement
  - May be due to hypersensitivity myocarditis, parasitic infections, malignancy, idiopathic HES
  - Dx: TTE (LV/RV apical dysfunction, signs of restriction, intracardiac thrombi) and cardiac MRI (+subendocardial LGE)
  - Tx: high dose steroids & remove culprit med (if hypersensitivity), treat underlying disorder (parasite, HES)
- Eosinophilic coronary arteritis: rare complication of EGPA; may mimic ACS

### Pulmonary: ([Clin Microbiol Rev 2012;25:649](#); [Chest 2014;145:883](#); [J Allergy Clin Practice 2014;2:703](#))

- Acute eosinophilic PNA: <7d fever, cough, SOB; a/w smoking; ↑periph. Eos often absent at presentation; Dx: BAL Eos ≥25%
  - Chronic eosinophilic PNA: subacute fever, cough, SOB, wt loss; a/w asthma; Dx: BL periph/pleural infil, UL-predom; BAL Eos ≥25%
  - Allergic bronchopulmonary aspergillosis (ABPA): asthma/CF c/b recurrent exacerbations w/ fever, malaise, brown mucus plugs; Dx: ↑Eos, ↑total IgE, ↑Aspergillus IgE & IgG, imaging w/ central bronchiectasis, UL/ML consolidations; Tx: steroids + itraconazole
  - Loeffler syndrome: transient/migratory pulm. opacities, ↑Eos 2/2 helminth larvae; Dx: larvae in resp secretion (stool usually ⊖)
- GI:** (AGA EoE: [Gastro 2020;158:1776](#); [NEJM 2015;373:1640](#); [Clin Rev Allergy Immunol 2016;50:175](#))
- Eosinophilic esophagitis (EoE): dysphagia, food impaction, GERD-like sx/refractory GERD, assoc w/ allergic conditions; Dx: EGD w/ bx, exclude other causes (GERD, motility d/o, Crohn's, infxn, CTD, etc.); Tx: dietary Δs, PPI, topical steroids (MDI/neb, PO liquid)
  - Eosinophilic gastroenteritis (EGE): stomach/duod. ± esoph., colon; Sx: n/v/d, abd. pain, ascites; Tx: dietary Δs, PO steroids

## PRIMARY HYPEREOSINOPHILIC SYNDROMES (HES) ([Am J Hematol 2017;92:1243](#); [Hematology 2015;2015:92](#))

- **Myeloproliferative HES** (~20% of HES in US): acute/chronic eosinophilic leukemia; 80% pts have *FIP1L1-PDGFRα* fusion gene
  - Dx: anemia, thrombocytopenia, ↑tryptase, ↑B12, special slide (dysplastic eosinophils), BM Bx (fibrosis, hypercellularity)
  - Tx: if PDGFR+, imatinib ± steroids if cardiac sxs; if JAK2+, JAK2 inhibitor; if FGFR1+, chemo.
- **Lymphocytic HES:** clonal T-cell expansion → ↑IL-5 → ↑Eos. Often p/w skin/soft tissue involv., polyclonal hyper-IgG, ↑IgE.
  - Dx: flow cytometry for CD3, CD4 (clonal IL-5-secreting CD3+ CD4+ T-cells); Tx: steroids; 2<sup>nd</sup> line: IFN-α, hydroxyurea, anti-IL-5
- **Idiopathic HES/Hypereosinophilia of Uncertain Significance (HE<sub>us</sub>):** eosinophilia w/o identified cause +/- organ involvement → consider ANCA-neg EGPA, suggested all pts get f/u to ensure no end-organ involvement even if asx at dx. Tx: Steroids only if sx.

# Hematology

# Coagulation Disorders

## HYPERCOAGULABLE STATES ([NEJM 2017;377:1177](#))

### Workup of VTE by provocation/features:

- Provoked VTE:** Triggers: surgery/trauma, immobility, Ca, pregnancy/OCP/estrogen, SLE, IBD, nephrotic sx, MPN, HIT, COVID, Paget-Schroetter/May-Thurner. Workup: NO role for hypercoag testing, age-appropriate cancer screening.
- 1<sup>st</sup> unprovoked VTE:** typically no need to test as inherited thrombophilia does NOT sig. ↑ risk of recurrent VTE ([JAMA 2005;293:2352](#))
- Unprovoked DVT and recurrent, young age, OR strong FHx:** Consider testing (below) if will alter med mgmt (i.e. OCPs, AC duration/agent, family planning); APLAS w/u if young or recurrent events.
- Arterial:** Send APLAS testing
- Cerebral/splanchnic veins:** Hypercoag. workup for inherited thrombophilia, APLAS, JAK2, PNH

### Hypercoag testing considerations:

- DO NOT test at time of event.** If performed, should be **>2w following d/c of AC** to avoid confounded results
- Testing** includes: Activated Protein C (APC) resistance (reflexes to Factor V Leiden), protein C/S (reflexes to FVIII/fibrinogen), ATIII, aPL Abs, prothrombin mut G20210A (PTG). **Only Factor V Leiden, PTG mutation, and aPL Ab are reliable in acute VTE or on AC**

INHERITED CONDITIONS		
Condition	Clinical Pearls	Testing
<b>Factor V Leiden</b>	- Most common inherited cause of hypercoagulability	- APC resistance assay (reliability iso heparin products depends on assay) → reflex FVL genetic test
<b>Prothrombin gene mutation</b>	- 2 <sup>nd</sup> most common cause of hypercoagulability - ↑ prothrombin (FII)	- PCR for PTG G20210A mutation (most common)
<b>Protein C/S deficiency</b>	- Activated protein C/S inactivate FVa and FVIIIa; ↓ level (more common) or function leads to hypercoagulability - A/w warfarin-induced skin necrosis (screen if hx)	- Free protein C/S functional assays - ↓ by acute thrombosis, VKA, liver dz, DIC, chemo, uremia (Prot C), pregnancy/OCP/nephrotic sx (Prot S) - ↑ by DOAC (Prot C/S), HLD and nephrotic sx (Prot C)
<b>Antithrombin III deficiency</b>	- ↓ level or function - Heparin works via ATIII to inactivate FIIa and FXa; if ATIII def., will be heparin-resistant & require ↑↑↑doses	- ATIII functional assay assessing FXa inhibition - ↓ by acute thrombosis, UFH/LMWH, liver dz, nephrotic - ↑ by DOAC, direct thrombin inhibitors
<b>Others</b>	Homocysteine and MTHFR mutational analysis should <b>NOT</b> be performed	
Acquired Conditions		
<b>APLAS</b>	- <b>Sapporo criteria</b> = 1 lab + 1 clinical criterion (venous/arterial thrombosis, pregnancy complications) - <b>Catastrophic APLAS:</b> ⊕ aPL w/ 3+ organ thromboses in <1w, mortality ~50% ( <a href="#">Autoimm. Rev 2010;10:74</a> ) Tx: LMWH → warfarin ± ASA (if arterial) ( <a href="#">Lupus 2015;23:301</a> ). If VKA ± ASA fails, consider split dose LMWH 25% above standard dose ( <a href="#">Blood 2021;137:299</a> )	- <b>Lab criteria:</b> ⊕ LA, anti-cardiolipin, or anti-β2 glycoprotein >2x ULN, twice <b>12w apart</b> - LA unreliable on AC (false ⊕) and acute thrombosis (false ⊖); anti-CL and β2GP not affected - ⊕ aPL Ab can be seen in infx, rheum dz, malig, meds, ↑D-dimer w/o clinical APLAS; unclear significance - False ⊕ VDRL ( <a href="#">NEJM 2018;378:2010</a> )

## COAGULOPATHY ([NEJM 2014;370:847](#))

Disorders of **1° hemostasis** (↓ platelet # or function, VWD → mucocutaneous bleeding, petechiae, menorrhagia) or **2° hemostasis** (factor deficiency/↓ activity → deep tissue bleeding, joint, organ, brain; prolonged PT/PTT)

- Rule out **artifact, anticoagulant use, or systemic disease** (cirrhosis, DIC, abx, malnutrition, renal disease, cancer)
  - Consider diseases affecting vascular function (e.g. HHT, scurvy, EDS)
- If prolonged PT/PTT and etiology is not clinically apparent, order **mixing study** w/ normal plasma ([JAMA 2016;316:2146](#))
  - If PT/PTT corrects: supports **clotting factor deficiency** (confirm w/ factor specific assays)
  - If no/partial correction: supports **presence of inhibitor** (confirm w/ inhibitor specific assays)
    - Types: drugs (e.g. heparin), acquired factor inhib (VIII, V>>IX, XI; autoimmune d/o, malig), nonspecific inhib (e.g. LAC)
  - If work-up is unrevealing, consider VWD testing, platelet function testing, thrombin time (TT), fibrinogen, factor XIII
- Tx: replace missing factor, eliminate inhibitor (immunosuppressants), treat underlying condition

**Hemophilia:** most common severe bleeding disorder, X-linked. Caused by Factor VIII (Hemophilia A) or Factor IX (Hemophilia B) deficiency → reduced clot formation and stabilization → bleeding (joint damage from recurrent bleeds common cause of morbidity)

- Dx:** ↑PTT (can be normal in mild def) → 1:1 mixing study (if PTT corrects = factor def) → factor specific assay to distinguish A and B
- Tx:** Concentrates of FVIII/FIX ppx for bleeding events or on-demand w/ bleeds. Emicizumab (bispecific ab which functions like Factor XIII) approved for prophylaxis in Hemophilia A. Multiple novel gene therapies currently under investigation ([Blood 2019;133:389](#)).

Coagulation Defect	Normal aPTT	Prolonged aPTT
<b>Normal PT</b>	<b>Platelet dysfunction</b> (VWD, other platelet disorders), ↓ Factor XIII	<b>Intrinsic pathway:</b> ↓VIII, IX (hemophilia), XI (Ashkenazi); VWD; ↓XII, PK, HMWK (no bleeding); LAC (prothrombotic)
<b>Prolonged PT</b>	<b>Extrinsic pathway:</b> ↓Factor VII, warfarin, liver disease, Vit K deficiency	<b>Common pathway:</b> liver disease, DIC, Vit K deficiency, warfarin. Rarely common pathway deficiency/inhibitor

**DIC:** massive activation of coag cascade caused by various inflamm. etiologies (sepsis, CA, trauma, pancreatitis). Consumption of coag. factors → **bleeding**, microvascular **thrombosis**, MAHA, organ ischemia.

- Dx:** ↑PT/PTT, ↑D-dimer, ↓fibrinogen, ↓plts, +schistos, ↑LDH, ↓haptoglobin (often normal coags in chronic DIC). Can differentiate DIC from liver dz w/ ↓FVIII (FVIII present in endothelium, not liver), [DIC score](#)
- Tx:** treat underlying cause, transfuse plts if <10k (or serious bleeding <50k), cryo if fibrinogen <100, FFP if INR >2. Amicar generally contraindicated

# Hematology

# Anticoagulation Agents

ORAL AGENTS (ASH: [Blood Adv 2018;2:3257](#); CHEST: [Chest 2012;141:e152S](#); [Chest 2012;141:e44S](#))

Agent	Dosing	Bridging/Switching/Reversal
<b>Warfarin</b> (Coumadin) - Vitamin K antagonist: inhibits vitamin K-dependent gamma-carboxylation of F <sub>2</sub> , II, VII, IX, X, & Protein C+S - t <sub>1/2</sub> 40h (variable)	- Initiation: 5mg qd x2d; frail, HF, kidney/liver dz: consider 2.5mg; BMI >40: consider 7.5mg - Adjust by INR, which lags 48h behind dose Δ Monitoring: ( <a href="#">UW Dosing Nomogram</a> ) <b>INR &lt;2:</b> ↑ up to 10-20%/w or consider booster dose <b>INR 2-3:</b> no change <b>INR 3-4:</b> ↓ 10%/wk or consider holding 0.5-1 dose <b>INR &gt;4:</b> hold until INR 2-3, restart ↓ 5-15%/week <b>If overlap with direct thrombin inhibitor:</b> check chromogenic FXa: goal 20-40%	Bridging: (see below to bridge from parenteral AC): To parenteral AC: start IV w/o bolus when INR <2 Reversal: IV vitamin K faster than PO at 6h; ~ at 24h - Active bleeding: 1) IV vit K 10mg + FFP ( <a href="#">10mL/kg</a> ; 1U = 200-250mL) 2) Kcentra (4-factor PCC) 50U/kg if life-threatening ( <a href="#">Circ 2013;128:1234</a> ; <a href="#">Transfusion 2016;56:799</a> ) - No active bleeding: 1) INR >10 → PO vitamin K 2.5-5mg OR IV 1-2.5mg 2) INR <10 → hold warfarin, no need for reversal
<b>Dabigatran</b> (Pradaxa) - Direct thrombin (IIa) inhibitor, t <sub>1/2</sub> 12-17h - 80% renal clearance - P-gp substrate - Other: ↑ dyspepsia, ?↑ coronary events	- <b>Non-valvular AF:</b> 150mg PO BID if GFR >30, 75mg PO BID if GFR 15-30 ( <a href="#">RE-LY, NEJM 2009;361:1139</a> ); some use 100mg PO BID dose if high bleeding risk - <b>VTE:</b> 150mg PO BID after 5d UFH/LMWH ( <a href="#">RE-COVER, NEJM 2009;361:2342</a> ) - <b>PPX:</b> 110mg x1 then 220mg PO QD ( <a href="#">RE-NOVATE II, Thromb Haemost 2011;106:721</a> )	Bridging/switching: To parenteral AC: start 12h after last dose (24h if CrCl <30). From parenteral AC: start <2h before next dose. <b>To warfarin:</b> start 3d before dabigatran ⊖ if CrCl ≥50; 2d if CrCl 31-50, 1d if GFR 15-30; bridge PRN. From warfarin: hold and start when INR < lower limit of therapeutic range Reversal if life threat.: can be dialyzed, lipophilic - Idarucizumab 5g ( <a href="#">RE-VERSE, NEJM 2017;377:431</a> )
<b>Rivaroxaban</b> (Xarelto) - Direct Xa inhibitor - t <sub>1/2</sub> 5-9h; 11-13 in elderly - 66% renal clearance - Avoid with CYP3A4 and P-gp dual inhibitors	- <b>Non-valvular AF:</b> 20mg PO QD if GFR >50, 15mg if GFR 15-50 ( <a href="#">ROCKET AF, NEJM 2011;365:883</a> ) - <b>VTE:</b> 15mg PO BID x21d, then 20mg QD. After 6mo, consider ↓ to 10mg QD if ongoing risk for VTE ( <a href="#">NEJM 2010;363:2499</a> ; <a href="#">NEJM 2012;366:1287</a> ; <a href="#">NEJM 2017;376:1211</a> ) - <b>PPX:</b> 10mg PO QD ( <a href="#">MAGELLAN, NEJM 2013;368:513</a> )	Bridging/switching: ( <a href="#">J Thromb Thrombolysis 2016;41:206</a> ) - To parenteral AC: start when next DOAC dose due - From LMWH/fonda: start w/in 0-2h of next dose - From UFH: start immediately after ⊖ gtt (for <b>edoxaban</b> , start 4h after stopping UFH) - From warfarin: <ul style="list-style-type: none"><li>• Start <b>rivaroxaban</b> when INR &lt;3</li><li>• Start <b>apixaban</b> when INR &lt;2</li><li>• Start <b>edoxaban</b> when INR ≤2.5</li></ul> - To warfarin: (NB all ↑ INR; ✓ just before dose if able) <ul style="list-style-type: none"><li>• <b>Rivaroxaban/apixaban:</b> co-administer until INR ≥2</li><li>• <b>Edoxaban:</b> cut edoxaban dose by ½ and begin warfarin, ⊖ edoxaban once INR ≥2</li></ul> - DOAC to DOAC: start when next dose due Reversal if life-threat.: not dialyzed off, protein-bound - Andexanet alfa (recombinant FXa): bolus → 2h gtt ( <a href="#">NEJM 2015;373:2413</a> ; <a href="#">NEJM 2019;380:1326</a> )
<b>Apixaban</b> (Eliquis) - Direct Xa inhibitor - t <sub>1/2</sub> 12h - lower renal clear. (25%) (can use in ESRD)	- <b>Non-valvular AF:</b> 5mg PO BID, 2.5mg BID if 2/3: Cr ≥1.5, Wt ≤60kg, age ≥80; some use 2.5mg BID if CrCl 15-29 ( <a href="#">ARISTOTLE, NEJM 2011;365:981</a> ) - <b>VTE:</b> 10mg BID x7d, then 5mg BID x6mo; after 6mo, consider ↓ to 2.5mg BID ( <a href="#">NEJM 2013;369:799</a> & <a href="#">368:699</a> ) - <b>PPX:</b> 2.5mg BID ( <a href="#">NEJM 2009;361:594</a> )	
<b>Edoxaban</b> (Savaysa) - Direct Xa inhibitor - t <sub>1/2</sub> 10-14h - 50% renal clearance - Avoid if CrCl >95 or <15 - P-gp substrate	- <b>Non-valvular AF:</b> 60mg PO QD; 30mg if CrCl 15-50 or wt ≤60kg; do not use if CrCl >95 ( <a href="#">ENGAGE AF, NEJM 2013;369:2093</a> ) - <b>VTE:</b> 60mg QD after 5d UFH/LMWH, 30mg QD if CrCl 15-50, ≤60kg, or taking P-gp inhibitor ( <a href="#">NEJM 2013;369:1406</a> )	

## PARENTERAL AGENTS

Agent	Dosing/Monitoring	Bridging/Switching	Reversal	Other
<b>Heparin (UFH)</b> - Binds & activates ATIII → inactivates Xa & IIa - t <sub>1/2</sub> 60-90min	- <b>ACS:</b> 60U/kg → 12U/kg/h; PTT 63-83 - <b>VTE:</b> 80U/kg → 18U/kg/h; PTT 70-100 - <b>PPX:</b> 5,000U SC q8-12h - <b>Monitoring:</b> PTT; anti-Xa (goal 0.3-0.7) if baseline ↑ PTT or high doses; ACT if 11)	- <b>To LMWH:</b> give LMWH & ⊖ UFH at same time - <b>To warfarin:</b> ⊖ UFH once therapeutic ≥2d	- <b>Protamine:</b> 1mg per 100U heparin or 1mg LMWH (max 50mg). 60% reversal for LMWH, most effective if last dose within 8h - Do NOT give FFP (has ATIII, which potentiates AC effect)	- Preferred in renal failure (CrCl <30), peri-procedure, poor absorption, pregnancy  - Acute VTE: LMWH > UFH ( <a href="#">Cochrane Rev 2017</a> ) - Prolonged t <sub>1/2</sub> in renal failure
<b>Enoxaparin (LMWH, Lovenox)</b> - Binds & activates ATIII → inact. Xa>>IIa - t <sub>1/2</sub> 4.5-7h	- <b>ACS/VTE:</b> 1mg/kg BID; QD if GFR <30 - <b>PPX:</b> 40mg SC QD; 30mg BID if ↑ risk; ↑ 30% if BMI ≥40; 30mg QD if GFR <30 - <b>Monitoring:</b> not routine; can check anti-Xa 4h after 4 <sup>th</sup> dose, goal 0.5-1.0	- <b>To UFH:</b> ⊖ LMWH & start UFH w/o bolus 1-2h before LMWH dose due - <b>To warfarin:</b> ⊖ LMWH once therapeutic INR ≥2d		
<b>Fondaparinux (Arixtra)</b> - Binds & activates ATIII → inact. Xa only - t <sub>1/2</sub> 17-21h	- <b>VTE:</b> <50kg → 5mg QD   50-100kg → 7.5mg QD   >100kg → 10mg QD - <b>PPX:</b> 2.5mg SC QD - CrCl <30: contraindicated - <b>Monitoring:</b> not routine; can check 4h anti-Xa	- <b>To warfarin:</b> ⊖ fonda. once therapeutic INR ≥2d - <b>To UFH:</b> start UFH (no bolus) 1-2h before due - <b>From UFH:</b> start 1h after UFH ⊖	- No reversal agent	- ↑ aPTT at therapeutic doses - If CrCl 30-50, consider Δ agents
<b>Argatroban</b> - Direct IIa (thrombin) inhibitor - t <sub>1/2</sub> 45min	- <b>HIT:</b> 1-2mcg/kg/min - <b>Monitoring:</b> PTT, goal 1.5-3x baseline - Caution in critically ill, cardiac dysfunction, liver disease	- <b>To warfarin:</b> ⊖ once chromogenic factor Xa 20-40% (argatroban ↑ INR)	- No reversal agent	

Factor XI/XII inhibitors under investigation ([Blood 2022;1:495](#)): antisense oligonucleotides (ASO), antibodies (abelacimab [NEJM 2021;385:609](#), osocimab, small molecules (milvexian, asundexian)

# Hematology

# Anticoagulation Management

## CHOOSING AN ANTICOAGULATION AGENT

**Guidelines:** CHEST for VTE: [Chest 2021;160:2247](#), ASH for VTE: [Blood Adv 2021;5:927](#), ASCO for VTE in CA: [JCO 2020;38:496](#); ACC/AHA/HRS for AF: [JACC 2019;74:104](#), CHEST for AF: [Chest 2018;154:1121](#); AHA/ACC for Valvular HD: [JACC 2021;77:e25](#)

VTE	Obesity	Avoid DOAC if BMI $\geq 40$ or wt $\geq 120\text{kg}$ , but rivaroxapix. may be ok. If use, ✓ peak/trough level (ISTH: JTH 2021;19:1874)
	Active Malignancy	Apixaban ( <a href="#">CARAVAGGIO, NEJM 2020;382:1599</a> ), edoxaban ( <a href="#">NEJM 2018;378:615</a> ), rivaroxaban ( <a href="#">JCO 2018;36:2017</a> ), LMWH > warfarin ( <a href="#">CLOT, NEJM 2003;349:146</a> ). Edox/rivarox ↑ bleeding risk vs LMWH, avoid in GI/GU CA w/ intralum. lesions. DOAC > LMWH for short-term VTE tx, either long-term. Apix/rivarox ppx ↓ VTE in high-risk outpts, suggest in mod-risk: consider if <a href="#">Khorana ≥2 (AVERT, NEJM 2019;380:711; CASSINI, NEJM 2019;380:720)</a> . LMWH ppx OK in high-risk outpts
	Recurrent	If on non-LMWH: switch to LMWH. If on LMWH: increase LMWH dose and check Xa level
	All Others	DOACs > warfarin > LMWH
AF	Non-valvular	DOACs > warfarin for stroke risk, mortality, and bleeding risk
	Valvular	Warfarin if mod/severe MS (regardless of CHADS2VASC)
	+ PCI	Dual (P2Y12i+OAC) v triple therapy (+ASA): dual w/ ↓ bleeding, likely no ↑ events ( <a href="#">Annals 2020;172:474; EHJ 2019;40:3757</a> )
		Dual therapy: DOAC + clopidogrel x-6-12mo. Rivaroxaban 15mg qd (some use 20mg) ( <a href="#">PIONEER AF, NEJM 2016;375:2423</a> ) & dabigatran 150mg BID ( <a href="#">RE-DUAL PCI, NEJM 2017;377:1513</a> ) in guidelines, also data for apixaban (5mg BID unless 2.5mg indicated) ( <a href="#">AUGUSTUS, NEJM 2019;380:1509</a> ) & edoxaban 60mg QD (*though didn't ↓ bleeding v VKA) ( <a href="#">ENTRUST-AF PCI, Lancet 2019;394:1335</a> ). Warfarin + clopi or ticag also option ( <a href="#">WOEST, Lancet 2013;381:1107</a> ). Ticag may be used in-hospital or if very high thrombotic risk. After 12mo, can likely Δ to OAC alone ( <a href="#">AFIRE, NEJM 2019;381:1103</a> )
		If triple therapy chosen (high thrombotic/low bleed risk), typically d/c ASA & transition to P2Y12i+OAC therapy at 1-6 wks
Valve	Mechanical	Warfarin (+ASA for aortic On-X valve). DOACs not approved. INR for AVR 2.5 (3 if +AF, VTE, etc.); MV/TV = 3
	Bioprosthetic	SAVR: Warfarin (INR 2.5) + ASA 3-6mo → ASA. TAVR: ASA/clopi 3-6mo → ASA. If AF/VTE, OAC+clopi → OAC (evolving)
CAD	APLS	Warfarin. Warfarin > rivaroxaban in high-risk APLS ( <a href="#">TRAPS Blood 2018;132:1365; AIM 2019; 171:685</a> )
	ACS (PCI)	Very low dose rivaroxaban (2.5mg BID) added to ASA/clopidogrel → ↓ CV mortality but ↑ major bleeding ( <a href="#">NEJM 2012;366:9</a> )
	2° prevention	Very low dose rivaroxaban (2.5mg BID) + ASA → ↓ MACE vs. ASA alone; ↑ major bleeding but no Δ in ICH or fatal bleeding ( <a href="#">COMPASS, NEJM 2017;377:1319</a> ). Can consider if high risk for events & low bleeding risk
s/p PCI	12 mo DAPT	new research w/ 1-3 mo DAPT+12 mo clop non-inf to 12 mo DAPT ( <a href="#">STOPDAPT-2, JAMA 2019;321:2414</a> ); can integrate DAPT score into clinical decision making

## ANTICOAGULATION BRIDGING

**Guidelines:** ACC: [JACC 2017;69:871](#); ASH: [Blood Adv 2018;2:3257](#); CHEST: [Chest 2012;141:e419s](#)

Indication Thrombotic Risk	AF		VTE		Mechanical Valve	
	Risk Factors	Bridge?	Risk Factors	Bridge?	Risk Factors	Bridge?
High	- CHA <sub>2</sub> DS <sub>2</sub> -VASc $\geq 7$ (or CHADS2 5-6) - CVA/TIA, or systemic embolism <3mo - Rheumatic valvular dz	Yes, unless major bleed/ICH <3mo	- VTE <3 mo - Severe thrombophilia: protein C/S or ATIII def, APLAS, multiple abnormalities	Yes	- Any mechanical MV - Caged ball/tilt disc AVR - Any mechanical valve w/ CVA/TIA <6mo	Yes
Moderate	- CHA <sub>2</sub> DS <sub>2</sub> -VASc 5-6 (or CHADS2 3-4) - CVA/TIA or systemic embolism >3mo	Likely bridge if prior CVA/TIA and if no ↑ risk of bleeding	- VTE 3-12mo - Recurrent VTE - Active malignancy - Non-severe thrombophilia: heterozygous factor V Leiden, PTG mutation	No	- Bileaflet AVR w/ ≥1 CVA risk factor: age >75, AF, prior CV/TIA, HTN, DM2, CHF	Consider against risk of procedural bleeding ( <a href="#">UpToDate table</a> )
Low	- CHA <sub>2</sub> DS <sub>2</sub> -VASc ≤4 (or CHADS2 0-2) - No prior CVA/TIA or systemic embolism	No	- VTE >1y & no other risk factors	No	- Bileaflet AVR w/o AF or CVA risk factor	No

- BRIDGE trial ([NEJM 2015;373:823](#)) demonstrated ↑ risk of bleeding w/ bridging in pts with AF undergoing invasive procedure requiring interruption of VKA (NB: excluded pts w/ mech. valves, stroke/TIA <12w, major bleeding <6w, CrCl <30, plt <100k)
- Bridging Vitamin K Antagonist (VKA) w/ UFH or LMWH:
  - Stop VKA 5d prior to procedure if therapeutic INR. Start UFH or LMWH when INR <2
  - Stop UFH 4-6h prior to surgery and LMWH 12 or 24h prior to surgery (depending on dosing interval)
  - Restart UFH/LMWH at 24h postop. if low postprocedural bleeding risk or 48-72h if high risk. ⊖ when INR >2
  - Resume VKA w/in 24h postop if no bleeding complications (will not ↑ early bleeding risk because effect takes 24-72h)
- DOACs: no bridging required; most can be stopped 24-72h prior to surgery, depending on procedural bleeding risk & renal function

Drug	High Bleed Risk*		Low Bleed Risk*	
	CrCl >50	CrCl <50	CrCl >50	CrCl <50
Dabigatran	≥48h (4 doses)	≥96h (8 doses)	≥24h (2 doses)	≥48h (4 doses)
Rivaroxaban	≥48h (2 doses)	≥48h (2 doses)	≥24h (1 dose)	≥24h (1 dose)
Apixaban	≥48h (4 doses)	≥48h (4 doses)	≥24h (2 doses)	≥24h (2 doses)
Edoxaban	≥48h (2 doses)	≥48h (2 doses)	≥24h (1 dose)	≥24h (1 dose)

\*For bleeding risk stratification use procedural bleeding risk + HAS-BLED score.

○ If low bleeding risk, can resume 24h after procedure. If high bleeding risk, wait 48-72h. No PO or 2<sup>nd</sup> procedure use UFH/LMWH.

\*\*See Peri-Procedural Anticoagulation for MGH-specific peri-procedural guidance for cardiac cath. lab & IR procedures\*\*

# Hematology

# Transfusion Medicine

## TRANSFUSION MEDICINE TERMINOLOGY

- **ABO typing:** front type: **A/B antigens** (pt's RBC + reagent anti-A or B); back: anti-A or B in plasma (pt's plasma + reagent RBCs)
- **Rh(D) typing:** tests for **D antigen** on RBC (pt's RBC + reagent anti-D) – *NB: anti-D is not a naturally occurring antibody*
- **Screening (T&S):** tests for **unexpected antibodies** in pt's plasma (pt's plasma + **screening** RBC + Coomb's reagent), “active”  $\times 3d$
- **Crossmatching (T&C):** final confirmation test by mixing pt's plasma & **donor** RBC; performed just prior to transfusion
- **Direct antiglobulin test (DAT/Coomb's Test):** tests for Ab or complement on RBCs (RBCs + Coomb's reagents [anti-IgG, anti-C3])

## BLOOD PRODUCTS

Product	Description	Indications	Notes
Red Blood Cells	1U ~ 330cc <u>Processing</u> 1. Leukocyte reduction 2. Irradiation 3. Washing (rarely)	- Hgb <7 ( <a href="#">NEJM 2014;371:1381</a> , <a href="#">NEJM 2013;368:11</a> ) - Hgb <8 if CAD/ACS, ortho/cardiac surgery (although threshold still being studied in MI, [ <a href="#">JAMA 2021;325:552</a> ]) - Acute hemorrhage (>15% intravascular volume) - AIHA (no specific Hgb threshold) - Sickle cell disease (see <i>Sickle Cell Disease</i> )	- Each unit: Hct ~55% - 1U ↑Hgb ~1 - Rate: if active hemorrhage, give over 60-90min
Platelets	1U = 6pk = 300cc <u>Types</u> 1. Apheresis platelets derived from 1 donor 2. Pooled platelets from multiple donors <u>Processing</u> 1. Leukocyte reduction 2. Irradiation	<b>Low platelets or functionally abnormal platelets (consider checking citrated platelets)</b> - <10k: PPX spont bleeding ( <a href="#">NEJM 1997;337:1870</a> ), antifibrinolitics in refractory thrombocytopenia in CA - <50k: major bleed, intra- or post-op bleed, ppx prior to invasive operative procedures (<30k bedside procedures) - <100k: post-bypass bleed, ICH/ophthalmic (no data) - <b>ITP:</b> only if life-threatening CNS/GI/GU bleed (often preceded by wet purpura, mucus membrane bleeding)	- Response at 30-60m: 1U ↑PLT ~30K - No evidence that apheresis > pooled plt - No evidence that platelets reverse anti-platelet agents ( <a href="#">Lancet 2016;387:2605</a> ) - CI: TTP/HUS, HIT
Fresh Frozen Plasma	1U = 250cc Typical starting dose 2U Non-cellular portion of blood containing all coag factors; separated and frozen after collection	- <u>Active bleed d/t deficiency in multi coag. factors</u> or isolated coag factors for which concentrate is not available - <u>ALF:</u> consider for ↓plt or ↑INR only if bleed or pre-op - <u>Cirrhosis:</u> <b>cryo preferred</b> , as treating INR w/ FFP can ↑bleeding due to ↑portal pressures, and has prothrombotic effect ( <a href="#">J Thromb Haemost 2021;19:664</a> ) - Trauma, DIC in presence of bleeding, congenital TTP - Ppx prior to bedside invasive procedures for INR >2.0 (low quality evidence [ <a href="#">Cochrane 2019;11:CD012745</a> ])	- Response: 2U ↑coag activity ~10% - Max correction: INR 1.7 - Effect <6h due to short t <sub>1/2</sub> of FVII - Potentiates effect of heparin by providing ATIII
Cryoprecipitate	10U = 150cc Contains factor VIII, factor XIII, VWF, and fibrinogen	- <u>Fibrinogen &lt;100:</u> 50-100mg/dL, give 10U; <50, give 20U - <u>Massive transfusion</u> w/ ↓fibrinogen or abnl ROTEM/TEG - <u>Complex cardiac surgery</u> ( <a href="#">JAMA 2017;217:738</a> ) - <u>Postpartum hemorrhage</u> ( <a href="#">Br J Anaesth 2015;114:623</a> ) - <u>FVIII deficiency, VWD</u> - <u>Cirrhosis:</u> fibrinogen <100-120 or c/f dysfibrinogenemia	- 10U cryo should ↑fibrinogen ~85mg/dL - Fibrinogen t <sub>1/2</sub> 3-5d - FVIII or vWF replacement: cryo is last resort therapy
Coagulation Factors	VIII, IX, rFVIIa, ATIII; combo: II+IX+X (Profilnine); PCC = II+VII+IX+X (Kcentra), FEIBA (anti-inhib. complx), vWF/FVIII (Humate-P), vWF/FVIII (Humate-P)	- Coagulation factor deficiency/inhibitor - Von Willebrand's disease (Humate-P, NovoSeven) - VKA reversal (IV VitK first, for severe bleed PCC > FFP)	- Blood Transfusion Service approval required - S/E: allergic rxn, thrombosis
Antifibrinolytics	Contain Lysine derivatives that bind to plasminogen to ↓fibrinolysis and ↑hemostasis <u>Types</u> (topical, PO, IV): Aminocaproic acid (Amicar), Tranexamic acid (TXA)	- <u>Trauma</u> ( <a href="#">Health Tech 2013;17:1</a> ) - <u>Postpartum hemorrhage</u> ( <a href="#">Lancet 2017;389:2105</a> ) - <u>Cardiac surgery</u> ( <a href="#">NEJM 2017;376:136</a> ; <a href="#">J Thor C Surg 2019;157:644</a> ), ECMO - <u>Cirrhosis:</u> when hyperfibrinolysis suspected (see ESLD) - Major orthopedic surgery, platelet refractoriness due to HLA alloimmunization, fibrinolysis of serosal surface and closed space bleeding, coagulation factor inhibitor	- Amicar: load 4-5g over 1h → 1g/h for 8h or until bleeding controlled - TXA: load 1g over 10min → 1g over 8h cont. infusion - S/E: risk of seizures w/ high dose TXA
Albumin	<u>Types</u> 1. 5% (iso-oncotic) 2. 25% (hyper-oncotic) Both contain 12.5g albumin & 154mEq Na (isotonic)	<b>5% if hypovol/intravasc depl., 25% if fluid/Na restricted</b> - <u>Cirrhosis:</u> HRS, SBP, LVP (see ESLD) - <u>Shock:</u> 4% albumin similar to 0.9% NS for IVF resuscitation (when alb. >2) ( <a href="#">SAFE, NEJM 2004;350:2247</a> ) - <u>ARDS:</u> 25% albumin (25g) q8h x3d + lasix gtt x3d → ↑O <sub>2</sub> , neg. TBB (when alb. <2) ( <a href="#">Crit Care 2005;33:1681</a> )	- C/I: traumatic brain injury (Also see <i>IV Fluids and Electrolyte Repletion</i> )
IVIG	<u>Types</u> Polyclonal IgG and trace plasma contaminants Dose adjust for obesity	- <u>Immunodeficiency:</u> hypogammaglobulinemia IgG <400 - <u>Immunosuppression</u> in autoimmune disease (e.g. ITP, AIHA, post-transfusion purpura, acquired VWS) - <u>Neuro:</u> CIDP, myasthenia gravis, GBS - <u>ID:</u> toxic shock syndrome, Kawasaki disease	- SE: infusion reactions, aseptic meningitis, hyperosm renal tubular injury, thrombosis

## TRANSFUSION MODIFICATIONS

- **Leukoreduction (LR):** filters leukocytes to (1) ↓ HLA sensitization in chronically transfused pts / **heme malignancies**, bone marrow / kidney / heart / lung **transplant candidates** (not liver transplant) (2) ↓ CMV risk & (3) ↓ febrile non-hemolytic transfusion reaction
- **Irradiation:** prevents proliferation of donor lymphocytes from attacking the recipient (transfusion-associated-GVHD in 1<sup>st</sup> degree directed donors); indications: **heme malignancy** & BMT to prevent GVHD; not indications: solid tumor, solid organ transplant, HIV
- **Saline-washing:** removes anti-IgA Ab & plasma proteins; indications: severe anaphylaxis to blood products (w/ or w/o IgA def.)

## ADMINISTERING BLOOD PRODUCTS

- **Consent:** required for administration of all blood products, discuss type of product, indication, benefits/risks, possible alternatives
- **Ordering:** “Prepare RBC” (or platelets/FFP/cryo) → select number of units to prepare, indication, applicable modifications (see below) and “Transfuse RBC” → select number of units to administer, and rate of admin (usually over 2-4h)
- **Monitoring response:** order post-transfusion CBC to be drawn 15-30min after transfusion (if not actively bleeding)

## MASSIVE TRANSFUSION: call Blood Bank (x63623) & physically run down w/ pick-up slip to **Gray/Bigelow 2** to pick up cooler

- Activate when anticipate transfusing 50% TBV (~5U pRBC) in 2h OR 100% TBV (~10U pRBC or 5L plasma) in 24h
- Occurs most commonly in trauma, GI bleeding, cardiac surgery, obstetric complications, rupture of major blood vessel
- Emergency release un-crossmatched pRBCs (O- for pre-menopausal females, O+ ok for males and older females)
- **No universally accepted ratio:** for 2-4U pRBCs, transfuse 1U FFP, 1U PLT, & 10U cryo (can modify to goals below as stabilizes)
  - Goals: Hb >7-10, INR <2.5, PLT >50k, fibrinogen >100
  - No evidence for 1:1:1 transfusion protocol ([JAMA 2015;313:471](#))
  - Excessive FFP a/w ARDS in pts not requiring massive transfusion
- Correct coagulopathy → IV vit K, FFP 15cc/kg; platelet dysfunction (ASA, plavix, uremia) → PLTs, DDAVP 0.3mcg/kg
- Consider IV amicar or IV TXA (dosing on previous page)
- **Complications:** dilutional coagulopathy, hypothermia, hypo-Ca<sup>2+</sup> (citrate), metabolic alkalosis (citrate metabolized to bicarb), hyper-K<sup>+</sup>

## PLATELET REFRACTORINESS: failure to achieve acceptable ↑ platelet count following transfusion. Normal t<sub>1/2</sub> of 3 days

- **Alloimmune: Ab to class I HLA antigens** (e.g. +PRA) or PLT-specific antigens. RFs for HLA alloimmunization: multiple pregnancies, prior transfusions with non-leukoreduced blood products, organ transplants ([NEJM 1997;337:1861](#)). Drug-associated ITP (heparin, sulfa, vanc, linezolid, piperacillin, rifampin, thiazide, anti-GpIIb/IIIa)
- **Non-alloimmune: non-HLA Ab-mediated;** 2/3 of cases; Ddx: sepsis/DIC, HIT, TTP, CVVH/bypass/IABP, splenomegaly, liver dz, HSCT, viral infection (HIV/HCV) & drugs (amphotericin)
- **Evaluation:** check plt post-transfusion on 2 occasions and assess plt recovery (15min-1h later) & plt survival (18-24h later)
  - Inadequate plt recovery: corrected count increment <5k on 2 occasions; also usually indicated by plt ↑ <10k x2 → alloimmune refractoriness ([JCO 2001;19:1519](#))
  - Normal plt recovery but ↓ survival → non-alloimmune refractoriness
- **Alloimmune refractoriness workup:**
  - Consult Blood Transfusion Service [p21829](#). Studies will *not* be processed without discussing w/ them first
  - Send Panel Reactive Antibody: HLA class I Ab screen; test for alloreactivity against HLA antigens. Normal is 0%, range 0-100%
  - **If platelets required urgently** (i.e. actively bleeding), notify Blood Bank and ask for send out to Red Cross
- **Management:** with each platelet transfusion, **must** check a post-transfusion CBC w/in 15-60min of completion
  - Compatible platelets (specific HLA-antigen negative) or crossmatch compatible
  - ABO/HLA-matched apheresis single-donor plts from Red Cross. Takes days to process. Each unit has a shelf life ~3 days
  - Consider Amicar if bleeding (contraindicated in thrombotic DIC); correct coagulopathy with DDAVP if e/o uremia

## MANAGEMENT OF ANEMIA IN JEHOVAH'S WITNESSES ([Am J Hematol 2017;92:1370](#))

- Discuss management with patients on a **case-by-case basis**; consider using a checklist of blood product types
- **Acceptable products:** hematins (iron, folate, B12, recombinant human EPO), non-blood volume expanders (NS, LR, hydroxyethyl starches), hemostatic agents (amicar, TXA, DDAVP, albumin-free clotting factors)
- **Acceptable to some:** autotransfusion, HD/apheresis/bypass/ECMO, hemostatic products w/ blood fractions (coag. factors, PCC), plasma-derived products (albumin, cryo, Ig), products potentially containing albumin (rhEPO, vaccines), BM/organ transplantation
- **Unacceptable products:** whole blood, pRBCs, platelets, FFP, cryo, autologous blood transfusion
- Bleeding, preop: consider IV iron + rhEPO to speed up erythropoiesis → rhEPO onset 2-6 days if Fe/folate/B12 replete
- **Critically ill:** no expert consensus, consider rhEPO 200-300U/kg IV q24h or 250-500U/kg SQ q48h for goal periop Hb >10-12 → can be extrapolated to hemodynamically unstable/bleeding pts

## THERAPEUTIC APHERESIS

- **Plasmapheresis (plasma exchange):** removes plasma, replaces with saline, albumin or plasma (depending on pt. condition) Indications: TTP (replace ADAMTS13, [NEJM 1991;325:393](#)), hyperviscosity, cryo, Guillain-Barre, CIDP, MG, ANCA, anti-GBM
- **Cytapheresis:** removes abnormal or excessive # blood cells Indications: leukapheresis for hyperleukocytosis (goal WBC <100, controversial); erythrocytapheresis for sickle cell crisis, severe babesiosis (high grade parasitemia >10, severe hemolysis, or pulm/liver/renal dz); platelet removal for thrombocytosis rarely done (goal plts <1000)

# Hematology

# Transfusion Reactions

**INITIAL EVALUATION:** Blood Bank (x63623, p21829) ([Br J Haematol 2012;159:143](#))

- S/Sx: f/c/rigors, hives/flushing, infusion site pain, shock/oliguria, wheezing, crackles
- STOP** transfusion, ABCs, VS q15min, notify blood bank
- If only urticarial sx or isolated T ≤39C → treat sx, resume once symptoms resolved
- Initial workup to consider:
  - High suspicion for hemolysis: DAT, Bili, LDH, haptoglobin, crossmatch, UA, smear
  - High suspicion for sepsis: GS/BCx of both pt & blood product
  - High suspicion for TRALI/TACO: JVP, NT-proBNP, ABG, portable CXR

	Acute	Delayed
Immune-mediated	AHTR, FNHTR, Urticaria/hives, Anaphylactic, TRALI	DHTR, TA-GVHD, post-tx purpura
Non-immune mediated	Cold toxicity, citrate toxicity, sepsis, TACO	Viral infection

Reaction/Per-Unit Risk	Presentation/Diagnosis	Pathophysiology	Treatment/Prevention
<b>ACUTE TRANSFUSION REACTIONS (&lt;24H)</b>			
<b>Acute Hemolytic (AHTR)</b> 1/76,000-137,000	<b>Sx:</b> 15min to 2-4h; <u>fever/chills</u> , back/flank pain, bleeding, DIC <b>Dx:</b> +Hb (blood/urine), +DAT, +Bili/LDH, +smear (spherocytes)	- ABO/Kidd incompatibility (preformed Abs) → <u>intravascular hemolysis</u> (IgM), cytokine/complement activation - Rh/Duffy incompatibility → less severe <u>extravascular hemolysis</u>	<b>Tx:</b> IVF (± diuresis) for goal UOP >100cc/hr x24h - Monitoring: HoTN, AKI, DIC, mortality ∝ volume transfused <b>PPX:</b> careful crossmatch
<b>Febrile Non-Hemolytic (FNHTR)</b> 1/14 (PLT) 1/200-2,500 (RBC)	<b>Sx:</b> 1-6h; <u>low-grade fever</u> , chills, HA, flushing <b>Dx:</b> hemolysis workup negative	- Donor WBCs produce TNFα, IL1, IL6 - <u>RBC</u> : donor WBCs activated by recipient anti-HLA Abs - <u>PLT</u> : donor WBCs make cytokines before transfusion	<b>Tx:</b> APAP ± meperidine <b>PPX:</b> leukoreduction, little evidence for pre-medication
<b>Sepsis (Bacterial Contamination)</b> 1/75,000 (PLT)	<b>Sx:</b> 15-60min; <u>high fever, rigors</u> , abd sx, HoTN/shock <b>Dx:</b> GS/BCx of both pt & bag	- Bacteria >> viruses in donor blood - RBC: <u>Yersinia, PsA</u> (endotox-GNRs) - PLTs: <u>Staph epi</u> (GPCs)	<b>Tx:</b> antibiotics, quarantine all other similar products <b>PPX:</b> routine screening
<b>Urticaria/Hives</b> 1/33-100	<b>Sx:</b> <u>anytime</u> during/after transfusion; localized or diffuse hives & redness <b>Dx:</b> no work-up necessary	- IgE-mediated hypersensitivity to donor plasma proteins	<b>Tx:</b> <u>pause</u> → diphenhydramine → resume if urticaria resolves <b>PPX:</b> <u>washed</u> products, no evidence for pre-medication
<b>Anaphylactic/Anaphylactoid</b> 1/20,000-50,000	<b>Sx:</b> <u>within min</u> ; acute <u>HoTN</u> , angioedema, urticaria, wheezing, abd pain <b>Dx:</b> clinical; consider IgA def.	- IgE-mediated hypersensitivity in recipient lacking IgA or <u>haptoglobin</u> - Bradykinin-mediated flushing/HoTN in pt taking <u>ACEi</u> or neg charged filters (e.g. plasma exchange w/ albumin)	<b>Tx:</b> ABCs, O2, IVF ± pressors, <u>epi</u> IM Q15min, methylpred 125mg, diphenhydr. 25-50mg <b>PPX:</b> <u>washed</u> products
<b>Transfusion-Related Acute Lung Injury (TRALI)</b> 1/12,000 (RBC) 1/38,000 (PLT)	<b>Sx:</b> <u>1-6h</u> ; noncardiogenic pulm edema (ARDS); ± fever <b>Dx:</b> NT-proBNP nml, bilateral CXR infiltrates w/o CHF	- Pre-transfusion stress activates lung endothelial cells & primes PMNs - Donor anti-HLA Abs/bioactive factors attack primed PMNs of recipient	<b>Tx:</b> ABCs, O2, contact blood bank, intubation <b>PPX:</b> male donor plasma (fewer anti-HLA, anti-PMN Abs); defer donors w/ prior assoc. TRALI
<b>Transfusion-Assoc. Circulatory Overload (TACO)</b> 1/100 (RBC)	<b>Sx:</b> <u>1-6h</u> cardiogenic pulm. edema 2/2 vol. overload <b>Dx:</b> elevated NT-proBNP, CXR	- Highest risk in elderly, HF, CKD, chronic anemias	<b>Tx:</b> O2, IV diuretics, ± nitrates, NiPPV <b>PPX:</b> <u>slower</u> rate (1cc/kg/hr)
<b>IVIG Transfusion Reactions</b> 5-15% of infusions	- <u>Inflammatory rxn</u> : fever, chills, flushing, myalgias - <u>Anaphylactoid rxn</u> : urticaria, flushing, chest pain, N/V, HTN	- <u>Inflammatory rxn</u> : Ab/Ag interaction i/s/o concurrent infxn - <u>Anaphylactoid rxn</u> : unknown, potentially kinin-mediated, rare	<b>Tx:</b> IVF, sx mgmt <b>PPX:</b> slow & space out infusions
<b>DELAYED TRANSFUSION REACTIONS (&gt;24H, &lt;28D)</b>			
<b>Delayed Hemolytic (DHTR)</b> 1/2,000	<b>Sx:</b> ~3d; <u>fever</u> , anemia, jaundice, flu-like illness <b>Dx:</b> +DAT, +DBili/LDH, +smear w/ spherocytes	- <u>Anamnestic IgG</u> against previously exposed antigen ( <u>Kidd/Duffy/Kell</u> ) → extravascular hemolysis	<b>Tx:</b> none <b>NB:</b> delayed <u>serologic</u> transfusion reaction is the same except w/o hemolysis
<b>TA-GVHD</b> Rare (typically immunosuppressed)	<b>Sx:</b> 2-30d; <u>fever</u> , rash, mucositis, diarrhea, hepatitis, pancytopenia	- Donor T cells attack non-HLA matched recipient organs in s/o immunosuppression or 1 <sup>st</sup> degree relative donor	<b>PPX:</b> <u>irradiation</u>
<b>Post-Transfusion Purpura (PTP)</b> Rare (women>>>men)	<b>Sx:</b> 3-14d; <u>purpura</u> , mucocutaneous bleed <b>Dx:</b> PLT <10,000, anti-HPA-1A	- HPA-1A (common in donor PLTs) HPA-1A neg women develop Abs to	<b>Tx:</b> 1 <sup>st</sup> line: IVIG   2 <sup>nd</sup> : PLEX <b>PPX:</b> <u>HPA-1A negative</u> PLTs

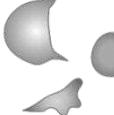
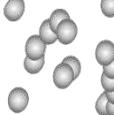
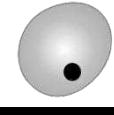
# Hematology

# Peripheral Smear Interpretation

## GENERAL APPROACH ([NEJM 2005;353:498](#); [MGH Slide Rounds](#))

- Special slide: 5<sup>th</sup> floor Bigelow building, first left off elevators, then another left, proceed down the hall past the Core lab, then second door on your left is the heme lab. Inside heme lab, second enclave on the right has the microscope and special slides next to it.
- Low power (20x): scan slide for WBC distribution. Identify the “thick” edge and the “feathered” or thin edge where RBCs are just apart
- Med power (40x): examine feathered edge for rouleaux, parasites, abnormal WBC, platelet aggregation/microsatellites
- Oil Immersion (100x): assess the size, shape, and morphology of major cell lineages:
  - RBC:** examine where RBCs are close but not touching. Assess size (compare to a lymphocyte nucleus for scale), morphology (membrane irregularities, fragmentation), color (pallor, reticulocytes)
  - WBC:** examine at edges and thin end of film. Assess distribution of normal WBC, size, shape, cytoplasm (including granules and vacuolation), and inclusions (such as Dohle bodies). Evaluate neutrophils for nucleus segmenting (average is 3).
  - Platelet:** assess for appropriate number (1 plt per HPF = 20K platelets in CBC), giant platelets, check for granulation

## COMMON QUESTIONS ANSWERABLE BY PERIPHERAL SMEAR ([NEJM 2005;353:498](#); [Harrison's 18th Ed.](#))

RBC Lineage				
Question	Findings	Example	Clinical Significance	Next Steps
Intravascular hemolysis occurring?	Schistocytes (helmet cells, fragments, micro-spherocytes)		>1% schistocytes in HPF + absent alt diagnoses suggests TMA ( <a href="#">Int Lab Hematol 2012;34:107</a> )	- Correlate with CBC, haptoglobin, LDH - Assess for clinical causes of TMA, valve hemolysis. Consider calculating PLASMIC score if concern for TPP
Intra-erythrocytic forms present?	Ring forms in RBCs; less often, tetrad (Babesia)		84% Sn for babesiosis ( <a href="#">Ann Rev Pub Health 1998;19:237</a> ); 65-74% Sn for malaria ( <a href="#">Malar J 2008;7:22</a> )	- Thick and thin smears for confirmation/parasite burden - Babesia, Lyme, Anaplasma testing
Evidence of iron deficiency?	Hypochromic, microcytic cells; “pencil” cells		>5% hypochromic cells gold standard for functional IDA, incl in pts with active inflammation ( <a href="#">Clin Chem 2002;48:1066</a> )	- Iron studies if not yet sent - Supplementation if no contraindication
Are there rouleaux?	Linear aggregations of RBCs throughout smear (may be artifact at edges)		Sn but not Sp for MM ( <a href="#">Arch Int Med 2002;162:1305</a> ). Reflects presence of + charged proteins, incl. Ig & fibrinogen ( <a href="#">Blood 2006;107:4205</a> )	- Correlate for causes of elevated Ig/decreased albumin, incl. infection, inflammation, cirrhosis - Consider quant Ig, SPEP/UPEP. Correlate for CRAB criteria
Functional asplenia?	Howell-Jolly bodies		Sn only for severe splenic hypo-function; inversely prop to functional splenic volume ( <a href="#">AJH 2012;87:484</a> )	- Assess for causes of hyposplenism; consider vaccination & antibiotic adjustment accordingly
WBC Lineage				
Question	Findings	Example	Clinical Significance	Next Steps
Are PMNs hyper/hyposegmented?	Hyper: any 6-lobed or >3% w/ 5 lobes. Hypo: 2 lobes		Hyper: 98% Sn megaloblastic anemia, 77% Sp B12 def ( <a href="#">Acta Haematol 1989;81:186</a> ). Hypo: 92% Sn MDS ( <a href="#">Br J Haematol 1986;63:665</a> )	- Check folate/B12, consider supplementation (hyper); MDS workup (hypo)
Are lymphocytes atypical?	Large lymphocytes, extra cytoplasm, prominent nucleoli		≥10% atypical lymphs +LR for infectious mononucleosis ( <a href="#">JAMA 2016;35:1502</a> ); part of RegiSCAR score for DRESS	- Apply to RegiSCAR; consider EBV/CMV, HIV, Toxoplasma infection
Platelet Lineage				
Question	Findings	Clinical Significance		Next Steps
Are giant platelets present?	Large plt ≥ size of RBC	Large plt suggest marrow response to destruction; incr. plt numbers may suggest myelo-proliferative dx; clumps suggest pseudo-thrombocytopenia		- Consider peripheral causes of thrombocytopenia incl drug-induced, hemolysis, sequestration - Consider MYH9 and other hereditary plt disorders

## OTHER COMMON FINDINGS AND IMPLICATIONS ([Harrison's 18th Ed.](#))

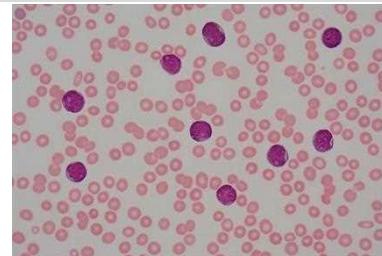
Target Cells	Acanthocytes (Spur Cells)	Echinocytes (Burr Cells)
 Membrane redundancy due to liver disease, thalassemia, HbC disease	 Irregular, dense membrane projections present in severe liver disease	 Small, uniform membrane projections present in uremia and MAHA

## GENERAL ADMISSION APPROACH

- History:** sibling status (for donor search), family history (for inherited syndromes), and if pre/peri menopausal, obtain date of LMP
- Peripheral smear:** anemia, thrombocytopenia, variable WBC, circulating **blasts** ("other cells"), Auer rods (*indicates myeloid origin*)
- Peripheral flow cytometry:** Collect in yellow top. In Epic, order "Flow cytometry labs (blood)" → fill in Clinical hx; select "Leukemia Panel." To **RUSH case (e.g. for new dx)** send page to *Group 549 - Leukemia Pathology Team* (if not on your directory, call MGH operator and ask for access). Sample is sent to BWH and interpreted by MGH Hemopath. FYI **Routine (non-rush)** are sent to Mayo
- Screening:** LFT, lipase, B12, folate, HBV/HCV/HIV serology, CMV IgG, T&S, G6PD, urinalysis, quantitative bHCG (if applicable)
- Monitoring (initially q8h): TLS:** BMP (if ↑WBC, use blood gas K), LDH, uric acid, iCal, Phos, Mg. Cairo-Bishop requires 2 lab (↑uric acid, ↑K, ↑phos, ↓Ca) + 1 clinical (AKI, arrhythmia, seizure); see *Oncologic Emergencies* | **DIC:** PT/INR, PTT, fibrinogen, D-dimer
- BMBx:** aspirate+core, flow, cytogenetics (+/- FISH), molecular diagnostics (e.g. BWH Rapid Heme Panel, MGH Heme Fusion Assay)
- Imaging:** CXR, TTE (prior to induction due to cardiotoxic chemotherapies), **CT head** (if CNS sx)
- Access:** Coordinate with attending: double-lumen **Hickman** vs. triple-lumen **PICC** if induction anticipated, not needed for venetoclax
- LP ± intrathecal chemo:** indications for LP → all ALL, AML w/ CNS or ocular symptoms, APL with systemic relapse
  - CT or MRI before LP: AMS, focal neurologic signs, papilledema, seizure within the last week
- HLA typing:** Initiate allo-HCT work-up if ≤80 yo. In Epic, order "HLA Lab" → select "Specimen Type: Blood," "Patient: Recipient," "Test: Bone Marrow/HSC, Allograft - Initial workup." Coordinate w/ RN, as it is difficult to tell if HLA typing is pending in Epic.
- Use Leukemia Admission Order Set:** Neutropenic precautions | **TLS ppx:** allopurinol 300mg qd (*HLA-B\*5801* ↑prevalence in Southeast Asian, black populations, ↑risk of SJS/TEN, consider testing ([ACR guidelines](#)) | **GI ppx:** omeprazole 20mg qd | **HSV/VZV ppx:** acyclovir 400 mg bid or famciclovir 500mg qd | Hibiclens daily | Peridex mouthwash | **No VTE ppx** (thrombocytopenia)

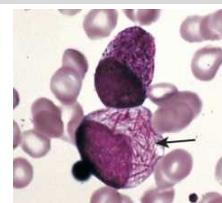
## ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

- Epi:** Bimodal. Peak incidence in children, but another peak in >45yo (68% 5y survival)
- S/Sx:** pancytopenia sx (pallor, petechiae/bruises, infections), bone pain, B symptoms, masses (LAD, HSM; anterior mediastinum in T-ALL), CNS sx (CN palsy, n/v, HA), TLS, DIC
- Smear:** lymphoblasts with scant cytoplasm, large nuclei containing nucleoli
- Subtypes:** B-cell lymphoblastic leukemia/lymphoma (B-ALL/LBL) & T-cell ALL/LBL
  - LBL = lymphoblastic lymphoma → pts w/ extramedullary mass(es) w/ <20% BM blasts
- Risk stratification for AYA and Adults** ([Lancet 2020;395:1146](#); [Blood 2021;138:948](#)):
  - B-ALL/LBL** (subtyped by clinical/molecular features):
    - Favorable:** ↓WBC, young, hyperdiploidy (>50 chromosomes), *ETV6-RUNX1*, *TCF3-PBX1*, *ERG* del, *DUX4*-rearrangement
    - Unfavorable:** ↑WBC, older, CNS/testicular involvement, hypodiploidy (<44 chromosomes), *KMT2A* rearrangement, *BCR-ABL1* (Ph+), *BCR-ABL1*-like (Ph-like, e.g. JAK-STAT pathway abnormalities), *TCF3-HLF*, *MEF2D* rearrangement, *ZNF384* rearrangement, *iAMP21*, *IKZF1* alterations, complex karyotype (≥5 chromosome abnormalities)
  - T-ALL/LBL:** **Favorable:** *NOTCH1* or *FBXW7* mut. **Unfavorable:** ↑WBC, CNS disease, complex karyotype, *RAS/PTEN* mut.
  - Measurable residual disease (MRD):** search for leukemic cells using flow cytometry, NGS or RT-PCR of gene fusions. MRD-positivity correlates w/ risk of relapse. MRD evaluation → dynamic risk assessment, therapy decisions (e.g. allo-HCT)
- Treatment** ([NEJM 2006;354:166](#); [JCO 2011;29:532](#)):
  - General:** no single best regimen, many (e.g. CALGB 10403, R-Hyper-CVAD, BFM). Incorporate (1) induction (2) consolidation (3) intensification [if needed] (4) CNS therapy [if needed] (5) maintenance (6) allo-HCT [for relapse or unfavorable-risk disease]
    - If pt is AYA (age 15-39), pediatric-inspired regimen often used (usually incorporating asparaginase + ↑corticosteroids)
      - Asparaginase toxicities: hypersensitivity (20-30%), pancreatitis (5-8%), coagulopathy (2-5%) ([Leukemia 2010;24:320](#))
    - If *BCR-ABL1*-positive, TKI is used in conjunction w/ chemotherapy (e.g. R-HyperCVAD plus dasatinib)
    - If elderly, low-intensity or chemotherapy-free regimens often used (e.g. dasatinib + blinatumomab, [NEJM 2020;383:1613](#))
  - CNS ppx:** **intrathecal** MTX/cytarabine vs. **systemic** high-dose MTX w/ leucovorin rescue
  - Maintenance:** weekly **MTX/6-MP** + monthly **Vinc/Pred** x2-3y (POMP); TKI maintenance if *BCR-ABL1*-positive
  - Relapsed/refractory B-ALL:** **blinatumomab** (CD19 BiTE), **inotuzumab ozogamicin** (CD22 ADC), **CAR T-cells**, allo-HCT



## ACUTE PROMYELOCYTIC LEUKEMIA (APL)

- Subtype of AML with distinct biology and excellent prognosis ([NEJM 2013;369:111](#))
- S/Sx:** pancytopenia sx (fatigue, anemia, ecchymoses, infection); very high risk for DIC and bleeding
- Smear:** **atypical promyelocytes** (large, "dirty" granular, bilobed nuclei), **+Auer rods** (see image to right)
- Cytogenetics:** t(15;17) → **PML-RARA** (>97%), rarely t(11;17), t(5;17)
- Treatment** ([JCO 2017;35:583](#)):
  - Immediately start ATRA** (all-trans retinoic acid) if **any** suspicion for APL given early mortality secondary to coagulopathy and low toxicity. Dose: 45 mg/m<sup>2</sup> in 2 divided doses daily.
  - Induction:** if low-risk (WBC ≤10K): ATRA + arsenic trioxide. If high-risk (WBC >10K): ATRA + anthracycline or cytarabine. **Consolidation:** ATRA + ATO/anthracycline → **complete molecular remission** (absence of *PML-RARA* on RT-PCR)
- Complications of ATRA:**
  - Differentiation syndrome:** fever, rising WBC, hypoxemia (pulmonary infiltrates, effusions), peripheral edema, weight gain, AKI → high-dose steroids (dexamethasone 10mg q12h), supportive care, temporary cessation of ATRA if severe.
    - Consider primary ppx w/ steroids in highest risk patients (e.g. WBC >10K) ([Blood 2014;123:2777](#)).
  - Hyperleukocytosis:** see *Oncologic Emergencies*
  - Idiopathic intracranial hypertension:** HA, vision loss, papilledema → hold ATRA, pain control ± steroids/acetazolamide



# Oncology

# Acute Leukemia

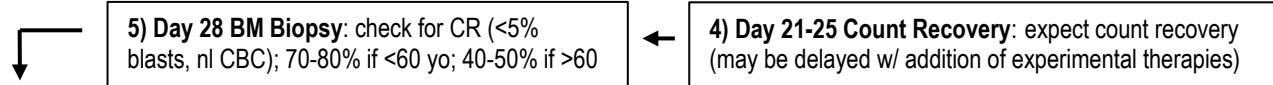
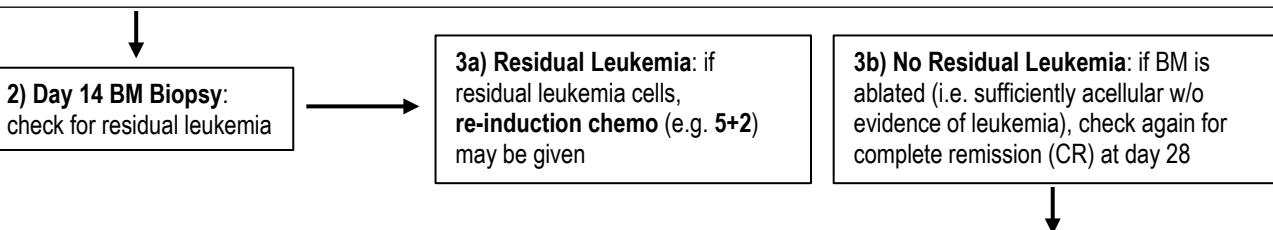
## ACUTE MYELOID LEUKEMIA (AML)

- Pathophysiology:** clonal disorder of hematopoietic progenitor cells w/ infiltration of BM, blood, & other tissues. Significant heterogeneity in underlying molecular abnormalities (see *Risk Category table*)
- Epi:** most common leukemia in adults (80%). Median age 68 at dx. 5-10% w/ familial syndrome.
- S/Sx:** **pancytopenia** (fatigue, petechiae, ecchymoses, infections), myeloid sarcoma, **leukemia cutis** (non-tender red/brown papules/nodules), **neutrophilic dermatosis** (i.e. Sweet syndrome: tender red/violet papules/plaques), gingival hypertrophy (due to leuk. infiltration), joint pain/swelling (leuk. infiltration, gout), **leukostasis** (AML > ALL; typically WBC >50-100K; SOB, HA, blurry vision, stroke), spurious ↑K (check blood gas K); falsely low PaO<sub>2</sub> (check pulse Ox) (see *Onc Emergencies*)
- Dx:** ≥20% blasts in BM or characteristic translocation (e.g. t(8;21)(q22;q22.1)) or myeloid sarcoma (extramedullary tumor of AML cells). Recent schism in classification ([ICC vs. WHO 5<sup>th</sup>](#)).
- Complications** (see *Onc Emergencies*): (1) **DIC** → keep fibrinogen >150, INR <1.5, plt >30-50, add ATRA if any c/f APL [see *APL*] (2) **febrile neutropenia** (3) **TLS** → allopurinol, IVF, rasburicase if uric acid >10 (4) **leukostasis** → hydroxyurea, IVF, leukapheresis, avoid transfusions (can ↑viscosity, worsen)
- Subtypes:** t-AML (therapy-related from prior chemo, RT), s-AML (secondary from preceding heme disorder, e.g. MDS, MPN, PNH)
- Risk stratification:** based on cytogenetics, mutations, performance status ([Karnofsky/ECOG](#)), gero assessment ([Blood 2013;121:4287](#))
- Tx:** intensive (see below, [NEJM 2009;361:1249](#)) vs. non-intensive (HMA+venetoclax, [NEJM 2020;383:617](#)), blurred distinction w/ emergence of ven.
  - Many factors including: cytogenetics, mutational profiling, patient characteristics (performance status)

**1) Day 1 Induction Chemotherapy:** standard regimen for “medically fit” pts: “7+3”, cytarabine continuous infusion days 1-7 + ida/daunorubicin (bolus/short infusion) on days 1-3.

Additional/alternative agents for pts with certain subtypes of AML:

- Midostaurin (tyrosine kinase inhibitor) added to 7+3 in AML with *FLT3* mutations ([NEJM 2017;377:454](#))
- Liposomal cytarabine/daunorubicin (Vyxeos): ↑survival in t-AML & MDS-related AML, but longer neutropenia ([JCO 2018;36:2684](#))
- Gemtuzumab ozogamicin added in CD33-positive core-binding factor AML (*RUNX1* or *CBFB* translocations, ([Blood 2017;130:2373](#)))
- Venetoclax + HMA (azacitidine or decitabine) instead of 7+3 if older and/or adverse risk e.g. *TP53* mut. ([NEJM 2016;375:2023](#))



**6) Consolidation Therapy:** initiated soon after first complete remission. Goal to eradicate residual disease for sustained complete remission. Options include chemo and/or allo-HCT. In general, allo-HCT preferred in poor-risk disease if patient is candidate and has suitable donor. Chemo alone is used in lower-risk disease & if not allo-HCT candidate.

**Risk stratification determines management** (see table above) ([Blood 2017;129:424](#)):

- Favorable risk: **HiDAC (high dose Ara-C)** x3-4 cycles
- Intermediate risk: chemo (HiDAC) vs. allo-HCT
- Poor/adverse risk: **allo-HCT** vs. clinical trial

**7) Surveillance:** CBC q1-3mo for 2y, then q3-6mo up to 5y

**8) Survivorship:** cardiac, psychosocial, vaccines, etc.

**Salvage Therapy:** If residual disease on surveillance (relapse) or persistent disease after induction (primary refractory), initiate salvage therapy with goal of inducing complete remission and bridging to **allo-HCT**. *IDH1* mutated → Ivosidenib ([NEJM 386\(16\):1519](#)) | *IDH2* mutated → Enasidenib ([Blood 2017;130\(6\):722](#)) | *FLT3* mutated → Gilteritinib ([NEJM 2019; 381:1728](#)) |

**Chemotherapy** → 7+3 (esp. if earlier durable response), HiDAC, mitoxantrone + etoposide + AraC (MEC), fludarabine + AraC + G-CSF + idarubicin (FLAG-Ida), others | **HMA ± venetoclax** | consider clinical trial enrollment

# Oncology

# Lymphadenopathy & Lymphoma

## EVALUATION OF LYMPHADENOPATHY (AFP 2016:94:896)

- Generalized LAD: HIV, EBV/CMV/toxo, mycobacteria, SLE, meds (e.g. phenytoin), sarcoid, lymphoma, Castleman's, Kikuchi dz, IgG4
- Localized LAD: cervical (EBV/CMV/toxo, mycobacteria, lymphoma), supraclav. (malignancy), axillary (infection, breast), inguinal (STI)
- Hx: exposures, travel, meds, B Sx (fever, drenching night sweats, >10% unintentional wt loss in 6mo), other s/sx of infxn/malignancy
- Exam: localization (think about area of nodal drainage), size (abnormal >1cm), consistency, fixation, tenderness (inflammation)
- Labs: CBC/diff, LDH, HIV (PCR if acute), HBV, HCV. Depending on pre-test probability: T-spot, RPR, ANA, EBV/CMV/toxo serologies
- Imaging: CT C/A/P w/ contrast, PET/CT can define node size, distribution, monitoring of response/progression (w/ Deauville scoring)
- Biopsy: consider if large (>2cm), persistent 4-6w, or increased size, w/ immunophenotyping & cytogenetics. Empiric steroids may decrease yield of biopsy. Excisional (cells & nodal architecture) > core needle (tissue for molecular studies) > FNA (high false neg.)

## LYMPHOMA GENERAL PRINCIPLES

Lymphoma Staging: if Hodgkin lymphoma (HL), add "B" if B Sx. PET Deauville score (1-5): 1 = no FDG uptake; 5 = markedly FDG-avid

Stage I: 1 LN region, or single extralymphatic organ      Stage III: LN groups above and below diaphragm

Stage II: ≥2 LN groups on same side of diaphragm      Stage IV: disseminated ≥1 extralymphatic organs

LN region: cervical (R/L), axillary (R/L), subpectoral (R/L), mediastinal, hilar (R/L), celiac, paraaortic, mesenteric, iliac (R/L), inguinal (R/L)

Workup: PET/CT, HBV/HCV/HIV serology, G6PD, quantitative bHCG (if applicable), PFTs (+DLCO), TTE (prior to anticipated chemo)

Fertility Preservation: semen, oocyte or ovarian tissue cryopreservation. Menstrual suppression: GnRH agonists if ↓ platelet expected

## HODGKIN LYMPHOMA (NCCN; 2023)

Bimodal age distribution ([Lancet 2012;380:836](#)). Reed-Sternberg cells (**CD15+** **CD30+** CD20- CD45- PAX5+ PD-L1+) in inflammatory milieu

**S/Sx**: neck LAD, mediastinal mass, pruritis, constitutional sx, ↑Eos. Rare: burning pain w/ alcohol, nephrotic syndrome (i.e. minimal change disease), liver dysfunction, skin lesions

**WHO classification**: nodular sclerosis (70%), mixed cellularity (25%), lymphocyte rich (5%), lymphocyte depleted (<1%). Nodular lymphocyte-predominant HL is distinct entity.

**Treatment**: note long-term risk of cardio- and pulm-toxicity, 2° malignancy (t-AML)

- Stage I-II**: ABVD ± XRT. **Stage III-IV**: ABVD vs. BV-AVD ([NEJM 2018;378:331](#)) vs. BEACOPP ± XRT. Interim PET/CT helpful for escalating vs. de-escalating tx
- Relapsed/refractory**: salvage chemo + auto-HCT; brentuximab vedotin (BV); PD1 inhibition (pembrolizumab or nivolumab), bendamustine, allo-HCT

HL International Prognostic Score (IPS)		
1 point/factor ( <a href="#">JCO 2012;30:3383</a> )		
Age >45	Points	5y PFS
Male	0	88%
Stage IV	1	84%
Albumin <4	2	80%
Hb <10.5	3	74%
WBC ≥15,000	4	67%
Lymphocytes <600 <8%	≥5	62%

## NON-HODGKIN LYMPHOMA

Most common blood cancer, a/w immunosupp., autoimmunity, infection (EBV, H. pylori, HCV, HIV, HHV8, HTLV1) ([Lancet 2012;380:848](#))

**Indolent** (e.g. FL): incurable, but better prognosis vs. **Aggressive** (e.g. DLBCL): higher chance of cure, but worse prognosis overall

Diagnosis	Prevalence	Clinical Features	Treatment
<b>Diffuse Large B-cell (DLBCL)</b>	~35%	Aggressive, rapid growth, nodal/extranodal <i>BCL2</i> , <i>BCL6</i> , or <i>MYC</i> translocations common Prognosis: <a href="#">IPI</a> , cell-of-origin (GCB > ABC) <b>Double-hit lymphoma (DHL)</b> : more aggressive subtype w/ <i>MYC</i> + either <i>BCL2</i> or <i>BCL6</i> translocations. Triple-hit = ultra-HR.	- Stage I-II: R-CHOP + RT; Stage III-IV: R-CHOP; if DHL, consider more aggressive Tx (i.e. R-EPOCH); if old/frail, R-mini-CHOP - CNS ppx <b>controversial</b> ; some give high <a href="#">CNS-IPI</a> IT MTX - Relapsed/refractory: CD19 CAR T-cells preferred ( <a href="#">Lancet 2022;399:2294</a> , <a href="#">NEJM 2022;386:640</a> ) vs. salvage chemo + auto-HCT - Trials adding drugs to R-CHOP failed in most phase III RCT so far, except polatuzumab ( <a href="#">NEJM 2022;386:351</a> )
<b>Follicular (FL)</b>	~25%	Generally indolent; occasionally aggressive t(14:18) <b>BCL2+</b> . High grade = more centroblasts. <a href="#">FLIPI</a> score prognostic	- Stage I/contiguous II: RT preferred; Stage II-IV: observation, anti-CD20 ± bendamustine (BR), lenalidomide (LR), CHOP, or CVP - Monitor for transformation (rapid LN growth, ↑LDH, B symptoms)
<b>Small or chronic lymphocytic (SLL/CLL)</b>	~5%	Often indolent, painless LAD, IgM M-protein No risk of leukostasis unless WBC >400k Prognosis: <a href="#">Ra/Binet</a> ,IGHV unmutated (HR), ZAP70+ (HR), CD38+ (HR), FISH (del17p = HR), genetics (TP53 mut. = HR)	- Only treat when "active" ( <a href="#">Blood 2018;131:2745</a> ), i.e. cytopenia, bulky disease, progressive lymphocytosis w/ increase >50% over 2mo, autoimmune dz (AIHA, ITP), significant constitutional symptoms - Evolving combinations with BTKi (zanubrutinib, acalabrutinib, ibrutinib), anti-CD20 (obinutuzumab, rituximab), and venetoclax
<b>Mantle Cell (MCL)</b>	~5%	Wide clinical spectrum, can involve spleen, GI, BM. Leukemic (SOX11-) often indolent t(11;14), cyclin D1+. <a href="#">MIPI</a> score prognostic	- Stage I/non-bulk II: BR, VR-CAP, R-CHOP, or LR + R maintenance - Stage II-IV: RDHA + platinum, R-CHOP, NORDIC or HyperCVAD + auto-HCT w/ R maint. Relapsed/refractory: BTKi, CD19 CAR T-cells
<b>Marginal Zone (MZL)</b>	~10%	<b>Extranodal MZL (MALT)</b> : a/w sites with chronic inflammation, e.g. stomach w/ <b>H. pylori+</b> t(11;18), salivary glands (Sjogren's), thyroid (Hashimoto's), small intestine, etc. <b>Splenic MZL</b> : often HCV+, cryoglobulinemia <b>Nodal MZL</b> : generally indolent, similar to FL	- Gastric MALT: if H. Pylori+, quad Tx can cure; if H. Pylori-, RT - Nongastric extranodal localized: RT, observation - Advanced nodal: observe, rituximab + chlorambucil/bendamustine - Splenic MZL: if HCV+, HCV Tx can lead to regression. If HCV-, Rituximab (preferred) or splenectomy (definitive for diagnosis to differentiate from splenic diffuse red pulp small B-cell lymphoma)
<b>Burkitt (BL)</b>	~1%	Aggressive, extranodal sites (jaw if African). ↑spont. TLS. t(8;14), c <i>MYC+</i> , EBV/HIV	- More aggressive than DLBCL treatment: R-EPOCH, R-CODOX-M/IVAC, R-HyperCVAD. Relapsed: chemo + auto- or allo-HCT
<b>T-cell lymphoma</b>	~15%	Diverse varieties. Peripheral T-cell (PTCL) NOS most common. Cutaneous T-cell (CTCL) i.e. Mycosis fungoides, Sezary syndrome (disseminated). Anaplastic large cell (ALCL) a/w ALK, breast implants. Adult T-cell leukemia/lymphoma (ATL) a/w HTLV-1, geography (e.g. Caribbean). Enteropathy-associated T-cell (EATL) a/w celiac disease	

**ABVD** = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine

**BEACOPP** = Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone

**CHOP** = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone

**COODOX-M/IVAC** = Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide, Cytarabine

**CVP** = Cyclophosphamide, Vincristine, Prednisolone

**DHA + platinum** = Rituximab, Dex, Cytarabine and Carbo-, -Cis- or Oxali-platin

**EPOCH** = Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin

**HyperCVAD** = Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, alternated w/ methotrexate & cytarabine, followed by maintenance POMP

**VR-CAP** = Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone

# Oncology

# Plasma Cell Disorders

## EVALUATION OF PLASMA CELL DISORDERS ([Leukemia 2009;23:215](#))

Evaluation	Utility	When to Send
Ig Levels	Quantify immunoglobulin (Ig) levels in blood (IgG, IgM, IgA, IgD, IgE). Will not discern monoclonal vs. polyclonal	If suspecting a 1° (e.g. B cell deficiency) or 2° humoral immunodeficiency <i>Consider retesting w/ IVIg if IgG &lt; 400 mg/dL</i>
SPEP	Detect/quantify M-protein (monoclonal protein = M-spike = paraprotein), Ig from an abnormally expanded B/plasma cell	If suspecting a monoclonal B-cell or plasma cell disorder, <b>send SPEP &amp; FLC</b> . FLC ↑ sensitivity. "SPEP panel" order contains quantitative IgG/A/M, total protein, SPEP & reflex IF. <b>Serum FLC is separate order</b> . At MGH lab, cannot force SIFE if no M-spike on SPEP (FLC assay should be sufficient in most of these cases)
Serum IF	Identify the type of M-protein (intact Ig [G, M, A, D, E], light chain only [LC: κ or λ], or heavy chain only)*	
Serum FLC Assay	Identify light chain abundance (outside normal κ/λ ratio 0.26-1.65) Normal ratio w/ ↓LC = immunosuppression Normal ratio w/ ↑LC = infection/inflammation or ↓renal clearance**	
UPEP	Detect/quantify Bence Jones Protein (BJP, i.e. urine monoclonal protein, which is typically κ or λ LC). UA/dipstick will miss BJP	Not needed unless high suspicion (+M-prot/abnl FLC). If UPEP+, can use 24h UProt to quantify
Urine IF	Identify the type of BJP (κ or λ)	If UPEP+ for BJP (reflex)

\*Some therapeutic antibodies may show up in above assays as false positives (e.g. daratumumab)

\*\*Kidney dysfunction decreases clearance of LC and can skew ratio. Icelandic iStopMM study has helped to re-define normal FLC ratio w/ CKD: eGFR ≥60, κ/λ 0.26-1.65 | eGFR 45-59, κ/λ 0.46-2.62 | eGFR 30-44, κ/λ 0.48-3.38 | eGFR <30, κ/λ 0.54-3.30 ([BCJ 2022;12:133](#))

## CLASSIFYING PLASMA CELL DISORDERS ([Lancet Oncol 2014;15:e358](#))

CRAB criteria: **Ca<sup>++</sup> (>11mg/dL)**, **Renal dz (Cr >2)**, **Anemia (Hgb <10)**, **Bone lesions (≥1 focal lytic lesion on whole body-CT, MRI or PET)**  
All those with **M-protein ≥1.5g/dL**, **Non-IgG M-protein** of any size, **abnormal FLC assay**, or **CRAB** should have **BM biopsy** to work-up

	MGUS	Smoldering MM	Multiple Myeloma (MM)	Waldenström (WM)	AL Amyloid
<b>BM Involvement (%)</b>	<10	10-60	≥10 (or plasmacytoma)	≥10	<10
<b>Serum M-protein (g/dL)</b>	<3	≥3	Present	Present (IgM)	<3
<b>Clinical Signs</b>	Absent	Absent	CRAB, unless SLiM*	Hyperviscosity, etc. (see below)	Present

- Approach to abnormal asymptomatic SPEP ([IMWG](#)):
  - If M prot > 3g/dL, classified as **SMM**: If 1-2/3, **Intermediate-Risk MGUS**; If 0/3, **Low-Risk MGUS**
    - Risk Factors: (1) ≥1.5 g/dL (2) non-IgG (3) +/- abnl. FLC ratio
  - If **SMM**: Refer to Oncology
  - If **Intermediate-Risk MGUS**: Refer to Onc. If SPEP/SFLC stable in 6mo, repeat annually, consider stopping if ↓functional status.
  - If **Low-Risk MGUS**: Repeat SPEP/SFLC in 6mo, if stable Q2-3Y or if CRAB crit develop, consider stopping if ↓functional status.
- Smoldering MM (SMM)**: prog. to MM 10%/yr for 5y, then ↓. "20-2-20" risk strat ([BCJ 2018;8:59](#)). Tx: controversial ([JCO 2020;38:112](#))
- MM**: ≥10% BM clonal PC & CRAB symptoms. \*If ≥60% BM PC or involved/uninvolved FLC ratio ≥100 or >1 bone lesion on MRI (w/ <10% BM PC) → MM dx w/o CRAB ("SLiM"). Rarer MM types: ~20% LC-only; ~5-10% oligo-secretory (low M-protein); ~3% non-sec.
- Solitary Plasmacytoma**: single biopsy-proven tumor w/ clonal PC, imaging w/o other lytic lesions, no CRAB. Tx: RT, monitor for MM
- WM**: lymphoplasmacytic lymphoma (LPL) in BM/lymph node + IgM M-protein. **S/Sx**: LAD/HSM, anemia, hyperviscosity (HA, vertigo, dizzy, Δ vision, AMS), bleeding (acq VWD), cryoglobulins, cold agglutinins. Measure viscosity. Tx: anti-CD20, BTKi, plasmapheresis
- AL amyloid**: **S/Sx**: cardiomyopathy, purpura, nephrotic sx, polyneuropathy, orthostasis, HSM, macroglossia. Congo-red stain (apple-green birefringence) on affected organ or fat-pad. Send for mass spec. Tx: Daratumumab-CyBorD, early auto-HCT if candidate
- Monoclonal Gammopathy of Renal Significance (MGRS)**: collection of disorders leading to kidney disease, including light chain & heavy chain deposition disease, proliferative GN w/ monoclonal immunoglobulin deposits, C3 glomerulopathy ([NEJM 2021;384:1931](#))
- POEMS syndrome**: (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes), ↑VEGF, sclerotic bone lesions, & Castleman's disease. ~λ only. Polyneuropathy & MGUS required for dx. Endocrinopathy: hypo-gonad, -thyroid, -adrenal, etc. Tx: ~MM
- Other**: Cryoglobulinemia, CANOMAD, DADS-M, Scleromyxedema, Schnitzler's, Clarkson's (cap. leak), TEMPI ([ASH 2020;2020:380](#))

## MULTIPLE MYELOMA WORKUP AND MANAGEMENT ([Nat Rev Dis Primers 2017;3:17046](#); [NCCN 2021 MM Guidelines](#))

- Lab findings/workup**: ↓AG ratio, ↑globulin, ↑ESR, peripheral smear (rouleaux), ↑LDH, ↑β2M, SPEP/IFE/FLC, whole body low-dose CT ± PET or MRI. BMBx (IHC, flow, cytogenetics/FISH, rapid heme panel). 10% w/ concurrent amyloid. 10-30% w/ extramedullary dz
- Risk stratification**: by age, performance status, comorbidities, [R-ISS staging](#) (incorporates cytogenetics/FISH, LDH, β2M, albumin). High-risk features: t(4;14), t(14;16), t(14;20), amp1q, **del17p**, extramedullary dz, circulating PC. **≥2 HR FISH** = "double-hit" (ultra-HR)
- Treatment agents**: most common induction regimens combine a proteasome inhibitor, immunomodulator, & steroids/chemo:
  - Proteasome inhibitors**: bortezomib (Velcade – V, Bor), carfilzomib (K), ixazomib (Ix)
  - Immunomodulatory agents (IMiDs)**: lenalidomide (Revlimid – R), pomalidomide (Pom), thalidomide (T), ibandronate
  - Steroids/chemo**: dexamethasone (low dose = d), prednisone (P), melphalan (M), cyclophosphamide (Cy), doxorubicin (dox)
  - Monoclonal Abs**: anti-CD38 daratumumab (D, Dara; [NEJM 2019;380:2104](#)) & isatuximab (Isa); anti-SLAMF7 elotuzumab (Elo)
- Induction & consolidation**: NOT curative. Standard risk median OS approaching 10y. High risk median OS ~3y
  - Induction: triple w/ VRd most common; CyBorD if renal failure at diagnosis; DaraRd if frail; quad (DaraVRd) ↑use, esp. if HR
  - If candidate for autoHCT, usually performed early, but can delay until relapse w/o detriment in OS ([NEJM 2017;376:1311](#))
  - Maintenance (e.g. **R** +/- **V**) following auto-HCT, or after induction if no HCT. A/w ↑OS ([JCO 2017;35:3279](#)), but ↑2° cancers
- Response criteria**: ↑depth a/w better outcomes: partial resp. (↓M-protein 50-90%); very good partial resp. (↓M-protein >90%); complete response (no M-protein, <5% BM PC); measurable residual disease-negative (<1 PC in 10<sup>6</sup> cells on flow/VDJ sequencing)
- Relapsed/refractory MM**: mix-match combos, **CAR-T** (anti-BCMA, anti-GPRC5D), BiTE (teclistamab), venetoclax if t(11;14), chemo
- Other Tx**: aimed at reducing skeletal lesions/fractures (bisphosphonates, denosumab, XRT), hyperCa<sup>++</sup>, renal damage, hyperviscosity, infections (PCP, HSV, fungal, VZV; depending on Tx), VTE (aspirin vs. AC for IMiD-induced thrombotic risk), anemia (EPO-analog)

# Oncology

# MDS & MPN

**MYELODYSPLASTIC SYNDROME (MDS):** clonal mutation → ineffective/dysmorphic hematopoiesis → risk of transf. to AML

- Presentation:** median age 65-75, s/sx of anemia (fatigue, malaise), less commonly infections/bleeding, most are asymptomatic with unexplained cytopenias (~90% anemia), can be associated with AI disease (rheumatic heart, RA, pernicious anemia, psoriasis, PMR)
- RF:** male, exposures (benzene, tobacco), chemotherapy, XRT, genetic syndromes (Down, Li-Fraumeni, Diamond-Blackfan), PNH
- Diagnosis:** cytopenias, dysplasia >10% of nucleated cells in at least one lineage, <20% blasts, cytogenetics
  - Initial eval: CBC/diff, retic, EPO, Fe studies, folate, B12, copper (deficiency can mimic MDS), TSH, LDH, HIV, BMBx w/ iron stain, cytogenetics, molecular testing (e.g. BWH Rapid Heme Panel) for somatic mutations, flow cytometry to r/o PNH and LGL
  - Classified by [WHO](#) or [ICC](#) (recent schism). DDx: cytopenias, myelofibrosis, AA, PNH, CHIP, AML, MPN, MDS/MPN syndromes
- Prognosis:** [IPSS-M](#) > [IPSS-R](#), used to predict progression to AML and survival, which ranges from < 1yr in "very high" risk to ~10 yrs in "very low" risk. TP53 multi-hit (not monoallelic), *FLT3*, *KMT2A* partial tandem duplication, and other mutations confer risk.
- Treatment:** based on IPSS-R, performance status & age
  - Low/intermediate risk:** Supportive care. Based on Epo levels (major decision point). Epo, ATG +/- CyA, G-CSF, hypomethylating agents (azacitidine/decitabine), alloHCT considered in select pts. Luspatercept for ringed sideroblastic ([NEJM 2020;382:140](#)).
  - Intermediate/high risk:** If alloHCT candidate, transplant +/- induction or hypomethylating prior (alloHCT improves outcomes even up to age 75, per [JCO 2021;39:3328](#)). If not alloHCT, azacitidine or decitabine. Ongoing trials with venetoclax plus azacitidine.
  - Special variants:** del(5q) = lenalidomide; hypoplastic MDS with PNH+ cells, HLA-DR15 or age <60 = ATG + cyclosporine

**OTHER MYELOID DISORDERS:** involve smaller clones w/ leuk-assoc. genes (*DNMT3A*, *TET2*, *ASXL1*, *JAK2*, *PPM1D*, *TP53*)

- Clonal Hematopoiesis of Undetermined Potential (CHIP):** risk factor for MDS/AML and cardiovascular disease, variant allele frequency (VAF) ≥2% of leukemia-associated gene, normal counts, blasts on BM Bx <5%, rate of progression to AML 0.5-1%/yr
- Clonal Cytopenia of Unknown Significance (CCUS):** unexplained cytopenia + CHIP
- Idiopathic Cytopenia of Unknown Significance (ICUS):** unexplained cytopenia, but not CHIP (either VAF <2% or no mutation)

**MYELOPROLIFERATIVE NEOPLASM (MPN):** clonal expansion, 1+ myeloid lineages, often involve activation of JAK-STAT

Chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF). Sequelae vary; PV/ET can progress to 2° MF (~10-20%) or straight to AML (<5%). MF progression to AML is more common (10-20%). **Tx goals:** improve quality of life (e.g. constitutional symptoms, splenomegaly w/ JAKi), prevent thrombosis (aspirin), prevent progression to AML (alloHCT)

	PV (↑Hgb ↑WBC ↑Plt)	ET (↑Plt)	Primary MF (↓Hgb ↓WBC ↓Plt)	CML (↓Hgb ↑WBC ↑Plt)
<b>Sx</b>	VTE (Budd-Chiari, PVT, etc.), CVA, ACS, <u>aquagenic pruritus</u> , erythromelalgia, ruddy complexion, GI (epigastric pain, ulcers), HA, dizziness, Δ vision, gout flare	Thrombosis, <u>bleeding</u> (acquired vWF, consider if plt >1 mil), vasomotor sx (HA, syncope, Δ vision, CP, paresthesia erythromelalgia, livido)	Fatigue, night sweats, weight loss, bone pain, <u>massive hepatosplenomegaly</u> , abdominal pain, early satiety, thrombotic/hemorrhagic events, anemia,	Fatigue, weight loss, night sweats, bleeding, <u>splenomegaly</u> , abdominal pain (LUQ), L shoulder pain (Kehr's sign), gout flare. 20-50% are asymptomatic at diagnosis.
<b>Dx</b>	<b>Major WHO criteria:</b> <ul style="list-style-type: none"> <li>- Hgb &gt;16.5 (♂), Hgb &gt;16 (♀)</li> <li>- BMBx showing trilineage proliferation</li> <li>- <u>Mutations:</u> <i>JAK2</i> V617F (95-97%) or <i>JAK2</i> exon 12 mut.</li> </ul> <b>Minor WHO criteria:</b> <ul style="list-style-type: none"> <li>- Low Epo (below reference)</li> </ul> <u>Note:</u> sig. overlap between PV, ET, MF on BMBx	<b>Major WHO criteria:</b> <ul style="list-style-type: none"> <li>- Plt &gt;450k</li> <li>- BMBx w/ enlarged megakaryocytes with hyperlobulated nuclei</li> </ul> <u>Mutations:</u> <i>JAK2</i> 60-65%, <i>CALR</i> 20-25%, <i>MPL</i> 5%	<b>Major WHO criteria:</b> <ul style="list-style-type: none"> <li>- BM Bx w/ "dry" tap showing reticulin or collagen fibrosis</li> <li>- <u>Mutations:</u> <i>JAK2</i> 50%, <i>CALR</i> 40%, <i>MPL</i> 5%</li> </ul> <b>Minor WHO criteria:</b> <ul style="list-style-type: none"> <li>- Leukoerythroblastic smear (left-shift, nucleated and teardrop RBCs), ↑LDH, anemia, splenomegaly</li> </ul>	<b>Mutation:</b> <i>BCR-ABL1</i> + <ul style="list-style-type: none"> <li>(by FISH, RT-PCR), CBC with ↑ granulocytes of all maturities (myelo, metamyelo, bands), basophilia, eos. Can be in <b>chronic</b>, <b>accelerated</b> (10-20% blasts), or <b>blast phase</b> (&gt;20% blasts). Blast phase can be consistent with AML (80%) or ALL (20%)</li> </ul>
<b>Tx</b>	<b>All:</b> phlebotomy (goal HCT < 45), ASA81 (if no bleeding), allopurinol, antihistamine <b>If &gt;60, ↑risk thrombosis:</b> Hydroxyurea (HU) > IFN-α, <b>2<sup>nd</sup> line:</b> ruxolitinib (JAK2-inhib, <a href="#">NEJM 2015;372:426</a> )	<b>All:</b> ASA81 (unless vWF syndrome). <b>If age&gt;60 or ↑risk thrombosis:</b> HU > interferon-α > anagrelide (PDE inhib, blocks plt production) ( <a href="#">NEJM 2005;353:33</a> )	AlloHCT (only cure), transfusion, hydroxyurea, ruxolitinib (JAK2 inhibitor, primary benefit is symptom reduction, splenomegaly) ( <a href="#">NEJM 2012;366:787</a> ). Fedratinib is another JAKi.	<b>Chronic phase:</b> TKI: imatinib, dasatinib, nilotinib. Ponatinib or asciminib if T315I. Consider alloHCT if TKI intolerant, resistance. <b>Blast phase:</b> Tx as AML/ALL w/ induction + TKI, alloHCT
<b>DDx</b>	↑Epo: hypoxia-induced (heart/lung dz, carboxy-Hb, smoking) vs. Epo-producing tumor (rare). ↓Epo: activating epo receptor mutation (rare)	Infection, inflammation, iron deficiency, splenectomy, bleeding, other MPN (PMF), MDS (e.g. 5q-), solid cancers	AML, CML, ET, PV, MDS/MPN overlap syndromes, MDS, hairy cell leukemia, other malignancies (e.g. w/ bone metastases)	Leukemoid rxn (↑LAP), drugs (steroids, GCSF, ATRA), infection (C. diff, mono), bleeding, splenectomy, DKA, organ necrosis, other MPN

**OTHER MYELOID DISORDERS:** [WHO 2016 classification](#). Variety of conditions ranging from aggressive to indolent

- MDS/MPN syndromes:** CMML (see below); MDS/MPN with ring sideroblasts & thrombocytosis; Atypical CML (*BCR-ABL1* negative); Juvenile myelomonocytic leukemia (JMML); MDS/MPN, unclassifiable
- Chronic myelomonocytic leukemia (CMML):** characterized by peripheral blood moncytosis (≥1x10<sup>9</sup>/L or ≥10%) and MDS/MPN features. Proliferative (WBC ≥13k) vs. dysplastic (<13k). Prognosis: [Mayo Molecular](#). ↑Prog. to AML. **Tx:** supportive, HU, alloHCT
- Blastic plasmacytoid dendritic cell neoplasm (BPDCN):** skin lesions, w/ or w/o marrow involvement and leukemic dissemination
- Mastocytosis:** includes cutaneous and systemic mastocytosis. Associated w/ *KIT* D816V. +Darier's sign. Recurrent anaphylaxis
- Other:** Myeloid/lymphoid neo. a/w eosinophilia & rearrang. of *PDGFRA/B* or *FGFR1* or w/ *PCM1-JAK2*; Chronic neutrophilic leukemia

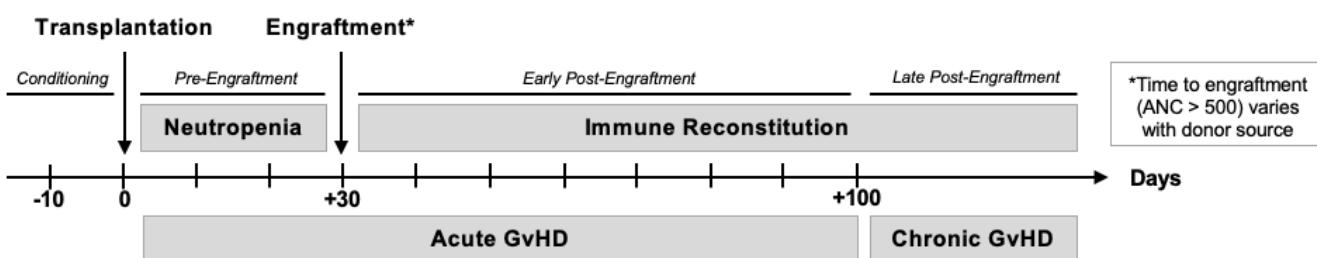
# Oncology

# Hematopoietic Stem Cell Transplantation

## TYPES OF TRANSPLANT

	Allogeneic Transplant	Autologous Transplant
Definition	Transplant of <b>non-self (donor)</b> hematopoietic cells	Transplant of <b>self (patient)</b> hematopoietic cells
Goals	<b>Reconstitute hematopoiesis</b> after conditioning chemo and <b>graft-versus-tumor (GVT) effect</b> to kill malignant cells. Also used for bone marrow failure syndromes. Always curative intent.	<b>Reconstitute hematopoiesis after high-dose chemotherapy.</b> Intent generally curative except in plasma cell disorders, where goal is to prolong remission
Indications	↑ risk <b>AML</b> (40-60% 5YS), <b>ALL</b> (40-50% 5YS), <b>MDS</b> (45% 5YS), ↑ risk <b>myelofibrosis</b> , TKI-resistant <b>CML</b> , <b>relapsed lymphoma</b> , <b>aplastic anemia</b> , thalassemia, sickle cell disease, primary immunodeficiency (SCID), inborn errors of metabolism	<b>1<sup>st</sup> relapsed lymphomas</b> (40-50% 5YS), <b>MM</b> (35% 5YS); <b>relapsed Waldenström, AL amyloidosis</b> , select solid tumors (germ cell, neuroblastoma, Ewing sarcoma), autoimmune disease (MS, SS, Crohns, SLE)
Source of cells	Mostly <b>peripheral blood</b> , but some centers use more <b>bone marrow</b> given lower risk of chronic GVH. Umbilical cord blood is occasionally used	Usually <b>peripheral blood</b> given less invasive harvest, more rapid engraftment
Time to engraftment	14-28 days (time for CB > BM > PBSC)	10-14 days
Graft-versus-host disease (GVHD)	<b>Yes</b> , skin, liver, GI most commonly affected <b>Acute</b> (within 100 days) <b>Chronic</b> (>100d, morbidity/mortality mo/ys later)	<b>No</b> , but rare “GVHD-like” syndrome occurs in ~0.5% of auto-transplants ( <a href="#">BMT 2020;55:1879</a> )
Graft-versus-tumor (GVT)	<b>Yes</b> , major therapeutic goal is for donor T cells to engraft and attack host tumor cells	<b>Likely no</b> , but mechanism via CD8+ T cells under investigation ( <a href="#">JCI 2019;129:48</a> )
Pharmacologic Immunosuppression	<b>Yes</b> (sometimes for 1-2y)	<b>No</b>

## ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT ([NEJM 2006;354:1813](#))



- **Donor types:** matched to pt by HLA typing to **minimize GVHD**; matching at alleles **A, B, C, DR, DQ**
  - **Matched-related donor (MRD):** compatible siblings, matched at 10/10 HLA alleles
  - **Matched-unrelated donor (MUD):** NMDP database, matched at 8-9/10 HLA alleles
  - **Haploidentical:** any parent/sib/child (~universal), match at 5/10 HLA alleles, ↑ GVT via NK cells ([Front Immun 2020;11:191](#))

Cell Source	Collection	Engraft	GVHD Risk	Notes
Bone marrow (BM)	Aspirated from iliac crest	18-21d	(Reference)	Less often used despite lower cGVHD risk, due to slower/less effective engraftment
Peripheral blood (PBSC)	Mobilization and peripheral apheresis	12-15d	Higher risk	Generally preferred source due to faster engraftment ( <a href="#">Cochrane Rev 2014</a> )
Cord blood (CB) ( <a href="#">Blood 2013;122:491</a> )	Immature cells from umbilical cord at delivery	28d (variable)	Lower risk	↑ txp-mortality compared to MUD (similar DFS/OS); allows for more HLA disparity

- **Conditioning regimens** ([Blood 2014;124:344](#)): determined by underlying condition, disease status, and performance status
  - **Myeloablative conditioning:** complete disease eradication & ablation of host BM/immune cells
    - Used for young healthy patients, in remission or with measurable residual disease (MRD) ([JCO 2020;38:1273](#))  
↑ toxicity, ↑ immunosuppr, ↑ txp-mortality, ↓ relapse
  - **Reduced intensity conditioning (RIC):** tumor debulking & allows for engraftment
    - Permits transplant in elderly w/ co-morbidities; ↓ toxicity, ↓ txp-mortality, ↑ relapse ([JCO 2017;35:1154](#))
  - **Conditioning agents:** chemo (ex. alkylating agents – fludarabine, busulfan, cyclophos., melphalan) ± total body irradiation

## TERMINOLOGY

- One-liners include: underlying diagnosis; **autologous vs allogeneic** transplant; **day since transplant** (transplant = d0, day before = d-1, day after = d+1); **conditioning regimen** (myeloablative vs RIC/non-myeloablative); **donor type** (MRD, MUD, haploidentical), **cell source** (BM, PB, CB), **GVHD prophylaxis** regimen (tac vs. cyclosporine, methotrexate, etc.)
- Example one-liner: 35M w/ AML (FLT3-mutated) who is now day +4 from his **myeloablative** (Bu/Cy) matched related donor (**MRD**) peripheral blood hematopoietic-cell transplant (**PBHCT**) with tacrolimus/methotrexate GVHD prophylaxis (day 0 = 1/1/21).

# Oncology

# Hematopoietic Cell Transplantation

INFECTIOUS COMPLICATIONS: 2/2 chemo-related pancytopenia & immunosuppression (ASBMT/IDSA: [BBMT 2009;15:1143](#))

Immune Defect	Day 0-30 Pre-Engraftment	Day 30-100 Early Post-Engraftment	Day 100+ Late Post-Engraftment
	Neutropenic, mucositis, lines, acute GVHD	Poor cellular immunity, acute GVHD	Poor cellular and humoral immunity, chronic GVHD
Bacterial	GPCs & GNRs (F&N) Neutropenic enterocolitis ( <b>typhlitis</b> )	GPCs & GNRs	<b>Encapsulated bacteria (SHiN)</b> Nocardia
Viral	Resp/enteral (adeno, flu, RSV, paraflu), HSV	Resp/enteral (adeno, flu, RSV, paraflu), EBV (risk of PTLD), CMV, HHV6 (screen for in CB tx)	Resp/enteral (adeno, flu, RSV, paraflu), EBV (PTLD), VZV, BK (hemorrhagic cystitis), JC (PML)
Fungal	Aspergillus, candida	Aspergillus, candida, <b>PJP</b>	<b>Aspergillus, PJP</b>
Parasitic	-	<b>Toxo</b>	Toxo (can mimic PJP PNA)

- **Neutropenic enterocolitis (typhlitis):** polymicrobial infxn leading to necrotizing enterocolitis, most often involving cecum
  - S/Sx: fever, ANC <500, abdominal pain (often RLQ), n/v, watery/bloody diarrhea
  - Micro: polymicrobial (GPC/GNR/anaerobes/fungal), clostridium septicum a/w fulminant course & high mortality rate
  - Dx: CT (I+/O+) w/ bowel wall thickening, mesenteric stranding, bowel dilatation, mucosal enhancement, pneumatoisis
  - Tx: pip/tazo vs -penem vs cefepime/MNZ + **surgery c/s** + add fungal coverage if persistently febrile >72h
- **Infectious PPX:** items with asterisks (\*) have well-established benefit and are employed at all institutions
  - **Bacterial:** cipro 500mg BID or levofloxacin 500mg qd (day -1 to ANC >500)
  - **Viral (HSV/VZV)\*:** acyclovir **400mg BID** or famciclovir 500mg qd (day -1 to +365 [auto]; 1y min & until off IS [allo])
  - **CMV:** **intermovir 480mg qd** (dose-reduced w/ cyclosporine) used in CMV-seropositive recipients (day +7 to +100)
    - Alternative: monitor weekly CMV VL (from day -1 to +100), with pre-emptive therapy for CMV viremia with IV ganciclovir or PO valganciclovir
  - **Fungal\***: fluconazole **400mg qd**, vori 200mg BID, posaconazole 200mg TID (day -1 to ANC>500 [auto] or 3-6mo [allo])
    - Anti-mold (vori-, posa-, isavu-conazole) prophylaxis is considered in patients with AML, lengthy neutropenia
  - **PCP/Toxo\*:** Bactrim **SS qd** (start after engraftment as outpatient for 6mo [auto], >1y or off IS [allo])

## GRAFT VERSUS HOST DISEASE

- **Acute GVHD:** D0 to +100. ~40% in MRD, ~60% in MUD (cellular immune response, T<sub>H</sub>1 cell-mediated) ([NEJM 2017;377:2167](#))
  - Risk factors: ↑HLA mismatch, ↑age, female donor/male recipient, donor parity, TBI-myeloablation, PBSC > BM > CB
  - Cause: (1) Short-lived donor T cells react immediately; (2) Post-engraft, chronic infl → DAMPs/PAMPs → organ damage
  - S/Sx: skin (rash, graded by biopsy findings, % body surface, desquamation), liver (cholestatic injury, graded by bilirubin), GI (diarrhea, graded by volume of diarrhea/day). Grading [here](#).
  - DDx: skin (viral, drug, engraftment), liver (viral, drug, SOS, TPN), GI (C. diff, CMV, adeno, GNR, typhlitis, drug)
  - Tx: Grade I topical, II-IV **methylpred 1-2mg/kg**; if severe or steroid-refractory: vedolizumab, MMF, ruxolitinib ([NEJM 2020;382:1800](#)), antithymocyte globulin (ATG). Trial enrollment for cell therapies (MSCs, Tregs) ([Blood 2020;136:410](#))
- **Chronic GVHD:** 30-70% of patients s/p allo-HSCT (humoral immune response, T<sub>H</sub>2 cell-mediated) ([NEJM 2017;377:2565](#))
  - Cause: Pro-inflammatory environment iso graft-vs-tumor response, infx → iatrogenic thymic dysfx in training new T cells + Treg depletion → chronic inflammation w/ T/B cells → aberrant tissue repair after multiple injurious cycles → fibrosis
  - Risk factors: prior acute GVHD, HLA mismatch, ↑age, PBSC > BM
  - S/Sx: resembles **scleroderma** (sicca, dysphagia, arthritis, skin tightening, malar rash), lung (bronchiolitis obliterans), liver (cholestasis), cytopenias/immunodeficiency; any organ system (see NIH consensus scoring sheet in [BBMT 2015;21:389](#))
  - Tx: **steroid** ± broad immunosuppression, **photopheresis** for skin; novel therapies including ruxolitinib, ibrutinib & belumosudil (ROCK2 inhibitor) have shown responses in steroid-resistant disease; cell therapies ([BBMT 2020;26:835](#))
- **GVHD PPX:** day -3 to indefinite (tapered over months to years), goal to prevent graft rejection & acute/chronic GVHD
  - **Immunosuppression regimens:** combined tacrolimus/methotrexate or tacrolimus/sirolimus most common; obinutuzumab
  - **T cell depletion regimens:** (ATG, decreased T-cell dose) no longer favored; ↓ chronic GVHD but no effect on OS
  - **Post-transplant cyclophosphamide:** combined with tacro/MMF, used more widely for haplo and MMUD, ↓a/cGVHD

Immunosuppressant	Mechanism	Dosing	Toxicities
Tacrolimus	Calcineurin inhibitor	Trough goal: 5-10ug/L	AKI, ↑K, ↓Mg, ↑LFTs, n/v, TMA, tremor, DM risk
<b>Sirolimus (Rapamycin)</b>	mTOR inhibitor	Trough goal: 3-12ug/L	AKI, sinusoidal obstruction syndrome (SOS), leukopenia, TMA, HLD, cytopenias
<b>Methotrexate (MTX)</b>	Anti-metabolite (inhibits thymidine)	Given on day +1,3,6,11 w/ tacrolimus	<b>Mucositis</b> , myelosuppression, hepatitis, AKI
<b>Mycophenolate (MMF/Cellcept)</b>	Anti-metabolite (inhibits purines)	N/A	Myelosuppression, n/v/d
<b>Post-transplant cyclophosphamide (PTCy)</b>	Expands Treg, limits allo-reactivity ( <a href="#">JCI 2019;129:2357</a> )	Given days +3 and +4, particularly for haploididential	<b>Hemorrhagic cystitis</b> , mucositis, cardiac toxicity

# Oncology

# Hematopoietic Cell Transplantation

**NON-INFECTIOUS COMPLICATIONS:** immune-mediated organ damage, toxic effects of chemo, or immunosuppression

QUICK REFERENCE (day -8 conditioning to day +30 engraftment)			
Monitor S/Sx	DDx fever	DDx abdominal pain	DDx dyspnea/hypoxemia
<ul style="list-style-type: none"> <li><b>Chemo toxicity:</b> mucositis, N/V/D, S/Sx of infection</li> <li><b>GVHD:</b> rash, jaundice, diarrhea (24h volume)</li> <li><b>SOS:</b> RUQ pain, jaundice, ascites, edema</li> <li><b>Engraftment syndrome:</b> fever, dyspnea, edema</li> </ul>	<ul style="list-style-type: none"> <li>Infection (bacterial, viral, fungal, parasitic)</li> <li>Drug reaction</li> <li>Engraftment syndrome (day 7-9 for auto, day 14-21 for allo)</li> <li>Tumor (initial lysis &amp; cytokine release)</li> <li>Immobility (aspiration, DVT/PE)</li> <li>GVHD</li> </ul>	<ul style="list-style-type: none"> <li>Neutropenic enterocolitis</li> <li>Colitis: <i>C. difficile</i>, CMV</li> <li>SOS</li> <li>GVHD</li> <li>Obstruction, ileus, constipation</li> </ul>	<ul style="list-style-type: none"> <li>Existing disease: CHF, COPD, asthma</li> <li>PNA: bacterial, fungal, aspiration</li> <li>Volume (often on mIVF, transfusions)</li> <li>Drug: chemo-induced lung injury or cardiotoxicity</li> <li>Engraftment (pulmonary edema from capillary leak)</li> <li>Pneumonitis</li> <li>Alveolar hemorrhage</li> <li>PE, TRALI, GVHD</li> </ul>

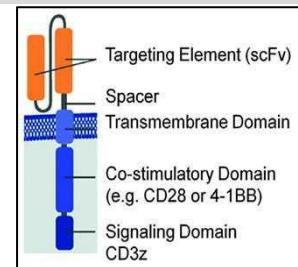
- **Pre-Engraftment (day 0-30):** common to have mucositis, nausea/vomiting, alopecia, rash, diarrhea
  - **Mucositis:** most HSCT patients get some degree of mucositis; duration & severity are worse in allogeneic HSCT. Treatment is focused on pain & caloric intake. **WHO grade:** (1) erythema (2) ulcer, solid+liquid PO (3) liquid PO (4) NPO
    - **Pain:** topical/IV opiates; low threshold for PCA
    - **Nutrition:** TPN initiated if PO intake impaired by mucositis & expected to continue for ≥1w
    - **Palifermin** (recombinant keratinocyte growth factor): might reduce duration & severity with select ablative regimens
  - **Engraftment syndrome:** sudden PMN recovery causing cytokine storm and vascular leak
    - **S/Sx:** fever, rash, weight gain, bone pain; if severe – pulmonary edema, ↑LFTs, AKI, seizures
    - **Dx:** diagnosis of exclusion (DDx: infection, drug reaction, acute GVHD)
    - **Tx:** high-dose IV steroids (discuss with attending prior to initiation of steroids)
  - **GI – nausea/vomiting:** optimal management varies based on timing relative to chemo initiation
    - **Immediate** (day 0-1): 5-HT<sub>3</sub> blockade (Zofran, Aloxi), neurokinin-1 antagonists (Emend), steroid (decadron)
    - **Delayed** (day 2-5 post chemo): dopamine (D2) blockade (Compazine, Reglan, Haldol)
    - **Late** (5+ days post chemo): lorazepam, steroids, dronabinol (more helpful in younger pts, marijuana users)
  - **Pulm – idiopathic interstitial pneumonitis/diffuse alveolar hemorrhage (DAH):**
    - **Cause:** direct cytotoxic injury to alveoli
    - **S/Sx:** fever, hypoxemia, diffuse lung infiltrates (**ARDS**)
    - **Dx:** bronchoscopy w/ serial lavage (r/o infection, blood) – progressively bloodier on serial lavage c/w DAH
    - **Tx:** high-dose steroids; + for DAH: FFP to correct coagulopathy, maintain plt >50k; limited data for recombinant FVIIa
  - **Liver – sinusoidal obstruction syndrome (SOS)** (previously called **veno-occlusive disease [VOD]**):
    - **Cause:** direct cytotoxic injury to hepatic venules leading to hypercoaguable state and microthrombi
    - **S/Sx:** RUQ pain, jaundice, ascites/edema; ↑ALT/AST/TBili, ↑INR/Cr (if acute liver failure or HRS)
    - **Dx:** Doppler US c/w reversal of portal vein flow, liver bx; **Dx criteria:** Tbili >2mg/dL, hepatomegaly/RUQ pain, sudden weight gain (fluid) >2-5% baseline body weight
    - **PPX:** ursodiol 300mg TID (admit to day +30); **Tx:** defibrotide
  - **Renal – AKI** (DDx: ATN, hepatic SOS, aGVHD, thrombotic microangiopathy (TMA), TLS, ABO-mismatched transplant)
    - **Nephrotoxins:** calcineurin inhibitors, acyclovir, amphotericin, aminoglycosides
    - **TMA:** subacute onset ~ day 20, caused by endothelial damage 2/2 calcineurin inhibitors, conditioning, & GVHD
    - **TLS:** considered in pts with significant disease burden at time of transplant; **PPX:** allopurinol 300mg qd
  - **Heme – graft failure, cytopenias, bleeding:**
    - **Primary graft failure:** persistent neutropenia without engraftment
    - **Secondary graft failure:** delayed pancytopenia after initial engraftment (immune or infectious)
    - Rx: graft failure may require re-transplantation (CD34 boost); transfusions with irradiated & leukoreduced products
  - **Post-Engraftment (day +30):**
    - **PTLD** (post-transplant lymphoproliferative disease): ~1% in allo-SCT; median **day +70-90** ([NEJM 2018;378:549](#))
      - **Cause:** IS leads to EBV reactivation (dormant in B cells) & clonal B cell proliferation (usually donor-derived)
      - **Risk factors:** T cell depleted donor graft, treatment with ATG, HLA-mismatch, CB transplant
      - **Dx:** rising plasma EBV DNA level, biopsy with immunophenotyping for definitive diagnosis
      - **Tx:** reduce IS, anti-viral, rituximab-based chemo (if systemic) vs surgery/RT (if localized), DLI, EBV-targeted T cells
    - **Pulm** – bronchiolitis obliterans (cGVHD), pulmonary veno-occlusive disease
    - **Liver** – cGVHD, drug-induced liver injury, viral hepatitis reactivation, iron overload (secondary hemochromatosis)
    - **Renal** – TMA (chronic onset ~ day 100), drug toxicity (calcineurin inhibitors), nephrotic syndrome

**DISEASE RELAPSE:** #1 cause of death post-HCT. **Mechanisms:** immune escape, resistant clones that survive conditioning

- Treatment: donor lymphocyte infusion (DLI), salvage chemo, then second allo-HCT, clinical trials for novel therapies, hospice

## MECHANISM OF ACTION ([NEJM 2018;379:64](#))

- Chimeric antigen receptor T cells autologous cell therapy whereby T cells are collected from patient, genetically modified with construct encoding a chimeric antigen receptor (CAR) that directs T cells against a tumor antigen. CAR T cells are infused into patient, where they persist *in vivo*
- CAR:** transmembrane engineered protein consisting of extracellular immunoglobulin (antibody)-derived domains (ScFv), which binds a tumor antigen (e.g. CD19). The ScFv is fused to signaling (CD3z) and costimulatory domains (CD28 or 4-1BB) that cause T cell activation and proliferation



## FDA-APPROVED CAR T CELL THERAPIES

- Yescarta** (axicabtagene ciloleucel - "axi-cel"; anti-CD19, CD28 co-stim domain)
  - Relapsed/refractory **large B-cell lymphoma**: ZUMA-1 → 82% ORR (54% CR) ([NEJM 2017;377:2531](#))
  - Relapsed/refractory **follicular lymphoma**: ZUMA-5 → 92% ORR (74% CR) ([Lancet Oncol 2022;23:91](#)).
- Kymriah** (tisagenlecleucel - "tisa-cel"; anti-CD19, 4-1BB co-stim domain)
  - Relapsed/refractory **B-ALL** age <25y: ELIANA → 81% CR ([NEJM 2018;378:439](#)). Adult phase 2: [NEJM 2018;378:449](#)
  - Relapsed/refractory **large B-cell lymphoma**: JULIET → 52% ORR (40% CR), 65% w/o relapse at 1y ([NEJM 2019;380:45](#))
- Tecartus** (brexucabtagene autoleucel - "brexu-cel"; anti-CD19, CD28 co-stim domain)
  - Relapsed/refractory **mantle cell lymphoma**: ZUMA-2, Phase 2, 93% ORR (67% CR) ([NEJM 2020;382:1331](#))
  - Relapsed/refractory **adult B-ALL**: ZUMA-3 → 71% CR ([Lancet 2021;398:491](#))
- Breyanzi** (lisocabtagene maraleucel - "liso-cel"; anti-CD19, 4-1BB co-stim domain, 1:1 ratio of CD8+:CD4+ CAR T cells)
  - Relapsed/refractory **large B-cell lymphoma**: TRANSCEND NHL 001 → ORR 73% (CR 53%) ([Lancet 2020;19;396:839](#))
- Abecma** (idecabtagene vicleucel - "ide-cel"; anti-BCMA, 4-1BB co-stim domain)
  - Relapsed/refractory **multiple myeloma**: KarMMa → 73% ORR (33% CR) ([NEJM 2021;384:705](#))
- Carvykti** (ciltacabtagene autoleucel - "cilte-cel"; anti-BCMA, 4-1BB co-stim domain, 2 anti-BCMA camelid nanobody domains)
  - Relapsed/refractory **multiple myeloma**: CARTITUDE-1 → 98% ORR (83% CR), 27-month PFS 55% ([Lancet 2023;41:1265](#))
- Under investigation: combo w/ PD1-axis blockade ([Cancer Cell 2019;36:471](#)) & other cell types, e.g. CAR-NK cells ([NEJM 2020;382:545](#))

## TOXICITIES ([JNCCN 2020;18:230](#); [BBMT 2019;25:625](#))

- Cytokine-release syndrome (CRS)**
  - At least Grade 1 occurs in majority of patients, <10% Grade 3. Typically 1-3d post-infusion, lasts ~7d. Caused by fulminant cytokine release (IL-2, sIL2R, IFNy, IL-6, GM-CSF) triggered by CAR T cell engagement of antigen and *in vivo* expansion. Risk: bulky disease, baseline ↓ platelets, ↑CRP. Axi-cel > Tisa-cel
  - Signs/Sx:** fever, ↓BP, ↑HR, ↓SpO<sub>2</sub>, malaise, rigors, anorexia, myalgia. Can affect any organ (CV, lung, GI/liver, renal, CNS), arrhythmias, capillary leak syndrome, HLH
  - Dx:** monitor for 7d post infusion for FDA-approved therapies (inpt or possibly close outpt); VS, basic labs, ferritin, coags, CRP, TLS labs. When suspicious, make sure to rule-out infection
  - Tx:** See table. Tocilizumab (anti-IL6R) 8mg/kg over 1h (<800mg); siltuximab (anti-IL6) and/or anakinra (anti-IL1R); 2nd line: steroids. If plan to treat CRS with steroids or anti-IL6, **first get clear approval by the treating attending** (even if overnight).
  - Broad-spectrum antibiotics (cefepime) if fever + neutropenia
- Immune effector cell-associated neurotoxicity syndrome (ICANS)**
  - Etiology:** unclear; cytokine diffusion into brain (IL-1, IL-6, IL-15 a/w neurotoxicity), BBB disruption, CAR T cell trafficking to CNS
  - Timing:** typical onset 4-10d post-infusion, duration variable. Can be concurrent w/ CRS or after. CRS is not necessary for ICANS.
  - S/Sx:** aphasia, impaired fine motor skills, seizure, motor weakness, toxic encephalopathy (see ICE & ICANS grade), rare parkinsonism w/ BCMA CAR T cells ([Nat Med 2021;27:2099](#))
  - Dx:** neuro c/s, ICE score, ICANS grade. If grade ≥3: MRI brain w/ w/o contrast, EEG, LP (r/o infection, e.g. HHV6), fundoscopy
  - Tx:** See table. Seizure prophylaxis starting on day of infusion (levetiracetam 500-750 mg q12h for 30d). Generally, dexamethasone +/- anakinra, treat CRS if present (i.e. toci), but **first get clear approval by the attending** (even if overnight)
  - Prognosis:** generally reversible, rare fatal cases
- Persistent Hematologic Toxicity**
  - CAR T cells can cause prolonged grade ≥3 anemia, neutropenia, thrombocytopenia that persists months-years
  - Mechanism unclear, a/w with decreased baseline hematopoietic reserve and inflammation ([Blood 2021;138: 2499](#))
- Hemophagocytic lymphohistiocytosis (HLH):** Rare, 1% develop (see *Pancytopenia/Anemia* page) ([TCT 2023](#) HLH guidelines)

ASTCT CRS Grade		Treatment
1	<b>Fever</b> (≥38C)	Tylenol, supportive. If >3d, consider tocilizumab
2	Fever & <b>HoTN</b> not requiring pressors or hypoxemia on NC	<b>Tocilizumab</b> q8h PRN up to x4, add steroids as below if still ↓BP after 1-2 doses, IV fluids
3	Fever + ↓BP requiring <b>pressor</b> or ↓SpO <sub>2</sub> requiring <b>HFNC, NRB</b>	<b>Tocilizumab</b> as above, <b>dexamethasone</b> 10mg IV q6h (or equivalent)
4	Fever + ↓BP requiring <b>multiple pressors</b> or ↓SpO <sub>2</sub> requiring <b>BIPAP, MV</b>	<b>Tocilizumab + dex</b> as above. If refractory, consider <b>methylpred</b> 1g/d IV x3d w/ taper

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool	
Max score: 10	A&Ox3 [+ hosp] (4 pts), naming [clock, pen, button] (3 pts), follows commands (1 pt), writes sentence (1 pt), serial 10s from 100 (1 pt)

ASTCT ICANS Grade		Treatment
Grade 1	ICE = 7-9, awakens spontaneously	Supportive
Grade 2	ICE = 3-6, awakens to voice	Dex 10mg IV x1
Grade 3	ICE = 0-2, awakens to tactile stimulus, or focal edema on neuroimaging, or brief seizure	Dex 10mg IV q6h or methylpred 1mg/kg IV q12h
Grade 4	ICE = 0,unarousable, seizure >5min or w/o return to b/l, or deep focal motor deficit, or diffuse cerebral edema, or ↑ICP	Methylprednisolone IV 1g/d x3d or equivalent w/ taper

# Oncology

# Solid Organ Malignancies

Organ	Risk factors/screening	Diagnostics	Treatment
<b>Breast</b> <ul style="list-style-type: none"> <li>Infiltr. ductal (76%)</li> <li>Invas. lobular (8%)</li> <li>Ductal/lobular (7%)</li> <li>Mucinous (2%)</li> <li>Tubular (1.5%)</li> <li>Medullary (1%)</li> <li>Papillary (1%)</li> </ul> <p><a href="#">NCCN Guidelines Breast Cancer 2023</a></p>	<p><b>Risk factors:</b> Age, genetics (<i>BRCA1/2, CHEK2, ATM, PALB2</i>), FHx, obesity after menopause, menopause, &gt;55, chest RT, 1<sup>st</sup> birth &gt;30, nulliparity, HRT, menarche &lt;13y, EtOH, benign breast disease, tobacco, DES exposure</p> <p><b>Screening:</b></p> <ul style="list-style-type: none"> <li><b>USPTF:</b> q2y mammo 50-74</li> <li><b>NCCN:</b> q1y mammo &gt;40 or 10y before earliest FHx if &gt;30 or 10y after RT if &gt;30</li> </ul>	<ul style="list-style-type: none"> <li>H&amp;P</li> <li>Dx bilateral mammogram (Bi-RADS), US, FNA or core Bx (&gt; excis. Bx), breast MRI if young or to assess extent (good Sn, but Sp 72%)</li> <li>Path review (include Ki-67)</li> <li>Genetic testing and counselling</li> </ul>	<p><b>Early stage (I, IIA, IIB through T2N1):</b></p> <ul style="list-style-type: none"> <li>Breast Conserving Surgery ± RT (<a href="#">NEJM 2023;388:585</a>) vs. mastectomy ± RT, HR tx, HER2 tx, chemo if high risk</li> </ul> <p><b>Locally advanced (Stage IIB T3N0, IIA-IIIC):</b></p> <ul style="list-style-type: none"> <li>Surgery + RT w/ (neo)adj. chemo &amp; HR/HER2 tx</li> </ul> <p><b>(Neo)adjuvant therapy:</b></p> <ul style="list-style-type: none"> <li><b>ER/PR+, HER2-</b>: tamoxifen or aromatase inhibitors (AI) (anastrozole, letrozole, exemestane); no AI if premenopausal; ± ovarian suppression if high risk.</li> <li>Chemo: AC-T (doxo, cyclophos [CYC], paclitax.) or TC</li> <li><b>HER2+:</b> TCH(P) (trastuzumab, carboplatin, docetaxel, ± pertuzumab) or ACTH(P) (doxorubicin, CYC, paclitaxel, trastuzumab ± pertuzumab) + ER/PR tx if HR+</li> <li><b>Triple Neg</b> (<a href="#">NEJM 2017;372:2147</a>): capecitabine</li> </ul> <p><b>Metastatic/recurrent (Stage IV):</b></p> <ul style="list-style-type: none"> <li><b>ER+:</b> as above ± fulvestrant (ER antagonist); ± CDK4/6 inhibitor or everolimus (mTOR inhibitor)</li> <li><b>HER2+:</b> THP (1<sup>st</sup> line) or T-DM1 (trastuzumab-drug conjugate), trastuzumab+lapatinib</li> <li><b>BRCA mutation</b> (<a href="#">NEJM 2017;377:523</a>; <a href="#">NEJM 2018;379:753</a>): olaparib or talazoparib</li> <li><b>Triple neg:</b> systemic tx</li> </ul>
<b>Colon and rectum</b> <ul style="list-style-type: none"> <li>AdenoCa (98%)</li> <li>Neuroendocrine</li> <li>Lymphoma</li> </ul> <p><a href="#">NCCN Guidelines Colon Cancer 2023</a></p>	<p><b>Risk factors:</b></p> <ul style="list-style-type: none"> <li>FHx, genetic (FAP, HNPCC), IBD, obesity, tobacco, red/processed meat, EtOH, adenomat. polyps, age</li> <li>↑ death w/ R-sided (<a href="#">JAMA Oncol 2018;4:e173695</a>)</li> </ul> <p><b>Protective factors:</b> ASA for 50-59yo and ≥10% CVD risk (<a href="#">Annals 2016;164:814</a>)</p> <p><b>Screening (45-75yo):</b> colo, flex sig, CT colo, FIT, FOBT for 50-75yo</p>	<ul style="list-style-type: none"> <li>Colonoscopy w/ polyp, bx for path</li> <li>CT C/A/P, CEA</li> <li><b>MRI for liver mets</b></li> <li>Pelvic MRI or endorectal US for rectal CA</li> </ul> <p><b>Genetic testing:</b> MSI/MMR status in all, K/N-RAS, BRAF, HER2</p>	<p><b>Colon:</b></p> <p><b>I-IIA:</b> surgery + observation, or capecitabine or 5-FU/leucovorin (IIA)</p> <p><b>IIB-IV:</b> surg, RT, <b>systemic tx:</b> FOLFOX (oxaliplatin, leucovorin, 5-FU), CAPEOX (capecitabine, oxaliplatin), FOLFIRI (irinotecan, leucovorin, 5-FU), FOLFOXIRI (irinotecan, oxaliplatin, leucovorin, fluorouracil), ± bevacizumab; nivo ± ipi or pembrolizumab</p> <p><b>BRAF V600E:</b> encorafenib + EGFR inhib. (cetuximab, panitumumab)</p> <p><b>MSI-H/dMMR:</b> immuno tx (pembrolizumab, nivolumab)</p> <p><b>HER-amp +RAS/BRAF WT:</b> trastuzumab + pertuzumab/lapatinib</p> <p><b>Rectal:</b> low anterior (LAR) v abdominoperineal resection (APR) ± neo v adj chemoRT. Chemo as in colon cancer</p>
<b>Lung</b> <ul style="list-style-type: none"> <li>NSCLC (84%): adeno, large&gt;SCC</li> <li>SCLC (13%)</li> </ul> <p><a href="#">NCCN Guidelines NSCLC 2023</a></p> <p><a href="#">NCCN Guidelines SCLC 2023</a></p>	<p><b>Risk factors</b> (<a href="#">Nat Rev Ca 2007;10:778</a>):</p> <ul style="list-style-type: none"> <li>Age, male, tobacco, asbestos, occup. exposures, lung fibrosis or COPD, prior cancer history, exposure to infectious agents (TB, fungal)</li> <li>25% lung cancer worldwide not due to smoking → more likely single mutation</li> </ul> <p><b>Screening</b> (<a href="#">Annals 2014;160:330</a>):</p> <ul style="list-style-type: none"> <li>Annual low dose CT chest for pts aged 50-80 with ≥20 pack-year hx and smoking within last 15 years</li> </ul>	<ul style="list-style-type: none"> <li>CT C/A/P, FDG-PET/CT, brain MRI</li> <li>PFTs</li> <li>Evaluate pathologic LNs with biopsy</li> <li>Molecular testing for NSCLC (EGFR, ALK, ROS1, NTRK1/2/3, MET exon14 skipping, RET, PD-L1) before systemic tx</li> </ul>	<p><b>NSCLC: IA:</b> surgery ± RT; <b>IB-IIIA:</b> surgery if able ± adjuv chemoRT ± osimertinib or atezolizumab. <b>IIB/IIIA unresectable, IIIB:</b> definitive chemoRT + adjuvant durvalumab (<a href="#">NEJM 2018;379:2342</a>). <b>IV:</b> systemic tx as below:</p> <ul style="list-style-type: none"> <li><b>ChemoRT:</b> cisplatin + docetaxel/etoposide/ pemetrexed; carboplatin + pemetrexed/paclitaxel/gemcitabine/docetaxel</li> <li><b>Targeted inhibitors:</b> EGFR (osimertinib 1<sup>st</sup> line, erlotinib, afatinib, gefitinib, dacomitinib); ALK/ROS1 (alectinib, crizotinib, ceritinib, brigatinib, lorlatinib); BRAF/MEK (dabrafenib/trametinib); TRK (larotrectinib, entrectinib)</li> <li><b>Immunotherapy (PD-L1+)</b> (<a href="#">Lancet 2016;387:1540</a>; <a href="#">NEJM 2018;378:2078</a>): pembrolizumab ± chemo. ipi/nivo, atezolizumab+ platinum+ taxane + bevacizumab (anti-VEGF)</li> </ul> <p><b>SCLC:</b></p> <ul style="list-style-type: none"> <li><b>Limited:</b> surgery + chemo ± mediastinal RT</li> <li><b>Extensive</b> (<a href="#">NEJM 2018;379:2220</a>): chemo &amp; atezolizumab v durvalumab ± RT for lobar obstruction, SVC syndrome, bone/brain mets</li> <li><b>Chemo:</b> platinum agents, etoposide, irinotecan</li> </ul>

# Oncology

# Solid Organ Malignancies

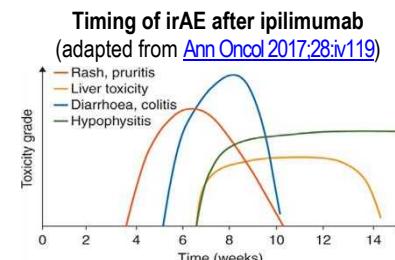
Organ	Risk factors/screening	Diagnostics	Treatment
<b>Melanoma</b> <ul style="list-style-type: none"> <li>▪ Superficial spreading (75%)</li> <li>▪ Nodular (15-30%)</li> <li>▪ Lentigo maligna (10-15%)</li> <li>▪ Acral lentiginous (&lt;5%)</li> <li>▪ Amelanotic (2-10%)</li> <li>▪ Ocular (5%)</li> <li>▪ Mucosal (~1%)</li> </ul> <p><a href="#">NCCN Guidelines Cutaneous Mel 2023</a></p> <p><a href="#">NCCN Guidelines Uveal Mel 2023</a></p>	<p><b>Risk factors:</b></p> <ul style="list-style-type: none"> <li>▪ Sun exposure (UVB &gt; UVA), atypical nevi, high nevi count, FHx or personal hx, immunosuppression</li> <li>▪ Familial melanoma with germline CDKN2A, CKD4, POT1 mutations</li> </ul> <p><b>Most common somatic mutations:</b></p> <ul style="list-style-type: none"> <li>▪ BRAF (V600E, V600K) 50%, NRAS 15-20%, KIT 10-15% (acral). Genetic testing for stage II-IV disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Biopsy of primary tumor (Breslow depth prognostic), LN sampling, CT C/A/P, brain MRI, &amp; serum LDH for active surveillance and treatment response</li> <li>▪ Liver MRI for ocular/uveal melanoma – liver most common metastatic site</li> </ul>	<p><b>Localized disease:</b> wide excision of primary tumor ± sentinel lymph node biopsy. Topical imiquimod or RT if surgery contraindicated or as adjuvant tx.</p> <p><b>Metastatic disease:</b> Systemic therapy ± excision (if feasible) ± RT (for sympt. localized disease, e.g. brain mets) ± talimogene laherparepvec (T-VEC, intralesion injection of HSV → tumor cell lysis &amp; GM-CSF expression) (<a href="#">JCO 2015;33:2780</a>).</p> <p>Systemic therapy:</p> <ul style="list-style-type: none"> <li>▪ <b>Immunotherapy</b> (<a href="#">NEJM 2015;373:23</a>; <a href="#">NEJM 2015;372:2521</a>): anti-PD-1 (pembrolizumab); anti-CTLA4 (ipilimumab), ipi+nivo (<a href="#">NEJM 2019;381:1535</a>)</li> <li>▪ <b>Targeted tx</b> (<a href="#">NEJM 2014;371:1867</a>): If BRAF/MEK mutated, combined inhibitors (dabrafenib+trametinib, vemurafenib+cobimetinib, encorafenib+binimetinib). If KIT mutant, imatinib.</li> </ul>
<b>Pancreas</b> <ul style="list-style-type: none"> <li>▪ Exocr./adeno (~95%)</li> <li>▪ Endocrine (&lt;5%)</li> </ul> <p><a href="#">NCCN Guidelines Pancreatic 2023</a></p>	<p><b>Risk factors:</b></p> <ul style="list-style-type: none"> <li>▪ Tobacco, EtOH, obesity, DM, chronic pancreatitis, age, male, FHx, HNPCC, chemical/heavy metal exposure, germline mut. (BRCA1/2, TP53, STK11, MLH1, MSH2/6, PMS2, CDKN2A).</li> </ul> <p><b>Genetic mutations:</b></p> <ul style="list-style-type: none"> <li>▪ KRAS, TP53, SMAD4, TGFbR1/2, CDKN2A, MLL2/3, KDM6A, ATM, NTRK, ALK, ROS1, BRAF, HER2, PALB2</li> </ul>	<ul style="list-style-type: none"> <li>▪ CT C/A/P pancreas protocol, EUS+Bx, MRCP ± ERCP, MRI for indeterminate lesions, PET/CT in high risk patients</li> <li>▪ CA19-9, LFT</li> <li>▪ Germline testing +molecular profiling of tumor tissue</li> <li>▪ Bx metastatic site if metastatic disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ <b>Resectable/Borderline:</b> surgery ± systemic tx: 1<sup>st</sup> line FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin), gemcitabine+nab-paclitaxel, gem+capecitabine, ± chemoRT</li> <li>▪ <b>Locally advanced:</b> systemic tx as above or stereotactic body radiation (SBRT)</li> <li>▪ <b>Metastatic:</b> systemic tx ±: <ul style="list-style-type: none"> <li>• BRCA1/2: olaparib (<a href="#">NEJM 2019;381:317</a>);</li> <li>• <b>NTRK fusions:</b> larotrectinib, entrectinib</li> <li>• <b>MSI-H/dMMR/TMB-H:</b> pembrolizumab (<a href="#">NEJM 2015;372:2509</a>)</li> <li>• <b>BRAF V600E:</b> dabrafenib + trametinib</li> </ul> </li> </ul>
<b>Prostate</b> <ul style="list-style-type: none"> <li>▪ Adenocarcinoma (95%)</li> <li>▪ Transitional, basal cell, intraductal carcinomas; neuroendocrine, carcinosarcoma, lymphoma, stromal sarcoma</li> </ul> <p><a href="#">NCCN Guidelines Prostate Cancer 2023</a></p>	<p><b>Risk factors:</b></p> <ul style="list-style-type: none"> <li>▪ Age, black race, genetic factors (BRCA1/2 and family history), smoking</li> </ul> <p><b>Screening with PSA:</b></p> <ul style="list-style-type: none"> <li>▪ 55-69: individualized risk-benefit discussion</li> <li>▪ 70 and above: no testing (<a href="#">JAMA 2018;319:1901</a>)</li> </ul>	<p><b>Diagnosis: Bx After diagnosis:</b></p> <ul style="list-style-type: none"> <li>▪ TRUS, MRI, biomarkers, CT C/A/P, bone scan</li> </ul> <p><b>Germline testing:</b></p> <ul style="list-style-type: none"> <li>▪ High/very high NCCN risk</li> <li>▪ Any risk level if + FHx or intraductal histology</li> </ul>	<p><b>Low risk:</b> surveillance (PSA, DRE ± Bx) vs external beam radiation therapy (EBRT) ± brachytherapy (BT) vs radical prostatectomy</p> <p><b>Intermediate/high risk:</b> combination of EBRT, BT ± prostatectomy w/ lymph node dissection, and androgen deprivation therapy (ADT):</p> <p><i>Orchiectomy, Androgen R blocker:</i> enzalut-, apalut-, darolut-, flutamide. <i>Androgen synthesis inhib:</i> abiraterone. <i>GnRH agonist:</i> leuprolide, gose-, hist-, triptorelin, <i>GnRH antagonist:</i> degarelix, relugolix</p> <p><b>Metastatic/recurrent:</b> ADT, if fail, ADT+doxetaxel. <b>Bone mets:</b> radium-223 or denosumab/zoledronic acid, palliative RT. <b>MSI-H/dMMR:</b> pembrolizumab</p>
<b>Cancer of Unknown Primary</b> <ul style="list-style-type: none"> <li>▪ Adenocarcinoma or carcinoma not otherwise specified (85%)</li> <li>▪ Squamous cell carcinoma (5%)</li> <li>▪ Undifferentiated carcinoma (5%)</li> <li>▪ Neuroendocrine tumors (5%)</li> </ul> <p><a href="#">NCCN Occult Primary Guidelines</a></p>	<p><b>Pathologic Diagnosis:</b></p> <ul style="list-style-type: none"> <li>▪ Core needle biopsy (preferred) and/or FNA from most accessible site</li> <li>▪ MSI/MMR testing</li> </ul> <p><b>Initial Evaluation:</b></p> <ul style="list-style-type: none"> <li>▪ Immunohistochemistry</li> <li>▪ Gene expression profiling</li> <li>▪ Tumor serum markers: β-hCG (testicular), AFP (testicular, hepatocellular carcinoma), CEA (CRC), CA-125 (ovarian)</li> </ul>	<p><b>Workup:</b></p> <ul style="list-style-type: none"> <li>▪ Complete H&amp;P (breast, GU, pelvic, rectal, skin exams)</li> <li>▪ Routine labs (CBC, electrolytes, LFT, Cr)</li> <li>▪ Occult blood stool testing</li> <li>▪ CT C/A/P with IV contrast +/- PET</li> <li>▪ Endoscopy, UA, LDH (if indicated)</li> </ul>	<p><b>Adenocarcinoma:</b> paclitaxel + carboplatin ± etoposide; gemcitabine + cisplatin or docetaxel; capecitabine + oxaliplatin (CapeOx); fluorouracil + leucovorin + oxaliplatin (FOLFOX) or irinotecan (FOLFIRI); docetaxel + carboplatin or cisplatin</p> <p><b>Squamous cell carcinoma:</b> Paclitaxel + carboplatin or cisplatin; gemcitabine + cisplatin; docetaxel + carboplatin or cisplatin; cisplatin + fluorouracil; docetaxel + cisplatin+ fluorouracil (DCF)</p> <p><b>Adenocarcinoma and SCC:</b> capecitabine, fluorouracil, pembrolizumab, selpercatinib</p> <p><b>Neuroendocrine tumors:</b> paclitaxel + carboplatin + etoposide; cisplatin + etoposide; temozolomide ± thalidomide.</p>

## IMMUNE CHECKPOINT INHIBITORS (ICI)

- Mechanism of Action:** **block** receptors that **down-regulate** T cell activation → CTLA-4, PD-1 (on T-cell), or its ligand PD-L1 (on cancer cell) → ↑ antitumor immune response ([Nat Rev Clin Oncol 2016;13:473](#); [NEJM 2018; 378:158](#); [NEJM 2016;375:1767](#))
- Indications:** >17 cancers. PD-1i FDA-approved for **any** microsatellite instability-high (MSI-H) or mismatch-repair deficient tumors (dMMR). Pre-existing autoimmunity not absolute contraindication, but can flare ([JCO 2018;36:1905](#); [Ann Oncol 2017;28:368](#))

## IMMUNE RELATED ADVERSE EVENTS (IRAEs) ([NEJM 2018;378:158](#); [Ann Oncol 2017;28:iv119](#); [J Immunother Cancer 2017;5:95](#))

- Definition:** systemic autoimmune/inflammatory event 2/2 immune activation by ICI
- Grading:** 1-4 (mild to life threatening), guides treatment regimen
- Risk factors:** combination (anti-CTLA-4 + anti-PD-1) a/w earlier onset, ↑ incidence and severity; anti-CTLA-4 > anti-PD-1
- Timing:** highly variable, can present weeks-years after use
- Tx:** based on expert consensus (ASCO [J Oncol Pract 2018;14:247](#)). 1<sup>st</sup> line corticosteroids. If refractory: infliximab, MMF, tacrolimus, MTX, ATG, tocilizumab. IVIg/plasmapheresis in autoAb-mediated/neurologic irAEs



## SELECTED IRAE DIAGNOSIS, GRADING, AND MANAGEMENT (ASCO: [JCO 2018;36:1714](#); [NCCN Guidelines 2022](#))

Consult SIC (Severe Immunotherapy Complications) Service for inpatient questions regarding concern for irAEs

**Skin toxicity:** rash, pruritis, rarely SJS/TEN. Common, up to 30-40% of patients (CTLA-4 > PD-1/L1 blockade). Vitiligo seen in melanoma, rarely in other malignancies, a/w response to immunotherapy ([JAMA Dermatol 2016;152:45](#))

- Timing:** early, within the first few weeks after tx initiation
- S/Sx:** four types (1) Inflammatory: psoriasisiform or lichenoid reactions; (2) Immunobullous: dermatitis herpetiformis or bullous pemphigoid; (3) Keratinocyte alteration: acantholytic dyskeratosis; (4) Immune reaction mediated by alteration of melanocytes
- Dx:** exam; r/o other etiologies (infection, DRESS, SJS/TEN); grading based on BSA (<10% Gr 1, 10-30% Gr 2, >30% Gr 3)
- Tx:** topical steroids, oral antihistamines for inflammatory/pruritic reaction. If severe, consider systemic steroids + derm c/s

**Colitis:** more common w/ anti-CTLA-4; grade 3/4 colitis is higher with ipilimumab (<10%) than with anti-PD-1 agents (1-2%).

- Timing:** 6-8w after initiation of therapy
- S/Sx:** diarrhea, weight loss, abdominal pain/urgency/rectal bleeding if severe
- Dx:** lactoferrin/calprotectin; r/o other etiologies (*C diff.*, stool Cx, CMV PCR). CT A/P can show mild diffuse bowel thickening or segmental colitis. EGD/flex sig/colo for Grade ≥2 sx, path w/ active acute colitis.
- Tx:** antidiarrheal agents, budesonide 9mg PO or prednisone PO vs. high dose steroids w/ taper, infliximab in refractory cases

**Pneumonitis:** more common w/ anti-PD-1, serious toxicity rare. Higher risk w/ combination or targeted therapy ([Chest 2017;152:271](#))

- Timing:** highly variable, can be later
  - S/Sx:** dyspnea, cough, fever, AIP/ARDS; 1/3 asymptomatic ([JCO 2017;35:709](#); [Clin Cancer Res 2016;22:6051](#))
  - Dx:** r/o other etiologies, consider BAL, PCP, CT often non-specific though can show GGOs and/or nodular infiltrates
  - Tx:** oxygen, glucocorticoids w/ prolonged taper, diuresis, infliximab, mycophenolate mofetil or IVIg if severe or refractory
- | irAE Severity | Management   |
|---------------|--|
| Grade 1       | <ul style="list-style-type: none"> <li>Continue checkpoint inhibitor</li> <li>Increased monitoring</li> <li>Supportive care</li> </ul>   |
| Grade 2       | <ul style="list-style-type: none"> <li>Delay checkpoint inhibitor</li> <li>Oral corticosteroids (0.5-1 mg/kg) as outpatient, taper over 2-4 wks</li> <li>Re-challenge with ICI if returned to grade 1 toxicity</li> <li>Increased monitoring</li> </ul>  |
| Grade 3       | <ul style="list-style-type: none"> <li>Delay checkpoint inhibitor, consider rechallenge if benefits outweigh risks</li> <li>Oral corticosteroids (1-2 mg/kg) as outpatient, IV if symptoms persist 48-72 hours, taper over 4-6 wks</li> <li>Consider organ specialist consultation (GI, pulm, etc.)</li> </ul> |
| Grade 4       | <ul style="list-style-type: none"> <li>Discontinue checkpoint inhibitor (except for endocrinopathies managed with hormone replacement)</li> <li>Hospitalize for IV steroids</li> <li>Consider additional immunosuppressive agents if no response to IV steroids</li> <li>Consult organ specialist</li> </ul>   |

**Hypophysitis** ([JAMA Oncol 2018;4:173](#)): primarily w/ anti-CTLA-4 (3%), rarely w/ anti-PD-1/PD-L1 (0.5%). Mechanistically distinct from other irAEs; possibly by direct binding of ipilimumab to CTLA-4 on normal cells of anterior pituitary ([Sci Transl Med 2014;6:230](#)).

- Timing:** median onset ~8w
- S/Sx:** HA (common, can be severe), fatigue, n/v, dizziness, weight changes, hot flashes, cold intolerance, hyponatremia (anterior hypopituitarism), vision changes; usually without central diabetes insipidus (posterior pituitary spared)
- Dx:** MRI brain/pituitary shows diffuse pituitary enlargement (generally resolves by 2mo); **test hormonal axes:** 8AM serum cortisol + ACTH and/or cort stim; TSH w/ FT4/total T4/T3; PRL; LH/FSH, serum testosterone/SHBG (in men); IGF-1
- Tx:** hormone substitution: **Hypocortisolism:** glucocorticoid replacement (prednisone 3-5mg daily) ([Cancer 2018;124:3706](#); [Oncologist 2016;21:804](#)). **Central hypothyroidism:** levothyroxine. **Hypogonadism:** consider testosterone replacement.

**GH deficiency:** GH theoretically contraindicated due to active malignancy, although little clinical evidence

**Myocarditis** ([JACC 2018;71:1755](#)): rare but serious AE a/w high mortality (46% in severe myocarditis); risk higher w/combo tx

- Timing:** generally within 3mo ([Oncologist 2018;23:874](#); [Lancet 2018;391:933](#))
- S/Sx:** heart failure, arrhythmia (high grade AV block, ventricular tachycardia)
- Dx:** EKG/tele; troponin, NT-proBNP, TTE; **endomyocardial Bx**.
- Tx:** discontinuation of ICI; high dose or pulse-dose steroids (1g IV, then PO pred 1mg/kg) ([J Am Heart Assoc 2020;9:2](#)); 2<sup>nd</sup>-line consider ATG/IVIg or infliximab/MMF/tacro ([Oncologist 2018;23:879](#)). GDMT for HFrEF. PPM for new conduction delay.

**Other irAEs** ([JCO 2019;36:1714](#))

Inflammatory arthritis, nephritis, hepatitis, myasthenia gravis, Guillain-Barré, peripheral neuropathy, autonomic neuropathy, aseptic meningitis, encephalitis, AIHA, ITP, TTP/HUS, aplastic anemia, acquired hemophilia, pericarditis, uveitis/iritis, episcleritis, blepharitis

# Oncology

# Oncologic Emergencies

## TUMOR LYSIS SYNDROME ([NEJM 2011;364:1844](#); [JCO 2008;26:2767](#))

- **Pathophys:** TLS 2/2 tx initiation or spontaneous in cancers w/ high turnover → release of intracellular metabolites (i.e. uric acid, K+, phos) → AKI (uric acid causes renal vasoconstriction, precipitates in tubules), seizure, CaPhos crystal deposition ( $\uparrow$  phos →  $\downarrow$  Ca)
- **Presentation:**  $\downarrow$  UOP, weakness/cramps/tetany, seizure, arrhythmia
- **Risk factors:** high risk: ALL/AML (WBC  $\geq 100k$ ), CLL (on venetoclax &  $\uparrow$  uric acid), stage 3/4 Burkitt/lymphoblastic NHL, bulky DLBCL; intermediate risk: ALL (WBC  $< 100k$ ), AML (WBC 25-100k or  $< 25k$  &  $\uparrow$  LDH), Burkitt, DLBCL, CLL (chemo-specific &  $\uparrow$  WBC), rare chemo-sens bulky solid tumor; low risk: HL, indolent NHL, CML, CLL (on alkylating tx & WBC  $< 50k$ ), MM
  - High risk substrate: WBC  $> 50k$ , LDH  $> 2x$  ULN, bulky tumor ( $> 10$ cm), hypovolemia, uric acid  $> 7.5$ , renal failure
- **Labs/workup:** BMP (electrolytes, Cr, iCa), Mg, phos (calculate Ca-phos product), uric acid, LDH, CBC/diff, ECG
- **Diagnosis (Cairo-Bishop criteria):**
  - Laboratory diagnosis:  $\geq 2$  criteria within 3d before or 7d after cytotoxic therapy: uric acid  $\geq 8$ mg/dL, K  $\geq 6$ mEq/L, phos  $\geq 4.5$ mg/dL, or Ca  $\leq 7$ mg/dL. Criteria also satisfied if 25% change from baseline.
  - Clinical diagnosis: laboratory dx &  $\geq 1$  clinical criteria: Cr  $1.5x$  ULN, arrhythmia, or seizure
- **Prophylaxis and treatment:** while treating, labs q2-4h & telemetry (electrolyte abnormalities)
  - **Hydration:** 2-3L/m<sup>2</sup> per day. D5-1/2NS or NS if hyponatremic/hypovolemic. Maintain **UOP  $\geq 100$ cc/hr** for excretion of uric acid and phos; diuretics PRN (prefer loops to  $\downarrow$  K) to maintain UOP and treat hypervolemia
  - **Urinary alkalization:** w/ NaHCO<sub>3</sub>, only indicated if metabolic acidosis, contraindicated in hyperphos ( $\uparrow$  CaPhos precip)
  - **Treat abnl electrolytes:** hyperK tx, phos binders, **delay tx of hypoCa** until phos nml or severe sx to avoid  $\uparrow$  CaPhos precip
  - **Allopurinol** ( $\downarrow$  uric acid formation): 300-600mg/day (adjust dose if renal dysfunction)
    - $\downarrow$  clearance of other meds (cyclophosphamide, MTX, 6-MP, azathioprine, ampicillin)
    - *HLA-B\*5801*  $\uparrow$  prev. in Southeast Asian, black pts,  $\uparrow$  risk of SJS/TEN, consider testing ([ACR guidelines](#)) + alternative tx
  - **Rasburicase** ( $\uparrow$  uric acid clearance; discuss w/ attending): 0.2mg/kg IV (but 3-6mg IV usually effective), administer if high risk, baseline renal failure,  $\uparrow$  baseline or rising uric acid or Cr despite allopurinol/saline, or cannot hydrate (volume overload)
    - Risk of anaphylaxis, methemoglobinemia. Contraindicated in G6PD deficient (can cause hemolysis); **check G6PD early**
  - **Renal replacement therapy:** indicated if Ca-phos product  $\geq 70$ mg<sup>2</sup>/dL<sup>2</sup> (albumin-corrected Ca  $\times$  phos)

## HYPERVISCOSITY SYNDROME/LEUKOSTASIS ([Blood 2012;119:2205](#); [Blood 2018;132:1379](#))

- **Etiology:** (1) **hyperproteinemia** from monoclonal gammopathies (Waldenström's macroglobulinemia [IgM]  $>$  MM [IgG]) or polyclonal (cryoglobulins, HIV, Sjögren's,  $\uparrow$  RF, IgG4, IVIg or rituximab) (2) **hyperleukocytosis/leukostasis** seen in AML/ALL with blasts  $> 50k$  (leukostasis rare in CLL unless very high counts  $> 400k$  WBC) (3) **other**: polycythemia vera, sickle cell, spherocytosis
- **S/Sx:** pulm (SOB, infiltrates) & CNS (blurry vision 2/2 retinal vein engorgement, HA, dizziness, ataxia, confusion, coma), fever, epistaxis → page **Heme/Onc fellow & Clin Path resident for emergency viscosity study**, notify attending to discuss pheresis
- **Diagnosis:** serum viscosity ( $\uparrow$  Ostwald tube), SPEP, SFLC, **WBC** (often  $> 100k$ , but can be lower if AML/ALL blast crisis)
  - Lab artifacts from hyperleukocytosis: **spurious  $\uparrow$  K** (use blood gas K), **falsely low arterial pO<sub>2</sub>** (use pulse oximeter)
- **Treatment:** always start with plasma volume expansion with **IV NS**
  - **Hyperproteinemia:** **plasmapheresis** (aiming for resolution of symptoms); reduces viscosity by 20-30% per session
  - **Leukostasis:** **leukapheresis**; cytoreduce (**hydroxyurea**); **induction chemo**; avoid RBC & plt transfusion ( $\uparrow$  viscosity)

## METASTATIC EPIDURAL SPINAL CORD COMPRESSION ([Seminars in Neurology 2010;30:245](#); [Lancet Neurology 2008;7:459](#))

- **Primary CA:** lung, prostate, breast  $>$  non-Hodgkin's lymphoma, renal cell, multiple myeloma, Hodgkin's lymphoma
- **Location:** T (60%)  $>$  L (25%)  $>$  C (15%); multiple sites in 30%; ESCC score for spinal level ([JNCCN 2016;14:70](#))
- **S/Sx:** **back pain** (usually 1<sup>st</sup> sx; radicular, localized, worse at night/recumbent/Valsalva) → weakness, gait instability → sensory deficits (saddle anesthesia in cauda equina lesions), bowel/bladder dysfunction (urinary retention, incontinence)
- **Exam:** pain precedes other sx by ~7w, weakness/ataxia, paresthesia,  $\uparrow$  reflexes,  $\oplus$  Babinski,  $\downarrow$  anal sphincter tone
- **Diagnosis:** STAT total spine MRI with cord compression/metastasis protocol, CT myelography if MRI not possible
- **Treatment:** call Spine Surgery & Radiation Oncology ASAP → more effective than chemo (except for heme, germ cell malignancies)
  - Neuro deficits/pain: **dexamethasone 10mg x1 IV**, then 16mg PO daily (divided), taper once definitive tx

## BRAIN METASTASES WITH INCREASED INTRACRANIAL PRESSURE ([Ann Palliat Med 2015;4:225](#); [JCO 2015;33:3475](#))

- Intracranial tumors present in ~10-30% of patients with metastatic disease; call Neurosurgery & Radiation Oncology
- **Primary CA:** lung  $>$  breast  $>$  melanoma  $>$  RCC, osteosarcoma, head and neck, thyroid, colorectal
- **S/Sx:** HA (40-50%; "tension", bifrontal, worse w/ Valsalva and forward bending, n/v), focal neuro deficits (20-40%, hemiparesis most common), cognitive dysfunction (30-35%), new onset seizures (10-20%), stroke (5-10%)
- **Diagnosis:** MRI w/ contrast  $>$  non-enhanced MRI or CT with contrast
- **Treatment:** control vasogenic edema (**dexamethasone 10mg IV x1, then 8mg IV/PO BID**), consider AED (usually not recommended for 1° ppx); avoid AC if concern for active hemorrhage; definitive treatment will  $\downarrow$  local recurrence: for multiple mets, stereotactic radiosurgery  $>$  whole-brain XRT ( $\uparrow$  neurocognitive impairment can be mitigated w/ hippocampal avoidance/memantine)  $>$  surgery

## SUPERIOR VENA CAVA (SVC) SYNDROME ([NEJM 2007;356:1862](#); [Mayo CP 2017;92:609](#))

- **Etiology:** external compression of SVC from mediastinal mass (commonly lung CA or NHL) causing  $\uparrow$  upper body venous pressure
- **Symptoms:** cerebral edema (HA, confusion, herniation), narrowing of larynx/pharynx (dyspnea, stridor, cough, dysphagia, hoarseness), head/neck swelling (visually striking, often not clinically significant), hemodynamic instability ( $\downarrow$  venous return)
- **Diagnosis:** CT venography (SVC syndrome protocol), **obtain/ensure tissue diagnosis ASAP to guide definitive tx**
- **Treatment:** secure airway, RT/chemo, intravascular stent (emergent/refractory), steroids (stridor/resp distress only, d/w attending)

## DEFINITIONS AND ETIOLOGY ([J Oncol Pract 2019;15:19](#); [NCCN Prevention and Treatment Guidelines](#))

- **Definition:**  $T \geq 100.4$  with  $ANC < 500 \text{ cells/mL}$  or expected to decrease to  $< 500$  over the next 48h
  - Functional neutropenia: defective PMNs, common in leukemia ( $\downarrow$  neutrophil function despite  $ANC > 500$ )
- **Microbiology:** ~30% have infectious source identified; others attributed to translocation of intestinal bacteria
  - When organisms identified: 40% 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  $\downarrow ANC$ , broad-spectrum abx use, or TPN

## EVALUATION

- **H&P:** prior micro data, time since last chemo, recent antibiotic therapy/ppx, major comorbid illness, use of devices
- **Exam:** mouth (mucositis), skin, perineum/rectal (**visual inspection, avoid DRE**), indwelling lines/port (erythema/tenderness)
- **Studies:** BCx x2+ sites ( $\geq 1$  periph, 1 per CVC lumen), UA/UCx, CXR, SCx/GS, resp viral panel/COVID-19 PCR, CMV PCR (SCT)
  - **Fungal markers:** LDH,  $\beta$ -D-glucan; galactomannan if high risk for Aspergillus (SCT, GVHD, neutropenia  $> 10-14d$ )
- **Further site-specific studies to consider:**
  - **GI symptoms:** CT A/P (evaluate for neutropenic colitis/typhlitis); stool culture, O&P, C. diff if diarrhea
  - **Pulmonary symptoms:** CT chest  $\pm$  bronch/BAL (especially if prolonged F&N)
  - **Headache/sinus pain:** CT face/sinus
- **Risk stratification:** ([J Oncol Pract 2019;15:19](#); [NCCN Prevention and Treatment Guidelines](#))
  - **MASCC Risk Index** ([JCO 2000;18:3038](#)) and **CISNE** ([JCO 2015;33:465](#)) can measure risk of F&N-related complications
  - **High risk:** anticipated  $ANC \leq 100$  for  $\geq 7d$ , inpt status, co-morbidities/infections (renal/hepatic impairment, PNA, central line infxn), allogeneic HCT, mucositis grade 3-4, alemtuzumab use within past 2mo  $\rightarrow$  inpatient management
  - **Low risk** ([JCO 2018;36:1443](#)): anticipated  $ANC \leq 100$  for  $< 7d$ , no co-morbidities, good performance status (ECOG 0-1), strong home social support  $\rightarrow$  treated with PO antibiotics after brief inpatient stay versus strictly outpatient

## TREATMENT/PROPHYLAXIS

- **MGH Guideline:** Alternate guidelines: ([NCCN guidelines](#), [Clin Infect Dis 2011;15:e56](#), [J Oncol Pract 2018;14\(4\):250](#))
- **Empiric abx:** within 1h; up to 70% mortality if delayed abx ([Antimicrob Agents Chemother 2014;58:3799](#))
  - **Gram-negatives (PsA dosing):** broad Gram-negative coverage (including PsA) within 60min of presentation
    - **Cefepime 2g q8h** (or ceftazidime 2g q8h), pip/tazo 4.5g q6h, or meropenem 1g q8h
    - **PCN allergy:** confirm allergy; use [Penicillin Hypersensitivity Pathway](#) and test-dose cefepime or meropenem; consider allergy consult. If true allergy, use aztreonam (avoid in ceftazidime allergy) + levofloxacin
    - **High-risk ESBL:** meropenem 1g q8h (2g q8h if meningitis)
    - **Low risk:** IV  $\rightarrow$  PO regimen (discuss w/ attending); cipro/levoflox + amox-clav vs clinda (if PCN allergy); avoid if prior FQ ppx
  - **Gram-positives:**
    - First line: vanc; VRE: daptomycin (unless pulmonary process, inactivated by surfactant) or linezolid
    - **Indications:** HoTN/severe sepsis, GPC bacteremia, catheter-related infxn (rigors with infusion, erythema on exam), SSTI, PNA on imaging, MRSA colonization (esp in HCT), severe mucositis + prior FQ ppx + GNR coverage with ceftaz
    - **Vancomycin is NOT part of FN empiric regimen** ([JAC 2005;55:436](#); [Clin Infect Dis 2011;52:56](#)), consider w/ suspicion as above
  - **Anaerobes:**
    - **Indications:** intra-abd source, C. diff, oral ulcer/periodontal infxn, post-obstructive PNA, necrotizing ulceration
  - **Fungi:**
    - **Indications:** F&N  $> 4-7d$  despite abx,  $\oplus$  fungal biomarkers,  $\oplus$  CT chest (circumscribed, air crescent, cavity),  $\oplus$  BAL Cx
    - Micafungin 100mg q24h or Amphotericin 3mg/kg (admin after 500cc NS)
- **Modification/duration:** Note recommended duration of empiric therapy varies between guidelines ([Ther Adv Infect Dis 2022;9](#))
  - **Resolution of fever:**
    - **Documented infxn:** narrow abx and tx for recommended course, then switch to FQ ppx until  $ANC > 500$
    - **Culture negative:** continue empiric treatment until afebrile &  $ANC > 500$  vs narrow to FQ ppx if afebrile x4-5d
  - **Fever continues  $> 4-7d$ :**
    - **Clinically stable:** do not broaden abx or add vanc, consider other causes (e.g. engraftment, differentiation, GVHD, TLS, drug fever, thrombophlebitis, hematoma, hepatosplenic candidiasis), discuss w/ ID
    - **Clinically worsening:** broaden abx  $\pm$  fungal coverage, consider CT chest  $\pm$  bronch to evaluate for fungal infxn
  - **Catheter-associated infection:** also see [Bloodstream Infections & Endocarditis](#)
    - **Coag-negative staph, non-VRE Enterococcus:** can keep line if IV abx + abx lock x2w
    - **Staph aureus, PsA, fungi:** must remove line. For gram negative, d/w ID/attending, consider line removal vs. lock therapy
    - **Complicated infxn:** (endocarditis, septic thrombosis, bacteremia/fungemia  $> 72h$ ), remove line, abx x4-6w
- **Prophylaxis:**
  - **Anti-microbial ppx:** refer to NCCN guidelines for more specific indications, also see [Hematopoietic Cell Transplantation](#)
    - **Antibacterial (FQs):** high-risk pts (heme malignancy) and attending discretion for intermediate-risk pts
    - **Antifungal (azole vs echinocandin):** select heme malignancies during neutropenia and early post-alloHCT
    - **PJP (TMP-SMX, atovaquone):** if  $\geq 20\text{mg}$  prednisone daily for  $\geq 1\text{mo}$ , purine analog, bendamustine, post-CAR T, or post-HCT
    - **HSV/VZV (acyclovir vs famciclovir):** heme malignancy on therapy, post-CAR T, or post-HCT (1-2 years)
  - **G-CSF:** ppx reduces incidence and duration of FN when risk  $> 20\%$  but does NOT decrease mortality ([JCO 2006;24:3187](#)); consider adding if critically ill, anticipated prolonged neutropenia, PTLD, or HIV. Caution if leukemia (d/w attending)

# Oncology

# Inpatient Leukemia & Lymphoma Regimens

Regimen*	Protocol	Supportive Care
	Leukemia	
Decitabine (5-aza-2'-deoxycytidine, Dacogen)  28-day or 42-day cycle until disease progression or toxicity	<b>MDS/AML:</b> 20 mg/m <sup>2</sup> IV over 60 minutes daily on Days 1-5  <b>AML with unfavorable cytogenetic and/or TP53 mutation:</b> 20 mg/m <sup>2</sup> IV over 60 minutes daily on Days 1-10	<b>Premedication:</b> PPx or tx symptoms with bowel regimen, antidiarrheals, IVF and/or electrolyte replacement <b>Emetic Risk:</b> Minimal-to-low; PRN for breakthrough <b>Neutropenia Risk:</b> Moderate <b>Growth Factor:</b> Filgrastim or Pegfilgrastim until count recovery
5-Azacytidine (5-Aza, Azacytidine, Vidaza, Azadine, Onureg)  28-day cycle until disease progression or toxicity	<b>AML:</b> 300mg PO qday on D1-14  <b>MDS:</b> Cycle 1: 75mg/m <sup>2</sup> /day for D1-7; Subsequent Cycles: 75 mg/m <sup>2</sup> /day q4weeks (Dose may be increased to 100 mg/m <sup>2</sup> /day if no benefit after 2 cycles)	<b>Premedication:</b> During first 2 PO cycles, administer an antiemetic 30 min prior to each dose; antiemetic ppx may be omitted after 2 cycles if no n/v <b>Emetic Risk:</b> Moderate, Cycle 1-2 <b>Neutropenia Risk:</b> Moderate <b>Growth Factor:</b> Filgrastim or Pegfilgrastim until count recovery
HiDAC (High-Dose ara-C)  (ara-C, Cytarabine)	<b>Consolidation:</b> <b>HiDAC:</b> 1.5-3 g/m <sup>2</sup> over 3h q12h on Day 1, 3, 5 -OR- Day 1, 2, 3 for 3-4 cycles	<b>Premedication:</b> Corticosteroid eye drops throughout consolidation <b>Emetic Risk:</b> Moderate <b>Neutropenia Risk:</b> Moderate <b>Growth Factor:</b> Filgrastim or Pegfilgrastim until count recovery
Hyper-CVAD  <u>Dose-intensive phase:</u> 8 cycles of Hyper-CVAD alternating with High-Dose Methotrexate and Cytarabine (HD MTX-ara-C) + intrathecal (IT) PPx each cycle for 16 IT treatments.  <u>Maintenance phase:</u> Dependent upon clinical response	<b>Hyperfractionated Cyclophosphamide (CP):</b> 300 mg/m <sup>2</sup> IV over 3h q12h for 6 doses on days 1-3, given with Mesna 600 mg/m <sup>2</sup> as continuous infusion ending 6h after last dose <b>Vincristine:</b> 2 mg IV Days 4 and 11 <b>Doxorubicin:</b> 50 mg/m <sup>2</sup> IV on Day 4 <b>Dexamethasone:</b> 40 mg daily on Days 1-4; 11-14  <b>HD MTX-ara-C:</b> <b>MTX:</b> 200 mg/m <sup>2</sup> IV over 2h followed by 800 mg/m <sup>2</sup> IV over 24h on Day 1; Leucovorin rescue starting 24h after completion MTX; dose according to MTX level <b>ara-C:</b> 3 g/m <sup>2</sup> over 2h q12h x 4 on Days 2-3 <b>Methylprednisolone:</b> 50 mg IV twice daily Days 1-3  <b>CNS PPx:</b> <i>Risk-stratified CNS ppx with alternating intrathecal (IT) high-dose methotrexate (MTX) and cytarabine (Ara-C)</i> <b>MTX:</b> 12 mg IT on Day 2 <b>ara-C:</b> 100 mg IT on Day 8	<b>Premedication:</b> NS 100mL/hr prior to chemotherapy. Continue through cyclophosphamide <b>Emetic Risk:</b> Day 1-5, high <b>Neutropenia Risk:</b> High; Median times to granulocyte and platelet recovery were 18 and 21 days, respectively <b>Growth Factor:</b> Filgrastim or Pegfilgrastim on Day 5 (24h after chemotherapy)
ATRA/ATO  <u>Induction:</u> ATRA should be continued until CR is achieved. Restage with BM aspirate and biopsy on Day 28	<b>Induction:</b> <b>All-Trans Retinoic Acid (ATRA):</b> 45 mg/m <sup>2</sup> in divided doses daily, starting Day 1. <i>Start ATRA upon first suspicion of APL</i> <b>Arsenic trioxide (ATO):</b> 0.15 mg/kg IV daily, starting after cytogenetics confirmation  <b>Consolidation:</b> <b>ATRA:</b> 45 mg/m <sup>2</sup> /d for 2 weeks q4weeks for a total of 7 cycles <b>ATO:</b> 0.15 mg/kg IV 5d/wk for 4 weeks q8weeks for a total of 4 cycles	<b>Premedication:</b> none <b>Emetic Risk:</b> Moderate <b>Neutropenia Risk:</b> High <b>Differentiation Syndrome:</b> maintain a high index of suspicion (fever; WBC >10k; SOB; hypoxemia; pleural or pericardial effusions). Discuss steroid use with attending, supportive <b>Growth Factor:</b> Myeloid growth factors should not be used during induction. May be considered during consolidation for life-threatening infection, sepsis, etc.
Hydroxyurea (Hydrea; HU)	<b>HU:</b> Starting dose 500 mg BID or 1000 mg QD; dose adjusted to ANC 500-1000; cytoreduction and WBC count goal based on disease and therapy regimen	<b>Premedication:</b> none <b>Emetic Risk:</b> Minimal-to-low <b>Neutropenia Risk:</b> Moderate <b>Growth Factor:</b> count recovery within days of stopping agent

Lymphoma		
R-CHOP  14-day cycle, restage after 2-4 cycles, total 3-6 cycles +/- radiation	<b>Rituximab:</b> 375 mg/m <sup>2</sup> IV Day 1 <b>Cyclophosphamide:</b> 750 mg/m <sup>2</sup> IV over 30 min Day 1, combined oral and IV hydration 2-3L on day of chemo <b>Doxorubicin:</b> 50 mg/m <sup>2</sup> IV Day 1 <b>Vincristine:</b> 1.4 mg/m <sup>2</sup> (max 2 mg) IV over 5-10 min Day 1 <b>Prednisone:</b> 100 mg PO Days 1-5  <b>CNS PPx:</b> 4-8 doses of IT MTX and/or cytarabine or high-dose MTX during the course of treatment	<b>Premedication:</b> Diphenhydramine and acetaminophen prior to rituximab <b>Emetic Risk:</b> Day 1, high <b>Neutropenia Risk:</b> High <b>Growth Factor:</b> Filgrastim or Pegfilgrastim on Day 6 or 3-4 days after completion of chemotherapy until count recovery
Dose-Adjusted R-EPOCH  21-day cycle, 6 cycles (dose adjustments based on ANC counts from BID CBC during previous cycle)	<b>Rituximab:</b> 375 mg/m <sup>2</sup> IV Day 1 <b>Etoposide:</b> 50 mg/m <sup>2</sup> infusion over 24h daily on Days 1-4 <b>Doxorubicin:</b> 10 mg/m <sup>2</sup> continuous infusion over 24 hours daily on Days 1-4 <b>Vincristine:</b> 0.4 mg/m <sup>2</sup> continuous infusion over 24 hours daily on Days 1-4 <b>Cyclophosphamide:</b> 750 mg/m <sup>2</sup> IV over 30 min Day 5, combined oral and IV hydration 2-3L on day of chemo <b>Prednisone:</b> 60 mg PO BID Days 1-5  <b>CNS PPx:</b> 4-8 doses of IT MTX and/or cytarabine or high-dose MTX during the course of treatment	<b>Premedication:</b> Diphenhydramine and acetaminophen prior to rituximab <b>Emetic Risk:</b> Days 1-5, high <b>Neutropenia Risk:</b> High <b>Growth Factor:</b> Filgrastim or Pegfilgrastim after completion of chemotherapy until count recovery
R-ICE  14-day cycle, 3 cycles	<b>Rituximab:</b> 375 mg/m <sup>2</sup> IV Day 1 <b>Ifosfamide:</b> 5,000 mg/m <sup>2</sup> IV continuous infusion over 24h on Day 2 with NS at 1.5-3 ml/kg/hr beginning 2 hours prior and ending 2-4h after infusion <b>Mesna:</b> 5,000 mg/m <sup>2</sup> IV infusion over 24h on Day 2 <b>Carboplatin:</b> Dose ~ AUC 5 IV over 30 minutes on Day 2 <b>Etoposide:</b> 100 mg/m <sup>2</sup> daily on Days 1-3	<b>Premedication:</b> Diphenhydramine and acetaminophen prior to rituximab <b>Emetic Risk:</b> Day 1, 3 – Low; Day 2 High <b>Neutropenia Risk:</b> High <b>Growth Factor:</b> Filgrastim or Pegfilgrastim on Day 4 or 3-4 days after completion of chemotherapy until count recovery
ICE	See R-ICE above, hold rituximab	
R-DHAOx  21-day cycle	<b>Rituximab:</b> 375 mg/m <sup>2</sup> IV Day 1 <b>Dexamethasone:</b> 40 mg PO daily on Days 1-4 <b>Cytarabine:</b> 2,000 mg/m <sup>2</sup> IV Day 2 (2 doses) <b>Oxaliplatin:</b> 130 mg/m <sup>2</sup> IV over 2 hours on Day 1	<b>Premedication:</b> Diphenhydramine and acetaminophen prior to rituximab <b>Emetic Risk:</b> Moderate <b>Neutropenia Risk:</b> High <b>Growth Factor:</b> Filgrastim or Pegfilgrastim on Day 5 or 3-4 days after completion of chemotherapy until count recovery
R-Bendamustine  28-day cycle, 6 cycles	<b>Rituximab:</b> 375 mg/m <sup>2</sup> IV Day 1 <b>Bendamustine:</b> 90 mg/m <sup>2</sup> IV over 10 minutes or IV over 30 minutes daily on Days 1-2, CVC recommended for administration	<b>Premedication:</b> Diphenhydramine and acetaminophen prior to rituximab <b>Emetic Risk:</b> Moderate, Day 1-2 <b>Neutropenia Risk:</b> High
High-dose Methotrexate (MTX)  Dependent on chemotherapy regimen and count-recovery for 1-8 cycles	<b>CNS PPx:</b> <b>MTX:</b> 3,000-3,500 mg/m <sup>2</sup> over 4h on Day 1 on alternate days of chemotherapy regimen <b>Leucovorin:</b> 25 mg IV over 15 minutes or PO on Day 2 starting 24h from initiation of MTX and q6h until MTX < 0.05 uM.	<b>Hydration:</b> Alkaline hydration with 5% Dextrose in sodium bicarbonate 100 mEq/L at 150 cc/hr 4 hours prior until 72 hours after completion of MTX infusion <b>Emetic Risk:</b> Days of MTX, moderate <b>Neutropenia Risk:</b> High <b>Growth Factor:</b> Filgrastim or Pegfilgrastim on Day 4 or 3-4 days after completion of chemotherapy until count recovery

\*Chemo regimens may be modified based on genetics, risk stratification level, cardiac history, QTc prolongation. For further details on stratification and protocol details see [NCCN.org](http://NCCN.org)

# Geriatrics & Palliative Care

# Pain Management

## GENERAL APPROACH TO PAIN MANAGEMENT ([NEJM 2015;373:2549](#); [Lancet 2011;377:2236](#); [Fast Facts app for pearls](#))

- Pain history and etiology can guide therapy. Goal is to maximize level of functioning and quality of life.
- Step-wise approach to pain management: ([WHO Guidelines](#); [CDC guidelines](#); [DFCI Pink Book](#))
  - Mild to moderate pain: non-opioids and adjuvants
    - Acetaminophen: max dose 4g daily, 2-3g safe in liver disease ([Br J Clin Pharmacol. 2016;81:210](#))
    - NSAIDs: celecoxib best if ↑GIB risk, ketorolac if severe pain [10 –15 mg recommended, no added analgesia with higher doses ([Am Fam Phys 2017;96:262](#)]), use with caution in CAD, renal disease, IBD]
  - Moderate to severe pain: schedule non-opioid options, try topicals, then consider short-acting opioids PRN
  - Severe pain: requiring round-the-clock opioids. Discuss w/ attending, consider adding extended release (ER) meds
    - Avoid ER opioids if pain source is expected to resolve (e.g., bone fracture, hematoma, abscess, post-procedural)
- “Basal-bolus” strategy: Obtain basal level of pain control throughout the day with scheduled oral doses + PRNs for breakthrough pain

## PAIN ARCHETYPES AND USEFUL ADJUVANT ANALGESICS

- Somatic/musculoskeletal: easily localized, sharp, aching, gnawing
  - Bony pain: high dose NSAIDs or steroids\*. Consider palliative XRT (if cancer-related) or surgery
  - Muscle spasm: topical lidocaine, capsaicin, methyl salicylate-menthol ointment; muscle relaxants (cyclobenzaprine, baclofen, tizanidine (*watch for sedation & delirium*))
- Visceral: deep tissues and internal organs, vague, referred or difficult to localize
  - Visceral distension (e.g., hepatic capsular stretch from liver mets, malignant bowel obstruction): depends on etiology but steroids\* can be helpful. Can consider plexus block with Chronic Pain
- Inflammatory: associated with other signs of inflammation (swelling, erythema, warmth)
  - NSAIDs (systemic or topical), steroids\*
- Neuropathic: burning, stinging, allodynia, hyperalgesia
  - Topical capsaicin, camphor/menthol, lidocaine, diclofenac gel
  - Pregabalin, gabapentin, clonidine, SNRIs (duloxetine, venlafaxine), TCAs (amitriptyline, nortriptyline, desipramine)
- Non-pharmacologics: PT/exercise/activity, heat or ice, CBT, treating comorbid psych dx, massage, acupuncture, other integrative therapies (note: for inpatient, massage and acupuncture currently only available for heme and onc patients)

\*Considerations with steroids: in cancer patients, may interfere with treatment (e.g immunotherapy) and/or diagnostics. If prolonged course, will need GI and PJP ppx; determine who will manage taper plan at discharge

## OPIOIDS ([CDC app for guidelines & MME calculator](#))

- Opioid-tolerant defined as total daily dose (TDD) x7d: morphine 60mg/oxycodone 30mg/hydromorphone 8mg/fentanyl 25mcg/h
- Patients on buprenorphine/methadone for OUD, or active non-Rx OUD → treat pain w/ full agonists if needed, See [OUD & Withdrawal](#) for strategies for each scenario. Can consult ACT if needed for assistance.
- Avoid using combo pills (limits titration flexibility). See Opioid Pharmacokinetics Chart for sample initial dosing.

## OPIOID PHARMACOKINETICS CHART

	Route	Sample Initial PRN Doses* (dose reduce ~50% for elderly)	Onset (min)	Peak Effect (min)	Duration of Effect (hr)	Clearance/Metabolites**
Morphine	IV	2-4mg q3-4h prn	5-10	10-30	3-5	AVOID in renal disease
	PO	7.5-15mg q3-4h prn	15-60	90-120	4	
HYDROmorphine	IV	0.2-0.4mg q3-4h prn	5-20	15-30	3-4	Safer in renal and liver disease
	PO	2-4mg q3-4h prn	15-30	90-120	4-6	
OxyCODONE	PO	5-10mg q3-4h prn	15-30	30-60	4-6	2 <sup>nd</sup> line for renal disease
FentaNYL	IV	25-50mcg q15-30m prn	<1	5-7	45m to 2+ hr	Safer in renal and liver disease
Methadone	IV	Consult pain and/or pall care	10-20	60-120	4-6	Safer in renal and liver disease
	PO		30-60	90-120	4-12	

\* For opioid naïve patients in moderate or severe pain. If opioid tolerant, consider home PO breakthrough dose or 10-20% of ER dose

\*\*If concern for hepatic or renal metabolism, would use wider dosing intervals and be more cautious with uptitration

## METHADONE AND FENTANYL: initiate with assistance of Palliative Care or Pain consult

- Methadone: both a mu agonist and NMDA antagonist
  - Beneficial in neuropathic pain
  - Cannot be converted linearly from other opioids
  - Safety concerns: bimodal short and long half-life (up to 150 hours), QTc prolongation (monitor K, Mg)
  - TID dosing for pain vs daily for OUD
  - Takes several days to reach steady state. Would not titrate more frequently than every 4-5 days
- Fentanyl:
  - Safer in both liver and renal dysfunction
  - Safety concerns: must remove patch if febrile (cutaneous vasodilation → faster transdermal absorption)
  - Less effective in cachexia (less subq fat for absorption)
  - Requires 18-24h to reach therapeutic level (patch)

## OPIOID UPTITRATION/ROTATION

- No max dose. Goal is to find minimum dose needed to control sx w/ minimal SE
- If pain only moderately controlled with scheduled doses (not in pain crisis), ↑ total daily dose by 30-50%
- If taking ER opioid and needing >3-4 rescue doses daily, ↑ ER dose by 50-100% of total rescue dose used in past 24h
- Rotate opioids if side effects, dose reduce by 25-50% when rotating

## CONVERTING OPIOIDS

Ex: Pt takes morphine ER 60mg PO q12h + morphine IR 15mg PO breakthrough doses 2x/ day

### Step 1) Calculate total daily opioid requirement

$$TDD = (60\text{mg} \times 2 \text{ doses}) + (15\text{mg} \times 2 \text{ doses}) = 150\text{mg morphine}$$

### Step 2) Convert TDD to equivalent dose of new opioid

$$\frac{30\text{mg morphine}}{20\text{mg oxycodone}} = \frac{150\text{mg morphine}}{x} \quad x = 100\text{mg oxycodone}$$

### Step 3) Reduce dose by 25-50% to account for incomplete cross-tolerance

$$\rightarrow \sim 60\text{mg oxycodone total daily dose}$$

### Step 4) Divide TDD by number of doses per day

- If initiating or converting to long-acting opioid, divide TDD into ER doses and add breakthrough dose (10-20% of TDD of ER opioid)

Final dose: oxycodone ER 30 mg q12h with 10 mg oxycodone q4h prn breakthrough

Opioid Equianalgesic Doses		
Drug	PO (mg)	IV (mg)
Morphine	30	10
OxyCODONE	20	n/a
HYDROcodone	20	n/a
HYDROMorphone	7.5	1.5
FentaNYL*	n/a	0.1 (100 mcg)
Fentanyl patch (mcg/hr)	Morphine PO (mg/day)	
25	50	

\*Use caution converting to fentanyl (short duration of action)

## PAIN CRISIS MANAGEMENT

Severe worsening of pain; while treating, pursue reasonable diagnostic workup for etiology (e.g., bowel perforation/peritonitis, procedural complication, bleeding). **Goal is reduction in pain score by at least 50%**. In sickle cell disease VOE, **follow patient's guidance/acute care plan**; opioid needs may be higher due to lifelong course of disease.

- 1) **Opioid-naïve:** give morphine IV 2-5mg or hydromorphone IV 0.2-0.4mg bolus dose  
**Opioid-tolerant:** convert usual breakthrough PO dose or 10-20% of total daily ER dose to IV and administer
- 2) Assess for response after 15min:
  - o No pain relief and no side effects → increase dose by 50-100%
  - o Minimal relief and no side effects (<50% reduction in pain score) → repeat the same dose
  - o Pain reduced >50% and no side effects → reassess in 2-3h, use this dose as new breakthrough dose
  - o Side effects with no pain relief → rotate to different IV opioid (no dose reduction if uncontrolled pain)

## PATIENT-CONTROLLED ANALGESIA (PCA)

- Appropriate for patients who are alert & oriented and able to use equipment. Families may NOT use PCA by proxy at MGH
- Quickest relief if episodes sudden and severe (pain onset prior to drug administration; do not have to call/wait)
- Can reduce burden on nursing for patients who need frequent administration of pain medications (generally q1-2h is the most frequent a PRN can be ordered on the floor)
- Medicine residents can order "General PCA" (for opioid-naïve patients) or "High Risk PCA" (BMI >40, hx OSA, RASS -2 to -5, age >65). If opioid-tolerant, requiring continuous infusion, or pain difficult to control, consult Palliative Care or Pain (may consider low dose naloxone gtt with PCA for reduced nausea and pruritis without reducing analgesic effect)

General Opioid-Naïve PCA Dosing		
	Morphine	Hydromorphone
<b>Patient Administered (PCA) Dose</b>	1.5mg	0.2mg
<b>Lockout Interval (in minutes)</b>	10-15min	10-15min
<b>One-Hour Dose Limit</b>	6mg	1.4mg
<b>RN/Clinician Bolus Dose (for breakthrough)</b>	2mg q30min PRN	0.3mg q20min PRN
<b>Continuous Infusion Rate</b>	0mg/hr	0mg/hr

## ADVERSE EFFECTS OF OPIOIDS AND MANAGEMENT

- **Respiratory depression:** hold opioid, consider low doses of naloxone but CAUTION if on high dose ER opioids
  - o Dilute 0.4mg naloxone (1ml) in 9ml saline, give 1-2ml q2min until ↑RR or mental status improves
  - o Naloxone half-life is shorter than many opioids, watch for **recurrence** of resp depression and consider naloxone gtt
  - o All patients being discharged on opioids should also be given a naloxone prescription
- Respiratory depression occurs AFTER opioid-induced sedation; watch out for sedation in patients receiving opioids
- **Constipation:** ALWAYS start **standing senna and/or Miralax** when initiating opioids; use other laxatives if needed; methylnaltrexone QOD if failed laxative therapy (but can cause severe nausea and cramping; avoid if concern for GI obstruction)
- **Opioid-induced hyperalgesia:** seen with high doses leading to increased pain, consider rotating opioids and involving Palliative Care
- **Myoclonus:** reduce dose or rotate opioid, increase hydration/IVF; can give low dose BZD, baclofen, or gabapentin
- **Nausea/vomiting:** start prochlorperazine, metoclopramide, haloperidol; **avoid ondansetron** (constipating)
- **Pruritus:** mediated by mu receptor (not histamine – thus Benadryl ineffective, unless rash/allergic reaction); consider opioid rotation, ondansetron, nalbuphine 5mg IV q6h, or naloxone gtt
- **Sedation:** consider CNS stimulants (dextroamphetamine, methylphenidate although rarely prescribed)
- **Delirium:** reduce dose or rotate opioid; IV Haldol 1-2.5mg BID-QID or IV/PO Zyprexa 2.5-5mg PO QD-BID

# Geriatrics & Palliative Care

# Adv Care Planning & Code Status

## SERIOUS ILLNESS CONVERSATIONS

When? Preferably early in disease course as outpatient, or:

- New, progressive, or life-altering serious medical illness such as advanced cancer, ESRD, ESLD, HF, COPD
- Prognosis trigger: "Would I be surprised if this patient died in the next year?" ([J Palliat Med 2010;13:837](#)). Life expectancy <6mo ([UCSF calculator](#), [J Palliat Med 2012;15:175](#))
- Age >80 and hospitalized; see *Frailty and Polypharmacy*

Why? Ascertain how the patient wants to **live** and what they **value**. Can be used for the purposes of Advanced Care Planning, discussion of transition to hospice/CMO, or referral to palliative care (more than just code status)

How? Conversations can be planned or may happen spontaneously in any setting ([NEJM 2014;370:2506](#))

Preparation for planned meetings:

- Identify time and location to accommodate all meeting participants. Include patient and their preferred participants, primary team, RN, SW, and other providers as appropriate.
- **Pre-meet** with team, including subspecialty consultants, to discuss: **goals, unified assessment of clinical scenario, if a clinical decision needs to be made urgently, and if so, what are treatment options and team recommendations**
- If complex decisions/psychosocial issues/family conflict, consider palliative care consult

MGB Serious Illness Conversation (SIC Guide):

Step	Suggested Prompts
Open the conversation	"I'd like to talk about what is ahead with your health. Would that be ok?"
Assess prognostic awareness	"What is your understanding of your health?" "Looking to the future, what are your hopes about your health? What else?" "What are your worries? Tell me more."
Share worry	"Would it be ok if we talked more about what may lie ahead?" "I hear you're hoping for ____ and I worry the decline we've seen will continue" or "I worry something serious may happen in the next few wk/mth/ yrs." "It can be difficult to predict what will happen with your health."
Align	"I wish we didn't have to worry about this"
Explore what's important	"What gives you strength as you think about the future of your health?" "If your health worsens, what is most important to you?" "How much do your family or friends know about your priorities and wishes?"
Make a recommendation	"It sounds like ____ is very important to you." "Given what's important to you, I would recommend ____"

Document Serious Illness Conversation in Epic:

- Patient ID banner (top left of storyboard): click "Code: \_\_\_\_" → "Advance Care Planning Activity" → "Serious Illness Conversation" in left tab; fill out SIC form "Close"
- Open a note with type "Advance Care Planning" and use the dot phrase to insert the SIC → type .seriousillnesslast
- Consider filling out ACP forms if not already filled out (see Advanced Care Planning Forms)

## ADVANCE CARE PLANNING FORMS

- **Health Care Proxy (HCP)/medical power of attorney:** an advance directive document that designates a healthcare agent to make future medical decisions if patient loses capacity. Expressly authorized in MA by statute
  - *If no HCP:* surrogate hierarchy: see Section 3, bullet 6 of [MA: An Act Improving Medical Decision Making](#)
- **Living Will:** an advance directive document in which a competent person specifies future medical treatments in the event of incapacity (usually at end-of-life or if in a persistent vegetative state). Can be used as evidence of a person's wishes, but not considered to have legal authority (no MA statute that expressly authorizes)
- **MOLST** (MA Medical Orders for Life-Sustaining Treatment; pink form available on all medical units): medical orders for patients with advanced age or serious illness that documents preferences for CPR, intubation, hospital transfer, artificial nutrition, dialysis, and more
  - Transferrable to outside facilities; must complete MOLST prior to discharge to rehab/SNF if patient DNR/DNI
  - Remember that you **do not** have to fill out or discuss everything on the back page (clinical discretion)
  - Remember that these decisions **can be changed** (fill out a new MOLST if decisions change)
- **Links to existing MOLST/HCP forms** are found in Advance Care Planning Activity tab or scanned into the Media tab
  - If filling out a new form, provide patients with a copy and scan into Epic for future documentation

## CODE STATUS DISCUSSIONS

General Considerations

- Confirm directly with the patient/HCP, MOLST, and/or prior documentation by outpatient providers
- Readdress if a patient's clinical status changes, or if code status is deemed inappropriate for the clinical setting, but do *not* need to routinely readdress on admission if has been recently addressed by outpatient providers
- Code status ≠ ACP. Code status is a medical procedure for which harms/benefits should be weighed iso clinical context.
- Many procedural teams (i.e. cards, surgery) require temporary reversal of DNR/DNI periop, often 30d ([JAGS 2022;70:3378-3389](#)):

# Geriatrics & Palliative Care

# Adv Care Planning & Code Status

- If changing code status pre-op (i.e. TAVR), ensure your discharge documentation includes changing status back/date of conditional code status end
- If changing code status during early post-procedure or during chemotherapy, notify procedural team/primary oncologist

## Survival Outcomes ([Circulation 2019;139:e56](#))

- *Out-of-hospital cardiac arrest:* survival to hospital discharge 10.4%; survival with good neurologic function 9.9%
- *In-hospital cardiac arrest:* survival to discharge 25.6%; survival with good neurologic function 22%
  - Favorable prognostic factors: ACS, drug overdose, drug reaction (up to 40% survival)
  - Unfavorable factors: age >80 (<10% survival), multi-organ failure, sepsis, advanced cancer, ESRD, ESLD, dementia
  - Post-arrest complications: hypoxic-ischemic brain injury, rib fractures, pulmonary contusion, prolonged ICU care

Code status options:

Full Code	The patient would want all resuscitative measures to be used
DNR/Ok to Intubate	The patient would not want chest compressions but would want to be intubated in the event of impending respiratory failure
DNR/DNI	In the event of a pulseless cardiac arrest or respiratory failure, the patient would not want chest compressions or intubation
DNR/DNI/LLST Comfort Measures	The patient would want their care team to orient care around comfort only, and care not oriented around comfort may be withdrawn while still treating the patient's symptoms
<b>Do not offer "Full Code Except Do Not Intubate."</b> Cardiopulmonary arrest requiring CPR nearly always necessitates intubation, and thus this is not an appropriate code status.	

## Conducting Code Status Discussions ([JAMA 2012;307:917](#))

- Suggested framing: "CPR is a medical procedure we would perform if you were to die, that is, if your heart were to stop and you were to stop breathing. CPR includes pressing down on your chest to pump the heart and inserting a breathing tube through your mouth and using a breathing machine to help you breathe." Approaches to discussion of code status based on scenario (Indication and goal based on [NEJM 2020;382:2450](#))

Scenario/Indication	Approach/Goal	Example
The patient has a stable condition and is likely to benefit from CPR/Intubation	Make sure the patient does not strongly prefer to avoid these medical interventions	"Have you ever discussed CPR and intubation with your medical team?" "What are your thoughts about it?" "Right now, if your heart were to stop, you would receive CPR. Is this consistent with your goals?"
The patient already has a preference to limit CPR and intubation that needs confirmation	Confirm an already established preference	"Your records show that you made an emergency plan with your outpatient doctor to focus on comfort and allow for a natural death. This means that we would not use chest compressions to start your heart or a use a breathing machine. Based on my medical assessment, I think we should continue this plan now. Does that sound right to you? We will do everything else we can to help you get through this."
The patient has an advancing illness, and it is unclear whether the benefits of CPR and intubation would outweigh the burdens (the decision depends heavily on the patient's values and goals)	Shared decision-making	"Have you ever discussed CPR and intubation with your medical team? What have you discussed?" "If an emergency were to occur and your heart were to stop, it is difficult to predict what would happen if you received CPR or a breathing tube. Recognizing this uncertainty, if your heart were to stop and you were to stop breathing, what would you want your medical team to know about what is important to you?" "Given what's important to you, I would recommend _____"
The patient is at risk for decompensation/death, unlikely to benefit from CPR and intubation	Informed Consent	<b>Introduce/assess:</b> If urgent: "I wish we were meeting under different circumstances." <b>Share information:</b> "Unfortunately, we are in a different place now." (Discuss medical situation, share concerns using hopes/concerns) <b>Explore goals:</b> "Given where we are, what is most important to you?" <b>Make a recommendation:</b> - "I recommend we make a plan to help you meet your goals and avoid treatments that are unlikely to help." - "I recommend that if your heart and lungs were to stop working, we focus on your comfort. This means having treatments such as oxygen and medication. This also means we would not use CPR or a breathing machine. Does this plan sound OK to you?"

# Geriatrics & Palliative Care

# Death & Pronouncement

## PRIOR TO DEATH

- Involve family ± chaplaincy (available 24/7), longitudinal care team members (e.g. PCP). Ask about religious/cultural traditions
- When passing off patient who may pass away, prep the “Report of Death” form; form available w/ OA
  - Consider asking families about autopsies in advance when appropriate
- Consider whether you will need to notify medical examiner. Common reasons:
  - Any death associated with acute or chronic use of alcohol or drugs (including alcohol-related cirrhosis)
  - Death associated with diagnostic or therapeutic procedures
  - Death by accidental/unintentional injury (including falls), criminal violence, suicide, or uncertain circumstances

## WITHDRAWING VENTILATORY SUPPORT (palliative extubation, discontinuation of NIPPV)

- Prior to extubation, refer to MGH MICU Policy and ATS Guidelines ([AJRCCM 2008;177:912](#)). Review plan with the following people:
  - Family: ask if they want to spend time privately with patient prior to extubation. As appropriate, review expected signs of dying process (agonal breathing/rattle' of pooled secretions, mottled extremities), expected timeline (usually minutes to hours [[Chest 2010;138:289](#)]), and plan for symptom control
  - RN: ensure adequate PRNs for air hunger/pain (IV opioids), anxiety (IV haldol, IV benzo), and secretions (glycopyrrolate) at bedside (see *End of Life Care*); can use CMO order set. May need continuous infusions depending on requirements. Stop paralytics
  - RT: determine plan for immediate withdrawal vs down-titration of vent support
- Do not withhold appropriate sx management because of concern for hastening death or concern for increased sedation
  - “*The Rule of Double Effect*” ([NEJM 1998;338:1389](#)): focus on managing sx. If in doubt, ask for help
  - The goal is adequate pain, dyspnea, and anxiety relief; dose based on ongoing symptoms and prior dose effectiveness

## ORGAN DONATION

- Eligibility: after family and medical team decide to discontinue medical support, medical team notifies New England Organ Bank (NEOB), (800) 446-6362, who coordinates consent and donation. This process can take up to 24h. DO NOT broach topic of potential organ donation with family; NEOB is specifically trained to do this
- Care prior to donation: maintaining organ viability during severe autonomic/inflammatory responses following severe neurologic injury. Key goals: MAP 60-110, normothermia, UOP 0.5-1.0cc/kg/hr, LTVV ([CCM 2015;43:1291](#); [NEJM 2004;351:2730](#); [JAMA Surg 2014;149:969](#))
- OR Preparation: Death paperwork must be signed by declaring MD (prepare in advance). After ventilatory withdrawal (usually extubation in OR), MD/RN coordinate symptom management until time of death, declare death based on irreversible cessation of circulatory/respiratory function

## DEATH PRONOUNCEMENT

- **PRONOUNCEMENT**: Introduce yourself to the family, explain what you are doing, express condolences
  - FEEL for pulse, LISTEN for heart sounds/breath sounds (> 60 sec), SHINE light to determine absence of pupillary light reflex, and NOTE time at the end of your exam, which becomes the time of death (do NOT need to say out loud)
- **QUESTIONS FOR NEXT OF KIN (Not HCP, but Next of Kin [NOK])**: Spouse > Children > Other Family
  - If no NOK in room, call NOK to notify of patient’s death
  - Ask the family if they would like to see a chaplain or social worker
  - Ask if family would want an autopsy (consent with NOK in MA, not HCP unlike other medical consent)
  - If family accepts autopsy, ask about disposition of organs (i.e., would they like MGH to retain organs for further testing, education, research?)
  - Are there other family members whom they would like you to inform?
  - Will anyone else be coming to view the body prior to transport to morgue?
  - **What you can tell family**: body is kept at MGH until the funeral home calls MGH and arranges for pickup. Family should select and contact funeral home directly.

**AUTOPSIES** are **free** and do not delay funerals (can still have open casket). In addition to helping determine cause of death, they can be instrumental in advancing research.

## ONCE YOU LEAVE THE ROOM:

- **Notify ATTENDING and PCP**. Email acceptable if death was expected
- Obtain “Report of Death” form from OA. **Fill out in BLACK ink**. If any mistakes, **you will need to START OVER**
  - Log into Epic before calling the numbers listed on the form
  - In the “Cause of Death” section of form, cannot write “cardiac arrest” or “respiratory arrest.” Fill out as many **underlying causes** as applicable—you do not need to fill in all the lines. See [CDC guide](#) for examples.
  - Call the **Medical Examiner** if necessary (see above “Prior to Death”). Document the first name of the staff member
  - Call **New England Organ Bank**: 800-446-6362: will need patient’s demographics, cause of death. May require history of cancer, recent infections, recent labs, hx dementia, other PMHx
  - Call the **Admitting Office** (x6-3393) to inform them of the death. They will ask cause/time of death, Med Examiner, NEOB
  - The “Report of Death” goes to **Admitting with the patient/chart**. Cannot leave the floor until the Report of Death is completed
- **Document a brief “note of patient death”**: SmartPhrase “.MGHDOMDEATHNOTE”
- Complete short **discharge summary** using “Deceased Patient” portion of the Discharge tab in Epic
- **Debrief** process and death with team or Night Teach

# Geriatrics & Palliative Care

# End of Life Care & Hospice

## END OF LIFE CARE GENERAL PRINCIPLES

- The focus of EOL care is to enhance patient's comfort & optimize palliative care management. Code status change to DNR/DNI or CMO (Comfort Measures Only) is **not a requirement**.
  - Note that EOL is a medical state while code status reflects patient goals/values
  - EOL care includes physical, emotional, social, and spiritual support to maximize comfort (treating pain, anxiety, dyspnea, N/V, delirium), enable loved ones' time with patient, and facilitate EOL rituals as feasible. **Offer chaplaincy and social work services**
- Communicate expected signs of dying and time course to loved ones. **Any clinical provider** (MD, NP, RN, SW, chaplain) **can make an EOL visitation policy exception irrespective of code status** if passing is expected during admission
- Prepare paperwork and logistical planning as feasible prior to death (see *Death and Pronouncement*)

## PRACTICAL CMO TIPS: DISCONTINUE NON-BENEFICIAL CARE (PALLIATIVE CARE ORDERSET)

- CMO (Comfort Measures Only): Does not mean all treatments are stopped, but instead means tailoring care to **maximize comfort**. Some patients may benefit from thoracenteses, paracentesis, or venting G tube if within pt's goals.
- Lines/tubes: Maintain PIV access as possible, d/c central line if feasible.
- Supplemental O<sub>2</sub>: Not shown to have benefit if not hypoxicemic. Instead, offer fan therapy, HOB elevation, IV/PO opioids ([Am J Hosp Palliat Care 2020;37:294](#))
- Foley: Can maintain for comfort; discuss w/ RN.
- Stop labs, routine VS: Reassure family that we can use RR, temp, & appearance as symptom management guide
- Medications: Continue meds contributing to patient comfort, those that will prevent uncomfortable events (e.g., maintain rate control to avoid AFRVR, AEDs for seizure control), or that have a withdrawal syndrome (e.g., SSRIs)
- Tube feeds, TPN/PPN, IVF: Generally avoid; may cause volume overload without meaningful benefit ([JCO 2013;31:111](#))

### Example PRN Orders: if questions or concerns, consult Palliative Care for support

\*Always treat acute symptoms with boluses rather than changing drip rate. Drips effectively act as long-acting meds

\*\*If uncontrolled acute symptoms despite IV bolus, can repeat after 20-30min at same dose or doubled dose and change PRN dose

	IV access	PO only (No IV access)
<b>Analgesia/Dyspnea</b>	Opioids: see <i>Pain Management</i> . Can dose more frequently (up titrate dose q30 min PRN for uncontrolled air hunger/pain) at EOL when goal is for aggressive symptom management (discuss w/ RN). Dyspnea: Start with 2-5mg IV morphine equivalents for the opioid naive	
<b>Secretions</b> *Stop TF, lay on side, pharm trial, reassure fam	Glycopyrrolate 0.2-0.4mg IV/SC q4-6hrs PRN	Glycopyrrolate 1mg PO q4-6hrs PRN or atropine 1-2 drops SL q6hrs PRN
<b>Delirium, Nausea, Restlessness, Anxiolysis</b>	Haldol 0.5-1mg IV q4-6hrs PRN	Haldol 0.5 mg PO q4-6 hrs PRN or Olanzapine 2.5-5mg SL q6h PRN
<b>Anxiolysis associated with dyspnea</b>	Lorazepam 0.5-1mg IV q4-6hrs PRN (increase as needed)	Lorazepam 0.5-1 mg PO q4-6hrs PRN (increase as needed)

Resources: Palliative Care Network of Wisconsin [Fast Facts](#) and app; DFCI resources: [Pink Book](#) for pain, [Green Book](#) for nausea/vomiting

## HOSPICE OVERVIEW

- Hospice**: multidisciplinary care for patients with advanced illness and life expectancy <6mo with goal of providing comfort rather than reversing underlying disease. Paid through Hospice Insurance Benefit (most often through Medicare)
- Can be provided in multiple locations**, including home (most common), SNF, residential facility, or acute care hospital depending on patient's care needs and caregiver support
- Services include intermittent nursing care (~1-2 visits with 24/7 on-call emergency support), social work, chaplaincy, all medications and supplies related to terminal illness or comfort, equipment (bed, commode, wheelchair etc.), home health aide (avg 1 h/d), bereavement support, short-term respite care (provides relief for caregivers), and short-term inpatient care for symptoms that cannot be managed at home. **Caregiving most often provided by family and friends**
- DOES NOT** cover room/board at facilities or 24/7 nursing care. Hospice sometimes covers treatments like abx, IVF if it will contribute to pt's comfort. Determined on case-by-case basis

## GENERAL INPATIENT HOSPICE (GIP)

- GIP Hospice: inpatient care plan for a hospice pt who has short-term symptom mgt needs that cannot be provided adequately in any other setting (e.g., high flow O<sub>2</sub>, uncontrolled sx requiring IV medications, high RN needs for wound care/suctioning). Most appropriately offered at hospice house & this DC plan should be prioritized if pt can be transported.
- Consider GIP at MGH for pts who are actively or imminently dying (days to short weeks) and/or cannot safely transport. If admitted to GIP at MGH, pt will be "Discharged to Hospice" and Pall Care becomes primary team
- Discuss w/ floor CM team (for insurance benefit screen and coordinate w/ hospice liaison), Care Dimensions, and Pall Care if pt is appropriate for GIP Hospice and, if so, which location

# Geriatrics & Palliative Care

# Frailty & Polypharmacy

## FRAILTY AND FALLS

**Screening for frailty/falls:** consider for all admissions: >70yo, frequent falls/admissions, “failure to thrive” or “admit for placement,” significant delirium (may signal underlying cognitive impairment), polypharmacy

- Reframe “failure to thrive” as **frailty**, which has evidence-based assessment criteria and diagnostic approach
- Definition of frailty:** “medical syndrome with multiple causes and contributors characterized by **diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability** for developing increased dependency and/or death” ([JAMDA 2013;14:392](#)). **Older age is risk factor but not necessary/sufficient for the dx**
- Most cited tool is **Phenotype of Frailty** ([J Geront 2001;56:M146](#); [BMC Geriatr 2013;13:64](#)), but can use quick screen below:

FRAIL screen (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?

**Scoring:** frail = 3 or more  $\oplus$  answers; pre-frail = 1-2  $\oplus$  answers

- Other quick screens that can easily be done in any setting include:
  - Subjective answer to “Are you afraid of falling?” ([PLoS One 2018;13\(3\):e1743](#))
  - Gait speed: below 1m/s is associated with higher fall risk ([J Geriatr Phys Ther 2009;32\(2\):46-9](#); [Physiother Res Int 2019;24\(1\):e1743](#))

## Inpatient frailty assessment: find the root cause!

- Assess cognitive decline, physiology of aging, and manageable medical pathologies (see *Geriatric Assessment*), medications
- Ddx:** anemia, infxn, cancer, HF, COPD, cirrhosis, CKD, DM, autonomic dysfunction, PMR, thyroid dz, nutrition deficiencies (incl vitamin D), depression, cognitive impairment, adverse medication side effect
  - If concern for frailty, initial workup: CBC, BMP, TSH/T4, vitamin studies (empirically replete when appropriate), fall screen, cognitive screen, functional assessment including collateral info from family or facility, foot exam!

## Interventions for frailty ([Age Ageing 2017;46:383](#))

- Screen for and treat high-risk comorbidities (e.g. urinary incontinence, osteoporosis, vision/hearing impairment, driving risk)
- Establish **patient- and family-centered goals** to guide treatment plan
- Exercise:** PT; exercise programs (e.g. Tai Chi) can reduce fall risk ([JAMA 2018;319:1705](#); [BMC Geriatr 2020;20:108](#))
- Consults:** Geriatric consult for additional help (p22161), Nutrition consult particularly for patients with weight loss
- Cognition training:** inpatient: delirium precautions (limiting overnight VS/interventions, labs, lines/tethers, physical/chemical restraints); outpatient: OT consult (improve short-term memory, info processing, problem-solving, driving evaluation)
- Environment assessment and modifications:** consider social work consult, OT consult, iCMP referral, home PT evaluation (Home Health includes PT (can specify home safety eval), OT, Speech, and SW, Home-Based Palliative Care team)
- Referral to OP geriatrics/palliative care for regular review of medications and **reduction in polypharmacy** (see below)
- Address advanced directives/HCP/Code Status

## POLYPHARMACY AND INAPPROPRIATE MEDICATIONS

**Preadmission Medication List (PAML) on admission:** review prior discharges for meds added/removed; look over hard copies of paperwork from nursing homes; ask about medication administration system at home (blister packs, family help, eg)

- 24/7 pharmacies: CVS 781-391-2668 (dial 1, 2, “staff”); Walgreens 781-321-1765 (dial 2, #, “other question”)
- Ask about OTC meds and herbal/dietary supplements, which can be easily missed culprits of drug-drug interactions
- Coordinate discharge Rx planning** and education with patient, pharmacy, PCP → lower risk of readmission with intensive pharmacist intervention (med rec and education) and coordination with PCP ([JAMA IM 2018;178:375](#)), MGH Home Health

## Inappropriate medications for elderly patients ([Medication Appropriateness Index](#); [MedStopper](#); [deprescribing.org](#))

- Classes to AVOID in geriatric patients:** See Beer’s list ([J Am Geri Soc 2019;67:674](#)) and **STOPP-START** for further details
  - Anticholinergics:** delirium, falls, blurred vision, urinary retention, tachycardia. Avoid antihistamines, TCAs, MAOIs, antimuscarinics (oxybutynin), muscle relaxants (cyclobenzaprine), prochlorperazine. *Long term use linked to increased risk for dementia* ([JAMA IM 2015;175:401](#); [Anticholinergic Risk Scale](#) to quantify risk burden)
  - Benzodiazepines:** delirium, falls, cognitive impairment, etc. (also risk w/ non-BZD hypnotics e.g. zolpidem)
  - Antipsychotics:** ↑ mortality with antipsychotics in the elderly with underlying cognitive impairment ([JAMA Psych 2015;72:438](#))
  - Peripheral alpha blockers and central alpha-agonists:** -zosins and clonidine → risk of orthostasis and falls
  - Long-acting sulfonylureas and rapid/short acting insulin:** hypoglycemia
  - PPIs:** C. diff, bone loss/fracture (switch to H2 blockers unless clear indication for PPI)
  - NSAIDs:** CVD, GI bleed, AKI (especially in elderly patients with decreased CrCl)
  - Aspirin for primary CVD prevention:** bleeding (use with caution and reevaluate at age >70) ([NEJM 2018;379:1509](#))
- Parkinson’s disease:** ondansetron is antiemetic of choice. **Avoid antipsychotics**, metoclopramide, prochlorperazine
- Dosage adjustments:** ensure appropriate renal and weight-based dose adjustment for anticoagulants (enoxaparin, apixaban, rivaroxaban, dabigatran), antibiotics, etc.

# Geriatrics & Palliative Care

# Geriatric Assessment & Elder Abuse

## GENERAL APPROACH TO THE COMPREHENSIVE GERIATRIC ASSESSMENT

- Overview:** The comprehensive geriatric assessment (CGA) systematically identifies medical and psychosocial factors that lead to functional limitations for older adults and should be approached by an interprofessional team. One widely accepted framework is the "Geriatric 5Ms" (mind, mobility, medications, matters most, multicomplexity) ([JAGS 2017;9:2115](#)).
- Outcomes:** CGA associated with increased likelihood that inpatients will be alive and in their own homes 3-12 months following discharge ([Cochrane 2017;9:CD006211](#)) & predicts operative/procedural risk ([JAGS 202:68:1235-41](#), [EJSO 2016;42:1890-7](#)). Outpatient, serial CGA provides opportunity to tailor care to the evolving needs of patients ([JAH 2021;33:469](#)).

Topic	Examples	Tools
Mind	Vision, hearing, mood, sleep, memory	PHQ-2 or Geriatric Depression Scale ( <a href="#">English</a> , <a href="#">Spanish</a> ) MOCA ( <a href="#">English</a> , <a href="#">Spanish</a> ) Mini-Cog ( <a href="#">English</a> , <a href="#">non-English languages</a> ) <a href="#">RUDAS</a> (minimizes effects of cultural learning and language in assessing cog fxn)
Mobility	Pain, feet, falls/fear of falling	<a href="#">Timed up and go test</a> (<12s) <a href="#">Gait speed test</a> (4m/5sec = 0.8m/sec)
Medications	High risk meds, polypharmacy, immunizations	See <a href="#">Frailty &amp; Polypharmacy</a>
Matters most	Social history, HCP, code status	<a href="#">Massachusetts HCP</a> Resources for patients: <a href="#">Prepare for your care</a> (5-step program for patients), <a href="#">The Conversation Project</a> See <a href="#">ACP &amp; Code Status</a> for further info
Functionality	Appetite/nutrition/weight Dentition/swallowing Constipation/incontinence Sexual history Substance use ADLs: bathing, dressing, toileting, transferring, continence, feeding, etc iADLs: cleaning, cooking, finances, etc	Mini-Nutritional Assessment ( <a href="#">English</a> , <a href="#">Spanish</a> ) <a href="#">Home Safety Assessment</a>

## COMMON SIGNS OF ELDER ABUSE

- Generally includes persons 60 years or older (although this definition is state-dependent)
- Definition ([CDC](#)): "An intentional act or failure to act by a caregiver or another person in a relationship involving an expectation of trust that causes or creates a risk of harm to an older adult."
- Signs of abuse** may include physical, emotional, sexual, neglect, abandonment, and/or financial abuse. In addition to common signs of abuse in all populations, look for:
  - Withdrawn affect, deferring to others to answer
  - Unwashed hair, dirty clothes, appearing unkempt (don't forget to look at feet and nails!)
  - Unclean or unsafe living conditions, mismatch in level of social supports/services vs needs based on physical or cognitive disability, tension w/ family around financial planning to help with care needs
  - Worsening of pressure ulcers, skin tears, weight loss
  - Lack of necessary medical aids (walkers/canes, adult-pull ups)
  - Unpaid bills, eviction notices, inability to hire more services/help or transition to a new level of care etc. despite adequate financial resources
- Risk Factors ([NCEA](#)): advanced age, female sex, non-white race, disability, cognitive impairment
- Screening
  - [AMA](#) recommends regular screening but USPSTF did not identify sufficient evidence ([Screening tools](#) validated in various settings are available for use, consider using comprehensive geriatric assessment above)
  - Concerns should prompt cognitive testing, functional assessment, and obtaining collateral to screen for unrecognized dementia as an underlying cause of these signs and symptoms (See "[Dementia](#)")
- Guardianship** ([Gerontology 2007;47:591-603](#)): legal process that gives a guardian permission to take care of and make decisions for an incapacitated adult who does not have a pre-designated HCP. Consider guardianship in situations where the patient does not have capacity regarding **high-risk decisions** and no HCP identified. Pt may be determined to lack **competence** (legal status) by a court.

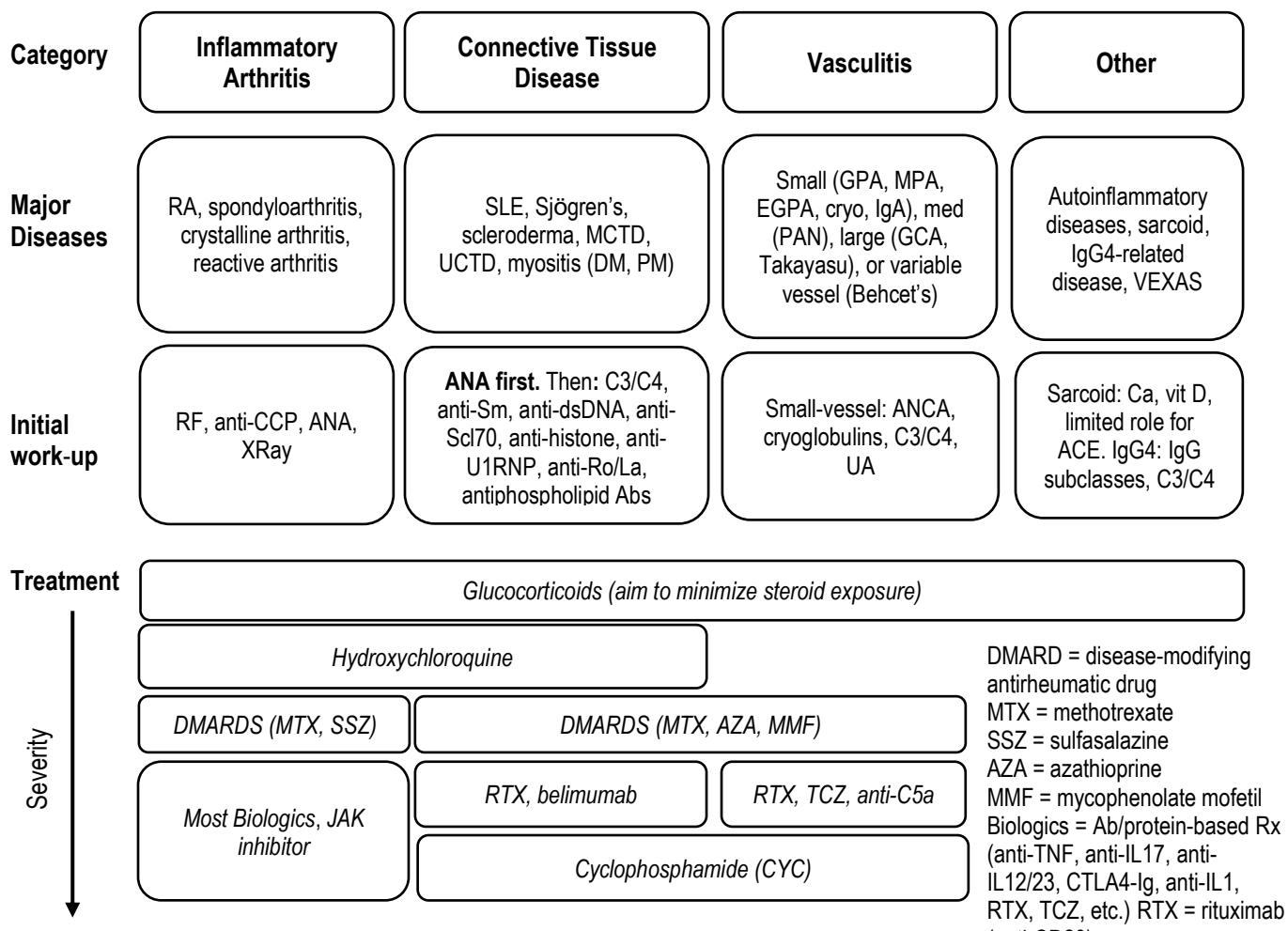
## REPORTING LOGISTICS

- Making a report through the Massachusetts Executive Office of Elder Affairs (can be made by any member of the healthcare team)
  - Report can be made [online](#) or via phone: (800) 922-2275
  - If you make a report via phone, must submit a [mandated reporter form](#) to the local Protective Services agency within 48h
  - To report abuse of a patient by nursing home or hospital staff, reach out to the other providers/institutions first to discuss and obtain collateral and understand greater clinical/social context. If continued concern, can contact the Massachusetts Department of Public Health: (800) 462-5540
- Similar to CPS reports, this is an ask to an objective, multi-disciplinary team to investigate concerns rather than a condemnation
- Documentation: No template currently available in Epic. Findings and report may be documented as part of a progress note or in a separate documentation encounter. Remember to be objective and detailed in describing your subjective and objective findings suggestive of abuse or neglect.

# Rheumatology

# Approach to Rheumatologic Disease

OVERVIEW: rheumatologic diseases may be roughly separated into 4 categories



\*\*Nuances of treatment not encapsulated by this figure – see following pages

## RHEUMATOLOGIC ROS

Fever, arthritis, rashes/photosensitivity, alopecia, nail/nailfold Δ, sicca symptoms, conjunctivitis, uveitis, episcleritis/scleritis, Raynaud's, acrocyanosis, oral/genital ulcers, polychondritis, enthesitis, serositis sx, thromboses, neuropathy, pregnancy loss

## LABS

CBC/diff, BMP, LFTs, UA, ESR/CRP, TSH. Target serological testing to positive items on rheum ROS

## DDx

Consider malignancy (including paraneoplastic phenomenon) and infection as alt. diagnoses

## COMMON INPATIENT RHEUM CONSULT QUESTIONS

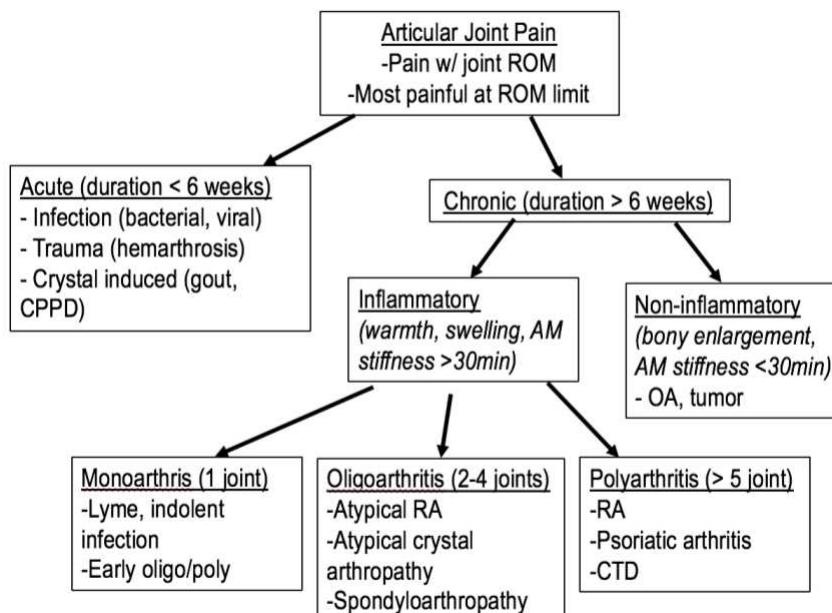
1. Inpatient inflammatory arthritis: should this patient have a joint aspiration/injection?
2. Guidance on interpretation/further work-up of positive rheumatologic serologies (i.e., positive ANA (>1:80), +RF, etc.)
3. Work-up/management of FUO
4. Patient with history of established rheumatological disease and c/f exacerbation or complication
5. Concern for new onset vasculitis, myositis, or connective tissue disease
6. Work-up/management of new interstitial lung disease (in conjunction with pulmonology)
7. Work-up/management of inflammatory eye disease
8. Guidance on immunosuppressive meds for pt w/ established rheumatologic dz & c/f new infection or malignancy

## HEALTHCARE MAINTENANCE FOR RHEUM PATIENTS

If prolonged steroids: Ca<sup>++</sup>/vitD (for bone health), pneumocystis ppx (if ≥20mg prednisone for ≥4 weeks; see ID: *Opportunistic Infections*), PPI (GI ulcer ppx), risk stratification for bone density screening, and ✓ A1c (see Endocrine: *Steroid Pearls*).

Consider reproductive planning (many meds teratogenic), immunizations, skin exam/sun protection if anti-TNF or MTX (↑skin cancer), increased pap smear frequency ([J Low Genit Tract Dis 2019 Apr;23\(2\):87-101](#)), and optimizing CV risk (↑risk w/ chronic inflammation ([Lancet Rheumatol 2021;3:e58](#))). Modified ASCVD from UK includes RA: [QRISK](#)

## APPROACH TO THE PATIENT WITH ARTHRITIS



## ACUTE ARTHRITIS SYNDROMES

Arthritis	Joint pattern	Presentation	Diagnosis	Treatment
Gout	- Mono > poly - 1 <sup>st</sup> MTP joint (also called Podagra; 1 <sup>st</sup> sx in 50% pts) - hindfoot, fingers, ankle, knee, wrists	- Triggers: diuretics, meat, seafood, EtOH, HTN, DM2, CKD - Acute flares → chronic arthropathy (tophi) - Urate nephrolithiasis, chronic nephropathy	Gold std: <u>Arthrocentesis</u> : neg birefringent needle-shaped crystals, WBC 10k-100k/uL - <u>ACR-EULAR Criteria for Gout</u> can help establish likelihood of dx in absence of joint aspiration - At first dx should obtain plain films to evaluate for erosions/tophi as this changes management - US if dx remains uncertain	<b>Acute:</b> colchicine (1.2mg x1, 0.6mg 1h later, 0.6mg 1-2x daily until 2-3d after resolved) or pred (40mg QD until resolved then taper) or NSAIDs (naproxen 500mg BID, indomethacin 50mg TID for ~5-7d), or <b>intra-art steroids</b> (if 1-2 joints). Choice driven by pt and side effect profile ( <u>UTD algorithm</u> to help choose initial therapy). <b>Anti-IL1 if above contraindicated.</b> If already on allopurinol, should continue in acute attack. In AKI renally dose.  <b>Chronic:</b> urate lowering tx indicated if ≥2 attacks/yr, disabling attacks, tophi, or erosions. Check b/l uric acid outside of flare as it can be falsely low during flare. Start ~2 wks after flare resolution. <b>Allopurinol</b> 1 <sup>st</sup> -line; start low to ↓ hypersens risk, flare ppx x 3-6 m w/ colchicine or NSIADS, ✓HLA-B*5801 if Korean/Han Chinese/Thai descent before starting allopurinol ( <u>Clin Pharm Ther. 2013;93:153</u> )
CPPD (pseudo-gout)	- Mono > poly - Knee > wrist, shoulder, ankle - Neck "crowned dens syndrome"	- Can be asymptomatic - Can coexist with gout, OA	- <u>Arthrocentesis</u> : small pos birefringent rhomboid crystals, WBC 10k-100k/uL - Chondrocalcinosis	- <b>Acute:</b> if ≤2 joints → <b>intra-art steroids</b> (1 <sup>st</sup> line). 2 <sup>nd</sup> line same as gout (colchicine w/in 24h sx onset) - <b>Chronic:</b> NSAIDs, colchicine, HCQ, low-dose pred, MTX. Anti-IL1 if refractory - Screen for 2° causes: hyperPTH, hypoMg, hemochromatosis, ?low phos
Bacterial septic arthritis	- Mono (50% knee), >1 joint (20%) - Gonococcal: mono or oligo	- Hematogenous spread most common - ↑risk in RA - Gonococcal: fever ± tenosynovitis & skin lesions	- <u>Arthrocentesis</u> : WBC 50-150k/uL, ↑PMNs, GS/Cx; blood cx - staph>strep>GNR - Gonococcal: GU NAAT, often ↓ synovial WBC + neg cx - XR ± CT/MRI	- <b>Antibiotics</b> for 3-4w (CTX x7-14 d for gonococcal) - Joint drainage/washout (ortho c/s) - Often requires hardware explant and longer antibx if prosthetic joint
Viral arthritis	- Varied, but often symmetric poly small joint (e.g. parvo) ± large joint	- Often a/w fever & fatigue	- IgM/IgG/PCR per ddx: parvo, HBV, HCV, HIV, rubella virus or vaccine, chikungunya, dengue, enterovirus, mumps, Herpesviridae	- NSAIDs - Antivirals if able - Many etiologies self-limited

# Rheumatology

# Arthritis

CHRONIC ARTHRITIS SYNDROMES				
Arthritis	Joint pattern	Presentation	Diagnosis	Treatment
Osteoarthritis	- Poly - Knees, hips, MTP, CMC, PIP, DIP, C-spine, L-spine	- Age >45 - AM stiff <30min, slow progression, no warmth, muscular wasting	- Clinical dx - Bony swelling, joint deformity, limited ROM - XR joint space narrowing, osteophytosis, subchondral sclerosis	- PT, braces, weight loss - Topical NSAIDs, PRN NSAIDs - Intra-articular steroids - If severe, refer to ortho, PM&R - Not recommended: duloxetine, glucosamine, bisphosphonates, PRP ( <a href="#">ACR Guideline 2019</a> )
Infectious	- Mono (Lyme: knee, TB: hip), oligo/poly ( <i>T. whipplei</i> )	- Late Lyme - immunox or RFs: fungal, TB (indolent monoarthritis) - <i>T. whipplei</i> : arthralgias > arthritis, diarrhea, ↓weight	- Arthrocentesis, Lyme serology, T spot, fungal cx/BDG/GM/Ags, SI biopsy ( <i>T. whipplei</i> )	- Lyme: 4w of doxy or amox - TB, endemic or other fungal: see ID pages - <i>T. whipplei</i> : 2w CTX + 1y TMP/sulfa
Rheumatoid Arthritis	- Mono in early stage, then poly - Small peripheral (MCP, PIP, wrists, MTP) - Symmetric	- F>M, age 35-65 - AM stiff >30min - Joint deformity - RA nodules	- RF, anti-CCP - Joint XR - Exclude other causes	- Acute: <b>prednisone</b> or <b>NSAIDs</b> , initiate DMARD if not on already - Chronic: <b>DMARD</b> (MTX > HCQ, SSZ, leflunomide); 2 <sup>nd</sup> line combo or <b>biologic</b> (infliximab, abatacept, TCZ)
Spondyloarthritis (SpA): - Ankylosing spondylitis (AS) - Psoriatic arthritis (PsA) - IBD-assoc. (IBDa)	<b>AS:</b> mostly axial (spine, SI) <b>PsA:</b> can be distal [DIPs], asymm oligo, symm poly, arthritis mutilans, axial <b>IBDa:</b> distal oligo or poly arthritis > axial	- AM stiff >30min - Extra-articular: tenosynovitis, enthesitis, dactylitis, uveitis, pyoderma gangrenosum <b>AS:</b> Pain in low back, buttock <b>PsA:</b> nail pits/onycholysis, 70% with psoriasis <b>IBDa:</b> oligo varies with IBD activity, poly or axial has independent course	- Clinical dx - 1ESR/CRP (not Sn) - HLA-B27 <b>AS:</b> ↓ spine mobility, bamboo spine + <b>sacroiliitis</b> (XR or MRI) <b>PsA:</b> <a href="#">CASPAR criteria</a> (91% Sn, 99% Sp), pencil-in-cup DIPs	- <b>NSAIDs</b> (1 <sup>st</sup> line) <b>AS:</b> <b>TNFα inhibitor</b> (2 <sup>nd</sup> line), anti-IL17, JAKi <b>PsA:</b> If mod, <b>MTX</b> > SSZ or leflunomide, apremilast (PDEI). - If severe/erosive, <b>TNFα inhibitor</b> . If non-response, anti-IL17 or anti-IL12/23. <b>IBDa:</b> SSZ > MTX or AZA, <b>TNFα inhibitor</b> , anti-IL-12/23
- Reactive arthritis (ReA)	- Oligo > mono > poly (small joints) - Asymmetric - LE > UE	- 1-4w post-infxn*: - Conjunctivitis, urethritis, cervicitis, oral ulcers, circinate balanitis, keratoderma blennorrhagica, SpA sx	- Preceding infection* - <u>Arthrocentesis</u> : GS/Cx - Stool cx (if diarrhea) - GC/Chlamydia	- If GU infxn, treat. If GI infxn, may not need to treat - <b>Acute:</b> <b>NSAIDs</b> > intra-articular steroids > prednisone - <b>Chronic:</b> if >6mo, <b>MTX</b> or SSZ

\* Causes: Enteric: *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C. diff*; GU: *Chlamydia*, *E. coli*, *Ureaplasma*, *Mycoplasma*

SYNOVIAL FLUID ANALYSIS					
	Normal	Non-Inflammatory	Inflammatory	Septic	Hemorrhagic
Clarity	Clear	Clear	Clear-opaque	Opaque	Bloody
Color	Pale yellow	Yellow	Yellow to opalescent	Yellow to green	Red to brown
Viscosity	High	High	Low	Variable	Variable
WBC (per mm <sup>3</sup> )	<200	0-2,000	2,000-100K	50-150K	200-2,000
PMNs (%)	<25	<25	≥50	≥75	50-75
Major Ddx		OA, trauma, AVN, mechanical dysfunction	Many: inflammatory and infectious arthritides, rheumatic diseases, gout/CPPD	Septic arthritis; occasionally, noninfectious: gout, reactive arthritis, RA	Trauma, coagulopathy, iatrogenic, tumors, scurvy

# Rheumatology

# Connective Tissue Diseases

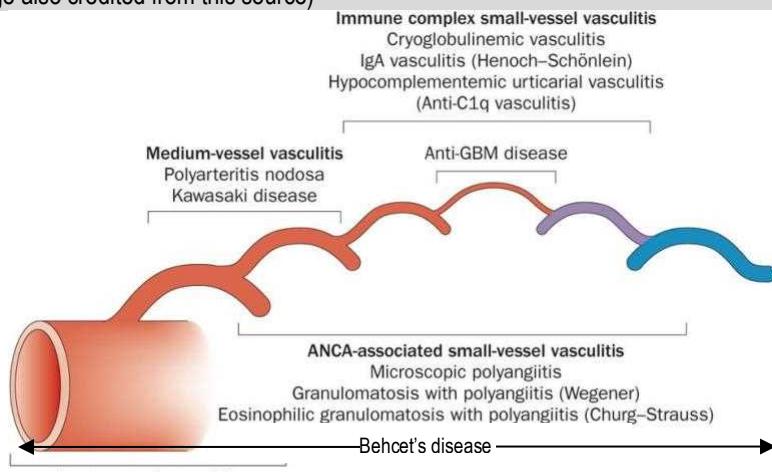
Disease	Clinical Presentation	Work-up	Treatment	Complication
SLE	<ul style="list-style-type: none"> <li>- F&gt;M, 15-40yo, Afr./Latino-a/Asian descent &gt; White</li> <li>- <b>Constitutional sx</b> (fever, wt loss, fatigue, myalgia), <b>malar rash</b> (spares NL fold), <b>discoid lesions</b>, <b>photosensitivity</b>, oral/nasal <b>ulcers</b> (often painless), <b>cytopenias</b>, serositis, <b>nephritis</b>, pneumonitis/DAH/ILD, seizure/CVA/neuropsych, vasculitis</li> <li>- <b>Arthritis/arthralgia</b>: migratory, polyarticular (knees, carpal joints, PIPs &gt; other), symmetric, nondeforming.</li> <li>⊕ Morning stiffness.</li> </ul>	<ul style="list-style-type: none"> <li>⊕ ANA (&gt;95%; Sn not Sp)</li> <li>+ <b>anti-dsDNA</b> (~70%; active dz &amp; lupus nephritis) ⊕ anti-Sm (30%, Sp, remains ⊕ in remission); ⊕ anti-RNP (30-50%); ⊕ anti-SS-A/Ro, anti-SS-B/La (35%, 15%)</li> <li>⊕ antiphospholipid Abs (40%)</li> <li>- CBC/diff, BMP, Coomb's, C3/4, ESR/CRP, UA/UPCR; consider RF, CCP if sig. arthritis, (<a href="#">2019 EULAR/ACR Criteria</a>)</li> </ul>	<ul style="list-style-type: none"> <li>- <b>All (incl. pregn)</b>: HCQ (↓ flares, clots, death)</li> <li>- <b>Flare: steroids</b>. If nephritis or severe end organ dz + (<b>MMF +/- CNI (voclosporin) or CYC</b>) → <b>MMF &gt; AZA</b>.</li> <li>- If refractory, consider add MTX, AZA, MMF, anti-B cell (RTX, belimumab), anti-IFN (anifrolumab), CNI. Early trials of anti B cell CAR T tx (<a href="#">Nat Med 2022;28:2124</a>)</li> </ul>	<ul style="list-style-type: none"> <li>- CVD (<a href="#">Semin Arthritis Rheum 2013;43:77</a>); ↑ risk <b>VTE/ATE</b> (APLS)</li> <li>- Preg. (neonatal death, pre-eclampsia, prem delivery)</li> <li>- Osteonecrosis (2/2 SLE and steroids)</li> </ul>
Drug-induced lupus (DIL)	<ul style="list-style-type: none"> <li>- Fever, arthralgias/arthritides, myalgias, rash, serositis. Other SLE complic. uncommon. Isolated subacute cutaneous lupus drug-induced in ~1/3 of cases (<a href="#">Br J Dermatol 2012;167:296</a>)</li> <li>- <b>Months-years</b> exposure (<a href="#">Ann NY Acad Sci 2007;1108:166</a>)</li> <li>- High risk: <b>procainamide</b> (15-20% per y), <b>hydralazine</b> (5-10% / y). Mod: quinidine. Low: TNFi, penicillamine, carbamazepine, methyldopa, others</li> </ul>	<ul style="list-style-type: none"> <li>*Serologies/clinical features often <b>unique to the offending drug</b></li> <li>⊕ <b>ANA</b> (almost all cases)</li> <li>⊕ <b>Anti-histone</b> (Sn but not Sp for DIL, also in up to 80% idiopathic SLE) ⊕ <b>anti-dsDNA</b> (exc. TNFi, IFN) ⊕ <b>anti-SS-A/Ro</b> (not Sp) Others: ANCA, anti-RNP</li> </ul>	<p><b>Treat sxs, not antibodies</b></p> <ul style="list-style-type: none"> <li>- <b>Withdraw</b> offending agent: resolution may take weeks-months</li> <li>- Occasionally NSAIDs, HCQ, steroids for sx</li> <li>- Avoid common drugs in patients with known dx SLE; consider SLE dx if end-organ involvement</li> </ul>	<ul style="list-style-type: none"> <li>- Generally good prognosis; life threatening disease is rare and should prompt workup for SLE or other CTD</li> </ul>
Sjogren's	<ul style="list-style-type: none"> <li>- F&gt;M, 40-60y. <b>Sicca</b> (dry mouth/ eyes), caries, parotid enlargement, vag. dryness. Extraglandular: fatigue, myalgia, vasculitis, nephropathy, neuropathy, cytopenias, pulm, RA/SLE w/ 2° sjogren's</li> </ul>	<ul style="list-style-type: none"> <li>⊕ ANA ⊕ <b>anti-SS-A/Ro</b></li> <li>⊕ <b>anti-SS-B/La</b></li> <li>- Schirmer test, parotid US, salivary gland bx, (<a href="#">2016 EULAR/ACR Criteria</a>)</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Sicca only</b>: sx mgmt.; regular eye, dental care</li> <li>- <b>Extraglandular</b>: HCQ, MTX, AZA, RTX, CYC, steroids</li> </ul>	<ul style="list-style-type: none"> <li>- 5-10% lifetime risk of NHL, MALT lymphoma</li> </ul>
Inflammatory myopathies (polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM))	<ul style="list-style-type: none"> <li>- F:M (2:1), 40-50yo. Symm proximal&gt;distal muscle weakness (IBM may be distal/asymm)</li> <li>- <b>Extramuscular</b>: constitutional, arthralgias, dysphagia, pulm (cough, DOE, ILD), HTN, DM2.</li> <li>- <b>DM skin findings</b>: heliotrope rash, poikiloderma (chest: V-sign; back: shawl; thigh: Holster), scalp rash, Gottron's papules, nail fold changes</li> </ul>	<ul style="list-style-type: none"> <li>⊕ <b>ANA</b> (50%), ⊕ <b>anti-Jo1</b> (20%, → <b>anti-synthetase syndr</b>: acute DM/PM, rapidly progr ILD, mechanic's hands, arthritis, Raynaud's), ⊕ anti-Mi2 (15-20%, acute, shawl, good prog.), ⊕ anti-MDA5 (↑ rapidly progr ILD, amyopathic)</li> <li>- CK/aldolase (can be wnl), myositis panel 3, LDH, AST/ALT</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Induction</b>: <b>prednisone</b>, ***IBM generally not responsive to immunosx</li> <li>- <b>Maintenance</b>: <b>AZA, MTX</b></li> <li>- <b>Resistant/severe</b>: pulse steroids, AZA, MTX, MMF, IVIG, RTX, CYC if ILD</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Occult malignancy</b> in DM (9-32%): ovarian, breast, colon, lung, NHL</li> <li>- ILD in 10%</li> <li>- Upper esoph. dz</li> <li>- ↑ risk of MI</li> </ul>
MCTD	<ul style="list-style-type: none"> <li>- 80% Female</li> <li>- Overlap of SLE, SSc, polymyositis; Raynaud's; non-erosive arthritis</li> </ul>	<ul style="list-style-type: none"> <li>⊕ ANA (often <b>speckled</b>)</li> <li>⊕ <b>anti-U1 RNP</b> (100%, not Sp)</li> </ul>	<ul style="list-style-type: none"> <li>- <b>SLE fts</b>: <b>steroids</b>, RTX.</li> <li>- If scleroderma sxs, ↓ responsive to steroids</li> </ul>	<ul style="list-style-type: none"> <li>- Main cause of death is <b>PAH</b></li> </ul>
UCTD & Overlap Synd	- Early Raynaud's, incomplete SLE	Dx of exclusion; not meeting criteria for dx of specific ds	Per 1° features	Per 1° features
Systemic Sclerosis (scleroderma, SSc)	<ul style="list-style-type: none"> <li>F:M 4:1, 30-50yo. <b>Limited cutaneous</b> (67%, hand/face skin thickening, freq. CREST sx, PAH) or <b>diffuse cutaneous</b> (33%, diffuse skin thickening, multi-organ dz, ↓ freq. CREST sx). <b>CREST</b>: Calcific nodules, Raynaud's, Esophageal dysmotility, Sclerodactyly, Telangiectasias.</li> <li>- <b>Other systemic sx</b>: renal crisis, ILD (&gt;70%), PAH (10-40%), fatigue, MSK.</li> <li>- SSc sine scleroderma = <u>no skin findings</u> (~10%)</li> </ul>	<ul style="list-style-type: none"> <li>⊕ <b>ANA</b> (95%)</li> <li>⊕ <b>anti-centromere*</b> (a/w limited)</li> <li>⊕ <b>anti-Scl-70*</b> (a/w diffuse)</li> <li>⊕ <b>anti-RNA pol III*</b> (a/w diffuse, is risk factor for scleroderma renal crisis)</li> <li>- HRCT, PFT, TTE (ILD, pHTN)</li> <li>*Ab are &gt;99% specific (<a href="#">Arthritis Rheum 2013;11:2737</a>)</li> </ul>	<ul style="list-style-type: none"> <li>- <b>ILD</b>: MMF, CYC (AZA or TCZ) induc. → MMF, AZA, TCZ maint. If progressive: anti-fibrotic, RTX. <b>PAH</b>: CCB, riociguat, ERA, PDEi, prostacyclin ag</li> <li>- <b>MSK</b>: pred, HCQ, MTX</li> <li>- <b>Raynaud's</b>: CCBs</li> <li>- <b>Skin</b>: MMF, MTX</li> <li>- <b>GI</b>: PPI &amp; promotility</li> </ul>	<ul style="list-style-type: none"> <li>↑ risk of multiple cancers. <b>Renal crisis</b> (&lt;20%): <b>avoid steroids if at risk (can trigger)</b>. AKI, abrupt HTN; a/w anti-RNA-pol III; tx w <b>ACEi</b> (captopril)</li> </ul>

# Rheumatology

# Vasculitis

**DIAGNOSTIC OVERVIEW** ([Arthritis Rheum 2013;65:1](#), image also credited from this source)

- Classified by size and type of blood vessel involved. Large vessels (aorta + branches) vs. medium-sized vessels (named visceral arteries) vs. small vessels (vessels w/o names)



## STEP 1 – SUSPECT VASCULITIS

- No “typical” presentation, consider in constitutionally ill pt w/ multisystem organ involvement & evidence of inflammation
- LARGE** vessel: aorta/branches, e.g. ext. carotid, temporal, ophthalmic → limb claud., bruits, asymm. BP, absent pulses, HA, vision loss
- MEDIUM** vessel: renal/hepatic/mesenteric arteries, etc. → cutaneous nodules, “punched out” ulcers, livedo reticularis, digital gangrene, mononeuritis multiplex (e.g. foot/wrist drop), renovascular HTN, mesenteric ischemia
- SMALL** vessel: vessels of skin, small airways, glomeruli → petechiae, palpable purpura, glomerulonephritis, alveolar hemorrhage/ hemoptysis, mononeuritis multiplex, scleritis

### General work-up:

- Inflammation?** → CBC/diff (anemia of chronic disease, thrombocytosis, neutrophilia, eosinophilia), ESR, CRP
- Organ involvement?** → BMP, LFTs, UA + sediment, CXR, brain MRI/MRA (if neurologic symptoms)
- Suspected large vessel?** → if c/f GCA (HA, jaw claud., vision Δ), see below. If other sx (GI, claudication), consider CTA/MRA C/A/P
- Suspected medium vessel?** → consider CTA/MRA c/a/p, deep biopsy of cutaneous findings (derm c/s)
- Suspected small vessel?** → ANCA (will reflex to MPO/PR3 ELISA if ⊕), immune complex w/u (C3/C4, RF, cryo), rash biopsy (derm c/s) (NB: ANA/RF not ⊕ in 1° vasculitis; ⊕RF may suggest cryoglobulinemia/endocarditis; ↓C3/C4 in cryo, SLE, 25% of PAN)

## STEP 2 – RULE OUT MIMICS and assess for SECONDARY CAUSES: based on presentation ([Int J Rheumatol. 2020:8392542](#))

- Infections:** (endocarditis, *Neisseria*, chronic osteomyelitis → immune complex deposition; HBV → PAN; HIV, HBV, & HCV → cryoglobulinemia, EBV-associated vasculitis; syphilis & TB → aortitis). **Inflammatory ds:** sarcoidosis, amyloidosis, Susac Syndrome
- Malignancies/lymphoproliferative:** lymphoma, myeloma, MGUS, IgG4-Related Disease (see *Misc Rheum* page)
- Coagulopathy/vasculopathy:** APLAS, TTP. If skin necrosis of lower ext., consider cholesterol emboli, calciphylaxis, pyoderma gangrenosum. If renal/internal carotid/vertebral art. involvement/dissections, consider fibromuscular dysplasia.
- Meds/drugs:** esp. hydralazine, PCN, sulfa, PTU, levamisole in cocaine, immunotherapy, post radiation (see ANCA in *Autoantibodies* and Drug-Induced Lupus in *Connective Tissue Diseases*)
- W/u:** BCx, HBV (med-v), HCV/HIV (small-v), syphilis/Tspot (large-v), SPEP/SFLC, tox screen. Consider IgG4, TTE, APLAS panel

## STEP 3 – CONFIRM DIAGNOSIS

Tissue biopsy: may be required to secure diagnosis. Sites: skin, sural nerve and muscle (PAN, ANCA), temporal artery (GCA), kidney (ANCA, IgA), lung (ANCA). Less common: testicle (PAN), rectum/gut, liver, heart, brain (1° CNS vasculitis), sinus (GPA)

Additional imaging: may help support med/large vessel involvement if CTA/MRA non-dx and/or tissue bx infeasible. Consider PET (GCA, Takayasu) or catheter-based angiogram (of celiac/SMA, renal (PAN), chest (Takayasu, GCA), limbs (Buerger's), brain (1° CNS vasculitis))

## LARGE-VESSEL VASCULITIS ([NEJM 2003;349:160](#), [Arth Rheum 2021;1349-1365](#), [Ann Rheum Dis. 2020;19-30](#))

**GIANT CELL ARTERITIS**: inflammation of aorta & extracranial branches (i.e., spares ICA), often temporal artery (TA). Most common primary systemic vasculitis. Age >50, 3:1 F:M. If <50 yo, rare → consider alternative dx

- Sx:** constitutional (low grade fevers, fatigue, wt loss, anorexia), new/different HA (incl. scalp tenderness), abrupt visual disturbance (amaurosis fugax, blindness, diplopia), jaw claudication (most specific; fatigue with chewing, NOT PAIN), current/recent PMR
- Exam:** asymm. BP/pulse; tender/thickened/pulseless TA; bruits; limb/jaw/tongue claud.; formal eye exam
- Dx:** combination of s/sx should prompt Doppler US & Rheum c/s. ESR (usually high but <50 in 10%), ↑CRP, ↑IL-6. **Gold standard = temporal artery biopsy** w/ granuloma (c/s surg). Start w/ unilateral; if ⊖, consider bilateral (↑yield by 5%); up to 30-45% of bx may be false ⊖ due to “skip areas”. If concern for large-vessel GCA or biopsy neg: vessel imaging (PET> CTA/MRA> US)
- Rx:** 1st line: High-dose steroids (PO pred 40-60mg qd; if c/f vision Δ, higher dose/IV immediately if ↑suspicion; NEVER delay Rx for bx. Steroid-sparing: TCZ > MTX=LEF=TNFi > abatacept ([Arthritis Care Res 2021;73:1349](#)) ↑ sust. remission w/ TCZ ([NEJM 2017;377:317](#)).

**POLYMYALGIA RHEUMATICA (PMR)**: seen in 50% of GCA pts; 10% develop GCA, peak age 70-80. 2:1 F:M.

- Sx:** symmetrical AM stiffness/pain in neck, b/l shoulders/prox arms, hips/prox thighs, constitutional sxs (malaise, fatigue, depression, anorexia, weight loss, and low-grade fever)
- Rx:** prednisone 12.5-20 mg/d w/ slow taper, consider addition of MTX or TCZ if refractory ([Ann Rheum Dis. 2022;838-844](#)).

**TAKAYASU ARTERITIS**: “pulseless disease,” granulomatous inflamm. of thoracoabd. aorta & branches. Age <40, 8:1 F:M, Asian descent

- Sx:** constitutional (fever, arthralgias/myalgias, wt loss, night sweats), vessel inflammation (carotidynia, limb claudication), vascular dz (TIA/stroke/sz/dizziness/syncope, MI/angina, HF, mesenteric ischemia). **Exam:** ↑BP, unequal pulses/BPs (LE>UE), ↓pulses, **bruits**
- Dx:** MRA or CTA; arteriography will show occlusion, stenosis, aneurysms; consider carotid US/Doppler studies, PET-CT
- Rx:** prednisone 1mg/kg/d; 50% of patients will need 2<sup>nd</sup> agent for chronic sx (MTX, AZA, TNFi > tocilizumab)

## MEDIUM-VESSEL VASCULITIS

**POLYARTERITIS NODOSA:** systemic necrotizing vasculitis that primarily affects the kidneys, skin, muscles, nerves, GI, joints, but **almost always spares lungs**. Age 40-60, a/w HBV ([Arthritis Care Res. 2021;73\(8\):1061-1070](#))

- **Sx:** systemic symptoms (fever, fatigue, weight loss); mononeuritis multiplex (~70% of pts); GI distress (mesenteric ischemia), myalgias; AKI (though GN suggests alternate etiology); gonadal pain (>10%), seizures
- **Exam:** HTN, skin lesions (erythematous nodules, purpura, livedo reticularis, ulcers, bullous eruption, palpable purpura), neuropathy
- **Dx:** gold standard = biopsy ( $\ominus$  granulomas; inflammatory infiltrates of vessel wall and fibrinoid necrosis); HBV/HCV, C3/C4, CTA/MRA w/ focal stenosis or microaneurysm (renal/mesenteric)
- **Rx:** prednisone 1mg/kg/d  $\pm$  MTX or AZA (IV steroids and CYC if severe); antivirals if HBV-related

**THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE):** segmental inflammatory nonatherosclerotic occlusive intravascular thrombi of small-med arteries and veins of extremities. Age  $\leq$ 50, 70-90% ♂, strongly a/w tobacco use. ([Cochr Syst Rev. 2016\(3\): CD011033](#))

- **Sx:** claudication (arch of foot, calf); Raynaud's (40%), ulcers and digital gangrene; livedo reticularis (hands, feet, & digits); typically ischemic symptoms start in distal vessels and progress more proximally.
- **Dx:** biopsy (rarely) or dx criteria: age, tobacco, distal ischemia (+ABI, thrombophlebitis),  $\oplus$  angiogram/CTA/MRA (segmental dz, abrupt cutoffs, corkscrew collaterals), r/o mimics (autoimmune, thrombophilia, DM, embolic)
- **Rx:** **smoking cessation!** Immunotherapy ineffective. Iloprost (PG analog, dec. amputation rates), pneumatic compression for pain, CCB for Raynaud's

## ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS (AAV)

**c-ANCA** = cytoplasmic staining (proteinase 3 [PR3]), **p-ANCA** = perinuclear staining (myeloperoxidase [MPO])

**GRANULOMATOSIS WITH POLYANGIITIS (GPA)** (Formerly Wegener's Granulomatosis): necrotizing granulomatous vasculitis commonly affecting the upper respiratory tract (upper and lower airways [90%]), and kidneys (80%),  $\pm$  cutaneous leukocytoclastic vasculitis (LCV).

- **Sx:** upper respiratory: (sinusitis/crusting rhinitis, subglottic stenosis, saddle nose, otitis media, mastoiditis, hearing loss); lower respiratory: (alveolar hemorrhage, large pulmonary nodules); kidney involvement (crescentic necrotizing glomerulonephritis)
- **Dx:** sinus CT ( $\pm$  bone erosions), Bx w/ granulomatous inflammation of vessel walls,  $\oplus$  PR3-ANCA 90%. R/o anti-GBM
- **Rx:** limited disease: MTX + prednisone; severe disease: induction w/ steroids + RTX > CYC ([NEJM 2010;363:221](#); [Arthritis Care Res 2021;73\(8\):1088](#)). Adding avacopan allows  $\downarrow$  steroids ([NEJM 2021;384:599](#)). Maintenance w/ RTX > AZA

**MICROSCOPIC POLYANGIITIS (MPA):** necrotizing vasculitis of small vessels without granulomas. All ages (mean 50-60). Similar sx to GPA w/o ENT/upper airway dz; most common cause of pulmonary-renal syndrome ([NEJM 2012;367:214](#))

- **Dx:**  $\oplus$  p-ANCA 70%,  $\oplus$  c-ANCA rare; BAL; gold standard = skin/renal biopsy; r/o HIV, cryo, anti-GBM, HBV, HCV. **Rx:** as for GPA

**EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)** (formerly Churg-Strauss Syndrome): necrotizing granulomatous inflammation of vessels in lungs, skin, nerves, heart (major cause of mortality); ↑ asthma/allergic rhinitis (asthma precedes vasculitis)

- **Dx:**  $\geq$  4 of: asthma, >10% periph. eos, neuropathy, migratory lung infiltrates, paranasal sinus dz, consistent Bx. 50%  $\oplus$  MPO-ANCA
- **Rx:** steroids  $\pm$  CYC or RTX (if severe disease) or mepolizumab (anti-IL5, if not severe, [NEJM 2017;376:1921](#)). Do not delay Rx if c/f mononeuritis (risk of nerve infarction). Screening TTE for all new dx ([Arthritis Care Res 2021;73\(8\):1088](#))

## IMMUNE COMPLEX-ASSOCIATED SMALL-VESSEL VASCULITIS ([Arth Rheum. 2019;1904-1912](#), [N Engl J Med. 2021:1038-1052](#))

**IgA VASCULITIS (HENOCH-SCHÖNLEIN PURPURA):** 90% in children; ♂>♀; preceding URI (~10d prior); in adults, ↑ severity ( $\uparrow$  nephropathy) and  $\uparrow$  a/w meds or malignancy

- **Sx:** classic tetrad of 1) palpable purpura (100%, LEs/buttocks = dependent areas), 2) colicky abdominal pain (50-65%, adults w/ ↓ intussusception), 3) arthritis (75%), 4) renal involvement (50%, proteinuria, microscopic hematuria, RPGN) ([AFR 2020;102 \(4\):229](#))
- **Dx:** clinical dx in children; in adults, confirmation w/ biopsy (leukocytoclastic vasculitis w/ vessel wall IgA dep.) preferred
- **Rx:** children: usually self-limited; adults: may require immunosuppression (orchitis, cerebral vasculitis, pulmonary hemorrhage, severe abd pain/ bleeding) w/ 1-2 mg/kg/day of prednisone or dapsone. ([Rheumatology \(Oxford\). 2019 Sep 1;58\(9\):1607-1616](#))

**CRYOGLOBULINEMIA:** 2/2 immunoglob. that precip. at  $\downarrow$  temp & redissolve w/ rewarming. Most common extrahepatic HCV manifestation.

- **Type 1:** monoclonal (usually IgM or IgG), a/w MGUS, Waldenstrom's, MM. S/Sx:  $\uparrow$  hyperviscosity ( $\uparrow$  in cold)  $\rightarrow$  acrocyanosis, digital ischemia, livedo reticularis, HA, transient CN sx; peripheral neuropathy, GN. Consider sending serum viscosity.
- **Type 2:** "mixed" monoclonal IgM against polyclonal IgG (IgM with RF activity), a/w infx ([HCV/HIV/HBV/EBV, endocarditis](#)), autoimmune dz, malign.
- **Type 3:** "mixed" polyclonal Ig (IgM or IgG) against polyclonal Ig (IgM or IgG), a/w autoimmunity (CTDs, RA, PAN), HCV. S/Sx (type 2 +3): immune complex dep.  $\rightarrow$  **Metzler triad** (palpable purpura, arthralgias, weakness), mononeuritis multiplex, GN.
- **Labs/Dx:** Send C3, C4, RF, HCV, HBV, CBC w/ diff  $\pm$  infx/rheum labs per sx above. Note: blood samples for serum cryoglobulins need to be received warm by lab, wrapped w/ hot pack, w/i 30 min of collection.
- **Rx:** avoid cold in type 1. Tx underlying cause (e.g. HCV, malign.); prednisone  $\pm$  RTX/CYC; consider plasma exchange in Type 1

## VARIABLE-VESSEL VASCULITIS

**BEHÇET'S DISEASE:** vasculitis affecting vessels of all sizes, both venous and arterial; characterized by recurrent oral and genital ulcers and skin/GI/neuro/joint/ocular sx. Age 20-40, more common in Turkey, Middle East, and Asia, a/w HLA-B51

- **Dx:** clinical dx of recurrent painful oral ulcers and ≥2 of painful genital ulcers (specific), ocular disease (uveitis, retinitis), skin lesions (pustules, folliculitis, papules, erythema nodosum),  $\oplus$  pathergy test (small needle prick elicits red pustule). May have: GI sx (similar to IBD), neurologic sx (migraine, CN abnl, venous sinus thrombosis), vascular dz (ATE/VTE, aneurysms [PA]), arthritis (nonerosive asymmetric large jnt). May have  $\uparrow$  ESR, CRP. R/o HSV as cause of ulcers.
- **Rx:** ([Ann Rheum Dis. 2018;77:808](#)) Mild (arthritis, ulcers): **colchicine**, topical steroid, low dose pred. Apremilast for ulcers ([NEJM 2019;381:1918](#)); Severe: **pred** 1mg/kg/d,  $\pm$ : AZA, TNF $\alpha$ , IFN, CYC, MTX; organ failure (esp ophth.): IV pulse steroids

# Rheumatology

# Miscellaneous Rheumatologic Diseases

## POLYMYALGIA RHEUMATICA

- Inflammatory condition characterized by proximal muscle aches and AM stiffness. Exclusively in pts >50yrs, peak 70-80yrs.
- **Sx:** abrupt onset symmetrical aching/stiffness in shoulders, hip girdle, neck, & torso, worst in AM. Stiffness with inactivity is severe. Can also have fever, malaise, weight loss. Often have limitation of active shoulder abduction.
- **Dx:** Nearly all pts have ↑ESR/CRP. Autoantibodies are negative. No agreed upon diagnostic criteria by ACR; it is a clinical dx.
- **Tx:** Steroids are mainstay of tx, low dose with prolonged taper (sometimes over years). Start w/ prednisone 15mg qd. Taper by 2.5mg every 2-4 wks if sx controlled; once at 10mg qd taper by 1mg/month. If no relapses w/ taper, can be off steroids in ~1 yr. ([ACR 2015](#))
- **10% of patients with PMR will be diagnosed w/ GCA at some point.** Screen at initial dx and routinely at f/u visits. See GCA

## IGG4-RELATED DISEASE ([Ann Rheum Dis. 2015;74:14](#); [Arth Rheum 2020;72:7](#))

- Fibro-inflammatory condition, involving pancreas, biliary tree, salivary/lacrimal glands, RP, thyroid, & orbits. Mean age ~60. M>F
- **Sx: pancreatitis** (w/ otherwise unclear etiol); sclerosing **cholangitis**; sialadenitis; lacrimal gland hypertrophy; **retroperitoneal fibrosis**; orbital pseudotumor; **mass-like** enlargement of pancreas, lungs, kidneys, or any of above organs. Often insidious.
- **Dx: tissue biopsy** (storiform ["strawlike"] fibrosis, lymphoplasmacytic infiltrate (↑IgG4+ plasma cells), obliterative phlebitis, tissue eosinophilia); ↑ serum IgG4 levels (90% Sn, 60% Sp, NPV 96%). May have ↑ serum IgE and ↓ C3/C4
- **Tx:** if sx and/or progressive imaging, **steroids ± biologics (RTX)** to induce remission. RTX often for maintenance as well

## SARCOIDOSIS ([Int Emerg Med 2018;13:325](#); [Lung 2016;194:91](#); [Am J Resp Crit Care Med 2020;201:e26](#))

- Systemic inflammatory d/o characterized by granulomatous inflammation of virtually any tissue, most commonly **hilar lymph nodes**, pulmonary parenchyma, skin, liver, eyes. F>M, young adults. ↑ in Northern pop, ↑ in Black patients
- **Sx:** fever, arthralgias, ↓ wt, fatigue; dyspnea, cough; rash; HSM, LAD; uveitis; cytopenias (BM involvement); pHTN; restrictive CM (sudden death); arrhythmias (AVB; ventricular>atrial); nephrolithiasis; neurosarcoid (CNopathy, periph. neuropathy, meningitis, seizures, hypothalamic dysfn); Lofgren syndr (↑ Sp) = hilar adenopathy, arthritis, erythema nodosum
- **Dx:** definitive dx usually requires **non-caseating granulomas on bx** (skin, LN, EBUS), compatible clinical findings, r/o of mimics. Obtain CXR (CT if atypical). No need to bx isolated asx incidental hilar LAD or if classic syndr w/ ↑ pretest prob of sarcoid (e.g., Lofgren). ↑ serum ACE 41% Sn, 90% Sp. Mimics: TB/NTM, fungal, lymphoma, GPA, IgG4, CVID, Berylliosis/Silicosis. Check Cr, alk phos, Ca<sup>2+</sup> ± 1,25-/25-vitD, CBC and baseline eye exam & EKG if new dx.
- **Tx:** many do not need tx and can be monitored for resolution/stability. If sx, oral **steroids ± MTX, TNFi, other DMARDs**

## ADULT ONSET STILL'S DISEASE (AOSD) ([J Rheumatol 1992;19:424](#))

- Rare systemic inflamm d/o w/ fevers, arthritis, rash. Monophasic, intermittent, or chronic. F=M, bimodal (15-25, 36-46 yo)
- **Sx:** fever (often spikes 1-2x daily); arthralgias; evanescent **salmon-colored maculopapular rash coinciding w/ fever**, often truncal, trauma may precipitate (Koebner phenom.); pericarditis; pleuritis; **HLH/macrophage activation syndrome**
- **Dx:** Yamaguchi criteria require **≥5 features**, including **≥2 major criteria**
  - **Major:** fever ≥39°C for ≥1w; arthralgias/arthritis ≥2w; salmon-colored rash; ↑WBC (≥80% PMN)
  - **Minor:** sore throat; LAD; HSM; ↑AST/ALT, ↑LDH; negative ANA/RF
  - **Other labs (non-criteria):** ↑ESR/CRP; **ferritin >3000** (if >10,000, consider [HLH/MAS](#), see *Hematology*); ↑plt; ↓Hgb
- **Tx:** Mild: **NSAIDs** 1<sup>st</sup> line, then glucocorticoids/DMARDs. Severe: **anakinra, pred** 0.5-1mg/kg/d +/- MTX, TNFi, anti-IL6

## RELAPSING POLYCHONDRITIS ([Rheumatology 2018;57:1532](#))

- Rare immune-mediated d/o a/w inflammation of cartilaginous structures (ears, nose, trachea, joints) & other tissue (eyes)
- **Sx:** bilateral auricular chondritis (sparring lobe), nasal chondritis (saddle-nose), arthritis, laryngeal/tracheal chondritis, valvulopathy; eye inflamm; cochlear/vestib dysfunction. **Dx:** ↑ESR/CRP; eval resp/card (CXR/CT ± bronch, PFTs, ECG/TTE)
- **Tx:** **steroids** first-line; NSAIDs for arthritis; MTX, AZA, biologics for steroid-sparing; CYC if organ-threatening

## VEXAS SYNDROME ([NEJM 2020;383:2628](#))

- Vacuolated myeloid/erythroid cells; E1 enzyme loss of fnx; **X-linked (M>F)**; Autoinflammatory; Somatic mutations in *UBA1*
- **Sx:** recurrent fever (92%); alveolitis; auricular/nasal chondritis; neutrophilic dermatosis; small to medium vessel vasculitis; cytopenias, macrocytic anemia; thromboses. 60% meet criteria for relapsing polychondritis
- **Dx:** Genetic testing. **Tx:** High-dose steroids. DMARDs not effective; poor prognosis

## FAMILIAL MEDITERRANEAN FEVER ([Am J Med 1967;43:227](#))

- Autoinflammatory disorder of recurrent fever & serositis. ↑ in Mediterranean descent, onset <10 yo (65%), <20 yo (90%)
- **Sx:** recurrent acute attacks (1-3d, resolve spontaneously) of fever a/w peritonitis (often mistaken for surgical abdomen); unilateral pleuritis; arthritis (monoarticular); skin lesions (erysipelas-like); exertional myalgia; pericarditis; testicular pain; aseptic meningitis.
- **Dx:** During acute attack: ↑ WBC, ↑ ESR/CRP. Check UA for amyloidosis (proteinuria). Genetic testing for confirmation.
  - **Diagnostic criteria:** requires 1 major or 2 minor criteria ([Arthritis Rheum 1997;40:1879](#))
- **Tx:** **colchicine** (to prevent acute attacks and progression to amyloidosis). 2<sup>nd</sup> line: anti-IL1 ([Ann Rheum Dis. 2016;4:644](#))

## FIBROMYALGIA ([JAMA Intern Med. 2021; 181\(1\):104-112](#))

- Central pain processing disorder manifesting as chronic widespread MSK pain, often w/ fatigue, sleep disturbance, and multiple somatic sx. F>M, 20-55 yo. Can coexist with other inflammatory dz like SLE, RA. Often psych. comorbidities.
- **Sx:** widespread MSK pain; fatigue; cognitive disturbance; psych. sx; HA; paresthesia; IBS. "Pan-positive" ROS not uncommon
- **Dx:** clinical: >3 mo of sxs; multiple tender points. [Newer criteria \(J Pain 2019;6:611\)](#). Labs: normal (ESR, CRP, TSH, CBC, BMP)
- **Tx:** Initial: patient education; CBT for pain; graduated **exercise program**; sleep hygiene. **Pharmacologic:** 1<sup>st</sup> line amitriptyline, duloxetine, milnacipran; may consider cyclobenzaprine, gabapentin, pregabalin (monotherapy > combo). Avoid opioids

# Rheumatology

# Autoantibodies

Antibody	Antigen (ANA Pattern if +)	Disease	Comments (See Approach to Rheum Disorders for when to order)
<b>Inflammatory polyarthritis</b>			
RF (IgM)	Fc gamma	RA (50-75%), Sjogren's (60+%), Cryoglobulinemia (90%), others	- Not Sp despite name: RA, CTD, cryoglobulinemia, chronic infxn (e.g. HCV, SBE) - + in 10% of healthy patients - RA: "seropositive", a/w erosive & extraarticular manifestations (nodules, scleritis, ILD, pleuritis, rare rheumatoid vasculitis)
CCP	Citrullinated peptides	RA (50-75%)	- Most Sp test for RA, + in 50-75% ("seropositive RA"), a/w erosive dz & extraarticular manifestations. Used for dx only, <u>NOT</u> marker of dz activity
<b>Connective tissue diseases (SLE, Sjogren's, SSc, MCTD, UCTD, DM/PM)</b>			
ANA	<p><b>When to order:</b> clinical suspicion for SLE or other ANA-+disease (<u>not</u> a screening test given high prevalence of false +; <b>not</b> to track disease activity). In populations with low prevalence of SLE (e.g. elderly), PPV low given high false + rates</p> <ul style="list-style-type: none"> <li>- ANA = antinuclear antibodies (<b>ENAs</b> ("extractable nuclear antigens") specify Ag and are a subset of ANAs). Low titer ANA ≤1:160 often false +. If ANA +, order specific autoantibodies guided by clinical presentation; 5% healthy people test +</li> <li>- + ANA: MCTD (100%), SLE (98%), scleroderma (90%), drug-induced lupus (DIL, 90%), Sjogren's (60%), PM/DM (50%)</li> <li>- Ddx for + ANA: <b>Autoimmune</b>: autoimmune hepatitis, PBC, IBD, myasthenia gravis, Graves', <b>Hashimoto's</b>; <b>ID</b>: malaria, SBE, syphilis, HIV, HSV, EBV, HCV, parvo-B19; <b>systemic inflammation</b>: lymphoproliferative d/o, IPF, asbestososis; <b>Medications</b></li> </ul>		
dsDNA	ds/mtDNA (homogenous)	SLE (40-60%)	- <u>Sp</u> for SLE, a/w SLE <b>activity</b> (follow titers) & lupus nephritis, consider TNFi DIL
Histone	Histones (homogenous)	SLE, drug-induced lupus (90%), Felty's	- <u>Sn</u> but not <u>Sp</u> for DIL - <u>Common meds</u> : procainamide, hydralazine, minocycline, phenytoin, lithium, INH, quinidine, terbinafine, TNFi
Smith	snRNP (speckled; ENA)	SLE (30%)	- <u>Sp</u> for SLE, <u>not</u> indicative of dz activity
RNP	U1-snRNP (speckled; ENA)	MCTD (100%), SLE (30%)	- <u>MCTD</u> : high-titer anti-U1 RNP. Also seen in systemic sclerosis (20%)
SS-A/Ro	Ro52, Ro60 (speckled; ENA)	Sjogren's (75%), SLE (40%)	- Can be seen with myositis, PBC, SSc. In SLE, a/w skin dz & congenital heart block. <b>2% SLE pts have - ANA but + anti-Ro</b>
SS-B/La	La (speckled; ENA)	Sjogren's (40%), SLE (10-15%)	- In SLE a/w congenital heart block
ACA	CENP A-F (centromere)	IcSSc (15-40%)	- A/w limited systemic sclerosis, <u>↑ risk of PAH</u> , <u>↓ risk of ILD</u> , esophageal disease
Scl-70	Topo-I (speckled)	dcSSc (10-40%)	- A/w diffuse systemic sclerosis; <u>↑ risk of ILD</u> , scleroderma renal crisis
RNA pol III	RNA pol. III (nucleolar)	dcSSc (4-25%)	- A/w <u>scleroderma renal crisis</u> , rapidly progressive skin disease, cancer
Fibrillarin	U3-RNP (nucleolar)	dcSSc (<5%)	- A/w PAH, pulmonary fibrosis, & myositis, esp. in African-Americans
PM-Scl	Exosome (nucleolar)	SSc (5-10%)	- A/w limited systemic sclerosis, <u>↓ risk of pulm. &amp; renal dz</u> , <u>↑ risk inflamm. myositis</u>
APL	Phospholipids (on plasma membranes)	SLE (10-44%)	- Most common: lupus anticoagulant, anticardiolipin, anti-B2-glycoprotein; ≥1 must be present ≥2 occasions at least 12 weeks apart to meet laboratory criteria
<b>Myositis</b>			
Jo-1*^	tRNA synthetase (His) (cytoplasmic)	PM/DM (30%), anti-synthetase syndrome (~20%)	- <u>Antisynthetase syndrome</u> : myositis (DM/PM), ILD (70%), polyarthritis, mechanic's hands, Raynaud's, fever
Mi-2*	Mi-2 HDAC factor (homog., speckled)	DM (15-20%)	- More likely in acute DM, good prognosis
MDA-5*^	MDA-5 dsRNA binder	DM	- Clinically amyopathic dermatomyositis, <u>rapidly-progressive ILD</u>
TIF1g*	TIF1y (fine speckled)	Juvenile DM	- A/w malignancy in adult DM
SRP*	Signal recog. particle (cytoplasmic)	PM	- Immune-mediated <u>necrotizing myopathy</u> (degenerating, regenerating, and necrotic cells on bx), rapidly progressive disease course
HMGCR	HMG CoA reductase	myositis	- Immune-mediated <u>necrotizing myopathy</u> , 70% with <u>statin</u> exposure (at any time in past), ≠ statin myopathy (does not respond to discontinuation of statin), very high CPK, often steroid-refractory, good response to IVIG
<b>Vasculitis</b>			
PR3 (c-ANCA)	Proteinase 3	GPA (90%)	- Poor correlation of titer with disease flare/remission - Antibody frequency lower in GPA <u>without</u> renal involvement
MPO (p-ANCA)	Myeloperoxidase	MPA (70%), EGPA (50%), Renal-Limited, DIV (95%)	- Poor correlation of titer with disease flare/remission - Drug-induced <u>vasculitis</u> (DIV): high-titer + for MPO (hydral, PTU, minocycline) ( <a href="#">Arthritis Rheum 2000;43:405</a> ) - <u>Levamisole vasculitis secondary to cocaine use</u> : MPO or PR3/MPO
Cryo-globulins	Fc gamma	Cryoglobulinemic vasculitis	- HCV > HBV, HIV, CTDs, lymphoproliferative disease - A/w low C4, glomerulonephritis, +RF

\* ordered as part of "myositis panel 3"; panel also includes other less common myositis antibodies

^ order separately for faster results if desired

# Rheumatology

# Rheumatologic Medications

DRUGS	INDICATIONS	COMMON TOXICITIES/NOTES
Ibuprofen, indomethacin (short act.) naproxen (long acting) celecoxib (COX-2 selective inhibitor) diclofenac ( <i>Voltaren</i> , topical)	OA, SpA, RA, gout, CPPD, SSc, SLE	Gastropathy ( $\uparrow$ w/ age; $\downarrow$ w/ PPI/misoprostol ppx, celecoxib), kidney injury (AKI, AIN, papillary necrosis), CV mortality (naproxen may $\downarrow$ risk, celecoxib noninferior, <a href="#">NEJM 2016;375:2519</a> )
Colchicine; microtubule inhibitor	Gout/CPPD, FMF, Behcet's	Diarrhea, myopathy, myelosuppression, neutropenia, med interactions ( $\downarrow$ dose if $\downarrow$ GFR)
NON-BIOLOGIC DMARDs		
Hydroxychloroquine (HCQ, Plaquenil)	SLE, RA, Sjogren's, APLAS	N/V, retinopathy (baseline & q1y retinal exam), dizziness, rash, alopecia, myelosuppr., QTc
Methotrexate* (MTX, <i>Rheumatrex</i> ); DHFR inhibitor (antifolate)	RA (first line), PsA	Myelosupp. (add <u>folate</u> ), $\uparrow$ LFTs, pneumonitis (baseline CXR), GI, stomatitis, rash, teratogen. Monitor: CBC + LFTs q12w
Azathioprine* (AZA, <i>Imuran</i> ); purine synthesis inhibitor	DM/PM, SLE nephritis, vasculitis (maintenance), RA	GI, $\uparrow$ LFTs; myelosuppression, lymphoproliferative d/o, bruising. Check TPMT deficiency and avoid XO <i>i</i> (allopurinol) as can $\uparrow$ toxicity ( $\uparrow$ 6-MP)
Mycophenolate* (MMF, Cell/Cept); purine synthesis inhibitor	AAV, DM/PM, PsA, Scleroderma, SLE	Cytopenias, $\uparrow$ LFTs, nausea, diarrhea, HA, insomnia, rash, teratogen, lymphoma/skin cancer
Leflunomide* (Arava); pyrimidine synthesis inhibitor	PsA, RA	N/V, alopecia, rash, diarrhea, HTN, hepatotoxicity, URI, dizziness/HA, teratogen
Sulfasalazine* (5-ASA, SSZ, Azulfidine)	AS, IBD, JRA, Psoriasis, RA	Sore throat, stomatitis, rash, HA, N/V, myelosuppression; check G6PD
Cyclosporine* (CsA); Voclosporin* ( <i>Lupkynis</i> ); calcineurin inhibitor (CNI)	SLE nephritis (voclosporin); RA	HTN, AKI, HA (both); N/V, GI, gum hyperplasia, hirsutism, edema, tremor (CsA); $\downarrow$ HTN & AKI and no level monitoring w/ voclosporin
Cyclophosphamide* (CYC, Cytoxin); DNA alkylation	Severe organ-threatening dz (SLE nephritis, ANCA)	Myelosuppression, lymphoma, hemorrhagic cystitis (MESNA ppx), infertility (cumulative dose, leuprolide ppx), teratogen, <1% pneumonitis
Apremilast (Otezla); PDE4 inhibitor	PsA/severe psoriasis, Behcet	N/D, URI, HA, depression, wt loss
Tofacitinib* ( <i>Xeljanz</i> ); JAK1&3 inh. Upadacitinib* ( <i>Rinvoq</i> ); JAK1 inhib. Baricitinib* ( <i>Olumiant</i> ): JAK1&2 inh.	RA, AS, psoriasis	Malignancy and CV events ( <a href="#">NEJM 2022; 386:316</a> ). Infection, $\uparrow$ LFTs, diarrhea, $\uparrow$ VTE, death (black box warning)
BIOLOGICS		
Adalimumab* ( <i>Humira</i> ); anti-TNF Infliximab* ( <i>Remicade</i> ); anti-TNF Golimumab* ( <i>Simponi</i> ); anti-TNF Certolizumab ( <i>Cimzia</i> ); anti-TNF Etanercept ( <i>Enbrel</i> ); sol. TNF-R	AS, IBD, Ps/PsA, RA	CHF (contraindicated in HF), HA, nausea, rash, infection, drug-induced lupus, skin cancer. Monitor: CBC, LFTs q3-6 mo NB: <u>safe</u> w/ HCV ( <a href="#">Expert Opin Biol Ther 2012;12:193</a> )
Rituximab* (RTX, <i>Rituxan</i> ); anti-CD20 Obinutuzumab* ( <i>Gazyva</i> ); anti-CD20	APLAS, ANCA, IgG4, Scl-ILD, SLE	Infection, HTN, infusion reaction (use premeds), PML, fever, rash/pruritus, LE edema
Belimumab* ( <i>Benlysta</i> ); anti-BAFF	SLE	Depression, HA, infusion reaction, PML, GI
Abatacept* ( <i>Orencia</i> ); soluble CTLA4	PsA, RA	Infection, HA, nausea, dizziness, HTN, dyspepsia
Tocilizumab* ( <i>Actemra</i> ); anti-IL6R	GCA, RA, PMR	Infection, hepatotoxicity, HLD, GI perforation
Anakinra* ( <i>Kineret</i> ); anti-IL-1R; Canakinumab* ( <i>Ilaris</i> ); anti-IL1 $\beta$	Gout/CPPD, AOSD/MAS	Myelosupp./neutropenia (anakinra), rash/inj. rxn/pain, HA, arthralgia, fever, N/D (canakinumab)
Secukinumab* ( <i>Cosentyx</i> ); Ixekizumab* ( <i>Taltz</i> ); anti-IL17A	AS, Ps/PsA	Infection, IBD flare, diarrhea; neutropenia (ixekizumab)
Ustekinumab* ( <i>Stelara</i> ); anti-IL-12/23 Guselkumab* ( <i>Tremfya</i> ); anti-IL23 Risankizumab* ( <i>Skyrizi</i> ); anti-IL23a	Ps/PsA, IBD	Infection; RPLS, seizures (ustekinumab); HA, diarrhea
Anifrolumab*, anti Type I IFN-R	SLE	Infection, bronchitis/URI, heme malignancies, hypersensitivity
Mepolizumab* ( <i>Nucala</i> ); anti-IL5	EGPA	Inj rxn, HA
Avacopan* ( <i>Tavneos</i> ); anti-C5aR	ANCA (GPA, MPA)	HA, N/V/D, HTN, rash, $\uparrow$ LFTs
Intravenous immunoglobulin	APLAS, DM/PM, IMNM, Kawasaki's	Transfusion reactions/anaphylaxis, aseptic meningitis, thromboembolism, HA

\*Can  $\uparrow$  HBV/TB reactivation and chronic infection risks (check HBV/HCV serologies, HIV, and IGRA or PPD prior to starting)

# Endocrinology

# Outpatient Type 2 Diabetes Mellitus

## SCREENING ([Diab Care 2023:46;S19](#))

- ADA recs: Begin at age  $\geq 35$  years, repeat q3y if normal. Repeat q1y if pre-DM. All adults at higher risk = 1) BMI  $\geq 25$  ( $\geq 23$  in Asian-Americans) + RF (1<sup>st</sup> degree relative with T2DM, nonwhite, history of CVD, HTN, HDL <35, triglycerides >250, PCOS, sedentary lifestyle, severe obesity, acanthosis nigricans) or 2) History of gestational DM or 3) HIV prior to starting/switching ART. ([ADA 2022](#)).

## PRE-DIABETES ([Diab Care 2023:46;S19](#))

- Diagnosis: A1c 5.7-6.4%; fasting plasma glucose (FPG) 100-125; or 75g OGTT w/ 2h glucose 140-199
- Monitoring: A1c at least q1y; if A1c 6-6.4%, screen q6mo (25-50% 5-year risk of progression to diabetes if A1c 6-6.5%)
- Treatment: **lifestyle**  $\Delta$  most effective; **metformin** also effective, esp. if BMI  $\geq 35$ , age  $< 60$ , or GDM hx ([Cochrane Rev 2019](#))

## DIABETES ([Diab Care 2023:46;S19](#)) ([Diab Care 2023:46;S97](#))

- Diagnosis: A1c  $\geq 6.5\%$ ; FPG  $\geq 126$ ; 75g OGTT with 2h glucose  $\geq 200$ ; or random BG  $\geq 200$  & symptoms. Unless diagnosis is made by symptoms & random glucose  $> 200$ , **confirm with repeat or additional test**.
  - For **T1DM**, check TSH at dx and q1y. Screen for celiac at dx, and again if signs/sx develop. ([Diab Care 2023:46;S49](#))
  - Use plasma blood glucose criteria and not A1C if high RBC turnover: sickle cell disease, 2nd/3rd trimester of pregnancy,  $\downarrow$  G6PD, HD, recent blood loss/transfusion, EPO tx.
  - A1c less reliable post-partum, with certain HIV drugs, thalassemia and sickle cell (high cell turnover), and anemia ([UTD list](#))
- Tx goal A1c  $< 7\%$ ; can liberalize to  $< 8-8.5\%$  if life expectancy  $\leq 10$  years or high risk for hypoglycemia

## Healthcare Maintenance for Diabetic Patients ([Diab Care 2023:46;S49](#)) ([Diab Care 2023:46;S158](#))

Every visit	<ul style="list-style-type: none"><li>Review blood sugar log: <b>goal AM FPG 80-130</b>, postprandial (1-2h) <math>&lt; 180</math>; screen for <b>hypoglycemia awareness</b></li><li>Review medication regimen and medication-taking behavior</li><li>Blood pressure: <b>goal &lt;130/80</b> (if it can be safely attained). ACEi/ARB first line.</li><li>Weight, BMI: weight center referral if BMI <math>\geq 40</math> or <math>\geq 35</math> with poor control; nutrition referral for all (Obesity Meds)</li><li><b>Foot exam</b> (inspect skin, joints, pulses, sensation) esp. if known neuropathy or PVD; ABIs/vascular referral if PVD</li><li>Screen for tobacco, alcohol, and substance use and provide appropriate counseling</li></ul>
Q3-6mo	<ul style="list-style-type: none"><li>A1c <b>q6mo</b> if controlled; q3-6mo if A1c above target</li></ul>
Annually	<ul style="list-style-type: none"><li>Lipids: Age 20-39 consider statin if additional risk factors. Age 40-75: moderate-intensity <b>statin for all DM pts regardless of lipid panel</b>. If CVD or 1+ ASCVD risk factor then <b>high intensity statin</b> w/ target LDL-C <math>&lt; 70</math>.</li><li>Urine mAlb/Cr, Cr/eGFR; ACEi/ARB if hypertensive w/ proteinuria <u>or</u> GFR <math>&lt; 60</math>; refer to renal if GFR <math>&lt; 30</math></li><li>Neuropathy exam: 10g monofilament (+ if no sensation at 4/10 sites, see <a href="#">PCO1</a>); pinprick, vibration, or reflexes</li><li>Retinopathy screen w/ dilated eye exam or retinal photography; can consider q2-3y if normal exam(s)</li><li>LFTs: consider elastography and/or hepatology referral if elevated to evaluate for NASH</li><li>Other: B12 for those on metformin. T1DM – yearly TSH.</li></ul>
Vaccines	<ul style="list-style-type: none"><li>Influenza annually, Hepatitis B series if age <math>&lt; 60</math> and not immune, Zoster, TDAP, Pneumococcus (<a href="#">CDC</a>)</li></ul>

## Basal Insulin Management ([Diab Care 2023:46;S140](#))

Criteria for initiation	<ul style="list-style-type: none"><li>Consider if <b>A1c <math>\geq 9\%</math></b>, random BG <math>\geq 300</math>, fasting BG <math>\geq 250</math>, or symptomatic; suspicion for T1DM or LADA; <math>&lt; 65</math>yo on two agents with A1c <math>&gt; 8\%</math> (or <math>\geq 65</math>yo and A1c <math>&gt; 8.5\%</math>) on two occasions <math>&gt; 3</math> mo apart; or A1c rising quickly.</li><li>Able to perform self-monitoring with glucometer; consider referral to DM educator</li></ul>
Initial dose	<ul style="list-style-type: none"><li><b>Starting dose:</b> 0.1-0.2U/kg/d or 10U/d (if weight <math>&gt; 80</math>kg, may consider starting at 20U/d)</li><li><b>Choice of agent:</b> choose long-acting (glargine/qd) <b>or</b> intermediate-acting (NPH BID <math>\rightarrow</math> cheaper)</li><li><b>Route:</b> pen (easier to use, more expensive) vs needle/syringe</li></ul>
Titration	<ul style="list-style-type: none"><li>Increase by 2-4U or 10-15% q3d until AM fasting BS is 80-130 without hypoglycemia; savvy patients can self-titrate.</li><li>If hypoglycemia occurs or FPG <math>&lt; 80</math> without clear reason, decrease dose by 10-20% or 4U, whichever is greater.</li></ul>

## Prandial Insulin Management

Criteria	<ul style="list-style-type: none"><li>Consider if A1c still not at goal with basal insulin <math>&gt; 0.5</math>U/kg/d and fasting glucose within target range (80-130).</li></ul>
Initial dose	<ul style="list-style-type: none"><li><b>Strategy 1:</b> add 1 rapid-acting insulin before largest meal <math>\rightarrow</math> start w/ 4U or 0.1U/kg or 10% basal dose</li><li><b>Strategy 2:</b> change to mixed insulin (e.g. fixed 70/30, NPH + regular) BID (before breakfast and dinner). Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM. Confirm w/ pt they eat 3 meals regularly if choosing this.</li></ul>
Titration	<ul style="list-style-type: none"><li>Increase dose by 1-2U or 10-15% q3d until target glucose reached (pre-prandial: 80-130; 1-2h post-prandial <math>&lt; 180</math>)</li><li>If A1c still not controlled: add rapid-acting insulin to another meal and titrate as above</li><li>If hypoglycemia occurs or FPG <math>&lt; 80</math> without clear reason, decrease dose by 10-20% or 4U, whichever is greater</li></ul>

## INSULIN SUPPLIES

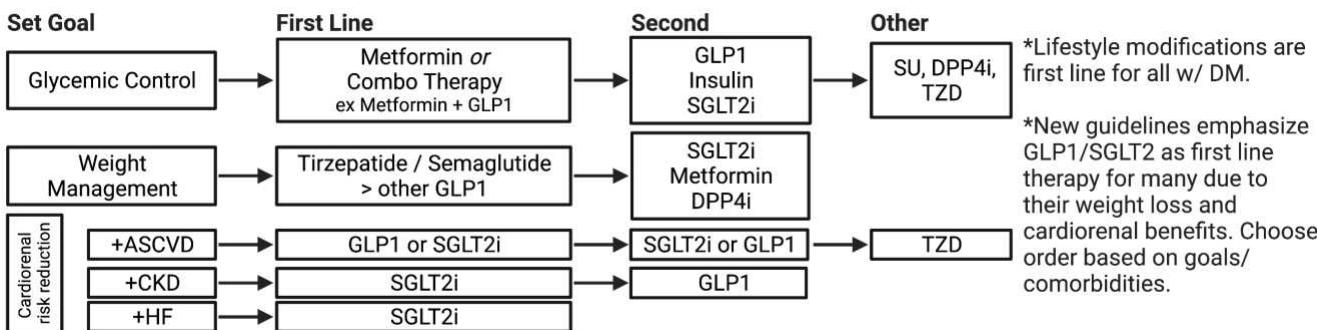
- Needles: Pen needles for pts on insulin pen or 2)needle+ syringe 32G 4mm is less painful (higher gauge = thinner and shorter needle), but larger patients and high insulin doses often require longer/wider needle.
- Syringes: boxes of 100. Choose smallest syringe that will hold the dose (smaller barrel  $\rightarrow$  clearer scale markings)
- Alcohol swabs (or patients can wash hands/skin with soap and water)
- Glucometer & test strips: Many choices, each with own strip brand. Most test strips come in boxes of 50-100. Some glucometers can read BG aloud (helpful for visually impaired). Tip: MassHealth only covers FreeStyle. Otherwise OneTouch Verio usually covered.
- \*\* All durable medical equipment including test strips and glucometers requires an ICD-10 code on the script itself\*\***

Use this barrel size...	With this dose range...
3/10 mL	30U or less
1/2 mL	31-50U
1 mL	51-100U

# Endocrinology

# Outpatient Type 2 Diabetes Mellitus

## ALGORITHM FOR ORAL ANTI-DIABETIC THERAPY ([Diab Care 2021;44:S111](#)) (PCOI)



## NON-INSULIN AGENTS

Drug/Dose Range	%↓ A1c	Indications/Benefits	Contraindications	Side Effects/Considerations
<b>Metformin:</b> 1 <sup>st</sup> line anti-diabetic medication; many effects, primary mechanism is decreasing hepatic glucose production				
<b>Metformin (Glucophage)</b> 500-1000mg BID	1-2	<b>First line therapy</b> Weight loss Improvement in lipids	GFR cutoffs: <45mL/min don't initiate <30mL/min discontinue Metabolic acidosis	<b>Nausea, bloating, diarrhea</b> B12 deficiency <b>Lactic acidosis</b> in severe liver/renal disease or hypoperfusion state
<b>Metformin pearls:</b> discuss GI sx (decrease over time). Minimize by advising slow titration (250-500mg/wk), taking <u>WITH</u> food, or switching to XR formulation. Benefits/side-effects are dose-dependent – <u>maintain highest dose tolerated</u> .				
<b>SGLT-2 Inhibitors:</b> block renal glucose reabsorption, increase glucosuria				
<b>Canagliflozin (Invokana)</b> 100-300mg qd <b>Empagliflozin (Jardiance)</b> 10-25mg qd <b>Dapagliflozin (Farxiga)</b> 5-10mg qd	0.8-0.9	<b>↓CV events, ASCVD mortality, CHF hospitalization, CKD progression</b> ( <a href="#">NEJM 2019;380:2295</a> ) <b>Weight loss</b> ↓ risk of hypoglycemia ↓ BP 3-5mmHg	GFR cutoffs: <45mL/min new data suggests ok to initiate <30mL/min discontinue *Prior DKA	<b>UTI &amp; GU fungal infections</b> Small risk of <b>euglycemic DKA</b> (hold in pts 3-4 days prior to surgery & post-op until take PO) Risk of dehydration/HoTN Risk of fracture (canagliflozin) May ↑ LDL cholesterol ? ↑ risk amputation w/ canagliflozin
<b>SGLT2i pearls:</b> Discuss diuretic effect, replace water loss to avoid euglycemic DKA. Initiate 1 mo low dose, then titrate to effective dose. For potency, empagliflozin > canagliflozin > dapagliflozin. HF benefit is probably not a function of A1c lowering.				
<b>GLP-1 Receptor Agonists:</b> stimulate glucose-dependent insulin release from beta cells. Slow gastric emptying, promote satiety and w/l				
<b>Liraglutide (Victoza)</b> 0.6-3mg qd <b>Dulaglutide (Trulicity)</b> 0.75-4.5mg qwk <b>Semaglutide (Ozempic)</b> 0.25-2.4mg qwk	0.5-2 *	<b>↓ CV events, ASCVD</b> <b>Weight loss</b> First line injectable therapy (before basal insulin) ↓ risk of hypoglycemia ↑ dose ↑ efficacy (wt/A1C)	<b>FDA Black Box Warning:</b> ↑ risk medullary thyroid ca. in rodents, not yet demonstrated in humans. Avoid if hx MTC/MEN2	<b>GI: n/v, diarrhea</b> <b>Injection site reactions</b> Delayed gastric emptying ↑ risk of pancreatitis Low starting dose is to avoid GI side fx. Up titrate for effective wt loss/A1C lowering
<b>GLP-1 RA pearls:</b> for weight loss, semaglutide > dulaglutide > liraglutide > others. Up-titrate to effective dose in 1mo intervals.				
<b>DPP-4 Inhibitors:</b> inhibit degradation of endogenous GLP1, ↑ glucose-dependent insulin secretion and ↓ glucagon secretion.				
<b>Sitagliptin (Januvia)</b> 25mg-100mg qd <b>Linagliptin (Tradjenta)</b> 5mg qd	0.5-0.8	Linagliptin preferred if CKD/ESRD ↓ risk of hypoglycemia Weight neutral	No contraindications, but very weak	Saxagliptin, alogliptin: ↑ hosp for <b>CHF</b> Joint pain
<b>Insulin Secretagogues:</b> stimulate release of insulin from pancreatic beta cells, thus only effective in pts who still have beta cell function				
<b>Sulfonylureas:</b> <b>Glipizide</b> 2.5-20mg qd <b>Glimepiride</b> 1-8mg qd	1-2	Affordable	T1DM, DKA Low cross-reactivity in pts with sulfa allergy	<b>Weight gain</b> <b>Hypoglycemia</b> (esp. glyburide) Possible ↑ CV mortality
<b>Meglitinides: Repaglinide</b> (Prandin) 0.5-4mg qAC	0.5-0.7	Use like bolus insulin (short-acting) <b>CKD</b> ↓ nocturnal hypoglycemia	Severe liver disease Concurrent gemfibrozil therapy	<b>Weight gain</b> <b>Hypoglycemia</b> ↑ serum conc. w/ clopidogrel TID dosing
<b>Thiazolidinediones:</b> increase insulin sensitivity by acting on adipose, muscle, and liver to ↑ glucose uptake, ↓ ectopic lipid deposition				
<b>Pioglitazone (Actos)</b> 15-30mg qd	1-1.6	↓ risk of hypoglycemia Possible benefit in NASH	Hx of bladder cancer, renal impairment NYHA Class III/IV HF	<b>FDA Black Box Warning:</b> ↑ risk of <b>CHF</b> (2/2 ↑ fluid retention) <b>Weight gain;</b> ↑ risk of fracture

# Endocrinology

# Inpatient Diabetes Mellitus Management

## INSULIN NOMENCLATURE

Type (Onset)	Formulation	Peak	Duration
Rapid (10min)	lispro (Humalog) aspart (Novolog) glulisine (Apidra)	30-60min	~4h
Short (30min)	Regular insulin (Humulin R, Novolin R)	2.5-5h	~6h
Intermediate (1-2h)	Insulin NPH (Humulin N, Novolin N)	4-12h	~12h
Long (3-4h)	glargin (Lantus) qD detemir (Levemir) qD degludec (Tresiba) qD	none	24h

**Basal insulin:** standing (NOT PRN) fixed intermediate/long-acting for basic metabolic requirements

**Prandial insulin:** standing (NOT PRN) rapid/short-acting to cover meals

**Correctional insulin:** sliding scale (can be standing or PRN depending on pt) rapid/short-acting to correct hyperglycemia from prior meal

**Pre-Mix** (avoid in hospital, but consider for transition to outpatient regimen): combine basal and prandial insulin into one injection

**Insulin gtt:** use in ICU if BG >180 x2 and anticipated ICU LOS >3 days; reference [MICU Insulin Protocol](#) in Partners Handbook. Always overlap with SC insulin by 2-3h before stopping insulin gtt

## INPATIENT MANAGEMENT ([Diabetes Care 2021;44:S211](#))

- Glycemic targets: **Floor:** fasting 100-140mg/dL, random <180 mg/dL. **ICU:** 140-180mg/dL (NOT stricter) ([NEJM 2009;360:1283](#))
- Check BG in: (1) diabetics (2) non-diabetics with gluc >140mg/dL (3) pt w/ therapies a/w hyperglycemia (glucocorticoids, octreotide)
- How to check: **FSBG qAC** (at least for 24-48h) initially OR **FSBG q6h if NPO** or on **continuous TF or TPN**.

Note: FSBGs less accurate in hypotension (esp. on pressors), hypothermia, and Raynaud's/ altered blood flow to skin. Confirm with BMP.

### Admission Orders ([NEJM 2006;355:1903](#))

- Hold home oral antihyperglycemic agents when patients are acutely ill (**NEVER hold basal insulin for T1DM**)
- Check A1c** in all patients with DM/hyperglycemia if not done in last 3 months
- If on insulin at home: 25-50% reduction given expected change in diet while hospitalized and initiate ISS for correction and **then adjust basal-bolus dosing over the hospitalization** ([Diabetes Conversion Guidelines](#))
- If **not** on home insulin:
  - Well-controlled: start with **lispro ISS and change to basal-bolus** once TDD established. Prolonged use of ISS as only anti-hyperglycemic tx is **discouraged (SSI-only reg. suboptimal unless pt well-controlled on orals)** ([J Hosp Med 2019;2:114](#))
  - Not well-controlled (BG >180mg/dL): start w/ **basal (0.25U/kg)**, use 0.15U/kg in pts with ESRD, elderly, and low BMI. Then add prandial insulin (0.05-0.1U/kg) qAC PLUS correctional insulin qAC.
- If NPO:** 50% dose reduction or 0.1U/kg/day for basal. Hold prandial & change correctional ISS and FSBG from TID qAC to q6h
- Correctional insulin sliding scale:** use low-dose if insulin-sensitive/ESRD/ESLD/frail, always do TID qAC and MAKE SURE no HS

**Adjusting Insulin Dosing:** in general, adjust insulin requirement by no more than **20%**.

Fasting/AM BG ↑ (or ↓) from qHS glucose	→	↑ (or ↓) basal insulin dose*
Fasting BG high + qHS BG high but are the same	→	↑ dinner prandial insulin dose (no Δ basal)
BG rises with each meal over the course of the day	→	↑ prandial insulin dose at each meal
Pre-lunch or dinner BG high (w/ other BGs in range)	→	↑ prandial insulin dose of preceding meal

\*Avoid titrating basal insulin more than q2-3d (d/t long half life, requires time to reach steady state) to avoid "stacking" and hypoglycemia

- Glucocorticoids:** NPH 0.1U/kg/d for every 10mg pred (or equivalent), up to 0.4U/kg/d (dose BID); if dexamethasone, use glargin qD
- Tube feeds:** if not on insulin, start with **regular ISS q6h**. Convert to NPH BID based on needs. **If on insulin, use ½ basal (NPH BID) + ½ bolus (regular insulin q6h) + ISS.** If TF stopped, give D5W at TF rate until next NPH dose would have been due, and ↓ NPH dose by 50% or more based on pre-TF insulin requirements. **TPN:** regular insulin can be added to TPN (discuss w/ nutrition)
- Insulin pumps:** consists of basal rate (units/kg/h) which replaces glargin, carb ratio (units insulin:gram carbs) which replaces standing prandial, sensitivity factor (units insulin:mg/dL above target which is just SSI, & insulin action time). **Complications:** site infection, pump failure interrupting infusion. **Endocrine consult required** and will develop a contingency plan in case of pump failure
- Patient's Home CGM:** Can be used to titrate insulin while inpatient but note that often the BG reading is 20-30 minutes delayed and should be cross-checked with FSBG initially. **Can consult endocrine for help with this.**

**Discharge:** if new home insulin → nutrition c/s + floor RN teaching and outpatient f/u. Using discharge order set, send rx for glucometer, test strips, lancets, syringes/vials or pens/needles to MGH outpatient pharmacy and bring up to floor for RN teaching ([MGH video link](#)).

## INPATIENT HYPOGLYCEMIA

↑ Risk: T1DM, brittle DM, malnutrition, emesis, ↓ body weight, ↓ PO intake, ↓ steroid dose, AKI (↓ insulin clearance), CKD (esp. dialysis)

### Beware of hypoglycemia unawareness in T1DM and longstanding T2DM

**Manifestations:** BG<70: Adrenergic component: shakiness, anxiety, diaphoresis, acute hyperphagia. Neuroglycopenic component: AMS, malaise. <55 with risk of seizure, coma

**Treatment:** PO (15g gel, tabs, juice) > IV (12.5-25g D50) > IM/SQ (1mg glucagon); recheck in 15min, chase with PO if due to insulin OD

If sulfonylurea OD: 50-75mcg octreotide SQ. **Review and adjust insulin**

**Ddx:** If ill/medicated: drugs (insulin [secretagogues], EtOH), sepsis, ESLD, ESRD, HF, adrenal insufficiency, non-islet cell tumor

If well-appearing: post-gastric bypass (post-prandial, or "reactive", hypoglycemia), insulin or insulin receptor antibodies, insulin (secretagogues), insulinoma (particularly if fasting hypoglycemia)

**Workup:** must meet **Whipple's Triad** to merit eval! Triad of 1) sx c/w ↓BG, 2) reliably ↓BG whene sx present, 3) sx relief once euglycemic

- Mixed-meal with postprandial eval (q30min labs for 5h post-meal, or fasting eval with admission for 72h fast)
- Check: serum glucose, insulin level, C-peptide, βHB, proinsulin, sulfonylurea/meglitinide screen at time 0

Insulin	Pro-Insulin	C-Peptide	Ddx
↑	↑	↑	Insulinoma, oral hypoglycemic, autoimmune
↑	↓	↓	Exogenous insulin administration
nl	nl	nl	Non-islet cell tumor, e.g. IGF-2-secreting tumor

## DIABETIC KETOACIDOSIS (DKA)

**Pathophysiology:** think about each element of Diabetic Keto-Acidosis

- Diabetes: ↓insulin & ↑opposing hormones (glucagon, catechols, cortisol) → hyperglycemia → osmotic diuresis → hypovolemia
- Ketones: ↓insulin → ↑lipolysis → ↑free fatty acids → ↑ketones (acetooacetate, β-hydroxybutyrate, acetone)
- Acidosis: ↑β-hydroxybutyrate and acetooacetate, and contraction alkalosis with total body HCO<sub>3</sub> deficit ([NEJM 2015;372:546](#))

**Precipitants (the “I’s”):** infection (30-40% of cases, commonly PNA or UTI), initial presentation of DM (20-25% of cases), insulin non-adherence, inflammation (pancreatitis – but can see ↑amylase/lipase in DKA even w/o this), infarction (MI, CVA, gut), intoxication (EtOH, cocaine), iatrogenesis (e.g., SGLT2 inhibitors, steroids, thiazides, dobutamine/terbutaline, atypical anti-psychotics), infant (pregnancy)

**Presentation:** dehydration, polyuria/polydipsia, weight loss, n/v/abd pain, AMS, Kussmaul's respirations, fruity breath (acetone)

**Dx:** BG 250-800, pH <7.3, HCO<sub>3</sub> < 18, AG >10, ketonemia. Consider euglycemic DKA in pt on SGLT2i, EtOH liver dz, pregnancy

- Check BMP, CBC/diff, UA, SOsm, serum β-hydroxybutyrate, ABG/VBG (if serum bicarb reduced or hypoxemic). Consider hs-trop, EKG, BCx/UCx, CXR, lipase/amylase
- **Na correction** → use absolute sodium value when calculating anion gap. Use corrected value to assess for underlying hypotonic hypoNa: Corrected Sodium = Measured sodium + 0.02 \* (Serum glucose - 100).
- UA ketone **does not** test for β-hydroxybutyrate, which is the predominant ketone in DKA (must measure from **serum**)

**Management:** prioritize ABCs, volume status, identifying precipitant → THEN electrolytes (especially K+) → THEN glucose

Labs: BMP q2h until AG closes, then q4h until normal K<sup>+</sup>; VBG, β-hydroxybutyrate q2-4h; FSBG q1h while on insulin gtt

**Step 1: volume resuscitation** (typically 5-8L deficit) ([QJM 2012;105:334](#); [JAMA Netw Open 2020;3:e2024596](#))

- Bolus LR 15-20cc/kg/h for initial resuscitation in first 1-2h (unless CHF, ESLD, ESRD, hypoxemia)
- Corrected Na → if low, start NS/LR±K<sup>+</sup> at 250-500cc/h; if **normal/high** or hyperCl acidosis, start ½NS/LR±K<sup>+</sup> at 250-500cc/h
- Add D5 to IVF at 150-200cc/h once BG<200 (DKA) or <300 (HHS)

**Step 2: potassium repletion and management**

Potassium	Action	
K <3.3	Give 20-40mEq KCl IV per hour + <b>hold insulin!</b>	
3.3≤K≤5.3	Add 20mEq K to IVF	
K >5.3	Continue to monitor q2h	K <sup>+</sup> may be normal/elevated at presentation, but total body K <sup>+</sup> is low. Multifactorial causes: solute drag of K <sup>+</sup> into extracellular space, osmotic diuresis, ↓insulin not driving K <sup>+</sup> into cells. <b>Aggressive K<sup>+</sup> repletion</b> is critical: HYPOkalemia will limit your ability to administer the necessary insulin!

**Step 3: insulin therapy**, see [flow chart](#) ([Diabetes Metab Syndr Obes. 2014;7:255](#))

The #1 goal of insulin therapy in DKA is to stop ketogenesis and close the AG

- **Don't start insulin until you have control of K<sup>+</sup>**
- **Don't stop the insulin gtt unless true hypoglycemia (<65 mg/dL) or hypokalemia (<3.3 mEq) occurs**
- **Initial:** bolus 0.1U/kg regular insulin, then start 0.1U/kg/h IV regular insulin gtt; OR no bolus and start 0.14U/kg/h IV gtt
  - Goal is to ↓BG by 50-75mg/dL each hour
  - For mild DKA, subcutaneous insulin regimens may be used instead of IV ([Cochrane Rev 2016](#))
- **Titrating insulin drip: MICU insulin gtt protocol is NOT for DKA**
  - If BG does not ↓ by 10% in 1<sup>st</sup> hr, re-bolus (DKA) or double the gtt (HHS), no evidence for hourly titration afterwards
  - If BG >250 and falling: increase gtt by 25% if drop is <40, no change if drop is 40-80, decrease by 50% if drop >80
  - Once BG <200 (DKA) or <300 (HHS), ↓gtt to 0.02-0.05U/kg/h and add D5 to fluids
  - Goal BG is 150-200 (DKA) or 250-300 (HHS)

**Other electrolytes:**

- **HCO<sub>3</sub>:** no proven benefit w/ pH > 6.9. If pH <6.9, give 2 amps HCO<sub>3</sub> dissolved in 400mL sterile water w/ 20mEq KCl over 2h
- **Phos:** total body deficit but serum phos may be ↑/nl; will ↓ w/ insulin; **only replete if <1.0** to prevent cardiac dysfunction

**Transitioning to SQ insulin:** start if BG <200 and pt is able to eat and two of the following are met: AG <12, HCO<sub>3</sub> ≥15, pH >7.3

- **Basal** regimen w/ either: home glargine dose OR glargin at 0.25-0.4 U/kg/d OR glargin at (# units on IV gtt over past 6h x 4 x 0.7). Consider NPH 0.25-0.4U/kg/d in pts presenting with newly diagnosed DM for easier titration (split dose as 2/3 AM dose, 1/3 PM dose).
- **Bolus** regimen w/ either: 0.25-0.4U/kg/d divided (if T1DM or unknown) OR ISS only (if T2DM). **Overlap IV gtt/SQ insulin by 2-4h.**

**Ketosis-prone diabetes:** characterized by DKA w/ hx T2DM or atypical substrate for T1DM (older age, overweight). Patients should be discharged on insulin and see an endocrinologist for antibody (GAD65, IA2) and β-cell function (C-peptide levels) testing to determine diabetes subtype (antibody, β-cell function). Patients may not require long-term insulin therapy.

For BG <150	Δ Insulin gtt and glucose source
BG 91-149	↓gtt by 25% + 1D5 gtt by 50cc/hr
BG 66-90	↓gtt by 50% + ½ amp D50 + continue D5 gtt
BG ≤65	hold insulin + 1 amp D50 + continue D5 gtt

## HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)

**Pathophysiology:** hyperglycemia → osmotic diuresis → volume depletion; ketogenesis suppressed by low (but present) insulin levels

**Precipitants:** same as DKA (note: pts w/ T2DM and burnt-out pancreas can also present with DKA)

**Presentation:** AMS (25-50%), obtundation, seizure, focal neuro def, volume depletion, evolves over days-weeks (vs hours-days in DKA)

**Dx:** glucose >600mg/dL (frequently >1000), osmolality >320mOsm/kg, pH >7.3, absent or minimal ketones

**Management:** as above for DKA w/ modifications: more aggressive IVF (~8-10L deficit); **goal glucose 250-300mg/dL** (in DKA, 150-200); transition to SQ insulin when BG <300 and mental status improved, and patient is able to eat. Mortality >> DKA ([Diab Care 2014;37:3124](#))

# Endocrinology

# Adrenal Insufficiency

## Etiology ([Lancet 2014;383:2152](#); [NEJM 2009;360:2328](#))

Primary AI (Addison's disease): ↓ all adrenal hormones → ↑ ACTH. Lesion localizes to bilateral **adrenal glands**

- Causes: autoimmune (80-90% cases in developed countries; anti-21-hydroxylase Ab+ in 86%, autoimmune polyglandular syndromes) >> infection (TB, HIV, CMV, meningococcus, histoplasmosis, fungi except *Candida*; most common cause worldwide), bilateral adrenal hemorrhage (infection, DIC, APLAS), infiltration (hemochromatosis, primary amyloidosis), malignancy (mets), genetic

Secondary AI: ↓ ACTH → ↓ adrenal hormone (**glucocorticoids only**). Lesion localizes to **pituitary gland or hypothalamus**

- Causes: Abrupt cessation of chronic supraphysiologic glucocorticoids, meds, pituitary/hypothalamic lesions (see *Pituitary Disorders*)

## Clinical Manifestations ([Lancet 2003;361:1881](#))

Primary AND Secondary:

- Signs/symptoms: weakness, fatigue, anorexia, nausea, abdominal pain, psychiatric sx, orthostasis, ↓ wt
- Lab abnormalities: **hyponatremia**, hypoglycemia, hypercalcemia, non-AG acidosis, anemia, eosinophilia, lymphocytosis

Primary only (↓ serum aldo): **hyperK (only 65%)**, salt craving, **hyperpigmentation** (↑ MSH), n/v, abdominal pain, ↓ BP, ↑ HR, shock

Secondary only (RAAS intact): ± hypopituitarism, hypoglycemia (more common than in primary AI)

## Diagnosis

- Preferred test: cosyntropin stimulation test (aka "cort stim") ([JCEM 2016;101:364](#)). Can be performed any time of day
  - Check serum cortisol and ACTH → give cosyntropin (ACTH) high-dose 250 µg IV → repeat serum cortisol **30 and 60min later**
  - Normal response: serum cortisol >15 µg/dL (note: this rules out all cases of 1° AI + chronic cases of 2° AI)
    - In acute 2° AI, adrenal glands have not had time to atrophy, so cort stim test will be normal
  - If abnormal cort stim, consult endocrine
- Second line: If cort stim is not possible, check AM cortisol and ACTH as a preliminary test to suggest AI
  - 6-8 AM cortisol: highly suggestive of AI if ≤3 µg/dL (<5 µg/dL suggestive); AI ruled out if ≥15 µg/dL (18 µg/dL on older assays).
    - Falsey low: ↓ albumin (cirrhosis, nephrotic syndrome, critical illness; ↓ bound and total cortisol, but free cortisol may be nml); PM testing (cortisol level is highest in morning)
    - Falsey high: pregnancy, estrogen tx (↑ cortisol binding globulin, ↑ bound/total cortisol, free cortisol may normal)
- Testing for primary AI: ↑ ACTH >2x ULN; ↓ aldo, ↑ plasma renin, 21-OHase Ab; TB test, VLCFA. Consider CT A/P
- Testing for secondary, tertiary AI: ↓ or normal ACTH, normal aldo

## Adrenal Crisis

- Acute-onset AI with distributive shock in s/o major stressor (infxn, trauma, major surgery, critical illness). **Consult endocrine**.
- No known AI: draw ACTH/cortisol but don't delay empiric treatment; defer cort-stim until stable
- Known AI or taking chronic steroids: start treatment; diagnosis can be presumed by history; no role for cort stim test

## Treatment ([JCEM 2016;101:364](#); [NEJM 2019;381:852](#))

- Adrenal crisis → stress dose steroids (**hydrocort 100mg IV x1**) & **>2-3L NS or D5NS** (if hypoglycemic). BMP, cortisol & ACTH. Follow w/ hydrocort 50mg IV q6-8h. Start fludrocortisone 0.1mg QD when off IV fluid (in primary AI & hydrocort dose <50mg in 24h).
  - Consider in any patient taking glucocorticoids (>5 mg pred eq/day for ≥4 wk or >40 mg pred eq/day for ≥1 wk)
  - May taper once patient's clinical status improves and underlying precipitant is adequately addressed
- AI → glucocorticoid: hydrocortisone 15-25mg/day PO (2/3 AM, 1/3 early PM) > prednisone 3-5mg/day (QD or BID) >> dexamethasone (significant Cushingoid side effects) 1° AI: add fludrocortisone 0.05-0.1 mg PO QD (n.b. hydrocortisone has mineralocorticoid activity; dose adjust appropriately); Dose monitoring: hypoK, HTN, edema → reduce dose; New dx: use plasma renin activity (PRA), goal upper normal range; Liberal salt intake, esp. with exercise or exposure to temps >85 °F (>29 °C). Consider ↑fludrocortisone dose in summer; Consider DHEA replacement for 3-6 month trial in women with impaired mood 2° AI: assess other pituitary hormone deficiencies (treat AI before hypothyroidism to ↓ risk adrenal crisis)
  - If minor illness (e.g., URI) or minor surgery → sick dose: "3x3 rule" = 3x daily glucocorticoid dose for 3 days
  - If severe illness → stress dose: emergency hydrocortisone injection (as below)
  - Supply patients with medical alert bracelet + card and glucocorticoid injection kit (100 mg hydrocortisone) for emergency use
  - Consider screening for AI diseases (unknown optimal frequency) including DM, thyroid dz, premature ovarian failure, celiac dz

## Steroid Pearls

- Taper: not necessary if steroid use <3w (independent of dose) → low risk of HPA suppression. Usually the patient's specialist prescribing the steroid a slow taper if underlying disease might flare with an abrupt decrease in steroid dose. Otherwise can drop steroid dose to 5mg pred equivalent and perform a cort stim. If AI present, continue pred 5 mg for 6-8 weeks then repeat cort stim
- Ppx: PJP: if taking pred ≥20mg for ≥4w + 2<sup>nd</sup> reason for immunocompromise; PUD: if taking aspirin/NSAIDs; **osteoporosis**: calcium 1200mg/d + vitamin D 800IU/d if on any dose >3mo (consider bisphosphonates for pts at intermediate/high risk of fracture); **DM2**: monitor glucose/A1C, consider insulin dosing (cover with NPH 0.1 U/kg per 10 mg prednisone equivalents up to 40 mg)

Steroid	Equivalent Anti-inflammatory Dose (mg)	Relative Anti-inflammatory Activity	Relative Na Retention Activity	Duration (hrs)
Hydrocortisone	20	1	2	8-12
Prednisolone	5	4	0.8	12-36
Methylprednisolone	4	5	0.5	12-36
Dexamethasone	0.75	30	0	36-72
Fludrocortisone	n/a	10	125	12-36

# Endocrinology

# Pituitary Disorders

## HYPOPITUITARISM

**Definition:** ↓ pituitary hormone production/release resulting from diseases of pituitary (1°) or hypothalamus/stalk (2°)

**Causes:** surgery, radiation, infection (TB, fungal, meningitis), infiltration (sarcoid, hemochromatosis, Langerhans cell histiocytosis, lymphocytosis), TBI, genetic, tumors (1°: pituitary tumors, mets; 2°: external stalk compression [e.g., craniopharyngioma, meningioma, mets])

- 1° only: Sheehan's (infarction), apoplexy (hemorrhage), meds (immune checkpoint inhibitors)

## Clinical Manifestations & Diagnosis:

Hormone Deficiency	Signs/Symptoms	Laboratory Tests
Prolactin (rarely isolated)	Reduced lactation	PRL
ACTH (2° adrenal insufficiency)	Weight loss, anorexia, nausea, dizziness	AM cortisol, cort stim test, ACTH
GH	Low energy, central obesity, ↓ bone mineral density, ↓ exercise performance, psych (depression, immaturity)	IGF-1, insulin tolerance test
TSH (2° hypothyroidism)	Weight gain, bradycardia, hair loss, dry skin, hyporeflexia	TSH, free T4
LH/FSH	amenorrhea/oligomenorrhea, decreased libido, ED, infertility	LH, FSH, estradiol, AM testosterone

**Treatment:** replace deficient hormone ([JCEM 2016;101:3888](#)) and **endocrine consult**. Most sensitive issue is cortisol/thyroid hormone replacement: if concurrent deficiencies **treat AI before hypothyroidism** as can otherwise precipitate adrenal crisis.

## HYPERPITUITARISM

**Definition:** excess of any of the hormones secreted by the anterior pituitary gland (PRL, ACTH, GH, TSH, LH/FSH)

**Causes:** (1) hyperfxn pituitary adenoma (2) elevated prolactin 2/2 disruption of pituitary stalk, med (e.g. dopamine antagonists)

**Clinical Manifestations & Diagnosis:** if pituitary adenoma → headaches, visual field deficits (bitemporal hemianopia)

- **Imaging:** MRI brain w/ and w/o contrast (ask rads for pituitary protocol)

Hormone Excess	Signs/Symptoms	Laboratory Tests
Prolactin (Prolactinoma)	Infertility, amenorrhea, galactorrhea (F>M), erectile dysfunction	PRL
ACTH (Cushing's disease)	Weight gain, depression, insomnia, easy bruising, poor wound healing, central obesity, acne, hirsutism, wide violaceous striae, prox muscle weakness, HTN, osteoporosis, DM	Overnight 1 mg dex suppression test, late-night salivary cortisol, or 24h urinary free cortisol excretion
GH (Acromegaly)	Arthralgias, paresthesias (carpal tunnel syndrome), hyperhidrosis, OSA, CHF, enlarged jaw/hands/feet, coarse facial features, deepening of voice, skin tags, hirsutism, HTN	IGF-1, confirm with GH level after glucose tolerance test
TSH (2° hyperthyroidism)	Tremor, palpitation, heat intolerance, weight loss, increased bowel movements, dyspnea	TSH, free T4, total T3

## Treatment:

- **Prolactinoma:** if >1cm or symptomatic, first-line treatment is **dopamine agonist** (cabergoline > bromocriptine [preferred in pregnancy]). If <1cm and asymptomatic, can monitor closely with MRI and prolactin levels ([JCEM 2011;96:273](#))
  - Use lowest dose possible to restore prolactin to normal (men and post-menopausal women: <20 ng/mL, pre-menopausal women: <30 ng/mL); TTE **not required** prior to initiation ([JCEM 2016;101:4189](#))
- For all other hypersecreting pituitary adenomas, treatment is **transsphenoidal pituitary surgery ± radiation therapy**
- For GH secreting adenomas in pts who are poor surgical candidates or w/ persistent dz, can tx with somatostatin analog (octreotide)

## DIABETES INSIPIDUS (DI)

**Definition:** polyuria (>50mL/kg/day in DI) in setting of insufficient amount of (central) or response to (nephrogenic) ADH

**Causes:** Central: trauma, surgery, hemorrhage, infarction, neoplasm, infiltrative (sarcoidosis, histiocytosis), infection, autoimmune, drugs (EtOH, phenytoin) || Nephrogenic: drugs (lithium, cisplatin), hypoK/hyperCa, infiltrative (sarcoidosis, amyloidosis, MM), sickle cell

**Diagnosis:** confirm polyuria (24 h urine volume >3 L) prior to referral/evaluation

- **Water deprivation test:** normal physiology: water restriction → ↑SOsm → ↑ADH → ↑UOsm ([JCEM 2012;97:3426](#))
  - Check Na, SOsm, UOsm, UVol q2hr. Urine dipstick for glucose should be negative.
  - If UOsm > 700 mEq/kg, stop test due to appropriate vasopressin response (dx: **primary polydipsia**)
  - Once (1) **SOsm > 295 mEq/kg**, (2) **Na ≥145 mEq/L** (adequate ADH stimulus) → administer **desmopressin 4 mcg IV**, then check UOsm, UVol q30min x 2hr. judge reponse:
    - UOsm ↑ to <300 mEq/kg → ↑ by <15% **complete nephro DI** || ↑ by 15-45% → **partial nephro DI**
    - UOsm ↑ to >300 mEq/kg → ↑ by >100% **complete central DI** || ↑ by 15-100% → **partial central DI**

**Treatment:** correct hypernatremia (see *Sodium Disorders*). Allow patient to drink to thirst. PO preferred to avoid rapid Δ in serum Na.

- Central: **desmopressin** (exogenous ADH) given intranasal (5mcg qhs + 5mcg qd to tid) or PO/SC, can augment with adjunctive meds. If **impaired thirst** or no access to water, high risk of hypernatremia.
- Nephrogenic: if partial, may try desmopressin; if complete, use adjunctive meds
- Salt/protein restriction: low solute intake reduces thirst, thereby reducing free water intake
- Adjunctive meds: **HCTZ** (volume depletion → increases proximal Na/water reabsorption, decreasing distal Na delivery where ADH acts), **amiloride** (mechanism similar to HCTZ, beneficial in Li-induced nephrogenic DI by blocking entry of Li across ENaC), **NSAIDs** (enhance renal response to ADH), **chlorpropamide** (enhances renal response to ADH)

# Endocrinology

# Calcium Disorders

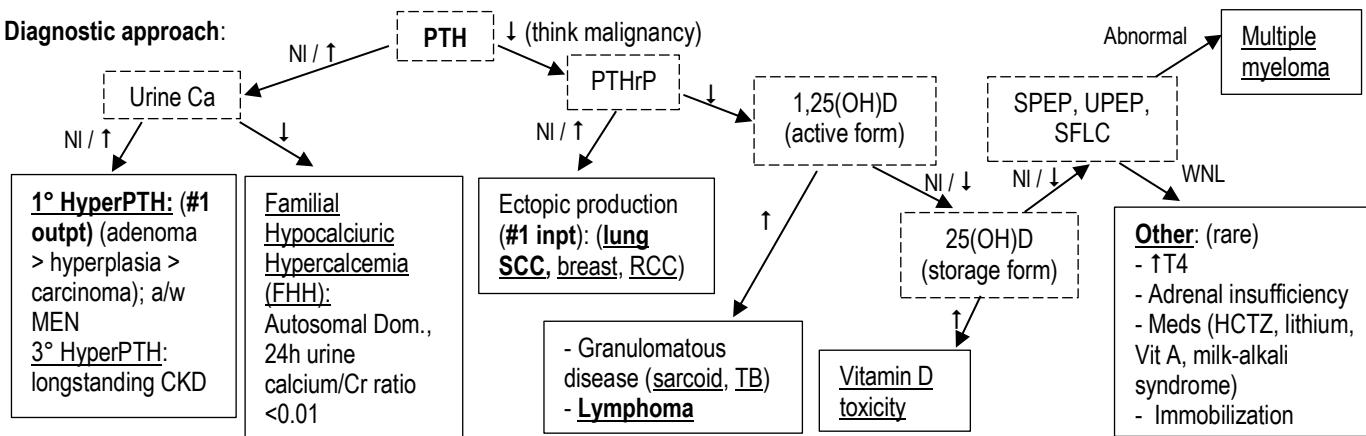
## HYPERCALCEMIA

\*FIRST CORRECT CALCIUM FOR ALBUMIN: Corrected Ca = Serum Ca + 0.8 x (4-Alb). Use iCa iso major acid-base disturbances.\*

**Definition:** mild (corrected Ca 10.5-12; iCa 5.6-8); moderate (corrected Ca 12-14; iCa 8-10); severe (corrected Ca >14; iCa >10)

**Clinical signs/symptoms:** MSK ("bones") → osteitis fibrosa cystica (1° hyperPTH), arthralgia, osteoporosis/fractures, weakness; Renal ("stones") → polydipsia, polyuria, nephrolithiasis, Type 1 RTA, AKI/CKD; GI ("groans") → n/v, anorexia, constipation, ileus, pancreatitis, peptic ulcers; Neuropsych ("overtones") → fatigue, depression, anxiety, confusion, stupor, coma; CV → bradycardia, short QTc, AV block, valve/vessel calcification, HTN

### Diagnostic approach:



**Management:** ([BMJ 2015;305:h2723](#); [NEJM 2005;352:373](#))

In **mild-moderate** hyperCa: avoid contributory meds; oral hydration; oral PO4 repletion to 2.5-3.0 (IV could lead to hypoCa)

In **symptomatic or severe** hyperCa (>14): **should be admitted** for treatment and have an endocrine +/- renal consult to assess HD needs

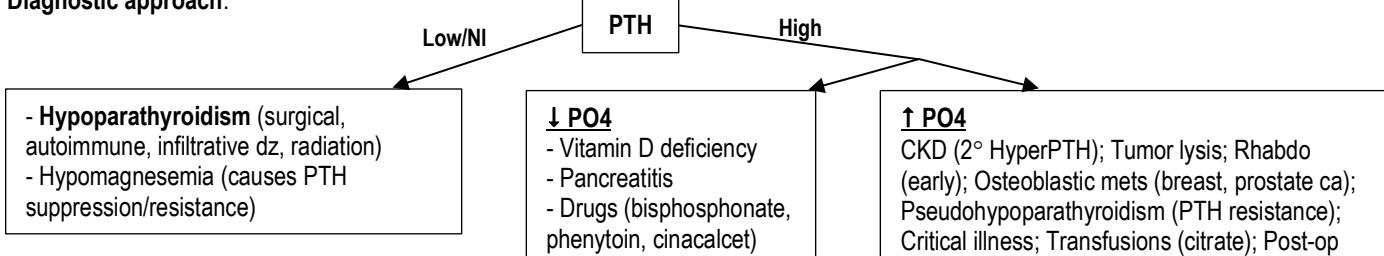
- **1<sup>st</sup> line treatment:** IVF and subQ calcitonin (faster but transient) + IV zoledronic acid (for delayed but sustained effect after 2-4d)
  - **Volume resuscitation:** pts are typically very dehydrated; bolus NS then gtt @ 200-300cc/h with goal UOP 100-150cc/h.
  - **Calcitonin:** 4-8U/kg subQ BID x 48 hrs (substantial Ca reduction within 12-24h). Possible tachyphylaxis within 48-72h.
  - **Bisphosphonates:** zoledronate >> pamidronate (**except in MM**). Takes 2-4d for effect. SE: hypoCa (check vit D, replete prior), hypoPhos, flu-like illness, impaired renal fxn. Reduce rate or dose if CKD (Cr>4.5). Avoid if CrCl <30.
- Other treatments:
  - **Loop diuretics:** **ONLY** if concurrent HF, CKD (once volume replete), elderly; otherwise avoid 2/2 worsen dehydration
  - **Denosumab:** monoclonal Ab against RANKL → blocks pre-osteoclast maturation. Good option in patients with CKD or hypercalcemia of malignancy refractory to zoledronate. Requires careful monitoring as hypocalcemia risk >> than with bisphosphonates. Check 25(OH)D + replete prior to admin.
  - **Glucocorticoids:** for calcitriol mediated etiologies [i.e. granulomatous diseases], takes 2-5 days to take effect.
  - **HD:** if life-threatening or Ca >18 at onset AND neuro sx.

**Special considerations for 1° hyperPTH:** surgery is curative. Indicated if (1) symptomatic OR (2) asymptomatic with Ca >11.5, osteoporosis/vertebral fracture, CrCl <60, nephrolithiasis, 24-hr urinary Ca > 400mg/day, or age <50. If poor surgical candidate, consider **cinacalcet**, bisphosphonate, HCTZ, raloxifene ([JAMA Surg 2017;152:878](#); [JCEM 2014;99:3607](#))

## HYPOCALCEMIA

**Clinical signs/symptoms:** neuromuscular (paresthesias, muscle cramps/spasms, tetany, Trousseau sign [carpal spasm w/ BP cuff inflation 94% Sn, 99% Sp], Chvostek sign [circumoral muscle twitch w/ facial nerve tapping poor Sn, 85% Sp]); **seizures**; ↑QTc, AMS, laryngospasm, bronchospasm, abdominal pain, dysphagia ([BMJ 2008;336:1298](#))

### Diagnostic approach:



### Management:

**Replete Mg** (hypoCa can be hard to correct w/o first correcting hypoMg (<0.8 mEq/L) → causes PTH resistance and ↓ secretion)

**IV Ca repletion:** if severe (**corrected Ca <7.5, iCa <1**) or no PO access. Not indicated for asymptomatic hypoCa in CKD.

- 1-2g IV **Ca gluconate** (preferred) or CaCl<sub>2</sub> (in codes: via central line, risk of skin necrosis if extravasates) over 10-20 min (slowly to mitigate cardiac risk)-> can repeat in 10-60 min if no effect; **Trend iCa q4-6h** (more reliable given frequent changes in pH in ICU)
- IV therapy↓ serum levels for **only 2-3h**, chase with gtt or PO; can do sliding scale repletion in ICU

**PO Ca repletion:** if Ca >7.5 (iCa>3) or asx: 1-2g **elemental** Ca QD in divided doses (Ca citrate better absorbed vs CaCO<sub>3</sub> esp. if pt on PPI)

**Vitamin D repletion:** See **Vitamin D**; often need to give calcitriol for primary hypoparathyroidism.

## OSTEOPOROSIS

**Definitions:** fragility fracture or BMD T-score  $\leq -2.5$  on DXA. **Osteopenia:** T-score  $-2.4$  to  $-1.1$ . BMD threshold based on fracture risk in postmenopausal white females, applicable to postmenopausal women and men  $\geq 50$  yo ([ISCD 2019](#)).

- T-score: SD compared to mean for young, healthy adults of same sex and race
- Z-score: SD compared to mean for age, sex, ethnicity-matched population (preferred younger patients)
- Fragility fracture: occurring spontaneously or from minor trauma (e.g. fall from standing height); fractures of hands, feet, ankles, cervical spine, face, skull typically do not count.

**Etiology:** ([Osteoporos Int 2022;33:2049](#))

- 1° osteoporosis most common. RFs: age (women  $\geq 65$ , men  $\geq 70$ ), low body weight ( $<57.6$  kg), FHx of hip fracture, smoking, early menopause, excessive EtOH use
- Many 2° causes, including: kidney and liver dz, hyperthyroidism, hyperPTH,  $\downarrow$ vit D, hypogonadism, hypercalciuria, myeloma, malabsorption, RA, SLE, COPD, drugs (e.g. glucocorticoids, PPI, AED, heparin, aromatase inhib, MTX, GnRH agonists)

## Diagnosis:

- FRAZ score estimates 10-year fracture risk with or without BMD data. In the US, clinical dx of osteoporosis when FRAZ 10-year risk of major osteoporotic fracture  $\geq 20\%$  or hip fracture  $\geq 3\%$ . ([Osteoporos Int. 2014;25:1439](#))
- **Indications for DXA Scan** (spine and hip +/- forearm): all women age  $\geq 65$  (USPSTF) and men  $\geq 70$  (rec by some groups); younger if RFs; fracture and age  $\geq 50$ ; hx condition or meds assoc. with  $\downarrow$ bone mass or bone loss ([Osteoporos Int 2022;33:2049](#))
- **Initial labs for 2° causes:** CBC, BMP/Ca/Mg/Phos, LFTs, 25(OH)-vitD, PTH, testosterone (men), 24h urinary Ca and Cr
  - Consider TSH, SPEP+sFLC, tTG-IgA, iron/ferritin, homocysteine, prolactin; Urine (UPEP, free cortisol, histamine)

**Management:** ([JCEM 2012;97:1802](#); [JCEM 2019;104:1592](#); [Osteoporos Int 2022;33:2049](#))

- **Lifestyle measures:** all patients with  $\downarrow$ BMD: weight-bearing exercise 3-4x/wk, smoking cessation,  $\downarrow$ EtOH intake, calcium 1200mg qd (diet+supplement). Replete Vit D to goal 30-50 ng/ml (usually 800-1000 IU/day).
- **Pharmacologic therapy:** initiate in postmenopausal women with hip/vertebral fracture; those with osteoporosis; or those with osteopenia and FRAZ 10y risk  $\geq 20\%$  for any fracture,  $\geq 3\%$  for hip
  - **Bisphosphonates:** normal Ca, Vit D  $>20$  prior to initiation. Reassess fracture risk in 3-5 years ([JCEM 2019;104:1592](#))
    - **PO alendronate** 70mg or **PO risedronate** 35mg weekly. Avoid if GFR  $<30$ , esophageal dysmotility or h/o bariatric surgery. Strict instructions: sit upright and take on empty stomach w/ full glass of water 30 min prior to other meds/food.
    - **IV zoledronic acid** 5mg annually if esophagitis/GERD with PO treatment, hx bariatric procedures (Roux-en-Y) or otherwise unable to tolerate PO. Can experience flu-like symptoms after infusion.
  - **SERMs (tamoxifen/raloxifene):** less effective compared to bisphosphonates and reserved for use if unable to tolerate bisphosphonate/denosumab or in postmenopausal women with increased risk of breast cancer. Side effects:  $\uparrow$ risk endometrial ca (tamoxifen only),  $\uparrow$ risk DVT/PE, edema, hot flashes, muscle cramps
  - **Referral to Endocrine** for advanced therapies, refractory disease, severe osteoporosis (T score  $\leq -3.0$  or  $\leq -2.5$  with fragility fracture) or age  $< 50$ : **denosumab** (RANKL mAb; if discontinued should be started on antiresorptive, preferably a bisphosphonate) ([NEJM 2009;361:756](#); [JCEM 2020;106:264](#)), teriparatide and abaloparatide (recombinant PTH and PTHrP analog, respectively) ([Lancet 2018;391:230](#))
- **Inpatient following fragility fracture:** assess need for surgical treatment and **consult Fracture Liaison Service (p25656)**. Bisphosphonates decrease rate of new clinical fracture and mortality post-hip fx ([NEJM 2007;357:1799](#))

**Monitoring:** variable recommendations; can repeat follow-up DXA hip/spine after 2 years; if stable, can space out scans

## VITAMIN D

**Definitions:** Measured by **25[OH]D (calcidiol)** in serum ([JCEM 2019;104:234](#)). No consensus cutoff but most groups use: Vit D

Sufficiency:  $>20$ ng/mL; Insufficiency: 12-20ng/mL; Deficiency:  $<12$ ng/mL; Risk of toxicity  $>100$ ng/mL +  $\uparrow$ Ca intake

## Diagnosis:

- Population screening not recommended, only screen high-risk patients (Choosing Wisely; [JCEM 2011;96:1911](#)): Rickets, osteomalacia, osteoporosis, hyperPTH, inadequate PO,  $\downarrow$  cutaneous synthesis ( $\downarrow$ sunlight i.e., institutionalized or northern latitudes, sun pigmentation, aging), malabsorption (gastrectomy, IBD, CF, celiac, pancreatobiliary disease),  $\downarrow$ synthesis (ESLD, CKD), change in catabolism (AEDs, steroids, HAART, immunosuppressants)
- If deficient, obtain PTH, BMP/Phos, ALP, TTG. Consider if insufficient AND concern for secondary cause e.g., IBD

**Management** ([NEJM 2007;357:3](#); [J Am Geriatr Soc 2014;62:147](#)):

- Supplement with D3 or D2 (D3 slightly more preferred but D2 more readily available); recheck levels in 3-4 months
  - $<12$ ng/mL: 50,000IU weekly x6-8w followed by 800-1000IU qd; 12-20ng/mL: 800-1000 IU qd
- For patients  $\geq 65$ y at high fall/fracture risk: Vit D  $\geq 1000$ IU + calcium 1000mg qd with goal of serum 25(OH)D  $>30$ ng/mL
- For patients with malabsorption: up to 10,000 to 50,000IU qd and/or UVB irradiation
- For patients with ESRD, ESLD, or vitamin D-dependent rickets (poor conversion of 25(OH)D): calcitriol 0.25-1.0  $\mu$ g qd
- Intermittent, high dosing of Vit D associated with increased falls in older adults and is generally avoided ([JAMA 2010;303:18](#))

# Endocrinology

# Thyroid Disorders & Male Hypogonadism

## INPATIENT TFTs

**Testing:** If thyroïdal illness suspected, TSH alone is inadequate; should also test for FT4 & T3. TSH reflects changes within 4-6 wks.  
**Routine screening on admission not indicated.** Only send if related to CC or suspect thyroid disease ([J Hosp Med 2020;15:560](#))

- **Undetectable TSH (<0.01)** suggests true hyperthyroidism, and **TSH >20 + low T4** suggests true hypothyroidism
- **Nonthyroidal illness "euthyroid sick":** alterations in thyroid fxn due to illness, not 1° endocrine disorder; may be adaptive (anti-catabolic); no indication to treat; most likely cause of abnormal TFTs among inpatients ([Lancet Diab Endo 2015;3:816](#))
- **Typical pattern:** (1) acute illness: ↓↓ T3, ↓T4, ↓/nl FT4, ↓/nl TSH. (2) recovery phase: ↑TSH → recovery of T4, T3
- Sequential FT4 should ↑ in recovering sick euthyroid but remains low in 1° hypothyroid. rT3 can differentiate central hypothyroidism (↓) from sick euthyroid (↑), but rarely needed. FT3 only helpful to dx hyperthyroidism w/ altered TBG.

## HYPOTHYROIDISM

**Definition:** elevated TSH with low T4 (primary) or inappropriately low/normal TSH with low T4 (2°/central)

**Signs/symptoms:** general (fatigue, cold intolerance, constipation, dry skin, myalgias, weight gain), neuro (depression, cognitive dysfunction, carpal tunnel), CV (bradycardia [severe], diastolic HTN), irregular menses

- Exam: delayed relaxation phase of DTRs, non-pitting edema, lateral eyebrow thinning, macroglossia

**Labs:** ↑LDL, ↑triglycerides, macrocytic anemia, ↓Na

- Check other pituitary axes if concern for central hypothyroidism

**Workup:** TSH with reflex, anti-TPO ab. No role for thyroglobulin or anti-thyroglobulin ab (only useful for monitoring thyroid Ca)

**Causes:**

- **1°: Hashimoto's** (most common, ⊕**TPO Ab**), infiltrative dz (hemochromatosis, sarcoid), transient thyroiditis (Hashimoto's, granulomatous, postpartum), drugs (lithium, amio, TKIs, contrast), iatrogenic (thyroidectomy, radiation), iodine deficiency
- **2°: see Pituitary Disorders**
- **↑ T4 requirement:** pregnancy, estrogen (↑THBG), weight gain, malabsorptive (e.g., celiac disease), nephrotic syndrome (↑ excretion), rifampin, phenytoin, carbamazepine, phenobarbital

**Tx:** levothyroxine (T4) starting dose ~1.4mcg/kg/d PO (use 25-50mcg QD for elderly or comorbidities); IV = 50-75% PO

- Take on an empty stomach 1h before food/meds; several hrs apart from calcium, aluminum hydroxide, iron, cholestyramine
- **Check TSH q4-6 weeks and adjust by 12-25mcg** until normal TSH. If pituitary insufficiency/2° hypothyroidism, track FT4s as TSH is not an accurate reflection of thyroid function. **Once on stable dose**, check TSH q6-12 months

	TSH	FT4
Primary	↑	↓
Central	↓/Normal	↓
Subclinical	↑	Normal

**Subclinical hypothyroidism:** elevated TSH with normal FT4 (biochemical dx)

- Dx: can check anti-TPO Ab (if ⊕, monitor TFTs because at ↑ risk for Hashimoto's)
- Treatment: tx all patients with **TSH ≥10**. If TSH>7 and age<65 OR if age>65 and symptomatic, tx. If TSH 5-6.9, consider risk factors (e.g., CV disease, HLD) to guide tx
- Elderly patients often have higher TSH levels, can be nl, tx if symptomatic.

TSH	Age<65	Age>65
5-6.9	Consider RFs to guide tx	No tx
7-9.9	Tx	Tx only if sx
≥10	Tx	Tx

## MYXEDEMA COMA

**Definition:** Manifestation of severe hypothyroidism, **STAT endo consult**; mortality >30%, commonly 2/2 hypercarbic resp failure

**Precipitants:** infection, MI, cold exposure, surgery, sedative drugs (esp. opioids) in a poorly controlled hypothyroid patient. Most common in older women with hypothyroidism

**Signs/symptoms:** **AMS** (lethargy/obtundation, not always coma), **hypothermia**, **hypotension**, bradycardia, ventricular arrhythmias, hypercarbic resp failure, seizure

- Exam: puffy hands and face, swollen lips, enlarged tongue

**Labs:** ↓Na (be careful with IVF), ↓Glu, ↓T4, ↑TSH

**Treatment:** do not wait for lab confirmation to start tx!

- **Test and empirically treat adrenal insufficiency:** **hydrocortisone** 100mg q8h until AI ruled out. Give steroids **BEFORE T4** (if concomitant AI, replacing thyroid first will catabolize residual cortisol and cause HoTN/death). Draw serum cortisol prior to rx.
- **Levothyroxine (T4)** Loading dose 200-400 mcg IV followed by 50-100 mcg IV QD until able to take T4 orally. Favor low end of range if elderly or at risk of cardiac complications (MI, arrhythmia).
- **Liothyronine (T3)** Loading dose 5-20 mcg followed by 2.5-10 mcg q8h, watch for rebound hypermetabolism.
- Monitor FT4 and T3 Q1-2 days, avoiding very high T3 levels.
- Patients are **hypometabolic**: use lower drug doses at lower frequency, avoid mental status-altering meds.

## AMIODARONE-INDUCED THYROID DISEASE

Check TSH prior to treatment, q4-6 mo while on amio, and for 1 yr after amio discontinued

- Typical response to amio acutely: ↑TSH (2-3x nl), ↑T4 and FT4, ↓T3, ↑rT3 → levels return to normal in 3-6 months

**Amiodarone-induced hypothyroidism:** due to Wolff-Chaikoff or thyroiditis

**Amiodarone-induced hyperthyroidism**

- **Type 1:** ↑synthesis of T4 and T3 due to ↑iodine, usually will see in pts with latent Graves' or goiter. Seen early during amiodarone Rx Tx: methimazole
- **Type 2:** direct toxicity of drug causing thyroiditis, stored hormone release w/o synthesis. Seen late during or after amiodarone Rx. Tx: ~60 mg/day prednisone x 1-3mo followed by taper
- **If unknown:** tx with methimazole and prednisone. Rapid response → Type 2, taper methimazole. Poor response → Type 1, taper steroid
- **Okay to continue amiodarone**, esp. if Type 1 (amiodarone prevents T4 → T3 conversion)

# Endocrinology

# Thyroid Disorders & Male Hypogonadism

## HYPERTHYROIDISM ([Thyroid 2016; 26:1343](#))

**Definition:** low TSH with high T3/T4 (primary) or high/normal TSH with high T3/T4 (secondary/central)

**Signs/symptoms:** general (↓ weight, ↑ appetite, heat intolerance, tremor, weakness), CV (palpitations, afib, systolic HTN), hyper-defecation, dyspnea, sweating, anxiety, emotional lability, urinary frequency, abnormal menses, osteoporosis

- Exam: goiter +/- thyroid bruit, lid lag, exophthalmos and pretibial myxedema (Graves' only), hyperreflexia and tremor
- Apathetic thyrotoxicosis: depression, weakness seen in elderly

**Labs:** ↑HDL, ↓LDL, normocytic anemia, ↑Ca, ↑AlkP, ↑Glu

**Workup:** 1) TSI and TBII (+ in Graves'), 2) RAIU (not for amio-induced or if recent IV contrast), 3) thyroid US w/ Doppler

**Causes:**

- 1°: **Graves' disease** (most common, **positive TSI or TBI establishes diagnosis**), toxic adenoma (TA), toxic multinodular goiter (TMG), transient thyroiditis (lymphocytic, granulomatous, postpartum, viral), drugs (amio, iodine, lithium), iatrogenic (radiation, palpation), exogenous T3 or T4 ingestion (low thyroglobulin), HCG-mediated, struma ovarii.
- 2°: see *Pituitary Disorders*

**Treatment:** β-blocker for adrenergic symptoms (e.g., metoprolol, propranolol)

- **Graves' disease:** thionamides (methimazole > PTU due to hepatotoxicity, though PTU preferred in 1<sup>st</sup> trimester of pregnancy), radioiodine (risk of ophthalmopathy), thyroidectomy (watch for hypoparathyroidism). Monitor total T3 and fT4 q6wks.
- If using **thionamides**: obtain baseline CBC w/ diff (10% of patients have neutropenia that resolves with tx ([Clin Endo 2021;94:473](#))); **risk of agranulocytosis:** routine ANC monitoring not recommended but CBC w/ diff recommended at earliest sign of febrile illness + discontinue drug until result available
- Toxic adenoma or multinodular goiter: radioiodine, surgery, less commonly thionamides

## THYROID STORM ([Thyroid 2016; 26:1343](#))

**Definition:** Manifestation of severe thyrotoxicosis, **STAT endocrine consult**. Mortality rate 10-30%, 2/2 cardiovascular collapse

**Precipitants:** surgery (any), trauma, infection, iodine load (incl. amiodarone), irregular use/cessation of antithyroid drugs

**Signs/symptoms:** AMS (agitation, delirium, psychosis, coma), **hyperpyrexia, tachycardia**, atrial arrhythmias, CHF

- Exam: goiter, tremor, warm/moist skin, exophthalmos (Graves')

**Labs:** ↑T4/T3, ↓TSH

**Dx:** Burch-Wartofsky Point Scale ([BWPS](#)) ≥ 45 highly suggestive

**Treatment:**

- **Beta blocker:** e.g., **propranolol 60-80 mg PO Q4-6H** (only propranolol decreases T4→T3 conversion), doses up to 2g/d. Titrate to sx and HR (i.e., <80). Can also use esmolol gtt for rapid titration (esp. pts who may not tolerate propranolol, e.g., HF)
- **Anti-thyroid meds:** only stop formation of new hormone, not release of stored hormone
  - **Methimazole** (20mg q4h-q6h) is preferred unless pt is critically ill. **PTU** (200mg q4h-q6h) decreases T4→T3 but higher rates of fulminant hepatic necrosis.
- **Iodine** (100-250mg q6h-q8h) blocks release of thyroid hormone, must be given at least 1h after thionamide to prevent use as substrate for new hormone synthesis in TA/TMG; can cause Jod-Basedow (iodine-induced hyperthyroid) in toxic adenoma and Wolff-Chaikoff (iodine-induced hypothyroid) in Graves
- **Hydrocortisone** (100mg q8h) to reduce T4→T3 conversion
- **Cholestyramine** (4 g PO qid) to reduce enterohepatic recycling of thyroid hormone
- **Plasmapheresis** for those unable to take thionamides and urgently being prepared for thyroidectomy
- Patients are **hypermetabolic** and will clear drugs quickly

## MALE HYPOGONADISM ([J Clin Endocrinol Metab 2018;103:1715](#))

**Definitions:** Clinical syndrome that results from a failure of the testes to produce physiologic levels of testosterone and/or normal number of spermatozoa due to pathology at the testicular level (1°), hypothalamus/pituitary (2°), or both

- 1° causes: Klinefelter, cryptorchidism, testicular radiation, orchitis, myotonic dystrophy, HIV
- 2° causes: hyperprolactinemia, obesity, Fe overload, opioids, glucocorticoids, androgens, progestins, GnRH agonists

**Signs/Symptoms:** loss of axillary/pubic body hair, reduced libido, erectile dysfunction, gynecomastia, low sperm count, decreased energy, depressive mood, normocytic anemia, reduced muscle bulk, increased body fat

**Diagnosis:**

- Measure 8am-10am fasting total testosterone x2 (nl total T range ~ 300-800)
  - Measure free testosterone only if c/f Δ in SHBG (obesity, nephrotic syndrome, steroids, HIV, cirrhosis, thyroid dz)
- If testosterone level is low on both measurements, measure LH/FSH to determine 1° vs 2° etiology
  - If 2° measure Fe studies, other pituitary hormones, & consider imaging (see *Pituitary Disorders*); for 1° consider karyotype

**Management:**

- **Testosterone therapy** is the mainstay of treatment to induce and maintain 2° sex characteristics and address symptoms
  - Formulations: intramuscular (weekly, q2w, and monthly), transdermal gel, patches, tablets
  - SE: site reactions, acne, oiliness of skin, no large RCT to study cardiovascular risk/MACE or VTE
  - Contraindications: prostate ca, breast ca, erythrocytosis, severe BPH, untreated OSA, severe LUTS, planning fertility

**Monitoring:**

- Evaluate around 3-6mo after initiation to assess response to treatment and measure concentrations, then annually
  - Goal level is mid-normal physiologic range (300-800)
- Check baseline Hct and 3-6mo after tx, if Hct >54% stop therapy, re-initiate at reduced dose once Hct reaches safe level
- If patient chooses to monitor for prostate ca, perform DRE and measure PSA before treatment and 3-12mo after starting

# Allergy & Immunology

# Drug & Contrast Allergy

## ADVERSE DRUG REACTIONS (ADRs) ([JACI 2010;125S126](#))

**KEY History:** Drug, date, dose, route, doses/days into course, co-administered meds, coincident infections, sx, severity (home/office/ED/hospital/ICU), treatment given, exposures since

Document appropriately in EPIC allergy section. Include rxn, date, intolerance v. reaction, other meds tolerated

ADRs defined by WHO as any noxious/unintended/undesired drug effect that occurs at doses used for prevention, diagnosis, or treatment.

- **Type A = predictable** (75-80%): dose-dependent reactions related to a drug's known pharmacological action which occur in otherwise healthy patients if given sufficient dose and exposure (e.g., gastritis after NSAIDs)
- **Type B = unpredictable** (20-25%): dose-independent, unrelated to pharm action, occurs only in susceptible pts
  - **Drug intolerance:** undesirable effect that occurs at low and sometimes subtherapeutic doses w/o abnormalities of metabolism/excretion/bioavailability (e.g., tinnitus after aspirin)
  - **Drug idiosyncrasy:** abnormal effect caused by underlying abnormalities of metabolism/excretion/bioavailability (e.g., hemolysis after antioxidant drug in G6PD deficiency)
  - **Pseudo-allergic reaction** (formerly known as anaphylactoid): direct release of mediators from mast cells and basophils rather than IgE antibodies (e.g., flushing during vancomycin infusion, exacerbation of asthma/rhinitis w/ aspirin in AERD, opiate pruritis)
  - **Drug allergy** (5-10% of all ADRs): immunologically-mediated hypersensitivity reactions, including IgE mediated

## HYPERSENSITIVITY REACTIONS (Gell and Coombs Classification) ([Clin All 1998;18:515](#))

Type	Reaction	Mechanism	Presentations	Timing
I	IgE-mediated, Immediate	Ig-E mediated degranulation of mast cells due to antigen binding and cross-linking of IgE	Anaphylaxis, allergic rhinitis, allergic asthma, urticaria, angioedema	Min-hrs
II	Antibody	IgM/IgG antigen interactions on target cell surfaces	Drug-induced cytopenia	Varies
III	Immune-complex	Immune complex formation & deposition in tissues → complement activation → local/systemic inflammation	Serum sickness, vasculitis, drug induced lupus	1-3 wks
IV	Cell-mediated, delayed	Ag activates T cells → Ag later binds to activated T cells → cytokine release → macrophage & cytotoxic T cell accumulation	Contact dermatitis, SJS/TEN, DRESS, AGEP	2-7 days

## CLINICAL MANIFESTATIONS OF DRUG ALLERGY ([AACI 2018;14:60](#))

Organ	Manifestation	Clinical Features	Timing	Causative Drugs
Skin	Urticaria, angioedema, drug exanthem, SJS/TEN, AGEP	For information on skin manifestations of drug allergy, see <i>Dermatology: Drug Eruptions</i>		
Blood	Hemolytic anemia, thrombocytopenia, leukopenia	Varies, but in general: -Hemolytic anemia: acute -Drug-induced TMA: acute or subacute		PCN, sulfa drugs, AEDs, cephalosporins, quinine, heparin, thiazides
Liver	Hepatitis, cholestatic jaundice	Varies, can be acute or chronic		Sulfonamides, phenothiazines, anti-TB drugs, carbamazepine, erythromycin, allopurinol
Kidney	Interstitial nephritis, glomerulonephritis	Varies, days to months		PCNs, sulfonamides, allopurinol, PPIs, ACEi, NSAIDs
Multi-organ	Anaphylaxis	Urticaria, angioedema, bronchospasm, GI, hypotension	Immediate (usually within 1 hr)	Abx, NM blockers, anesthetics, contrast, recombinant proteins (e.g., omalizumab)
	DRESS	Rash, fever, eos, hepatic dysfunction, LAD	2-8 weeks	AEDs, sulfa drugs, minocycline, allopurinol, mAB (monoclonal Ab)
	Drug induced lupus erythematosus	Arthralgias, myalgias, fever, malaise	Months to years	Hydralazine, procainamide, INH, quinidine, minocycline, abx, anti-TNF
	Serum sickness	Arthralgias, urticaria, fever	1-2 weeks	Heterologous Ab, infliximab, mAbs, allopurinol, thiazides, abx, bupropion
	Vasculitis	Cutaneous or visceral vasculitis		Sulfa abx and diuretics, mAbs, hydralazine, levamisole, PTU

# Allergy & Immunology

# Drug & Contrast Allergy

## DIAGNOSIS ([Drug Allergy Practice Parameter 2010](#))

- **Labs** (sometimes helpful): CBC w/ diff (eos), tryptase (if anaphylaxis), auto-Abs (e.g., anti-histone in drug induced lupus)
- **Skin testing:** evaluates for drug-specific IgE antibodies for a limited # of meds. NPV of penicillin skin testing = 95%.
- **Deliberate rechallenge = graded challenge = test dose procedure**
  - Used when there is a **low suspicion for true allergic reaction** to a medication. Does NOT assess cross-reactivity of structurally-related drugs. **Contraindication** = severe non-IgE mediated HSR (ex: DRESS, SJS, etc.)
  - **How to order: Antibiotic Test Dose** in Epic order sets (can also type "penicillin" "allergy" "test dose")
    - Automatically orders the rescue medications, nursing communication orders, and fills in doses of desired med (FYI test dose = 1/10 of rx dose for IV meds and 1/4 of rx dose for oral meds)
  - If **no reaction**: patient is *not* allergic to that agent and can safely receive it, please update allergy list
    - If agent was a related agent (e.g., CTX administered in PCN-allergic pt): update "comments"
    - If agent was same agent as recorded allergy (e.g., PCN administered in PCN-allergic pt): remove allergy
  - If **⊕ reaction**: Epi 1:1000 IM (0.3 mg), Benadryl 50mg IV/PO, page allergy fellow, & complete a Medication Safety Report.

## DRUG DESENSITIZATION ([JACI 2010;125:S126](#)) | [Ellucid-Drug Desensitization and Test Dose Administration](#)

- **Indications:** ⊕skin test, ⊕test dose, or h/o severe type I HSR **AND** no alt. tx. ONLY for Type I (IgE-mediated) rxns
- **Method:** administer drug with increasing doses over hours such that it induces state of **TEMPORARY tolerance**
- At MGH, consult Allergy. Generally, desensitization needs to be done in the ICU but there are exceptions (e.g., chemo, aspirin)
- **If patient discontinues medication:** procedure must be performed again if pt stops medication for >2-3 half-lives

## PENICILLIN & CEPHALOSPORIN ALLERGY | [Ellucid -Penicillin and Cephalosporin Hypersensitivity Pathway](#)

- 10% of pts report a PCN allergy, but **90%** of patients with a h/o PCN allergy can tolerate PCN ([JACI 2010;125:S126](#))
- 70-80% of pts with IgE-mediated allergy to penicillin will lose their penicillin sensitivity over 10-year period ([Drug Allergy Practice Parameter 2010](#))
- Patients with PCN allergy have a **<1% cross reactivity to carbapenems** ([CID 2014;59:1113](#)); and **<2% of patients w/ skin test-proven sensitivity to PCN will react to cephalosporins** ([Annals 2004;141:16](#))
- Allergic determinants of cephalosporins can be derived from the **beta-lactam structure**, but in later (3rd/4th gen) cephalosporins, they are most commonly derived from the R-group.

## OTHER COMMON DRUG ALLERGIES

- **Taxanes/platinum-based Chemotherapy:** differentiate *infusion reaction* (SIRS response) from anaphylaxis (type I HSR). Platinum agents assoc with IgE HSR. Taxanes generally non-IgE mediated w/ premed usually effective ([AAAAI 2009;102:179](#))
- **Allopurinol hypersensitivity syndrome:** rash, fever, hepatitis, AKI usually within 4-8 wks. Testing for *HLA-B5801* in pts at elev risk (patients of Southeast Asian descent and African American) recommended prior to starting ([ACR Guideline 2020](#))
- **Aspirin/NSAIDs** ([JACI 2010;125:S126](#)): wide spectrum of drug-induced allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis
  - **Management:** avoid NSAIDs (COX-1 inhibitors). If NSAIDs are necessary, consult Allergy.
  - **Aspirin-Exacerbated Respiratory Disease (AERD)** (aka Samter's Triad): triad of asthma, rhinosinusitis w/ nasal polyps, and ASA/NSAID sensitivity (nasal congestion, bronchospasm). **Tx:** Avoidance of NSAIDs, desensitization and daily uninterrupted therapy, leukotriene-modifying drugs, or biologics (omalizumab, mepolizumab, dupilumab) ([JACI 2017;5:3](#))

## IV CONTRAST MEDIA ([ACR Guidelines 2021](#)) | [Ellucid -Allergy Premedication](#) | See Contrast for details on contrast reactions

Type/Path	Epidemiology	Presentation	Clinical pearls	Pre-Treatment (MGH protocol)
<b>Pseudoallergic</b> Direct stimulation of mast cells / basophils	Mild rxn: 0.6% pts  Severe rxn: 0.04% pts	Immediate pruritus, urticaria, angioedema, airway obstruction, HoTN, abd pain	<b>Seafood allergy is NOT</b> a contraindication.  <b>Oral contrast is NOT</b> contraindicated in a patient with IV contrast allergy, very rare pseudo-allergic reactions.	<b>Elective</b> (13h protocol) Prednisone 50mg PO at 13, 7, & 1h prior <b>AND</b> Benadryl 50mg PO 1h prior  <b>Urgent</b> (4-5h) Methylprednisolone 40mg IV now & q4h until scan <b>AND</b> Benadryl 50mg IV 1h prior  <b>Emergency (no data)</b> (1h) Methylpred 40mg IV AND Benadryl 50mg IV @ 1h prior
<b>Delayed</b> T cell-mediated	0.5-14% of patients	>1h - 1 wk. Usually mild, skin eruption.	<b>Tx:</b> Supportive care	

# Allergy & Immunology

# Angioedema & Anaphylaxis

## ANGIOEDEMA (Allergy 2018;73:1393)

- Definition:** localized non-pitting swelling of skin or mucosal tissue due to interstitial edema; may affect face, throat, lips, extremities, genitals, bowels. Often asymmetric. Occurs in min-hrs and resolves within 1-3d.
- Common triggers: food, insect bites, drugs, heat, cold, delayed pressure, solar, vibratory, cholinergic, contact, and aquagenic

Type	Urticaria/Pruritus	Triggers
Histamine (mast-cell mediated)	Usually (may have angioedema only)	ASA, NSAIDs, CCB, opioids, contrast dye, platinum-based chemo, $\beta$ -lactams, metoprolol, sirolimus/everolimus, risperidone, idiopathic/spontaneous
Bradykinin	Never, often more prolonged time course (in 24-36 hrs)	<b>ACEi:</b> 0.1-0.7% pts; may occur any time during treatment and recur 4-6 wks after cessation. Consider also in ARBs, DPP-4 inhibitors. <b>C1 inhibitor deficiency:</b> Either due to AD inheritance (present at early age) or acquired. Screen: $\downarrow$ C4.

- Work up:** CBC w diff, BMP, LFTs, CRP, ESR, C4 level, tryptase (see below)
- Treatment:** in ALL patients **ABCs, secure airway**
  - If urticaria: identify & remove exposure → if anaphylaxis (treat as below) → H1 antihistamines (IV Benadryl vs high-dose PO cetirizine) + steroids
  - If no urticaria/pruritis (bradykinin-mediated angioedema does not respond to epinephrine):
    - On ACEi: stop ACEi → supportive care (if severe, consider treating similar to Hereditary Angioedema [mixed evidence]), add ACEi to allergy list
    - Known hereditary or acquired angioedema: page Allergy for C1-inhibitor, ecallantide, icatibant. FFP 2<sup>nd</sup> line.
    - Not on ACE; no known disorder: H1 antihistamines + methylpred → PO pred (5-7 d taper) + H1 antihistamine

## ANAPHYLAXIS (AAAI 2015;115:341) | (World Allergy Org J 2011;4:13)

**Definition:** acute, life-threatening, multi-system syndrome due to allergy or hypersensitivity

Type	Mechanism	Triggers
Immunologic	IgE mediated	Food (e.g., nuts, shellfish, milk, eggs), insect venom, meds (e.g., NSAIDs, $\beta$ -lactams, biologics), latex, occupational allergens, aeroallergens
	Non-IgE mediated	NSAIDs, HMW dextrans, biologics, contrast
Nonimmunologic	Direct mast cell activation	Physical factors (exercise, heat, cold, UV light, XRT), EtOH, meds (opioids)
Idiopathic	No apparent trigger	Mastocytosis/clonal mast cell disorder, previously unrecognized allergen

**S/Sx:** (1) Cutaneous = angioedema, urticaria, flushing, pruritis; (2) Respiratory = dyspnea, wheeze, upper airway angioedema, rhinitis; (3) GI = nausea, vomiting, diarrhea; (4) Cardiovascular = hypotension

- **Biphasic reaction:** resolution w/ return of symptoms 1-72h (usually <12) after initial symptom resolution despite no further exposure to trigger (4-20% pts)
- **Diagnostic criteria:** **1 of 3** must be met
  - 1) Acute onset (min-hr) of **skin  $\pm$  mucosal** involvement **AND** either **respiratory sx OR hypotension (age appropriate)**
  - 2) Two or more of the following after exposure to **LIKELY allergen**: skin/mucosa swelling, respiratory sx, HoTN, persistent GI sx
  - 3) **Low BP** (SBP<90 or >30% drop from baseline) after exposure to **KNOWN allergen** for pt
- **Labs:** **tryptase** (within 15min-3h of symptom onset & 24h after sx resolve to establish baseline). Values  $\geq 1.2x$  baseline + 2ng/dL = mast cell activation. Normal levels do not rule out anaphylaxis (normal in 37%). Consider plasma histamine (peaks in 5-15 min).
- **Treatment:**
  - Establish and maintain airway, administer oxygen/IVF (1-2L) and lie pt flat/Tberg for hypotension, remove trigger if possible
  - **Epinephrine:** **1<sup>st</sup> line.** ONLY medication that reverses airflow obstruction & prevents cardiovascular collapse
    - **Dosing:** prefer 0.3-0.5mg IM (1:1000 dilution, 1 mg/mL) in mid-outer thigh. Can also use 0.1-0.3mg IV (1:10,000 dilution, 0.1mg/mL). May repeat q5-15min; if >3 doses required, consider continuous epi gtt (1-10mcg/min)
    - If on beta blockers AND resistant to epinephrine, administer glucagon (1-5mg bolus → gtt @ 5-15mcg/min)
  - Adjunctive agents:
    - **Albuterol** (stacked nebs x 3) PRN wheezing/cough/SOB
    - **H1 antihistamines:** PRN for pruritis/urticaria. Does NOT treat airway obstruction or hypotension! Benadryl 25-50mg
    - **H2 antihistamines:** famotidine 20mg IV given over 2 min
    - **Methylprednisolone 125 mg IV.** No evidence to prevent biphasic rxn. May be beneficial if (1) severe sx requiring hospitalization (2) known asthma (3) significant and persistent bronchospasm
  - **Make sure to discharge home with EpiPen & refer to Allergy**
  - If h/o anaphylaxis to stinging insect, refer for skin testing. If +, consider SQ venom immunotherapy, which decreases risk of subsequent anaphylaxis from 50-60% to 2-3% (NNT = 2) ([NEJM 2014;370:1432](#))

# Allergy & Immunology

# Mast Cell Disorders

## MAST CELL BASICS ([NEJM 2015;373:163](#))

- When activated, mast cells degranulate and release **vasoactive & pro-inflammatory** mediators such as histamine, heparin, serotonin, leukotrienes, prostaglandins, proteases (including tryptase), cytokines (including TNF), etc.
- Signs and symptoms associated with mast cell activation are similar to those of allergic & anaphylactic reaction. However, **angioedema, hives and wheezing are uncommon in mastocytosis.**
  - Cutaneous: flushing, pruritis, urticaria, angioedema
  - GI: heartburn & nausea (histamine → hypersecretion of acid from parietal cells), diarrhea, abdominal cramps
  - Cardiovascular: tachycardia, hypotension, presyncope, and syncope
  - Neuro: fatigue, lethargy, memory and concentration problems, headache
  - Respiratory: wheezing (bronchospastic cough), nasal congestion
- Triggers for mast cell activation:** temp changes (e.g., hot showers), exercise, alcohol/spicy food ingestion, mechanical irritation, stress, insect stings, certain medications (opioids, NSAIDs, muscle relaxants). *Can also be spontaneous.*

## MASTOCYTOSIS ([Blood 2017;129:1420](#))

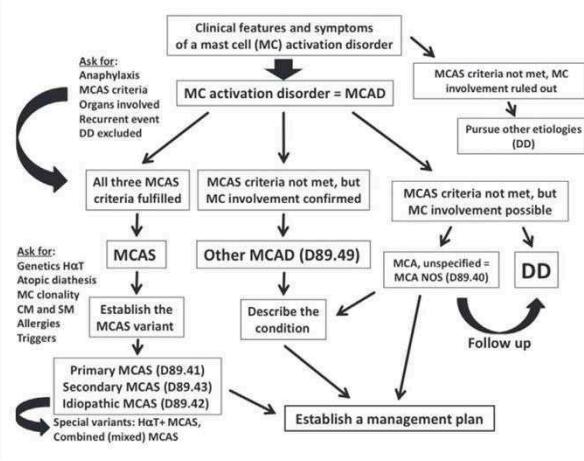
- Heterogenous group of **rare** disorders (~1:10,000) characterized by excess mast cell proliferation and accumulation.
- Symptoms are primarily related to episodic release of mast cell mediators (lasts 30 min – few hours)

Mastocytosis	
<b>Epidemiology</b>	Primarily presents as systemic mastocytosis (SM) Rare presentations of cutaneous mastocytosis (primarily in infants and young children)
<b>Organ systems</b>	Multifocal <b>infiltration of mast cells</b> in various internal organs <b>Bone marrow</b> is involved in virtually <u>all patients</u> <b>Skin</b> more common with indolent systemic mastocytosis.
<b>Variants</b>	<ol style="list-style-type: none"> <li>Indolent SM (most common): no end-organ dysfunction</li> <li>Smoldering SM</li> <li>SM associated with non-mast cell hematologic neoplasm</li> <li>Aggressive systemic mastocytosis: + end-organ dysfunction</li> <li>Malignancy: mast cell leukemia, mast cell sarcoma</li> <li>Cutaneous only: urticaria pigmentosa (UP), mastocytoma of skin, diffuse cutaneous mastocytosis</li> </ol>
<b>Cutaneous manifestations</b>	Due to mediator release = flushing, pruritis, urticaria Due to mast cell infiltration = maculopapular cutaneous mastocytosis (most common; fixed, salmon/tan lesions; predominate on trunk/limbs), bullous eruptions, mastocytomas, telangiectasis
<b>Systemic manifestations</b>	<ul style="list-style-type: none"> <li>GI (50%): n/v/bloating, chronic diarrhea, chronic abdominal pain, steatorrhea, GERD, gastroduodenal ulcers, hepatomegaly. Liver infiltration: ↑alk phos, AST, ALT, GGT, portal HTN, ascites if advanced SM.</li> <li>MSK: fibromyalgia-like pain, osteoporosis (due to prolonged TNF/IL-6), sclerotic/lytic lesions</li> <li>CV: episodes of tachycardia, hypotension, vasodilation</li> <li>Heme (50%): anemia (most common), thrombocytopenia, eosinophilia, LAD, splenomegaly</li> <li>Neuro: anxiety, mood disorder, insomnia, depression, headache, hypersomnolence, irritability</li> <li>Systemic: fatigue, cachexia</li> </ul>
<b>Characteristic clinical presentations</b>	<ul style="list-style-type: none"> <li>Recurrent symptoms of mast cell degranulation</li> <li>Urticaria pigmentosa (UP) +/- Darier's sign*</li> <li>Hypotensive anaphylaxis, especially with stinging insects</li> <li>Unexplained osteoporosis and pathologic bone fractures</li> <li>Sclerotic or lytic bone lesions prompting malignancy eval</li> <li>Suspected hematologic disease (heme abnormalities, splenomegaly, fatigue, weight loss)</li> </ul> <p style="margin-left: 20px;"><b>*Darier's Sign:</b> If UP detected, rub affected skin. Erythema/urticaria around lesion within 5 mins suggestive of mast cells within lesion.</p>
<b>Lab findings</b>	Elevated baseline serum tryptase (>20ng/mL) in <b>non-symptomatic state</b> strongly suggestive of SM.
<b>Diagnosis</b>	BMBx/aspirate. A/w KIT gain of function mutation. If cutaneous lesions present, skin biopsy (see <a href="#">WHO dx criteria</a> )

## MAST CELL ACTIVATION SYNDROME (MCAS) ([JACI 2022;10:1941-50](#))

Recurrent episodes of symptoms of anaphylaxis (hives, swelling, HoTN, diarrhea, SOB) w/o consistent trigger and w/o clonal population of mast cells.

- Dx criteria: 1) **episodic, objective s/s of mast cell release involving ≥2 organ systems AND 2) corresponding elevations in mast cell mediators** (preferred: tryptase 120% bl + 2ng/mL) AND 3) **respond to medications that stabilize MC/inhibit MC mediators/block mediator release** (e.g., anti-histamines, cromolyn, anti-leukotrienes)
  - Less-preferred for #2: urine histamine/PGD2 metabolites >200% individual's baseline, less specific
- Tx: anaphylaxis tx as indicated, otherwise H1/H2 blockers, ASA, anti-leukotrienes, omalizumab (blocks IgE) per Allergy
- For those w/o clear dx, provisional dx "Other MCAD" while search for other causes of sx (see diagram, [JACI 2022;10:1941-50](#))
- DDx "other MCAD": other urticaria, angioedema, food intolerance/aversion & GI d/o, rheum/joint d/o, acute/chronic infx, endocrine/neuro d/o, intoxication/poisoning/med effects, psych d/o.



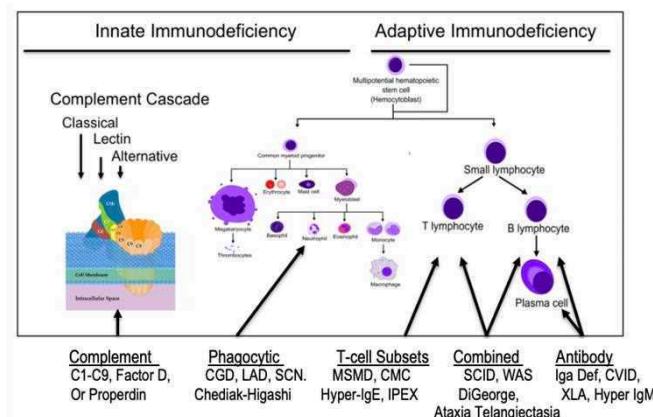
# Allergy & Immunology

# Primary Immunodeficiency

## PRIMARY IMMUNODEFICIENCY DISORDERS ([JACI 2015;136:1186](#), [JCI 2015;35:696](#))

**Definition:** inherited deficits of immune system →

- increased incidence/severity/frequency of infections
- Prevalence:** 1/1200-2000 pts
- Warning signs in adults:** ≥4 infection requiring antibiotics per year (ear infxn, sinusitis, bronchitis, PNA, otitis media), infection not responsive to antibiotics, ≥2 severe infections (osteo, septic arthritis, meningitis, sepsis), ≥2 PNA within 3 years, chronic diarrhea, recurrent deep abscesses, persistent fungal infection, persistent thrush, recurrent need for IV abx, infxn w/ benign mycobacteria, relevant FH
- H&P:** developmental hx, FH, age at onset, frequency & type of infections, syndromic features, autoimmune dz
- Need to r/o 2<sup>o</sup> causes of immunodeficiency (HIV, immunosuppressants, malignancy, cirrhosis, diabetes, nephrotic syndrome, SLE, RA, asplenia)
- General principles of management:** vaccination, abx ppx, ↑risk of malignancy, immunoglobulin replacement, HSCT



	Disorder (% Total)	Presentation	Infectious Organisms	Advanced Testing ( <a href="#">JACI 2010;125:S297</a> )
INNATE	<b>Complement (5%)</b>	Any age - Sinusitis, PNA, meningitis - Lupus-like syndrome - Rheumatoid disorders	<u>Bacteria:</u> encapsulated esp. Neisseria, gonococcal infections	Complement levels CH50+AH50 (alt pathway)
	<b>Phagocytic (10%)</b>	Infancy/childhood - Oral, lymphadenitis, skin and soft tissue, liver, lung, bone, anorectal - Unusually severe infections - Granulomas, poor wound healing	<u>Bacteria:</u> S aureus, PsA, Serratia, Klebsiella, non-TB mycobacteria, nocardia <u>Fungi:</u> Candida, Aspergillus	ANC (↓SCN, ↑LAD), ELANE gene in SCN Oxidative burst via DHR/NBT test for CGD
ADAPTIVE	<b>T cell subset defects (5%)</b>	Infancy - Oral thrush	<u>Bacteria:</u> Mycobacteria <u>Viruses:</u> CMV, adenovirus <u>Fungi:</u> Candida, PJP	Flow cytometry Anergy/proliferation tests STAT1, AIRE if chronic mucocutaneous candidiasis or APECED
	<b>B cell / Antibody (65%)</b>	>6 mos, can present in adulthood - Recurrent sinusitis, otitis media, PNA, bronchiectasis - Chronic GI malabsorption, diarrhea - Autoimmune disease (29% in CVID) ( <a href="#">Blood 2012;119:1650</a> ) - Anaphylaxis to blood products (IgA deficiency)	<u>Bacteria:</u> H flu, Strep, Staph, Moraxella cat, PsA, mycoplasma pneumoniae <u>Virus:</u> Enterovirus (esp. with IgA deficiency) <u>Parasites:</u> Giardia	SPEP (IgG, IgA, IgM), IgG subclasses, flow cytometry <b>Vaccine response</b> <b>Polysaccharide PPSV23 titers:</b> ≥70% of serotypes ≥1.3 = adequate. If not, give PPSV23 & repeat titers in 4-6 wks <u>Protein:</u> tetanus, diphtheria IgG <u>Conjugated:</u> Hib IgG
	<b>Combined B &amp; T cell (15%)</b>	<6 mos old, FTT - Oral thrush, viral infections - Chronic diarrhea - Absent thymus - Active disease to live vaccines	<u>Bacteria:</u> Salmonella, Listeria, non-TB mycobacteria <u>Viruses:</u> CMV, EBV, VZV <u>Fungi:</u> Candida, Aspergillus, cryptococcus, histoplasmosis <u>Parasites:</u> PJP, toxoplasmosis, Cryptosporidium	As above for B & T cell deficiencies Adenosine deaminase deficiency Avoid live vaccines

## IMMUNOGLOBULIN REPLACEMENT ([JACI 2017;139:S1](#))

- Manufactured using donor pools of donated human plasma & contains IgG antibodies, administered as IVIG or SQ Ig
- In addition to **antibody replacement**, it also has **anti-inflammatory** effects at higher doses ([Science 2008;320:376](#))
- Starting doses:** 400-800 mg/kg q3-4 wks for trough level >500-600 mg/dL (higher in pregnancy & bronchiectasis)
- Consider HBV serologies prior to IVIG: can't check for 3-4 mo after IVIG. If patient already got IVIG, consider HBV PCR
- IVIG in infection** depends on host & infection. If CVID w/ infection, can check SPEP for IgG trough. Beneficial in CMV pneumonitis in solid organ tx recipients, rotavirus enterocolitis & bacterial infections in lymphoproliferative dz (e.g., CLL)

## THERAPEUTIC USE OF VACCINES IN PATIENTS WITH PID ([JACI 2018;141:474](#))

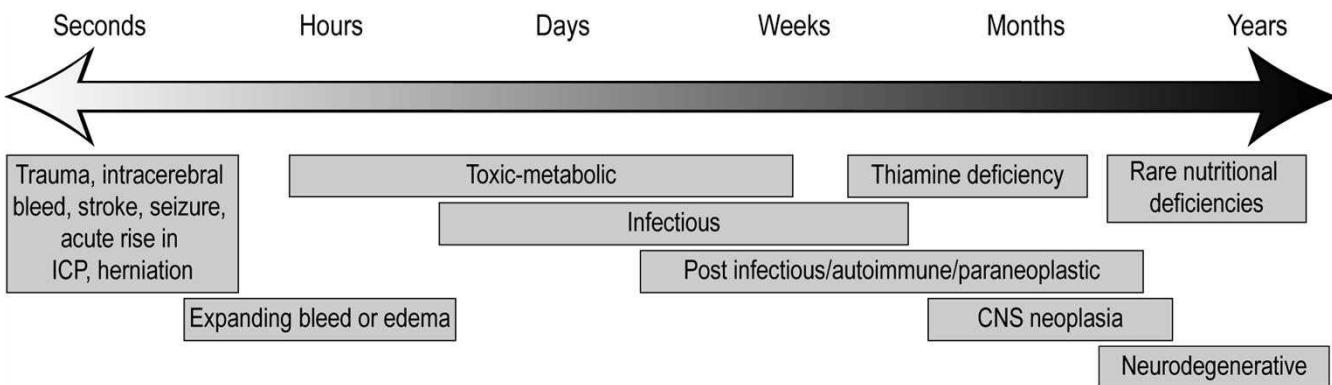
- ALL** patients with PID can receive **INACTIVATED** vaccines according to routine schedule. Prioritize flu, HPV, PNA. For **LIVE ATTENUATED** vaccine safety/benefit, see [UpToDate Table](#)
- Pts on **IVIG** have adequate titers to measles, mumps, varicella, rubella, pneumococci, Hib, and meningococcus (variable). If exposed to an infection requiring "hyperimmune" Ig (rabies, HBV, tetanus), should still receive pathogen-specific Ig.

# Neurology

# Altered Mental Status

## CAUSES OF AMS

- AMS is any change in patient's baseline mental status and can include obtundation/non-responsiveness, agitation, lethargy, disorientation, hypoactivity, hyperactivity, etc.
- Major categories include 1) Metabolic, 2) Infectious, 3) Drugs/Toxins/Medications, 4) Primary CNS, 5) Delirium
- Duration: flow diagram (below)
- AEIOU TIPS:** Alcohol (intox, HE, withdrawal, DTs, Wernicke's)/Arrhythmia, Electrolyte/Endocrine (gluc, thyroid, adrenal), Infection, Oxygen (hypoxia, hypercarbia)/Overdose (opiate), Uremia/Urine retention, Trauma/Tumor/TPP/Temp, Iatrogenic (meds including anticholinergics, BZDs, antidopaminergics), Psych/Poison, Seizure (+post-ictal)/Stroke/Syncope



## APPROACH TO ACUTE AMS

- ABCs & vitals:** if GCS <8, call **Rapid Response & RICU** for intubation. Include **breathing pattern, FSBG, EKG**
- Hx:** last known well, baseline functional status, acuity, time course, previous AMS, recent clinical events, **MAR/toxins** (stopped, started, withdrawal, overdose), past medical history
  - MAR:** insulin, benzo, opioid, steroid, anticholinergic, antihistamine, antihypertensive, AED, anti/dopaminergic, digoxin, Li, ASA, OTCs, abx (incl. **cefepime**, other cephalosporins, PCNs, FQs) ([Neurology 2016;86:963](#))
  - Consider catatonia, NMS, serotonin syndrome and see **Catatonia, NMS, & Serotonin Syndrome**
- Neuro Exam:**
  - Arousable (**GCS**): commands, attention, cranial nerve or focal weakness, abnormal movements, meningismus, tongue biting
  - Not arousable: coma exam: pupils, nystagmus, doll's eyes, corneal, grimace, cough/gag, w/d to pain, posturing ([JNNP 2001;71:13](#))
  - Other helpful findings: **trauma** (c-spine, hip frx, fat embolus), **asterixis/myoclonus** (toxic, metabolic), **volume status**, **cherry red discoloration** (CO), findings c/f **toxicodromes**, **incontinence** (seizure)
- Dx:**
  - FSBG, CBC/diff, BMP, LFTs, lactate, VBG, UA, CXR, bladder scan
  - Consider based on initial assessment: cultures, toxicology, drug levels, CK, CTH ± CTA head/neck, EEG, etc.

NEUROLOGIC EXAMINATION		
Arousal/Mentation	Brainstem Functions	Motor Sensory
<u>Arousal level:</u> "AVPU scale" 1) Alert 2) Verbal stimuli 3) Painful stimuli 4) Unresponsive	<u>Pupils (CN 2/3):</u> <ul style="list-style-type: none"><li>- Absent light reflex (upper brainstem injury, excessive sedation)</li><li>- Bilateral fixed, dilated (upper brainstem injury/compression)</li><li>- Unilateral fixed, dilated (herniation w/ CN III compression)</li><li>- Pinpoint (opioids, pontine injury)</li></ul> <u>Blink to threat or visual field testing if able (CN 2)</u> <u>Corneal reflexes (CN 5/7):</u> absent (upper brainstem injury, deep sedation), normal, or forceful closure <u>Extraocular eye movements (CN 3/4/6):</u> <ul style="list-style-type: none"><li>- Conjugate lateral deviation (destructive or irritative lesions)</li><li>- Vertical disconjugate ("skew deviation"; structural)</li><li>- Roving eyes (esp. if conjugate suggests metabolic cause)</li></ul> <u>Facial symmetry (CN 7):</u> test at rest and on activation (smile) <u>Oculocephalic reflexes (CN 8):</u> doll's eye movement <u>Cough/gag (CN 9/10):</u> if intubated, suction	<u>Muscle strength:</u> Observe spont. movements (e.g., symmetric? Antigravity?); if mental status allows, perform confrontational testing
<u>Orientation</u>		<u>Sensory:</u> compare sensation to light touch
<u>Attention</u> (days of week backwards)		<u>Response to noxious stimuli in each extremity:</u> (localizing > withdrawal > extension)
<u>Language:</u> more detailed exam: comprehension, fluency, repetition, naming		

## APPROACH TO SUBACUTE AMS:

 consider Neurology consult prior to further extensive work-up

- Hx/Exam similar to above. **DDx** also includes: infection (HIV, Lyme, syphilis), autoimmune (anti-NMDA, sarcoid), metabolic (thyroid, B1, B3, B12, Wilson's), medications, toxicodromes, HTN encephalopathy, hepatic encephalopathy, PRES (tacro/cyclosporine), adrenal insufficiency, porphyria (urine PBG)
- Dx:**
  - rEEG:** for non-convulsive status epilepticus (NCSE); **LTM:** for intermittent seizures
  - MRI with contrast:** for stroke, malignancy, infxn/inflammatory process, Wernicke's
  - LP (CTH to r/o herniation first):** see *Lumbar Puncture*, discuss advanced testing with Neuro

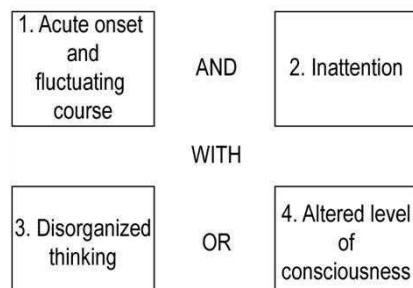
## TREATMENT OF AMS:

 diagnose and treat underlying cause; see disease-specific pages

## DELIRIUM: definition per DSM-5

- 1) Impairment in **attention**;
  - 2) change from baseline, develops over a short period of time (usually hours to days), tends to fluctuate during the course of the day
  - 3) additional disturbance in **cognition** (memory, disorientation, language, visuospatial ability, or perception);
  - 4) **not better explained by another preexisting neurocognitive disorder** and does not occur in the context of a severely reduced arousal/coma;
  - 5) clinical and/or lab evidence that the disturbance is **caused by a medical condition or substance**
- RFs: age >65 (~50% have delirium inpatient), hx delirium/TIA/CVA/dementia, long hospitalization, critical illness, recent surgery (esp. orthopedic), EtOH, infection, visual/hearing impairment, depression, HIV, h/o TBI
  - Exam: test inattention: reciting **months of the year backwards** (Sn 84%); **days of the week backwards** (Sp 82%) ([JHM 2018;13:551](#))
  - Complications: a/w ↑ mortality ([JAMA 2010;304:433](#)), ↑ institutionalization ([Lancet 2014;383:911](#)), ↓ cognition ([NEJM 2012;367:30](#))

## Confusion Assessment Method (CAM)



Sn 94-100%, Sp 90-95%, high inter-rater reliability ([Annals 1990;113:941](#))

## AVOID DELIRIUM BY PREVENTING IT IN VULNERABLE PATIENTS

- **Minimize deliriogenic meds:** anticholinergics, antihistamines, benzodiazepines, opioids
- **Ensure:** no urinary retention, regular bowel movements, and adequate pain management
- **Precautions:** frequent reorientation, mobilize with PT/OT, OOB to chair, **glasses/hearing aids**, minimize lines/telemetry/catheters, early volume repletion if c/f dehydration. **Avoid** room changes or physical restraints
- **Anticipate circadian dysfunction:** standing melatonin 3mg **q6PM**, lights on during day and off at night, schedule meds for earlier in evening, avoid late diuresis, reduce noise

## DELIRIUM MANAGEMENT

- Both HYPERactive and HYPOactive delirium warrant treatment
- Behavioral management: implement delirium precautions, modified deliriogenic medications, treat circadian dysfunction
- Identify & treat **UNDERLYING CAUSE** w/ special attention to life-threatening conditions (see *Altered Mental Status*)
- **Monitor QTc daily** (goal <550ms); daily repletion of K>4 & Mg>2 (in anticipation of pharmacotherapies)
- Reserve pharmacologic agents for **dangerous behavior ONLY** i.e. if **danger to self or others**; no evidence for altering duration of delirium ([NEJM 2018;379:2506](#)), severity, hospital or ICU LOS ([JAGS 2016;64:705](#)) with increased potential for adverse effects (e.g. QTc prolongation and drug interactions)

### Medical Management

1:1 sitter (re-orient) >> meds >> restraints (deliriogenic)

- **For HYPERactive delirium/AGITATION → start PRN, escalate to scheduled** ([Nat Rev Neurol. 2009;5:210](#)). (see *Agitation*)
  - Haloperidol 2-5mg IV q3h PRN vs. 0.5-1mg PO q4h PRN vs. IM q1h PRN (NB: can lead to EPS/acute dystonias in Parkinsonism)
  - Quetiapine 12.5-50mg PO q6-12h PRN
  - Olanzapine 2.5-10mg SL/PO/IM qd-q4h PRN
- **If continued severe agitation → consider Psych/Geri consult:**
  - Haloperidol PRN: double PRN dose q20 min until effective, ~5-20mg IV, consider standing or gtt (ICU)
  - Quetiapine PRN: standing 25-50 mg TID, extra dose HS
  - Olanzapine PRN: standing 2.5-10 mg BID, extra dose HS
- QTc ↑ severity: haloperidol > quetiapine > olanzapine; Δ tx if QTc ↑ by 25-50%, QTc>500, ⊕U-wave/T-wave flattening
- **Discontinue when able, avoid benzos. Prolonged antipsychotic use in elderly can increase mortality**
- For patients with prolonged QTc or refractory symptoms to medications, consider IV valproic acid (discuss with psychiatry)

## WHEN TO CONSIDER PSYCHIATRY/GERI CONSULTATION

- **Escalating/persistent delirium**, hx agitated delirium, underlying neurodegen. disorder (esp. PD), hx TBI
- **Co-morbid EtOH or other substance use disorders**
- Significant co-morbidities (CV disease/critical illness)
- At risk for disinhibition/impulsivity

## WHEN TO CONSIDER NEUROLOGY CONSULTATION

- New **focal** finding suggesting stroke: *Stroke Neuro p20202*
- Other **concerning** findings (convulsions, meningismus, e/o elevated ICP, abnl spot EEG/LP): *General Neuro p20702*
- **Know the following prior to calling:** last seen well, baseline deficits, anticoagulation

# Neurology

# Dementia

**INITIAL EVALUATION:** should almost always be in the outpatient setting, can assess over time without acute illness or delirium

- Obtain collateral, determine symptom onset, ADLs/IADLs, assess safety, screen for depression
- Review medications for those with cognitive SEs (e.g., analgesics, anticholinergics, psychotropic medications, sedative-hypnotics)
- Assess cognitive impairment (**MOCA >> MMSE**), track score at subsequent visits
- Labs: CBC, TSH, BMP, B12; consider: tox screen, syphilis, Lyme, HIV, UA, metals, ESR, LFT, folate, B1 ([AFP 2005;71:1745](#))
- Imaging: NCHCT or **MRI brain (preferred)** to r/o structural lesion (tumor), assess **atrophy pattern** and vascular dementia
- Inpatient eval considered for 1) any rapidly progressing dementia syndrome (c/s Neuro to discuss LP → RT-QuIC 14-3-3 in CSF (CJD), ACE (sarcoid), autoimmune encephalitis, or 2) new dementia diagnosis in pts <55yo or with new focal deficit (eval stroke)
- **Outpatient Neurology referral to Memory/Cognitive clinic** (and formal neuropsychological testing)

**DEMENTIA SYNDROMES** ([Prog Neurol Psych 2012;16:11](#); [BMJ Neurol Neurosurg Psych 2005;76:v15](#); [Ann Neurol 2008;64:97](#))

\*\*Clinical phenotypes often overlap and may require years to differentiate\*\*

Syndrome	Presentation	Exam	Imaging	Treatment
<b>Gradually Progressive</b>				
Alzheimer Dementia	<ul style="list-style-type: none"> <li>• <b>Short term memory loss early</b>; language &amp; visuospatial deficits</li> <li>• Apraxia in later stages</li> </ul>	<ul style="list-style-type: none"> <li>• Nml neuro exam (excluding mental status)</li> <li>• Neuropsych: amnesia w/ short memory span, alexia, agraphia</li> </ul>	Hippocampal (± global) atrophy; ?microhemorrhages (CAA)	<ul style="list-style-type: none"> <li>• AChE-inhibitors (mild-severe dz)</li> <li>• NMDA-inhibitors (mod-severe dz)</li> </ul>
Lewy Body and Parkinson's Dementia	<ul style="list-style-type: none"> <li>• <b>Fluctuations</b> in attention/alertness</li> <li>• <b>Visual hallucinations (LBD)</b></li> <li>• <b>REM behavior d/o</b></li> <li>• Falls/syncope</li> <li>• Neuroleptic intolerance</li> <li>• Memory problems late</li> </ul>	<ul style="list-style-type: none"> <li>• Parkinsonism: resting tremor (can be absent), cogwheel rigidity, bradykinesia, stooped/shuffling gait</li> <li>• <b>Parkinson's dementia</b> if motor sx &gt;1y before dementia</li> <li>• Neuropsych: fluctuations w/ intrusions and confabulation, visuospatial impairment</li> </ul>	Global volume loss	<ul style="list-style-type: none"> <li>• AChE-inhibitors (esp. rivastigmine) for memory sx</li> <li>• Carbidopa/levodopa trial for motor sx</li> <li>• Sx management of <b>autonomic dysfxn</b></li> <li>• Avoid typical antipsychotics</li> </ul>
Frontotemporal Dementia	<p><b>Behavioral type</b></p> <ul style="list-style-type: none"> <li>• Personality Δ (<u>disinhib.</u>, apathy, poor insight)</li> <li>• Stereotyped behaviors</li> <li><b>1° prog aphasia type</b></li> <li>• Dysnomia, dysfluency, poor comprehension</li> </ul>	<ul style="list-style-type: none"> <li>• May have <b>frontal release signs</b> (non-specific)</li> <li>• 15-20% get motor neuron dz</li> <li>• Neuropsych testing: poor impulse control, difficulty in organization</li> </ul>	Atrophy predominantly in <b>frontal and temporal lobes</b>	<ul style="list-style-type: none"> <li>• Management of behavioral sx (consult psych)</li> <li>• AChE-inhibitors not helpful</li> <li>• <b>Avoid</b> NMDA-inhibitors</li> </ul>
<b>Stepwise Progressive</b>				
Vascular Dementia	<ul style="list-style-type: none"> <li>• <b>Abrupt focal sx, stepwise progression</b></li> <li>• Depression common</li> <li>• Hx: CVA, HTN, HLD, AF</li> </ul>	<ul style="list-style-type: none"> <li>• Focal deficits (depends on stroke location), can include: weakness, dysarthria, ataxia, gait changes</li> <li>• Often look older than age</li> </ul>	Cortical or subcortical <b>punctate lesions</b> , <b>white matter disease</b> , and <b>volume-loss</b>	<ul style="list-style-type: none"> <li>• Secondary stroke prevention and risk factor modification</li> <li>• AChE-inhibitor for memory deficits</li> </ul>
<b>Rapidly Progressive</b>				
Prion Diseases (Sporadic, Variant Creutzfeldt-Jacob Disease)	<ul style="list-style-type: none"> <li>• <b>Rapidly progressive</b> sx in memory, concentration, judgment</li> <li>• Mean onset age ~60 for sporadic, 28 for variant</li> <li>• Younger → ↑psych sx</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Myoclonus, exaggerated startle response</b></li> <li>• EPS (bradykinesia, nystagmus, ataxia), UMN (hyperreflexia, Babinski, spasticity)</li> <li>• <b>LP: RT-QuIC&gt;&gt;14-3-3</b></li> </ul>	<b>MRI:</b> cortical ribboning on DWI, subcortical hyperintensity on FLAIR <b>EEG:</b> 1-Hz periodic epileptiform discharges	<ul style="list-style-type: none"> <li>• No tx</li> <li>• Death w/in 1y (median disease duration 6mo)</li> </ul>
Limbic Encephalitis (Autoimmune, Paraneoplastic)	<ul style="list-style-type: none"> <li>• Sx evolve days-weeks (more indolent possible)</li> <li>• <b>Short-term memory sx</b></li> <li>• <b>Psych sx:</b> agitation, delusions, hallucinations</li> <li>• <b>Focal seizures</b></li> </ul>	<ul style="list-style-type: none"> <li>• Prominent psych features</li> <li>• Dyskinesias, rigidity</li> <li>• Autonomic instability</li> <li>• <b>LP:</b> lymphocytic pleocytosis, oligoclonal bands, <b>autoantibodies</b> (CSF + serum)</li> </ul>	<b>MRI:</b> FLAIR hyperintensity or contrast enhancement (esp. in temporal lobe) <b>EEG:</b> extreme delta brush very specific	<ul style="list-style-type: none"> <li>• Immunotherapy: <b>steroids, IVIG, PLEX, rituximab, cyclophosphamide</b></li> <li>• <b>Tumor resection</b></li> </ul>

**TREATMENT:** can treat symptoms, but treatment does not slow the progression of disease

- Inpatient Considerations:
  - For patients with Parkinson's, **do NOT stop/change** home medications (NGT if needed). Stopping sinemet can cause NMS.
  - If patient has or may have LBD, avoid antipsychotics. If necessary, atypicals (olanzapine, quetiapine) or trazadone preferred
- **AChE (acetylcholinesterase) inhibitors:** donepezil (first line), rivastigmine (patch), galantamine. Small effect on decreasing rate of cognitive decline, ADLs. Major side effects: GI (n/v/d); less common bradycardia and heart block (increased vagal tone)
- **NMDA inhibitors:** memantine. Can precipitate agitation and exacerbate neuropsychiatric sx (caution in pts with significant behavioral sx)
- **Anti-amyloid Abs:** For patients w/ confirmed amyloid (by LP or amyloid PET). Aducanumab clears amyloid, uncertain clinical sig. Lecanemab binds to inhibit formation of AB plaques. ([NEJM 2023; 388; 9-21](#)). Amyloid-Related Imaging Abnormalities (ARIA) associated with edema (-E) or hemorrhage (-H). CMS does not yet reimburse for anti-amyloid abs, but remains an evolving discussion.

# Neurology

# Headache & Vertigo

## HEADACHES

**Approach:** distinguish **primary HA** (tension, migraine, etc.) from **secondary HA** (tumor, ↑ICP, etc.)

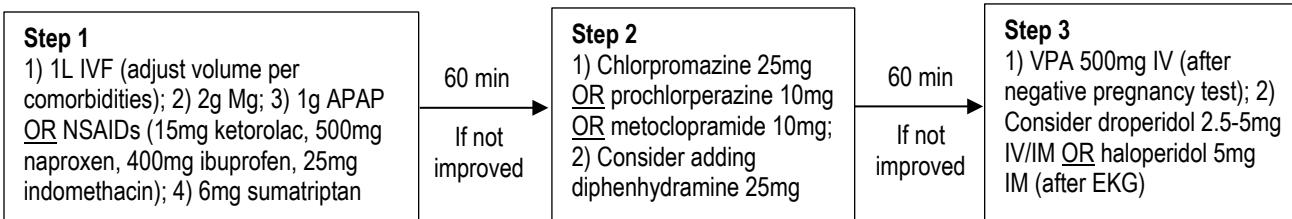
**Red Flags (consider neuro c/s or neuroimaging):** new onset HA (in pt with c/f trigeminal autonomic cephalgia, hx of SCD, or >50 yo); positional or sudden+severe onset HA; headache with maximal intensity at onset, PMH immunocompromised, TB, cancer, or VPS; abn neuro exam, fever/nuchal rigidity

**Tension HA:** ~40% population, ♀>♂, band-like, forehead radiating to occiput, mild-mod severity, duration 30min to 7d ([AFP 2002;66:797](#))

**Migraine HA:** >3/5 "POUND" criteria (Pulsating, 4-72h hOurs, Unilateral, Nausea, Disabling) ([JAMA 2006;296:1274](#))

- Migraine with aura: 1 unilateral/reversible sx [visual/retinal (scintillating scotoma, visual field deficit), sensory (tingling, numbness), speech/lang (aphasia), motor (weakness), brainstem (dysarthria, vertigo, ataxia, diplopia)] lasting minutes, usually followed by HA

**ED/Inpt Management:** for migraine/tension HA w/o red flags



## Outpatient Management:

Migraine HA	
Preventatives (if >4d/mo, long duration, or disability)	Rescue (max 2d/w, treat early)
<b>BB/CCB:</b> propranolol 20mg BID up to 160mg/d; metoprolol 25mg BID up to 200mg/d; verapamil 80mg TID, ↑ gradually	<b>NSAIDs/APAP</b>
<b>Antidepressants:</b> amitriptyline/nortriptyline 10mg qhs, ↑ to 150mg; venlafaxine 37.5mg qd, ↑ to 75-150mg	<b>Triptans:</b> sumatriptan [5-20mg q2h (max 40mg/d) intranasal, 4-6mg q1h (max 12mg/d) SC, 25-100mg q2h (max 200mg/d) PO]; zolmitriptan [5mg q2h (max 10mg/d) intranasal, 1.25-2.5mg q2h (max 10mg/d) PO]; <b>C/I:</b> CAD/PAD, liver dz, basilar migraine, MAOIs w/in 2w; risk of serotonin syndrome
<b>Anticonvulsants:</b> topiramate 25mg qd, ↑ gradually to 100mg BID; VPA 500-1500mg qd (avoid both in young ♀)	<b>CGRP antagonists:</b> ubrogepant 50-100mg q2h (max 200mg/d) PO
<b>CGRP antagonists:</b> erenumab 140mg monthly	
<b>Supplements:</b> Mg 400mg qd, riboflavin 400mg qd, melatonin, feverfew	
<b>Botox:</b> referral to HA clinic	

- Tension HA:** prevention - smoking cessation, treat OSA, TCA, SSRI; rescue - NSAIDs **OR** APAP +/- antiemetic, max 2 d/w
- Menstrual migraine:** before/during menstruation → NSAIDs or sumatriptan ([Neurology 2008;70:1555](#)). Consider preventive tx perimenstrually w/ slow triptan (frovatriptan) 2.5mg QD/BID (begin 2d premenstrually, for total 6d/month)
- In pregnancy:** NO gadolinium contrast, NSAIDs, VPA. C/s OB/Neuro if ? re: med safety/efficacy ([Continuum 2022; 28: 72-92](#))

## VERTIGO

**Definition:** illusion of motion of self or world secondary to vestib dysfunction; a/w n/v, postural/gait instability

**Approach:** distinguish **central vs peripheral** ([AFP 2017;95:154](#))

- Hx/Exam:** duration of sx, episodic/persistent, triggers (position Δ), prior sx, assoc sx (5D's for brainstem: dysarthria, diplopia, dysphagia, dysphonia, dysmetria). Obtain orthostatics. Perform Dix-Hallpike. [HINTS exam video](#).
- HINTS exam:** each test *must be c/w peripheral to be reassuring*. In **acute, ongoing** vertigo, Sn 97%, Sp 85% for stroke (>[MRI](#))
  - Head Impulse** (pt looks at your nose, passively rotate head ~20°. No saccade = ambiguous. Catchup saccade = peripheral)
  - Nystagmus** (unidirectional e.g., always left-beating = peripheral; direction changing = central, any vertical = central)
  - Test of Skew** (cover one eye, then other, any vertical skew/correction = central) ([Acad Em Med 2013;20:986](#))

**Tx (peripheral):** metoclopramide, prochlorperazine, meclizine (≤2w, vestib suppression), lorazepam, or diazepam, **AND** vestibular PT

	Symptoms	Ddx	Imaging
<b>Peripheral</b>	Severe nausea, mild imbalance, hearing loss/tinnitus	Benign positional paroxysmal vertigo (BPPV), infxn (labyrinthitis, vestibular neuritis, herpes zoster oticus), Meniere's, vestibular migraine, otosclerosis, trauma (perilymphatic fistula)	If exam reassuring, none
<b>Central</b>	Mild nausea, severe imbalance, rare hearing sx	Vertebrobasilar ischemia/TIA, ICH, toxic, cerebellopontine mass (vestib schwannoma, ependymoma, brainstem glioma, medulloblastoma), NF, MS, vestibular migraine	<b>MRI</b> brain w/ contrast (coronal DWI reformats), <b>MRA</b> head & neck

### MGH ED Approach to Acute Dizziness



**Consider stroke for any sudden-onset focal neurologic symptoms**		IV tPA/TNK
ACUTE STROKE ACTIVATION		
1) If high suspicion and onset of sx <u>within past 24h</u> , activate the code pager by <b>calling the operator at 6-3333</b> . This will notify the stroke resident and fellow. Stroke resident will activate stroke group pager if needed (pharmacy, radiology, NSGY, IR, ICU RN, resource RN)		<b>Inclusion:</b> 1. Severe or disabling neurological deficit 2. Age $\geq 18$ 3. Time since <b>last seen well &lt;4.5h or wake up symptoms</b>
2) <b>BE AT BEDSIDE.</b> Consider this a code equivalent. Ensure 18g PIV is in place and bed is ready for travel with travel monitor in place		<b>Exclusion:</b> History: stroke/head trauma in last 3mo; recent head/spine surg; prior ICH; intracranial malignancy, AVM, aneurysm; incompressible arterial puncture last 7 days; GIB last 21 days
3) <b>ABC/Vs, check EKG, telemetry, glucose, keep NPO &amp; HOB <math>&gt;30^\circ</math>. Do not treat HTN unless BP <math>&gt;220/120</math>, ACS, or ICH (see below)</b>		<b>Clinical:</b> $BP \geq 185/\geq 110$ ( <b>treat!</b> ); BG $<50$ ; active internal bleeding; bleeding diathesis
4) Be ready to provide the following information: a) <u>Last seen well (LSW) time</u> (last time patient confirmed to be normal) – this is NOT the time that sx were noticed by you or patient		<b>Heme:</b> plt $<100K$ , PTT $>40s$ , PT $>15s$ ; current AC (warfarin w/ INR $>1.7$ ; therapeutic heparin use w/in 48h w/ ↑PTT; DOAC w/in 48h)
b) AC or antiplatelets, CrCl, allergies, code status		<b>Head CT:</b> hemorrhage; large, established infarct (e.g., 1/3 MCA territory, <b>ASPECTS &lt;6</b> )
c) Contraindications to tPA/TNK - <u>even if present, call an acute stroke (patient may be candidate for thrombectomy)</u>		
d) Physical exam findings: most predictive findings incl. facial paresis, arm drift/weakness, and abnormal speech ( <a href="#">JAMA 2005;293:239</a> )		
e) Premorbid disability (e.g., walks w/ assistance, bedridden)		
5) <b>Order STAT CTA Head/Neck</b> (only need to order CTA; includes NCHCT). If unable to receive contrast, stroke team will consider STAT MRI ± MRA		
6) <b>Obtain Labs:</b> BMP, LFTs, CBC, PT/PTT, trop, UA/UCx, tox screen, & AED levels (if appropriate)		
7) Neurology will perform <b>NIHSS</b> at bedside		
ACUTE STROKE INITIAL MANAGEMENT ( <a href="#">in-house stroke pathway</a> )		
Stroke team will provide guidance, but IV tPA/TNK may be given by any physician		
<b>1. ISCHEMIC STROKE</b>		<b>Inclusion:</b> 1. Clinical: NIHSS $\geq 6$ , LSW $\leq 24h$ , age 18-90, baseline mRS $\leq 2$ , life expectancy $>12$ mo 2. Radiological: ICA or MCA M1/2 occlusion, basilar/vert occlusion, small infarct core volume Note: Proven benefit w/ these inclusion crit; probable benefit w/ NIHSS $\geq 4$ , mRS $\leq 3$ , prox occlusion w/ <b>ASPECTS <math>\geq 5</math></b> . Discuss all cases w/ Neuro, may opt for IAT w/o strict criteria.
• <b>IV thrombolysis: tPA or TNK:</b> <u>0.25mg/kg</u> (max 25mg); tPA given as infusion, TNK given as bolus. TNK is now preferred thrombolytic at <b>MGB</b> .		<b>Exclusion:</b> Clinical: anaphylaxis to contrast, acute ICH
○ <b>LSW 0-3h:</b> goal to start IV tPA/TNK w/in 60min of ED arrival (AHA/ASA: <a href="#">Stroke 2018;49:e46</a> )		
○ <b>LSW 3-4.5h:</b> IV tPA/TNK recommended but w/ relative exclusion criteria including age $>80$ , AC (regardless of INR), NIHSS score $>25$ , h/o both stroke & DM2 ( <a href="#">ECASS III NEJM 2008;359:1317</a> )		
○ <b>Wake-up or Unknown Onset:</b> consider IV tPA if DWI lesion $<70$ mL w/o FLAIR changes ( <a href="#">WAKE-UP NEJM 2018;379:611</a> )		
• <b>Intra-arterial therapy (thrombectomy, thrombolysis):</b>		
○ Patients with disabling deficit & large vessel occlusion with <b>LSW &lt;6h</b> ( <a href="#">MR CLEAN NEJM 2015;372:11</a> )		
○ May extend time to <b>LSW 6-24h</b> based on imaging criteria ( <a href="#">DAWN NEJM 2018;378:11; DEFUSE 3 NEJM 2018;378:708</a> )		
• <b>BP control:</b> low SBP ( $<150$ ) a/w poor outcome ( <a href="#">Arch Intern Med 2003;163:211</a> )		
○ If tPA/TNK candidate: goal BP $\leq 185/110$ prior to thrombolysis ( <b>treat STAT if higher!</b> ); goal BP $\leq 180/105$ after tPA for 24h		
○ If no tPA/TNK: goal BP $\leq 220/120$ (allow auto-regulation) for 1d; gradually reduce BP goal subsequently		
○ If anticoagulated: goal SBP $\leq 180$		
○ If active cardiovascular disease (ACS) & requires tighter BP control, discuss w/ neuro		
○ <b>Monitor neuro exam:</b> sx worse at low BP c/f ongoing ischemia → <b>lay bed flat, give IVF bolus, STAT page neuro</b>		
<b>2. HEMORRHAGIC STROKE</b> (see <i>CNS Emergencies</i> )		
INPATIENT POST-STROKE CARE		
• Frequent <b>neuro checks</b> q1-2h x 24h if unstable/ICU; q4h if stable/floor pt, <b>STAT</b> head CT if change in exam		
• Consult PT, OT, SLP (NPO until bedside swallow eval). Keep <b>euthermic</b> (antipyretics), <b>euglycemic</b> (FSG $<180$ )		
• Post tPA/TNK: <b>NCHCT 24h post-tPA</b> → if no e/o hemorrhagic transformation and etiology cryptogenic, start antiplatelet + DVT ppx		
• If did not receive tPA/TNK: <b>ASA 325mg x1</b> , followed by long-term antiplatelet or AC (may delay antiplatelet and/or AC for large ischemic strokes). Start DVT ppx if ischemic stroke (unless large volume hemorrhagic conversion)		
• <b>Discuss 2° prevention plan w/ Neuro</b> (depends on suspected etiology, size of infarct, NIHSS, ABCD <sup>2</sup> , etc.)		
• <b>Antiplatelet long-term 2° prevention</b>		
○ <b>ASA</b> 81mg qd (50-325mg/d effective; $\leq 200$ mg/d lower risk of major bleed) ( <a href="#">Am J Cardiol 2005;95:1218</a> )		
○ <b>Clopidogrel</b> 75mg qd (may be superior to ASA for atherosclerotic vascular dz) ( <a href="#">CAPRIE Lancet 1996;348:1329</a> )		
○ <b>DAPT (ASA + clopidogrel OR ticagrelor)</b>		
▪ <b>High-risk TIA (ABCD<sup>2</sup> <math>&gt;3</math>) or minor stroke (NIHSS <math>&lt;4</math>):</b> ASA 81mg + clopidogrel 300mg load → 75mg for 3w followed by clopidogrel or ASA alone ( <a href="#">CHANCE NEJM 2013;369:11</a> ). May replace clopidogrel with ticagrelor ( <a href="#">NEJM 2020; 383:207</a> )		
▪ <b>Symptomatic intracranial stenosis:</b> consider ASA 325mg /clopidogrel 75mg for 3mo → ASA 325 qD ( <a href="#">SAMMPRIS NEJM 2011;365:993</a> )		
▪ <b>Recurrent stroke on ASA or clopidogrel alone + significant athero:</b> consider DAPT long-term; however, no clear evidence & higher bleed risk ( <a href="#">CHARISMA NEJM 2006;354:1706; MATCH Lancet 2004;364:331</a> )		
• <b>Anticoagulation long-term 2° prevention</b> (embolic infarcts from AFib, paradoxical embolus, LV thrombus, VST, or hypercoag state)		
○ <b>Warfarin or DOAC</b> for pts w/ AF (start immediately for TIA, wait 2-14d for small infarct, generally 2-4w if c/f large hemispheric stroke or hemorrhagic transformation)		

- Typically, no need for both antiplatelet & anticoagulation for 2° stroke prevention
- Start atorvastatin 80mg with LDL goal <70 ([TST NEJM 2020;382:9](#))
- Work up/secondary prevention (see below):
  - **Labs:** See Acute Stroke above, plus lipids, A1c, TSH, ESR, CRP , if **cryptogenic stroke**: consider RPR, HIV +/- bloodstream or CNS infectious w/u +/- hypercoagulability (d/w Neuro). ([STROKE 2021;52:364](#))
  - **Imaging:** MRI brain w/o contrast; head and neck CTA or MRA (TOF if low GFR); carotid US PRN
  - **Cardiac:** EKG, TTE (w/ bubble if <60yo), tele then 30d MCOT vs LINQ ([STROKE-AF JAMA 2021;325:2169](#)) if tele neg for AF

CARDIOEMBOLIC STROKE	
<b>SUSPECT WHEN:</b> <ul style="list-style-type: none"> <li>● ACA/MCA/PCA occlusion w/o sig vascular dz</li> <li>● Infarcts in multiple vasc territories or cerebellar stroke</li> <li>● Known risk factors (LA/LV thrombus, AF, LVEF&lt;35%, aortic arch athero, R→L shunt)</li> <li>● Hypercoagulability/hyperviscosity (malignancy, HbSS, cryo, clotting d/o)</li> </ul>	<b>DIAGNOSTIC WORKUP:</b> <ul style="list-style-type: none"> <li>● <b>TTE (w/ bubble if &lt;60yo):</b> if PFO, r/o venous thrombus (LENIs/ MRV pelvis), consider closure (<a href="#">RESPECT NEJM 2017;377:1022</a>)</li> <li>● If no hx of AF: <b>tele followed by 30d MCOT vs. LINQ</b> at discharge</li> </ul> <b>ACUTE MANAGEMENT CONCERNS:</b> <ul style="list-style-type: none"> <li>● Unless c/f hemorrhagic transformation, trans to long-term AC in 2d-14d. If concerned, delay 2-4w (d/w Neuro).</li> </ul>
SYMPTOMATIC CAROTID STENOSIS	
<b>SUSPECT WHEN:</b> <ul style="list-style-type: none"> <li>● Carotid stenosis present on ipsilateral side</li> <li>● H/o amaurosis fugax</li> </ul> <b>DIAGNOSTIC WORKUP:</b> <ul style="list-style-type: none"> <li>● <b>CTA vs. MRA head &amp; neck, carotid US</b> typically needed prior to carotid endarterectomy (CEA)</li> </ul>	<b>ACUTE MANAGEMENT CONCERNS:</b> <ul style="list-style-type: none"> <li>● If <b>stroke/TIA and either stenosis &gt;50% or high-risk plaque features</b>, consider revascularization (stent/angioplasty/CEA) ideally w/in 2w of sx (<a href="#">NASCET II NEJM 1998;339:1415</a>)</li> <li>● Consider temporary <b>anticoagulation</b> (d/w neurology)</li> <li>● Consider <b>induced HTN</b> if symptoms fluctuate with BP</li> </ul>
INFECTIVE ENDOCARDITIS	
<b>SUSPECT WHEN:</b> <ul style="list-style-type: none"> <li>● Unexplained fever w/ stroke or pt with valvular dz</li> </ul> <b>DIAGNOSTIC WORKUP:</b> <ul style="list-style-type: none"> <li>● <b>Blood cultures, TTE</b> followed by <b>TEE</b> if neg</li> <li>● <b>CTA head +/- conventional angio</b> to identify mycotic aneurysms (↑ bleeding risk)</li> </ul>	<b>ACUTE MANAGEMENT CONCERNS:</b> <ul style="list-style-type: none"> <li>● <b>Immediate antibiotics; tPA contraindicated</b></li> <li>● Early cardiac surgery if small non-hemorrhagic stroke; delayed cardiac surgery (2-4w) if large or hemorrhagic stroke</li> <li>● <b>Avoid anticoagulation or antiplatelet</b> w/o a separate indication</li> </ul>
CAROTID AND VERTEBRAL DISSECTIONS	
<b>SUSPECT WHEN:</b> <ul style="list-style-type: none"> <li>● &lt;60yo or posterior circulation stroke in pt w/o RFs</li> <li>● Neck pain, HA, or Horner's syndrome</li> <li>● Trauma (vertebral fx), chiropractor, coughing spells</li> </ul> <b>DIAGNOSTIC WORKUP:</b> <ul style="list-style-type: none"> <li>● <b>CTA vs. MRA with T1 fat saturation</b></li> <li>● Consider eval for comorbid conditions (Marfan's, FMD)</li> </ul>	<b>ACUTE MANAGEMENT CONCERNS:</b> <ul style="list-style-type: none"> <li>● Goal of tx is to prevent stroke: highest risk in first few days</li> <li>● <b>Anticoagulation vs antiplatelet</b> (<a href="#">TREAT-CAD Lancet Neurol 2021;20:341</a>). Prefer antiplatelet if: sx onset &gt;3d ago, dissection extends intradurally (no AC due to risk of SAH), large infarct (risk of hemorrhage)</li> <li>● High rate of recanalization → tx 3mo then re-image vessel</li> </ul>
CEREBRAL VENOUS SINUS THROMBOSIS	
<b>SUSPECT WHEN:</b> <ul style="list-style-type: none"> <li>● Positional HA, vomiting, papilledema, vision Δ</li> <li>● P/w seizure (common, may be difficult to control)</li> </ul> <b>DIAGNOSTIC WORKUP:</b> <ul style="list-style-type: none"> <li>● <b>NCHCT:</b> hyperdensity in torcula (<a href="#">dense delta sign</a>)</li> <li>● <b>CTV vs. MRV</b> to assess intracranial venous system</li> <li>● Consider <b>hypercoagulable workup</b></li> </ul>	<b>ACUTE MANAGEMENT CONCERNS:</b> <ul style="list-style-type: none"> <li>● <b>Immediate anticoagulation (heparin or LMWH)</b> even in presence of hemorrhage</li> <li>● AEDs if seizures (not indicated for ppx)</li> <li>● IV fluids, avoid dehydration, modify risk factors (smoking, OCPs)</li> <li>● <b>Long term anticoagulation (warfarin or DOAC)</b> for 3-6 months, then reimagine (<a href="#">RE-SPECT CVT JAMA Neurol 2019;76:1457</a>)</li> </ul>

## TRANSIENT ISCHEMIC ATTACK (TIA)

- **Definition:** transient neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia w/o acute infarction
- **Causes:** atherosclerotic 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 within 24h of sx onset and vessel imaging of head and neck for large vessel occlusive disease (e.g. [MRA head and neck w/ contrast](#) [w/o contrast TOF if low GFR] vs. [CTA head and neck](#) vs. carotid ultrasound)
- **Cardiac w/u:** [TTE](#) (w/ bubble if age <60) to excl thrombus & PFO, [MCOT vs. LINQ](#) monitoring to exclude AF if suspected embolic TIA
- **ABCD<sup>2</sup>** score (Age, BP, Clinical features, Sx Duration, Diabetes): used to identify pts w/ high risk of ischemic stroke w/in 1w of TIA
- **Management:** immediate intervention reduces the risk of recurrent stroke (1.5-3.5% risk w/in 48h), see 2° Prevention above

## POST-DISCHARGE STROKE/TIA CARE

- **Work up:** follow up labs pending at time of discharge (e.g. hypercoag panel), repeat APLAS labs after 12w if pos, f/u MCOT/LINQ, f/u repeat brain/vessel imaging as noted
- **Management:** discontinue short term meds as appropriate (e.g. d/c ASA or Clopidogrel after 21d if treating per CHANCE trial); start AC as noted in d/c sum (e.g. 2w after large ischemic stroke due to AF); ask about depression (common post-stroke), consider treating w/ fluoxetine ([FLAME Lancet Neurol 2011;10:123](#)); remind pts that deficits may continue to improve for >1yr

## INTRACRANIAL HEMORRHAGE (ICH)

- Causes:** trauma (all), ruptured aneurysm/AVM (SAH, IPH), IPH also caused by HTN, cerebral amyloid, tumor (most common w/ met breast CA, lung CA, melanoma, RCC, choroid, thyroid CAs), cortical vein/venous sinus thrombosis, hemorrhagic transformation of ischemic stroke
- Presentation:** acute focal neuro deficit ± progressive ↓ consciousness, n/v. **SAH:** thunderclap HA, N/V, meningismus; **EDH/SDH:** s/p trauma, lucid interval with EDH; **IPH:** focal neuro symptoms (may mimic ischemic stroke clinically); often with HA
- Tests:** STAT imaging (NCHCT for all; +CTA head if SAH/IPH), coags/PLTs; repeat CT head after 6h to assess progression
- STAT management:**
  - STAT Neurosurg (p21111) if SAH/SDH/EDH; otherwise, Neuro (inpatient: p20202; ED: p20000)
  - Elevate HOB to 30-45° to reduce ICP and prevent aspiration
  - BP control:** strict SBP <140 (studied in SAH or ICH due to ruptured aneurysm/AVM, to prevent re-bleeding), use **IV labetalol** or **nicardipine drip** (avoid hydralazine and nitropaste if possible), place arterial line ([Lancet Neurol 2008;7:391](#)); consider less restrictive BP goal (ie. SBP <160) for pts presenting with SBP >200 ([NEJM 2016;375:1033](#)). For aneurysmal SAH, PO nimodipine. ([Stroke. 2022;53\(6\):1993-2005](#))
  - Correct coags:** warfarin/INR>1.5 (vitamin K 10mg IV x1 AND 3-5U FFP or 4-factor PCC/KCentra); ↓plt (transfuse, goal >50); uremia/antiplatelet use (consider DDAVP 0.3mcg/kg IV); heparin/LMWH (protamine sulfate, consider heme c/s); s/p tPA (check fibrinogen, give cryo, ± amicar 4-5g → 1g/hr); rivaroxaban/apixaban (4-factor PCC/KCentra OR andexanet alfa, page pharmacy)
  - Venous sinus thrombosis (VST):** AC w/ LMWH/UFH despite ICH ([Lancet 1991;338:597](#)). Manage seizures (see *Seizures*) & ↑ICP.
  - Prognosis depends on age, GCS, pre-ICH cognitive impairment, and ICH volume/location ([FUNC Score; Stroke 2008;39:2304](#))
  - Typically, acceptable to restart DVT ppx in smaller hemorrhages **48h after** last stable NCHCT, confirm w/ Neurology
  - Start prophylactic levetiracetam 500mg BID x7d for traumatic SDH or SAH ([Neurocrit Care 2010;12:165](#))

## ELEVATED INTRACRANIAL PRESSURE (ICP)/HERNIATION

- Etiologies:** mass (tumor, abscess, hemorrhage), cerebral edema (infarction, inflammation, hyperammonemia, DKA), hydrocephalus (tumor, intraventricular hemorrhage, leptomeningeal disease, meningitis), PRES, VST. High ICP may cause compression/ischemia. Severe local swelling or CSF drainage with large space-occupying lesions causes herniation (displacement & compression of brain).
- Signs of herniation:** fixed/dilated/asymmetric pupil accompanied by nausea, somnolence/confusion, or limited upgaze; flexor/extensor posturing; ipsilateral hemiparesis (uncal herniation); **Cushing's triad (bradycardia, ↑SBP, irreg. breathing)**
- Tests:** STAT head CT, blood gas, BMP, CBC
- Management:**
  - STAT Neurosurgery for ICP monitor/EVD placement/decompressive hemicraniectomy, Neurology to discuss need for Neuro ICU
  - Secure ABCs, elevate HOB to 30-45°, keep head midline (to secure venous drainage), treat pain/agitation, maintain BP to avoid CPP <50mmHg.
  - If c/f herniation, **hyperventilate** to PaCO<sub>2</sub> ~ 30-35 mmHg (transiently reduces ICP)
  - Hyperosmolar therapy:** Check BMP, Sosm q6h. Start with 23% saline boluses, then use mannitol, or both staggered 3h apart (discuss with Neuro) ([Emerg Med J 2014;31\(8\):679-83](#))
    - 23% saline 30cc q6h (requires central line → better option for patients with AKI/CKD, use with caution in HF)
      - Hold if Na >160
      - IV mannitol therapy 1g/kg q6h (max 100g, use with caution in pts on HD). Hold if osm gap >15, Na >160, serum osm >340
  - If edema 2° to malignancy or bacterial infection, give 10mg IV dexamethasone x1, then 4-8mg BID
  - Complications during LP:** if sx of herniation or opening pressures >40cm H<sub>2</sub>O with space occupying lesion, consider STAT head CT. Immediately replace stylet into needle, only drain CSF from manometer, STAT Neurosurgery consult.
  - Do not use hypotonic solutions for resuscitation (i.e. LR) as this can worsen edema. Use 0.9% NaCl (NS) instead. ([J Neurosurg 1995;83\(6\):949-62](#)).

## HYPERTENSIVE ENCEPHALOPATHY

- PRES (posterior reversible encephalopathy syndrome)
- Dx of exclusion w/ (sub)acute onset, varied neuro sx, vasogenic edema, & severely elevated BP. ([J Neurol 2017; 264\(8\): 1608-16](#)).
  - Typically associated with:** severe HTN, but also relative HTN in setting of eclampsia/pre-eclampsia, cytotoxic/immunosuppr meds (cyclosporine, tacrolimus, cisplatin, bevacizumab), acute/chronic renal failure, uremia, sepsis, vasculitides, TTP → due to impaired cerebral autoregulation and endothelial dysfunction, hypoMg ([NEJM 1996;334:494](#))
  - Symptoms:** thunderclap HA, confusion, decreased consciousness, visual disturbances, seizures, ICH and ↑ICP
  - Tests:** MRI brain w/ contrast: FLAIR w/ vasogenic edema w/in white matter in the posterior cerebral hemispheres; DWI/ADC typically nl (though can have strokes); additional regions can be affected incl. brainstem, cerebellum, basal ganglia, frontal lobes
  - Management:** ICU if severe, strict BP control (goal SBP <140, reduce by 210-15% 1<sup>st</sup> hour then 5% daily, if severe use nicardipine or labetalol drip), treat seizures, Mg<sup>2+</sup> (esp. in eclampsia), remove inciting factor (i.e stop medication, dialyze if needed, treat infx)
  - Prognosis:** often fully reversible; complications include progressive cerebral edema, ICH, stroke, death

## CORD COMPRESSION

- high level of suspicion in cancer or injection drug use patients with back pain, urinary sx or LE weakness
- Etiologies:** subacute (tumor/mets, abscesses) vs acute (disc herniation, trauma, hemorrhage)
  - Symptoms:** back pain (worse at night/Valsalva), motor weakness, **hyperreflexia** below lesion if chronic (**hyporeflexic** if acute, cauda equina), ⊕Babinski, loss of sensation ("sensory level"), bowel/bladder incontinence OR retention, loss rectal tone, saddle anesthesia
  - Imaging:** **STAT MRI C/T/L w/ contrast** (cord compression protocol), call ED (x63050) or inpt MRI (x64226) to prioritize
  - STAT page** NSGY/Ortho spine for decompression ± Rad Onc for possible XRT if tumor related (see *Oncologic Emergencies*)
  - Dexamethasone:** 10mg IV x1 then 4mg IV Q6H, esp in malignancy ([Cochrane Database Syst Rev. 2015 Sep 4;2015\(9\):CD006716](#))

DEFINITIONS [Epilepsia 2017;58:522](#) [Continuum 2019;25:306](#) [Continuum 2022;28\(2 Epilepsy\):230-260](#)

- Classification of seizure (sz): describe onset and semiology
  - Focal onset: unilateral, occurring in one hemisphere, ± impaired awareness, may evolve to bilateral tonic-clonic
  - Generalized onset: occurring in & rapidly engaging bilateral distributed networks, impaired awareness
  - Motor: limb stiffening (tonic), limb jerking (clonic), brief muscle contraction (myotonic), loss of tone (atonic), or automatisms
  - Non-motor: autonomic changes, staring/behavioral changes, cognitive changes, sensory phenomena
- Epilepsy: ≥2 unprovoked sz >24h apart or 1 unprovoked sz + recurrence risk ≥60% over the next 10y or dx of an epilepsy syndrome
- Status epilepticus: ≥ 5min of continuous sz or 2+ sz w/ incomplete recovery of consciousness in between ([Epilepsia 2015;56:1515](#))
- Non-convulsive status epilepticus: electrographic sz ≥10s or EEG & clinical improvement w/ tx ([Epilepsy Behav 2015;49:158](#))
- Psychogenic non-epileptic sz (PNES): most prevalent phenotype of fxnl neuro disorder (FND). Long & fluctuating course, asynchronous/side-to-side mvmts, closed eyes, preserved awareness of spell. ([Ann Neurol 2011;69:997](#))

ETIOLOGY: provoked vs unprovoked?

- Causes/RFs: primary epilepsy, vascular (ischemia/hemorrhage), withdrawal (EtOH/BZD), masses (tumor, abscess), trauma, metabolic (↓BG, ↑CO<sub>2</sub>, ↓O<sub>2</sub>, ↓Ca, ↑/↓Na), meds, infxn (systemic, CNS), HTN/HoTN, high fever, eclampsia, PRES
- Ddx: syncope, TIA, migraine, PNES (~30% have epilepsy, [Brain Behav 2022;12](#)), myoclonus, dystonia, cataplexy, tremor, catatonia
- H&P: sz history, prodrome (headache, confusion, anxiety, irritability), med list (↓sz threshold), triggers (exertion, pain, fatigue, stress, cough, urination/defecation, infxn), tongue biting (lateral), incontinence, lateralizing signs, EtOH/BZD. GET COLLATERAL.
- Labs: FSBG, Utox & Stox, UA, CXR, AED lvs, BMP, Mg, Phos, CBC, LFTs, VBG, CK, INR, lactate, b-hCG. Prolactin rarely helpful.
- Monitoring: tele (↑risk for ictal bradycardia/aystole), pulse O<sub>2</sub> ([NEJM 2013;368:2304-12](#))
- Neuroimaging: epilepsy protocol MRI w/ contrast for unprovoked 1st sz ([Continuum 2022;28\(2 Epilepsy\):230-260](#)), focal seizure, focal neuro exam, h/o trauma, malignancy, or HIV. 10% found to have relevant structural lesion ([Neuro 2007;69:1996](#)).
- LP/BCx: if febrile, HIV/immunocompromised, 2° autoimmune encephalitis (anti-NMDA) ([Epilepsia 2020;61:1341](#))
- EEG: within 24-48h if not seizing, emergent if seizing. DO NOT wait for EEG to manage. If emergent, contact EEG fellow (p16834).

SEIZURE PPX [Neuro 2015;84:1705](#) [Neuro 2006;67:s45](#) [Cochrane 2008;CD004424](#) [Stroke 2016;47:2666](#)

- No AED in 1<sup>st</sup> sz unless prior TBI, abnml EEG, or abnml imaging. Early AED ↓short term recurrence (<2y), not remission (3+y).
- ETOH seizure: ppx not indicated for intox/withdrawal, ICH: only if clinical sz or traumatic etiology, levetiracetam 500mg BID x7d
- Brain tumor: no ppx. If sz, levetiracetam > lacosamide (fewer chemo interactions), Severe TBI: levetiracetam 500-750mg BID x7d
- PNES: Outpatient, CBT & Psychiatry. Inpatient, educate about functional neurological sx, c/s social work.
- In MA, no driving (for LOC event) until 6mo event free. Counsel pt, include in d/c summary. Restrictions vary by state.

TREATMENT

- Seizures that are NOT status epilepticus: tx if a) GTC > 2-3min or b) patient has several focal seizures within 24h ("clustering")
  - Lorazepam 1-2mg IV (1mg if elderly or low weight), can repeat x1 if needed. Then discuss possible ASM load with Neurology.
- Treatment of status epilepticus ([MGH status epilepticus treatment protocol](#))
  - Lorazepam 4mg IV q5min x1-2 → levetiracetam 60mg/kg x1 (max 4500mg/dose) vs. valproate 40mg/kg x1 (max 3000mg/dose) vs. fosphenytoin 20 PE/kg (over 10 min) → intubation w/ propofol/midazolam/(3<sup>rd</sup>-line) ketamine ([NEJM 2019;381:2103](#)). Add 4mg Mg for suspected eclamptic seizure. Discuss with Neurology.
  - If no IV access, midaz 10mg IM/nasal/buccal or diazepam 20mg PR
- Suspected preeclamptic seizure: 4mg IV Mg x1, consider mag sulfate infusion (2g/h)

AED	Loading	Dosing	Goal Level	Side Effects
Levetiracetam (Keppra)*	40-60mg/kg Max 4.5g	1:1 PO:IV	No goal, level to check adherence	Psych (aggression, anxiety/depression, psychosis)
Valproic acid (Depakote) <sup>†</sup>	20-40mg/kg Max 3g	1:1 PO:IV	50-100mcg/mL (>1h post load)	↑ weight, hepatitis, N/V, tremor, alopecia, encephalopathy (↑NH3), ↓platelets. Good w co-morbid mood disorder.
Phenytoin (Dilantin) <sup>†</sup> , Fosphenytoin	20 mg/kg Max 1.5g	1:1 PO:IV	10-20mcg/mL, correct for alb, (2h post load)	HoTN/arrhythmia (if run >50mg/min; fosphen. has ↓cardiotox, gingival hypertrophy, nystagmus/ataxia/slurred speech, blood dyscrasias, DRESS, rash (TEN/SJS))
Lacosamide (Vimpat)	200-400mg	1:1 PO:IV	10-20mcg/mL	HA, diplopia, dizziness, ataxia, nausea. Get EKG before & after load (PR prolongation, flutter/fib).
Lamotrigine (Lamictal)*	No Load	Only PO	3-15mcg/mL	Rash (TEN/SJS), DRESS, nausea, drowsiness, ↓PMNs, HLH, aseptic mening. Good w co-morbid mood disorder.
Topiramate (Topamax) <sup>†</sup>	No Load	Only PO	N/A	↓ weight, drowsiness, glaucoma, NAGMA→nephrolith., cognitive dysfxn, aggression, anxiety/depression
Carbamazepine (Tegretol)	No Load	Only PO	4-12mcg/mL	SIADH, N/V blood dyscrasias, ataxia, blurred vision, DRESS. Screen for HLA-B*1502 if Asian descent for ↑risk of TEN/SJS ( <a href="#">Epilepsia 2019;60:1472</a> ).
Clobazam (ONFI)	No Load	1:1 PO:SUSP	N/A	Drowsiness, resp. depression (BZD), ataxia, URI, fever
Perampanel (Fycompa)	No Load	1:1 PO:IV	N/A	Aggression/irritability, dizziness, drowsiness, weight gain

Others include: Brivaracetam, Cenobamate, Ethosuximide (absence), Phenobarbital (historical), Vigabatrin, Zonisamide

\*Preferred in pregnancy, <sup>†</sup>Teratogenic

# Neurology

# Weakness & Neuromuscular Disease

## CHARACTERIZATION OF A PERIPHERAL PROCESS

- **Weakness:** ask about **function** (rising from a chair, stairs, brushing hair, tripping while walking, opening jars, zippers/buttons). Clarify vs. generalized fatigue or systemic symptoms (i.e. of anemia, infection, electrolyte abnormalities, thyroid/adrenal issues)
- **UMN signs:** spasticity, increased tone, hyperreflexia,  $\oplus$  Babinski; **LMN signs:** fasciculations, atrophy, decreased tone, hyporeflexia
- **Patterns:** UMN (UE extensors, LE flexors), LMN (length pdnt, myotomal), myopathy (proximal), bulbar (dysphagia, dyspnea, dysarthria)
- **Sensory sx:** negative ( $\downarrow$  temp/pin (small fibers), vibration(proprio (large fibers), imbalance) or positive (tingling, allodynia, hyperalgesia)
- **Autonomic sx:** orthostasis, constipation, urinary retention, sexual dysfxn, changes in sweating, post-prandial nausea or early satiety
- **Exam:** 0/5 - no mvmt, 1/5 - flicker, 2/5 - mvmt if no gravity, 3/5 - mvmt vs. gravity only, 4/5 - dec. power vs. resistance, 5/5 - nml
- **EMG/NCS:** localization (radicular, nerve, junction, muscle), motor vs. sensory, axonal vs. demyel (guides tx), severity (guides prognosis). **Higher yield if sx for  $\geq 2-3w$  (do as outpatient).**

Localization	Associated Signs/Sx	Diagnostics	Important/Common Causes
<b>Brain</b>	Cortical (lang., visual field, neglect), cerebellar, UMN	<b>MRI Brain</b> (with contrast if c/f cancer, infection, demyelinating dz)	<b>Vascular</b> (hemorrhage, ischemia), <b>tumor, trauma, demyelinating dz</b>
<b>Spinal Cord</b>	Truncal sensory level, bowel/bladder dysfxn, UMN (if chronic)	<b>MRI Spine</b> (level from exam, contrast if c/f cancer, infxn, demyelinating dz); <b>CSF</b> if c/f inflammatory or infxn	<b>Transverse myelitis</b> (MS, NMO, sarc/Sjo/SLE), infxn (viral myelitis, abscess, TB, AIDS, HTLV, syph.), paraneop, neoplasm, $\downarrow$ B12/Cu, vascular, <b>trauma, toxic, myelopathy</b>
<b>Anterior Horn Cell</b>	LMN; if motor neuron dz, UMN & LMN	<b>NCS/EMG</b> $\pm$ MRI brain and spine	<b>ALS, SMA, poliomyelitis, acute flaccid myelitis</b>
<b>Radiculär</b>	Motor/sensory corresponding to nerve root. Radiating pain.	<b>MRI Spine</b> (nerve root from exam) LP if polyradiculopathy <b>NCS/EMG</b> can aid in localization if sx $>3w$	Nerve root compression 2/2 disc herniation, spondylosis; <b>polyradiculopathy</b> $\rightarrow$ DM (thoracic, lumbosacral), AIDP/CIDP, infxn (Lyme, HIV, CMV), malignancy (leptomeningeal, chemo)
<b>Peripheral Neuropathy</b>	Motor/sensory; autonomic dysfxn. Often symmetric/ length dependent.	<b>Labs:</b> A1c, B12/MMA, S/UPEP <b>Consider:</b> Lyme, syphilis, HIV, B1, B6, vit E, B3, Cu, ANCA, ANA, ESR, CRP, RF, TSH, C3/C4, celiac w/u <b>NCS/EMG:</b> localization & pattern (not for eval of small fiber dz)	<b>Symmetric, length dependent:</b> toxic/metabolic/nutritional (DM, chemo, EtOH, $\downarrow$ B12, critical illness), hereditary (CMT), <b>AIDP/CIDP, paraprotein-related</b> <b>Mononeuropathy:</b> compression/trauma <b>Multiple mononeuropathy:</b> <b>vasculitis</b> , DM, amyloid, RA/SLE/sarcoid/Sjogren, leprosy
<b>NM Junction</b>	Motor only; weakness fluctuates with use; a/w ptosis, diplopia.	<b>Ice pack test</b> <b>Labs:</b> MG panel (below) <b>NCS/EMG:</b> repetitive stim, single fiber EMG. <b>CT chest</b> if above c/w MG	<b>Myasthenia gravis</b> , Lambert-Eaton, botulism, tick paralysis, meds (imm checkpt inhib, penicillamine, aminoglycosides), snake/spider venom
<b>Myopathy</b>	Proximal weakness most common. Pain uncommon.	<b>Initial labs:</b> CK/aldolase, LDH, LFTs, TSH/ft4, PTH, ESR/CRP <b>EMG:</b> e/o muscle irritability, chronicity <b>May need muscle biopsy</b>	<b>Critical illness, meds (steroids, statins, colchicine, cyclosporine, NRTI), inflammatory</b> (inclusion body, dermatomyositis, polymyositis)

**Sx tx:** Pain: gabapentin, pregab, TCA, SNRI; Dysautonomia: compress. hose, abd binder, fludrocort, midodrine, droxidopa, pyridostigmine

## ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (GUILLAIN-BARRÉ SX)

- **Symmetric, progressive** numbness & weakness, **hypo/areflexia,  $\pm$ bulbar weakness, autonomic dysfxn, acute resp failure (10-30%)**
- **Causes:** recent infxn (Campylobacter, HIV, COVID, CMV, EBV, Zika), vaccine (rare), meds (TNF-alpha antag, tacro, imm checkpt inhib)
- **Dx:** LP w/ albuminocytologic dissociation ( $\uparrow$ protein, nml WBC), **NCS/EMG (2-4 wks after symptom onset), RT consult for mechanics**
- **Tx:** IVIG or plasmapheresis; monitor resp with NIF/VC (RT); glucocorticoids not effective
- **Elective intubation 20-30-40 Rule:** VC  $<20mL/kg$ , NIF weaker than  $-30cm H2O$ , MEF  $<40cm H2O$ , or  $\geq 20\%$  decline in ~24h
- **Mimics:** CIPD, myelopathy, trans. myelitis, ALS, polio, myositis, tick paralysis, vasculitis, paraneop, toxin/vit def, hexacarbon expos., AIP
- **AIDP less likely:** persistent asymmetric weakness, bowel/bladder dysfxn at onset,  $>50$  CSF PMN, sensory lvl, severe pulm dysfxn w/o limb weakness at onset, fever at onset, nadir of weakness in  $<24h$  or  $>4w$ , purely sensory

## MYASTHENIA GRAVIS/LAMBERT EATON (MG/LEMS)

- Weakness of voluntary muscles. MG: **worse w exertion**, repetitive mvmts, & in the evening. LEMS: transient improvement w activity.
- Typically involves ocular (ptosis, diplopia), bulbar, respiratory, neck, proximal>distal limb muscles
- **Cause:** auto-Ab against postsynaptic ACh-R in skeletal muscle (MG) or voltage-gated calcium channels (LEMS); **imm. checkpt. inhib.**
- **Exam:** **ptosis w up-gaze** after 1min. Ice pack test: after observing ptosis, place ice on eyes for 1min, ptosis will improve. Fatiguable diplopia. (Historical: tensilon test, requires atropine at the bedside. Only improves MG not LEMS).
- **Monitor for respiratory failure:** track number counting in single breath, worry if  $<20$ , assess cough/swallow. Trend mechanics with RT: NIFs/Vc as above (20-30-40 Rule). Aggressive pulm toilet. **HOLD** pyridostigmine if bulbar sx and/or intubated (2/2  $\uparrow$ secretions)
- **Dx: Ach-R Ab** (80-90% seropositive in generalized dz, 40% in ocular dz,  $\sim 100\%$  sp); if  $\ominus$ , check anti-MuSK. **EMG/NCS w repetitive stim:** decremental response (MG) or potentiation (LEMS). **Chest CT:** r/o thymoma. Find **underlying malignancy** in LEMS.
- **Tx:** sx (pyridostigmine); immune: rapid (IVIG, plasmapheresis), chronic (steroids  $\pm$ AZA/MMF); thymectomy (thymomatous MG or  $<65yo$ )
- **Myasthenic crisis:** exacerbation requiring intubation or noninvasive vent. Triggers include surg, infxn, pregnancy, **meds** (abx incl FQs, macrolides, AGs; AEDs; antipsychotics, BBs, CCBs, Mg, iodinated contrast rarely). **AVOID** succinylcholine.

# Neurology

# Neuroprognostication

Neurological prognostication after cardiac arrest is challenging and uncertain ([Semin Neurol 2017;37:40](#)). The introduction of targeted temperature management (TTM: see *Cardiac Arrest & TTM*) alters the timeframe for neurological recovery and the interpretation of prognostic markers.

## CEREBRAL PERFORMANCE CATEGORY (CPC)

- Original CPC scale ([NEJM 1986;314\(7\):397-403](#)) is commonly used, though does not always reflect patient/family values ([Resusc 2016;100:6-10](#))
- Good Outcome:
  - CPC 1. Able to work. May have mild neurologic/psychologic deficits
  - CPC 2. Moderate deficits. Capable of independent activities of daily life. Able to work in sheltered environment
- Poor Outcome:
  - CPC 3. Severe deficits. Conscious but dependent on others. Ranges from ambulatory to severe dementia/paralysis
  - CPC 4. Coma (no wakefulness) or vegetative state (wakefulness but unawareness)
  - CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

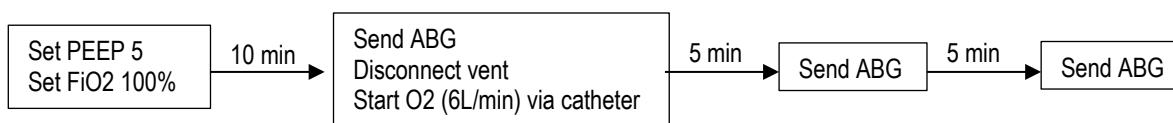
## POST-CARDIAC ARREST DIAGNOSTICS

- Critical Caveat:** each of the below tests has a FPR > 0 (i.e. will be “positive” for prediction of poor outcome in some patients who would have a good outcome); FPRs are likely underestimated due to “self-fulfilling prophecy” bias; use of prognostic indicators in combination may reduce FPRs and withdrawal of life sustaining treatment in patients who otherwise would have had a good outcome ([MGH Neuroprognostication Guidelines](#))
- Clinical exam
  - Poor prognosis: **status myoclonus** (spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs, axial musculature ± EEG correlate) <48h post arrest or rewarming. **Absent brainstem reflexes** (esp. bilateral pupillary/corneal) 3-7d post arrest or rewarming.
- Electroencephalography (EEG): started immediately post arrest, continued for 24h post rewarming
  - Poor prognosis: absence of EEG reactivity, seizures/status, discharges, voltage attenuation, alpha or delta coma patterns, burst suppression ([Neurology 2013;80:339](#))
- Neuron specific enolase (NSE): check serially at 24, 48, 72h post arrest
  - Non-specific marker of neuronal injury (also found in RBC and platelets)
  - Poor prognosis: >70mcg/L at 24-48h, >59mcg/L at 48-72h ([Neurology 2022;98:e62](#))
- Somatosensory evoked potentials (SSEP): 48h post cardiac arrest or rewarming
  - Measurement of brain activity in response to somatosensory stimulation
  - Poor prognosis: bilateral absence of N20, which reflects the integrity of thalamocortical projections
- CT head: 48h post cardiac arrest or rewarming
  - Poor prognosis: widespread hypodensity in combination with poor clinical exam
- Brain MRI: 2-6d post cardiac arrest or rewarming (not useful <48h post arrest/rewarming)
  - Poor prognosis: extensive restriction of diffusion in combination with other poor prognostic signs

## BRAIN DEATH

- Variability exists in prerequisites, clinical evaluation, apnea/ancillary testing to evaluate for [brain death](#) across hospitals
- Prerequisites:** irreversible CNS catastrophe; absence of severe acid-base, electrolyte, or endocrine abnormality; neg tox screen, clearance of CNS depressants (i.e., 5 half-lives since last dose or subtherapeutic level), absence of neuromuscl blockade, eucapnia, euolemia
- In principle, brain death = **coma + absence of brainstem reflexes + apnea** with irreversible etiology ([NEJM 2021;385:2554-61](#))
- Death by neuro criteria confirmed when all prerequisites met PLUS**
  - Consistent coma and brainstem reflex exams and positive apnea test OR
  - Incomplete brainstem reflex exams due to patient factors, positive apnea test, and one supporting ancillary test OR
  - Consistent coma and brainstem reflex exam, inconclusive/aborted apnea test, and one supporting ancillary test
- Clinical exam (by Neuro/NSGY attending or Neurocrit care fellow):** coma exam (i.e. absence of response to nox stim in extremities & head (incl. absence of decorticate/decerebrate posturing), absent brainstem reflexes (pupils, oculocephalic [doll's eyes], VORs [cold calorics], corneals, cough, gag)

### Apnea testing ([separate protocol for pts on ECMO](#))



Always perform in presence of RT AND Neurology/Neurosurgery Attending OR Neurocritical care fellow

Stop test and draw ABG for spontaneous respiration, ectopy, SpO2 <90% x30 sec, SBP <100

**Test pos if resp movements absent at PaCO2 >60 (or >20 inc from baseline if chronic retainer)**

- Ancillary tests (only if clinical exam/apnea test inconclusive): conventional angio, nuclear flow study, SPECT, EEG, TCDs
  - For EEG, order evoked potentials and ensure electrodes are tested (touched) at beginning of epoch (ask techs)

# Psychiatry

# Consent & Capacity

## THREE ELEMENTS OF VALID INFORMED CONSENT ([Psychosomatics 1997;38:119; NEJM 2007;357:1834](#))

1. Relevant clinical information: at minimum: diagnosis, proposed intervention, its purpose, its basic risks/benefits, alternatives, and risks/benefits of alternatives (including no intervention)
2. Voluntary decision: decision is voluntary and w/o coercion from hospital staff or family/friends (advice/discussion are NOT coercion)
3. Capacity: confirm patient has the ability to make a decision about the **specific question** being addressed at the time it is being asked

## EXCEPTIONS TO INFORMED CONSENT

1. Emergency in incapacitated patient: imminent risk of death or serious harm without medical intervention. All attempts should be made to find HCP/other surrogate decision-maker. Always discuss with team attending. Document emergent situation, lack of capacity, lack of available surrogate, need for emergent intervention. Consider 2<sup>nd</sup> opinion/consulting MGH lawyer-on-call (p26831) if time allows. If not, need to make a team-based clinical judgment of emergency.
2. Lack of capacity or competency: turn to the appropriate HCP/surrogate decision-maker; note **only a court-appointed surrogate can override an incapable patient's verbal refusal** or physical resistance in a non-emergency situation

## CAPACITY ASSESSMENT

- **Capacity**: person's ability to make an informed decision about a **specific question**. It **can change over time**
- **Competence**: legal designation made by a judge. When deemed lacking, the judge may make a global determination or define time and domain-based parameters within which a legally appointed surrogate can make decisions on the patient's behalf.
- **Any physician can make a determination of capacity**. Psychiatry should be consulted only for complex cases (i.e. neuropsychiatric illness impairing decision-making, disagreement between patient/family/medical team.) Be ready to tell consult: Pt decision, risk/benefit of intervention. Be prepared to accompany consultant during evaluation if needed.
- **The strictness of the capacity test varies as the risk/benefit ratio of a decision changes**: the more favorable the risk/benefit ratio, the lower the standard for capacity to consent and higher the standard to refuse, and vice versa

## CRITERIA FOR DETERMINING CAPACITY (ALL must be met for pt to have capacity) ([NEJM 2007;357:1834; NEJM 1988;319:1635](#))

Criterion	Approach in Physician's Assessment
Communicate a clear and consistent choice	Ask pt to indicate a choice. Inability to express one or to participate in assessment is equivalent to incapacity in a sufficiently high stakes situation. Frequent reversals of choice may also indicate lack of capacity.
Understand relevant information	Ask pt to describe understanding of the information given by the physician (dx, proposed intervention, purpose, risks/benefits, risks/benefits of alternatives including no intervention). Some cueing is OK here. Do not overestimate what is reasonable to expect from a lay person.
Appreciate the situation and its consequences	Ask pt to describe views of diagnosis, interventions, and likely outcomes. Is patient aware of their illness? Its seriousness? Consequences? What are the patient's non-medical priorities that factor into their decision?
Able to manipulate info in a rational fashion	Ask patient to compare treatment options, consequences, and reasons for choice. Does the patient weigh the risks and benefits logically? A rational choice may not be the same as a "good" one.

## SURROGATE DECISION-MAKERS

- Encourage each pt to sign [legal HCP form](#) specifying surrogate. "Confirmed" (court procedure) when pt lacks capacity and retains ability to refuse/resist medical activities. Confirmation of HCP is not needed if pt is incapable but agreeing, assenting, or unconscious.
- Surrogate's job is, ideally, to make the decision pt would have made for themselves if able — not what the surrogate wants. If a pt's wishes cannot be known, the surrogate should make the decision in the "best interests" of the patient
- HCP may be unconfirmed (most common) or confirmed. **Court-confirmed HCP is required when pt's surrogate is activated & pt actively objects to surrogate's decision**. If HCP confirmation required, contact MGH Guardianship team
- **Guardianship**: legal process where MA Probate Court grants a guardian the authority to make decisions on behalf of someone who a judge has ruled is not competent. **Required when there is no HCP identified & pt is unable to designate a HCP**. Note: a patient may not have capacity to make a certain medical decision and still have capacity to designate a HCP. For help: 'Guardianship Team'
- Emergency guardianship is not required to provide lifesaving treatment & should not delay care (see above).

## TEMPORARY INVOLUNTARY (PSYCHIATRIC) HOLD ([Section 12](#) in MA - MGL ch.123 §12): consult Psychiatry for all on 12a

- **Section 12a** (the front of the "pink paper"): MD, NP, psych RN, psychologist, SW, or police officer uses this 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, the use of restraint of the pt to maintain safety
- Issued when likelihood of serious harm to self and/or others is imminent (within 24-72h) AND:
  1. Is the result of a "serious mental illness": must be supported in writing with specific evidence. Symptoms caused solely by alcohol or drug intake, organic brain damage, or intellectual disability do not constitute a serious mental illness
  2. Meets ≥1 of the following 3 criteria: (1) substantial risk of **physical self-harm**; (2) substantial risk of **physical harm to others**; (3) very substantial risk of **physical self-impairment or injury** as manifested by evidence that the person's judgment is so affected (i.e., by serious mental illness) that they unable to protect themselves in the community.
- **Section 12b** (reverse side of the "pink paper," "72h hold"): completed by evaluating psychiatrist at the admitting psychiatric facility

## SAFETY (MEDICAL) HOLD ([PATIENTS LEAVING AMA POLICY](#))

- Order that can be placed that empowers staff to prevent pt from leave AMA when the following criteria are met:
  1. Patient lacks capacity to leave the hospital and is attempting to do so
  2. There is imminent risk of harm to self and/or others from leaving AMA
  3. Pt does not meet S12 criteria
  4. Physical restraint or chemical tranquilization would be excessive
- Staff may prevent a pt under a safety hold from leaving AMA using non-physical methods (e.g. verbal redirection, standing in a doorway or exit, preventing an elevator door from closing) but should not place themselves at risk or physically hold a patient.
- If the pt should escalate or become physically aggressive, then providers should follow restraint/seclusion protocols

## AGITATION MANAGEMENT 101

- Goals: 1) Safety of pt & staff, 2) Help pt manage distress (goal is not to put pt to sleep/punish pt), 3) Avoid restraints as able
- General Considerations:
  - Take notice early of anger/fear, yelling, pacing/restlessness, sweating. LISTEN to RN and PCA concerns
  - Address any easily/quickly reversible issues: hunger, thirst, pain, communication breakdowns. Consider urinary retention, & constipation as sources of discomfort. Work up/treat any other contributors (delirium, psych d/o, substance intox/withdrawal).
  - Offer PO medications early in escalation process. Think about standing medication if recurrent concerns.
  - If pt requires restraints, should **always** receive med to help ease/lessen time in restraints. Monitor for ongoing need and discontinue restraints ASAP. Restrained pts are at risk of aspiration, rhabdomyolysis, MSK injury, delirium.  
**Restraints/seclusion may be traumatizing, are associated with morbidity/mortality, and are the result of treatment failures. Any restraint episode warrants reassessment of treatment approach.**

## APPROACH TO VERBAL DE-ESCALATION: DEFUSE ([NUEMBLOG](#))

Decide if pt is appropriate for verbal de-escalation. Clues include a patient who is responsive, engageable, not an active threat to safety.

**Ensure safety.** Ensure adequate backup. Clear area of potential weapons (loose objects, supplies). Respect personal space (two arm's length between you and patient)

**Form relationship.** Introduce yourself by name and title. Ask what they like to be called. If they are responsive in conversation, consider asking, "Will you allow us to help?". Use short sentences and simple vocabulary.

**Utilize interests.** Identify patient's wants and feelings. Agree as much as possible, either in truth, principle, odds, or to disagree. Reinforce that you will let no harm come to patient.

**Set limits.** Speak matter-of-factly about consequences for bad behavior. Offer choices for behavior, even if it's between oral or IV meds. Use repetition as needed until you are heard by patient.

**Enforce/Evaluate.** If aggression escalates and violence seems imminent, withdraw and mobilize help. Once situation defused, by either verbal de-escalation or medication, debrief staff and/or patient.

## CHOOSING MEDICATIONS – CHART REVIEW:

- Consider current standing medications. Can any of these be used for acute agitation?
- Allergies/adverse reactions
- Major medical comorbidities (heart conditions, h/o arrhythmia, OSA, COPD, Parkinson disease, fall risk)
- MAR: previous medications for agitation, medication burden (is patient near max daily dose for an agitation medication?)
- QTc: if high overall load of QTc-prolonging medications or underlying heart disease, consider options with less QTc-prolonging potential. If no recent EKG, do not defer giving meds to obtain one– you can plan to obtain when next able.

## MEDICATION OPTIONS AND SPECIAL POPULATIONS: *always offer PO option first if pt able to safely take PO*

- General principle: Treat exacerbations of the underlying condition with the agent intended for it, within medical reason:
  - GABA withdrawal, catatonia, stimulant intoxication → benzodiazepines
  - Psychosis → antipsychotics
  - Mania → antipsychotics/mood stabilizers/benzodiazepines
  - AVOID antipsychotics in patients with catatonia and NMS
- Medication options: (MDD = Max Daily Dose, ODT = Oral Disintegrating Tablet)
  - Consider consulting psychiatry for pts requiring IM meds
  - **Quetiapine** (PO) 12.5-100mg. Can lead to orthostatic hypotension.
  - **Trazodone** (PO) 12.5-100mg. Good for elderly; no cardiac or delirium risks.
  - **Olanzapine** (PO, ODT, IM, IV) 2.5-10mg. MDD 20mg. NOTE: **do not** co-administer parenteral benzos with parenteral olanzapine within 4 hours (risk of lethal respiratory depression).
  - **Haloperidol** (PO, IM, IV) 2.5-10mg. MDD 30mg. IM haloperidol has greatest risk for EPS side effects (pair with lorazepam and/or diphenhydramine, although these meds may temporarily worsen delirium). IV haloperidol has greatest QTc-prolonging potential (check if QTc >550).
  - **Risperidone** (PO, ODT) 0.5-2mg. MDD 8mg. NOTE: highest risk of EPS among second generation antipsychotics.
  - **Chlorpromazine** (PO, IM, IV) 25-100mg. Can lead to hypotension (use cautiously in patients with borderline/low blood pressure). Can also lower seizure threshold. Avoid in pregnancy.
  - **Lorazepam** (PO, IM, IV) 0.5-2mg. Use cautiously in elderly and patients with COPD/OSA due to risk for delirium and respiratory depression, respectively. NOTE: **do not** co-administer parenteral benzos with parenteral olanzapine within 4 hours (risk of lethal respiratory depression).
- Special populations
  - **Geriatric:** PO, consider trazodone 12.5-25mg, quetiapine 12.5-25mg. If cannot take PO, consider olanzapine 2.5-5mg IM/IV
  - **<18 years of age:** If <35kg, can do clonidine 0.05mg PO. If >35kg, can do clonidine 0.1mg PO. If severe and unable to take PO, can do olanzapine (<25kg: 1.25mg olanzapine IM, 25-70kg: olanzapine 2.5mg IM, >70kg: olanzapine 5mg IM).
  - **Parkinson's/Lewy Body Dementia:** quetiapine 12.5-50mg PO, or lorazepam 1-2mg IM or 0.5-1mg IV.

# Psychiatry

# Psychosis

MENTAL STATUS: document daily if new AMS or worsening psychiatric sx ([AFP 2009:80:809](#))

- APPEARANCE/BEHAVIOR:** grooming/hygiene, eye contact, attitude/cooperation, abnormal mvmt (fidgeting, tics, TD)
- SPEECH/LANGUAGE:** mechanics: rate, volume, prosody, articulation, and fluency. Watch for speech latency, paucity of speech, mutism, echolalia (copying provider's speech), verbigeration (repeating meaningless phrase like a "broken record")
- THOUGHT PROCESS:** linear, logical, goal-directed vs. disordered. Types of thought disorder: circumstantial (non-linear; initially veers off but still goal-directed) > tangential (nonlinear, not goal-directed; ultimately loses topic entirely) > flight of ideas (rapid jumps between somewhat-connected thoughts) > word salad (incomprehensible speech). Disorganization: deficiencies in logical organizing of thoughts needed to achieve goal. Thought blocking: interruptions in thought causing inability to respond.
- MOOD/AFFECT:** Mood: subjective description of emotional state. Affect: physical expression of emotional state
- THOUGHT CONTENT/PERCEPTIONS:** SI/HI, delusions vs overvalued ideas, hallucinations, obsessions, poverty of content
- COGNITION:** level of consciousness, orientation, Luria sequence, MOCA
- INSIGHT/JUDGMENT:** insight: pt recognizes sx as pathological/accepts dx). Judgment (pt's action based on insight)

## PSYCHOSIS WORKUP AND DIFFERENTIAL DIAGNOSIS

- Characteristics:** delusions, thought/behavior disorganization, auditory > visual hallucinations (visual = often neuro/medical, esp. delirium, dementia, alc withdrawal)
- Ddx:**
  - Psychotic/mood disorder:** schizophrenia (no clinically significant mood episodes), schizoaffective (primarily psychotic disorder w/ some mood episodes), mood disorder w/ psychotic fx (primarily mood disorder w/ some psychotic symptoms)
  - Neurocognitive disorder:** intellectual disability, autism spectrum, dementia and neurodegenerative disorders
  - Medical mimics:** **delirium (visual hallucinations)**, migraine, steroid-induced, lupus encephalitis, porphyria, Wilson's, epilepsy, autoimmune/paraneoplastic encephalitis, Charles Bonnet syndrome
  - Substance induced:** Can exclude if hx of psychosis during sobriety. Alcohol withdrawal (VH, formication; 24hrs - 5d); cocaine/amphetamine intoxication (persecutory delusions, formication); cannabis intox (paranoia, persecutory delusions); hallucinogen intox (VH, paranoia). Note: isolated opioid intoxication/withdrawal does **not** typically include psychosis.
  - New-onset primary psychotic disorder in >50yo is rare. Medical causes (delirium, dementia, CNS pathology) more likely
  - Refer to psych:** outpatient = always, inpatient = if decompensated ± safety concerns
- Labs:** CBC, BMP, TSH, CRP, UA, tox screens, med levels, delirium w/u (see *Delirium*). Consider RPR, HIV, B12, ANA, pregnancy. Imaging not routinely indicated unless atypical presentation or neuro/medical etiology suspected.

## TREATMENT BASICS

- General principles:**
  - Confirm home antipsychotics/mood stabilizers early in admission & continue *only if* pt reliably taking; otherwise, dose reduce/hold pending psych consult. Ask if pt on long-acting injectable meds/date of last injection and which PRNs work well. Get collateral from DMH case manager, family, shelter, or Freedom Trail Clinic (if on clozapine) if pt can't give hx.
  - If on >1 standing antipsychotic, confirm before ordering (otherwise avoid). If on valproate, Li, clozapine, check level ASAP.
  - Continue home benzodiazepine, benadryl, propranolol, clonidine (if prescribed) to reduce EPS. Note: lamotrigine has SJS risk, if not taking for >2-3 days re-start at 25mg QD, uptitrate q2w (contact pharmacy/psych for questions).
- Clozapine:** Uniquely effective, but many SE. Continue inpatient (withdrawal catatonia if stopped suddenly).
  - Neutropenia agranulocytosis in <1% of pts (84% w/in first 3mo); weekly CBC for first 6mo, biweekly for next 6mo, then monthly. May need to DC if ANC <1.5k. **Requires REMS training/monitoring, consult psych/pharmacy w/ questions.**
  - Risk for myocarditis, withdrawal catatonia, constipation/bowel obstruction. Infx can ↓ metabolism and ↑ levels.
  - On admission: continue med to avoid w/d catatonia, ensure bowel reg, check levels if infection/altered metabolism
- Extrapyramidal symptoms (EPS):**
  - Dystonia:** muscle spasm incl. oculogyric crisis (**risk of rapid airway obstruction**), torticollis, trismus, opisthotonus, laryngospasm. **Tx:** anticholinergics (benzodiazepine, diphenhydramine)
  - Pseudoparkinsonism:** reversible; bradykinesia, tremor, rigidity, masked facies, shuffling gait. **Tx:** anticholinergics
  - Akathisia:** subjective feeling of inner restlessness, inability to stay still. **Tx:** low dose BB (e.g. propranolol)
  - Tardive dyskinesia (TD):** Involuntary, repetitive, arrhythmic movements: lip smacking, chewing, puckering, writhing. Occurs w/ long-term antipsychotic use, often irreversible.

## ANTIPSYCHOTICS & SIDE EFFECTS ([AFP 2010:81:617](#))

	Anti-cholinergic	Prolong QTc	EPS	NMS	Prolactin ↑	Postural hypoTN	Sedation	HLD	Wt gain	DM2	Sexual dysfxn
haloperidol	+	+	++	++	+++	+	+	+	+	+	++
chlorpromazine	+++	++	+	+	++	+++	+++	++	++	+	+++
ariprazole	0	+	+	+	0	+	+	0	0	+	+
olanzapine	+	+	+	+	+	+	++	+++	+++	++	+
quetiapine	+	+	0	+	0	++	++	++	++	+	+
risperidone	0	+	++	+	+++	++	+	+	++	+	++
ziprasidone	0	++	+	+	+	+	+	0	0	+	+
clozapine	+++	+	0	+	0	+++	+++	+++	+++	++	+

# Psychiatry

# Catatonia, NMS, & Serotonin Syndrome

## CATATONIA

- **Behavioral syndrome** due to underlying condition that can occur in the context of many psychiatric, neuro, or medical dx; marked by inability to move or communicate typically despite full physical capacity; pathophysiology incompletely understood
- **Subtypes:** stuporous: immobility, mutism, withdrawal; excited: hyperkinesis, stereotypy, disorientation; malignant (medical emergency): sx accompanied by hyperthermia, autonomic instability, rigidity ([Arch Gen Psych 2009;66:1173](#))

**Etiology:** ([Schizophr Bull 2010;36:239](#); [Behav Brain Sci 2002;25:555](#))

- **Psychiatric:** mood disorders (e.g. bipolar d/o) > thought disorders (e.g. schizophrenia, autism) > dissociative disorders
- **Neuro/medical:** seizures/NCSE, PRES, CNS lesion, infection, TBI, PLE, delirium, anti-NMDAR encephalitis, SLE
- **Drug:** dopamine-blockers, dopamine withdrawal, sedative/hypnotic withdrawal, hallucinogens, synthetic MJ, opiates

**Diagnosis:** ([Psych Scand 1996;93:129](#); DSM-5 TR 2022;6:135; [Arch Gen Psych 2009;66:1173](#)):

- Bush-Francis Catatonia Rating Scale ([BFCRS](#)) – 14-item screening (positive when ≥ 2 items) and 23-item rating scales (Positive when ≥ 4 items) OR the presence of 2-4 of the below signs for several hours:

Observed Signs	Elicited Signs
<ul style="list-style-type: none"><li>-<u>Immobility</u>: Hypo-akinetic not influenced by external stimuli</li><li>-<u>Stupor</u>: Decreased alertness, diminished r/ to voice/painful stimuli</li><li>-<u>Excitement</u>: Impulsive, stereotypic behavior</li><li>-<u>Mutism</u>: Verbally unresponsive while awake</li><li>-<u>Speech mannerisms</u>: Robotic speech, foreign accent, palilalia</li><li>-<u>Behavioral mannerism</u>: Odd, purposeful movements</li><li>-<u>Posturing</u>: Voluntarily maintaining a posture for a long time</li><li>-<u>Echophenomena</u>: Echolalia/echopraxia (mimic sound/movement)</li><li>-<u>Stereotypy</u>: Awkward non-goal-directed repetitive movements.</li><li>-<u>Staring</u>: Fixed gaze</li></ul>	<ul style="list-style-type: none"><li>-<u>Ambitendency</u>: Stuck on hesitant movement when the examiner verbally contradicts own nonverbal signal (extend hand and say "do not shake my hand")</li><li>-<u>Waxy flexibility</u>: rigid tone that is gradually overcome</li><li>-<u>Automatic obedience</u>: "Stick out your tongue. I want to put a pin in it" (pt will stick out tongue)</li><li>-<u>Negativism</u>: Opposite/no response to instruction.</li><li>-<u>Stimulus-bound behavior</u>: Behavior tied to certain stimuli</li></ul>

- Lab findings: Leukocytosis (15,000 - 25,000), CK ≥ 1000, and ↓ serum iron in malignant catatonia.
- Lorazepam Challenge: **2mg IV x1** (0.5-1mg in frail/elderly). Partial relief of signs after 5 -10 minutes after is consistent with a diagnosis of catatonia ([Arch Gen Psych 2009;66:1173](#)). Negative challenge test does NOT rule out catatonia.
- **Differential dx:** delirium, dementia, stroke, PD, stiff person & locked-in syndromes, NCSE, akinetic & elective mutism, anti-NMDAR encephalitis; If **malignant**: NMS, malignant hyperthermia, SS, DTs, CNS infection/vasculitis, anticholinergic toxicity

**Treatment:** ([Gen Hosp Psychiatry 2017;48:1](#))

- **Always consult psych. NO antipsychotics/other D2 blocking meds.** Trend CK, BMP; q4h VS; supportive care.
- **Treatment:** 2mg IV lorazepam q6-8h, uptitrate as tolerated. Hold for respiratory depression only, NOT sedation (catatonia sx can mimic sedation). If no response → **ECT, amantadine/memantine, anticonvulsants**

## NEUROLEPTIC MALIGNANT SYNDROME ([Am J Psych 2007;164:870](#))

- **Overview:** abrupt onset of 1) Δ in mental status 2) rigidity 3) fever 4) autonomic dysfunction (tachy, HTN, diaphoresis) associated with dopamine-blocking agent or withdrawal of pro-dopamine meds (med list: [Neurohospitalist 2011;1:41](#))
- **Risk factors:** initiation/increase of dopamine-blocking med (typically occurs within hours/days, but can be idiosyncratic), hx of NMS/catatonia, withdrawal from EtOH/sedatives, basal ganglia d/o, exhaustion, dehydration, agitation
- **Labs:** ↑WBC and CK>1000 (correlates w/severity) most common, ↓ serum iron, mild ↑LDH/alk phos/AST/ALT, ↑↓ electrolytes
- **Ddx:** serotonin syndrome, malignant hyperthermia, malignant catatonia (significant overlap), CNS infection, spinal cord injury, seizure, heat stroke, acute dystonia, CNS vasculitis, thyrotoxicosis, drug intoxication/toxicity, withdrawal states

Stage	Clinical Presentation	Intervention/Treatment
Early	Mild rigidity, confusion, T<100.4F, HR <100	<ul style="list-style-type: none"><li>• Stop offending agent &amp; contributors (serotonergics, Li, anticholinergics)</li><li>• Aggressive fluids/supportive care ± <b>lorazepam</b> 0.5-2mg IV q4-6h</li></ul>
Moderate (may require ECT)	Moderate rigidity, T100.4-104F, HR 100-120	<ul style="list-style-type: none"><li>• Cooling measures ± ICU</li><li>• <b>Bromocriptine</b> 2.5mg PO q8h or <b>amantadine</b> 100mg PO q12h</li></ul>
Severe (may require ECT)	Severe rigidity, ± coma, T >104F, HR >120	<ul style="list-style-type: none"><li>• ICU level of care (if intubation required, midaz &gt; propofol for sedation)</li><li>• <b>Dantrolene</b> 1-2.5mg/kg IV q6h x48h</li></ul>

## SEROTONIN SYNDROME ([NEJM 2005;352:1112](#))

- **Overview:** Exposure to serotonergic agent leading to 1) Δ mental status 2) neuromuscular hyperreactivity (tremor, clonus, hyperreflexia) 3) autonomic instability (tachycardia, tachypnea, diaphoresis, mydriasis, hyperthermia, shivering, sialorrhea, hyperactive bowel sounds, diarrhea). Watch for rhabdo/AKI. Note: n/v/d common in SS prodrome but rarely seen in NMS
- **Causative agents:** amphetamines, bupropion, buspirone, carbamazepine, carbidopa-levodopa, cocaine, cyclobenzaprine, diphenhydramine, fentanyl, linezolid, lithium, LSD, MAOIs, MDMA, meperidine, methadone, methylene blue, metoclopramide, ondansetron, SNRIs, SSRIs, TCAs, tramadol, trazodone, triptans, tryptophan, VPA
- **Diagnosis:** [Hunter's Criteria](#) 84% sensitive 97% specific ([QJM 2003;96:635](#))
- **Treatment:** 1) hold offending agent (generally will resolve within 24h), 2) use BZDs if agitation present (**lorazepam** 1-2mg IV, repeat PRN to effect), 3) if unsuccessful, can use **ciproheptadine** 12mg x1 then 2mg q2h until clinical response seen. Very severe cases with hyperthermia may require ICU level of care with cooling, intubation, sedation, and paralysis.

## MAJOR DEPRESSIVE DISORDER (MDD)

- Epidemiology:** common in general population. U.S. lifetime prevalence ~20%, F>M ([JAMA Psych 2018;75:336](#))
- Screening:** USPSTF recommends universal screening of adult primary care patients including pregnant and postpartum women (Grade B)
  - **PHQ-2:** in last month, have you 1) felt down/depressed/hopeless? 2) had little interest/pleasure in doing things?
    - ≥1 = + screen, 97% Sn, 67% Sp for MDD → **PHQ-9** to grade severity ([AFP 2012;85:139](#))
- DSM-5-TR criteria:** (mnemonic SIGECAPS): must have depressed mood and/or loss of Interest/pleasure + ≥4 of following sx: change in Sleep, worthlessness/Guilt, fatigue/decreased Energy, poor Concentration, change in weight/Appetite, Psychomotor agitation/slowing, thoughts of death (not just fear of death) or Si.
- **Sx** must be present over same 2w period & cause significant impairment/distress
- **Ddx:** other psych (e.g. bipolar, adjustment disorder, persistent depressive disorder, etc.), drugs/meds, OSA, hypothyroidism, stroke, TBI, delirium, vit def, dementia, MS, HIV
- **Tx:** therapy ± medication as determined through shared decision making; either alone is acceptable ([APA 2019](#))
  - SSRIs are 1<sup>st</sup> line: All second-generation antidepressants are roughly equivalent (consider starting with **sertraline & escitalopram** as efficacy/acceptability > paroxetine) ([Lancet 2009;373:746](#)).
  - Other common options: bupropion, mirtazapine, & SNRIs. Bupropion lowers seizure threshold and is contraindicated in pts with seizure disorders and eating disorders
  - Consider mirtazapine in elderly pt with frailty (increases appetite and treats insomnia, see below)
  - Use [Mayo Clinic Depression Medication Decision Aid](#) to choose meds based on side effect profile
  - Other common uses of antidepressants:
    - Anxiety disorders: SSRIs, SNRIs
    - Neuropathic pain: SNRIs, TCAs
    - Insomnia: trazodone, mirtazapine
    - Functional GI disorders: amitriptyline for IBS-D & dyspepsia, nortriptyline/fluoxetine for constipation ([WJG 2009;15:1548-53](#))

## Side Effect Profiles of Commonly Prescribed Antidepressants ([Can J Psychiatry 2016;61:540](#); [NEJM 2005;353:1819](#))

Class	Drug	Anti-Cholinergic	Sedation	Insomnia/Activation	Nausea/Vomiting/Diarrhea	Wt Gain	Sexual Dysfn	Orthostatic HoTN	↑ QTc	Usual Daily Dose (mg)
SSRI	Citalopram	-	-	+	+	+	+++	+	++	10-40
	Escitalopram	-	-	+	+	+	+++	+	+	5-20
	Fluoxetine	-	-	++	+	+	+++	+	+	20-80
	Paroxetine	+	+	+	+	++	++++	++	-	20-50
	Sertraline	-	-	++	++	+	+++	+	+	50-200
SNRI	Duloxetine	-	-	+	++	-	+	-	-	30-60
	Venlafaxine	-	+	+	++	-	+++	-	+	37.5-225
Atypical	Bupropion	-	-	++	+	-	-	-	+	150-450
	Mirtazapine	+	++++	-	-	++++	+	-	+	15-45*
Serotonin Modulator	Trazodone	-	++++	-	++	-	\$	++	++	100-400*
	Vilazodone	-	-	++	+++	-	+	-	-	10-40
	Vortioxetine	-	-	+	+	+	+	-	-	10-20
TCA	Amitriptyline	++++	++++	-	+	++++	++++	+++	+	25-300*
	Nortriptyline	++	++	-	-	+	+++	+	+	25-150*

\$ Risk of priapism

\* Usual doses for depression; lower doses are used for sleep or off-label uses (for mirtazapine, start at 7.5 - 15 mg nightly for insomnia. For trazodone, start at 25-50 mg nightly for insomnia).

## Dosing of Antidepressants

- Start at low dose, titrate q1-2 weeks. Adequate trial is 6-12 weeks at full dose; if poor tolerance/response after 4-6 weeks, augment with psychotherapy or other medications; consider switching SSRIs
- Advise pts of initial side effects that they will develop tolerance to (GI upset, headache, sedation/activation, dizziness, sexual effects). Advise pts that physical sx of depression (sleep disturbance, appetite changes) usually resolve first, within days-weeks. Mood sx may take weeks to resolve.
- Continue antidepressants for at least 6 months after symptom remission to prevent relapse
- Stopping any antidepressant requires tapering off over 2-4 wks to prevent discontinuation syndrome (affective sx, flu-like sx, sleep disturbance, GI upset, dizziness/balance/sensory sx, electrical sensation or 'brain zaps')
  - Paroxetine (short half-life, most likely to cause discontinuation sx): taper down 5-10 mg weekly over 4+ weeks
  - Fluoxetine (long half-life): taper may not be needed for doses < 40 mg daily; if >= 40 mg daily, taper over 2 wks
  - If pt develops discontinuation sx, taper more gradually over 6-12 weeks

**When to Refer to Psychiatry:** concern for bipolar disorder (any history of mania/hypomania), failure of 2 adequate rx trials, severe MDD with SI/HI, psychosis, or catatonia.

## GENERALIZED ANXIETY DISORDER (GAD)

- Epi: US lifetime prevalence ♀7.7% & ♂4.6% ([AFP 2015;91:617](#)). 90% will meet criteria for at least 1 co-morbid psych condition in their lifetime (MDD, dysthymia, AUD, simple phobia, social anxiety) ([Arch Gen Psych 1994;51:355](#))
- Excessive worry associated w/ poor CV health, ↑CAD, ↑CV mortality ([Nat Rev 2012;9:360](#))
- Screening: USPSTF recommends screening of adult primary care patients (Grade B). **GAD-7:** score ≥5 indicates mild GAD (97% Sn, 57% Sp, LR 2.2); score ≥10 indicates moderate GAD (89% Sn, 82% Sp, LR 5.1) ([Arch Intern Med 2006;166:1092](#)).
- DSM-5 criteria:
  - A) excessive anxiety/worry occurring most days for ≥6mo re: multiple life domains, that is
  - B) difficult to control, and
  - C) associated w/ ≥3 sx: restlessness, fatigue, poor concentration, irritability, muscle tension, sleep disturbance. Must also cause
  - D) significant distress/impairment; and
  - E/F) not better explained by drugs/meds/other psych disorders
- Tx: 1<sup>st</sup> 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; SSRIs have lower risk of insomnia/activation over SNRIs. **Escitalopram, citalopram, and sertraline** generally preferred due to fewer side effects.
  - Advise pts that symptoms may take 4-6 weeks to resolve. For first few days, anxiety and activation may worsen as SSRI takes effect. See *Depression* for dosing guidelines.
- Adjunctive therapy: Consider buspirone 7.5 mg BID, increase by 5mg/day q2-3days (note: little efficacy as an acute anxiolytic); hydroxyzine 50-100 mg QID; 0.5-1 mg BID PRN for 4-6 wks while SSRI takes effect. If refractory, psychiatry may start risperidone/quetiapine. Counsel pt on dependence of BZD, and consider non-BZD options first if history of substance use.

**Refer to Psych:** need for CBT, failure of 2 adequate SSRI/SNRI trials, severe GAD w/ recurrent panic, SI

## PANIC DISORDER

- Epi: US lifetime prevalence ♀7.0% & ♂3.3% ([AFP 2015;91:617](#))
- DSM-5 criteria: A) Recurrent unexpected panic attacks; B) >1 month of persistent worry about panic attacks or their consequences, or >1 month of significant maladaptive change in behavior related to attacks; C/D) sx not better explained by drugs/meds/other psych disorders (e.g. social anxiety disorder, specific phobia, OCD, PTSD)
- Workup for panic attacks: vitals, ECG, BMP, CBC, thyroid panel, HCG, tox screen. Consider testing for pheochromocytoma, seizures, OSA, asthma/COPD if any clinical suspicion
- Treatment: 1<sup>st</sup> line = CBT and/or SSRI (equally effective). See GAD above for adjunctive therapies during SSRI initiation

**Refer to Psych:** need for CBT, severe symptoms, failure of 2 SSRI trials, SI

## POST-TRAUMATIC STRESS DISORDER (PTSD)

- Epi: US lifetime prevalence 8%; trauma-exposed: ♂8%, ♀20%; higher in combat/severe disaster survivors ([AFP 2013;88:827](#))
- Screening: Primary Care PTSD Screen ([PC-PTSD-5](#)): screens for trauma exposure then for sxs based on DSM criteria; score >4 with Sn 100%, Sp 85.2% (J. Clin. Psychol 2022;78:2299), though cutoff of 3 may be more accurate for female pts due to higher false negative rates ([JAMANTW 2021;4](#))
- DSM-5 criteria:
  - A) exposure to trauma
  - B) intrusive sx (involuntary trauma memories/dreams, dissociative flashbacks, psych distress, marked physiological reactions to trauma reminders)
  - C) avoidance sx (of trauma reminders)
  - D) neg cognition & mood (incl amnesia of trauma, neg beliefs about self/others/world, inappropriate self-blame, neg emotional state)
  - E) hyperarousal (irritability/anger, reckless/self-destructive behavior, hypervigilance, exaggerated startle, sleep disturbance); lasting **>1mo** & causing significant distress
- Treatment: trauma-focused therapy + SSRIs/SNRIs; tx of psych/SUDs comorbidities; clonidine, atypical antipsychotics; prazosin 1mg nightly, increasing 3-15mg over few months for sleep disturbance. Counsel pt on risks of orthostasis and rebound HTN for prazosin/clonidine if discontinued abruptly. **All care/conversations should be trauma-informed, recognizing that not all patients are ready to discuss trauma (and avoid probing patients on their trauma if so).**

**Refer to Psych:** all should be referred for psychotherapy ± pharmacotherapy (depending on complexity of needs)

## OBSSESSIVE-COMPULSIVE DISORDER (OCD)

- Epi: US lifetime prevalence 2.3%. Mean age of onset ~19-20, rarely develops after early 30s ([AFP 2015;92:896](#))
- DSM-5 criteria: A) presence of obsessions (recurrent and persistent thoughts/urges/images that are intrusive and unwanted, and that pt tries to suppress) and/or compulsions (excessive or unconnected repetitive behaviors/mental acts that pt feels compelled to perform in response to obsessions or rigid rules to reduce or prevent anxiety/distress); B) obsessions/compulsions are time-consuming or cause significant distress/impairment; C/D) sx not better explained by drugs/meds/other psych disorders
- Treatment: 1<sup>st</sup> line = CBT and/or SSRI. Adequate trial of SSRI is maximum tolerated dose for 6 weeks. OCD pts typically require higher doses than for other indications. If good response to SSRI, duration of treatment should be *at least 1-2 years* with taper off over several months ([AFP 2015;92:896](#))

**Refer to Psych:** need for CBT, severe symptoms, failure to respond to 2 SSRI trials, SI

# Psychiatry

# Alcohol Use Disorder & Withdrawal

## SUBSTANCE USE - GENERAL PRINCIPLES

**Screening:** Ask all primary care pts & inpatients about current and lifetime substance use. USPSTF recs screening for *unhealthy use*.

- EtOH: [AUDIT-C](#) screens for unhealthy use, [CAGE](#) detects dependence
- Other substances: "How many times in the past year have you used a recreational drug or used a prescription medication for nonmedical reasons?" ([Arch Int Med 2010](#))

## History

- Most recent use, quantity, frequency, route of ingestion, triggers for use
- Benefits vs. harms of use; medical, psychiatric, and behavioral complications of use; harm reduction practices
- Age of first use, family hx of use disorders, periods of abstinence
- Treatment hx: Medications, structured treatment settings, mutual support groups. Current goals (↓ amt or freq of use vs. abstain).

## Diagnosis

- Use ≠ disorder.** Assess for use disorder of all substances reported by number of DSM-V criteria met: 2-3 = mild, 4-5 = moderate, ≥6 = severe. Once criteria for use disorder is no longer met, can classify as early remission (3-12 mo) or sustained remission (>1y).
- Polysubstance use disorder ≠ DSM diagnosis. Ask about 1° vs. 2° sub.
- Tox screens alone should not be used to diagnose SUDs. False positives and negatives are possible. It is not recommended to alter prescribing patterns for meds based on tox screens. Use tox to check for concomitant substance use, monitor opioid use, and initiate conversations around use with patients. See *Drug Testing*.

**Approach:** Person-first language and trauma-informed care. People w/ SUD experience bias and discrimination from healthcare providers. Address drivers of self-directed d/c: pain, agitation, discomfort, treating w/d, and allowing pts to leave the floor ([Subst Abus 2020;41:519](#)). Involve ACT early. Consider risks of escalation before directly involving security (ex: may have security in hall on standby).

**Treatment:** Counseling: MI, CBT, recovery coach, mutual help meetings (AA/SMART recovery). Medications: many can be prescribed by PCP, except for methadone. See [Boston Area and MGH SUD Resources](#).

## DSM-V Generalized Criteria for SUDs

- Substance taken in **larger amounts** and/or over a longer period than intended
- Unsuccessful efforts to cut down** or control use
- A **great deal of time is spent** to acquire, use the substance, or recover from effects
- Craving** or strong desire or urge to use the substance
- Recurrent use resulting in a **failure to fulfill major role obligations** at work, school, or home
- Continued use despite **persistent/recurrent social or interpersonal problems**
- Important social, occupational or recreational **activities given up** or reduced because of use
- Recurrent use in **physically hazardous situations**
- Use continued despite persistent or recurrent **physical or psychological problem** that is likely caused or exacerbated by the substance
- Tolerance**, defined as ↑ amount of substance to achieve desired effect; or ↓ effect w/ same amount
- Withdrawal**, defined as characteristic withdrawal syndrome for the substance; or pt is taking substance to relieve or avoid w/d sx

SUD Levels of Care					
Levels of care usually progress from hospitalization/"detox" " CSS " TSS " long-term residential tx " sober living					
Inpatient			Outpatient		
Medically Supervised Withdrawal/ "Detox"	Clinical Stabilization Service (CSS)/Transitional Support Service (TSS)	Dual Diagnosis Units	Long-Term Residential Treatment ("Halfway Houses")	Partial Hospitalization Program (PHP)	Intensive Outpatient Program (IOP)
-Medical mgmt of acute w/d in a hospital or standalone detox center. -Best for pts with risk of severe withdrawal sx. - <u>LOS:</u> 4-6d	-Inpt programs to transition from detox to longer treatment; very structured with counseling. -Usually go from CSS to TSS. -D/c coord: ACT SW - <u>LOS:</u> 14d (CSS), 30d (TSS) - <u>LOS:</u> 3-5d	-Inpt locked psych unit, address comorbid SUD + 1° psych disorders. -Often reserved for pts w/ severe comorbid sx +/- acute safety concern. (i.e mania, psychosis, SI) -D/c coord: Psych - <u>LOS:</u> 3-5d	-Covered by insurance -Offer groups, counseling and attendance at outside mutual support -Few offer meds esp in OUD ( <a href="#">JAMA 2020;324:804</a> ). -D/c coord: ACT SW - <u>LOS:</u> 6-12mo	-Highly structured outpt treatment, 6-8h/d for 5d/w. -Intensive group therapy; tx for both SUD and MH concerns. -D/c coord: Psych - <u>LOS:</u> 1-3w	-Outpt., less intensive than PHP; usually ~3h/d for 3d/w -Provides psychoeduc./therapy. -D/c coord: ACT SW - <u>LOS:</u> 1-3mo

## ALCOHOL USE DISORDER (AUD)

### Diagnosis and Health Effects

- Diagnose AUD w/ [DSM criteria](#). Quantify use to counsel re: risks. 1 standard drink = 14g ethanol (5oz wine, 12 oz beer, 1.5 oz spirits)
- Risky use ↑ risk for health consequences (not part of SUD criteria). Includes drinking while pregnant; binge drinking: >4 drinks/occasion for men, >3 for women; heavy drinking: >14 drinks/w for men & >7 drinks/w for women.
- Chronic use: Cytopenia (low Hb, WBC, Plt); low K/Mg/Ca/Phos/VitD (EtOH toxic to renal tubules and ↓ GI absorpt); ketoacidosis (↓ gluconeogenesis → rel. hypoglycemia → ↓ insulin → ketosis); lactic acidosis (↑ratio of NADH/NAD) ([NEJM 2017;377:1368](#))

### Treatments for Moderate-Severe AUD

- Psychosocial: See above. 12-step progs ↑ rate of continuous abstinence compared to other counseling methods ([Cochrane Rev 2020](#))
- FDA approved: naltrexone, acamprosate, disulfiram; data suggests disulfiram efficacy only if dosing is observed
  - Naltrexone (↓ reward/cravings) PO 25mg to start → 50mg daily or IM (Vivitrol) 380mg q4w (Cl: acute hepatitis/ALF, current opioid use or on bup or methadone). Naltrexone likely > acamprosate ([JAMA 2006;295:2003](#))
  - Acamprosate (↓ cravings) 666mg TID (Cl: CrCl<30, pregnancy)
- Non-FDA approved: topiramate, gabapentin ([Addiction 2019;114:1547](#)), baclofen ([Am J Psych 2018;175:86](#))

# Psychiatry

# Alcohol Use Disorder & Withdrawal

- Success can range from reducing heavy drinking days to abstinence ([Addiction 2021;116:1973](#)). Utilize principles of harm reduction.
- Set goal with patient and use benchmarks to assess treatment efficacy.
- Risk of **malnutrition**. Assess lytes. Consider prescribing MVI w/ thiamine 100 mg daily ([Drug Alcohol Depen 2017;179:229](#))

## Wernicke-Korsakoff Syndrome

- Wernicke encephalopathy (acute):**
  - Dx: Caine Criteria (85% Sn) requires ≥2: (1) dietary deficiency, (2) oculomotor dysfxn, (3) cerebellar dysfxn (LE ataxia), (4) AMS or poor memory. Note: Serum B1 NOT diagnostic ([J Neuro Nsgy Psych 1997;62:51](#))
  - Tx: Thiamine IV 500mg TID x5-7d (**dose 1 before glucose**, infuse over 30m) → PO 100mg TID x1-2w → 100mg qd
  - Ppx in those at risk: IV 200mg TID x3-5d → PO 100mg TID x1-2w → 100mg qd ([Intern Med J 2014;44:911](#))
- Korsakoff's (chronic):** Antero+retrograde memory deficits (confabulation), apathy, intact sensorium

## ALCOHOL WITHDRAWAL SYNDROME

**Pathophysiology:** GABA (inhibitory) and glutamate (excitatory) work in balance

- Chronic EtOH use:** ↑GABA stimulation → glutamate upregulation. After chronic stim, GABA receptors are less sensitive & require more EtOH to balance increased glutamate. **Abrupt cessation of EtOH:** ↓GABA → unbalanced excess glutamate activity → noradrenergic surge → ↑dopamine release → complicated withdrawal sx's.
- EtOH eliminated via approx 0<sup>th</sup>-order kinetics:** approx. 15-20 mg/dL/hour. [Blood EtOH clearance calculator](#).
- BAC effects vary widely by person and chronicity of EtOH use. For many, BAC can be approximated grossly as: <80 mg/dL: legal driving limit // 100 mg/dL: impaired judgment // 200 mg/dL: confusion/staggering // 300 mg/dL: stupor // 400 mg/dL: coma/death

## Evaluation:

- H&P:** Time of last drink, hx severe withdrawal & complications (ICU/intubation), hx of patient-initiated discharge, co-ingestions (including BZD), EtOH use hx and tx, including recent changes in use pattern
- Labs:** CMP, CBC, serum osm if HCO3 <15 or AGMA (2/2 ketoacidosis), CPK if found down (>5K = rhabdo), tox screen, serum EtOH (clear ~15-35 mg/dL/h, chronic = faster metab, higher tolerance) ([J Forensic Sci 1993;38:104](#))

**Subtypes and Management:** Sx vary by time after last drink ([Ind Psych 2013;22:100](#)), but often consistent btw episodes for a given pt.

- Initial Tx for all EtOH withdrawal:** IV thiamine (if concerned for Wernicke's), D5-LR (after thiamine) to fix ketoacidosis, replete lytes, folate 1mg qd, MVI, place on CIWA (must be responsive to CIWA questions), offer ACT c/s for AUD treatment
- Treat with rx if CIWA >10 or unable to CIWA:** BZD vs. phenobarbital. No difference in outcome or sedation ([Psychosom 2019;60:458](#)).
- Mild withdrawal** (CIWA-Ar <8): Defer tx, or can consider 4-day taper of gabapentin >> BZD ([Alcohol Clin Exp Res 2009;33:9](#)):
  - Gabapentin 300mg q6HR (day 1) -> 300mg q8HR (day 2) -> 300mg q12HR (day 3) -> 300mg qHS (day 4)
- Mild-moderate withdrawal** (CIWA-Ar 8-14): Within 48h; tremors, sweats, ↑HR, ↑BP, HA, anxiety, intact orientation.
  - Use EtOH withdrawal order set.** Typically BZD (lorazepam) >> phenobarbital (unless hx of comp. withdrawal).
- Severe withdrawal** (CIWA-Ar >15): **ALWAYS TREAT, can be fatal.** BZD vs. phenobarb using EtOH withdrawal order set, as detailed below. **Predictors:** age, comorbidities, hx of DT/sz, ↑BP, ↓Na/↓K, BUN >26, Plt <150 ([JAMA 2018;320:825](#)).
  - Seizures:** 6-48h; typically 1x GTC or burst of multiple GTCs in a short period. If status epi, consider other etiologies.
  - Alcoholic hallucinosis:** 24h-6d; visual/tactile >> auditory (pt typically aware that hallucinations are not real), clear sensorium.
  - Delirium Tremens (DT):** 48h-5d, up to 2w; tremors, sweats, ↑HR, ↑BP, fever, disorientation, inattention, hallucinations (pt typically unaware that hallucinations are not real), agitation; usually CIWA >20.

ALCOHOL WITHDRAWAL TREATMENT PROTOCOLS: <i>Use Epic Alcohol Withdrawal Order Set!</i>		
	Benzodiazepine (BZD)	Phenobarbital (PB)
When to use	Generally 1 <sup>st</sup> line. Mild-mod w/d sx, no hx of severe w/d, or PB is contraindicated	Hx or current DTs, seizures, prior ICU admissions for w/d; prior success w/ phenobarb; not responding to BZD
Notes	Cl: Acute angle closure glaucoma <u>Resistance</u> (>6mg lorazepam/h) or <u>BZD toxicity</u> (similar to DTs) w/ escalating dose. Consider switch to phenobarb if CIWA consistently >16 despite aggressive dosing & <30mg lorazepam equiv. in 24h	Cl: hx SJS/TEN; hx AIP; unstable respiratory status <u>Relative Cl:</u> received >30mg lorazepam equiv. in 24h (use 6-8 mg/kg PB loading dose); high likelihood of self-dir d/c interrupting therapy. <u>Side effects:</u> apnea, hypoventilation, ↓HR, ↓BP, laryngeal spasm <u>Medication interactions:</u> CYP3A4 inducer – decreases conc. of many rx including apixaban. May enhance effects of anti-HTN meds.
Mech.	GABA-ergic. t <sub>1/2</sub> varies by BZD	GABA-ergic and anti-glutamate receptor. Auto-taper, long half-life (1-4d), predictable effect, wide therapeutic window.
Dose	PO > IV if able to take PO <u>Lorazepam</u> >> <u>diazepam/chlordiazepoxide</u> (↑half-life, delayed toxicity, liver cleared) <u>PRN: use CIWA scale only if patient can communicate. Do not use HR/BP as only indicators of w/d.</u> ( <a href="#">JGIM 1996;11:410</a> ). <u>Standing:</u> if likely to have severe w/d	<u>Loading dose: Inpatient IM load (6-12 mg/kg IBW div in 3 doses 3h apart)</u> +/- PO taper. <u>ED IV load:</u> must stay 1h in ED after <b>NO MORE IM</b> after IV unless re-load (see below). <b>NO MORE BZD</b> after PB started. - <b>↓dose</b> (10-12 mg/kg) for <b>high-risk withdrawal</b> : past DTs ± sz AND EtOH use in <2w OR active w/d OR ⊕BAL with labs predictive of severe w/d) – - <b>↓dose</b> (6-8 mg/kg) if <b>sedation carries high risk</b> : age>65, liver dz, TBI, concurrent sedatives, recent benzos, lung dz
D/C	Monitor CIWA score, what sx they are scoring for, and total daily BZD requirements. Consult ACT team for assistance w/ pharmacologic and psychosocial mgmt of AUD, or if considering <u>standing</u> BZD taper and unsure of dosing sched.	<u>Assess frequently:</u> IM loading dose is split to allow monitoring: 40% 0h, 30% 3h, 30% 6h. If uncontrolled sx or sedation, call pharmacist. <u>Consider reload:</u> if breakthrough sx despite IM/IV load. Check 5h PB level (esp. if considering reload); target level=12-15. Consult psych/ACT/pharm. <u>Discharge:</u> phenobarbital increases sensitivity to BZDs/EtOH; <b>drinking after IV/IM load can be fatal.</b> If stable, can d/c pt before all doses complete, no earlier than day 3. No PO doses on d/c.

## OPIOID USE DISORDER (OUD)

- Chronic, relapsing disorder of opioid use due to dysfunction of brain reward circuits ([J Addict Med 2015;9:358](#))
- Screen** all patients. Confirm diagnosis using [DSM-5 Criteria](#) for opioid use disorder. Use ≠ SUD. See [SUD General Principles](#).
- Focus on building a **therapeutic alliance** and performing risk assessment ([Med Clin N Am 2018;102:587](#))
  - Assess **risk of withdrawal**: current opioids, frequency of use, last use PTA, g/day or \$ spent/day, recent withdrawal
  - Assess **treatment readiness**: treatment hx (medications, counseling, mutual-aid organizations), social circumstances (housing, food security, legal issues). Understand patient's current goals, including safer use vs abstinence
  - Assess for **high-risk injection practices**: history of bacterial/fungal complications (endocarditis, SSTIs, bone/joint infections), viral complications (HIV, HCV, HBV). If currently injecting, use [PCoI harm reduction conversation guide](#) to review injection practices. Consider PrEP for patients with high-risk injection practices (see [HIV/AIDS](#))
  - Assess **risk of overdose**: h/o OD, h/o psychiatric (i.e. mood) disorder or suicidality, ↓ tolerance from recent incarceration or abstinence-based treatment, access to naloxone, high-dose Rx'd opioids and/or other sedatives (check PDMP), incr alcohol use, injection use, respiratory disease, severe chronic pain ([Addiction 2015;110:996](#); [Lancet 2019; 393: 1765](#))
- Labs**: serum/urine tox (fentanyl now included in urine tox but may take days to result), LFTs, HIV, HBV/HCV, TB, syphilis, EKG.
- Tx**: agonist treatment with **buprenorphine** or **methadone** is 1<sup>st</sup> line tx for opioid withdrawal and OUD. Should be offered to **every patient with OUD**. Long-term agonist therapy for OUD decreases morbidity and mortality ([BMJ 2017;357:j1550](#)). When choosing bup vs. methadone consider long-term plan: methadone = daily observed administration at clinic. Buprenorphine = transmucosal TID vs. long acting injectable qmonth vs. subcutaneous injection q6mo prescribed by outpatient provider.
- Pain control**: pts w/ OUD and/or chronic opioids likely have developed tolerance and require high doses of opioids to treat pain
  - If using non-prescribed opioids: can initiate methadone for withdrawal & add short-acting opioids titrated to pain
  - If taking methadone: give usual dose (once confirmed) & add short-acting opioids (e.g. oxycodone) titrated to pain
  - If taking buprenorphine: there are several strategies:
    - For pain of short duration, may continue daily bup & add short-acting opioids (may need high doses, consider PCA)
    - Give total daily dose of bup divided 3-4x daily (e.g. 4-8mg q6-8h for mod-severe pain)
    - D/c bup & use short-acting opioids to tx acute pain. Blocking effects of bup wear off after 24-72h, so monitor for OD (initial opioid dose is higher than pt will need). After pain resolved, re-start bup ([CMAJ 2016;188:1232](#); [Annals 2006;144:127](#))

## ACUTE OPIOID OVERDOSE (OD) ([NEJM 2012;367:1372](#))

- Signs**: ↓ mental status, ↓ RR, ↓ tidal volume, miosis. Normal pupils do not exclude opioid toxicity → co-ingestions may be sympathomimetic/anticholinergic. **Rare**: hypoxic seizure. Acute toxicity is a clinical diagnosis; ⊕ tox screen does NOT confirm toxicity
- Acute stabilization**: assess airway (mental status). If apnea and/or stupor, bag valve mask (with O2). Administer **naloxone**
- Naloxone**: goal is to improve mental status, SpO2, and ensure RR>10, NOT to achieve normal level of consciousness
  - Dose: 0.4mg IV, if no response increase dose q2 min: → 0.5mg → 2mg → 4mg → 10mg → 15mg. Can administer intranasally or IM
  - Effect lasts 20-40min, but most opioids last longer. **OD can recur after naloxone wears off** so may need to redose or start gtt. Adulterants such as **xylazine** may cause prolonged OD w/ less response to naloxone, consider particularly if **necrotic ulcers**
  - NB**: too much naloxone will precipitate opioid withdrawal. Consider diluting 0.4mg in 10cc saline and push 1cc q2-3min
  - If failing to respond, consider **intubation** (STAT RICU consult)
- Post-resuscitation**: continuous O2 monitoring, CXR (post-OD pulmonary edema does NOT respond to diuretics, may evolve to ARDS), APAP level. Examine skin for fentanyl patch (remember fever + patch → overabsorption). Consider naloxone gtt

## ACUTE OPIOID WITHDRAWAL

- S/Sx**: dysphoria, restlessness/irritability, muscle twitching, yawning, piloerection, mydriasis, rhinorrhea, myalgia/arthritis, lacrimation, n/v/d, abd cramping. **Onset**: 6-12h after short-acting opioids, 24-48h after last methadone, variable for fentanyl analogs (long half-life)
- Buprenorphine**: **high affinity partial agonist** with lower risk of respiratory depression/OD than methadone
  - Wait until Clinical Opioid Withdrawal Scale ([COWS](#)) >10, usually 10-12h after last heroin use/short acting opioids. **Avoid precipitated withdrawal**—rapid, intense withdrawal due to displacement of full agonist by partial agonist
    - First dose: 4mg/1mg (1/2 of an 8mg/2mg bup/nal film). Second dose: if continued withdrawal sx, give another 4mg/1mg after 45-60min. Third dose: if recurrent withdrawal sx, give another 4mg/1mg after 6-12h
    - Maximum dose for Day #1 is 12mg buprenorphine (unless PDMP documented recent tolerance of higher doses)
    - Prescribe total from Day 1 for Day 2, then reassess later in the day. Can give additional 4mg/1mg for withdrawal symptoms. Max dose for Day #2 is 16mg buprenorphine
  - Microdosing** (Bernese Method): start w/ small initial dose of bup (0.5mg) & incrementally increase dose & freq over 7-10d while pts continue other opioids (prescribed or recreational) until therapeutic bup dose (>8mg daily) achieved ([CMAJ 2020;192:E73](#))
- Methadone**: **long-acting full agonist**. Check and trend ECG for QTc, use with caution with other QTc-prolonging meds.
  - Day 1 initial dose**: 10-20mg x1. COWS q2h: <6→observe; 6-12→5mg x1; ≥12→10mg x1. MUST call ACT if ≥40 mg daily dose
  - Day 2 Stabilization**: Cont day 1 dose if COWS <6; inc 20% if COWS 6-12. If not planning methadone maint, ↓ dose 20% per day
- If unable to initiate suboxone/methadone, offer symptomatic medications and short-acting opioids for pain:
  - Autonomic dysreg**: clonidine 0.1-0.2mg TID PRN/lofexidine 0.54-0.72mg QID PRN; avoid w/1st bup/methadone dose, watch BP
  - GI upset**: Bentyl 10-20mg q6h PRN abd cramps; ondansetron 8-16 mg q8-12 PO/IV PRN, promethazine 25-50mg IM PRN N/V; loperamide 2mg PRN diarrhea
  - Anxiety**: hydroxyzine 25mg q8h PRN or trazodone 50-100mg q8h PRN
- Discharge**: ensure pts have **insurance**, **PCP**, **provider** to prescribe bup/nal or methadone, **list of shelters/needle exchanges**, **PrEP**
  - Last dose letter** for patients on methadone maintenance (includes date/amount of last methadone dose)
  - Prescribe naloxone** and **teach** OD response. Emphasize that naloxone reverses OD for ~30min. After OD → EMS to the ED
  - Bridge Clinic**: call 617-643-8281 Mon-Fri 8am-4pm to schedule appt or present as walk-in

# Psychiatry

# Other Substance Use

## TOBACCO (USPSTF: Annals 2015;163:622; JAMA 2021;325:280)

**Screening:** Tobacco: 5A's framework: Ask about use, Advise to quit, Assess readiness, Assist if ready, Arrange follow up.

**Treatment:** For those ready and motivated to quit, combination of counseling and medication is most effective ([Cochrane Rev 2016](#)).

- Set a **quit date**, typically in 2-4w. Abrupt cessation more effective than taper ([Annals 2016;164:585](#)).
- **Counseling:** Individual, group, cessation coach, telephone support lines; [smoking cessation resources](#) at MGH.
- **Pharmacotherapy:** Start **varenicline** or **bupropion 1-2w prior to quit date**; can continue for duration of 3-6mo; monitor tobacco consumption while on pharmacotherapy to see decrease in use (harm reduction approach).
  - **Varenicline:** 0.5mg qd x3d → 0.5mg BID x4d → 1mg BID. **SEs:** nausea, insomnia/vivid dreams; avoid if hx PTSD/SI; monitor for neuropsychiatric symptoms (behavior changes, agitation/hostility, depressed mood, SI/SA).
  - **Bupropion:** 150mg qd x3d → 150mg BID. **Ses:** insomnia, agitation, HA, dry mouth. **Cl:** seizure disorder/predisposition.
  - **Nicotine Replacement Therapy (NRT):** long acting (patch) + short acting (lozenges/gum); efficacy >6mo not established.
- **E-cigarettes:** Evidence to suggest ↑quit rates e-cig w/nicotine> NRT or e-cig w/out nicotine ([Cochrane Rev 2021](#)). Unclear Ses. May be a helpful harm reduction tool if other therapies trialed/refused.

## CANNABIS

- **Intoxication:** Euphoria followed by relaxation; tachycardia; hallucinations (especially w/ high potency THC, e.g. wax/dab)
- **Drug interactions:** Research not definitive, [cannabis may increase warfarin levels](#) ([Basic Clin Pharm Tox 2019;124:28](#))
- **Cannabinoid hyperemesis syndrome:** Dysregulation of GI cannabinoid receptors → recurrent n/v, abd pain, sx relief w/ hot showers, mild leukocytosis. Tx: IVF, antiemetic, THC cessation; consider BZD, antipsychotic, capsaicin ([J Med Toxicol 2017;13:71](#)).
- **E-cigarette or Vaping Associated Lung Injury (EVALI):** Dx of exclusion in respiratory failure <90d after e-cigarette/vape use. GGOs in b/l lung fields; BAL with lipid laden macrophages. Thought to be due to Vitamin E acetate in THC cartridges ([NEJM 2020;382:903](#)). Suspected cases must now be [reported to MA DPH](#).
- **Tx:** No FDA-approved meds. Topiramate, NAC, gabapentin, dronabinol, nabilone may help cravings ([Pharmacotherapy 2016:511](#)).

## SYNTHETIC CANNABINOIDS (SPICE/K2/BATH SALTS)

- **Intoxication:** Agitation/violence, hallucinations, paranoia, anxiety, tachycardia, arrhythmia, myoclonus, diaphoresis. Variable time to symptom onset and recovery based on synthetic used, quantity consumed, and route of use (inhalation, ingestion).
- **Tx:** Low stimulation environment, IVF, consider IV/IM BZD to reduce agitation and prevent seizure ([Curr Psychiatry Rep 2016;18:52](#)).

## BENZODIAZEPINES

- **Intoxication:** Memory impairment, disinhibition, psychomotor slowing, depression, may be amplified with concurrent EtOH use.
- **Withdrawal:** ↑Anxiety, irritability, tremor, HA, nausea, autonomic instability, photo/phonophobia, seizures, paranoia, hallucinations, depersonalization, and delirium. Duration depends on half-life of agent, ranges from 2-10d ([NEJM 2017;376:1147](#)). **Can be lethal.**
- **Abstinence syndrome weeks after cessation:** Anxiety, tachycardia, restlessness.
- **Tx:** Manage severe w/d inpt, use BZD protocol (see [Alcohol Withdrawal](#)). Consider taper with same BZD used. Consider collaboration w/ outpt prescribers and pharmacy.

Commonly Used BZDs	~ Equiv Dose	Half-life (hours)
Alprazolam (Xanax)	0.5mg	6-27 (oral peak 1-2)
Chlordiazepoxide (Librium)	25mg	5-30 (oral peak 0.5-4)
Clonazepam (Klonopin)	0.25mg	18-50 (oral peak 1-2)
Diazepam (Valium)	5mg	20-50 (oral peak 0.5-1)
Lorazepam (Ativan)	1mg	10-20 (oral peak 2-4)
Temazepam (Restoril)	10mg	3-19 (oral peak 1-2)

## STIMULANTS: COCAINE, METHAMPHETAMINE, PRESCRIBED STIMULANTS

### Cocaine:

- **Intoxication:** Euphoria, hyperactivity, grandiosity, anorexia, anxiety, psychotic sx (formication, paranoia, AH/VH). ½ life ~1h.
- **Withdrawal:** Depression, fatigue, nightmares, cravings, ↑sleep/appetite. **Acute w/d tx:** Supportive care, BZD if symptoms severe.
- **Complications:** **Acute:** vasospasm, HTN emergency (Tx: BZD, phentolamine if refractory, nitroglycerin; avoid βB), ACS (Tx: ASA, nitro, BZD), arrhythmia, ischemic bowel. **Chronic:** LVH, cardiomyopathy ([NEJM 2001;345:351](#)). **Snorting:** nasal septum perforation, ulcers, chronic rhinitis. **Inhalation:** cough, SOB, hemoptysis, PTX. **"Crack Lung":** syndrome of fever, hemorrhagic alveolitis, respiratory failure, eosinophilic infiltration thought d/t levamisole additive. Additives & co-ingestion increase risk of harm. **Injection:** discuss safe practices, eg using vitamin C powder as acidifier over lemon juice (fungal infxn) or vinegar (damages veins), use PCOI guide

### Methamphetamine:

- **Intoxication:** Similar to cocaine. Sympathetic activation, executive dysfunction, memory impairment, ↑libido. ½ life ~6-12h.
- **Complications:** HTN, hyperthermia, rhabdomyolysis, may exacerbate existing psych sx. **Tx for severe agitation:** BZD first line.

**Stimulant Use Disorder Tx:** [Consult ACT](#). Limited psychosocial programs in community and mixed evidence for pharmacotherapy.

- **Psychosocial:** Contingency management is best supported; also consider CBT, community reinforcement, motivational interviewing.
- **Pharmacotherapy:** No FDA approved meds. Insufficient evidence for replacement therapy, opioid agonists or NAC to reduce use or improve tx retention across all stimulant use disorders ([PLOS ONE 2020;15: e0234809](#)). Replacement therapy may help sustain cocaine abstinence ([Cochrane Review 2016](#)). Consider topiramate and/or baclofen for cocaine cravings/dependence ([Psychiatry 2005;2:44](#)). IM ER naltrexone + PO ER bupropion may reduce meth use ([NEJM 2021: 384:140](#)).

## HALLUCINOGENS

**MDMA/Ecstasy:** **Intox:** Euphoria, HTN, hyperthermia, stimulant properties. ½ life ~2h. **Complications:** HypoNa, serotonin synd, seizure  
**LSD:** **Intox:** Euphoria, synesthesia, depersonalization. **Complications:** Frightening imagery. Rare vital sign abnormalities.

## CIVIL COMMITMENT FOR SUBSTANCE USE DISORDER TREATMENT ([Section 35](#) in MA - MGL ch.123 §35)

Process by which the court may involuntarily commit someone to inpatient SUD treatment when there is immediate likelihood of serious harm as a result of the SUD. Petition must be filed by MD, blood relative, spouse, guardian, police officer, or court official.

# Psychiatry

# Drug Testing

## MGH TOXICOLOGY SCREENS

- Basic serum toxicology screen:** Quantitative assay for EtOH, salicylates, acetaminophen; qualitative assay for TCAs.
- Urine drug screen (VDAU):** Qualitative screen for amphetamines, BZDs, cocaine, opiates, fentanyl, oxycodone. *Not included: THC, bupe, barbituates, methadone, meperidine, LSD, PCP, propoxyphene.* If a patient may need a THC test (often necessary for transfers to facilities such as McLean), it is much easier to include this in the original order than as an add-on later.
- SUD management panel (VPP2):** Same as VDAU + bupe, methadone (24h turn-around).
- Oral drug screen:** Amphetamines, buprenorphine, benzos, cocaine & metabolite, opiates, methadone, oxycodone, 6-MAM, fentanyl

Test	Turnaround
Serum tox	2 hours
Urine tox	2 hours
SUD	2-24 hours
Oral tox	2-3 days

## ORAL VS. URINE TESTS

- Oral drug mass spectrometry:** Used for outpatient testing for chronic opioids or buprenorphine. Differentiates BZD subtypes and opiates. Superior sensitivity/specificity of amphetamines, opioids and cocaine. More expensive than UTox screen.
  - ODS technique:** Rinse w/ 40 mL water for 30 seconds and swallow prior to test, repeated twice. Wait 10 minutes (early testing → false negative), then place swab under tongue.
- Urine drug screen:** Cheap, easy, noninvasive. Used more often on inpatient. Does not differentiate subtypes of BZDs or opiates. Superior sensitivity for BZDs but does not detect lorazepam. Superior sensitivity for buprenorphine (detects doses as low as 2mg/d). Fentanyl added recently; THC removed.
  - Tampering:** More common w/ UDS. Strategies include use of synthetic urine, smuggling urine, or storing urine in bathroom.

Strategies to minimize UDS tampering: direct observ, check specimen cup temp, ask pts to leave belongings outside bathroom

## Detection Time of Drugs in MGH Toxicology Screens\*

	Urine	Oral
<b>Urine Tox Panel (VDAU)</b>		
Amphetamine, methamphetamine	1-3 days	3-6 days
<b>Benzodiazepines</b>		
Alprazolam	2-3 days	1-2 days
Chlordiazepoxide	10-20 days	5-10 days
Clonazepam	5-10 days	5-10 days
Diazepam	10-20 days	5-10 days
Lorazepam	Not detected	1-2 days
Cocaine	2-5 days**	2-7 days**
Opiates (morphine, codeine)	2-4 days**	2-4 days**
Hydrocodone, hydromorphone	2-3 days	2-3 days
Fentanyl	2-3 days***	2-3 days***
Oxycodone	-2-3 days	2-3 days
<b>Urine SUD Panel</b>		
Buprenorphine	2-3 days	6-10 hours
Methadone	5-10 days	5-10 days

\*Estimates updated 3/2023 from MGH laboratories (James Flood, PhD and Sacha Uljon, MD PhD) Detection times are specific to MGH and are not hard cut-offs.

\*\*Longer in chronic/high-dose users

\*\*\*Best available estimates (detection time for chronic/high-dose fentanyl users over long period of time is unknown)

		Drugs Detected	False Positive	False Negative	Comments
Urine Tox Panel (VDAU)	Amphetamines	Amphetamine, methamphetamine, ecstasy/MDMA	Labetalol, ranitidine, bath salts, trazodone		Ritalin <u>does not</u> cause a false positive
	Benzos	Alprazolam, chlordiazepoxide, clonazepam, diazepam, triazolam		Lorazepam, temazepam	Clonazepam detected even at 1mg/day
	Cocaine metabolites	Benzoylecggonine	None		
	Opiates	Morphine, hydromorphone, codeine, hydrocodone, heroin	Poppy products, rifampin, levofloxacin	Oxycodone, oxymorphone	Fentanyl, methadone, naloxone, naltrexone <u>do not</u> interfere
	Fentanyl	Norfentanyl (metabolite), fentanyl			
	Oxycodone	Oxycodone and metabolite oxymorphone		Substances imparting color to urine (e.g., Flagyl)	
Urine SUD Panel	Buprenorphine	Parent drug and major metabolite			
	Methadone	Methadone	Quetiapine, tramadol, vortioxetine		<u>Does not</u> cause false positive for opiates

## INTERPRETING RESULTS

Tox screens alone should not be used to dx SUDs as they do not give information on frequency or intensity of use. False positives and negatives are possible. It is not recommended to alter prescribing meds based on positive tox screens; instead, use these tests to check for concomitant substance use, monitor opioid use, and initiate conversations around use with patients. **The best tox screen is a respectful history.**

Source: MGH Toxicology Lab and PCOI

# Primary Care

# Health Screening & Maintenance

## GENERAL SCREENING GUIDELINES [Evidence Grade] (<sup>a</sup>[USPSTF](#), <sup>b</sup>[ADA](#), <sup>c</sup>[AACE](#), <sup>d</sup>[ACC/AHA](#), <sup>e</sup>[ACCP](#), <sup>f</sup>[ACS](#))

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+														
<b>Cardiovascular Screening/Preventative Health Recommendations</b>																													
CVD Risk	Assess RFs Q4-6y [B] <sup>d</sup> (age, sex, Tchol/HDL, HTN, DM, CKD, smoking, FHx)						Estimate risk w/ <a href="#">ASCVD calculator</a> Q4-6y [B] <sup>d</sup> If ASCVD risk ≥20% consider high intensity statin* [B] <sup>a</sup>																						
ASA for 1° ppx							Low dose ASA in adults 40-70 with higher ASCVD risk but not higher bleeding risk <sup>d</sup> [A] <sup>a,d</sup>						Not rec for adults >70 [B] <sup>d</sup>																
DM	If HTN or BMI ≥25 (≥23 Asian) w/ ≥1 DM RF <sup>a</sup> , or GDM [B] <sup>b</sup>						A1c Q3y. ↓ interval if abnl result, ✓ annually in pre-DM <sup>b</sup>																						
HTN	Q3-5y; Q1y if elevated BP reading, obese, AA [A] <sup>a</sup>						Q1y [A] <sup>a</sup>																						
HLD	Screen once in age <20	Men 20-45, women 20-55: screen Q5yr, ↑ if RF [C] <sup>c</sup> Q1y in DM [B] <sup>c</sup>						Men >45, women >55 Q1-2y if no RF* [A] <sup>a,c</sup> , Q1y in DM [B] <sup>c</sup>						Screen Q1y [A] <sup>c</sup>															
Obesity	Annual BMI [C] <sup>d</sup> → refer for or offer comprehensive lifestyle program if ≥25 (see <i>Weight &amp; Weight Loss</i> ) [B] <sup>d</sup>																												
Diet	Intensive behavioral counseling if CVD RF* [B] <sup>a</sup>																												
Exercise	150min/wk moderate-intensity exercise or 75min/wk intense-exercise & 2d of muscle strengthening activity [A] <sup>d</sup>																												
<b>Universal Cancer Screening</b>																													
Colorectal CA	Start 10y prior to age of affected family member at dx**						Colo Q10y, flex sig Q5y, FIT or FOBT Q1y [A,B] <sup>a</sup>						+/-**																
Lung CA	Q1y low-dose CT if 20 pack-yrs & current smoker or quit w/in last 15y (age 50-80) [B] <sup>a,***</sup>																												
<b>Infectious Disease Screening</b>																													
HIV	Screen all age 15-65 at least once; repeat based on risk assessment [A] <sup>a</sup>																												
HCV	Screen all 18-79 at least once; repeat based on risk assessment [B] <sup>a</sup>																												
HBV	Born in endemic region, getting HD or immunosuppressed, HIV+, IVDU, MSM, close contact w/ HBV+ person [B] <sup>a</sup>																												
Latent TB	Screen if born or lived in high risk country (see USPSTF <a href="#">recs</a> ) or high risk setting (homeless, jail) [B] <sup>a</sup>																												
<b>Psych/SUD/Social Risk Factor Screening</b>																													
Depression	Q1y [B] <sup>a</sup> by PHQ-2: in 2w how often (a) little interest/pleasure doing things & (b) down/depressed/hopeless ( <a href="#">JAMA 2020;323:2290</a> )																												
Alcohol	Screen regularly with AUDIT-C [B] <sup>a</sup>																												
Tobacco	Every encounter [A] <sup>a</sup> . Advise to quit, Assist doing so (plan, quit date, QuitWorks, meds), Arrange f/u. Strong evidence to start varenicline (Chantix) over other tx options, despite psych comorbidities or readiness ( <a href="#">Am J Respir Crit Care Med. 2020;202:e5</a> )																												
Unhealthy Drug Use	Screening [B] <sup>a</sup> via asking questions about unhealthy drug use (not drug testing) is beneficial when services for accurate diagnosis, effective treatment, and appropriate care can be offered ( <a href="#">JAMA 2020;323:2310</a> )																												
Inter-partner Violence	Screen regularly in women of reproductive age [B] <sup>a</sup> . Use <a href="#">HITS tool</a> . Assess immediate safety & consider HAVEN referral. ↑ rates in LGBT population.						Consider screening for ongoing IPV, elder abuse screening [I] <sup>a</sup>																						
Fall Risk	PT, Vit D [B] <sup>a</sup>																												

\*If ASCVD borderline risk (5%-7.5%) or intermediate risk (7.5%-20%) use risk-enhancing factors [FHx, LDL-C ≥160, metabolic syndrome, CKD, S. Asian race/ethnicity, chronic inflammatory disease including HIV, menopause <40y, pre-eclampsia or pre-term delivery, abn biomarkers (e.g. hsCRP, Lp(a), apoB, ABI)] or coronary artery calcium score to guide decision about statin (see *Outpatient CV Health*)

°History of previous GIB or PUD or bleeding from other sites, thrombocytopenia, coagulopathy, CKD, and concurrent use of other medications that increase bleeding risk (NSAID, steroids, DOACs, Warfarin)

^DM RFs: prior abnl testing (A1c≥5.7), FHx, AA/Latinx/Asian/NA ancestry, Hx GDM, PCOS, CVD, HDL<35 or TG>250, physical inactivity

\*\*Begin at age 40 or 10y prior to earliest dx in fam (whichever comes first) for ≥1<sup>st</sup> degree relative dx<60 or two 1<sup>st</sup> degree relatives of any age; Age 40: ≥1<sup>st</sup> degree relative dx≥60; 75+: based on life expectancy. Early screening for special populations: hx of high-grade polyp, IBD, prior colon or rectal ca, hx prior pelvic/gut radiation, genetics.

\*\*\*Consider screening cessation if limited life expectancy or screening would impede surgical candidacy.

## ADDITIONAL SCREENING GUIDELINES FOR MEN [Evidence grade] (<sup>a</sup>[USPSTF](#), <sup>f</sup>[ACS](#), <sup>g</sup>[Endo](#), <sup>h</sup>[PCOI](#))

Age	18-40	40	45	50	55	60	65	70	75+
AAA									If +tobacco hx [B] <sup>a</sup>
Prostate CA*		FHx** Q1-2y <sup>df</sup>	FHx, AA Q1-2y <sup>df</sup>	Screen all men Q1-2y <sup>df</sup> if life expectancy ≥ 10y <sup>f</sup>					PSA 55-69y if pt preference [C] <sup>a</sup> , recommend against if >70y [D] <sup>a</sup>
Testicular CA	<i>Recommend against</i> routine screening in all men <sup>Σ</sup> [D] <sup>a</sup>								
Anal CA <sup>#</sup>	In MSM: anal Pap smears Q1y if HIV+ (space to Q3y after 3 neg Paps); consider Q2-3y if HIV- <sup>h</sup>								
Osteoporosis							If RF <sup>g</sup>		DXA <sup>g</sup>
STIs	In MSM: Q1y, Q3-6mo if multiple/anonymous partners or sex in conjunction w/ drug use; hx re: sexual practice can guide screening (pharyngeal, anal, urine). Discussion re: PrEP.								

\*Inform all patients of [uncertainties, risks, and potential benefits](#) before starting PSA screening

°Screening frequency varies based on level. PSA < 2.5ng/mL = Q2y. PSA ≥ 2.5ng/mL = Q1y; [Amer Urological Assoc](#) recs Q2y interval

\*\*>1 first-degree relative with history of prostate cancer at early age

^Low body weight, prior fracture, smoking

ΣIf higher risk (h/o cryptorchidism or orchioepoxy, testicular atrophy, or sxs), evaluate, educate & consider periodic testicular exams

#Lacking evidence to inform screening initiation age & intervals. [NYS DOH AI](#) includes follow-up algorithm. Stop when life expectancy <10y

# Primary Care

# Health Screening & Maintenance

## ADDITIONAL SCREENING GUIDELINES FOR NON-PREGNANT WOMEN [Evidence grade] (<sup>a</sup>USPSTF, <sup>f</sup>ACS)

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+	
Breast CA*	Consider BRCA counseling if +FHx. Screening tools <a href="#">available</a> [B] <sup>a</sup>				Discuss Q1y mammogram <sup>f</sup>	Q1y mammogram age 45-54 <sup>f</sup>		Q1-2y mammogram age 55-74. Stop if <10y life expectancy <sup>a,f</sup>								
Cervical CA <sup>a,b</sup>			Q5y 1° high risk HPV testing (preferred if available); if not available, Q5y cytology + hrHPV co-testing OR Q3y cytology alone <sup>f</sup>												If neg adequate screening, stop	
		Q3y cytology [A] <sup>a</sup>		Q5y 1° hrHPV testing (preferred) <sup>f</sup> OR co-testing (hrHPV & cytology) OR Q3y cytology alone [A] <sup>a,f</sup>												
Ovarian CA	<i>Recommend against</i> routine screening in asx women [D] <sup>a</sup> ( <a href="#">Lancet 2021;397:2182</a> )															
STIs	≤24: GC/CT annually [B] <sup>a</sup>		Screen based on risk assessment [B] <sup>a</sup>													
Contraception	Discuss with everyone including trans ♂ (see <i>Women's Health</i> for contraception guidelines). Start folic acid at reproductive age if planning/capable of pregnancy [A] <sup>a</sup>															
Osteoporosis	Consider earlier screening based on <a href="#">FRAX</a> assessment [B] <sup>a</sup> (see <i>Osteoporosis</i> )										DXA [B] <sup>a</sup>					

\*Discrepancy btw societal guidelines despite same evidence. USPSTF: 50-74 Q2y [B]; 40-49 discussion of risks/benefits [C]; >75 no recommendation [I]. ACS: 40 discuss initiation of annual screening; 45-54 Q1y; ≥55 discuss transitioning to Q2y screening until life expectancy <10y. ACOG: offer mammography at 40; start screening at 50; discuss cessation at 75; screen Q1-2 years

<sup>a</sup>All screening methods still accepted to promote access to adequate cervical cancer screening. USPTF recommends age 21 start whereas [ACS](#) recommends age 25. [ACOG](#) recommends start at age 21 due to underscreening in younger populations.

<sup>b</sup>Women w/ HIV require more frequent Paps & Paps preferred (HPV testing w/o cervical cytology is **not** approved). See [NIH guidelines](#)

<sup>c</sup>Subsequent screening dictated by age, prior screening results, and other factors. Use [ASCCP Web App](#) for algorithm of next steps.

## ADDITIONAL SCREENING GUIDELINES FOR TRANSGENDER INDIVIDUALS\*

Age	18-40	40	45	50	55	60	65	70	75+		
CVD Risk	As above; if patient has been on hormones for many years, use hormonal sex in the calculator										
Osteoporosis	Consider at any age if s/p gonadectomy and >5y w/o hormone tx				Consider based on <a href="#">FRAX</a> (no guideline on which sex to use)		DXA				
Breast CA	Trans ♀: Q2y after 5-10y hormone use Trans ♂: if natal tissue present (incl s/p partial mastectomy), screen per guidelines for non-trans ♀										
Cervical CA	Trans ♂: if natal tissue present (incl s/p subtotal hysterectomy), screen per guidelines for non-trans ♀ <sup>a</sup>										
Prostate CA	Trans ♀: screen per guidelines for non-trans ♂. Use lower ULN for PSA if on estrogen										

\*See *Transgender Health*

<sup>a</sup>Cells more likely to be "unsatisfactory" for interpretation on testosterone. On order, note that pt is on testosterone and/or amenorrheic. Self-collected vaginal swabs as sensitive as provider-collected swab ([PLoS 2018;13](#))

## VACCINES (CDC, <sup>a</sup>NYS DOH AI)

Immunizations	19-21	22-26	27-49	50-64	≥65		
Influenza		Annual flu vaccine		Annual high dose flu vaccine			
	No live (intranasal) if immunocompromised (or contact), pregnant, asplenia, cochlear implant, CSF leak, ≥50; OK for 65+ to get regular adult flu vaccine if high dose not available						
Tdap/Td	1 dose Tdap then Td booster every 10 years; extra Tdap dose during each pregnancy						
MMR*	1-2 doses based on indication (if born 1957 or later) 1 dose in ♀ of childbearing age; 2 doses if HIV & CD4≥200, healthcare personnel, or college students						
Varicella*	2 doses (if born 1980 or later)						
Zoster*	Immunocompromised: 2 doses of RZV 1-6 mo apart Administer RZV regardless of history of Zostavax (live, no longer available) administration						
HPV**	2-3 doses	27-45y SDM***					
	3 dose series to all people with HIV up to 45y <sup>a</sup>						
PCV15/PPSV23 OR PCV20	Chronic heart, lung, kidney, or liver dz; DM; AUD; smoking; nephrotic syndrome; CSF leak; cochlear implant; immunocompromising conditions: PCV20 x1 OR PCV15 x1 followed by PPSV23 x1 ≥ 8 wks (underlined) or 1 yr later				If never vaccinated, PCV20 x1 OR PCV15 x1 followed by PPSV23 x1 ≥1 yr later.		
Hep A	Travel to endemic country, HIV, MSM, <b>any</b> drug use (not just IVDU), chronic liver dz, undomiciled, work w/ HAV, close contact to international adoptee, settings for exposure, pregnancy at risk for infxn: 2 doses						
Hep B	Travel to endemic country, HIV, sexual exposure risk, IVDU, chronic liver dz, incarcerated, mucosal or percutaneous blood exposure (incl dialysis, DM <60y, work exposure), pregnancy w/ infxn risk: 2 doses						
Meningococcus** (MenACWY/MenB)	Functional/anatomical asplenia, HIV, ↓ complement (including by meds), travel to endemic country, freshmen in dorms, military recruits: 1-2 doses + Q5Y if risk remains (add MenB for asplenia, ↓ complements + Q2-3Y if risk remains)						
Hib	Functional or anticipated asplenia: 1 dose (if no prior); after HSCT: 3 doses (regardless of vaccination hx)						

\*Hold live vaccines in pregnancy, malignancy, and immunocompromised (incl HIV w/ CD4 <200, cochlear implant). Ok if CD4 ≥200

\*\*Wait until after pregnancy \*\*\*Shared decision making (SDM): most likely to benefit adults not yet exposed to HPV or w/ new sex partners

# Primary Care

# Transgender Health

## GENERAL CONSIDERATIONS ([NEJM 2019;381:2451](#))

### Gender Terminology

- Gender identity: a person's sense of one's gender; can be congruent with or differ from sex assigned at birth
- Transgender/trans: a person whose gender identity is different from cultural expectations based on their sex assigned at birth vs cisgender: sex assigned at birth and gender are congruent
- Non-binary, gender non-conforming, genderqueer: a person whose gender identity does not fall within the traditional gender binary. People who are non-binary may see themselves as being both male and female, neither male nor female, or as completely outside of or unrelated to these categories

**History:** use "Sexual Orientation/Gender ID" and "Demographics" activities in EPIC to update patient header w/ chosen name/pronouns

- Gender identity data: name and pronouns, gender identity + sex assigned at birth
- Organ inventory: guides screening and physical exam. Note natal and surgical anatomy. Confirm patient's preferred terms for organs
  - CA screening: per usual guidelines based on organs present; trans women [screen breast CA](#) if >50yo and 5yr HRT
  - Include present organs in ddx: e.g., PID, fibroids, endometriosis in trans M w/ uterus/fallopian tubes; prostatitis in trans F
- Sexual history: "What body parts do your sexual partners have?" "What body parts do you use for sex?" "What terms do you use to refer to your body parts?"
  - Use gender neutral language to use for natal parts (i.e., chest wall instead of breast, monthly bleeding instead of menses)
  - Self-collected rectal, oropharyngeal and vaginal swabs as sensitive as provider-collected swabs for STIs and HPV ([Cytology 2019;63](#)); useful for individuals who want to avoid an invasive exam
  - Offer HPV, HBV vaccine series; CDC [primary prevention](#) guidelines
  - Consider HIV PrEP for patients who use IV drugs or have multiple sexual partners: ([AETC prescriber guidelines](#))

### Physical Exam Considerations

- Skin: acne, hair, irritation/infection 2/2 chest binding or penile/scrotal tucking, tattoos at potential skin flap sites, silicone injections
- Abd: complications from tucking include prostatitis, cystitis, epididymo-orchitis,
- GU: pelvic exam in trans M can be traumatizing and painful 2/2 vaginal atrophy on testosterone. Tips: 1-2w vaginal estrogen before exam; pediatric speculum; [trauma-informed care](#) esp [physical exam](#); consider PO benzos 1h before; self-swab if possible.

## GENDER-AFFIRMING CARE ([WPATH Standards of Care](#); [UCSF Transgender Health](#); [Trans Line](#); [MGH Transgender Health](#))

**Gender dysphoria**: distress a person feels due to a mismatch between their gender identity and their sex assigned at birth

- Affirm gender identity and explore options below for expression of identity and alleviation of gender dysphoria
  - Psychotherapy: safe space to explore gender expression, impact of internalized transphobia, social support, body image, strategies for resilience. Not required to pursue hormone tx or surgery
  - Changes in name and gender marker on [identity documents](#); voice and communication [therapy](#); hair removal; chest [binding](#) or padding; genital tucking or packing; padding of hips or buttocks; hormone tx; surgery

**Hormone therapy**: initiate w/ informed consent & shared decision making w/ patient ([WPATH standard](#), [Endocrine Reviews Feb 2019;40:97-117](#))

- Anticipatory guidance: full effects can take 1-5y. Dose titration requires frequent labs and visits in the first year
- Feminization: 17-beta estradiol (PO/SL, transdermal patch, IM) + androgen blocker (spironolactone/leuprolide), +/- progesterone
- Masculinization: Testosterone (topical gel/transdermal patch, IM/SQ). Progestins, Aygestin early on may help stop menses
- Fertility: Discuss fertility preservation (egg/embryo freezing, sperm banking) before starting tx
- Testosterone ≠ contraception. If partner makes sperm, discuss birth control: pills, patches, Nexplanon and IUD are all options
- When monitoring treatment, indicate hormonal sex in lab requisition and interpret values using ranges for hormonal, not natal sex
- Reasonable to provide 1-6 mo of bridge Rx if patient is already on hormones and then refer to another provider who can prescribe

	Contraindication	Potential Risks	Irreversible changes	Reversible changes	Monitoring
MtF	Absolute: estrogen-sensitive neoplasm, ESLD	- VTE^ - Gallstones - ↑TG, liver enzymes - HTN - ↑prolactin - Migraines	- Chest growth - ↓ testicular volume	- ↓ muscle mass - fat redistribution - hair/skin softens - ↓ sex drive - ↓ libido, erections	- If spironolactone: BP, BMP baseline and q3 mo, then q1y - total T, E q3-6mo until at goal, then q1y - prolactin PRN if sxs
FtM	Absolute: ACS, polycythemia (Hct >55%), pregnancy, sex hormone sensitive neoplasm	- Erythrocytosis - HLD, ↑liver enzyme - Sleep apnea	- Deepening of voice - ↑ facial and body hair - Clitoromegaly - Vaginal tissue atrophy - Scalp hair loss**	- menses cessation - ↑ sex drive - ↑ muscle mass - acne	- Before tx: urine HCG - CBC q3mo, then q1y - total T q3mo, then q1y

<sup>^</sup>Strongly encourage smoking cessation to attenuate risk. Consult [UCSF guide](#) for risk-benefit analysis after VTE

<sup>\*\*</sup>Treatment with 5-alpha reductase inhibitors may reverse some testosterone effect

**Surgery:** may require 12 mo hormone tx and support letter from two mental health providers (depends on surgery type)

- Feminization: vaginoplasty, mammoplasty, voice feminization surgery, thyroid cartilage reduction, penectomy, orchietomy
  - Pre-op: no evidence to stop hormone therapy in otherwise low-risk transgender women, electrolysis for hair removal
  - Post-op considerations: tissue necrosis, fistulae, urethral stenosis, UTIs, anorgasmia; regular vaginal dilation/penetrative intercourse to maintain vaginal depth and width
- Masculinization: mastectomy, phalloplasty, metoidioplasty, scrotoplasty, hysterectomy, oophorectomy
  - Post-op considerations: tissue necrosis, urinary tract stenoses/fistulae, flap loss

# Primary Care

# Women's Health

## BREAST CONCERNs (PCOI – CRICO Guidelines)

- Nipple Discharge:** **bilateral/milky:** eval prolactin, Cr, TSH, bHCG. **Unilateral, bloody** (associated with mass): <30y U/S, ≥30y dx mammo and U/S. Surgery referral for concerning imaging, MRI vs surgery refer if imaging negative
- Palpable Mass:** <30y U/S; ≥30y diagnostic mammo and U/S. Surgery referral based on imaging findings
- Breast Pain:** rare presentation of BC. **Cyclical:** wait two cycles. **Focal:** <30y U/S, ≥30y U/S and BL dx mammo; **Diffuse:** unlikely ca, <30y sxs management (APAP, NSAID, hot/cold, eval for extramammary causes), ≥30y BL dx mammo

## VULVAR/VAGINAL CONCERNs (Obstet Gynecol 2020;135:e1; Obstet Gynecol 2020;136)

	Presentation	Dx	Tx
Vaginitis	<p><b>Bacterial vaginosis (BV):</b> most common; malodorous discharge, often asx; RF = sexually active, douching Recurrent vaginosis defined as: ≥3x/yr</p>	<ul style="list-style-type: none"> <li>- Amsel's criteria (≥3): 1) homogeneous, thin, grey-white discharge 2) &gt;20 % clue cells 3) +KOH whiff test/amine test 4) pH &gt;4.5 (less reliable if post-menopause)</li> <li>- Wet prep or "Genital culture female" (collect w/ rayon swab). Nugent score 7-10 = BV</li> <li>- Also test for HIV and STIs</li> </ul>	<b>Metronidazole</b> PO 500mg BID x7d or vaginal 0.75% x5d, clinda PO 300mg BID x7d or vaginal 2% x7d <b>Recurrent:</b> Metrogel x7d, followed by 2x/w maintenance for 4-6 mos
	<p><b>Candida:</b> curd-like discharge, no odor, pruritus, vulvar erythema ± edema, dysuria, dyspareunia  <b>Complicated:</b> severe sx, pregnancy, non-<i>c. albicans</i>  <b>Recurrent defined as:</b> ≥4x/yr</p>	<ul style="list-style-type: none"> <li>- pH normal (3.5-4.5), KOH microscopy</li> <li>- "Genital culture female" or yeast culture for fungal sensitivity if recurrent</li> </ul>	<b>Fluconazole</b> 150mg PO x1, miconazole 2% x7d if pregnant <b>Complicated*</b> : fluc 150mg q72h x 3 doses <b>Recurrent*</b> : fluc 150mg q72h x 3 doses + maintenance or fluc 150mg x 7-14d *test for DM2, HIV, fluconazole resistance, non- <i>c. albicans</i> infect
Other infections: Trichomonas, Gonorrhea, Chlamydia, HSV - see STI			
Painful	<b>Vulvodynia:</b> general or local pain, provoked or unprovoked, >3-6mo	Q-tip test to localize pain, exclude other etiology	TCA, gabapentin, lidocaine 5% before sex, steroid/lidocaine inj., sitz bath
	<b>Genitourinary Syndrome of Menopause:</b> vaginal dryness; pain w/ intercourse; thin, pale mucosa	Vaginal pH >4.5, parabasal cells on wet mount/GS	Topical estrogen (insert, ring), lubricants (prior to intercourse), Replens moisturizer, ospemifene
Dermatoses	<ul style="list-style-type: none"> <li><b>Contact dermatitis:</b> erythema, swelling, fissures, erosions → r/o candida, remove offending agent</li> <li><b>Lichen simplex chronicus:</b> intense pruritis + lichenified plaque → antihistamines, topical corticosteroids; stop itch/scratch cycle</li> <li><b>Lichen sclerosus:</b> onset 50-60s, pruritis, irritation, dysuria, dyspareunia; perianal or vulvar white, atrophic papules lead to skin thinning, labia minora fusion, &amp; clitoral hood phimosis. 5% incidence malignancy → bx to confirm; clobetasol 0.05% taper (qd x4w, qod x4w, 2x/w x4w), vulvar hygiene, monitor for SCC</li> <li><b>Lichen planus:</b> onset 50-60s, pain/burning, "purple, papular, pruritic," white lacy striae, vaginal involvement, ↑SCC risk → bx to confirm &amp; r/o malignancy; high potency steroids, monitor for SCC</li> </ul>		

## URINARY INCONTINENCE (Obstet Gynecol 2015;126; PCOI)

- Types:** **stress** (involuntary leakage w/ cough, laugh), **urge** (leakage w/ urge), **mixed** (stress + urge), **overflow** (incomplete emptying, constant dribble), **functional** (impaired mobility/cognition/neurologic); **DDx:** UTI, vaginal atrophy
- History:** systemic sx (fevers, dysuria, pain), meds (anticholinergics, diuretics, etc.), comorbid conditions (DM, vol overload), bowel habits, caffeine/EtOH use, voiding diary
- Exam:** check for prolapse, vulvar/vaginal atrophy, cough/valsalva stress test; rectal exam (fecal impaction, sphincter tone); neuro exam; **Dx:** UA/Cx, PVR (abnl >150cc); urethral mobility assessment and urodynamic studies if etiology unclear
- Initial tx:** incontinence products, bladder training (timed voiding), lifestyle interventions (e.g., wt loss, ↓ fluid/caffeine intake), pelvic floor exercises (e.g. Kegels; pelvic floor PT). **Stress/mixed:** pessary, vaginal estrogen (for vaginal atrophy), surgery. **Urgency:** antimuscarinics (many SE), β-agonists (e.g. mirabegron) – monitor for urinary retention
- Refer to Urogyn if:** hx surgery/radiation, c/f mass/pain/prolapse, no response initial tx, abnl PVR, pessary/surgery/intravesicular botox

## MENOPAUSE (J Clin Endo Met 2015;100:3975)

- Amenorrhea x12mo w/o alt etiology (no need to ✓ labs, can help s/p hysterectomy), avg onset at 51, suspect 1° ovarian insuff if <40
- Vasomotor sx** (hot flashes): **Systemic hormones** (estrogen + progestin, estrogen mono-Rx if hysterectomy) first line if <60yo, <10y since onset & <5y duration. **Avoid if:** hx or >10% risk CVD, hx/high risk of breast CA/endometrial CA, hx VTE/CVA/TIA, active liver disease, unexplained vag bleeding. **Side effects:** breast tenderness, vag bleeding; ↓CRC, fracture risk; ↑breast CA, CVD, VTE (equivocal if ↑risk attenuated with topical Tx); no mortality risk after 5-7y on therapy (JAMA 2017;318:927). **If not eligible/desiring systemic hormones:** SSRI/SRNI (paroxetine best), gabapentin, clonidine.
- Vaginal/vulvar sx** (now called **genitourinary syndrome of menopause**): see above; oral therapy not effective, use topical
- Psych sx:** sleep disturbance, poor concentration, new-onset depression. May improve with Rx for vasomotor sx

## AMENORRHEA (AFP 2019;100:39)

- In adults, most commonly **2° amenorrhea**: cessation of regular menses for 3mo **or** cessation of irregular menses for 6mo
- Hx:** wt Δ, diet/exercise, hot flashes, galactorrhea, hirsutism, stress, systemic illness; **Initial labs:** HCG, FSH, LH, E2, TSH, PRL

# Primary Care

# Women's Health

- DDx:** pregnancy, hypothalamic (eating disorder, excess wt loss/exercise, stress, prolonged illness), pituitary (hyperprolactinemia 2/2 adenoma, mass effect, meds, breastfeeding, apoplexy), ovary (1° ovarian insufficiency, PCOS), uterine (prior instrumentation → scar = Asherman Syndrome), other (hypo/hyperthyroidism, DM, celiac, excess androgens [exogenous, Cushing's])
- If nl/low FSH, consider progestin challenge: medroxyprogesterone acetate 10mg x10d. If no withdrawal bleed, suggests uterine abnl

## POLYCYSTIC OVARY SYNDROME (PCOS) ([J Clin Endo Met 2013;98:4565](#); [Obstet Gynecol 2018;131](#))

- Affects 5-10% of women of reproductive age; often comorbid w/ CVD, DM, HTN, NAFLD, HLD, OSA, depression and anxiety
- Rotterdam Criteria** (need 2/3): 1) oligo/anovulation, 2) clinical/biochemical hyperandrogenism, 3) polycystic ovaries on pelvic U/S
- Workup:** exclude other dx (hCG, 17-OHP [pre-8AM], prolactin, TSH); DHEAS, total testosterone, SHBG to confirm if dx unclear
- Tx:** wt loss, exercise, **C-OCP** (2<sup>nd</sup> line = oral progesterone or levo-IUD), spironolactone, metformin (if insulin resistant), fertility referral

## PRECONCEPTION COUNSELING/INFERTILITY ([Fertil Steril 2021;116](#))

- Preconception counseling (PCoI):** avoid tobacco, EtOH, drugs; multivitamin qd w/ 400-800mcg folic acid; review immunizations (Rubella, Varicella, HepB, COVID-19); optimize mgmt of wt, thyroid (TSH goal 0.5-2.5, recheck after conception), HTN (avoid ACEi/ARB, check b/l Cr, spot Ur protein/Cr), DM (↑ risk birth defects; metformin/insulin first-line), mood (avoid paroxetine; SSRI safety debated, engage Psych/MFM), VTE (LMWH preferred), asthma, OUD (methadone & suboxone safe in pregnancy)
- Infertility:** evaluate after 12mo unprotected intercourse in <35yo, 6mo in ≥35, sooner if >40; fertility tx covered by insurance in MA
- Hx:** prior OB/GYN hx (menstrual hx, pregnancies, PID, fibroids/polyps, abnl Pap, endometriosis, contraceptive use), sexual hx (timing, frequency, sexual dysfunction), hx chemo/XRT, meds, substance use, FHx. **Ddx:** see amenorrhea above
- Dx:** ovarian reserve tests, pelvic/transvaginal U/S, PCOS w/u, STI & fallopian tube patency testing, TSH, PRL, **semen analysis**
- Tx:** fertility awareness (intercourse qod cycle d9-14, or from 5d before and day of ovulation); refer to Repro-Endo for other w/u, induction of ovulation, IVF, or donor oocytes

## CONTRACEPTION ([CDC USMEC 2016](#); [CDC 2020 Summary](#); <sup>a</sup>Society of Fam Planning), resource for patients: [bedsider.org](#)

- 45% of pregnancies are unplanned → r/o pregnancy before initiating contraception → **LARCs (IUD, implant) are most effective**
- Hormonal methods (including LARC) take ~1w to take effect → always recommend backup method (condoms) for 7d

Use	1y Failure Rate*	Pros/Cons	Contraindications (A: Abs, R: Rel)
<b>Estrogen-progestin<sup>^</sup></b>			
Combined Pill	Daily	9% (0.3%)	
Vaginal Ring	3w in, 1w out	9% (0.3%)	
Patch (e.g. Xulane, Ortho Evra)	Weekly x3w, 1w off; apply to arm, torso, or buttock	9% (0.3%)	<p><b>Pros:</b> ↓menses, PMS, cramps, acne, endometrial/ovarian CA</p> <p><b>Cons:</b> n/v, breast tenderness, can ↑HTN/TGs, ↓libido, spotting for first few months, cannot start if &lt;21d PP (VTE risk), requires pt adherence</p>
<b>Progestin-only</b>			
IUD (hormone content Mirena/Liletta > Kyleena > Skyla)	M/L q8y Kyleena q5y Skyla q3y	0.2%	<p><b>Pros:</b> effective, long-acting, lighter periods, may reduce cramping/anemia, discreet, <b>emergency contraceptive (M/L)**</b></p> <p><b>Cons:</b> irregular bleeding, requires removal, physical complications (rare) Pt preference: amenorrhea (~18%)</p>
Implant (Nexplanon)	q3y to upper arm (q5y efficacy <sup>a</sup> )	0.05%	<p><b>Pros:</b> effective, long-acting, discreet</p> <p><b>Cons:</b> irregular bleeding; temporary ↓BMD; prolonged return to fertility (1y); may worsen HA, acne, mood</p>
Injection (Depo-Provera)	q3mo IM/SQ to arm, thigh, or buttock	6% (0.2%)	<p><b>Pros:</b> long-acting, discreet</p> <p><b>Cons:</b> irregular bleeding; temporary ↓BMD; prolonged return to fertility (1y); may worsen HA, acne, mood</p>
Pill (e.g. Micronor, Slynd)	Daily	8% (0.3%)	<p><b>Pros:</b> no effect on breastfeeding</p> <p><b>Cons:</b> irregular bleeding, HA, acne, mood sx, timing<sup>Σ</sup></p>
<b>Hormone-free</b>			
Copper IUD (Paragard)	q10y (12-20y efficacy <sup>a</sup> )	0.8% (0.6%)	<p><b>Pros:</b> effective, long-acting, safe in ESLD, emergency contraceptive</p> <p><b>Cons:</b> heavier bleeding, cramping</p>
Male condom	Every encounter	18% (2%)	<p><b>Pros:</b> STI prevention</p> <p><b>Cons:</b> requires pt adherence</p>
Tubal Ligation Vasectomy	Permanent	0.5% 0.15%	<p><b>Pros:</b> available to men and women</p> <p><b>Cons:</b> irreversible</p>

\* Typical use – i.e. % women who will have unplanned pregnancy in 1 year on this method (perfect use in parentheses)

<sup>a</sup>Estrogen-progestin methods can be used continuously to avoid withdrawal bleed. Skip placebo/iron pills or replace vaginal ring/patch every 3 weeks.

\*\* [NEJM 2021;384\(4\)](#) <sup>Σ</sup>Newer formulations like Slynd maintain efficacy with 24h missed window ([Curr Obstet Gynecol Rep 2022;11](#))

# Primary Care

# Women's Health

**Oral Contraceptives (OCPs)** ([Quick Start Algorithm](#)): start anytime (exclude preg + 7d backup method if not 1<sup>st</sup> day period)

- **OCP selection:** estrogen (ethynodiol) – 30-35mcg: less breakthrough bleeding. 20mcg: less estrogen SE. Progestin – 2gen (levonorgestrel, norgestrel): ↓VTE risk. 3gen (norgestimate, desogestrel): ↓androgenic SE, ↑VTE risk

**Emergency Contraception** ([Obstet Gynecol 2015;126:e1](#); [NEJM 2021;384\(4\)](#); [PCOI](#))

- **Plan B** (levonorgestrel 1.5mg x1 or 0.75mg q12h x2): OTC, use w/in 72h, less reliable if BMI >25. **Ella** (ulipristal 30mg x1): requires Rx, use w/in 120h, less reliable if BMI >30. **Paragard/Mirena/Liletta**: place within 120h (Paragard okay up to 160h), most effective
- In cases of **sexual assault**: refer pt to ED for an exam by a trained SANE RN. If IPV: ask if partner has access to online medical records prior to detailed documentation and prepare safety plan. **MGH HAVEN referral: 617-724-0054**

## OPTIONS COUNSELING (TEACH)

Options counseling is an opportunity for the pregnant person to consider, in conversation with her provider, whether she wants to continue the pregnancy and parent the child, continue the pregnancy with a plan for adoption, or have an abortion. Particular attention to neutralizing language to avoid potential coercion is imperative. For people who desire abortion, see [PCOI](#) or [abortionfinder.org](#) for list of providers in MA. Avg cost ~\$500, 50% pay out of pocket. Counseling: **1-866-4-EXHALE**.

**Medical Abortion (MAB)** (95-98% effective)

- **Eligibility:** ≤10 wks gestation, no ectopic risk (history alone or U/S if equivocal); **no** (1) IUD in place, (2) mifepristone or misoprostol allergy, (3) chronic adrenal failure/long-term corticosteroid use, (4) hemorrhagic disorders, on AC, symptomatic anemia, (5) porphyria
- **Workup:** serum or urine hCG test; **no routine pre-MAB lab testing needed if no underlying conditions; LMP can date pregnancy accurately & safely in most cases** (U/S NOT universally required); offer STI testing & immediate post-abortion contraception
- **Protocol:** PO mifepristone x1 → buccal or vaginal misoprostol in 24-48h → pt passes pregnancy at home over hrs. May experience cramping and bleeding. Tx with NSAIDs. F/u history and home urine pregnancy test OR serial bHCG testing OR U/S in 7-14d

**Surgical Abortion** (<24wks gestation, 99% effective): same-day office procedure → no f/u unless complications

**Parenting:** obstetrics

**Adoption:** [resources](#) for public and private agencies

## POSTPARTUM CARE ([ACOG Postpartum Toolkit, 2018](#))

**Key Screening Items:** proactive questions and anticipatory guidance about nl vs abnl mitigates complications and worry

- **Vaccines:** recommend all w/ baby contact receive flu & Tdap (unless contraindicated); all vaccines safe while breastfeeding except smallpox (give yellow fever and MenB only if benefits > risks)
- **Contraception:** can start progestin-only options (IUD, implant, injection, pills) immediately postpartum & estrogen-containing options 21-28d postpartum (42d if VTE risk factor).
- **Breastfeeding:** see [Lactmed](#) for restarting medications. Challenges: nipple pain (tx lanolin, breast shield), plugged ducts (aspiration if >72h), inadequate milk supply, mastitis (10% breastfeeding mothers; assoc w/ edema, erythema, ± fever/chills; if c/f infection, r/o abscess w/ exam (tx w/ I&D) and Rx dicloxacillin or keflex; encourage continued breastfeeding). Consider referral to lactation consultant. Remind mom federal law requires break time & dedicated space at work for lactation
- **SUDs/Analgesia:** postpartum period high risk for SUD/relapse. Methadone & buprenorphine safe w/ breastfeeding, should be continued. Screen for AUD. Encourage smoking cessation (pt & all household members). Acetaminophen and ibuprofen safe during breast feeding; avoid NSAIDs if HTN. Butorphanol, morphine, hydromorphone are preferred opioids if needed
- **Common sx (often self-resolve):** vaginal soreness & discharge, constipation, hemorrhoids, cramps, breast engorgement, urinary/fecal incontinence, hair loss (w/in 5mo), mood swings ("baby blues")
- **Persistent vaginal bleeding:** normal to have small amount of red-tinged discharge for 1-2w PP (w/ red, heavy discharge for 1-2d); if soaking through pad/tampon in <1h ± pain, fever, tenderness, may be signs of infection, refer to ED
- **Perineal pain, dyspareunia, and sexual dysfunction:** >10% report pain 1y post-vaginal delivery (RF = 3<sup>rd</sup>/4<sup>th</sup> degree tears, operative delivery, vaginal atrophy while breastfeeding). Tx: water-based lubricants, topical estrogen, pelvic floor therapy, scar tissue ablation. Decreased libido common and normal (50% at 3mo, 30% at 6mo)
- Postpartum depression: w/in 12mo after birth; incidence of 11-20%; screen with [PHQ9](#), Postpartum Depression Scale, or [Edinburgh Postnatal Depression Scale](#); tx with peer counseling, CBT, SSRI

## Pregnancy-Related Complications of Cardiovascular Disease and Endocrinopathies

- Postpartum period high risk for: flares of underlying autoimmune disease, peripartum cardiomyopathy
- Excessive gestational weight gain, obesity, preterm birth (<32w) ↑risk for CVD in mom; screen annually for modifiable RF

	Future Risk	Postpartum Screening	Risk Mitigation
<b>Gestational Diabetes/ Diabetes</b>	- ↑risk of recurrent GDM, pre-DM, T1DM, T2DM (7x higher), CVD, & metabolic syndrome (esp. w/in 5y) - Uncontrolled DM ↑risk birth defects	- 75g OGTT or fasting BG at 4-12w postpartum ( <a href="#">Diab Care 2021;44:S15</a> ). If ⊕, screen q1y. If ⊖, q3y for life - If T1DM, TFTs x1 (if never done)	- Encourage breastfeeding - If overt DM: target A1c 6-6.5, consider ASA 81mg qd in future pregnancies to ↓pre-eclampsia risk
<b>Pre-Eclampsia/ HTN</b>	- ↑risk of stroke 48h-10d postpartum - ↑risk of CKD in first 5y - ↑risk of ASCVD ( <a href="#">JACC 2019;74:1376</a> )	- Close BP monitoring up to 6w PP - Repeat UACR/UPCR to quantify baseline proteinuria	- Encourage breastfeeding - Early goal BP <160/100, later <120/80 - Add pre-eclampsia as ASCVD risk-enhancer - Consider ASA 81mg qd in future pregnancies to ↓pre-eclampsia risk

## BENIGN PROSTATIC HYPERPLASIA (BPH)/LUTS ([J Urol 2021;206:806; PCOI](#))

- Sx:** increased frequency or urge to urinate, difficulty initiating or weak stream, small amt urine with each void, leaking or dribbling, sensation of incomplete void. Present in >50% of men over 60 with increased incidence with older age (~90% > 85 years)
- DDx:** urethral stricture, bladder neck contracture, prostate ca, bladder ca, bladder calculi, UTI, prostatitis, neurogenic bladder
- If dx of BPH established via sxs/exam +/- optional testing (PVR, uroflowmetry), can f/u LUTS w/[International Prostatisim Symptom Score](#)
- Possible Complications:** urinary retention, persistent gross hematuria, bladder stones, recurrent UTI, hydronephrosis, renal failure
- Screening:** important to counsel patients and participate in shared decision making re: annual screening PSA at age 50 given high incidence of false positive (~70%) as well as risks/benefits of side effects vs medical therapy
- Rx:** if watchful waiting and behavior change (avoid alcohol/caffeine, limit PM fluid intake, avoid antihistamines/decongestants/allergy meds which can worsen symptoms), may consider medical therapies including:
  - Alpha-blockers** (terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin): initial therapy; relax muscles near the prostate, max efficacy in 1 month; SE: headaches, low blood pressure, dizziness, or feeling lightheaded or tired.
  - 5-alpha reductase inhibitors** (finasteride or dutasteride): inhibit testosterone to shrink prostate, max efficacy in 6-12 months; SE: decreased libido, problems with erection or ejaculation. Decreases PSA, double result to trend.
  - PDE-5 inhibitors** (tadalafil): preferred drug for men who experience erectile dysfunction. SE: headache and back pain.
  - Combination Rx (alpha blocker + 5-alpha reductase inhibitor):** consider addition of 5ARI if prostate >30cc, combination may be more effective for symptom reduction and decreasing risk of overall BPH progression than either agent alone
  - Saw Palmetto (plant extract):** limited data to support efficacy over placebo but anecdotally may help improve sxs
- Procedures:** **Transurethral resection of prostate (TURP):** Most common. Thin tube is inserted in the urethra and cuts away pieces of prostate causing blockage (often does not require complete removal of prostate). Additional minimally invasive procedures include transurethral needle ablation (TUNA) and transurethral microwave thermotherapy (TUMT).

Possible complications: reverse flow of semen (empties into bladder and not out of penis) – does not affect ability to orgasm but can affect fertility; less common side effects: urinary incontinence, inability to initiate or sustain erection.

## ERECTILE DYSFUNCTION ([HPyR 2022 Aug 20;10\(3\): 37533](#))

- Sxs:** inability to consistently attain or maintain erections rigid enough or sufficient quality for sexual intercourse. Affects ~22% men 60-69 and 30% men >69.
- DDx:** distinguish from decreased libido 2/2 testosterone deficiency (see *Endocrine section*), depression, use of prescription/illicit drugs; ejaculatory dysfunction (e.g., premature or retrograde ejaculation); anatomic anomalies (e.g., Peyronie's Dz)
- Risk Factors:** CVD, HL, HTN, obesity, smoking, sleep disorders (OSA, RLS), hyperglycemia, DM; should additionally perform complete medication review as many commonly prescribed medications can cause ED ([PCOI, Table 2](#))
- Rx:** lifestyle modifications for pts with above risk factors (e.g., tobacco cessation, EtOH reduction) first line, may consider pharm rx:

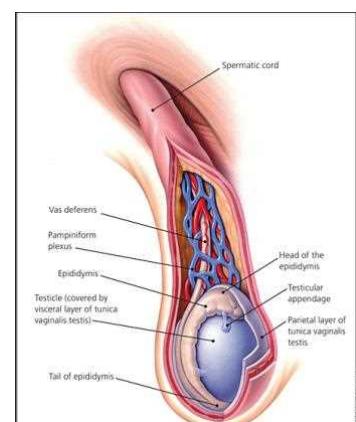
Medication	Dosing	Side Effects
Sildenafil (Viagra)	<ul style="list-style-type: none"> <li>Start: 50 mg, dose range 25-100 mg prn according to side effects.</li> <li>Take 1 hour prior to sex on empty stomach, effective for 4 hours.</li> </ul>	Rarely can cause blue-tinged vision.
Vardenafil (Levitra)	<ul style="list-style-type: none"> <li>Start: 10 mg, dose range 2.5-20 mg.</li> <li>Take 1 hour prior to sex, effective for 4 hours. Taking with fatty meals may cause reduced efficacy.</li> </ul>	Can cause QTc prolongation (avoid in congenital QT prolongation or with additional prolonging meds)
Tadalafil (Cialis)	<ul style="list-style-type: none"> <li>Start: 10 mg, dose range 5-20 mg.</li> <li>Take 30 minutes prior to sex, peaks at 2 hours, effective for 24-36 hours.</li> </ul>	More tolerable than other PDE-5 inhibitors with alpha-blocker tamsulosin 0.4 mg. Myalgias in 15% of users.
Avanafil (Stendra)	<ul style="list-style-type: none"> <li>Start: 100 mg, dose range 50-200 mg.</li> <li>Take 15-30 minutes prior to sex with or without food.</li> </ul>	Fastest onset. Limited side-effect profile.

**When to refer:** urology referral for adolescents/YA with primary ED (never been able to achieve erection); failure of initial first-line oral rx; contraindication to PDE-5 inhibitor therapy; other specialized testing warranted (e.g. penile vascular test, nocturnal penile tumescence)

## SCROTAL/TESTICULAR MASSES ([Am Fam Physician 2014; 89:723](#))

- Scrotal masses common presentation in primary care – scrotal pain ~1% of all ED visits.
- Normal exam: firm but not hard testes, nearly equal in size, smooth/ovoid, normal testicle length ~4-5 cm after puberty, epididymis is posterolateral to testicle, vas deferens exits via tail of epididymis and joins vascular pedicle of testicle to form spermatic cord.
- DDx:** helpful to begin assessment by distinguishing **painful vs painless**:
- Painful:** torsion (acute, N/V, abnormal cremasteric reflex, blue dot sign, CRP<24) vs epididymitis/orchitis (most common, +/- fever and dysuria, erythema, CRP>24) vs hematocoele/testicular rupture (rare, associated with trauma)
- Mixed pain/painless:** testicular cancer (males 15-34, firm unilateral nodule, hx of cryptorchidism in childhood or Klinefelter syndrome, test a-fetoprotein, b-HCG, LDH) vs hernia (painful with strangulation, test via Valsalva)
- Painless:** hydrocele (transillumination w/ pen light) vs varicocele (bag of worms, 15% of males affected, typically occurs in adolescence)

**Imaging/labs:** Ultrasonography is best to distinguish above ddx coupled with inflammatory vs ca markers as above if high index of suspicion.



## INSOMNIA

35-50% of population; chronic insomnia **>3mo.** difficulty initiating or maintaining sleep and compromised daytime function (UTD)

- **Hx:** evaluate chronicity, stressors, effect on fxn/mood, # awakenings and triggers, sleep hygiene; meds, PMH, sleep log for 1w
- **Ddx: Medical:** r/o mood disorder, pain, primary medical condition (e.g., pulm: COPD, asthma; CV: CHF; GI: GERD; GU: nocturia), SUDs, medications (e.g., stimulants, steroids, BBs, SSRIs, OCPs, opioids)
  - **Primary sleep d/o:** insufficient sleep syndrome (<7-8h allotted to sleep), psychophysiological (inability to sleep due to stress or anxiety about sleep), paradoxical (no e/o sleep d/o), RLS, Periodic Limb Movements of Sleep (PLMS), OSA, idiopathic (starting in childhood), circadian rhythm disorder (delayed sleep phase; advanced sleep phase-common elderly)
- **Tx:** **Sleep hygiene:** regular sleep schedule 7d/wk, exercise, if lying in bed awake get up till sleepy, reduce/eliminate caffeine/EtOH/nicotine, quiet/dark BR, elim bright lights/screens in pm; CBT-I (first line with strong evidence, hard to access), ([J Clin Sleep Med 2021;2:263](#)). **Meds:** scant evidence on safety/efficacy but often tried: low dose melatonin, trazodone (UTD); (WEAK evidence): sleep maintenance (DORA, doxepin), sleep onset (ramelteon, zaleplon, triazolam), both (eszopiclone, zolpidem, zaleplon, temazepam). Goal is Rx hypnotics for <4w only and careful risk/benefit for BZDR agents ([J Clin Sleep Med 2017;13:307](#)); treat mental health disorders

## SLEEP APNEA

Obstructive (upper airway occlusion) and/or central (↓ resp drive). OSA affects ~20% of adults ([JAMA 2020;14:389, PCOI](#))

- **Presentation:** daytime somnolence (use [Epworth Sleepiness Scale](#)), morning HA, witnessed apnea/gasping, snoring (Sn > Sp), depression, nocturia, pHTN; RF: obesity, anatomy, incr age, ♂, post-menopausal, EtOH, FHx, CHF. Screen for OSA w/ [STOP-BANG](#) (Sn 85%)
- **Dx: sleep study in-lab** (polysomnography (PSG); gold standard) vs **at home** cannot detect other sleep d/o or central apnea); both quantify apnea-hypopnea index (AHI) = sum of events/h (mild 5-15, mod 16-30, severe >30). Often found in inpatients, but PSG is o/p only. Also key is minimum O<sub>2</sub> Sat and percent of time below 90%.
- **Tx: behavioral:** weight loss, avoid ETOH/sedatives, position (avoid supine sleep, elevate HOB); **Positive Airway Pressure:** CPAP, BiPAP, ASV (for central, risky in CHF), APAP (most common, auto adjusts PAP); **other:** oral appliance (dentist referral), surgery, modafinil (for daytime sleepiness refractory to CPAP). Managed by PCP (HST then APAP), Sleep ENT (PAP, surgery, HGNS), Sleep Neurology (PAP, meds), or Pulmonary (pHTN). Important to identify preoperatively ([JAMA 2019;321:18:1788](#)).

## OBESITY HYPOVENTILATION SYNDROME (OHS)

- **Presentation:** **awake** alveolar hypoventilation not attributed to other conditions (dx of exclusion: r/o alt etiologies of hypercapnia and hypoventilation), in an obese individual ([AJRCCM 2019;200:3:e6](#))
  - RF: obesity (BMI>30) esp severe (BMI≥40, Class III), central obesity, severe OSA
- **DDx:** COPD, ILD, neuromuscular disorders, chest wall disorders, hypothyroidism, chronic sedative use
- **Dx:** VBG CO<sub>2</sub>>27, PaCO<sub>2</sub>>45, PaO<sub>2</sub><70; also BMP, CBC (polycythemia may be associated, monitor response to rx), TSH, PFTs (to exclude other causes – nml does not exclude OHS), CXR, PSG (identify sleep d/o breathing)
- **Tx:** BiPAP and weight loss. Assess for complications (PHtn, HTN, CHF, insulin resistance)

## RESTLESS LEG SYNDROME (RLS)

- **Presentation:** URGE: Urge to move legs, Rest induces symptoms, Getting active brings relief, Evening worsens sxs ([PCOI](#))
- **Common triggers:** caffeine, nicotine, ETOH, dopamine antagonists, most antidepressants, antihistamines
- **Assoc conditions:** iron deficiency (EGD/Colo!), CKD, pregnancy, tremor, Parkinson's, MS, movement disorders, OSA, w/d
- **Dx:** Clinical (PSG if unsure, PLMD), Fe/TIBC/Ferritin/CBC, BMP; DDx: MS, akathisia, myalgia, PMR/myositis, neuropathy, stasis/edema, PVD, arthritis, nocturnal leg cramps, positional discomfort, habitual foot tapping
- **Tx:** stop trigger meds, treat OSAS, iron supplement to ferritin >75; **DA agonists** (take 1-1.5h before trigger or qhs) - pramipexole, ropinirole, carbidopa/levodopa (<3x/w, high risk rebound), rotigotine patch; **a-2-d Ca channel ligand:** pregabalin, gabapentin; comorbidities may guide Rx (PCOI); last choice opiates (BZD no data), generally refer instead.

## OTHER SLEEP DISORDER

- **Narcolepsy:** chronic daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis (1/3 pts have all three symptoms so consider narcolepsy even if only chronic daytime sleepiness) ([NEJM 2015;373:2654](#)); PSG (exclude alternative causes) and Multiple Sleep Latency Test (MSLT), specialty managed. Basics: good hygiene, avoid BZD, Opiates, Antipsychotics, EtOH, Caffeine, Alpha1Antag.
- **Parasomnias:** complex movements and behaviors during sleep. Associated with NREM (sleepwalking, confusional arousal, sleep terrors, sleep related eating disorder), associated with REM (nightmare disorder, REM sleep behavior disorder), or other ([AJM 2019; 132:292](#)). Initial Rx improve sleep hygiene (EtOH, stress, sleep deprivation, Rx OSAS) and assess safety.

# Primary Care

# HEENT Concerns

## CHRONIC COUGH (AFP 2017;96:575; NEJM 2016;375:1544)

- Time course: acute ( $\leq 3w$ ) vs. subacute (3-8w) vs. chronic ( $>8w$ )
- Common causes: upper airway cough syndrome (UACS), asthma, GERD; these three account for 90% (18-62% pts have combo)
- General approach:
  - 1) History (smoking, URI, ACEi use, GERD sx); remove possible offending agent
  - 2) Consider CXR if cough  $>8$  weeks, especially if ↓ suspicion for UACS/asthma/GERD
  - 3) Start empiric tx for UACS/asthma/GERD sequentially until resolution → tx should be added to initial regimen
  - 4) Consider PFTs, esophageal pH monitoring, chest CT, sputum tests, cardiac studies if sx persist despite treatment of usual causes

Etiology	Characteristics	Treatment
Upper Airway Cough Syndrome (UACS)	Formerly post-nasal drip syndrome. Most common cause of subacute/chronic cough. Cough may be only sx. Exam: throat/nose may reveal cobblestoning. Common causes: allergic/non-allergic rhinitis, sinusitis	Avoid environmental triggers of allergic rhinitis. Steroid or antihistamine nasal spray, oral antihistamine/ decongestants, and saline nasal rinse for symptom relief. Improve in wks- 2 mos
Asthma	Typically p/w episodic wheezing & dyspnea. Cough variant asthma p/w only cough. Pt may have h/o atopy. Exam: ± nasal polyps. Need spirometry w/ bronchodilator response & bronchoprovocation (methacholine challenge) for dx	PRN bronchodilators ± inhaled corticosteroids. Some pts may use only seasonally. See Asthma for stepwise therapy
GERD	30-40% of chronic cough. Epigastric burning sensation, sour taste in mouth (although sx absent in $>40\%$ of patients)	Lifestyle modifications, moderate dose PPI/H2 blocker. Consider <i>H. pylori</i> testing
Respiratory tract infection	H/o recent viral illness. 2/2 postnasal drip/UACS or direct effect of virus on bronchial reactivity/cough receptors. Pts have been shown to experience transient bronchial hyperreactivity as well	UACS tx as above. 2 <sup>nd</sup> gen (cetirizine) or 3 <sup>rd</sup> gen (fexofenadine) antihistamine. If bronchial hyperreactivity, tx w/ usual asthma care
ACE Inhibitor	Produces cough in 3-20% of pts. 2/2 ACEi-mediated increase in bradykinin. Sx can occur 1w to 6mo after starting	Withdraw ACEi (resolves within 1-4w), change to ARB (not associated with cough)

**Other causes:** post-infxn (self-limited; can last 3+ months, treat sx), COPD, OSA, nonasthmatic eosinophilic bronchitis, chemical irritant (e.g., cigarette smoke), laryngopharyngeal bronchitis, psychogenic/habitual cough, bronchiectasis, CA, TB, sarcoid

## RHINOSINUSITIS (Otolaryngol Head Neck Surg 2015;152:598; NEJM 2016;375:962; Clin Infect Dis. 2012; 54(8):e72)

- Time course: acute (<1mo) vs. subacute (1-3mo) vs. chronic ( $>3mo$ ); recurrent (4 or more annual episodes)
- Dx: rhinorrhea (viral=clear, bact=purulent) + nasal obstruction or facial pressure/pain/fullness. A/w anosmia, ear fullness, cough, HA
- Acute rhinosinusitis is infectious while chronic is inflammatory (atopy, asthma, granulomatous disease, immunodeficiency, CF)

Etiology	Time Frame	Treatment
Viral: most common cause	7-10d	Symptom control, oral decongestant
Bacterial: only 0.5-2% of acute rhinosinusitis. <i>S. pneumo</i> (41%), <i>H. flu</i> (35%)	>10d, or worsening w/in 10d after initial improvement	Watchful waiting in pts w/ follow-up vs. amox-clav 875mg BID** or doxy 100mg BID x5-7d
Fungal: mucor (invasive) in DM, immunocompromised	Acute (invasive) to more chronic ( $>3mo$ )	Surgical removal of fungal mucin or "fungal ball" (mycetoma). ENT emergency if invasive (destruction of sinus, erosion into orbit or brain)

\*\* Higher dose Augmentin (2g BID or 90 mg/kg/d BID) in pts w/ RFs for resistance: regional resistance pattern, age 65+, hospitalized in last 5d, abx use in last month, immunocompromised, DM/cardiac/renal/hepatic disease, severe infxn (fever  $>102F$ , suppurative complication)

- Chronic rhinosinusitis: confirm diagnosis w/ CT or endoscopy; treatment varies by presence or absence of nasal polyps
  - No polyps → trial saline irrigation/intranasal steroid
  - + polyps → add short course of PO steroid ± ASA desens if concern for ASA-exacerbated respiratory disease
- Complications: meningitis, periorbital/orbital cellulitis (pain, edema, proptosis, painful eye movement, diplopia), subperiosteal/intracranial/epidural abscess, osteomyelitis of the sinus bones, septic cavernous sinus thrombosis
- Alarm symptoms: persistent fevers  $>102F$ ; periorbital edema, inflammation, or erythema; CN palsies; abnormal extraocular movements; proptosis; vision changes (diplopia, impaired vision); severe HA; AMS; meningeal signs

## PHARYNGITIS (JAMA 2012;308:1307; NEJM 2011;364:648; CID 2012;55:e86)

- Usually viral (suspect if +conjunctivitis, coryza, cough, diarrhea, hoarseness, discrete ulcerative stomatitis, viral exanthema)
  - Only 5-15% of adult sore throat visits are Group A Strep (GAS)
- Exclude dangerous etiologies: epiglottitis, peritonsillar abscesses, infxn in submandibular or retropharyngeal space, acute HIV
- Identify & treat GAS to ↓ risk of suppurative complications (peritonsillar abscess, cervical lymphadenitis, mastoiditis), prevent rheumatic fever (lower risk in adults), ↓ transmission, & improve sx. ASO titers useful only in dx of non-suppurative sequelae of GAS
  - **Centor Criteria:** 1 point for each - tonsillar exudates, tender ant. cervical LAD, fever, Ø cough; (-1pt if age  $\geq 45$ )
    - 0-2: no testing, treat sx. 3-4: send Rapid Strep antigen detection test (Sn 70-90%, Sp 95%) ± throat Cx (if neg rapid but ↑ clinical suspicion; not indicated for routine use in adults w/ neg rapid)
  - Tx: PO penicillin V 250mg QID vs 500mg BID x10d; amoxicillin 500mg BID x10d; IM benzathine penicillin G 1.2milliU x1
    - PCN-allergic: cephalaxin 500mg BID x10d
      - β-lactam sensitivity: clindamycin 300mg TID x10d; azithromycin 500mg QD x1d, then 250mg QD x4d
- Symptomatic tx: OTC lozenges (e.g. Sucrets, Capacol), throat sprays, NSAIDs/Tylenol for pain relief. No PO steroids
- Follow up: if no improvement in sx in 5-7 days, evaluate for other infectious causes (e.g., mono, HIV, GC/chlamydia) or suppurative complications such as tonsillopharyngeal cellulitis, abscess, or acute otitis media

# Primary Care

# HEENT Concerns

## EYE

**General Evaluation:** see *Ophthalmology*

- Initial eye exam: visual acuity (Snellen chart, w/ glasses if worn), pupils (reactivity, APD), confrontational visual fields, EOM, intraocular pressure (palpate for firmness), color vision ([Ishihara cards](#))
- Red Flags (urgent ophtho eval):** severe pain, HA/nausea, photophobia, severely decreased vision, abnormal pupil exam, corneal opacities, chemical injury, recent eye surgery or trauma, double vision, new onset flashes or floaters

## Vision Loss

- Acute, Painless (ED):** GCA; non-arteritic ischemic optic neuropathy (~60y, +APD); central retinal artery occlusion (vasculopathy, +APD, ± amaurosis fugax); central retinal vein occlusion (DM, HTN, hypercoag, glaucoma, OCPs, hyperviscosity, ± RAPD); vitreous hemorrhage (DM, retinal detachment/tear); retinal detachment (flashes of light, floaters, ± abnl red reflex); pseudosudden vision loss (gradual monocular loss misperceived as sudden if other eye occluded)
- Acute, Painful (ophtho w/in 24h):** optic neuritis (unilateral, <50y, blurry vision, flashes of light, +APD, pain worse w/ eye movt); acute closed-angle glaucoma (deep brow ache, ± n/v, halos around lights)
- Gradual, Painless (routine referral):** refractive error, cataracts (glare, halos, trouble night driving), open-angle glaucoma (RF: age, FHx, AA/Hispanic), diabetic retinopathy (c/b macular edema, vitreous hemorrhage, macular ischemia, tractional retinal detachment), age-related macular degeneration (central, RF: tobacco, poor diet, age, FHx), meds, idiopathic intracranial HTN (RF: ♀, obesity, steroids, OCPs, high-dose VitA, tetracyclines), mild amblyopia

**Red Eye** ([AFP 2010;81:137](#)): for tx see *Ophthalmology*

- Painless:** subconjunctival hemorrhage (unilateral, no vision Δ), episcleritis (painless w/o vision Δ or discharge, unilateral focal erythema, self-limited), dry eye syndrome (b/l itching, burning, photophobia, foreign body sensation, diffuse hyperemia), blepharitis/Meibomian gland dysfunction (b/l lid margin burning, itching, AM crusting)
- Painful:** conjunctivitis (itching, burning, FB sensation), keratitis (photophobia, tearing, hyperemia; 2/2 corneal ulcer or VZV/HSV), severe tear deficiency (Sjogren's, GVHD), iritis/uveitis (unilateral, photophobia, tearing, sluggish pupils; autoimmune), scleritis (HA, boggy red/pink sclera, tender globe, pain with EOM, no vision Δ), endophthalmitis (floaters, vision Δ, fixed dilated pupil, hypopyon; c/f fungemia), acute angle closure glaucoma (unilateral, HA, halos, n/v, vision Δ, fixed dilated pupil, globe firmness)
- Swollen eyelid** ([AFP 2015;92:106](#)): hordeolum = stye (tender nodule 2/2 occluded Meibomian gland), chalazion (painless nodule 2/2 chronic granulomas), contact dermatitis (caution w/ topical steroids), preseptal or orbital cellulitis (see *Orbital and Preseptal Cellulitis*)

## Conjunctivitis

- ([JAMA 2013;310:1721](#)):
- Viral > bacterial. Very contagious: strict hand hygiene, avoid contacts until sx resolves
  - Dx: PCR, GS, or Cx rarely needed – consider if severe purulence, refractory to tx, recurrent, immunocompromised, or c/f GC/CT
  - Avoid contact lenses, topical corticosteroids, OTC vasoconstrictors (rebound hyperemia)

Etiology	Presentation	Dx	Tx
Viral (most common)	<u>History:</u> sick contact, URI sx, watery d/c, gritty sensation, itching. <u>Exam:</u> intense hyperemia, ± periocular swelling, preauricular LAD	Typically adenovirus	Cool compresses, artificial tears. If c/f HSV/VZV: topical/PO tx + ophtho
Bacterial	<u>History:</u> mucopurulent d/c, pain/stinging. <u>Exam:</u> crusting, intense hyperemia, LAD rare	Typically <i>S. pneumo</i> , <i>S. aureus</i> , or <i>H. flu</i> ; consider GC/CT if RF	Erythromycin ointment 0.5% QID x7d (mild) or Polytrim 1-2 drops QID x7d (mod-severe, ↓ time to recovery). GC: PO abx + ophtho
Allergic	<u>History:</u> intense itching, painless tearing, hx atopy, allergic rhinitis. <u>Exam:</u> bilateral, mild hyperemia	Chronic or seasonal	Avoid allergens. Cool compresses, artificial tears. OTC anti-histamine/mast-cell stabilizer drops (e.g., ketotifen BID) ± PO anti-H1

## EAR

### Ear Pain

- Primary** (otitis externa/media, foreign body, Eustachian tube dysfunction, barotrauma, cellulitis, cholesteatoma, mastoiditis, Ramsay Hunt Syndrome 2/2 VZV) vs **Secondary** (TMJ, Bell's Palsy, sinusitis, dental work, GERD, tumor, GCA, MI, thoracic aneurysm)
- Red Flags:** signs of malignant otitis externa (HA/pain out of proportion to exam, fever, immunosuppressed, granulation tissue in floor of ear canal) or otitis media spread (mastoid pain/swelling, bloody otorrhea, facial weakness, vertigo, nystagmus, photophobia)

Etiology	Presentation	Dx	Tx
Otitis Externa	<u>History:</u> otalgia, itching. DM, water exposure, cerumen. <u>Exam:</u> tragus/pinna pain, ear canal edema/erythema, ± otorrhea/LAD/TM perf	Typically <i>PsA</i> or <i>S. aureus</i> . Assess for other skin conditions	Depends on if TM is intact and severity. <u>Topical:</u> acetic acid, steroid, abx (FQ) oto-drops ( <a href="#">UTD algorithm</a> )
Otitis Media	<u>History:</u> recent URI, smoking, hx Eustachian tube dysfunction. <u>Exam:</u> TM bulging ± immobile w/ erythema, conductive hearing loss	Viral > bacterial ( <i>S. pneumo</i> , <i>H. flu</i> , <i>M. catarrhalis</i> )	If mild-mod, consider Rx if no improvement at 2-3d. Amox-clav BID x5-10d (or amox 500 TID). ENT if ruptured TM does not close in 6w

**Tinnitus:** false perception of sound in the absence of acoustic stimulus ([NEJM 2018;378:1224](#); [AFP 2014;89:106](#))

- History: dizziness/vertigo (consider Meniere's), hearing loss, laterality (c/f schwannoma), meds (ASA, loops, abx), trauma, CVA, HA, depression/anxiety. Red flags: persistent + pulsatile, unilateral + hearing loss, vertigo, focal neuro deficits – consider audiology referral, imaging w/ CTA or MRA/MRV
- Tx: r/o underlying etiology. 20-50% have resolution spontaneously. If bothersome: CBT, sound therapy, tinnitus retraining therapy

**Hearing Loss:** RF - age, ♂, Caucasian, HTN, DM, CKD, immunosuppressed

- Conductive (mechanical):** cerumen impaction, otitis externa/media, otosclerosis, ruptured TM, cholesteatoma (middle ear cyst)
- Sensorineural (neuro):** presbycusis (age-related, gradual, symmetric, high frequency), noise-induced, Meniere's (asymmetric, +tinnitus, +vertigo), sudden sensorineural (acute, asymmetric, +tinnitus, **urgent eval**), barotrauma, tumor, meds, infxn

# Primary Care

# Nodules

## ADRENAL NODULES (>1 CM) ([Endocr Rev 2020;41:775](#))

- Is it malignant? (<5% 1° carcinoma, <2.5% mets): high-risk imaging findings: diameter >4 cm (93% Sn for adrenocortical CA), >10 HU on CT, heterogeneous, hypervascularity, irregular shape, calcification, ↑ T2 signal on MRI, delayed contrast washout
- Is it functionally active? (10-15%): exam & lab testing for all nodules >1cm (unless obvious myelolipoma) to r/o pheo & Cushing's syndrome (see table). Also test for hyperaldo if HTN, hypokalemia. Only test for production of excess sex hormones if clinical stigmata. AVOID testing inpatients due to high false + rates

Diagnosis	Suggestive Clinical Features	Laboratory Tests
Cushing's syndrome (~6-10%)	<ul style="list-style-type: none"> <li>HTN, metabolic syndrome, CVD, central obesity, prox muscle weakness, facial plethora</li> <li>Glucose intolerance, DM</li> <li>Decreased, normal, or increased bone formation</li> </ul>	1mg o/n dex suppression test (DST): if + send 24h urine free cortisol, then confirmatory 8mg o/n DST
Pheochromocytoma (~3-5%)	<ul style="list-style-type: none"> <li>HTN (5-15% don't have), palpitations, HA, diaphoresis, tremors</li> <li>≥20 HU on unenhanced CT, vascularity, cystic/hemorrhagic changes</li> <li>Cardiomyopathy</li> <li>"Pheo crisis": HTN/HoTN, psych d/o, multiorgan failure, hyperthermia</li> </ul>	Plasma free (after 30m supine) or 24h urine fractionated metanephrenes & catecholamines (Sn 98%, Sp 98%)
Hyperaldosteronism (~1%)	<ul style="list-style-type: none"> <li>HTN, hypokalemia</li> <li>↑ risk stroke, CAD, afib, HF</li> <li>↑ mortality (compared to matched population with essential HTN)</li> </ul>	Plasma aldo & renin activity (correct hypoK and d/c aldo antagonists before testing). May need adrenal venous sampling
Hyperandrogenism	<ul style="list-style-type: none"> <li>♀: virilization, hirsutism, acne, irregular periods</li> <li>♂: decreased libido, testicular atrophy, gynecomastia</li> </ul>	DHEAS, total testosterone, 17-OHP

- Consider adrenalectomy: if ↑ risk characteristics, >4cm, malignant, or hormonally active; surgery after hormonal eval
- Consider FNA: cannot distinguish between benign cortical mass & 1° adrenal CA. Useful if c/f adrenal met from another primary without known metastatic disease (**only** after excluding pheo)
- Follow up: repeat CT in 12mo. Consider annual DHEAS/1mg DST x4-5y (unknown effectiveness, guidelines do not recommend). Adrenalectomy if nodule grows >1 cm in 1 year, reaches 4cm, or becomes functional

## THYROID NODULES ([Thyroid 2016;26:1](#); [Endocr Pract 2016;22:622](#))

- Is it malignant? ↑ risk: h/o irradiation to head/neck, +family hx, h/o thyroid cancer syndromes (i.e., MEN 2), age <30

Workup: Thyroid Ultrasound, TSH	
TSH normal or high	TSH low
↓	↓
r/o hypothyroid (FT4/TPO Ab)	FT4/T3, Thyroid radionuclide ( <sup>123</sup> I) scan
↓	↓
"Cold nodule"	"Hot nodule"
↓	↓
U/S-guided FNA if criteria met	Consider tx for hyperthyroidism if sx

- FNA: any nodule w/ extrathyroidal extension, extrusion through rim calcs, abnormal cervical LNs, adjacent to laryngeal nerve/trachea OR >1cm + solid/hypoechoic w/ irregular margins, microcalcs, rim calc, or taller than wide shape. No FNA for pure cystic nodules. ACR uses **TIRADS**
- Follow up (benign): based on U/S characteristics. If highly suspicious U/S findings, repeat US & FNA w/in 6-12mo. If low-moderate suspicious U/S findings, repeat U/S 12-24mo, consider FNA if >1-2cm change. Stop f/u after 2 neg FNAs

## INCIDENTAL PULMONARY NODULES (<3 CM) ([Radiology 2017;284:228](#); [Chest 2013;143:e93S](#); [Thorax 2015;70 Suppl 2:ii1](#))

NB: these guidelines are for **incidental findings** (see [Fleischner Society Guidelines](#)); recommendations for f/u of nodules found on LDCT for lung cancer screening are different as that population is high risk (see [Lung-RADS classification](#))

- Ddx: malignant (primary, met, carcinoid) or benign (majority; infectious granuloma, hamartoma, AVM, inflammatory)
- Is it malignant? Pt characteristics: ↑ risk w/ **h/o smoking**, emphysema, pulmonary fibrosis, extra-thoracic cancer, asbestos exposure, age. Nodule characteristics: density (part-solid/ground glass>solid), larger size, faster rate of growth (increase >2mm on repeat CT), borders (irregular/spiculated>smooth), location (upper>lower lobe)
- Is it benign? demonstrates fat (pulmonary hamartoma) or characteristic calcification pattern (granuloma, hamartoma) or stability on CT for a defined period (>2y for solid and >5y for subsolid nodules)
- Follow-up: tailored to patient and type of nodule. **Subsolid** (entirely ground glass): if <6 mm, no routine f/u. If >6 mm, CT at 6-12mo, then CT every 2y until 5y. **Part solid**: if <6mm, no routine f/u. If >6 mm, CT at 3-6mo, then annual CT for 5y if unchanged and solid component <6 mm. **Solid nodules**: see below
- At MGH, consider referral to the **Pulmonary Nodule Clinic**: refer in Epic or call x38728 for appointment

Nodule type	< 6 mm	6-8 mm	> 8 mm
<b>Single solid nodule</b>			
<b>Low risk</b>	No routine follow up	CT at 6-12mo, then cons. CT at 18-24mo	Cons. CT at 3mo, PET/CT, or tissue sampling
<b>High risk</b>	Optional CT at 12mo	CT at 6-12mo, then CT at 18-24mo	Cons. CT at 3mo, PET/CT, or tissue sampling
<b>Multiple solid nodules</b>			
<b>Low risk</b>	No routine follow up	CT at 3-6mo, then cons. CT at 18-24mo	CT at 3-6mo, then consider CT at 18-24mo
<b>High risk</b>	Optional CT at 12mo	CT at 3-6mo, then at 18-24mo	CT at 3-6mo, then at 18-24mo

# Primary Care

# Musculoskeletal Pain

## KNEE PAIN

- History:** trauma, acute vs chronic, association with activity, constitutional sx, swelling, stiffness, instability, popping or catching sensation, sensory/motor changes, BMI, orthopedic or rheumatologic hx. Have pt point to area of pain with one finger

Knee Exam		
Test	Maneuver	Positive in
<u>Lachman</u> (sim. to anterior drawer)	Pt supine with knee flexed to 20-30°. One hand on pt's femur, just above knee. Other hand on pt's tibia. Apply slight flexion and pull sharply towards your abdomen. If tibia feels less restrained, $\oplus$ test	ACL injury
<u>Posterior Drawer</u>	Pt supine with knee flexed, can stabilize foot by sitting on it. Place hands around tibia, apply pressure backward in place parallel to femur. If less restrained motion, $\oplus$ test	PCL injury
<u>McMurray</u>	One hand over medial joint line with knee fully flexed. Externally rotate foot/tibia, apply valgus stress, and gently flex/extend knee. If clicking around medial joint line, $\oplus$ test	Meniscal injury

Location	Traumatic	Related to Activity	Atraumatic
Anterior	Quadriceps or patellar injury	<b>Patellofemoral syndrome*</b> , Osgood-Schlatter, bursitis, quadriceps/patellar tendinopathy	RA, gout, pseudogout, septic joint
Lateral	Lateral meniscal tear, LCL injury	Iliotibial band syndrome	Lateral OA
Medial	Medial meniscal tear, MCL injury, tibial plateau fracture	Anserine bursitis	Medial OA, saphenous nerve entrapment
Popliteal	PCL injury	Popliteal artery entrapment, Baker cyst	Popliteal artery aneurysm, DVT

\*Most common etiology in patients <45 yo (pain with patellofemoral joint palpation and compression of patella against femur)

- XR imaging:** if trauma <1w, XR indications per [Ottawa Knee Rule](#) - Sn 98%, Sp 49% ([Annals 2004;140:121](#))
  - If eval of chronic OA, get weightbearing views of both knees; patellar view for patellar problems
- MRI imaging:** if suspecting fracture, infection, or internal derangement (e.g. ACL, meniscal tear in younger patients) or pain refractory to 4w conservative care. [Asymptomatic meniscal tears: 13% <45 yo, 36% >45 yo \(Clin Ortho Rel Res 1992;282:177\)](#)
- Tx:** all benefit from rest, ice, NSAIDs  $\pm$  APAP, compression, PT, wt loss. For mod-sev OA, young ACL tear, or any pain refractory to conservative tx, consider surgery. For bursitis, popliteal cyst, or IT band, consider steroid injection

## SHOULDER PAIN

- General approach:** r/o shoulder mimics, then rotator cuff pathology, then bursitis, impingement, OA or tendinopathy

Etiology	History Findings	Physical exam
Shoulder Mimics	Consider cervical/neck pain, biceps pathology, cardiac or GI radiation	
Rotator Cuff	- Acute = trauma - Chronic = age, acromial spurring, overuse - Tendinopathy, partial or full thickness tears - Pain & weakness, often with overhead arm use - Ortho referral often needed	- $\downarrow$ ROM. Painful arc, impingement - <b>Internal lag test:</b> bring dorsum of patient's hand against lumbar region of back. Take forearm and hand away from the back (~20°). Ask pt to maintain position while supporting elbow. $\oplus$ if not maintained - <b>External lag test:</b> externally rotate shoulder 90°, flex elbow 90°. Ask pt to maintain position. $\oplus$ if not maintained - <b>Drop arm:</b> abduct arm to 90°. $\oplus$ if cannot smoothly adduct shoulder to waist-level - <b>Neer:</b> pronate forearm (thumbs point backwards), bring shoulder to full forward flexion. $\oplus$ if pain - <b>Hawkins:</b> flex shoulder to 90°, flex elbow to 90°, and internally rotate the shoulder. $\oplus$ if pain - <b>Ext rotation</b> (teres minor, infraspin): flex elbow 90°, externally rotate shoulder against resistance. $\oplus$ if pain - <b>Empty can</b> (supraspin): flex shoulder to 90°, internally rotate forearm. $\oplus$ if pain w/ resistance of downward push
Subacromial Bursitis	- Referred pain to deltoid - Overuse, heavy lifting	- Pain w/ arc 60°-120° abduction $\pm$ impingement - $\oplus$ Neer & Hawkins
Glenohumeral OA/ Adhesive Capsulitis	- OA: aching, stiff; age >60 - Capsulitis: ↑ risk w/ DM, thyroid disease, immobilization; age 40-60	- OA: crepitus - Capsulitis: loss of active/passive ROM in all planes
AC Joint Pain	- Young: traumatic sprain, fall with separation - Older: AC evolves into OA & impingement	- Pain, tenderness, swelling over AC joint - $\oplus$ cross arm test

- Imaging:** none for bursitis. **XR** if h/o trauma c/f fracture or dislocation, gross deformity, exam concerning for OA, RTC tear or joint involvement. Get true AP of glenohumeral joint, axillary lateral, & "Y view" of AC joint w/ stress views for trauma. **MRI w/o contrast** in pts w/  $\oplus$  internal/external lag tests, r/o full thickness RTC tear, previous abnl XR, persistent pain despite 2-3mo of conservative tx
- Tx:** **conservative tx** w/ activity avoidance, NSAIDs, PT/home exercises  $\pm$  short-term steroid injections; **surgery** for refractory instability, labral/full RC tear, AC joint separation

# Primary Care

# Musculoskeletal Pain

## Low BACK PAIN

- Incidence/Prognosis: 84% lifetime acute back pain, 50% sciatica ([Mayo Clin Proc 2015;90:1699](#)); 75-90% improve over 4w
- Exam: palpation of midline & paraspinal muscles, ROM spine/hip, LE strength/reflexes (L4-5 = foot dorsiflex; L5-S1 = foot plantarflex, ankle reflex), rectal tone (if c/f cauda equina), SLR/crossed SLR (pain radiates below knee, often to heel, when straight leg raised while supine; crossed SLR is radicular pain in opposite leg, ↑Sp)

	Origin	Signs and Symptoms
<b>Nonspecific MSK (85%)</b>	Paraspinal muscles, ligaments, discs, facets	<u>Muscle spasm:</u> paraspinal muscle tenderness w/ acute onset, usually unilateral. <u>Disc:</u> young, ↑ w/ spine loading (i.e. sitting). <u>Facet:</u> >40 yo, ↑ w/ extension, ↓ w/ sitting
<b>Radicular/Spinal stenosis (7%)</b>	Disc herniation w/ nerve compression (90% L4-S1), spinal stenosis	<u>Sciatica</u> 95% Sn, 88% Sp for herniation: leg > back pain w/ dermatomal distribution of lancing/burning pain, SLR +. <u>Spinal stenosis</u> causes neurogenic claudication: leg pain worse with walking (esp downhill) better with sitting/leaning forward
<b>Specific spinal disorder (8%)</b>	Vertebrae, discs, endplates, SI joints, facet joints	<u>Compression fx:</u> older, trauma, osteopenia, steroids. <u>SI pain:</u> MVA/falls, rheum. <u>Inflammatory:</u> AM stiffness, night pain. <u>Cancer:</u> PMH, weight loss, night pain. <u>Infection:</u> fever, night sweats, IVDU, immunosuppression

- Imaging: **early MRI** or XR if **RED FLAGS** – focal severe/progressive neuro deficits, cauda equina sx (b/l weakness, urinary retention/incontinence, saddle anesthesia); trauma; c/f fracture, osteopenia risk (age >50 or <20, PMH, steroids); c/f CA or infxn
  - Otherwise, **defer imaging until after initial 4-6w tx** ([Annals 2007;147:478](#); [Choosing Wisely](#)) as herniation, disc bulging, DJD common findings ([Am J Neuroradiol 2015;36:811](#)). See [STarT Back Screening tool](#) for further guidance
- Possibly effective and lower-risk therapies
  - Avoid bed rest.** Explore social/psychological stressors, psych comorbidities, coping mechanisms
  - Non-pharmacologic:** acute: heat/cold, massage, acupuncture; chronic: yoga, CBT, mindfulness, rehab ([Annals 2017;166:514](#)); **PT & exercise** (demonstrated benefit in sciatica ([Annals 2021;174:8](#)), though not other acute LBP)
  - NSAIDs** (ibuprofen 400-800mg TID or naproxen 220-440mg BID) are first line for limited duration if no contraindication
  - Muscle relaxants:** can add limited supply for acute pain if NSAIDs alone ineffective ([JAMA 2015;314:1572](#))
  - Duloxetine and TCAs for chronic LBP:** second line after NSAIDs ([Annals 2017;166:480](#))
  - Epidural steroids** (Pain Med/PM&R): for radicular pain refractory to 6w tx - limited evidence, benefits likely limited, short-term
- Therapies with questionable evidence and/or higher risk of harm
  - Acetaminophen:** if NSAIDs contraindicated; but little e/o effectiveness ([Lancet 2014;384:1586](#)). **Oral prednisone taper** for acute sciatica: inconclusive evidence ([Annals 2017;166:480](#)). **Gabapentin, pregabalin:** option for sciatica though efficacy inconclusive ([NEJM 2017;376:1111](#)). **Opioids** (see below): limited evidence of effectiveness & ↑ risk of harm ([JAMA 2018;319:872](#)). **Surgery:** short-term sx relief in disc herniation w/o clear long-term benefit, ↑ side effects in spinal stenosis w/o e/o improved fxn

## FOOT AND ANKLE PAIN

Etiology	History and Physical	Dx and Tx
<b>Ankle sprain</b>	- Trauma history - Pain/instability/swelling, bruising, focal tenderness over ligament (ATFL most common); squeeze test to r/o syndesmotic sprain	- Imaging: use <a href="#">Ottawa Ankle Rule</a> - Ice, elevation, rest followed by exercise (consider PT) - Grade I (stretch, no tear): elastic wrap; grade II (partial tear, swelling, bruising): aircast or other splint; grade III (complete tear, unstable): casting, sports med/ortho c/s
<b>Achilles tendinopathy</b>	- Overuse or change in activity common - Pain & thickening at insertion or 2-6cm proximally; calf squeeze to r/o complete rupture	- MRI only if uncertain - Rest, ice, tendon support, PT - Surgical c/s for complete tear
<b>Stress fracture</b>	- Overuse; more common in ♀ esp if amenorrheic, underwt (rel caloric deficiency/overtaining syndrome) - Insidious onset of pain after exercising, ± focal tenderness on exam (tibia > tarsal > metatarsal)	- XR insensitive esp early in course; if ⊖ MRI may be req - Rest/non-wt-bearing 2-6w - Consider ortho c/s if high risk for nonunion (anterior tibia, navicular, talus, 1 <sup>st</sup> or 5 <sup>th</sup> metatarsal)
<b>Plantar fascitis</b>	- Assoc w/ overuse, pes planus, overweight - Sharp anteromedial heel pain with activity after rest	- If uncertain, US may show thickening - Ice, stretching, NSAIDs, heel cups/OTC orthotics

Ddx: tarsal tunnel, **Charcot foot** (>40yo, obesity/neuropathy, swelling w/ minimal pain), hallux valgus ("bunion"), hallux rigidus (OA of 1<sup>st</sup> MTP), interdigital neuroma, non-Achilles tendinopathy, arthritis, gout/CPPD, derm (corns, calluses, warts, paronychia)

## LONG-TERM OPIOIDS FOR MUSCULOSKELETAL PAIN

- Before prescribing longer-term opioids:** (NB limited evidence; high risks of hyperalgesia, tolerance, dependence, addiction)
  - Exhaust non-opioid options. Avoid BDZ, hypnotics. Screen for OSA, SUD, mental health. Stress **complete pain relief is unlikely**. Set functional goals. Perform **risk assessment** ([SOAPP-R](#)). **Check PDMP**. Obtain prior records, speak to prior prescribers
  - Pain agreement** ([PCOI form](#)) is required. MA law: *Must check PDMP and limit 7 days for initial opioid prescription*. Discuss **6-8w initial trial & safe use, storage, & disposal of opioids**. Educate that random UTox and pill counts are for pt safety. Agree that **single prescriber will Rx**. Rx on 28d cycle ending on weekday to facilitate refills. **Rx naloxone**
- Follow-up for longer-term opioids:** See at least q1-3mo to review pain/function, side effects, adherence
  - Discontinue opioids if no significant benefit at 6-8w:** significant side effects, risk > benefit, non-adherence
  - Caution prescribing >50mg/d morphine equivalents (MME), avoid >90 MME (c/s pain)**
  - Early refill requests should trigger appointment to assess reason, obtain tox screen, discuss use

# Primary Care

# Immigrant & Refugee Health

## MEDICAL EXAMINATION (CDC)

**Interpreter Services:** In person - x66966, p27403 (M-F 7a-8p; S/Su 8a-6:30p) or via phone service [617-643-3344 Pin #1050]. Speak in short sentences & make sure to address the patient (not interpreter) when speaking.

**History:** obtain prior medical records if possible

- SHx: country of origin, travel hx, transit countries, residence in refugee camps/detention centers, time living in US, family structure/hx of separation, food security, housing stability, home/neighborhood safety, education/literacy, occupational hx
- PMHx: chronic diseases (incl. pain), surgeries, cancer screens, ♀ OBGYN hx, sexual hx, meds (incl traditional/herbal remedies), smoke/toxin/lead exposures, tobacco/substance use (incl. those legal in country of origin; inform of legality differences in US)
- Mental health: screen for PTSD, anxiety, MDD (on 2<sup>nd</sup> visit to ↓re-traumatizing). RHS-15 is a consolidated screening tool.
- ROS: fever, wt loss, night sweats, respiratory concerns, diarrhea, abdominal discomfort, pruritis, skin rashes/lesions

**Physical Exam:** reassure patients this exam is for their health & not regulatory purposes

- Vision, dental, hearing, BMI, BP. Eval for murmurs, hepatosplenomegaly, LAD, skin lesions (rashes, trauma, nutrient deficiency)
- See PCOI for low-cost referral options for dental and eye care: → “Health Care Access”

**Vaccinations:** if no documentation (translation guide), assume not vaccinated (see *Health Screening & Maintenance*)

- Can check titers for MMR/VZV. Incomplete HBV vaccination may result in transiently elevated titers

**Screening and Labs:** (CDC regional profiles)

- Gen: CBC/diff (eos, anemia), UA (hematuria), BMP (glucose, renal dz), ♀ hCG, lead screen if preg. or lactating; age-appropriate screens (lipids, HIV, HCV, etc.)
- STIs (see STI): syphilis, HIV, GC/CT if ♀≤24+sexually active or ♀>24+RF
- HBV: if from high prevalence country
- TB: ask yearly about sx, recent travel, sick contacts; retest PRN (see *Tuberculosis*)
- Malaria: Rx if from Sub-Saharan Africa w/o pre-departure Rx or from endemic country w/sx (Rx resistance info [here](#)). If preg/breastfeeding, Dx first (do not Rx empirically). Obtain thick/thin smears or PCR (↑Sn if no sx)
- Intestinal/tissue invasive parasites: varies by country & pre-departure tx. See [CDC guideline](#). No empiric ivermectin if from [Loa loa-endemic country](#)
- Micronutrients (Fe, D, B12, etc): if malnutrition, anemia, h/o food insecurity

Infection*	Signs & Symptoms
Strongyloidiasis, filariasis, schistosomiasis	Peripheral eosinophilia
Schistosomiasis	Hematuria, ♀ infertility, chronic pelvic pain
Malaria, schistosomiasis	Splenomegaly
Mycetoma, onchocerciasis, other filarial diseases	Chronic rash or itching
Chagas disease	Esoph. dysmotility, HF, conduction dz
Neurocysticercosis	Seizures, CNS sx

## LEGAL CONSIDERATIONS (Boston-area [legal services](#), MGH Chelsea LINC referral if pt @ MGH Chelsea CHC )

- **Do NOT** document immigration status in EMR
- MassHealth eligibility is NOT contingent on immigration status. Refer all uninsured pts to [PFS, Multilingual videos](#) for pts on the ACA
- Know your Rights re: ICE: multilingual infographics from [Immigrant Defense Project](#) & [Immigrant Legal Resource Center](#)
- Asylum screening questions (yes/no answers sufficient; obtain only as much detail as necessary to refer for legal support; re-telling or re-living experiences can be re-traumatizing & asylum seekers will have to tell their whole story to lawyers/doctors in the future)
  - What led you to leave your home country?
  - Were you ever a victim of violence or (verbal, sexual, physical) abuse there?
  - If so, was it due to your religion, race, political beliefs, nationality, or particular social group (gender, sexual identity)?
  - If so, did you face violence from anyone working for the government, military, or police?
    - If yes → refer to legal organization above, [PAIR](#), or the MGH asylum clinic
- Resources on conducting asylum evaluations and working with asylum seekers
- Resources within Boston area: [Refugeography](#) (Google map of various food pantries, job training, ESL, social support services, etc.)
- Additional tips: **Travel**: undocumented pts will now be able to apply for driver's license (DL) in MA ([H4805](#)), however, DL will likely not meet [REAL ID](#) requirements for air travel (to start: 5/7/25) – risk being detained by CBP agents stationed at any US international airport if trying to fly; **Legal**: can support pt's petition for legal status by providing documentation re: medical need for legal status (coordinate w/legal team if pt/team desires); **Advocacy**: consider joining Asylum clinic and/or IHC groups

Immigration Statuses	Details
Lawful Permanent Resident (LPR)	Green card recipient; pathway to citizenship. Family can get green card through “family based” immigration
U-Visa, T-Visa VAWA	Eligible if victim of human trafficking (T) or victim of certain types of crime (U). Violence Against Women Act: eligible if abused by spouse, child, or parent who is LPR/citizen
Temporary Protected Status (TPS)	Short list of countries where conditions preclude safe return. Cannot be deported while country of origin listed
Cancellation of Removal	Based on exceptional hardship anticipated to self or LPR/citizen, spouse, parent, child if deported; ineligible with certain criminal convictions
Asylum	Well-founded fear of persecution based on race, religion, nationality, membership in social group, or political opinion. Application due w/in 1y of date of entry. If granted, may apply to spouse/children if they are in US
Refugee	Same legal standard as asylum, based on persecution or well-founded fear, but granted prior to arrival in US. Maximum set annually by President (no limit to asylum)
Medical Deferred Action	Temporary reprieve from deportation for immigrants facing life-threatening medical conditions & other humanitarian circumstances
Withholding of Removal	Asylum/CAT/Withholding all part of same application. No 1y rule. Ineligible with certain criminal convictions. No path to citizenship
CAT	Convention Against Torture: similar to Withholding, but still eligible with criminal convictions
Undocumented	Patients should seek legal counsel to check for options to apply for alternative statuses

# Primary Care

# Climate Change & Health

Climate Change Drivers ([NASA Global Climate Change](#)): Atmospheric CO<sub>2</sub> & other greenhouse gases 2/2 human activities

Principal Climate Effects ([USGCRP CSSR 2017](#); [IPCC AR6 2021](#)):

↑temp, ↑sea level, precipitation pattern changes, ocean acidification, extreme weather

		Mediators of Climate-Related Health Risks ( <a href="#">NEJM 2019;380:263</a> )				
Access to quality healthcare Age & sex Agricultural practices		Baseline air & water quality Baseline nutritional status Ecosystem & land use change	Geography Occupation Pre-existing health conditions	Poverty & housing Racism & discrimination Warning systems		
Exposure	Extreme heat	Poor air quality	Climate-sensitive infectious disease	Extreme weather	Imbalanced water quality and quantity	Food insecurity
Health Effects	- Early death - CVD/resp dz exacerbations - Heat stress nephropathy - Fluid/electrolyte disturbances - Suicide - Mental health effects - ↑risk congenital heart defects	<i>PM</i> 2.5 (particulates ≤2.5 µm diameter): - Early death - CV disease ( <a href="#">NEJM 2021;385:1881</a> ) - Worsened resp dz - Low birth wt Ozone: - Early death - ↑ED visits <i>Aeroallergens</i> : - Exacerbation of asthma/allergic dz	- ↑habitability for Ixodes ticks → expanded Lyme distribution - ↑vectorial capacity for Aedes spp mosquitos → ↑dengue & malaria - ↑waterborne dz (Vibrio, Leptospira, Shigella, Campylobacter)	- Tropical storms: direct injury, trauma, flooding - Wildfire: burns & traumatic injury, inhalational injury, produces PM2.5 (see left) and other pollutants that can spread internationally	- Drought: resp effects of dust inhalation - Water insecurity → ↓nutrition, ↓sanitation, ↑susceptibility to violence - Flooding: ↑allergenic molds, diarrheal diseases, toxic algal blooms	- ↓nutritional content of staple crops - ↓productivity of fisheries - Undernutrition, underweight, & stunting - ↑susceptibility of food to spoilage & pests
Secondary Impacts	- Desertification - Missed work, 2° economic impact - Power outages	- Missed school, workdays - ↑healthcare costs ( <a href="#">Health Aff 2020;39:2113</a> )	- ↑strain on public health systems for dz control - ↑abx resistance w/ ↑temp ( <a href="#">Nat Clim Change 2018;8:510</a> )	- ↑cost of disaster relief & recovery - Disrupted health care delivery	- ↓crop yields 2/2 precipitation Δ, salt water intrusion - Wildfire risk - Forced migration	- ↑frequency of conflict - ↑food prices, ↓purchasing power of vuln. populations

## TREATMENT

		Counsel Patients on Climate & Health Co-Benefits	
Patient-Centered Actions			
<ul style="list-style-type: none"> <li>Educate patients: help patients understand links between climate and health (<a href="#">Ann Intern Med 2021;174(3):417</a>), develop an extreme heat plan (<a href="#">CDC Guide</a>, <a href="#">Boston Guide</a>) &amp; disaster-preparedness (<a href="#">PlanetReady</a>, <a href="#">ClimateCrew</a>)</li> <li>Co-Benefits: actions that both improve health &amp; mitigate emissions that drive climate change. Examples: <ul style="list-style-type: none"> <li>↓Red meat consumption → improved CV/renal health, ↓emissions (in 2017, excess red meat consumption contributed to 990,000 deaths worldwide, &amp; emissions from beef were &gt;400kg CO<sub>2</sub>e/person)</li> <li>Active transportation → improved CV health, ↓transport-related pollution &amp; emissions (<a href="#">BMJ 2020;368:l6758</a>)</li> </ul> </li> </ul>			
Institutional Actions	Improve Health Care Delivery in a Changing Climate		
<ul style="list-style-type: none"> <li>Improve resilience: 2019 global survey of climate vulnerability revealed 67% of surveyed cities reported climate change would seriously compromise their health infrastructure (<a href="#">Lancet 2021;397:129</a>) <ul style="list-style-type: none"> <li><a href="#">U.S. Climate Resilience Toolkit</a>: best practices for US health care facilities to withstand climate impacts</li> </ul> </li> <li>Deliver climate-smart healthcare (<a href="#">NEJM 2021;385:2117</a>): US healthcare-associated pollution comprised ~8.5% domestic greenhouse gas emissions &amp; drove comparable disease as deaths from preventable medical errors (<a href="#">Health Aff 2020;39:2071</a>). <ul style="list-style-type: none"> <li><a href="#">Health Care Without Harm</a> &amp; <a href="#">Practice Greenhealth</a> (free membership for MGH residents): resources to improve resource stewardship, decarbonize energy sources, &amp; procure food &amp; materials sustainably</li> </ul> </li> </ul>			
Policy & Advocacy Actions	Example Advocacy Topics in Climate and Health		
<ul style="list-style-type: none"> <li><i>Paris Agreement</i>: limits warming to 2°C above pre-industrial levels, with further goal to limit to 1.5°C in recognition that 2°C would be catastrophic for certain populations (<a href="#">IPCC SR1.5 2019</a>). U.S. rejoined on January 20, 2021. At start of 2022, we are on track to exceed 2.7°C warming by 2100 (<a href="#">UNEP EGR 2021</a>)</li> <li><i>Equity is critical</i>: countries least responsible stand to suffer most (<a href="#">Health Aff 2020;39:2056</a>). Locally, Black and Latinx Americans inhale disproportionately more PM2.5 than is caused by their consumption ("pollution inequity") (<a href="#">PNAS 2019;116:6001</a>)</li> </ul>			

Read [NEJM 2019;380:209](#) & [ACP Toolkit](#) for further resources for physicians, patients, and policymakers; [PCOI page](#) for tips in primary care

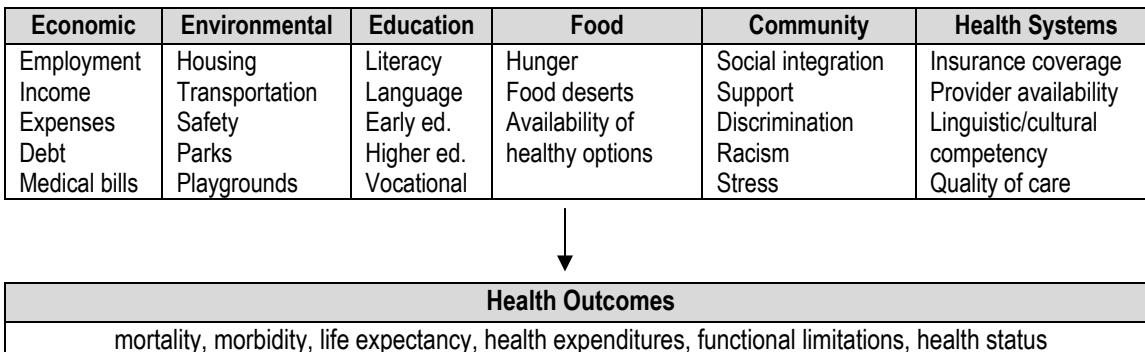
Shraddha R. Damaraju

# Primary Care

# Health Equity & Insurance

## SOCIAL DETERMINATES OF HEALTH ([AAFP EveryONE Project](#))

Accounts for 30-55% of health outcomes with up to 20-year gap in life expectancy between counties with lowest and highest life expectancy in the US. SDH primarily influence health outcomes through limiting opportunities to live a healthy lifestyle or chronic stress ([JAMA 2017; 117:1003](#)). Structural racism limits opportunities through discriminatory practices in labor, housing and educational systems with racism and stress being shown to affect both mental and physical health outcomes ([Lancet 2017; 389:1453](#)).



## STRATEGIES TO ADDRESSING HEALTH INEQUITY

- 1) Understand patient's community ([County Health Rankings and Roadmaps](#)); screen for SDOH (useful dot phrase: .SDOHSCREEN, if positive refer to MGH SDoH Services aka "Ambulatory Referral to MGH SDH")
- 2) Consciously address implicit bias ([Harvard Project Implicit](#)); reflect on gut reactions, ask if they are rooted in implicit bias
- 3) Address patient health literacy; utilize in-person interpreter services when available, schedule longer visits, employ teach back method, utilize dot phrase .MEDSS for a framework to optimize medication adherence.
- 4) Identify and utilize resources within your clinics to address SDOH; [AAFP Neighborhood Navigator, 211](#), and [FindHelp](#) can help identify local resources

## INSURANCE COVERAGE

- Open enrollment: limited time when one can buy a new insurance plan, varies by employer and insurance system; MassHealth ~Nov-Jan
- MassHealth: federal and state funded healthcare coverage, MA's interpretation of Medicaid and CHIP; can [apply online](#) (if age <65), by mail or fax, will take 45-90d for approval; must renew households annually
  - Basic eligibility requirements: MA resident, eligible citizenship/immigration status, valid SSN
    - Can apply for MassHealth Limited for patients who have an immigration status that keeps them from getting more services.
  - Several coverage options available with eligibility for age <65y determined by comorbidities and income, ranging from ≤133-300% federal poverty limit (FPL); age ≥65y eligible if income ≤100% FPL, more lenient for disabled seniors

# Consultants

# Calling Consults

## TIPS FOR CALLING CONSULTS

- To do BEFORE you call:
  - Place order in Epic for consult
  - Know your patient: review the H&P/chart and briefly see/examine the patient if you have not done so previously; recommend reviewing last clinic notes if applicable (Notes → Filters → Specialty); for all below, mention any outpatient providers
    - GI: melena/hematochezia, current/prior H/H, plts, coags, transfusions, past EGD/colo, vitals, IV access, NSAID/ASA use; for cirrhosis: any prior work-up, social history, complications, decompensation
    - Cards: recent and old ECG, telemetry, prior stress/echo/cath (know anatomy), dry weight, biomarkers, current cardiac meds
    - Renal: baseline Cr, CKD stage, on/off HD, dialysis access, electrolyte mgmt, current UOP, nephrotoxins
    - Onc: known cancers w/ stage/treatment history, clinical trial history, biopsy results (for new dx), current anticoagulants, special slide; if on immunotherapy, usually on SIC (Severe Immunotherapy Complications) service list at MGH
    - ID: current/past micro data, possible sources, current/prior abx (incl # of days), fever curve, hardware, travel, exposures
    - Pulm: imaging results, social hx, prior work-up (e.g., autoimmune), prior/current O2 requirements, PFTs
  - Know your question – Your senior should specify consult question in task list. If not there, ASK. It is always OK to clarify
- To do DURING the page/call: refer to order instructions in EPIC and phone directory when paging for service-specific instructions as some services prefer to call you rather than have you reach out first
  - Call as early in the day as possible (ideally before noon), find out how to page using the paging directory
    - At MGH: paging directory → find "On Call Directory"
  - In your page to consulting team, include: pt name, MRN, location, call back #, brief consult question +/- level of urgency
  - Avoid "curbside" questions unless official curbside consult service. If specific question about management, call a formal consult.
  - Tell the consultant a brief HPI, a clear explanation of the team's thinking, and a clear and specific question
- To do AFTER the call:
  - Invite the consultant to find you to relay their recommendations or tell them who will be covering for you

## CALLING EMERGENT CONSULTS

- Surgery: STAT = imminently life-threatening emergency (e.g. lost airway, hypotensive from hemorrhage); URGENT = high concern for urgent surgical question (e.g. acute abdomen, perforated bowel, etc.)
  - Page "Senior Resident on call" under Emergency Surgery/Trauma (Churchill) Team
- Psychiatry (e.g. pt actively trying to leave AMA w/ unclear capacity; security concerns, major behavioral issues)
  - 8am-6pm: p33061 (Emergency Consult Resident). If weekend/Holiday: p17911 (weekend rounding psychiatrist)
  - 6pm-8am: Call APS (6-2994) or page APS resident at 27792
- Toxicology ( ingestions/overdoses/exposures/interactions): call Poison Control Massachusetts (617-355-6607 or 800-222-1222).
- Cardiac Surgery: call "In-House fellow"

## CALLING SURGICAL CONSULTS AT MGH

- In the ED: ED surgery "pit team." They typically sit in Acute bay across from room #5
  - For patients in the Acute bay → pit senior (x44169; p13115)
  - For patients anywhere else in the ED → pit junior (x44187; p20491)
  - Once the patient is on the floor, page PGY1 on the consulting team (identified in the consult note)
- New surgery consult (floor or ICU): page the senior resident of the appropriate surgical service
  - If patient known to an MGH surgeon, consult senior resident on call for that team to discuss
  - If patient not known to a surgeon, do your best to elucidate the appropriate team based on disease state (Baker surgery teams). When in doubt, contact the senior resident of the most appropriate team to further triage
- Follow up on GENERAL surgery consults: page the PGY1 covering the consulted service
- Cardiac Surgery consult → if non-emergent (8:30am-5pm) place order and call referral coordinator 617-724-4833. Can page NP at 30010. All other times (5pm-8:30am, weekends) call "In-House fellow"
- Ortho consult → page "Floor resident" at 20296 under "Orthopedics" or if ED consult, page 22566
- Transplant Surgery consult → page "Intern" (6a-6p) or "House officer on call (6p-6a)" under "Transplant Surgery"

## CALLING OTHER SUBSPECIALTY CONSULTS

- ACT (Addiction Consult Team): place consult in Epic (no need to call), for EtOH or other substance use disorders, Suboxone, etc.
- AMS (Anticoagulation Management Service): for established pts: p30104, or click AMS icon in Epic to determine existing AMS RN. For discharge – place Epic consult; if urgent or questions, page Discharge Pathway Service: p30103
- Cardiology: non-urgent consults 7:30AM-4PM p25713 OR email [MGHcardiologyconsults@partners.org](mailto:MGHcardiologyconsults@partners.org) 24/7
- Chronic pain service for cancer pain, pain in addiction; for interventions (e.g., injections), patients often need to be able to travel to clinic from inpt side. Acute pain service for epidurals, periop pain.
- Diabetes nurse educator: service NP p20737; MD p14364
- ENT: page 22220. Backup/emergency number is 617-523-7900 (MEEI operator) and ask them to page ENT resident on call
- Optimum Care Committee ("OCC," Ethics): page ethics support pager: p32097 (Mon-Fri, 8am-4pm, except holidays)
- Ophtho: for all consults p21004. Backup/emergency number is 617-573-4063 (MEEI ED back desk). Determine whether patient can travel to MEEI for an exam and if ok to dilate prior to calling consult
- Psychiatry: for non-emergent floor consult: order psych consult in Epic
  - Weekday 8:30AM-4:30PM: call CL coordinators (6-2984). These consults will be seen within 24 hours.
  - Weekend or Holiday 8am-5pm: p17911 (weekend rounding psychiatrist)
- Transfusion reactions: page blood bank resident at 21829

# Consultants

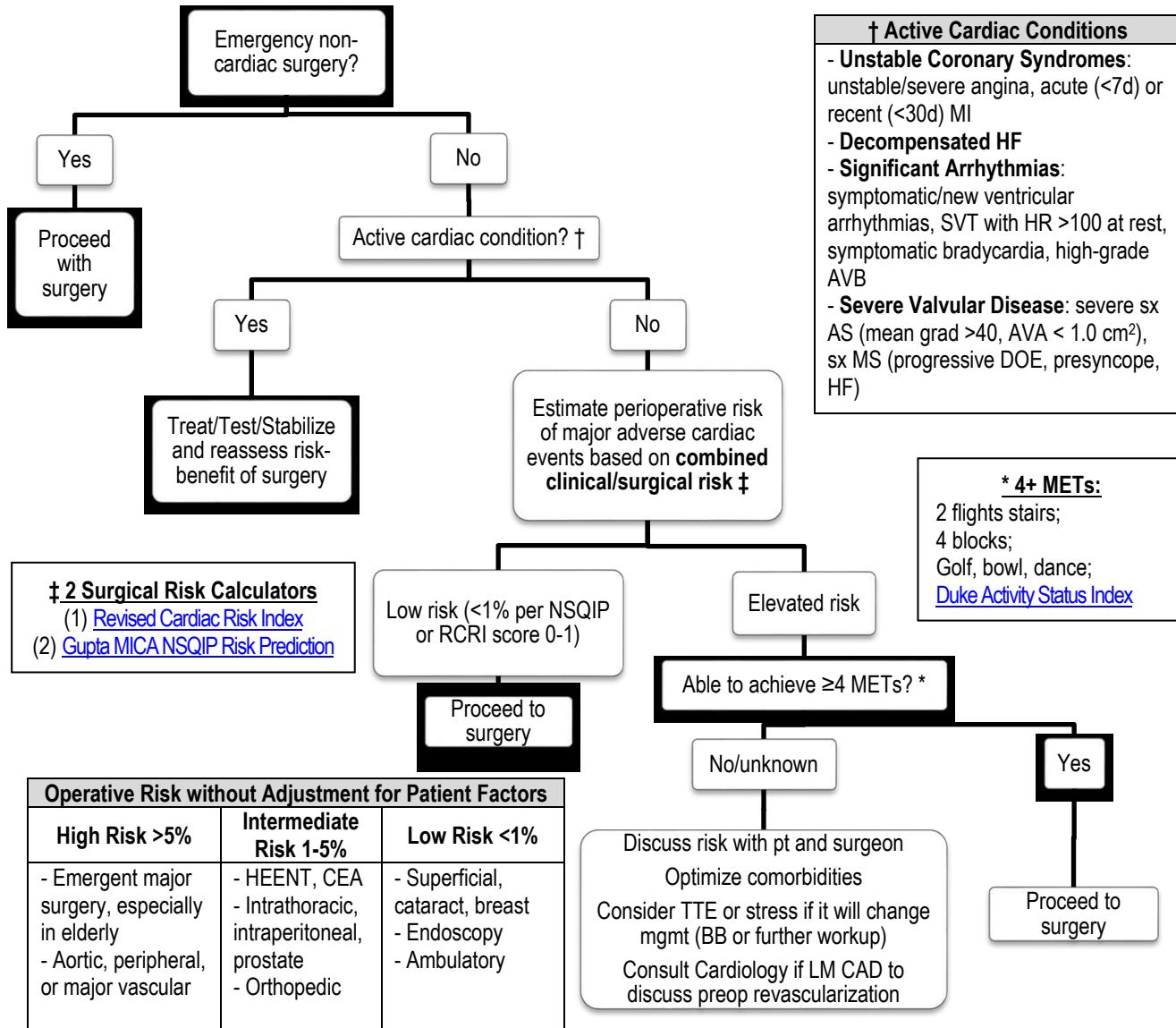
# Perioperative Medicine

## PERI-OPERATIVE CARDIAC RISK STRATIFICATION AND RISK REDUCTION

**GOAL:** to estimate risk, optimize, and pause for cardiac testing regarding peri-operative cardiac events, **NOT to "clear for surgery"**

- Peri-op cardiac events: **MI** (usually clinically silent, NSTEMI>STEMI, POD#0-3, not intraop), **CHF, VT/VF, cardiac arrest, death**
  - Major determinants include: (1) preceding condition of patient (2) risk of procedure (3) functional capacity
- Emphasis on risk stratification. **Very few patients need non-invasive/invasive testing**, only if testing would change cardiac optimization management (initiating medical management, PCI, Cardiac Surgery) even *in the absence of surgery*

## PERI-OPERATIVE CARDIOVASCULAR EVALUATION FOR NON-CARDIAC SURGERY (adapted [JACC 2014;64:e77](#))



## REVISED CARDIAC RISK INDEX (RCRI, GOLDMAN) ([Circ 1999;100:1043](#); [Can J Cardiol 2017;33:17](#))

- **Six independent predictors (risk factors) of major cardiac complications**
  1. High-risk noncardiac surgery (not a clinical RF but incorporated elsewhere in algorithm): OR 2.6
  2. CAD (MI, PCI, CABG, angina, nitrate use, ECG with pathologic Q waves, or + exercise stress test): OR 3.8
  3. HF (CHF, pulm edema, bilateral rales, or S3): OR 4.3
  4. Cerebrovascular disease (stroke or TIA): OR 3.0
  5. Diabetes mellitus with preop insulin therapy: OR 1.0
  6. Renal insufficiency with preop Cr >2.0 mg/dL: OR 0.9
- RCRI event rates were re-calculated (and partially validated) in 2017 after multiple trials included troponins ± emergent surgeries

Rate of cardiac death, MI, pulm edema, CHB, cardiac arrest/VF		
RCRI	1999 Event Rates (95% CI)	2017 Event Rates (95% CI)
0	0.4-0.5% (0.05-1.5) → ~0.5%	3.9% (2.8-5.4) → ~4%
1	0.9-1.3% (0.3-2.1) → ~1%	6.0% (4.9-7.4) → ~6%
2	3.6-6.6% (2.1-10.3) → ~5%	10.1% (8.1-12.6) → ~10%
≥3	9.1-11.0% (5.5-18.4) → ~10%	15.0% (11.1-20.0) → ~15%

# Consultants

# Perioperative Medicine

## ALTERNATIVE CARDIAC RISK ASSESSMENT ([MICA](#), [GUPTA](#)) ([Circ 2011;124:381](#))

- Identified 5 risk factors predictive of *risk of STEMI or cardiac arrest* w/in 30 days of surgery:  
1) Type of surgery/procedure, 2) preoperative functional status, 3) serum Cr >1.5, 4) ASA class, 5) increasing age
- Compared to RCRI, **better** discriminative predictive value
- Limitations:** likely underestimates actual risk because MI was defined in the study based on only ECG changes: STEMI or new LBBB; biomarkers were NOT monitored post-op, which is necessary to detect more than 50% of perioperative MIs

## PREOPERATIVE CORONARY REVASCULARIZATION ([NEJM 2004;351:2795](#))

- CARP:** multicenter RCT of 510 high-risk vascular surgery patients, showed prophylactic revascularization w/ BMS/CABG conferred no survival benefit; data extrapolated to lower risk non-vascular/non-cardiac surgeries
  - Exclusion criteria: EF < 20%, unstable angina, LMCA disease > 50%, severe AS

## PERI-OPERATIVE $\beta$ -BLOCKADE AND OTHER CARDIAC DRUGS

- Evaluate for peri-operative  $\beta$ -blockade ([Circ 2014;130:278](#))
  - Continue  $\beta$ -blocker: if already taking for other indication (e.g. CAD, arrhythmia, HTN) for goal HR 55-65 (Class I, LOE C)
  - Consider initiating  $\beta$ -blocker:  $\geq 3$  RCRI RFs or intermediate/high risk preop test (Class IIb, LOE B)
    - Do not start a  $\beta$ -blocker within 24 hours of surgery!** ([Lancet 2008;371:1839](#); [JACC 2014;64:2406](#))
  - Uncertain role of  $\beta$ -blocker: if  $\oplus$  stress test or long-term indication without other RCRI risk factors
- Anti-platelet:** ([NEJM 2014;370:1494](#); [Anesth Analg 2015;120:570](#))
  - 1° prevention: can generally be held prior to surgery
  - 2° prevention: continue ASA 81mg unless high risk of bleeding (intramedullary spine, intracranial, hip, knee, possibly prostate)
  - DAPT post-PCI: POBA <14d, BMS <30d, DES <6-12mo → discuss with Cardiology
- ACEi/ARB:** pts have more transient peri- and post-op episodes of HoTN; **no diff** in death, post-op MI, stroke; ↑ or ↓ AKI unclear
  - Discontinue ACEi/ARB night before surgery (unless used for HF and BP ok). At MGH hold prior to cardiac surgery
  - Failure to restart ARB within 48h ↑ 130d mortality ([Anesthes 2015;123:288](#))
- Other:** consider holding diuretics, other anti-hypertensives should be continued perioperatively to goal BP <180/100 to avoid bleeding
- Anticoagulation and bridging:** see *Anticoagulation Management*

## VTE PROPHYLAXIS ([Mayo Clin Proc 2014;89:394](#))

- Postop VTE risk assessment: [Caparini Score](#)
- Non-orthopedic surgeries: those undergoing **general or abdominal/pelvic surgery** are at highest risk
- Orthopedic surgeries: **all pts at high VTE risk** 2/2 tourniquet time + immobilization; minimum duration 10-14d (35d if higher risk)

## PERI-OPERATIVE MONITORING AND CONSIDERATIONS ([NEJM 2015;373:2258](#))

- ACS NSQIP Surgical Risk Calculator** can help estimate other post-operative complications including LOS, need for rehab, risk of non-cardiac post-operative complications ([Am J Cardiol. 2018; 121:125](#))
- ACS:** most MIs occur w/in 48h while patients are on analgesics that mask pain → some data show benefit of troponin monitoring ([JAMA 2012;307:2295](#)). Elevated post-op NT-proBNP can be used as a predictor of post-op MI and death ([JACC 2014;63:170](#))
  - Myocardial injury after noncardiac surgery (MINS) commonly asymptomatic; variable recommendations for screening with ongoing studies → MINS is an independent predictor of 30-day mortality ([Anesthesiology 2014;120:564](#))
- AF:** may be a more important risk factor than CAD for 30d post-op mortality ([Circ 2011;124:289](#)). Associated with higher preop # of preexisting comorbidities and increased postop LOS, cost, and mortality ([Am Heart J 2012;164:918](#)), as well as similar thromboembolism and death risk to pre-existing NVAF ([JACC 2018;72:2027](#))
  - If multiple episodes or lasts > 48h, recommend OAC and close follow up for further decision-making
- Pulmonary Disease:** numerous risk factors for postoperative pulmonary complications, including COPD, OSA, pHTN, low albumin. Multiple risk calculators for different outcomes, including [ARISCAT](#) ([Anesth 2010;113:1338](#)), [Gupta](#) (for resp failure), and [Gupta](#) (for PNA). Mitigation of risk usually supportive, including incentive spirometry and smoking cessation. Consider Pulmonology consult
- Post-operative PNA:** ~20% mortality; pre-op CXR or PFTs not recommended because rarely change management
  - Risk factors: COPD, age >60, ASA class  $\geq II$ , albumin <3.5, poor functional dependence, weight loss >10% over previous 6 months ([Annals 2006;144:575](#))
- Renal dysfunction:** increased risk of complications in ESRD; AKI also a/w high morbidity and mortality ([Ann Surg 2009;249:851](#))
- ESLD:** increasing risk of perioperative mortality with increasing [MELD](#) & [Child-Pugh](#) scores. If Child-Pugh B, optimize VIBES & consider TIPS for refractory ascites. If Child-Pugh C, optimize, consider transplant, & discuss risk/benefit nonsurgical options ([J Gastroenterol Hepatol 2012;27:1569](#); [Clin Gastroenterol Hepatol 2020;18:2398](#))
- Low albumin:** independent predictor of 30d post-op morbidity and mortality ([Arch Surg 1999;134:36](#))

# Consultants

# Dermatology

Before Consulting Dermatology: **upload photos of rash** (ideally pre-treatment) to media tab of EPIC using Haiku

- If consulting for drug rash, note exact timing of rash development and administration of suspect medications
- Note: Erythema in patients with darker skin types can present with a more violaceous or dark brown hue; textural changes are important to note. Applying gentle pressure to blanch involved skin or use of a bright light may accentuate subtle erythema.

Quick Steroid Guide	
• Face/intertriginous areas:	hydrocort. 2.5% cream, hydrocort. valerate 0.2% cream
• Body:	fluocinolone 0.025% cream if mild, clobetasol 0.05% ointment if severe → mid strength to super potent depending on severity
• Scalp:	0.01% fluocinolone scalp solution or oil (dermasmooth); oil better for dry scalp
<b>Counsel patients:</b>	Use BID x2 wks then 1 wk "off", avoid face (risk = skin thinning)

MGH topical steroid formulary by level of potency	
Super-potent	clobetasol 0.05%, betamethasone dipropionate 0.05%
Potent	fluocinonide-emollient 0.05%
Upper-mid strength	betamethasone valerate ointment 0.1%
Mid-strength	fluocinolone ointment 0.025%
Lower mid-strength	fluocinolone cream 0.025%, betamethasone valerate cream 0.1%
Mild	hydrocortisone valerate 0.2%, fluocinolone oil 0.01%
Least potent	hydrocortisone 2.5%, hydrocortisone ointment 1.0%
Over the counter	hydrocortisone cream 0.5%, 1.0%

Choice of vehicle: ointments ↑ potent, ↑ stickiness, ↓ irritation

## COMMON DERMATOLOGIC CONDITIONS

- **Allergic contact dermatitis:** appears as a geometric shape with well-demarcated borders (i.e. square tape). Usually localized but may generalize 2/2 autoeczematization (a.k.a. "id reaction", may also occur 2/2 tinea anywhere on the body). Identify and remove suspected trigger. Tx w/ high potency topical steroid for limited BSA (low to mid potency for face). Pred taper (>1wk) for more extensive BSA involvement.
- **Eczema/atopic dermatitis:** tx depends on severity. Intense BID/TID moisturization (plain hydrated petrolatum, Cetaphil®, CeraVe®). For affected areas, use mid-strength to super-potent topical steroids BID x 2wks. For face, use least potent to lower mid-strength steroids BID x 1-2wks. Scalp: mid- to high-potency steroid in solution, foam, or oil vehicles. Erosions/fissures: petrolatum or mupirocin ointment BID x 1-2wks if concerned for superinfection and/or MRSA positive.
- **Cellulitis:** consider **derm consult if not improved in 48h** to distinguish cellulitis mimickers (30% of cases)
  - Calculate ALT-70: 5-7 = 82.2% likely cellulitis; 3-4 = consider derm c/s if no improvement by 48h with abx. Consult reduces abx use + duration ([JAAD 2017;76:618](#); [JAMA Dem 2018;154:529](#)). **Bilateral LE cellulitis is rare.**
- **Pressure injury/ulcers:** document in H&P with Haiku pics.
  - **NPUAP Staging:** 1) non blanchable erythema of intact skin, 2) partial thickness skin loss with exposed dermis, 3) full thickness skin loss, 4) full thickness skin and tissue loss. Can be unstageable due to eschar/necrosis
  - **Wound Nurse consult** for: stage 3-4 pressure injury, device related injuries, moisture associated skin damage, edema drainage management, special bed surfaces (i.e. clinitron, bariatric). **Wound Service consult** (Plastics/Vascular) for: acute wound issues such as limb ischemia, wet gangrene, any wound requiring OR debridement. Consider derm c/s to confirm etiology.
- **Intertrigo:** chronic inflammation in skin folds usually superinfected with yeast or bacteria. Candidal intertrigo → outlying papules or pustules. Eliminate friction, moisture, heat with wicking fabric (Interdry), barrier cream (zinc oxide paste), avoid powders when active. Topical azole antifungal BID to reduce yeast burden, caution with topical steroids in thin/occluded areas. Immunocompromised patients with intertriginous lesions should prompt concern for deep fungal infections ([JAAD 2021;17:92](#)).

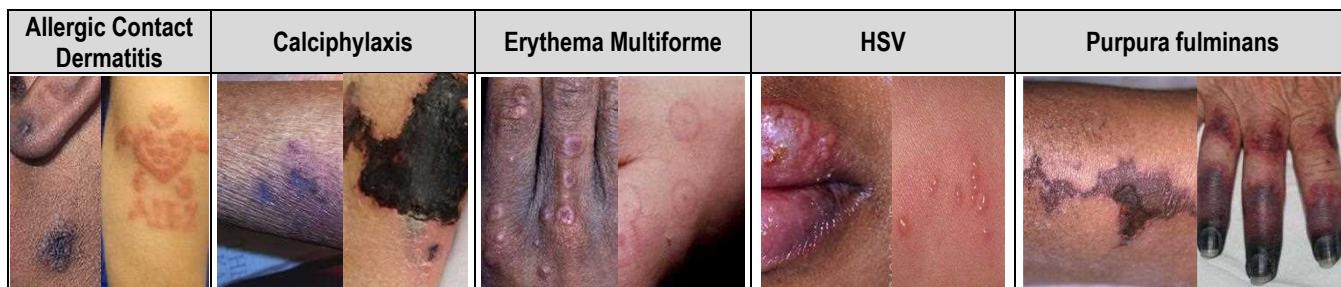
## OTHER DERMATOLOGIC CONDITIONS

- **Calciphylaxis:** extreme pain (may precede lesion), violaceous retiform patch/plaque +/- "woody" induration → necrosis, ulcer, eschar. Can appear at sites of trauma (injection sites, surgical debridement) ([JAAD;13:57](#)).
  - **Risk Factors:** ESRD on dialysis (most common), warfarin, 1° hyperPTH, malignancy, prior bariatric surgery
  - **Dx:** skin biopsy (gold standard, not sensitive); Ca<sup>2+</sup> x phos product, PTH; bone scan w/ increased uptake
  - **Tx:** normalize serum Ca<sup>2+</sup>/phos/PTH via non-Ca based phos binders (i.e. sevelamer) and cinacalcet; Intralesional or IV sodium thiosulfate; treat 2° infections (death from sepsis), consider hyperbaric O<sub>2</sub> (consult MEEI Hyperbaric Medicine), pain ctrl, wound care (Medihoney), nutrition consult. D/c warfarin if possible; consider AC if appropriate. **Calciphylaxis = indication for HD in CKD**
- **Cutaneous GVHD:** skin pain/pruritus can precede eruption, acral → central; acute vs. chronic based on morphology, *not* time course
  - **Acute:** follicular erythematous papules. **Chronic:** morphology varies, can be dry and scaly (asteatotic), pruritic and erythematous (eczematous), thickened and raised (lichenoid), tight and thick (sclerodermoid), pigment changes and atrophy (poikilodermatous)
  - **Stage 1:** <25% BSA, **stage 2:** 25-50% BSA, **stage 3:** >50% BSA, **stage 4:** erythroderma w/ bullae (TEN-like).
  - **Tx:** immunosuppression with corticosteroids +/- cyclosporine or tacrolimus, supportive care
- **Immunotherapy toxicity:** result of t-cell activation; most common on PDL-1 inhibitors, highest incidence of adverse immune related effects are mucocutaneous (~50% of immunotherapy patients, ~2% severe (>grade 2)); usually managed outpatient; variable timeline
  - Wide range of severity (grade 0->3)/presentations: maculopapular/lichenoid → pruritis → psoriasiform → bullous, SJS/TEN
  - Derm and/or SIC consult warranted if not controlled w/ topical high potency steroids inpatient +/- oral pred 0.5-1mg/kg
  - Grade > 2 = hold ICI + monitor, Grade >3 = hold ICI + dose reduction likely req. ([SITC Guideline 2021](#)).
- **Herpes simplex virus 1/2:** always confirm w/ DFA or PCR from vesicle base; cx possible but takes long to result

# Consultants

# Dermatology

- Uncomplicated orolabial: usually gingivostomatitis → acyclovir 400mg TID x7-10d; if recurrent → valacyclovir 2000 mg PO q12h x 1d or famciclovir 1500mg PO x1 at sx onset; periocular skin involvement warrants ophtho c/s to r/o herpetic keratitis
- Uncomplicated genital (immunocompetent): 1° ep (<72hr onset) → valacyclovir 1000mg PO BID x10d, acyclovir 400mg PO TID x10d, or famciclovir 250mg TID; recurrent eps (<24hr onset) → valacyclovir 500mg PO BID x3-5d or acyclovir 400mg PO TID x5d.
- Complications: sacral radiculitis (acute urinary retention), proctitis (MSM).
- Ppx for immunosuppressed patients: acutely immunosuppressed, e.g. transplant patients or patients with hematologic malignancies undergoing induction chemotherapy, HSV seropositive: acyclovir 5 mg/kg IV q8h X 7d → acyclovir 200-400 mg PO 3-5x daily x 1-3 mos; for prevention of recurrence in people living with HIV (NOT primary prevention): acyclovir 400-800 mg PO BID/TID or valacyclovir 500 mg daily or famciclovir 500 mg BID. Consider high lysine/low arginine diet to prevent HSV recurrence
- **Herpes zoster (shingles)**
  - Uncomplicated, <72 hr (immunocompetent): valacyclovir 1000mg PO Q8H x7d or acyclovir 800 mg PO 5x/d x7-10d
  - Disseminated: >20 vesicles and two 1° (non-adjacent) dermatomes; acyclovir 10mg/kg IV q8h; consider immunodeficiency w/u; droplet precautions
  - Immunosuppressed: acyclovir 10 mg/kg IV q8h; IVFs if hypovolemic/CKD to decrease risk of crystalline nephropathy; obtain DFA/viral culture; monitor for complications (PNA, encephalitis, aseptic meningitis, hepatitis)
  - Zoster ophthalmicus: urgent ophtho consult if c/f ocular involvement ("Hutchinson sign" = vesicle on nasal tip)
  - Post-herpetic neuralgia: risk ↓ w/ early antiviral treatment (<72 hr); if higher risk ( $\geq 50$ yo w/ mod-to-severe acute pain) consider preventive tx w/ gabapentin 300mg PO QD, titrate up to 3600mg QD, divided TID as tolerated
  - Consider post-episode vaccination
- **Erythema multiforme**: target lesions (well-defined, circular erythematous macules/papules w/ 3 distinct color zones + central bulla or crust) on palms/soles +/- mucosal involvement occurs within 24-72 hours; persist for 2wks
  - 90% triggered by infection (HSV, mycoplasma, GAS, EBV); less commonly drug rxn
  - Tx: treat underlying infxn, NSAIDs, cool compresses, topical steroids, antihistamines; systemic steroids only if severe
- **Erythroderma**: diffuse redness >90% BSA; caution: can progress to bullous/skin sloughing
  - Causes: psoriasis, atopic derm, cutaneous T-cell lymphoma (incl. Sezary), pityriasis rubra pilaris (islands of sparing), drugs
  - Work-up: detailed med rec, +/- HIV. Tx: derm c/s; liberal emollients, mid-potency topical steroids, antihistamines; fluids/lytes; monitor for 2° infections; d/c offending meds.
- **Purpura fulminans**: "DIC in skin" = true emergency; consult Hematology for possible factor replacement
  - Microvascular skin occlusion w/ platelet-fibrin thrombi → retiform purpura
  - Causes: infection (Strep, Staph, H. flu, N. meningitidis, Capnocytophaga, VZV, CMV, Babesia); catastrophic APLAS, CTD, malignancy, protein C/S deficiency
  - Work-up: DIC labs, blood cultures, skin bx w/ GS and culture. Tx: broad-spectrum abx + supportive care
- **Stasis dermatitis**: LE compression (ACE wraps, stockings) with elevation; mid-strength to super potent corticosteroid ointment BID x 1-2wks +/- occlusion with plastic wrap; mupirocin ointment BID x1-2wks to erosions; intensive moisturization (hydrated petrolatum); for hyperkeratosis can liberally apply ammonium lactate BID until improvement
- **Psoriasis**: depends severity; avoid PO steroids d/t post-tx flare. Short-term tx incl topical steroids, calcipotriene, intense moisturizing +/- occlusion w/ plastic wrap; Long-term tx incl phototherapy, acitretin, MTX, biologics w/ outpt derm f/u ([JAAD 2011;65:137](#))
- **Seborrheic dermatitis**: Face: least potent to lower mid-strength topical steroid BID x 1wk and/or ketoconazole 2% cream BID x4wks, then 1-2x/wk; Alternative: pimecrolimus cream, tacrolimus 0.03 or 0.1% ointment. Scalp: ketoconazole 2% shampoo QHS
- **Tinea pedis**: "moccasin distribution"; apply topical imidazole (econazole 1% cream QD or clotrimazole 1% cream BID x 2-4 wks) or allylamine (terbinafine 1% cream BID x 2 wks) to entire foot and webbed spaces between toes. Predisposes to LE cellulitis



## DRUG ERUPTIONS

- Step 1: Make timeline to determine time course of drug initiation and development of rash
- Step 2: Discontinue offending agent. Common drugs for each eruption listed, but any drug can be a culprit at any time

# Consultants

# Dermatology

	Time Course	Rash	Signs/Sx	Common Drugs	Treatment
Urticaria/ Anaphylaxis	Immediate (min-hr) – delayed (days)		Puritic, well-circumscribed, erythematous papules/plaques with central pallor. <b>Transient</b> lesions (circle and observe) +/- angioedema, wheezing, GI sx, tachycardia, HoTN	Any	Antihistamines (benadryl + H2) + steroids if severe + IM epi if s/s anaphylaxis - Allergy c/s
Fixed Drug Eruption	Minutes-hours		Solitary sharply demarcated round red-brown patch or edematous plaque recurring in <b>same location</b> each time drug ingested. Can evolve to bullae/become disseminated. Oral/anogenital mucosa commonly, can be anywhere. Usually ax.	Abx (sulfa, TMP, FQs, TCNs), NSAIDs, barbiturates	Topical steroids if symptomatic
Acute Generalized Exanthematous Pustulosis (AGEP)	2-14 days		Small non-follic. pustules on erythema/edematous plaques, begin on face/intertriginous areas → widespread. Usually w/in 24-48hrs med exposure. Burning, pruritus common. Fever, marked neutrophilia +/ oral mucosal erosions, facial edema	Abx (PCN, macrolides)	Anti-pyretic Topical steroids
Exanthematous/ Morbilliform	4-14d (if prev. exposed to the drug, could be sooner)		"Classic" drug rash. Pruritic, erythematous macules/papules. Start on trunk, spread centrifugally to symmetric extremities. May lead to erythroderma. ± low grade fever	Abx (PCN, sulfa), allopurinol, phenytoin	Topical steroids, antihistamines (Note: may take 7-14d after stopping drug to resolve)
SJS/TEN	4-21 days		Fever, malaise, myalgias, arthralgias. Pruritic atypical targetoid (amorphous, 2 color zones) macules → bullae → desquamation; <10% = SJS, 10-30% = SJS/TEN overlap, >30% = TEN. Mucosal bullae, erosions & crusting, conjunctivitis. + Nikolsky. Complications: 2° infection, resp. compromise, GIB, visual impairment	Abx (esp. sulfa), AEDs, NSAIDs, allopurinol, phenobarb.	Cyclosporine (preferred at MGH) Steroids possible mortality benefit ( <a href="#">JAMA Derm 2017;153:514</a> ) but controversial IVIG, anti-TNF <b>Burn level care if &gt;30% BSA</b> <b>Opho consult</b>
DRESS	3-6 wks		Morbilliform; spreads down symmetric. from face & mucosal involv. Face often swollen/painful (can help diff. from morbilliform drug) Fever, arthralgias, eos, internal organ involv. (liver, kidney, rarely lung, heart), LAD	Abx, AEDs, carbamazepine, ARTs (nevirapine, abacavir)	Dx: obtain CMP, CBC w/ diff, TSH, consider TTE - Supportive care - IV Solumedrol (decreased risk of bowel edema vs. PO), SLOW taper (3-6 wks), TSH check at 4-6 wks

See **Calling Consults** for details on how to call the appropriate surgical service

## SMALL BOWEL OBSTRUCTION ([J Trauma Acute Care Surg 2015;79:661](#))

- Causes: adhesions from any previous abd surgery, hernias, cancer >> intussusception, volvulus, foreign bodies, stricture
- Dx: abd distension, vomiting, obstipation. Labs normal or hypoK/hypoCl metabolic alkalosis from repeated emesis. Examine for evidence of hernia and abdominal scars. If severe pain, consider ischemia from strangulation (lactate, WBC)
- Imaging: KUB - air-fluid levels; **CT A/P +/- PO contrast** (only if tolerated) - dilated bowel proximal to & decompressed bowel distal to obstruction. **Caution:** sending patient with SBO to CT w/o an NGT = aspiration risk, empirically place prior to CT
- Tx: NPO (no meds via NGT), large bore **NGT** (18Fr always) to continuous low suction; consider gastrografin challenge (100 cc undiluted GG, KUB 4 hrs post). **Consider OR** if signs of strangulation/bowel ischemia, s/p RNY gastric bypass (internal hernia), closed loop, or if no improvement in 72 hours. **All pts need strict I/O and adequate IVF resuscitation, taking into consideration NGT output.**

## BENIGN BILIARY DISEASE ([Prim Care 2017;44\(4\):575-597](#)), see *Biliary Disease*

- Indications for cholecystectomy (CCY): symptomatic cholelithiasis; cholecystitis; gallstone pancreatitis; gallbladder polyps (>1cm or rapidly growing)
  - Post-cholecystectomy syndrome (PCS): abdominal pain, dyspepsia recurring/persisting after CCY; **early** (due to biliary injury, retained stones, retained cystic duct), **late** (due to recurrent CBD stones, strictures, stenosis, biliary dyskinesia), consider alternate non-biliary etiology ([Int J Surg 2010;8:15](#))
- Acute cholecystitis: persistent RUQ pain, cholelithiasis, caused by cystic duct obstruction. Dx: RUQUS.
  - Tx: early CCY during hospitalization assoc. with ↓ morbidity ([Br J Surg 2015;102:1302](#)). If critically ill, perc chole→delayed CCY.
- Gallstone pancreatitis: See *Pancreatitis*; findings include ↑lipase, ↑LFTs (**↑ALT > 3.5x ULN, 95% PPV**)
  - Consider Urgent ERCP (24 hrs) if cholangitis or CBD obstruction; same-admission CCY +/- IOC in mild cases associated with ↓readmission for gallstone-related complications compared to delayed CCY ([Br J Surg 2016; 103:1695](#))
- Acalculous cholecystitis: seen in critically ill ICU pts usually with prolonged NPO + biliary stasis, high mortality rate
  - Tx: perc chole + IV antibiotics
- Choledocholithiasis: CBD obstruction, jaundice. ↑AST,ALT (< 1000), ↑ALP, ↑direct bili. RUQUS with CBD dilation, MRCP.
  - Tx: GI c/s for ERCP with sphincterotomy, stone extraction, and surgery c/s for same-admission CCY. Can consider immediate CCY+IOC for select patients.
  - If concern for cholangitis (Charcot's triad – fever, RUQ pain, jaundice, Reynolds' pentad – AMS, shock) → IV abx (Zosyn or CTX/Flagyl), IVF, close monitoring and **urgent ERCP**. *Cholangitis can cause rapid clinical decompensation.*

## NECROTIZING SOFT TISSUE INFECTION ([CID 2007;44:705](#); [Front Surg 2014;1:36](#))

- Definition: progressive, rapidly spreading infection with secondary necrosis of skin and subcutaneous tissues, sometimes fascia
- Microbiology: majority of cases are polymicrobial (anaerobes, group A strep, *S. Aureus*, *Clostridium*, *Peptostreptococcus*, *Enterobacteriaceae*, *Proteus*, *Pseudomonas*, *Klebsiella*)
- Clinical signs: rapidly spreading erythema (hrs to days) → pain disproportionate to exam or beyond borders of erythema, dusky skin, turbid ("dishwater") discharge, crepitus
- Dx: CT w/contrast has a ~95-100% NPV. Labs for LRINEC score (CRP, WBC, Hg, Na, Cr, Gluc) → score ≥6 has a 96% NPV
- Tx: IV abx ([Vanc or Linezolid] + [Pip/Tazo or meropenem] + Clinda (to inhibit toxin production) + **urgent surgical debridement (consult Churchill service)**

## ACUTE LIMB ISCHEMIA ([NEJM 2012; 366:2198](#))

- **6 P's:** Pain, Poikilothermia (cool), Paresthesia, Pallor, Pulselessness, Paralysis
- Dx: check and document pulses AND Doppler signals in the entirety of the extremity and the contralateral extremity for comparison. Obtain ankle-brachial indices. Urgent if loss of arterial/venous Doppler signal
  - **Acute limb ischemia** → thrombotic or embolic (can be iatrogenic, e.g., s/p vascular access procedure), acute change in blood supply, needs **urgent surgical evaluation**
  - **Chronic limb ischemia** → chronic vascular disease from atherosclerotic changes. Exam with cool, hairless extremities, limited/no pulse that is not acutely painful. **Non-urgent** surgical eval
- Tx: if unsure, or acute limb ischemia, consider IV heparin (unless AC contraindicated); **consult Vascular Surgery immediately**

## COMPARTMENT SYNDROME (EXTREMITY) ([Lancet 2015;386:1299](#); [Musc Lig Tend J 2015;5:18](#))

- Definition: excessive pressure within a muscle compartment impairing perfusion; 2/2 crush injury, edema, bleed, ischemia, 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 w/ Stryker transducer needle (call Orthopedic or Churchill Service)
  - Arterial flow diminished once compartment pressure within 30mmHg of DBP (20mmHg in hypotensive patients)
  - Compartment syndrome is a **clinical diagnosis**, regardless of measured compartment pressure(s)
- Tx: surgical emergency (fasciotomy/decompression); **consult Churchill Surgery immediately**

## ABDOMINAL COMPARTMENT SYNDROME ([ICM 2013;39:1190](#))

- Definition: IAH = IAP >12. **Abdominal Compartment Syndrome** = IAP >20 **AND** end organ dysfunction (e.g., ↑airway pressures, ↓UOP/AKI, ↑lactate, acidemia). IAP measured via bladder pressure (most reliable if paralyzed, done in ICU)
- Typically occurs after massive resuscitation in ICU patients with trauma, burns, s/p liver txp, severe ascites, pancreatitis, sepsis
- Tx: **for medically refractory, true Abdominal Compartment Syndrome** → **laparotomy with temporary closure**
  - If IAP 12-20 w/o clinical instability, temporize w/NGT, rectal tube, paralytics, LVP, ↓tidal volume, diuresis, HOB elevation

# Consultants

# Urology

**Who to call:** page 11300 for Emergencies, Foleys, SPTs, & gross hematuria; page 10300 for other non-urgent inpatient consults

**Consults:** note urine color **in tube** (bag urine appears darker due to volume) before consulting Urology, place urine samples at bedside – use food/drink comparisons like “pink lemonade,” “fruit punch,” “cranberry juice,” and “merlot” to help characterize

## URETERAL OBSTRUCTION (MOST COMMONLY DUE TO KIDNEY STONES OR MALIGNANCY)

- **Evaluation/management:** Pain usually present only in **obstructing** stones. +hydronephrosis implies obstruction.
  - **Imaging:** stone-protocol CT scan (**I-**, **O-**): evaluates position, density/composition & presence of hydronephrosis
    - Alternative: MRI vs combined KUB+US; however, less diagnostic than stone-protocol CT. US helpful to r/o hydronephrosis
  - Vitals, CBC, UA/UCx: if concomitant UTI, decompress urgently with stent by urology or percutaneous nephrostomy (PCN) by IR
  - **Rehydration:** patients often volume down, bolus as tolerated and increase maintenance IV fluids → ↑ureteral clearance
  - **Alpha-Blockers:** **tamsulosin** 0.4mg PO qd (hold for SBP <90) → ureteral relaxation, +evidence for better **distal** stone passage
  - **Analgesia:** Tylenol, NSAIDs if Cr <1.5, add IV opioids if inadequate pain control; can also use diazepam (2mg Q8 PRN)
  - **Preoperative workup:** NPO, BMP/CBC, continue AC if plan for Urology stent; hold AC & obtain coags if plan for IR PCN
- **Urgent urology consults:** solitary or transplanted kidney with worsening AKI, UTI, urosepsis in setting of obstruction
- **Obstruction + sepsis:** Non-con CT A/P ASAP, BCx/UCx, urgent Urology consult; broad IV abx to cover GNRs + enterococcus
- **Non-stone hydronephrosis:** often stricture or malignancy, can require decompression for renoprotection or need for nephrotoxic chemo. Same options (stent vs PCN), same indications of urgent/emergent consult. Urology can help determine stent vs PCN
- **Relevant History:** renal colic is unilateral pain from CVA wrapping around flank radiating towards ipsilateral scrotum/labium
- **Indwelling ureteral stents:** Need exchange every 3-6 months; if +UCx, need abx treatment prior to exchange; can be done as outpatient

## HEMATURIA

- **DDx:** BPH, UTI, INR>3, traumatic catheter placement, bladder CA (5<sup>th</sup> most common neoplasm), upper urinary tract CA, prostate CA
- **Acute Management:** Obtain post-void residual bladder scan before consulting Urology. If +foley, can manually irrigate & aspirate
  - **DO NOT start CBI if active clot burden. If 3-way clots off, stop CBI and manually irrigate through 3-way until clear**
  - Manual irrigation removes clots that already exist, while CBI prevents new clots from forming by diluting active bleeding
- **Diagnostic Workup (4 C's):** 1) in-house **CT hematuria protocol**; 2) urine **Culture**, 3) urine **Cytology**, 4) outpatient **Cystoscopy**

## OBSTRUCTED CATHETER VS BLADDER SPASM/URGENCY FROM CATHETER

- **Obstructed Catheters:** bladder feels full, urine spasms around catheter, minimal/no urine through catheter, **bladder scan is high**
  - Tx: disconnect tube from drainage port, gently flush 50cc and aspirate with catheter-tip syringe and reconnect
- **Bladder Spasm:** bladder feels full, urine spasms around catheter but **continued flow through catheter, bladder scan is low**
  - Tx: antispasmodic agents – restart home meds if they have them normally, otherwise can start **tolterodine** (anticholinergic with fewer side effects than oxybutynin), Oxytrol patch and/or **belladonna-opium suppository** (local anticholinergic)
- **Note:** bladder scans are inaccurate when patients have ascites because they inappropriately detect the fluid around the bladder

## URINARY RETENTION

- **Etiology:** BPH, UTI, constipation, neurogenic (MS, cord injury), DM, immobility, **anticholinergics, opioids, benzos**, pelvic surgery
- **Treatment:** **bowel regimen**, treat UTI, **minimize opioids/anticholinergics**, encourage **ambulation**, (re)start **tamsulosin** or other α-blocker. Catheterize as necessary – clean intermittent “**straight cath**”, preferred long-term to Foley/SPT if possible

## URINARY INCONTINENCE

- **Classifications:** **stress** (Valsalva), **urge** (preceded by urgency), **mixed** (most common), **overflow** (PVR >150), **functional** (neurologic)
- **Treatment:** lifestyle interventions, bladder training (timed voiding), Kegel pelvic floor exercises for all types
  - **Stress:** vaginal estrogen (post-menopausal women w/ vaginal atrophy), pessaries (mixed data), surgery (urethral bulking, slings)
  - **Urge:** antichol (oxybutynin, tolterodine, beware side effects), β3-agonists (mirabegron, avoid w/ HTN, ESRD, ESLD), Botox
- **Note:** workup of “voiding dysfunction” (retention, incontinence) usually takes weeks/months of outpatient observation ± urodynamics.

## TUBES AND DRAINS: see *Tube Management* for placement and management

- **Foley catheter:** externally placed tube which travels through urethra and into bladder
  - Considerations: BPH, men >50yo → 16-18Fr Coudé (gentle curve directs catheter tip through curve of prostate), **all RNs are allowed to place Coudés – the tip (and balloon port) point “up” towards sky**; stricture → 12-14Fr
    - **Pro-tip:** use 8-10cc lubricant **instilled into the urethra** via syringe (urojet) for easier catheter placement in men
  - Urethral trauma: To avoid, fully hub foley on placement prior to balloon inflation; leave foley in 3-5d to allow for urethral healing
- **Suprapubic tubes (SPT):** externally placed tube travels percutaneously through ant abdominal wall into bladder
  - Placed by IR. First exchange done by IR, change q6-12w similar to Foley, **RNs do routine exchange, Urology assists PRN**
- **Percutaneous nephrostomy tube (PCN):** externally placed tube travels percutaneously through flank wall into renal pelvis
  - Placed by IR under local vs general anesthesia. Cannot be coagulopathic, thrombocytopenic, or on ASA/anticoag
  - Urine collects in external bag. If low UOP into bags, passage of blood or concern for malposition – flush>obtain US/CT>call IR
- **Ureteral stent:** internally placed tube travels from renal pelvis to bladder inside ureter to drain kidney into bladder
  - Placed by Urology in OR with general anesthesia or MAC, requires change every 3-6mo. May cause urinary urgency. NOT changed in setting of infection unless stent has failed (which becomes a ureteral obstruction c/b UTI, tx usually = PCN with IR)
- **Note:** if stents/PCNs/chronic catheter or SPT/ileal conduit or neobladder – UTIs diagnosed on symptoms over UCx/UA (colonized)
- **Note:** there are no good data that Foley/SPT exchange in UTI is helpful because the new tube goes into the same (infected) tract

# Consultants

ENT

## EPISTAXIS (NOSEBLEED)

Acute management: ([UpToDate Epistaxis](#))

1. Have patient **lean forward, pinch nostrils**, and hold **pressure for 20 min**
  - o Guidance: pinch over the soft portion of the nose; do NOT lean head back or pinch bony part of nose; **do NOT “peek”** – hold continuous pressure for 20 min; patient may be unable to hold pinch, best for RN/MD to do
2. **Afrin (oxymetazoline 0.025%)** nasal spray (after gently clearing clots)
  - o Guidance: **GENEROUSLY SPRAY (5-10 sprays) on both sides then hold pressure again for 20 min as above**
3. Control SBP (goal < 120) if much greater than baseline; correct coagulopathy if present and able to
4. **Consult ENT if continued bleed after above steps**
  - o Treatment: silver nitrate cauterization, resorbable nasal packing, non-resorbable nasal packing, Neuro IR embolization
  - o Non-resorbable nasal packing: risk of Toxic Shock very low; put patient on prophylactic cephalexin or clindamycin; packing typically removed after 5-7d (whether inpt or outpt – can be removed by anyone by pulling on string)

Location: most are anterior bleeds from Kiesselbach's plexus (90%); **posterior bleeds are more rare / serious / difficult to manage**

Hx: duration and frequency of bleeding; laterality; EBL; prior episodes (and txs); trauma (fingers, fists, foreign body, etc.); prior nasal surgery; PMHx or FHx of coagulopathy; medications (in particular **anticoagulation**); cocaine or intranasal drug use

Exam: rapidity of bleeding; inspect nasal septum and OP for originating site; **suction clots from OP to protect airway if rapid bleed**

Tests: CBC, PT, PTT, T&S (consider crossmatch pRBC if brisk bleed)

Epistaxis prevention: after resolution x 2 weeks: petroleum ointment; avoid nose blowing / digital manipulation / vigorous exercise; keep head above heart; sneeze w/ mouth open; humidification (saline nasal spray BID); Afrin / hold pressure PRN re-bleeding

## STRIDOR

Acute management:

1. Administer oxygen (low flow = NC, simple face mask, non-rebreather; high flow = venturi mask, HFNC); ensure IV access
2. Racemic epinephrine neb x 1 STAT (lasts ~2h); 10mg dexamethasone IV x 1 STAT (re-dose q8h)
3. Consider Heliox, abx, and humidification; IM / IV epinephrine and Benadryl if allergy suspected (see *Angioedema & Anaphylaxis*)
4. **If unstable → RICU & trauma surgery (x6-3333) for possible surgical airway; if stable → ENT for airway evaluation**

Hx: timing/evolution; inspiratory / expiratory / biphasic; inciting events, prior episodes; evidence of infection; allergy; hx EtOH/tobacco (cancer risks); hx subglottic stenosis; hx of known cancer of head and neck or radiation

DDx (in adults): iatrogenic / post-intubation (laryngeal / vocal cord edema or praxis of the recurrent laryngeal nerve from ET tube); infectious (epiglottitis, laryngitis, laryngotracheitis [croup], bacterial tracheitis, Ludwig's angina); allergic / angioedema; mass of larynx or trachea; neurological (vocal cord spasm / immobility); foreign body; trauma

Imaging: if stable, CT with contrast of head / neck / chest to localize source

## DEEP NECK SPACE INFECTION (see Head & Neck Infections)

Acute management: ([UpToDate Deep Neck Infection](#)):

1. **Ensure protected airway:** intubation or surgical airway for threatened airway → consider glucocorticoids
2. **Empiric antibiotics:** typically need **polymicrobial coverage** (ensure appropriate anaerobic coverage)
  - o E.g., amp/sulbactam vs 3<sup>rd</sup> gen cephalosporin + flagyl; consider vancomycin in pt with risk of MRSA or if sinogenic source
  - o Vancomycin/cefepime/flagyl if healthcare-associated, severe, or immunocompromised
3. **ENT consult for consideration of drainage** (localized infection) and airway monitoring

Symptoms: sore throat; **trismus (inability to open jaw)**; dysphagia / odynophagia; dysphonia; dyspnea / stridor

Exam: neck tenderness; lymphadenopathy; trismus, fullness / asymmetry of OP; crepitus; pooled saliva; stridor

Tests: CBC, PT, PTT, T&S; blood cultures; CT neck with contrast; MRI neck with contrast if c/f osteo

Complications: based on location: parapharyngeal: involvement of carotid sheath (CCA, IJV, CN X), carotid blowout (life-threatening), jugular thrombophlebitis (Lemierre's); retropharyngeal: extension along deep neck spaces/mediastinum (mediastinitis / empyema); prevertebral: spine osteomyelitis; submandibular/sublingual: Ludwig's angina (floor of mouth swelling, rapid resp compromise)

## ACUTE SINUSITIS (Otolaryngol Head Neck Surg 2015;152:S2)

Definition: up to 4 weeks of purulent nasal drainage + nasal obstruction or facial pain / pressure / fullness (or both); can be viral or bacterial (typically bacterial if symptoms > 10 days)

Symptoms: uncomplicated (confined to sinuses): facial pressure / pain, purulent nasal discharge, nasal obstruction, fever, malaise, anosmia, dental pain, ear fullness; complicated (extra-sinus extension): vision changes, proptosis, mental status changes, severe HA, facial soft tissue changes; in immunocompromised/critically ill: consider **invasive fungal sinusitis, a surgical emergency** (see *Invasive Fungal Infections*)

Workup: uncomplicated: no imaging required; complicated: CT w/ contrast ± nasal endoscopy to look for evidence of purulence

- If concern for invasive fungal sinusitis, consult ENT for consideration of nasal biopsy with STAT pathology

Treatment:

- Uncomplicated ABRS: amoxicillin ± clavulanate 5-10 days; nasal steroid spray / nasal saline irrigations for symptomatic relief; if no improvement after 7 days change antibiotic
- Invasive fungal sinusitis: **liposomal amphotericin**, urgent surgical debridement, ID consultation

## SUDDEN HEARING LOSS (Otolaryngol Head Neck Surg 2019;161:S1)

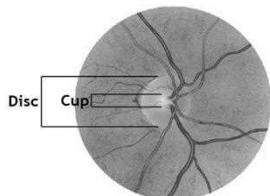
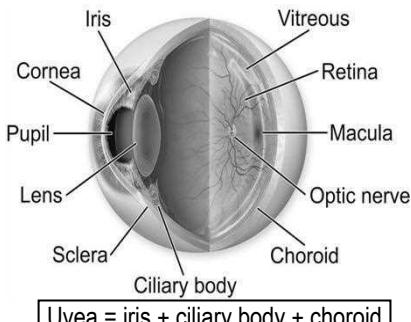
1. Use otoscope to examine ears and **ensure no cerumen impaction**
2. Determine conductive hearing loss vs sensorineural hearing loss – obtain **audiogram**, call 617-573-3266 at MEE to schedule
3. If sensorineural hearing loss, consult ENT for initiation of either high dose oral corticosteroids or intra-tympanic steroids if contraindication to systemic steroids; ideally start steroids within 2 weeks of symptom onset

# Consultants

# Ophthalmology

Check vision using vision card (or 'Eye Handbook' phone app) and pupils **prior to calling consult!**

General inpatient consult: check paging directory and page/call listed number; can also call MEEI ED desk 617-573-4063



## Basic Eye Exam: "Ocular Vital Signs"

- Visual Acuity (e.g. 20/200, CF)
- Pupils (4mm → 2mm OD, No APD)
- Confrontational visual fields
- Extra-ocular movements
- Intraocular pressure
- Color vision testing (Ishihara cards)

## Common Abbreviations:

APD	Afferent pupillary defect	NLP	No light perception (VA)
AT	Artificial tears	NPDR	Non-prolif. diabetic retinopathy
cc/sc	With/without correction (glasses)	NS	Nuclear sclerosis (i.e. cataract)
CE	Cataract extraction	OD/OS	Right eye, left eye
CF	Count fingers (VA)	OU	Both eyes
CWS	Cotton wool spot	PDR	Proliferative diabetic retinopathy
DES	Dry eye syndrome	PF	Pred Forte gtt (prednisolone)
EOM	Extraocular movement	PFAT	Preservative-free artificial tears
HM	Hand motion (VA)	PVD	Posterior vitreous detachment
IOL	Intraocular lens	RD	Retinal detachment
IOP	Intraocular pressure	SLE	Slit lamp exam
LP	Light perception (VA)	SPK	Superficial punctate keratitis/dry eye
MGD	Meibomian gland dysfunction	VA, VF	Visual acuity, 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 drops unavailable: fractionate combo meds, ask pharm for substitution advice, or have pt bring in home meds
- **Dilating drops:** 0.5% tropicamide (parasympathetic antagonist), 1-2 drops placed 15-20 minutes before exam; light-sensitive 4 hours
- **Finding the retina:** dilate the eye and use the ophthalmoscope; see example [Stanford Medicine fundoscopic exam video](#)

## COMMON EYE PATHOLOGY

- **Red Eye:** typically benign; refer to ophtho if no improvement or **any "ocular vital sign" changes** (see above)
  - **Viral conjunctivitis:** eyes "stuck shut" in AM, itchy, crusty discharge, ± URI symptoms, ± pre-auricular nodes, winter time
    - Tx: supportive/isolation (typically adenovirus, highly infectious). Wash hands thoroughly if you suspect this!
  - **Allergic conjunctivitis:** olopatadine 0.1% gtt bid x 5d. Clear Eyes/Visine not rec'd (rebound redness 2/2 alpha agonism)
  - **Anterior uveitis:** pain and true photophobia **must** be present ± eye injection. [Refer to MEEI ED](#)
  - **Contact lens keratitis:** have patients remove contact lens when admitted! Use glasses. P/w red/uncomfortable eye; infection until proven otherwise. [Refer to MEEI ED](#)
  - **Acute angle closure glaucoma:** common sx include nausea, aching pain, vision loss. Palpation of the eye will be "rock hard" or elevated pressure with tonopen. Exam: red eye, hazy cornea, mid-dilated pupil. **Urgent consult to MEEI.**
  - **Subconjunctival hemorrhage:** blood between conjunctiva and sclera from ruptured vessel. No vision changes, not painful. Can be 2/2 blood dyscrasia, valsalva, trauma, spontaneous. Resolves spontaneously. No need to consult if no significant trauma.
- **Blepharitis** (inflammation of eyelids): p/w crusting, red eye, gritty feeling
  - Tx: baby shampoo, warm compresses, abx ointments x 2 weeks, then daily lid hygiene. Tx for **hordeolum ("stye")** is same
- **Dry Eye Syndrome (DES):** p/w eye pain or "grit"/paradoxical tearing ± vague "blurriness"
  - Tx: artificial tears q1h prn first line tx, Refer to ophtho if no improvement
- **Corneal abrasion/exposure keratopathy:** unilateral, redness, mild light sensitivity, common after sedation
  - PPx: intubated patients require lubrication regimen (ophthalmic lubricating ointment QID) ± tape eyelids shut if partially open
  - Dx: apply fluorescein (order in Epic) to the affected eye, illuminate with a blue light (e.g. ophthalmoscope, smartphone screen with Eye Handbook App). Abrasion will light up green; keratopathy will look like "sandpaper" instead of smooth glass
  - Tx: abx ointment (Erythromycin 0.5%/bacitracin ophthalmic QID) + Lacrilube qhs. Consult if no improvement after 24h
- **Anisocoria (unequal pupils):** old (20% population has at baseline) vs. new (can be trivial 2/2 anticholinergic vs. catastrophic from herniation). Always ask for **h/o ocular surgery** as surgical pupil is a common benign cause

Miosis (Constricted Pupil)	Mydriasis (Dilated Pupil)
↑ Cholinergic (e.g. morphine, pilocarpine)	↑ Sympathetic (e.g. atropine, CNIII paralysis)
↓ Sympathetic (e.g. Horner's)	↓ Cholinergic (e.g. epinephrine, cocaine)

- If clinical suspicion for herniation (known bleed, CN3 palsy, obtundation, hemiparesis) → **STAT head CT**
- **Horner's Syndrome:** ptosis, miosis, ± anhidrosis. Wide ddx along pathway from posterior hypothalamus → C8-T2 → superior cervical ganglion → up sympathetic chain along internal carotid and into orbit. Requires head and neck angiographic imaging to r/o potential carotid dissection
- **Retinal detachment:** presents with flashes/floaters/curtain coming over vision. Risk factors: myopia (near-sighted), trauma, diabetic retinopathy, prior eye surgery. Tx: [Refer to MEEI ED](#) for likely vitreoretinal surgery
- **Orbital Cellulitis** (see *Orbital & Preseptal Cellulitis*): most common from sinus disease, periorbital edema/erythema + orbital signs (rAPD, color vision loss, motility disturbance, proptosis). Non-con CT face and orbits for stranding/abscess. [Consult MEEI](#), likely needs admission for IV abx. **Preseptal** negative orbital signs, negative scan, can treat with oral abx and reassess symptoms.
- **Endophthalmitis:** infection within globe. Can be 2/2 trauma, surgery, or endogenous source (bacteremia/fungemia)
  - Tx: [ophtho c/s](#), antibiotics/antifungals that will penetrate blood-brain barrier. May require vitrectomy (surgery)

# Consultants

# OB/GYN

## HOW TO CONSULT

- **Obstetrics:** if pt has pregnancy >20w or has established MGH OB provider (p32344)
  - If no response, call L&D 617-724-9410
- **MFM:** known high risk pregnancy (p17977)
- **GYN Onc:** if pt has biopsy confirmed GYN malignancy or established GYN onc provider (p31037)
- **GYN:** everyone else (e.g., pregnancy <20w, undifferentiated ovarian mass). Obtain pelvic vs. transvaginal **U/S**. If hCG+ but no confirmed intrauterine pregnancy, should be followed on **ectopic list** (p22346)

## ABNORMAL UTERINE BLEEDING

- **History:** verify source of bleeding is vaginal (as opposed to GI or GU), duration and quantity (#soaked pads, tampons), associated sx (pain, dizziness), triggers (e.g., postcoital), trauma history. Other history: estrogen contraindications (smoking, BMI, HTN, h/o coagulopathy), LMP/menstrual hx, full pregnancy hx, known GYN conditions (e.g., fibroids), meds (hormones, AC)
  - **Heavy bleeding = soaking through 1 pad per hour**, symptomatic, Δ VS, ↓ Hgb
- **Exam:** external vulvar exam, speculum exam (note how many scopettes required to clear bleeding, volume of blood in vault, cervical lacerations, blood actively coming from cervix). Do NOT do digital exam if pregnant.
- Postmenopausal bleeding is never normal and often warrants a workup to rule out malignancy. If premenopausal, rule out pregnancy and its complications.

### Differential Diagnosis for Abnormal Uterine Bleeding

Pregnant	Ectopic pregnancy, miscarriage (including incomplete and septic abortion), subchorionic hematoma, placental abruption, placenta previa/accreta, vasa previa, trophoblastic disease, cervical/vaginal/uterine pathology (e.g. polyp)
Not pregnant	PALM-COEIN: Endometrial/cervical polyp, adenomyosis, leiomyoma/fibroids, <b>malignancy</b> (e.g., endometrial, cervical), coagulopathy, ovulatory dysfunction, endometrial dysfunction, iatrogenic, not otherwise classified (thyroid disease, vaginal/vulvar etiologies [e.g., laceration, atrophy]).

- **Workup:** CBC, T&S, coags, pad count (Epic order, monitors bleeding quantity)
  - If premenopausal, first step is **urine hCG**
    - If +, obtain **serum quant hCG** and **pelvic U/S** (must **rule out ectopic pregnancy** in all pregnant women with bleeding)
    - If intrauterine pregnancy not confirmed on U/S, measure serial **serum hCG q48h** (should increase 35-50% in 48h) and repeat pelvic U/S. **Ectopic risk factors:** IVF pregnancy, h/o STIs, prior ectopic, h/o tubal surgery, IUD, smoking
  - If postmenopausal, **pelvic U/S**, consider endometrial biopsy if endometrial lining >4mm (difficult to do inpatient) \*Regardless of U/S result, postmenopausal bleeding warrants at least outpatient GYN follow up\*

## PELVIC PAIN

- **History:** timeline, severity, LMP, associated sx (N/V, GI, GU, fevers/chills, vag bleeding/discharge, wt loss), pain med requirement
- **Exam:** abdominal, CVA tenderness, bimanual exam, consider speculum exam if bleeding or discharge
- **Differential Diagnosis:** non-exhaustive list of most common causes of pelvic pain
  - **Ectopic:** see above; if peritoneal signs on exam or hemodynamically unstable, consider ruptured ectopic (**surgical emergency**)
  - **Adnexal lesions:** benign (simple, hemorrhagic, etc) vs malignant. If high c/f malignancy, obtain CA-125, CA19-9, CEA
  - **Ovarian torsion:** clinical dx, most predicted by acute unilateral pain (<8hr), vomiting, mass (>5cm) ([HuRepro 2010;25:2276](#))
  - **PID:** ascending (e.g., STI) vs descending (e.g., diverticulitis); fevers/chills, vaginal discharge, CMT; complications include TOA
  - **Endometriosis/chronic:** dysmenorrhea, dyspareunia, dyschezia; r/o acute causes, consider outpatient follow up
  - **Non-GYN:** nephrolithiasis, UTI/pyelo, appendicitis, diverticulitis, constipation
- **Workup:** hCG, pelvic U/S, GC/CT, CBC with diff, UA/UCx; consider alternative abdominal imaging pending H&P (e.g., CTAP)

## PREGNANCY AND ITS COMPLICATIONS

Gravida/para (GP), G= #pregnancies, P= #births; TPAL (T=term births, P=preterm births, A=abortions, L=living children)

- **Hypertensive complications:** BP  $\geq$ 140/90 is abnormal, **any BP  $\geq$ 160/110 is an OB emergency**
  - **Differential:** chronic HTN (HTN <20w), gestational HTN (HTN >20w), pre-eclampsia (new HTN + proteinuria), pre-eclampsia with severe features (unrelenting HA, vision changes, RUQ/epigastric pain, lab abnormalities), eclampsia (seizure), HELLP
  - **Workup:** CBC, BMP, LFTs, LDH, uric acid, urine protein/Cr ratio +/- coags and hemolysis workup
- **Hyperemesis:** standing meds most effective, see tx algorithm on [UTD](#)
- **OUD/SUD:** can refer to [HOPE Clinic](#).
- **References:** Normal lab values by trimester ([UTD](#)). Guide to OTC med use/symptom tx during pregnancy: [AFP 2014;90:548](#)

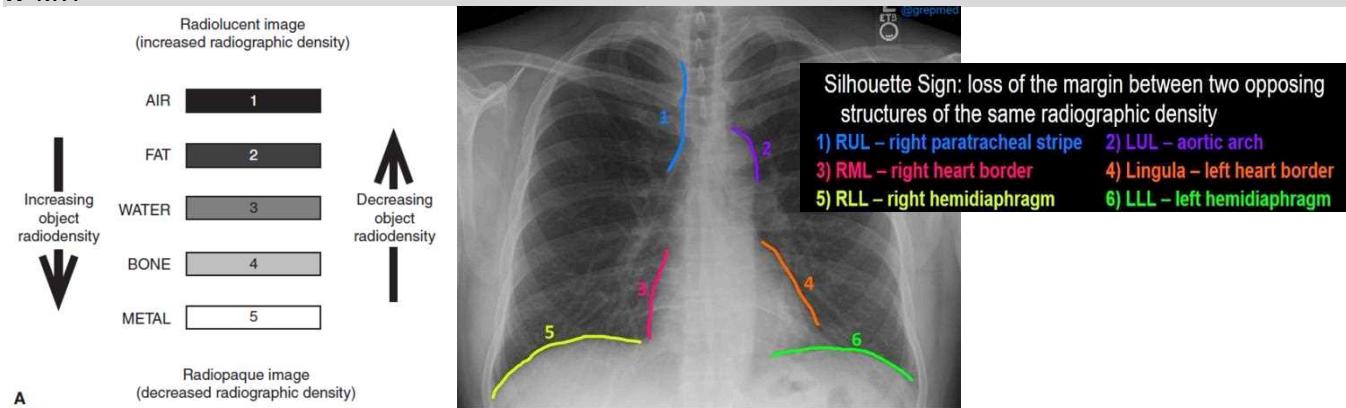
# Radiology

## IMAGING ORDERS

Always include *brief* clinically relevant information to inform the radiologist of your clinical question.

Think of the radiologist as a **consultant** with the goal of adding valuable diagnostic information to patient care via imaging.

## X-RAY



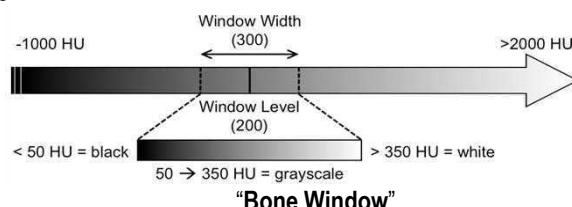
## COMPUTED TOMOGRAPHY (CT)

**Hounsfield Units (HU):** measurement of CT attenuation (see table for reference range)

**Windowing:** adjusting contrast (width) and brightness (level) to better visualize specific structures.

- **Window width ("contrast" - range of grayscale):** range of Hounsfield units.  $HU < \text{window} = \text{black}$ ,  $HU > \text{window} = \text{white}$ , within window = gray. Wide windows for large diff in density (i.e. air/vessel in lung), narrow for similar density (grey vs white matter)
- **Window Level ("brightness" - center of grayscale):** HU at center of window, corresponds to attenuation of structure of interest (e.g. high lvl for bone window, low lvl for lung window)

Phase	Time Post-Injection	Structures Evaluated
CT-PE	5-15 s	Pulmonary arteries
Arterial (CTA)	15-20 s	Systemic arteries, no organs
Late arterial	35-40 s	Arteries, renal corticomedullary differentiation
Late Portal	70-80 s	Organs (Routine abdomen)
Nephrographic	100 s	Renal parenchyma
Delayed (Vascular)	120 s	Active contrast extravasation (bleeding), peripheral veins
Delayed (Urogram)	10-15 min	Ureters, bladder



**"Lung Window"**  
**"Brain/Soft Tissue Window"**

Wide window 1500, Low level -40



Wide window 160, High level +500; Narrow window 80, Medium level +40



Substance	HU
Air	-1000
Fat	-100
Water	0
Blood	50
Soft tissue	100
Bone	1000
Metal	>2000

## MAGNETIC RESONANCE IMAGING (MRI)

MRI safety: search device compatibility at [mrismafety.com](http://mrismafety.com)

	T1	T2
Blood	○	●
Protein	●	○
Air	●	●
Calcium	●	●
Fat	○	○
Fluid	●	○
Gadolinium	○	

Basics of Common MRI Sequences	
Sequence	Purpose
T2 weighted +/- fat-sat	Identify fluid/edema (e.g. most pathology, malignancy). Fat sat refers to technique to make fat appear hypointense.
T1 weighted +/- contrast	Evaluate anatomy; identify T1 hyperintense products, including hemorrhage, fat, protein & contrast (gadolinium) enhancement.
STIR	T2W (fluid/edema) with technique to make fat appear hypointense (more consistent than fat-sat). Common in MSK MRIs.
MRCP	Heavily T2W sequence to eval gallbladder + intrahepatic, extrahepatic, and pancreatic ducts.
HASTE/SSFSE	T2W sequence that is rapidly acquired (fast sequence).
GRE	ID hypointense susc (blooming) artifact a/w blood & calcium.
SPACE	High resolution 3-D sequence (cor, sag, axial).
DWI	Identify restricted motion of intra-/extracellular water molecules (e.g. acute stroke, abscess, highly cellular tumors like lymphoma).

# Radiology

# Contrast

## INDICATIONS FOR CT CONTRAST ADMINISTRATION

- IV positive (I+): vast majority of studies more sensitive when given, particularly for **infection, tumors, and vessel imaging**
- IV negative (I-): urinary tract stones, retroperitoneal hematoma, pulmonary nodule follow-up
- PO positive (O+): bowel obstruction, bowel leak/perforation/fistula, differentiate bowel from other abdominal structures
- PO negative (O-): inflammatory bowel disease, GI bleed, mesenteric ischemia, retroperitoneal hematoma

## PREGNANCY AND BREASTFEEDING (ACR 2022 Manual)

- Contrast Use in Pregnancy:
  - Iodinated contrast for CT studies*: no need to withhold (no data to suggest potential harm to fetus, although limited data)
  - Gadolinium contrast for MRI studies*: do not use unless essential + no suitable alternative (radiology consultation). Req consent.
  - Written consent required if predicted fetal dose >0.05mGy. 1 CT = ~25mGy to fetus. No consent for CXR, C/T-spine, mammo
- Breastfeeding: Current rec: I & G\* safe for mother & infant, may choose to "pump and dump" for 24h after scan.
  - \***Exception – EOVIST**: unknown if Eovist excreted in milk. Consider "pump & dump", but likely safe to nurse after 10h

## RENAL FUNCTION (ACR 2022 Manual; MGPO 2020 (CIN); MGPO 2020 (NSF); JAMA IM 2020;2:223)

Contrast Induced Nephropathy / Post Contrast Acute Kidney Injury (PC-AKI)		Nephrogenic Systemic Fibrosis (NSF)
<u>Definition</u>	<ul style="list-style-type: none"> <li>Association between intravenous / intra-arterial contrast and development of renal impairment</li> <li>Occurs 48-72 hours after contrast admin</li> </ul>	<ul style="list-style-type: none"> <li>Association b/w Gad-based contrast (MRI) in pts with renal impairment &amp; development of systemic fibrosis</li> <li>Occurs weeks to months after contrast admin</li> </ul>
<u>Risk factors</u>	<ul style="list-style-type: none"> <li><b>CKD (consensus most important)</b></li> <li>Diuretic use</li> <li>&gt; 2x contrast doses in &lt;24 hrs</li> </ul> <ul style="list-style-type: none"> <li>Diabetes mellitus</li> <li>Dehydration</li> <li>Cardiovascular disease</li> <li>Age &gt;60 years</li> <li>Hyperuricemia</li> </ul>	<ul style="list-style-type: none"> <li>3 classes of contrast based on risk: I (highest risk), II (minimal risk), III (likely very low risk but limited data)</li> <li>Some risk with Group I and III (e.g., <b>Eovist</b>) in patients with <b>kidney disease</b> (acute or chronic) and/or <b>DM</b>.</li> <li>Risk "sufficiently low or possibly non-existent" w/ default Group II GBCAs (e.g. <b>Dotarem, Multihance</b>)</li> </ul>
<u>Screening</u>	<b>Screen if h/o kidney dz or diabetes mellitus</b> Outpatient: eGFR within 30d, ED: eGFR within 30d, Inpatient: eGFR within 24h	Outpatient: not necessary for most scans Inpatient/ED: eGFR within 24hr for class III agent (e.g. Eovist). None needed for class II agent
<u>Prevention</u>	eGFR ≥30: contrast per protocol (NO prehydration) eGFR <30 or AKI → I- or alternative study. Consult radiology if I+ is medically urgent. Consider prehydration. Dose reduction not considered effective prevention	<b>Group II GBCA</b> : given regardless of eGFR <b>Group I GBCA</b> : consult radiology if eGFR <30 <b>Group III GBCA</b> : do <u>not</u> give if eGFR <30
<u>On Dialysis</u>	If maintenance dialysis w/o possible renal recovery: administer contrast. If possible renal function recovery, (e.g temporary dialysis catheter): consult radiology	<b>Consult radiology. Typically Gad withheld.</b> Prompt post-scan HD suggested (PD inadequate)
<u>&lt;24h repeat studies</u>	Decision is clinical and subjective Insufficient evidence to hold contrast for 24h	No risk factors: proceed At risk patients: consult radiology
<u>Metformin</u>	eGFR ≥30: continue metformin eGFR <30 or AKI: hold for 48h after scan	Continue metformin
<u>Renal txplt</u>	Consult Radiology	Consult Radiology

\*Post contrast peak effect on creatinine occurs 48-72 hours after administration

## Pre-hydration protocol: (ACR 2022) \*If you want an I+ CT scan in a patient w/ eGFR <30, speak to radiology

- Prophylaxis indications: eGFR <30 (not on long-term HD), AKI
- PO hydration: Not well-studied. Historical MGH regimen: 1-2L PO non-caffeinated beverage 12-24h prior to scan
- IV hydration: Start 1 hr prior & cont 3-12 hrs after. Fixed volume (250-500 mL NS) before & after vs. weight-based (1-3 mL/kg/hr)
- N-acetylcysteine is **NOT** recommended for IV contrast prophylaxis

## CONTRAST REACTIONS (ACR 2022)

	Mild	Moderate	Severe
Allergic	Limited urticaria Itchy throat, congestion URI symptoms	Diffuse urticaria Facial/laryngeal edema w/o dyspnea or hoarseness Bronchospasm w/o hypoxia	Anaphylaxis Facial/laryngeal edema w/ dyspnea or hoarseness Bronchospasm w/ hypoxia
Physiologic	N/V, flushing/warmth HA/dizziness Mild HTN Transient vasovagal rxn	Protracted N/V HTN urgency Isolated Chest Pain Vasovagal rxn requiring tx	HTN emergency Arrhythmia Seizure Protracted vasovagal rxn

Standard contrast allergy pre-medication regimen: **13h**

- You *must* indicate standard premedication regimen in the imaging order
- Epic orderset – “Contrast Allergy Prophylaxis: Regular Protocol Order Panel”
- Urgent contrast allergy pre-medication regimen: 4h**
  - Requires discussion with a radiologist before starting regimen
  - Epic orderset – “Contrast Allergy Prophylaxis: Urgent Protocol Order Panel”
- See *Drugs and Contrast* section on pre-medication prior to scan

Indications for Premedication
<ul style="list-style-type: none"> <li>Prior mild-moderate allergic reaction</li> <li>Prior unknown contrast reaction</li> <li>None for prior physiologic reactions</li> <li>None for shellfish allergies</li> <li><b>No cross-reactivity b/w iodinated contrast and gadolinium</b></li> </ul>

## ORDERING STUDIES

- All cross-sectional studies are protocoled by radiology – simply provide the necessary information:
  - Body part: Head, abdomen only, abdomen and pelvis, etc.
  - Modality: Ultrasound, Radiograph, CT, MRI, Fluoroscopy, PET whole body, PET Brain, HIDA Scan, etc.
  - Indication: clinical history relevant to the study
  - Contrast: “per radiology discretion” unless specific reason otherwise (**I+ IV; O+ oral; R+ rectal**)
  - Contraindications for contrast: renal transplant, kidney injury or prior allergic reaction (see Contrast)
  - Questions? - call the appropriate division or page the appropriate on-call radiologist (see *MGH Directory*)
    - Inpatient study questions? - call ED reading room **after 7PM weekdays/5PM on weekends** (unless STAT study). Otherwise, call divisions during work hours (8am-7pm weekdays/8am-5pm on weekends; vascular 8am-noon weekend).
- **Level of Urgency:**
  - Routine: order of interpretation depends on acquisition time
  - Urgent: takes priority over routine studies (performed within 6 hours)
  - STAT: means **NOW, high acuity/life threatening emergencies (i.e., trauma patient may be removed from the scanner for your patient)**; these studies are typically (not always) performed in White 1 (ED scanners)
    - Must call the body or neuro ED radiologist for approval (*MGH Directory*)
    - Patient must be ready for immediate transport. Responding team must transport patient (no transport provided)
    - Patient must be accompanied by a responding clinician ( $\geq$ PGY-2) capable of providing emergency care
    - Responding clinician must be present for the entire exam
    - Radiology will provide preliminary read: phone call for XR/US, at the scanner for cross-sectionals

## OVERNIGHT READS BODY EXT.4-1533 | NEURO EXT.6-8188

- Full interpretation reads overnight: All ED studies
- Preliminary interpretation reads overnight (labeled “Imaging Note” found under the Imaging tab in Epic):
  - All acute CT-PE studies (inpatient and ICU)
  - By verbal request: inpatient and ICU studies
    - **Routine/Urgent ICU & inpt studies** only reviewed overnight if **urgent clinical question**. Consider face-to-face c/s in ED.
    - **STAT ICU and inpatient studies will receive a prelim interpretation**.
  - After communication with the primary team, all verbalized prelim reads for ultrasound and cross-sectional studies (CT/MRI) will be documented in the chart. Verbalized prelim reads for radiographs (XR) will be documented as needed.
  - All inpatient and ICU full interpretations will be generated the following morning by appropriate division

## ED PROTOCOLS BODY x4-1533 | NEURO x6-8188

- Trauma: I+ (IV contrast), single phase (combo of arterial/portal venous – images checked at scanner by rads to decide if need delays)
  - Blunt trauma: includes bone kernel reformats for better visualization of bones; +/- Delays for parenchymal bleed
  - Penetrating trauma: O+R+ (Oral contrast, rectal contrast) for increased sensitivity of bowel injury
  - CT Cystogram: retrograde filling of bladder with contrast via Foley catheter to evaluate for bladder rupture
- Cervical spine: I-, need for follow-up CTA head/neck determined by radiology, bone kernel reformats in all 3 planes
  - Images checked at the scanner by radiology only if IV contrast is required for another body part
- Appendicitis: I+, possibly O+ or R+ (if GI contrast requested, please specify PO or PR), image kidneys through pelvis only
- Retroperitoneal Bleed: I-O-
- Indications for MRI in the ED: Pediatric appendicitis after equivocal ultrasound || Appendicitis suspected in pregnancy || Rule out occult fracture || Osteomyelitis || Choledocholithiasis (MRCP)
- OB Ultrasound Studies: Covered up until 14 weeks

## ABDOMINAL PROTOCOLS x6-5162

- Stone protocol: I-O-, low dose, prone
  - Order contrast-enhanced (I+) CT if there is c/f ANYTHING else (e.g. pyelonephritis) as stones likely still visualized
- Retroperitoneal hemorrhage: Routine abdomen/pelvis I-O-
- Routine abdomen/pelvis vs renal mass vs bladder cancer vs hematuria:
  - Routine abdomen/pelvis: I+O+, single phase (portal venous) → workhorse protocol
  - Renal mass: I+O+, two phases (noncontrast, nephrographic), abdomen only → renal masses or cysts
  - Bladder cancer: I+O+, two phases (portal venous, delayed) → workup or monitoring of GU malignancy
  - Hematuria: I+O-, “three” phases (noncontrast, nephrographic, urogram) → hematuria, hydronephrosis
- CT urogram vs CT cystogram:
  - Urogram: antegrade filling of ureters and bladder via excretion of IV contrast (delayed phase)
  - Cystogram: retrograde filling of bladder with contrast via Foley catheter to evaluate for bladder rupture
- Arterially-enhancing tumors: add arterial phase along to usual CT protocol
  - MR CHIT: Melanoma, RCC, Choriocarcinoma, HCC, Islet cell (neuroendocrine) tumors, Thyroid
- Time to be NPO: IV contrast CT: 2h || Abdomen/pelvis CT: 8h. || Non-contrast CT: no NPO
- Fluoroscopy protocols:
  - Requisition: specify indication, h/o surgery or aspiration
  - Barium swallow vs modified barium swallow vs UGI series vs SB follow-through:
    - Barium swallow: eval esophagus, GE junction, proximal stomach → dysphagia, GERD
    - Modified barium swallow: eval mouth, pharynx, upper esophagus → dysphagia, **aspiration**

# Radiology

# Protocols

- UGI series: barium swallow plus stomach, pylorus, and duodenal bulb → bariatric surgery pre-op eval
- SB follow-through: small bowel, terminal ileum, and proximal LB ± UGI series beforehand

## CARDIOVASCULAR PROTOCOLS VASC x4-7115 | CARD CT x4-7132 | CARD MR x3-4457

- DVT imaging:
  - Compression ultrasound is the best initial test of choice ([ACR 2018](#)); Epic order “LENI” (Lower Extremity Non-Invasive)
  - CTV/MRV: primarily used for central venous thrombosis when initial US is equivocal or non-diagnostic
- Arterial imaging:
  - CTA: three phases (noncontrast, arterial, venous delays) → stenosis, dissection, aneurysm, active bleeding, systemic embolism/thrombosis (**not pulmonary embolism**)
  - Requisition: specify vessel of interest, field of view, and indication
- Coronary CTA:
  - ECG-gated study of the coronary vessels → only performed by cardiovascular CT
    - Requires beta blocker and vasodilator administration
    - **Not performed after 7pm on weeknights or noontime on weekends**, as cardiac techs are typically not in house
    - On call Cardiac CT Fellow is available for urgent questions after hours: p22122
  - Specify if body parts other than the heart should be imaged (thoracic aorta, CABG grafts, etc.)
- Other ECG-gated CTAs:
  - Indications: any eval of the heart or ascending aorta. ECG-gating unnecessary for descending thoracic/abd aorta & pulm arteries
- Noncontrast vascular studies:
  - Indications: Retroperitoneal hematoma, pre-op aortic calcifications, coronary calcium score, follow-up aortic size

## THORACIC PROTOCOLS X3-3899

- All chest CTs are high resolution
- Routine chest vs CT-PE vs CTA chest:
  - Routine chest: single phase (late arterial) → workhorse protocol (read by Thoracic)
  - CT PE: single phase (pulmonary arterial) → **pulmonary** arteries (read by **Thoracic**), prelim by ED during off-hours
  - CTA chest: three phases (non-contrast, arterial, delays) → **systemic** arteries (e.g. aorta) (read by **Vascular**)
- Double rule out studies: (Clinical concern for PE and aortic dissection)
  - Contrast can only be optimized for one (must pick CT-PE or CTA)
- Diffuse lung disease (a.k.a. misnomer “high res CT”):
  - Indications: ILD, lung transplant, air trapping, bronchiectasis
  - Phases: Inspiratory and expiratory images, plus prone images to differentiate between atelectasis and fibrosis
- Nodule follow-up: ([Radiology 2017:284:228](#); Please refer to Fleischner guidelines)
  - Indications: incidental nodule on prior CT, age >35y, **AND** no hx immune compromise, malignancy or recent infection
- Dual energy esophageal leak (I+/I-): Esophageal perf, postop leak; Tracheal Protocol: Tracheal stenosis, mass, stent

## NEURORADIOLOGY PROTOCOLS

- Inpatients: page Neuro IP on-call radiologist at p32535
- Inpatients/ICU Acute Stroke: call x6-3333 & page p21723 acute stroke consult fellow (ED: activated ED2CT group pager)
- Head CT: typically noncontrast
  - Indications for contrast-enhanced head CT: infection and/or tumor AND contraindication for brain MRI
- Spine MRI: for more than one segment, **please order total spine** and specify indication
  - Separate MRIs should not be ordered prior to neurology/NSGY consult
- Fluoroscopy-guided LPs: performed by neuroradiology fellows, NOT neuro IR
  - Indications: difficult anatomy, and only after LP is attempted on floor
  - Typically performed without conscious sedation, although this can be arranged if required for patient safety

## NUCLEAR MEDICINE PROTOCOLS NON-PET X6-1404 | PET X6-6737

- Tagged RBC study: BRBPR (**NOT** guaiac positive stools, melena, or massive bleeding)
  - Requirements: consult **IR BEFORE STUDY** to confirm angiogram will be performed if study is positive
- VQ scan: acute PE (**NOT** chronic PE), can happen overnight if results will alter management (i.e., AC tonight)
  - Technically just a perfusion (Q) scan since COVID; Ventilation (V) portion of the study is no longer performed.
  - Requirements: CXR or I-CT chest within 24h, patient stable and can tolerate laying supine for duration of scan (~4h)
- HIDA scan: acute cholecystitis
  - Requirements: NPO 4h prior to study, no opiates 12-24h prior to study, bilirubin <10, pt will need to tolerate lying supine
- PET: must be fasting, hold everything but meds and water (NO glucose containing fluids either ex: D5W)
  - Overnight is ideal for NPO, but at least 6h for non-DM patients
  - At least 4h for DM patients
    - Continue long-acting insulin, hold short-acting insulin 4h prior to scan
  - Blood sugar thresholds: FDG-PET brain < 175 mg/dL, FDG-PET whole body <250mg/dL
- Gastric emptying study:
  - Patient must tolerate PO (consume a standardized meal in 10 minutes), best performed as outpatient study

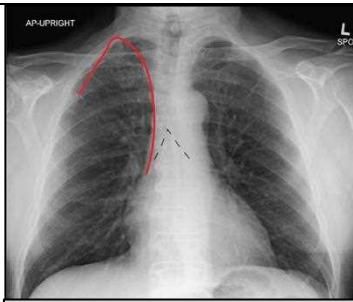
## MUSCULOSKELETAL PROTOCOLS

: if questions: page MSK IR on-call radiologist at p36321

## CHEST X-RAY

### 1. Line placement

- ETT positioning: tip 3 - 7 cm above the carina in an adult
- SVC: b/w R tracheobronchial angle and R heart border ([Chest 1998;114:820](#))
- Superior cavoatrial jxn: ~2 vertebral bodies below the carina ([JVIR 2008;19:359](#))
- Line positioning:
  - PICC or Central line: tip in the lower SVC or at the superior cavoatrial jxn
  - HD catheter: tip in the right atrium
- Post placement: check for pneumothorax, except with PICC/midline (see below)



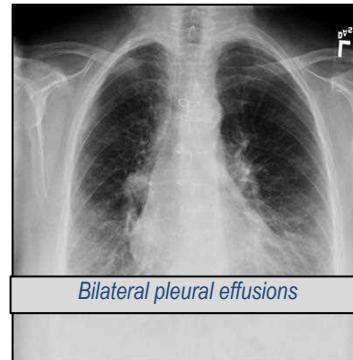
Red line outlines optimally placed central line. Dotted line denotes carina.

### 2. Pneumothorax

- Sensitivities:

Imaging Position	Detectable PTX Size	Imaging Findings
Supine/Portable	500 cc (LEAST Sensitive)	Deep sulcus sign, lucency along mediastinal border
Upright	50 cc	Sharp pleural edge, absence of distal lung vessels
Lateral decubitus	5 cc (MOST sensitive)	Nondependent collection of air

- Tension: contralateral mediastinal and tracheal shift, collapse of ipsilateral lung, flattening of ipsilateral hemidiaphragm, widening of ipsilateral rib spaces
- Artifacts that mimic visceral pleural lines: ([BMJ 2005;330:1493](#))
  - Skin folds: form an interface (not a line), extension beyond rib cage, presence of distal lung vessels
  - Medial border of scapula: extension beyond rib cage w/ rest of scapula



Bilateral pleural effusions

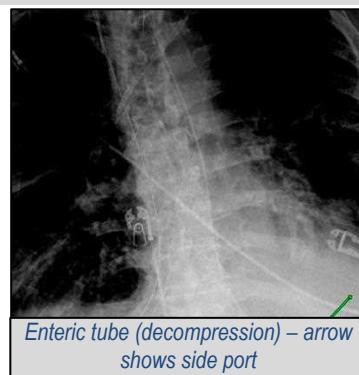
### 3. Pulmonary edema ([example images](#))

- Vascular redistribution (first sign): increased caliber of pulmonary vessels in upper lobes ("cephalization")
- Interstitial edema: incr. interstitial opacities, indistinct pulmonary vasculature, **Kerley B lines** (peripheral subpleural linear opacities), peribronchial cuffing
- Alveolar edema: perihilar/central opacities, pleural effusions, cardiomegaly
- Pearls: typically bilateral and symmetric, rapid appearance/resolution of findings
- Pitfalls: low lung volumes mimic increased interstitial opacities via crowding of normal vasculature

## ABDOMINAL X-RAY (KUB)

### 1. Line placement

- For Decompression: gastric fundus or dependent portion of stomach. Side-port AND tip should be 4-6 cm below the GE junction.
- For Feeding: distal duodenum or proximal jejunum; C-loop of duodenum is only reliable indicator of post-pyloric placement
- Post placement Assessment: check for endobronchial placement. Should descend vertically in midline, pass diaphragm, tip should be visualized



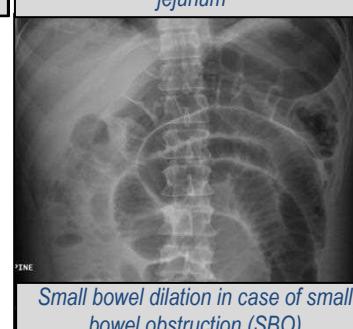
Enteric tube (decompression) – arrow shows side port



Feeding tube - weighted tip in proximal jejunum

### 2. Small bowel obstruction ([RadioGraphics 2009;29:423](#))

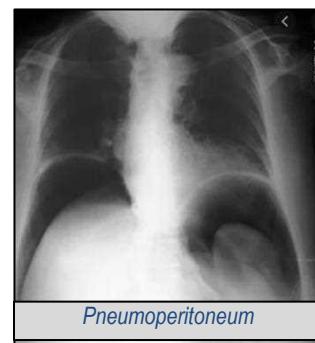
- **KUB**: preferred initial examination
  - Assess for: small bowel dilatation >3 cm, decompressed distal small/large bowel, air-fluid levels, stacked loops of bowel, free air as a complication
  - Main differential: post operative ileus → often large bowel is also dilated
- **CT**: equivocal cases / further evaluation
  - Findings: SB dilatation with collapse of distal bowel loops and transition point
  - Severity:
    - Partial: passage of air or contrast beyond the obstruction
    - Complete: no passage of air or contrast beyond the obstruction
  - Transition point: look for small-bowel feces sign (fecal material mixed with gas bubbles in small bowel just proximal to transition point)
  - Common causes: adhesions, Crohn's, malignancy, hernias; colon cancer most common cause in LBO
  - Closed loop obstruction: radially oriented bowel loops, engorged mesentery, whirl sign
  - Strangulated/incarcerated hernia (ischemia): bowel wall thickening, lack of bowel wall enhancement, pneumatoisis intestinalis, portal venous gas



Small bowel dilation in case of small bowel obstruction (SBO)

### 3. Pneumoperitoneum ([AJEM 2009;27:320](#))

- Upright: air beneath the diaphragm
- Left lateral decubitus: air overlying the liver
- Supine: **insensitive** exam



Pneumoperitoneum

## ULTRASOUND

### 1. Cholecystitis ([AJR 2011;196:W367](#))

- US is preferred initial examination
- Common findings: gallstones, gallbladder wall thickening >3 mm, gallbladder distension (>4cm transverse, >8cm longitudinal), peri-cholecystic fluid
- Sonographic Murphy's sign: 92% sensitivity (analgesics reduce sensitivity, unreliable if recent analgesics)
- Gallstones and gallbladder wall thickening: 95% positive predictive value for acute cholecystitis
- Key Differential - Gallbladder wall thickening without stones and without distension is more likely to be from third spacing (CHF/renal failure/cirrhosis) or underlying liver disease (hepatitis); much less likely cholecystitis

### 2. Deep venous thrombosis ([Cardiovascular Diagnosis and Therapy 2016;6:493](#))

- Compression U/S: noncompressibility of vein (key finding), echogenic thrombus within vein, venous expansion
- Venous duplex U/S: absence of color Doppler signal, flow phasicity, & response to augmentation maneuvers
- Non-obstructive vs. Obstructive thrombus: both are non-compressible, obstructive lacks color Doppler flow
- CT venogram:
  - Alternative to U/S in critically ill patients who have undergone CT PE
  - Pros: evaluation of pelvic veins and IVC, which are difficult to assess on US
  - Cons: invasive, requires contrast, radiation, possible streak or mixing artifacts

## CROSS SECTIONAL IMAGING

Excellent resources for anatomy, image interpretation, and sample cases:

<https://radiopaedia.org/>; <https://radiologyassistant.nl/>; <https://introductiontoradiology.net/>; <https://www.learnabdominal.com/> (GI/GU); <http://xrayhead.com/> (MSK)

### CT Head Example Search Pattern

1. **Brain parenchyma**
  - a. Mass lesion: brain window
  - b. Intraparenchymal hemorrhage: brain window
  - c. Infarction: stroke window
2. **Epidural / Subdural Hematoma**
3. **Vessels**
4. **CSF spaces**: ventricles, sulci, basal cisterns
5. **Midline shift or herniation**: coronals helpful
6. **Soft tissues** (great to start with for trauma head CTs)
7. **Bones/sinuses**

### MRI Brain Example Search pattern

1. **Brain parenchyma**
  - a. Mass lesion: T1, T2, FLAIR
  - b. Intracranial hemorrhage: SWI, T1, T2
  - c. Infarction: DWI, ADC
2. **Vessels**: T2 for flow voids, T1 post-contrast, TOF if non-contrast MRA
3. **CSF spaces**: T2
4. **Midline shift or herniation**: coronals helpful
5. **Soft tissues**
6. **Bones/sinuses**

### CT Chest Example Search Pattern

1. **Lines and tubes** (scout can be very helpful)
2. **Upper Abdomen**
3. **Soft tissues**
4. **Bones**
5. **Heart and mediastinum**: thyroid, lymph node stations, heart and pericardium, asc/desc aorta, great vessels, esophagus
6. **Pleura**: pleural effusion, pneumothorax
7. **Airways**: trachea, bronchi, bronchioles
8. **Lungs**: pathology manifests as changes to the secondary pulmonary lobule (see links)
  - a. Radiology Assistant → [Lung HRCT Basics](#)
  - b. Radiopedia → [Lobule Basics](#)

### CT Abdomen/Pelvis Example Search Pattern

1. **Lung bases and partially visualized heart**
2. **Liver/gallbladder**: focal lesions, biliary dilatation
3. **Spleen**
4. **Pancreas**: focal lesions, pancreatic ductal dilatation
5. **Adrenals**
6. **Kidneys/ureters**: hydronephrosis, stones, focal lesion
7. **Bladder/Prostate/Uterus/Adnexae**
8. **Peritoneum**: free air or fluid
9. **Lymph Node Stations**
10. **Vessels**: AAA
11. **GI tract**: bowel distension, bowel wall thickening, appendix, terminal ileum
12. **Soft tissues**
13. **Bones**

# Procedures

# Ultrasound Basics

**REMINDER:** do not base clinical decisions on POCUS exams unless the exam and decisions are supported by a supervising provider. Additionally, POCUS should be used in the setting of *limited and targeted clinical questions*.

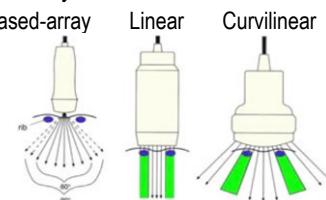
## EQUIPMENT (NEJM 2011;364:749)

### Basic Terminology:

- Frequency: 1Hz = 1 cycle/sec; medical US typically between 2-15MHz
  - High frequency (>5MHz): ↑resolution, shallow tissue penetration, ideal for **vascular, skin, breast, thyroid**
  - Low frequency (2-5MHz): ↓resolution, deeper tissue penetration, ideal for **abdominal, OB/GYN, cardiac**
- Gain: signal amplification; similar to brightness control. Higher gain = brighter image; lower gain = dimmer image
- Depth: depth of field of view (FOV). Excessively large FOV = ↓spatial resolution; tight FOV limits view of nearby structures
- Attenuation: reduced signal transduction through a medium = ↓signal intensity behind it (bone/air/stones have high attenuation)

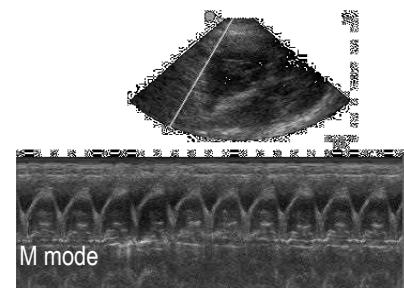
**Transducer (probe)**: converts electricity into sound waves → transmits sound wave into tissue → receives sound waves echoed back from tissue. Indicator (denoted by dot or notch on probe) displays on **left of the screen**. Exception: echocardiography → indicator displays on **right side**. For most indications, position probe with indicator to patient's right or cranially

- PHASED-ARRAY (cardiac) probe: good for looking in small windows (i.e. between inter-costal spaces for cardiac or pulm imaging); low resolution, fan-like image
- LINEAR (vascular) probe: good for shallow structures (i.e. vascular, soft tissue). Uses high frequency with good resolution, produces rectangular image
- CURVILINEAR (abdominal) probe: good for deeper structures (i.e. intra-abdominal). Uses lower frequency; combines linear and phased-array probe image qualities



## COMMONLY USED MODES

- B-mode (brightness mode): standard 2D gray-scale image
- D-mode (doppler mode): detects flow to or away from transducer. Useful to find and define vessels, or flow across valve
  - Color → direction and velocity are color coded and superimposed on B-mode image. "**BART**" (Blue is Away from probe, Red is Towards)
  - Power → detects very low flow but not direction, useful in vascular compromise
  - Spectral → velocity presented graphically on a timeline
- M-mode (motion mode): takes a slice of a B-mode image over time. Often used in TTE. Useful to assess lung sliding for pneumothorax



## GENERAL IMAGING CONCEPTS

### Typical Appearance of Normal Tissue:

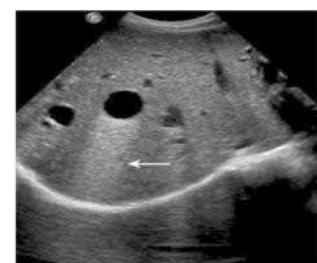
- Skin and pleura are smooth and brighter than surrounding tissue (**hyperechoic**)
- Fat and muscle are darker (**hypoechoic**), though varies depending on the tissue
- Fluid (e.g. blood, effusion, ascites) is black on US (**anechoic**), though thick fluids (e.g. pus) can be brighter than typical fluid
- Tendons and nerves are bright (**hyperechoic**) if perpendicular to probe, dark (hypoechoic) when angle is changed (anisotropy)
- Bone has a hyperechoic rim (due to reflection) with dark shadow beyond it



Acoustic Shadowing (gallstone)

### Artifacts: elements seen on ultrasound image that do not exist in reality

- Reflection: proportional to the difference in acoustic impedance between two tissues (↑difference = ↑reflection)
- Relative acoustic impedance: bone > solid organ > fat > lung > air
- Shadowing: signal beyond strongly attenuating/reflecting structure (e.g. stones, bone)
- Enhancement: signal posterior to weakly attenuating (hypo or anechoic) structure (e.g., cysts)
- Mirror image: structures in front of strong reflector (e.g. diaphragm) appear to lie behind it as well
- Reverberation: evenly spaced lines at various depths beyond a strong reflector (e.g. A lines beyond pleura)
- Comet tail: tiny, narrow reverberations beyond very strong reflector (e.g. metal pellet) blending into a line



Acoustic Enhancement (liver cyst)

# Procedures

# Ultrasound Basics

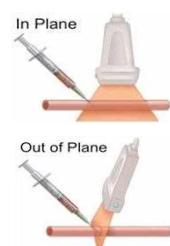
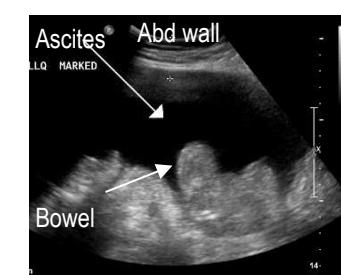
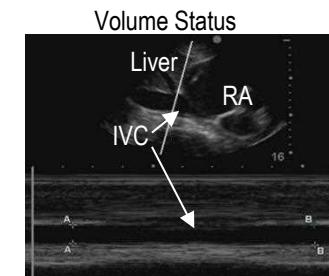
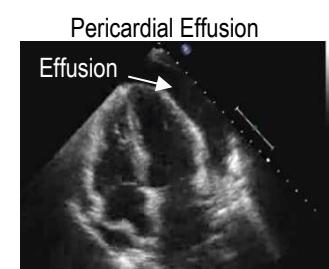
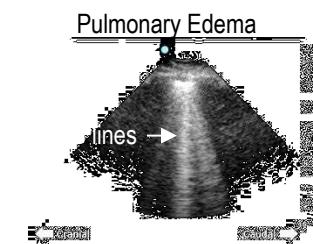
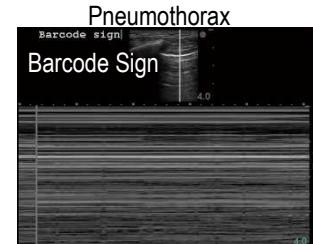
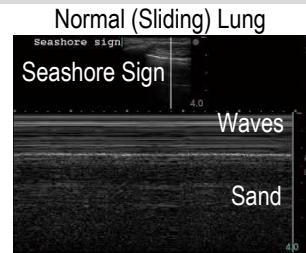
IMAGING AND TIPS (see [The POCUS Atlas](#) for reference)

Diagnostic Use:

- **Pneumothorax:** use LINEAR (vascular) or CURVILINEAR probe. In supine patient, look in 3rd intercostal space on anterior chest, pointing indicator cranially. Identify hyperechoic rims of the ribs with posterior shadowing. The pleura is the hyperechoic stripe that is within the intercostal space. Normal lung will slide along the pleural line with respiration, while pneumothorax will not. If ambiguous, use M mode to confirm. A lack of lung sliding will change the normal 'seashore' sign to a static 'barcode' sign. Sn 91%, Sp 98%, superior to CXR. Can also look for "lung point" (100% specific) ([J Emerg Trauma Shock 2012;5:76](#); [Annals EM 2013;61:207](#))
- **Pulmonary embolism:** use PHASED-ARRAY (cardiac) probe. Bedside US can be used to identify right heart strain. Look for RV size  $\geq$  LV size, septal bowing (D-sign in parasternal short), note Sn 53%, Sp 83% for PE. RV/LV ratio most easily visualized in apical 4 chamber view, can be misleading based upon slight changes in plane. Assess the cardiac septum vertical and in line with midpoint of probe. Combine with parasternal axes for better reliability ([J Am Soc Echocardiogr 2017;30:714](#))
- **Pulmonary edema:** use PHASED-ARRAY (cardiac) or CURVED (abdominal) probe. Evaluate the lung between rib spaces and across multiple lung fields similar to auscultation. Look for B-lines: comet like artifacts that shine perpendicular from the pleural line and obliterate A-lines.  $\geq 3$  in one interspace is consistent with interstitial fluid, and bilaterally suggests pulmonary edema. Ddx of B-lines is broad. Operator dependent but can outperform CXR ([Intensive Care Med 2012;38:577](#); [Acad Emerg Med 23:223](#))
- **Pericardial effusion:** use PHASED-ARRAY (cardiac) probe. Look for an anechoic collection between the heart and the hyperechoic pericardium. Hemorrhagic or purulent effusions may appear more complex. On parasternal long axis, pericardial effusion will be anterior to the descending aorta while a pleural effusion will be posterior. All four views are important but subxiphoid often used in emergencies. Look for chamber collapse indicating tamponade: RA is more sensitive; RV is more specific ([Resuscitation 2011;82:671](#))
- **Volume status:** use the PHASED-ARRAY (cardiac) probe. IVC collapsibility has been proposed as a proxy for CVP and fluid responsiveness, though data is mixed. There are no consensus guidelines. Start with subcostal view of RA/RV, then rotate probe to the sagittal plane to find the IVC draining into RA and abutting the liver. Look at IVC 2cm from RA: fluid responsiveness or an underfilled IVC is suggested by 1) IVC diameter  $\leq 1.5\text{cm}$  and 2) IVC collapses  $\geq \frac{1}{2}$  its diameter with inspiration. Can use M mode to assess collapsibility. IVC diameter  $\geq 2.1\text{cm}$  with  $\leq 50\%$  inspiratory collapse can indicate elevated CVP. Pair IVC POCUS w/ lung US for volume status evaluation. ([Crit Care 2012;16:R188](#); [CCM 2013;41:833](#); [Shock 2017;47:550](#))

Procedural Use: refer to pages on specific procedures for more details

- **Paracentesis:** use CURVILINEAR (abdominal) probe. Locate largest fluid collection, often in LLQ. Try rolling patient to side to increase pocket size. LINEAR (vascular) probe can help identify any overlying vessels (particularly inferior epigastric vessels). Bowel appears as hyperechoic finger-like projections within the anechoic ascites, ensure prior to procedure scanning in multiple locations and fanning to assess for bowel (to avoid perforation). Measure the depth of the abdominal wall and compare to your needle to determine when to expect flash.
- **Central venous access:** use LINEAR (vascular) probe. Reduces complications and quality of placement compared to landmark approach ([Crit Care 2017;21:225](#))
  - In-plane (longitudinal): can view entire tip, but harder to keep needle in view
  - Out-of-plane (cross sectional): easier to center needle, may underestimate depth
- **Peripheral IV:** use LINEAR (vascular) probe. Most of your time should be spent finding the best vein to go for. Evaluate anterior forearm prior to assessing the cephalic in upper arm. Track along vessel length to determine trajectory, look for large, superficial, compressible vessels that are not immediately adjacent to pulsatile, non-compressible arterial vessels



# Procedures

# Ultrasound-Guided Peripheral IV

## GENERAL CONSIDERATIONS

**Indications:** non-emergent access in a patient with difficult access. If emergent, obtain IO or central access

**Locations:** forearm first; then AC, cephalic, basilic, brachial; larger veins offer higher chance of success than smaller veins (see figure)

**Contraindications:** relative: sensory/motor deficits (clot risk), HD fistula, hx of LN dissection, overlying infection/cellulitis

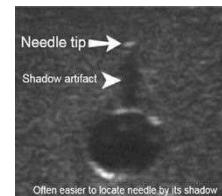
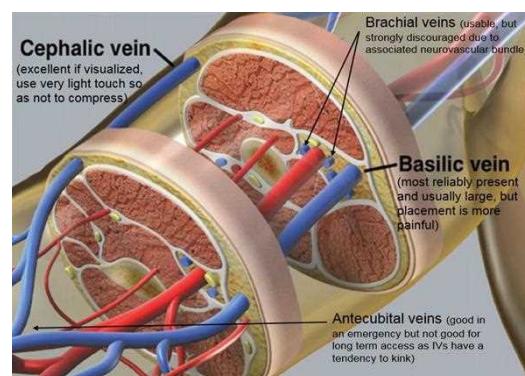
**Materials:** angiocath (18 or 20G best; small IVs not well visualized on US), vascular probe, gel/sterile lubricant, tourniquet, alcohol wipe/chlorhexidine, tegaderm, extension tubing, saline flush, ± vacutainer adapter and tubes/cultures (if labs needed)

- **Angiocath selection:** standard length (30mm) good for vein <0.8cm deep; long needle (48mm) preferred for ≥0.8cm deep (48mm 18G [green] stocked in most supply rooms, but 48mm 20G [pink] more difficult to find. Can try back of AMPS US cart as last resort.

## TRANSVERSE TECHNIQUE

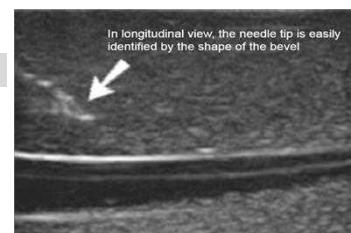
[NEJM 2012;366:e38](#): choosing a vein (8:45), transverse (10:05), longitudinal (12:28)

- 1) **Setup:** positioning is crucial. Place US on opposite side of pts bed, adjust bed to appropriate height, obtain seat if needed, abduct & externally rotate pts arm
- 2) **Place tourniquet:** place tourniquet proximal, near axilla if possible
- 3) **Confirm anatomy:** use vascular probe at minimum depth to locate adequate superficial veins, M-mode line can be helpful to stay centered
  - **Find vessels:** start at AC and move proximal first, then distal. Key is to find LARGE vessels (>0.4cm diameter) that are CLOSE to the surface (depth between 0.3cm – 1.5cm) ([J Emerg Med 2010;39:70](#)). Common veins: basilic, cephalic > deep brachial (see figure)
  - **Confirm venous circulation:** gentle pressure differentiates veins (fully compressible, non-pulsatile) and arteries (non-compressible, pulsatile); color doppler can confirm; recommend scanning both arms (if able)
  - **Trace vessel course:** follow the vessel course proximally and distally; recognize and avoid branch points, diving veins, and irregular coursing veins → identify the trajectory along which the ultrasound probe travels to maintain centered vessel
- 4) **Sterility:** use alcohol pad or chlorhexidine swabs to sterilize proposed venipuncture site; clean US probe, then cover with tegaderm; use sterile lubrication (or sterile US gel) as conduction medium for probe (can also put gel under tegaderm)
- 5) **Orient ultrasound:** center target vein on US screen, confirm with compression, confirm vein course is in line with proposed needle course, stabilize probe by anchoring hand on patient
- 6) **Insert angiocath:** with *bevel up*, puncture skin and advance angiocath 2-3 mm at a 45° angle
  - Angiocath needle tip should be *centered on US probe* – this will be directly over the vein if vein is centered on screen
  - Insertion site at skin is *distal* to the planned site of insertion into vein
  - At skin insertion, eyes should be on the *site of venipuncture*, not on the US screen, though after puncture, should be watching screen at all times and not hand
- 7) **Find tip and advance:** needle tip (and shadow) should appear on screen → advance PROBE until you lose needle tip → advance NEEDLE tip until it reappears on US screen; continue to advance until tip is “tenting” the roof of the vein
- 8) **Enter vein:** a quick short jab will allow you to enter vein; visualize needle tip as “target sign”
- 9) **Drop angle and advance:** drop your hand to flatten needle angle; continue to advance as above, keep needle in center of vein (always aim to get “target sign” with each probe then needle advancement) until angiocath is hubbed to skin, then retract needle
- 10) **Alternative: Slide off catheter:** once 3-5mm into vein, can slide catheter off needle into vein and hub, and retract needle
- 11) **Flush:** attach extension tubing, REMOVE TOUNIQUET, pull back on saline flush (ensure drawback), THEN FLUSH with saline → can also confirm lack of extravasation of saline under US visualization
- 12) **Secure:** secure catheter and tubing with tegaderm; nurses may redress IV



## LONGITUDINAL TECHNIQUE: use the following adjustments to the above technique

- 1) Identify target vein in the transverse view
- 2) **Rotate the probe to obtain a longitudinal view with the indicator towards your needle**
- 3) Align needle in the plane of the probe; puncture skin at 45 degrees, visualize needle tip
- 4) Advance needle until you can see that the tip of the catheter itself is fully within the vein
- 5) Do not go through the back wall. Advance the catheter under direct visualization



Technique	Pros	Cons
Transverse (short axis)	- Faster, requires less finesse with US probe - Allows visualization of adjacent structures	- Harder to visualize the needle tip - Risk of “through and through”
Longitudinal (long axis)	- Improved visualization of the needle tip - Can advance catheter under direct visualization	- Challenging to maintain probe/vein/needle in plane - Cannot see adjacent structures

## TROUBLESHOOTING (Transverse Video; Longitudinal Video; written guide: [West J Emerg Med 2017;18:1047](#))

- **Can't see needle:** gently bounce the needle tip to generate artifact or slight fanning of the ultrasound probe until the tip is in view
- **Too much loose tissue:** use tape or have someone assist by putting tension on the tissue w/o applying pressure over target vein
- **Vein rolls:** reposition directly over the middle of vein, use a slightly steeper angle to take advantage of the sharp edge of the needle
- **Trouble finding any veins:** try using a blood pressure cuff high in the axilla instead of a tourniquet, but give the patient frequent breaks

# Procedures

# Central Line

## GENERAL CONSIDERATIONS

**Indications:** hemodynamic monitoring (CVP, CVO<sub>2</sub>); admin. of noxious meds (pressors, chemo, hypertonic solution, TPN); rapid large volume resuscitation; inadequate peripheral access; HD/CVVH/pheresis; to introduce other devices (PA line, temp wire)

**Contraindications:** vein thrombosis or stenosis should prompt another site. Coagulopathy/thrombocytopenia are relative contraindications, if severe coagulopathy, avoid subclavian (not a compressible site & difficult to effectively monitor for bleed)

**Site selection:** general preference at MGH is RIJ > LIJ > subclavian/femoral due to historical concern for infection. However, more recent data suggests no difference between these sites with proper attention to sterile technique ([NEJM 2015;373:1220](#)). Additionally, it is helpful to check if RIJ may be needed for dialysis catheter, in which case LIJ placement may be preferred.

**Catheter selection:** select based on number of lumens and speed of infusion; if rapid infusion required → large bore, short length (Cordis). Right IJ catheter length: 16cm. Left IJ catheter length: 20cm

**Alternatives:** PICC (if no concern for bacteremia, often requires negative BCx >48hr) or IO (if emergent, should not be used for >24h)

**Infection control:** scheduled exchange of catheters without evidence of infection is **NOT** indicated. Cultures drawn from indwelling catheters have ↑false + rate; generally not done aside from time of sterile placement ([NEJM 2003;348:1123](#))

## INTERNAL JUGULAR VEIN ([Video: NEJM 2010;362:e57](#))

Advantages	Disadvantages
Compressible vein	Carotid artery puncture 2-10%
Lower risk of pneumothorax (< 1%) than subclavian	Less patient comfort
Ability to use real-time ultrasound	Anatomy not as consistent as subclavian

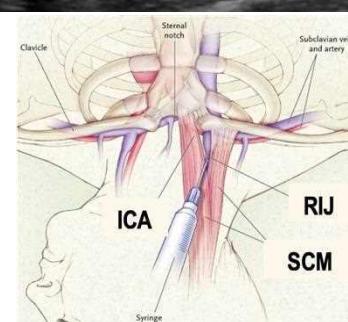
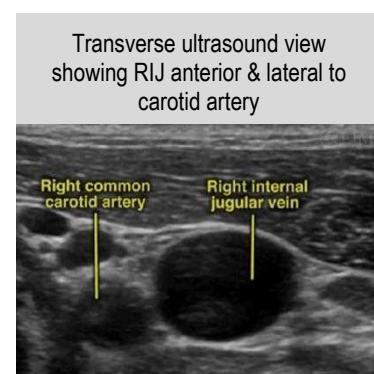
All IJ CVCs placed with real-time US guidance @ MGH: ↓first attempt failure, procedure time, and failure/complication rate

Positioning: supine + Trendelenburg to engorge veins & ↓risk of air embolus. Towel can be used to elevate shoulder to lateralize IJ. Site selection (typically R > L, unless preserving right side for HD line).

- Locate triangle formed by medial and lateral portions of SCM with the clavicle as base
- Find IJ, typically superficial and lateral to carotid, compressible; can also use color Doppler
- RIJ generally preferred due to direct course to SVC, LIJ ↑risk of PTX and thoracic duct injury

**Target:** aim at ipsilateral nipple, 45 degrees (map out trajectory of vessel using ultrasound)

- 1) Preparation and positioning are **ESSENTIAL**; ensure someone is always available to help
- 2) Obtain consent; perform TIME-OUT with RN; complete checklist with RN assistance
- 3) Use US to ensure your target anatomy is in good position. Assess LIJ & RIJ
- 4) Use 2% chlorhexidine solution to prep (in the kit); drape the entire patient in sterile field
- 5) Place caps on CVC, flush all lines with sterile saline, remove cap from brown port (**where wire will emerge**); ensure guide wire advances easily and syringe comes off needle easily
- 6) Locate IJ vein & carotid artery using ultrasound
- 7) Anesthetize with lidocaine; can make wheal & inject along tract (aspirate before injecting!)
- 8) Insert (bevel up) large bore needle at the apex of SCM/clavicle triangle, about 4-5 cm above suprasternal notch. Advance @ 45° towards ipsilateral nipple visualizing tip with US; apply negative pressure throughout. Once flash of blood is obtained → stop advancing the needle, continue to draw back venous flow (dark, non-pulsatile)
  - If arterial flow seen, remove needle and compress ~10 min
  - If air drawn back, suspect PTX → STAT CXR, 100% FiO<sub>2</sub>, decompress if tension
- 9) Once flow obtained, stabilize needle with your non-dominant hand, flatten needle angle while drawing back, remove syringe from locator (occlude hub with thumb to minimize risk of air embolism in non-ventilated patients)
- 10) Feed the curved end of the wire (*never feed the opposite end*), **NEVER LET GO OF THE WIRE**.
  - If any resistance, remove wire, assess for flow w/ syringe; if good blood flow, try twisting wire or flattening angle of needle
  - For RIJ → feed ~25cm of wire (between two and three dark lines) → watch for ectopy (suggests wire in RV → withdraw)
- 11) Remove needle
- 12) Confirm wire is in vein using US in transverse and longitudinal planes
- 13) Perform manometry confirmation → advance angiocath from kit over wire, remove wire, connect manometer tubing → leave fluid in manometer and hold vertically to avoid air embolism → venous blood should be non-pulsatile, dark, and rise <20cm → disconnect manometer tubing → replace wire through angiocath → remove angiocath
- 14) Extend puncture site with scalpel (face cutting edge away from wire to prevent cutting wire)
- 15) Thread dilator over wire (using twisting motion) until about 1/3 is inserted, then remove; goal is to dilate skin/subcutaneous tissue, NOT the vessel itself (increased bleeding); ensure the wire moves back and forth freely while dilating (may otherwise be kinked)
- 16) Advance catheter over wire (wire comes out brown port); remove wire
- 17) Draw back vertically off all ports through caps using saline flush (only small amount of flush needed), flush all lines clean, clamp ports
- 18) Secure with sutures; place Biopatch prior to securing with dressing
- 19) Order CXR (ASAP) to assess position, rule out PTX/hemothorax; **MUST look at the CXR yourself to confirm placement**; catheters should terminate in superior vena cava or cavo-atrial junction; may need to pull back if in RA (→ ectopy). If adequate position, put in order “OK to use”
- 20) Write procedure note (create note in notewriter, then select “Central Line”)



# Procedures

# Central Line

\*\*For subclavian or femoral vein access, please discuss with attending and ensure appropriate oversight prior to procedure!\*\*

## SUBCLAVIAN VEIN (Video: NEJM 2007;357:e26)

Advantages	Disadvantages
Anatomy more reproducible, incl obesity, w/ bony landmarks	Risk of PTX (1-8%), L side slightly > R, higher dome of L pleura
Improved patient comfort; easier to dress and maintain	<b>Not easily compressible;</b> more risk a/w bleed if coagulopathic
	Risk of subclavian artery puncture/hemothorax (0.5-1%)

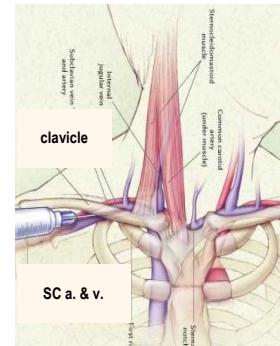
**Positioning:** place in Trendelenburg to engorge vein and consider placing a roll of towels between the scapula to expose subclavicular area (may distort anatomy for some)

**Entry:** at MGH → infraclavicular approach (as opposed to supraclavicular); puncture skin 1cm caudal to junction of medial 1/3 and middle 1/3 of clavicle (where vein flows just under the bone)

**Target:** bevel up and aim toward sternal notch, 30° to the skin; needle should advance just on the underside of the clavicle (~3-5cm depending on anatomy); some people “walk down” the clavicle to ensure this, but may lead to dulling or bending of needle as well as periosteal pain

**Pearls:**

- Turning head to ipsilateral side will kink IJ and facilitate wire going down the SVC
- Rotate bevel 90° caudal after needle is in the vein to help direct wire into the SVC
- Ultrasound not always helpful (given acoustic shadowing from bone)
- Subclavian vessels may be compressed with two fingers squeezing around the clavicle
- Guidewire usually only needs to advance 20cm (two dark lines)



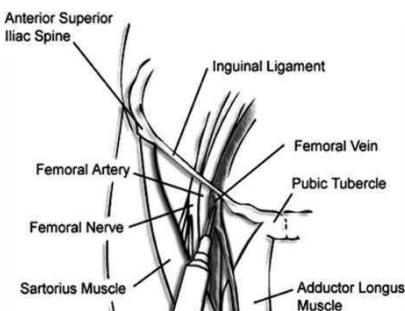
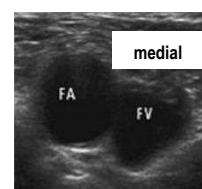
## FEMORAL VEIN (Video: NEJM 2008;358:e30)

Advantages	Disadvantages
Compressible	Femoral artery puncture 5-10%
No risk of PTX	Risk of development of DVT
Can be cannulated more easily during CPR	Less patient comfort in hip flexion, requires immobility
Large caliber vein technically easier to cannulate	May occlude flow if patient has obesity
	Caution in patients with inferior vena cava filters

**Positioning:** head of bed flat; abduct lower extremity and externally rotate the hip, generally use 20 cm line

**Entry:** bevel up, 2-3 cm below inguinal ligament, 1cm medial to palpated pulse → femoral vein lies medial & inferior to the femoral artery

- If non-urgent, best to use US to visualize
- **“NAVEL toward the NAVEL”** → Nerve, Artery, Vein, Empty, Lymphatics (alternative: venous → penis)
- Two fingerbreadths lateral to pubic tubercle if pulse not palpable
- DO NOT approach vein above inguinal ligament → increased risk for RP bleed & peritoneal perforation



**Target:** directly superior at 30-45°

\*No confirmatory imaging needed

## HEMODIALYSIS LINES

**Sites:** IJ (R preferred), subclavian vein, femoral vein

**Placement technique:** Same steps as CVC placement, additional dilation step is key difference (double dilation). For manometry, can use catheter from Arrow arterial kit. Note, the wire will come out of the blue colored port.

## CORDIS (AKA VENOUS INTRODUCER SHEATH)

Combined dilator and sheath w/ side port for IV access

**Indications:** rapid resuscitation, introducer sheath for PA catheter, temp wire placement

**Sites:** IJ (R preferred for PA line), subclavian vein, femoral vein

**Placement technique:** uses Seldinger technique (advance catheter over a wire) but dilator and sheath are advanced over wire together as unit; dilator and wire then removed together; side port aspirated and irrigated prior to use

## CVC COMPLICATIONS

**Arterial puncture:** hold pressure x10min; compress 1 inch inferior (IJ) or 2 inches superior (femoral) to puncture mark

\*Methods for ensuring venous placement include manometry/waveform measurement, ABG sampling

**Dilation/line placement in an artery:** consult vascular surgery BEFORE removing line; consider CT if pt stable

**Pneumothorax (IJ & subclavian):** suspect if hypoxemia, hypoTN, difficult stick; obtain STAT CXR → consult thoracic surgery if PTX or hemoTX; if tension physiology (shock) → immediate decompression with 16G angiocath at 5th ICS, mid-axillary line (enter above the rib)

**Retroperitoneal bleed (femoral):** suspect if hematoma or hypotension; STAT CT → consult vascular medicine

**Loss of wire or wire stuck in vessel:** DO NOT use excessive force to pull out wire if it is stuck → leave in place, hold pressure to prevent exsanguination → STAT KUB/CXR if wire loss → consult vascular medicine

# Procedures

## Arterial Line

### GENERAL CONSIDERATIONS

**Indications:** real-time BP monitoring (pressors, HTN emergency, CVA); frequent ABGs, softer indication for lab draws ( $\geq 3$  per day)

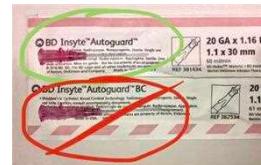
**Locations:** radial > femoral > dorsalis pedis > axillary; brachial not recommended given lack of collaterals unless placed by anesthesia

**Contraindications:** lack of collaterals (abnormal Allen test), h/o arterial grafts/stents, Raynaud's/scleroderma

**Risks:** pain, infection, bleeding, ischemia, vasospasm, arterial dissection, embolization, necrosis, loss of limb

**Materials:** arm board, tape, Chux, chlorhex prep, 4 x 4 sterile gauze, pack of sterile towels, sterile gloves, mask, eye protection, bouffant, 20G angiocaths, guide wire, Tegaderm, US probe cover (if needed)

- If pt awake → consider lidocaine w/o epi (small syringe and 25G needle)
- **Use PINK SOLID STRIPE angiocath:** do NOT use pink interrupted stripes, which has a one-way valve so can't pass wire
- Alt: use Arrow arterial line kit; the kit's longer catheter is preferable for femoral site

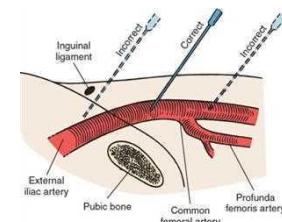


### RADIAL TECHNIQUE (Video: NEJM 2006;354:e13)

- 1) Obtain consent and perform TIME OUT; ask RN to prepare for A-line
- 2) Confirm anatomy by palpating pulses or with US. Test for collateral circulation of the hand:
  - **Allen test:** make fist for ~30sec, then occlude ulnar & radial arteries; pt opens hand (palm should be blanched); then release pressure from ulnar artery → palm should regain color within ~5-10 sec
  - **Modified Allen test:** place pulse oximeter on index finger or thumb; occlude radial and ulnar arteries until wave form lost; release ulnar artery → should get arterial tracing if good collateral flow
- 3) Proper positioning: adjust bed to appropriate height for operator comfort. Put Chux under wrist; extend pt's wrist; secure arm board (bendable arm boards in CCU and MICU). Consider taping hand to bed/table to stabilize; note the course the artery travels.
- 4) Sterilize wrist widely with 2% chlorhexidine swabs for ~30 seconds; open towel packet to create sterile field
- 5) Prepare field: drop angiocath & guide wire (and sterile US supplies) on sterile field; don sterile gloves and drape widely w/ sterile towels. Prepare US with gel and probe cover, if utilizing. Leave on sterile field
- 6) Prepare angiocath/guidewire: check angiocath to ensure catheter slides easily off needle; pull one side of wire *slightly* out of paper
- 7) Pick your target: palpate radial artery (or visualize with US) with non-dominant hand; plan to puncture distal to the pulse you palpate.  
*Note: Avoid catheterizing very distal (near angle of extension) as A-line more likely to displace later when pt moved*
- 8) Insert angiocath: with *bevel up*, advance angiocath needle at a 45° angle toward pulse until flash is obtained (similar to ABG)
- 9) Once flash obtained, go "*through-and-through*": advance ~0.5cm through artery; hold the top of the plastic catheter with non-dominant hand; push button to retract needle, while steadyng the catheter (should be no blood flow)
- 10) Hold guide wire close to head of angiocath w/ dominant hand
- 11) Level and pull back : lower angiocath as parallel to skin as possible and SLOWLY pull it back until pulsatile blood flow is obtained, then hold angiocath very still to avoid pulling out of vessel
- 12) Advance wire: insert the wire into the angiocath; should not feel resistance; if unable to advance wire, DO NOT LET GO OF GUIDE WIRE; TRY SPINNING THE WIRE → avoids side branches of artery (where wire commonly gets caught)
- 13) Advance angiocath into the artery over the wire (Seldinger technique)
- 14) Remove guidewire: apply pressure to radial artery proximal to cath; remove guide wire; occlude opening of the angiocath with finger
- 15) Connect transducer: ask RN for A-line setup and connect transducer to angiocath; RN will flush; confirm placement w/ art. waveform
- 16) Dress the area with a Tegaderm; MICU RNs will often re-dress afterwards, so ask their preference; in ED, suture to the wrist; NWH has snap dressings

### ALTERNATIVES AND TROUBLESHOOTING

- If using Doppler, mark out course of artery with marking pen
- If using US, can try advancing needle under US guidance and once firmly in vessel, advance catheter over needle (no guide wire; similar to PIV)
- After multiple attempts, the artery may spasm or hematomas may form. Pursue alternative site (or more distal site).
- If unable to thread guide wire after attempting spinning during insertion, consider micropuncture wire (with supervision). May help with atherosclerotic arteries at ↑ risk of perforation. Kit includes introducer needle, microwire, and microcatheter w/inner stylet.
  - Use micropuncture needle to puncture vessel under US guidance until flash, can walk forward in vessel, then drop probe
  - Thread microwire (more pliable end first) through needle, then remove needle
  - Thread microcatheter over the wire
  - Once hubbed, unscrew to remove inner stylet and microwire
- **Femoral artery access** can be considered in difficult cases. Use the long catheter in the Arrow arterial line kit. Puncture must occur distal to the inguinal ligament to prevent RP bleed. Too distal, however, and the femoral artery will bifurcate into superficial and deep femoral vessels. The femoral artery usually transverses the inguinal ligament ~1/3 distance from pubic symphysis to the ASIS. Optimal point of skin puncture is 1-2 cm below the inguinal ligament at point where pulse is palpated, or aiming to insert immediately proximal to femoral bifurcation (see graphic)



# Procedures

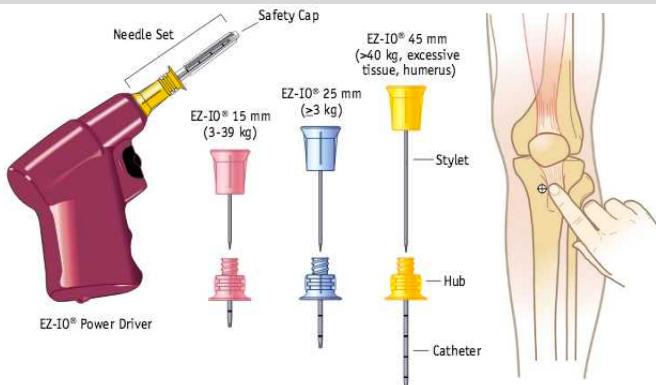
# Intraosseous Line

## GENERAL CONSIDERATIONS (Video: NEJM 2014;370:e35)

- **Anatomy:** veins that drain medullary sinuses of bones; veins supported by bones do not collapse in patients in shock
- **Indication:** patients without available IV access with urgent need (arrest, shock, status epilepticus, trauma, etc). Used for delivery of fluids/medications; labs (but tenuous – clots off quickly). Faster access than CVC, low complication risk ([Resuscitation 2012;83:40](#))
- **Contraindications:** fractured or penetrated bone (fluids exit site), local vascular compromise (e.g. trauma or cutdown). Should be avoided in areas of cellulitis, burns, osteomyelitis, bone disease (e.g. osteogenesis imperfecta), R→L intracardiac shunts (TOF, pulm atresia) due to risk of fat emboli, failed IO insertion within 24h at same site
- **Complications:** extravasation, compartment syndrome, fracture, growth plate injury, infection, fat emboli, osteomyelitis (rare)
- **Notes:** infusion rate roughly 160mL/min at tibia or humerus with use of pressure bag, half the rate without. IO samples only accurate for some studies (Hgb, T&S, drugs, Cx). NOT for PaO<sub>2</sub>, WBC, K, AST/ALT, iCal, after drug admin

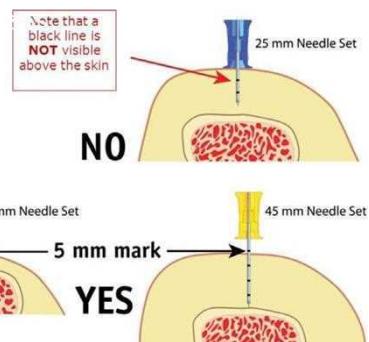
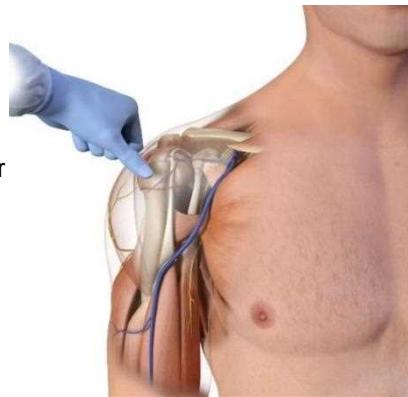
## SET-UP

- **Materials:** ALL IN KIT → EZ-IO Power Driver, IO needle-set, connector tubing, 10cc syringe with saline flush, chlorhexidine/povidone iodine, sterile gloves. If awake, 3cc syringe with 1% lidocaine via 25G needle
- **Replace:** Blake 7 MICU, Materials Management (Lunder LL019)
- **Location:**
  - Proximal tibia (preferred): find the flat surface 2cm below tibial tuberosity, 1-2cm medial along tibia
  - Proximal humerus: position pt palm on abdomen (elbow flexed, shoulder internally rotated), greater tubercle 2cm below acromion process
  - Other sites: distal tibia, distal femur, iliac crest



## PROCEDURE (Crit Care 2016; 20:102)

1. Don surgical mask, eye protection, sterile gloves
2. Flush connector tubing with NS or lidocaine if patient is awake
3. Identify injection site
4. Clean injection site with antiseptic (chlorhexidine or iodine)
5. If patient is awake, create wheal with 1% lidocaine
6. Choose proper needle size: generally blue (25mm); yellow (45mm) is for excess tissue or for humerus approach
7. Magnetic pole holds the needle in place; turn the safety cap clockwise for removal
8. Hold drill perpendicular to bone if proximal tibia; hold 45° to the anterior plane and posterior medial if proximal humerus
9. Manually press the needle through the skin until it touches the bone. Confirm you see one black line on the needle (5mm mark); if not, use a longer needle (see illustration)
10. Apply gentle, steady, downward pressure while holding the trigger; allow drill to do the work
11. Release trigger when decreased resistance felt ("give" or "pop") as you enter into medullary space
12. While holding catheter in place, pull straight up to remove driver
13. Unscrew the needle stylet by rotating counterclockwise (both stylet and needle are encased in colored plastic)
14. Aspirate marrow to confirm placement. Prior to attaching tubing, send labs; blood samples may only be obtained in patients with spontaneous cardiac activity or during initial CPR before drug and fluid infusion through the IO
15. Attach connector tubing and flush IO w/ NS or 1% lidocaine over 45s if the patient is awake (IO infusions are VERY painful); if the patient is unconscious, rapid 10mL NS. Look for superficial swelling and note that no flush means no flow!
16. Apply IO dressing stabilizer – FYI each size needle has a different dressing, will not fit if using dressing for different size needle
17. Administer rapid NS bolus/blood/pressor with a pressure bag or syringe
18. Always return the IO kit to unit for resource nurse to refill



## REMOVAL

Remove **within 24 hours** of insertion once other access is obtained (not good for long term access), or if signs of erythema, swelling or extravasation. To remove: don procedure mask, goggles, non-sterile gloves. Remove IV extension tubing from needle hub. Then, place sterile syringe on needle hub (acts as handle for removal). Grasp at needle hub and rotate clockwise while pulling gently at 90-degree angle from the bone. Do not rock the syringe. Once the needle hub is out, place needle hub in sharps container. Apply pressure over IO site until bleeding has stopped and dress with gauze and tegaderm.

# Procedures

# Paracentesis

## INDICATIONS (Video: NEJM 2006;355:e21)

- **Diagnostic:** new-onset ascites, unknown etiology of ascites, rule out SBP. Low threshold for inpatients with cirrhosis and often helpful to obtain concurrent RUQUS with Doppler to rule out hepatic or portal vein thrombosis
- **Therapeutic:** large volume paracentesis (>5L) → performed for abdominal pain/discomfort, diuretic-refractory ascites, respiratory compromise, abdominal compartment syndrome, adjunctive treatment of esophageal variceal bleeding (can lower portal pressures)

## CONTRAINDICATIONS

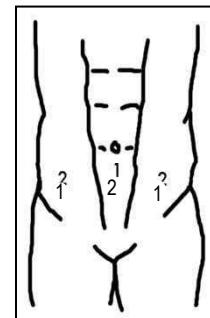
- Overlying cellulitis, inability to demonstrate ascites on US, bowel obstruction/distention, acute abdomen, 2<sup>nd</sup> or 3<sup>rd</sup> trimester pregnancy
- ↑INR, ↓plt are **NOT** contraindications in cirrhosis (INR in patients with cirrhosis is NOT reflective of the risk of bleeding). There is no need to correct coagulopathy w/ FFP or platelets unless severe DIC ([Hepatology 2021;74:1014](#))

## MATERIALS

- Sterile gloves, bouffant, face shield, chlorhexidine, sterile towels, US, 1% lidocaine (10cc syringe, SQ 25G needle, 1.5inch 20-22G needle), two 18G needles, 60cc syringe, diagnostic assay tubes as below, gauze, bandage or Tegaderm dressing
- **Diagnostic:** **20G two-way (pink) angiocath** or 18-22G 1.5inch needle. In obese pts, may use angiocath from femoral art line kit. Purple and green top tube, black top tube (for micro)
- **Therapeutic:** **safe-T-Centesis kit** (preferred, pigtail minimizes perforation risk) or paracentesis kit (straight rigid needle), 1L vacuum bottles, 25% albumin dosed 6-8g per liter of fluid removed if >5L ([Hepatology 2021;74:1014](#))

## SITE SELECTION/POSITIONING

- Position patient supine, turned slightly toward the side of the paracentesis, and angled upright at 30°
- Use abdominal probe to **identify fluid pocket ≥2-3cm in all dimensions** by rotating/fanning probe to ensure **absence of bowel loops**. Simulate planned angle of needle insertion with probe. Measure subcutaneous tissue and fluid pocket.
- Avoid superficial veins or prior surgical incisions and **use vascular probe with Doppler to avoid SQ vessels**
- **Approaches:**
  - **LLQ > RLQ (1): most commonly used;** LLQ ↓risk of bowel perf, use caution if pt with splenomegaly; **avoid inferior epigastric vessels** that run along lateral borders of rectus muscles
  - **Infraumbilical (2):** midline, 2cm below umbilicus; **must be certain to differentiate urine in bladder from intra-abdominal free fluid**



Approaches

## INSTRUCTIONS

1. Identify best site with abdominal US probe and mark site with pen or round base of needle
2. Open sterile OR towels package. Use light blue covering as sterile field to drop sterile supplies. Don PPE (gloves, mask, bouffant cap) & clean skin vigorously with chlorhexidine. Create sterile field over patient with OR towels or open kit and use dressing provided
3. Anesthetize overlying skin using ~0.5cc lidocaine (SQ 25G needle) to make a wheal. **For LVP**, use 1.5 inch 20-22G to anesthetize deeper tissues with lidocaine in 10cc syringe. **Use Z-line technique** (below) and aspirate while advancing needle. Once ascitic fluid begins to fill syringe, stop advancing the needle & inject remainder of lidocaine to anesthetize the highly sensitive parietal peritoneum.

**Z-line technique:** reduces risk of ascites leak. With non-dominant hand, pull skin ~2cm caudad to deep abdominal wall while para needle is being slowly inserted

### Therapeutic paracentesis instructions

- a) Prepare Safe-T-Centesis kit: place catheter on needle, attach syringe, and prep tubing
- b) Use scalpel to make small superficial incision (enlarge PRN)
- c) Advance needle/catheter while pulling back on syringe until ascitic fluid return is visualized, then advance 0.5 cm
- d) Advance catheter until hubbed (only with Safe-T Centesis kit!), hold rigid needle in place
- e) Retract needle, attach 60cc syringe for dx sample PRN
- f) Connect tubing to catheter and puncture vacuum bottles
- g) Withdraw catheter and apply gauze/Tegaderm dressing
- h) Give **25% albumin (6-8g/L removed) if >5L removed**

## DIAGNOSTIC ASSAYS: (see Fluid Analysis for interpretation)

Tube	Lab	Tests
Green top	Chem	Fluid albumin (send serum albumin to calculate SAAG), fluid total protein
Purple top	Heme	Fluid cell count
Blood culture bottles	Micro	Can send for aerobic & anaerobic fluid culture, clean top with alcohol and inoculate at bedside for max yield
Black top	Micro	Gram stain and culture plates

Other tests to consider: glucose, amylase, LDH, bilirubin, triglyceride, AFB smear, mycobacterial culture, adenosine deaminase, pH, cytology

## COMPLICATIONS

- **Flow stops/slows:** roll patient slightly to side of para, rotate catheter, slightly withdraw catheter, flush catheter, new vacuum container
- **Flash of blood in catheter:** use vascular probe to avoid SQ vessels → withdraw & insert new catheter at different site
- **BRB return:** injury to mesentery or inferior epigastries → stop, assess for hematoma w/ US, IR or surgery consult if HD unstable
- **Hypotension:** likely vasovagal or fluid shift (>1500cc tap) → Trendelenburg, hydrate, and consider 25% albumin
- **Bowel perforation:** may lead to polymicrobial baterascites/sepsis → surgery consult for potential laparotomy
- **Fluid leak:** prevent with Z-line technique or up-front Dermabond → apply pressure dressing, seal w/ Dermabond or single stitch

# Procedures

## Lumbar Puncture

### INDICATIONS

**Diagnostic:** suspicion for CNS infection (most common), CNS malignancy/mets, SAH, CNS demyelinating/inflammatory process, or ↑ICP

**Therapeutic:** idiopathic intracranial hypertension, NPH, ↑ICP in cryptococcal meningitis, intrathecal meds/chemotherapy/anesthesia

**Contraindications:** no absolute contraindications; high risk if skin infection over puncture site, epidural abscess, ↑ICP 2/2 mass lesion or obstruction (risk of brain herniation), spinal cord tumor or AVM, thrombocytopenia (<50K) or coagulopathy (INR>1.5) of any etiology

### Preparation:

- **Time frame needed to hold AC prior to LP:** IV heparin (4-6h, PTT<35), LMWH therapeutic (24h), LMWH ppx (12h), plavix (5-7d), DOAC (3d), warfarin (3d, goal INR <1.5). OK to proceed if on SQ heparin daily dose <10,000U, ASA, or NSAIDS. If urgent: weigh risks and benefits. For details (including when to restart AC): [Ellucid](#)
- **Head CT:** only obtain if ≥1 of the following: age >60, hx CNS disease, seizure <7d ago, immunocompromised, AMS, aphasia, cranial nerve deficit. If none of these, then 97% NPV for no mass lesion ([NEJM 2001;345:1727](#))

### TECHNIQUE (Video: [NEJM 2006;355:e12](#))

**Equipment:** LP kit, sterile towels, sterile gloves, face shield, pillows to position patient

- LP kit: 1% lidocaine (25G needle, 5cc syringe), sterile drape, iodine/chlorhex, 20-22G needle/stylet, 4 collection tubes, manometer

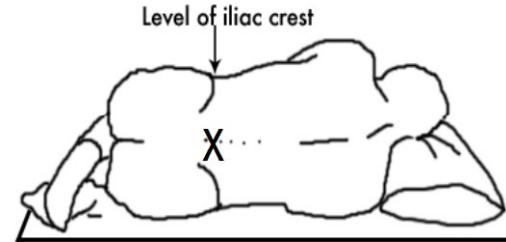
**Positioning:** proper positioning is the key to a successful and smooth LP!

- **Use L4-L5 (level of iliac crests), L5-S1, or L3-L4 interspaces (conus medullaris at L1-L2).**
- **Lateral** (if opening pressure needed): place pt in fetal position (maximize neck and hip flexion), no hip/shoulder rotation; keep back parallel to edge of bed
- **Upright** (easier): sit on bed, head/arms rest on table, spine flexed
- To identify target: place a hand on each iliac crest, mark where thumbs meet at midline or draw line between crests. Confirm location by palpating spinous processes above/below. Ensure needle midline before inserting
- Sitting while performing LP is often easier than standing, as the needle is in your line of sight

**Protocol:** ([JAMA 2006;296:2012](#))

- 1) Prep: sterilize and drape widely. Re-identify target with palpation (betadine will make this easier). Make lidocaine wheal w/ 25G, then inject track (aspiration before injecting, goal is **not** spinal anesthesia). Keep CSF collection tubes in order nearby. If checking pressure, have manometer connected and ready
- 2) Tap: check needle/stylet mobility. Bevel should face ceiling when pt is lateral. Needle angles slightly toward the head (as if aiming to umbilicus), straight at the back. Stabilize with your hand against the skin and advance with your dominant hand. Remove stylet frequently to check for CSF flow but **always keep stylet in place when advancing**
- 3) Troubleshoot: if hitting bone, partially withdraw (needle shouldn't leave skin), adjust angle, re-advance. Try space below if no luck. If patient has pain, DO NOT withdraw → ASK "where?" If pain is shooting down the left side, withdraw slightly and go slightly more to the right. If hitting bone early, more likely to be superior or inferior; if hitting bone late, more likely to be too lateral
- 4) Measure opening pressure: once flow is established, remove stylet and connect manometer to measure opening pressure (must be in lateral decubitus position). Pt must **extend legs** to obtain accurate pressure. If performing therapeutic LP, drain until pressure normal
- 5) Collect: collect CSF tubes 1 to 4; if flow slows, try rotating needle or minimally advancing or withdrawing with stylet in place
- 6) Finish: re-insert stylet prior to needle removal (associated w/ ↓post-LP headache)

\*If unable to obtain LP (ie overnight) and suspicion for meningitis is high, **empirically treat** while awaiting diagnostic study\*



DIAGNOSTIC ASSAYS (see Fluid Analysis)		
Tube	Lab	Tests
1 (1mL)	Heme	CSF cell count
2 (1mL)	Chem	Total protein, glucose
3 (3-5+ mL, depending on # of tests)	Micro	Gram stain/Cx. Consider: HSV PCR, VZV PCR, CrAg, viral Cx, AFB stain, VDRL. Ask lab to save extra CSF. <b>If you need flow cytometry, DO NOT FREEZE CSF!</b>
4 (1mL)	Heme	CSF cell count (should have fewer RBCs than tube 1 unless hemorrhage)

**Additional tests:** cytology & flow cytometry (meningeal carcinomatosis), oligoclonal bands (MS), paraneoplastic Abs, 14-3-3 & RT-QuIC (prion dz); **can collect extra black top tubes** for these purposes; **if c/f prion dz:** contact materials management for instruction on special disposal of materials (highly contagious!)

COMPLICATIONS	
<b>Cerebral herniation</b> (acute AMS, fixed pupils, ↑BP, brady, arrest)	Immediately replace stylet and do not drain more CSF beyond what is in manometer. STAT consult NSGY and treat with ICP-lowering agents (e.g. mannitol)
<b>Nerve root injury</b>	Shooting pains during procedure usually transient. Withdraw slightly and adjust position away from direction of pain. Consider dexamethasone if pain is persistent
<b>Post-LP headache</b> (10-30% incidence; likely 2/2 dural leak)	Onset 72h, lasts 3-14d. Give fluids, caffeine, and pain meds. No evidence for bed rest. If persistent, c/s anesthesia for epidural blood patch (65-98% success, often quick relief)
<b>Spinal hematoma</b>	Suspect if on AC w/ persistent back pain or neuro sx → STAT MRI → IV dex + NSGY c/s

# Procedures

## Thoracentesis

### INDICATIONS

**Diagnostic:** to establish etiology of  $\geq 1\text{cm}$  pleural effusion visualized by US (not necessary for small effusions w/ probable alternative dx)

- pleural effusions are visible on CXR when  $>200\text{mL}$  of fluid is present

**Therapeutic:** large effusions  $\rightarrow$  resp compromise or sx (e.g., dyspnea), hemothorax, empyema, complicated parapneumonic effusion

**Relative Contraindications:** no absolute ([Chest 2013;144:456](#))

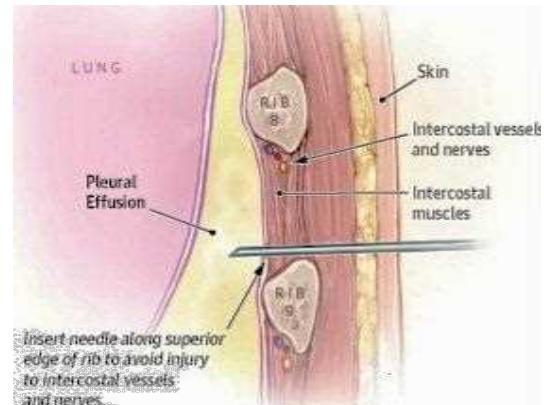
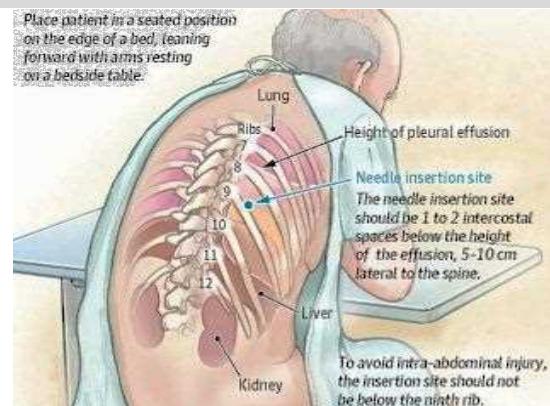
- Consider reversing coagulopathy (INR  $>1.5$ , recent LMWH) or thrombocytopenia (plt  $<50\text{k}$ ), but no data to support
- Skin infection (cellulitis or herpes zoster) over site of entry ↑ risk of pleural space infection
- Positive pressure ventilation ↑ risk of PTX by 1-7% ([Crit Care 2011;15:R46](#)). US guidance associated with lower risk.

### PREPARATION

- **Materials:** skin cleansing agent, gauze, sterile gloves/drape, hemostat, 1-2% lidocaine, 10cc syringe with 22 & 25G needle, thoracentesis kit with 18-20G over-the-needle catheter, 60cc syringe, 3-way stopcock, drainage tubing, specimen tube, evacuation container, occlusive dressing
- **At MGH:** IP (p23710), Pulmonary, or IR perform thoracentesis (not AMPS). Attending **MUST** be present for bedside thoracentesis

### TECHNIQUE (Video: [NEJM 2006;355:e16](#))

- **Position:** patient at edge of bed, leaning forward with arms resting on table
- **Identify:** height of effusion determined by auscultation & percussion of chest wall. Use **US** to confirm location of effusion
  - Mark 5-10cm lateral to spine & 1-2 ICS below effusion. **Lowest level recommended is 8<sup>th</sup> ICS** (above diaphragm)
  - In patients who cannot sit upright  $\rightarrow$  mid-axillary approach (patient supine) or posterior axillary with patient lateral decubitus
- **Prep & drape:** set up thoracentesis kit, put on sterile gown and gloves, sterilize patient w/ chlorhexidine, then drape
- Using 25G needle, place wheal 1% lidocaine over superior edge of the rib
- Using 22G needle, walk needle over superior aspect of the rib while intermittently aspirating and injecting perpendicular to the pleural space
- When pleural fluid aspirated, withdraw slightly then anesthetize the parietal pleura (highly sensitive) w/ 2-3cc of lidocaine. **Note penetration depth**
- Attach 18G over-the-needle catheter to syringe & advance over superior aspect of the rib, pulling back plunger while advancing
- When fluid aspirated, stop advancing & guide plastic catheter over needle **Catheter has valve preventing fluid or air from entering the pleural space, so may use both hands to prepare for your next step**
- Attach 60cc syringe to 3-way stopcock connected to catheter, withdraw full syringe of fluid, and put in appropriate tubes for lab & micro studies
- Attach tubing to 3-way stopcock, affixing longer tube to large evacuation container & shorter tube to the syringe. Tubing is all one-way
- Aspirate fluid slowly into the syringe and inject back into bag, never fully empty the syringe as it can lead to difficulty on repeat aspiration. **Stop if: patient experiences chest pain, dyspnea, cough.** Do not remove more than 1.5L fluid as ↑ risk of post-expansion pulm edema
- When done, withdraw catheter while patient is humming (to avoid air entry into pleural space); cover site with occlusive dressing
- Obtain **post-procedure CXR** to assess for pneumothorax or hemothorax



### DIAGNOSTIC ASSAYS (see *Fluid Analysis* for interpretation)

- **Send fluid for:** TP, LDH, chol, glucose, pH, cell count, Gram stain/Cx, anaerobic Cx, fungal wet prep w/ Cx
- **Consider:** TG (chyllothorax), Cr (urinotorax), amylase (pancreatitis, esophageal rupture), ADA (TB), AFB Cx, modified AFB Cx, cytology

### COMPLICATIONS

1. **Hemothorax/intercostal vessel injury:** ↑ risk if inferior approach to rib or elderly (tortuous vessels). CXR, H&H. Consider chest tube
2. **PTX:** 5-20% risk; most can be monitored with serial CXR; **monitor for signs of tension PTX** and obtain STAT expiratory CXR; if PTX is large or patient is symptomatic and/or in distress  $\rightarrow$  STAT page IP for bedside needle decompression with 16G angiocath at **5<sup>th</sup> ICS mid-axillary line** (always above nipple). A chest tube is indicated in 20% of cases  $\rightarrow$  **consult IP or thoracic surgery**
3. **Vasovagal syncope/pleural shock:** caused by needle penetrating parietal pleura. Tx: Supportive care
4. **Re-expansion pulmonary edema:** to avoid, stop thoracentesis if cough, CP, or dyspnea occurs. Limit volume removal to  $<1.5\text{L}$ . Do not attach to vacuum. Remove fluid slowly without excessive negative pressure. Tx: O2, diuretics, and/or BiPAP

# Procedures

## Pericardial Drain

### INDICATIONS

- Pericardial effusion with tamponade physiology (or if at high risk for development of tamponade physiology)
- Diagnostic or palliative drain of stable pericardial effusion

### RELATIVE CONTRAINDICATIONS: no absolute contraindications

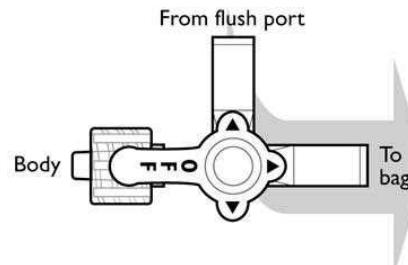
- Coagulopathy: INR>1.7, platelets<20, PTT>60 or on heparin gtt. Consider FFP/platelets when on call for procedure
- Effusion associated with aortic dissection or myocardial rupture, as decompression could lead to extension of injury
- Effusion associated with severe pHTN (controversial), as decompression could lead to RV dilation and acute RV failure / hemodynamic collapse ([Pulm Circ 2013;3:467](#))

### MANAGEMENT OVERVIEW: if in doubt about management, page the Cardiology team that placed the drain

- Pericardiocentesis does not completely evacuate a pericardial effusion. A pericardial pigtail catheter is often left in for 24-72h to allow for serial drainage, preventing re-accumulation and repeat pericardiocentesis
- Frequency of drainage depends on chronicity and size of the effusion, usually q6-q12h. Recommendations are often found in the report from the cath lab when the drain was initially placed
- **Post-procedural antibiotic prophylaxis not indicated per MGH guidelines** ([MGH peri-procedural abx guidelines](#))
- Monitor effusion resolution and recurrent tamponade. Check serial hemodynamics/pulsus paradoxus
- If >100cc output/d for 3d s/p placement, aggressive tx may be indicated (e.g. pericardial window, sclerosing agents, etc.)
- Consider removal of pericardial drain if <50cc output over 24h. Remove with cardiology fellow/attending present

### MATERIALS

- Sterile technique: sterile gloves, mask, hat
- Identify assistant (must be MD, NP, or PA)
- Sterile towels
- Chlorhexidine swabs (at least 3)
- 60cc Luer lock (screw-on) syringe (x2-3 if high output)
- New blue cap for 3-way stopcock
- Heparin (10U/ml) pre-mixed syringe (in MICU/CCU/SDU med rooms)



### TECHNIQUE: mask and hat required (gown is optional)

1. Open sterile towel wrap carefully. Open supplies onto sterile field. Don sterile gloves
2. Ask assistant to lift the catheter off the skin (holding end of port). Place sterile OR towels around and underneath pericardial drain. Sterilize distal exposed catheter and stopcock with chlorhex swab. Once finished, hold the recently sterilized area and take catheter from assistant to sterilize remaining distal portion. Once fully sterilized, lay the catheter down on the sterile field of blue OR towels.
3. **Ensure the stopcock is turned towards the patient.** This means the catheter line is closed.
4. Remove and throw away one blue cap (does not matter which). There will be one capped tip and one open tip
5. Sterilize open stopcock tip with iodine or chlorhex swab
6. Hold up flush port for the assistant to connect heparin syringe (syringe itself is not sterile) to open/sterilized tip. **Turn stopcock toward the remaining capped valve** (opens flush port/catheter), and assistant will infuse 2cc heparin
7. **Turn stopcock towards the patient**, remove (do not discard) heparin syringe, and connect 60cc Luer lock syringe
8. **Turn stopcock to the remaining capped valve** and slowly withdraw pericardial fluid. This may require significant negative pressure. Consider different patient positions (Trendelenburg, lateral decubitus, etc.) to mobilize pericardial effusion. Patient may experience chest discomfort. Monitor hemodynamics and telemetry throughout drainage
9. Can stop draining once fluid flow diminishes/ceases. **Turn stopcock towards patient** then remove syringe
10. Save/transfer pericardial fluid if needed for analysis. Otherwise discard
11. Repeat step 6 (flush port with another 2cc heparin). **Turn stopcock to the patient** (to close catheter)
12. Remove heparin syringe and attach new sterile blue cap to open flush port
13. Consider re-sterilizing distal exposed catheter and stopcock with chlorhex swab
14. Write a procedure note. **Be sure to deduct the 4cc infused heparin** (2cc from prior drainage, 2cc from current drainage) when calculating amount of fluid removed

### FLUID STUDIES: typically not needed routine, serial drainage

- Gram stain and bacterial/fungal culture
- Specific viral studies/PCR
- Cytology
- AFB stain, mycobacterial culture, adenosine deaminase, IFN-gamma, or lysozyme (if considering TB pericarditis)
- Protein, LDH, glucose, red/white cell count are not helpful for fluid characterization

# Procedures

# Fluid Analysis

LUMBAR PUNCTURE INTERPRETATION						
Condition	Pressure (cm H <sub>2</sub> O)	WBC/mL	Predominant cell type	Glucose (mg/dL)	Protein (mg/dL)	Further CSF Testing
Normal	9–18	0–5	Lymph	50–75	15–40	N/A
Bacterial meningitis	20–50	<100 to >10k	>80% PMN	<40	100–1000	Cx, Gram stain
Viral meningitis (Enteroviruses, HSV, VZV, arboviruses)	9–20	50–1000	Lymph; early echovirus/HSV can have 80% PMN	>45; low in LCM and mumps	<200	HSV/VZV PCR, consider further viral PCR or Ab if clinical suspicion; d/w ID
Lyme meningitis	9–20	10–300	Lymph	Normal	50–100	Ab testing paired with serum ab
TB meningitis	18–30	50–300	Lymph	<50	50–300 >2000 if subarach block	MTb Cx <60% Sn, NAAT not approved by FDA, discuss w/ ID
Fungal meningitis	18–30	< 300	Lymph	<50	40–300	Fungal wet prep + Cx, d/w ID
Cryptococcal meningitis	18–30+	5–500	Lymph	<40	>45	Fungal wet prep + Cx, CrAg; d/w ID need for India ink stain
Epidural/Brain abscess	18–30	10–300	Lymph	Normal	50–400	Gram stain not sensitive

WBC correction for RBCs (i.e. traumatic tap) = measured WBC – (measured RBC / 500)

PARACENTESIS INTERPRETATION (SEE ASCITES)		
	⊕ Ascites culture	⊖ Ascites culture
PMN ≥250/ $\mu$ L	Spontaneous Bacterial Peritonitis (SBP) (Secondary Peritonitis → polymicrobial)	Culture Negative Neutrocytic Ascites (CNNA)
PMN <250/ $\mu$ L	Non-neutrocytic Bacterascites (NNBA)	Normal

**CNNA:** has similar clinical presentation and prognosis as SBP, thus treat for suspected SBP after diagnostic PMN count without waiting for Cx (ddx: peritoneal carcinomatosis, tuberculosis, pancreatitis)

**Calculations:** # of PMNs = Total nucleated cells x % of PMNs  
Correction for RBCs (RBC count >50,000/mm<sup>3</sup>, seen in "traumatic tap") = measured PMN – (measured RBC / 250)

**Clues in Fluid Analysis for SBP vs. Secondary Peritonitis:**

- **Runyon's Criteria:** if ≥2 present, ↑ suspicion for secondary peritonitis: 1) ascitic total protein >1; 2) ascitic glucose <50; 3) ascitic LDH > ULN
- Fluid CEA >5 or Alk Phos >240 (92% Sn, 88% Sp for secondary peritonitis) ([J Hepatol 2001;34:215](#))
- Consider **repeat paracentesis after 48h of antibiotic treatment:** if PMN ↓ and only 1 org. on prior culture, likely SBP; if PMN ↑ and polymicrobial growth on prior culture, then likely secondary peritonitis. Higher risk for secondary peritonitis if recent operation, trauma, or perforation

	SAAG ≥1.1g/dL (etiology related to portal HTN)	SAAG <1.1g/dL (etiology NOT related to portal HTN)
Fluid total protein < 2.5 g/dL	Cirrhosis	Nephrotic syndrome
Fluid total protein ≥ 2.5 g/dL	Heart failure Budd-Chiari syndrome	Pancreatitis Peritoneal carcinomatosis TB

**SAAG** = Serum Albumin – Ascites Albumin (from samples obtained on the same day)

PLEURAL FLUID INTERPRETATION		
Transudate (due to Starling forces) vs. Exudate (due to increased capillary leak) ( <a href="#">NEJM 2002;346:1971</a> )		
<b>Light's Criteria:</b> exudate if ≥1 criteria present (98% Sn, 83% Sp)*	<b>If ≥ 1 of these, fluid is exudate with 98% Sn, 70% Sp:</b>	
1. Pleural fluid protein / serum protein >0.5	▪ Pleural fluid protein >2.9, LDH >95, cholesterol >45	
2. Pleural fluid LDH / serum LDH >0.6	<b>More specific criteria for confirming exudate:</b>	
3. Pleural fluid LDH >2/3 ULN of serum LDH (i.e. >140)	▪ Pleural fluid cholesterol >60 (54% Sn, 92% Sp)	
*Diuretics cause ~25% of transudates to be misclassified as exudates	▪ Serum albumin – pleural albumin ≤1.2 (87% Sn, 92% Sp)	
	▪ Pleural NT-proBNP <2,300pg/mL (>80% Sn, >70% Sp)	
• Other tests: adenosine deaminase, amylase, triglyceride, cholesterol, Gram stain/Cx, cell count, IFN-γ, NT-proBNP, pH, tumor markers		
• Complicated parapneumonic effusion/empyema = ⊕ Gram stain/Cx/purulent OR pH <7.2 OR glu <60 → drainage w/ chest tube		

# Procedures

# Tube Management

## NASOGASTRIC TUBES

### Indications:

- Decompression of SBO or minimize vomiting in ileus
- Enteral feeding/med administration; charcoal admin (OD), oral contrast or colonoscopy prep (if can't take PO)
- Lactulose (hepatic encephalopathy) (if can't take PO)

### Contraindications:

- Head/maxillofacial trauma, basilar skull fracture, or recent neurosurgical intervention
- Esophageal stricture or  $\geq$ grade 2 varices/recent banding (discuss w/ GI if uncertainty regarding varices/banding)

### Supplies:

- NGT, lubricant/viscous lidocaine ("UroJet"), Chux, emesis basin, cup of water with ice and straw, 60mL syringe, tape
- If NGT needed for decompression: use 14 to 16 Fr Salem sump NGT (larger diameter, ↓clogging)

### NGT Placement:

- Assess patency & symmetry of nares by direct visualization
- Consider topical anesthetic (e.g. 4% lidocaine) pre-treatment
- Position patient in upright "sniffing" position with neck flexed & chin to chest
- Estimate distance of NGT insertion by measuring from xiphoid process → earlobe → nose tip
- Apply lubricant/ice to tip of NGT and/or apply viscous lidocaine directly into the nares
- Insert NGT into nares along floor & apply pressure posterior & slightly inferomedial, not upward
- After passage of NGT into oropharynx (will feel curve & ↓ resistance), have patient swallow water via straw while advancing rapidly
  - If patient excessively coughs, gags, has change in voice or dyspnea, or increased resistance, **STOP** (never force), suspect improper location (in airway or coiled), & immediately withdraw. Look in posterior oropharynx for coiling
- Advance to predetermined depth. Can insufflate air w/ 60cc syringe while auscultating over stomach for rush of air. May also see return of gastric contents. Inspect oropharynx to ensure no coiling before securing tube w/ tape or bridle if ↑ risk removal (AMS)
- Confirming position: **MUST confirm placement with KUB prior to feeding/meds given risk of placement in trachea/lungs.** KUB will show NGT sideport below diaphragm. Optional for KUB if bilious return when NGT for decompression (bile = stomach)

### TYPES OF NGTs & USES

- Dobhoff: PO formula, meds
- 14, 16 Fr: decompression

### Dobhoff tube/Enteroflex:

thinner, more flexible; more comfortable but ↑ risk of placement into lung

- Requires 2-step 2-CXR placement method. Placement at MGH must be supervised by an attending
  1. Measure from nose to earlobe to mid-sternum → insert tube this distance → secure → obtain CXR
  2. If CXR shows tip (1) past carina & (2) midline → advance into stomach → repeat CXR → remove stylette once confirmed
    - Caution: never administer tube feeds or medications prior to confirmation. Dobhoff can pass into mainstem bronchus.

### General Troubleshooting:

- If tube coiling repeatedly in oropharynx on insertion, soak tip in ice water to make tube more rigid prior to insertion
- NGT to suction should "sump" – air should audibly enter blue port and exit main port; if not: (1) flush blue port with air (never fluids), (2) flush main port with water (not NS, does not need to be sterile), (3) aspirate from main port → if not able to withdraw flush, NGT needs to be advanced vs. withdrawn (KUB can guide)
- To prevent clogging or adherence to gastric wall, NGTs should be flushed with 30cc water & air q8h. If clogged, can try methods to unclog tube as below in "Gastrostomy Tubes"

### Complications (↑ with longer duration):

- GI: malposition, coiling, knotting anywhere along course of tube, nasal/GI tract perforation. ↑ risk acid/stomach content reflux and aspiration → consider PPI. Chronic suction → gastritis/pressure necrosis: consider removal if grossly bloody
- Pulm: insertion into lung → inadvertent med, contrast, TF administration → PNA, pulm abscess, tracheal perforation, PTX, death
- HEENT: nasal irritation, epistaxis, intracranial placement, skin erosion, sinusitis, alar necrosis, tracheoesophageal fistula/perf

### Removal:

- If for ileus/SBO, consider removal when passing flatus or resolved n/v. Alternatively, may remove when NGT output <1L over 24h. Consider clamp trial before removing (clamp 4h, then check residual. Remove if <150cc)
- Remove tape. Flush tube w/ 10mL air or NS. Turn OFF suction & clamp. Fold Chux around tube insertion site. Gently remove tube

# Procedures

# Tube Management

## GASTROSTOMY TUBES

### Description:

- Clear, soft, graduated tubing held in place w/ plastic mushroom-shaped ring/balloon in stomach (~3cm deeper in obese pts)
- May be replaced at bedside after epithelialized track forms (~2-4w; delayed by malnutrition, steroids, immunosuppression)
- Gastrojejunostomy (GJ) tubes have 3 access ports: G tube port, J tube port, & balloon port
- Secured with vertical Hollister device
- Venting means access port is attached to a foley bag so contents/gas can flow out as needed

### Troubleshooting:

- **Clogging:** only tube feeds & elixir meds should be given through J tube
  - Attach 3cc syringe w/ warm H<sub>2</sub>O to female Luer adaptor. Pulse plunger to force through debris. Flush w/ 30cc warm H<sub>2</sub>O to ensure not clogged
  - Can also try Seltzer, ginger ale, Coca-Cola. If persistent, can try pancrelipase (Viokase) with sodium bicarb
- **Leaking:** retract balloon or mushroom back to skin level; do NOT insert larger size tube (can cause stoma to enlarge); call service who placed G tube if persistent
- **Migration:** can cause n/v (w/ or w/o feeds), dumping syndrome. Confirm placement w/ *tube injection study* (30-60mL gastrograffin f/b KUB)
- **Falling out:** replace w/ similar-sized Foley or feeding tube. Obtain tube study
- **Local site infection:** try topical abx ± antifungal before PO (cephalexin, clinda)
- **Granulation tissue:** check tube size (not too long or short); tx w/ warm compresses & silver nitrate (w/ barrier cream on surrounding normal skin)

## FOLEY CATHETER

### Choosing Catheter:

- (order from Central Supply, ED, or Ellison 6 if not on floor)
- **Many contain latex**, use silicone if allergy; silicone also ↓ risk CAUTI
  - **2-way Foleys** (drainage & balloon ports):  
16F (stock), 12F if stricture, use an ~18Fr **coudé** if BPH or men >50yo → insert curve up toward umbilicus (balloon port points towards sky) – MGH RNs can place coudés
  - **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 viscous lidocaine ("UroJet") or other lubricant syringe into urethra (men)
3. In men, insert catheter to the hub. In women, insert until urine return + 5cm more
4. Fill balloon w/ 10cc sterile H<sub>2</sub>O only if catheter hubbed (in men) and urine return.
5. If no urine when inserted, can verify position by flushing/aspirating the catheter with a 50cc catheter-tip syringe ("GU gun"). Inability to aspirate suggests:
  - a. Bladder empty and catheter sucking against bladder mucosa (instill 50-100 cc if patient does not feel like bladder is full and re-aspirate)
  - b. Catheter in urethra or false passage (instill 50-100 cc – if catheter is in the urethra, what you flush in may come around catheter but you cannot aspirate)
  - c. Catheter outside bladder (undermined bladder neck in pt s/p prostatectomy/TURP – this is rare)
6. If in the bladder, gently withdraw catheter after inflating the balloon until balloon engages the bladder neck
7. Secure the catheter with a little slack to the leg (attach it in the inner thigh between balloon and drainage ports so the catheter can slide down the attachment)
8. Don't forget to reduce foreskin (if not, may cause paraphimosis = **urgent problem**)

### Continuous Bladder Irrigation (CBI): consult Urology to initiate

- Indications: gross hematuria (when you cannot see your hand through the foley due to presence of blood). DO NOT start CBI if urine has clots without manually irrigating the clots out first
- Titrate flow to "fruit punch" colored urine (should be able to see through)
- When d/c'ing, usually start with clamp trial to ensure resolution before removal

### Bladder Pressure: only done in the ICU

*Indications:* concern for intra-abdominal hypertension ( $\geq 12\text{mmHg}$ ) or frank abdominal compartment syndrome ( $>20\text{mmHg}$ )

1. Ensure patient position correlates between measurements (head position as flat as possible) and pressure transducer set-up is arranged
2. Drain bladder and clamp drainage tube of foley
3. Inject 25cc of NS into drainage port, wait 30-60s (allows detrusor muscle to relax)
4. Connect pressure transducer to aspiration port, measure pressure at end-expiration

Cath policy: <https://hospitalpolicies.elucid.com/documents/view/1207>

SPT policy: <https://hospitalpolicies.elucid.com/documents/view/21862>

### Special Circumstances:

**Required urology catheter consults at MGH:** any patient with an artificial urinary sphincter (AUS – prosthetic sphincter for men with incontinence), prostatectomy or other prostate/urethral surgery w/in past 3-4mo, known urethral stricture. See hospital policy below for full details

### Troubleshooting:

- **Difficulty in female patient:** likely poor positioning. Place sheets under hips & place pt in Trendelenburg
- **Urethral trauma:** blood at meatus. Leave catheter in for ~3-5 days (ensure balloon is in proper place)
- **Foley is leaking:**
  - Bladder spasms 2/2 infection, mucosal irritation, overactive bladder. Start anticholinergic (tolterodine 4mg qd PRN)
  - Foley obstructed 2/2 sediment, kinked, dome of bladder, clot. Flush catheter & bladder US
  - Urethra patulous (women w/ chronic indwelling catheters)

### Suprapubic Tubes:

- Many different types although usually a standard Foley catheter
- Know type & size catheter, who exchanges, how exchanged, how frequently
- First exchange performed by IR. Subsequent exchanges should be performed by RNs. Urology available to assist PRN
- If need to reinsert, decompress balloon and remove indwelling SPT tube. Use Foley kit, prep area, apply lubricant to new tube, insert through tract (may have to use some force) until urine return, inflate balloon and ensure tube is mobile, attach to Foley bag

## CHEST TUBES

**Indications:** drainage of air (PTX), blood (hemothorax), pus (empyema), or lymph (chylothorax)

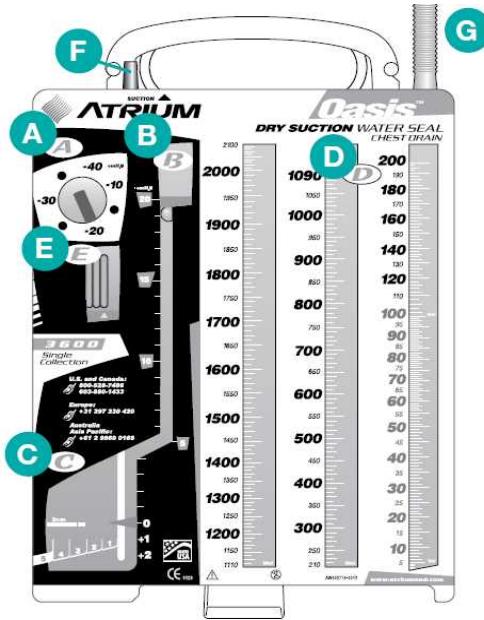
### Chest Tube Logistics:

- Drainage: measured by gradations in 3 columns; if significant drainage, watch for re-expansion pulmonary edema
- Daily CXR while hospitalized until removal
- Suction control: adjusts negative pressure applied to pleural space
  - Suction determined by setting on the device [A], NOT at the wall; if working properly, suction verification window [E] orange bellows will be at triangle marker
  - “Suction” vs “water seal”: if disconnected from wall suction, it is on water seal (i.e. “to gravity”) and will allow for one-way flow of air out of chest, [E] orange bellows not expanded

### Troubleshooting:

- Air leaks: if bubbles present in the water seal chamber [C], indicates air in pleural space. Higher level in chamber, greater leak. Ask patient to cough to assess for leak if bubbles are not continuous
  - Ddx: air in pleural space (parenchymal lung injury or bronchopleural fistula) vs leak in chest tube (check tubing and connections to Pleur-evac)
  - Note: “Tidaling” (movement w/ respiratory variation in water seal chamber) [C] is normal – i.e. not an air leak
- Clogging: look for debris in tube, lack of tidaling, can try “stripping the tube” by compressing it with your fingers while pulling TOWARDS the drainage system, helpful to have an alcohol prep pad for lubrication, might require tPA (alteplase) for clot or Pulmozyme (dornase) for fibrinolysis → involve IP/thoracic surgery (whoever placed tube)

- Ⓐ Dry suction control
- Ⓑ Water seal chamber
- Ⓒ Air leak monitor
- Ⓓ Collection chamber
- Ⓔ Suction monitor bellows
- Ⓕ Tube to suction
- Ⓖ Tube from patient



### Removal:

- General criteria: no active air leak, pt off positive pressure ventilation, <150cc of drainage over 24h
- Steps to removal: place on suction (-40mmHg to -10mmHg) → place on water seal → clamp trial (clamp tube with hemostat)
  - With each step, wait 4h, then obtain CXR to ensure stable or improving PTX
- After stable on clamp trial, tube should be removed during exhalation (patient humming). Large chest tubes often require surgical knot to close hole covered by occlusive dressing (xeroform, 4x4 gauze, large tegaderm) for 48h

# Procedures

# Exposures & Needle Sticks

Please follow the steps below **IMMEDIATELY** in the event of an exposure to bodily fluids while on duty

1. **Stop the procedure**
2. **Immediately clean the affected area**
  - Sharp stick: wash site immediately with soap/water. Alcohol-based agents are also virucidal to HBV, HCV, HIV
  - Splash to open wound: wash site immediately with soap/water
  - Splash to eye(s): irrigate liberally for up to 5 minutes
  - Notify your department supervisor as needed; the charge nurse is often a very helpful resource
3. **Call occupational health (OHS)**
  - Monday-Friday 7am-5pm call 617-726-2217, located at 165 Charles River Plaza (CRP) Suite 404 (4th floor)
  - If outside of normal business hours, page the on-call occupational health provider at p21272 and go to ED
  - **Have the following information available** for the OHS staff member at the time of your call:
    - Source patient: name, MRN, DOB, location, MD, diagnosis, known Hx, exposure to HBV/HCV/HIV, meds
    - Needle: brand, size, gauge, specific device/kit, device manufacturer, safety design type
4. **Test the patient for HBV, HCV, and HIV**
  - **HBV/HCV: one gold top tube**
    - Order HBsAg and HCV qualitative Ab; if patient known HCV+, also send HCV RNA
    - If using paper form (available from OA), mark with BILLING NUMBER CL00009 so pt not charged
  - **HIV: another gold top tube**
    - Order HIV 1/2 Ag/Ab (4<sup>th</sup> generation test)
    - **By law in Massachusetts (M.G.L. c. 111, §70F)**, written consent is required to release HIV results to a third party.  
In the event of an exposure, since HIV status is being released to the exposed individual, written consent is assumed to be required
  - **Send the HIV tube to STAT lab** (results ~60min once received), send HBV/HCV tube to standard core lab

If source patient HAS capacity to consent:	If source patient DOES NOT have capacity to consent:
<ol style="list-style-type: none"><li>1. Obtain a special HIV occupational exposure consent form/lab requisition from the OA</li><li>2. Write STAT result in the comment section</li><li>3. <u>Have the patient sign</u>, then sign it yourself</li><li>4. Ensure form is marked with <u>BILLING NUMBER CL00009</u> so patient is not charged</li></ol>	<ol style="list-style-type: none"><li>1. A valid and invoked health care proxy (you need paperwork!) can sign the occupational exposure consent form <b>OR</b></li><li>2. Facility legal staff can assume temporary guardianship</li></ol> <p>If the exposure occurs to a member of the <u>primary team</u>, the implication of the law is unclear, as that person is not technically a third party. Be conservative, obtain written consent anyway. If this is not possible, consider contacting HIV needlesticks fellow (p36222) or the chief residents for guidance</p>

## 5. Decide if you will initiate post-exposure prophylaxis (PEP)

\*\*\*Post-exposure prophylaxis is most effective if started within 1-2 hours of exposure\*\*\*

- Transmission factors increasing risk: hollow-bore needle, lack of barrier protection/direct skin penetration, depth of needle penetration, increased amount of blood on the needle
- **Starting PEP is recommended if**: patient has known HIV or testing is expected to take >2 hours
  - M-F 7a-5p, PEP can be obtained at the OHS office. At all other times, you must go to the Emergency Department (page the on-call OHS provider at p21272 to be fast-tracked in the ED for treatment)
  - **HIV fellow** can be paged to discuss PEP specifics at p36222

PATHOGEN	TRANSMISSION RISK	POST-EXPOSURE PROPHYLAXIS (PEP)
HIV	Percutaneous (blood): 0.3% Mucocutaneous (blood): 0.09%  <i>There has only been 1 confirmed case of occupational transmission since 1999 (CDC)</i>	PEP can vary but usually includes <u>3 anti-retroviral drugs</u> : <ul style="list-style-type: none"><li>• 2 NRTI <b>tenofovir PLUS emtricitabine AND INSTI raltegravir</b></li><li>• 28 days of treatment recommended but optimal length unknown</li><li>• Regimen usually well-tolerated, side effects include:<ul style="list-style-type: none"><li>◦ Common but mild: n/v/d, fatigue, HA</li><li>◦ Rare: hepatitis, hyperglycemia, fevers, rash, pancytopenia</li></ul></li><li>• Serial testing at 6w, 12w, and 6mo if patient has HIV</li></ul>
HCV	Percutaneous: 1-2%	No PEP; serial testing at 4w, 12w, and 6mo if patient has HCV
AHBV	Percutaneous: 30%	Positive immune titers usually are an employment requirement Vaccine non-responders should be seen in occupational health

## 6. Always file a safety report

# Logistics

# Monitoring & Prophylaxis

## CARDIAC MONITORING (MGH Clinical Guidelines for Cardiac Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	<ul style="list-style-type: none"> <li>Cardiac monitoring for diagnostic purposes only</li> </ul>	<ul style="list-style-type: none"> <li>Continuous cardiac monitoring</li> <li>May be off monitor ONLY in presence of licensed clinical personnel</li> </ul>	<ul style="list-style-type: none"> <li>Continuous cardiac monitoring</li> </ul>
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	<ul style="list-style-type: none"> <li>No cardiac monitor</li> <li>Unaccompanied</li> </ul>	<ul style="list-style-type: none"> <li>With cardiac monitor</li> <li>Accompanied by MD, PA, NP, or RN</li> </ul>	<ul style="list-style-type: none"> <li>With cardiac monitor</li> <li>Accompanied by MD, PA, NP, or RN</li> </ul>
Example indications*	<ul style="list-style-type: none"> <li>Indicated to make dx or guide treatment</li> <li>Post-op AF</li> <li>Post-stroke AF</li> <li>Routine syncope evaluation</li> <li>Low risk chest pain syndrome</li> </ul>	<ul style="list-style-type: none"> <li>Typical chest pain syndrome</li> <li>Acute decompensated HF</li> <li>Uncontrolled AF</li> <li>24 hrs s/p PPM/ICD placement and not PPM-dependent</li> <li>Suspected cardiogenic syncope</li> <li>Actual or risk for QTc prolongation</li> </ul>	<ul style="list-style-type: none"> <li>Early ACS</li> <li>S/p cardiac arrest</li> <li>Critical care patients</li> <li>Temporary PPM/pacing pads</li> <li>s/p PPM/ICD and PPM-dependent</li> <li>Advanced 2<sup>nd</sup> deg. HB, complete HB</li> <li>Unstable arrhythmias</li> </ul>

\*See 2017 AHA guidelines on ECG monitoring for more detailed indications/monitoring duration ([Circ 2017;136:e273](#)). See *Telemetry*.

## O2 SATURATION MONITORING (MGH Clinical Guidelines for O2 Saturation Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	<ul style="list-style-type: none"> <li>Spot check O2 sats as frequently as clinically indicated</li> </ul>	<ul style="list-style-type: none"> <li>Continuous O2 sat monitoring</li> <li>May be off monitor ONLY in presence of licensed clinical personnel</li> </ul>	<ul style="list-style-type: none"> <li>Continuous O2 sat monitoring</li> </ul>
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	<ul style="list-style-type: none"> <li>No O2 sat monitor</li> <li>Unaccompanied</li> </ul>	<ul style="list-style-type: none"> <li>With O2 sat monitor</li> <li>Accomp by MD, PA, NP, RN, or RRT</li> </ul>	<ul style="list-style-type: none"> <li>With O2 sat monitor</li> <li>Accompanied by MD, PA, NP, RN, or RRT</li> </ul>
Example Indications	<ul style="list-style-type: none"> <li>Stable chronic respiratory disease</li> <li>Post-procedure</li> <li>Opioid naïve patients receiving PO narcotics</li> </ul>	<ul style="list-style-type: none"> <li>COPD exacerbation</li> <li>OSA not on CPAP</li> <li>PCA use</li> </ul>	<ul style="list-style-type: none"> <li>Acute respiratory distress</li> <li>High-risk airway</li> <li>NIPPV or intubation</li> <li>Continuous narcotic infusion</li> </ul>

## DVT PROPHYLAXIS

	Low Risk	Moderate Risk	High Risk
Risk factors	<ul style="list-style-type: none"> <li>Ambulatory</li> <li>Estimated LOS &lt;48h</li> <li>Not meeting moderate- or high-risk criteria</li> </ul>	<ul style="list-style-type: none"> <li>Major surgery (&gt;45min, not craniotomy, ortho, spine, or for cancer)</li> <li>Acute illness; immobility w/ est. LOS &gt;48h</li> <li>H/o VTE, thrombophilia (incl. hormone tx)</li> <li>Active malignancy</li> </ul>	<ul style="list-style-type: none"> <li>Major surgery (craniotomy, ortho, spine, or for cancer)</li> <li>Critical illness in ICU</li> <li>2+ moderate risk factors</li> </ul>
Prophylaxis	Ambulation	Pharmacologic OR mechanical	Pharmacologic AND mechanical (SCDs)

- **30 / 30 / 30 Rule**

- Pharmacologic prophylaxis: can be administered if platelets >30K
- Mechanical prophylaxis: SCD boots should not be off the pt for >30% of the day
- Ambulation: pts should ambulate 30min/shift (60min/d)

- **Pharmacologic prophylaxis options:**

- Enoxaparin (Lovenox): 40mg SC q24h; default in patients with CrCl >30 and BMI <40
- Heparin (UFH): 5,000units SC q8h-q12h; preferred in pts with CrCl <30 or BMI >40; q8h pref. in cancer patients
- Fondaparinux: 2.5mg SC q24h (can be used if concern for HIT)
- Alternatives to UFH during shortage: apixaban 2.5mg PO q12h, rivaroxaban 10mg PO q24h (avoid if CrCl <30)
  - Do not use if critically ill (ICU), trauma/spinal cord injury; avoid if recent/high risk for bleeding, anticipated invasive procedure, GI/GU CA and active intraluminal lesions, Childs B/C cirrhosis or any liver disease with coagulopathy

## GI PROPHYLAXIS (MGH Stress Ulcer Prophylaxis Guidelines)

- **Indications** ([Crit Care Med 2016;44:1395](#)):

- Admitted to ICU AND one of the following: 1) mechanically ventilated >48h, 2) coagulopathy (plt <50, INR >1.5, PTT >2x ULN), 3) GI bleed in the last year, 4) TBI, spinal cord injury, or burns, 5) 2+ of the following: sepsis, occult GIB >6d, steroids >60mg prednisone daily (or equivalent), ICU LOS >7d

- Prophylaxis options (PO unless contraindicated): **PPI** (omeprazole, esomeprazole, pantoprazole) or **H2 blocker** (famotidine)

# Logistics

# Peri-Procedural Anticoagulation

## GENERAL ANTIPLATELET & ANTICOAGULATION GUIDELINES FOR ELECTIVE PROCEDURES

- ASA:** hold for 1 week prior if for primary prevention, continue if for secondary prevention
- P2Y12:** hold clopidogrel and ticagrelor 5 days prior; prasugrel 7 days
- Warfarin:** hold 5 days prior (see *Anticoagulation Management* for indications for and guidance on bridging)
- DOAC:** hold 1-3 days prior, depending on agent, renal function, & procedural bleeding risk (see below for guidance for Cath Lab & IR)
- Note:** NO SGLT2i for 72h prior to cases requiring cardiac anesthesia

## CARDIAC CATH LAB ANTICOAGULATION GUIDELINES

Medication	Hold Pre-Procedure*	Resume Post-Procedure
Heparin	<b>Therapeutic</b> (>15k U/d): 1h or on call to lab <b>Prophylactic:</b> continue	4h after sheath removal; no bolus
Enoxaparin (Lovenox)	<b>Therapeutic</b> (1mg/kg): 24h; <b>Prophylactic</b> (<60mg/d): 12h	Next morning
Bivalirudin	1h or on call to lab	4h after sheath removal; no bolus
Argatroban	1h or on call to lab	4h after sheath removal; no bolus
Dalteparin	<b>Therapeutic:</b> 24h; <b>Prophylactic</b> (<5000 U/d): 12h	Next morning
Warfarin	5 days or INR ≤1.8	Night of cath
Apixaban, rivaroxaban, edoxaban	$\text{CrCl} \geq 30: \geq 2 \text{ days}$ ; $\text{CrCl} < 30: \geq 3 \text{ days}$	Next morning
Dabigatran	$\text{CrCl} \geq 50: \geq 2 \text{ days}$ ; $\text{CrCl} < 50: \geq 5 \text{ days}$	Next morning
Fondaparinux	$\text{CrCl} \geq 50: \geq 4 \text{ days}$ ; $\text{CrCl} < 50: \geq 7 \text{ days}$	Next morning

\*Guidelines for endomyocardial biopsy differ. See [MGH Cardiac Cath Lab Anticoagulation Guidelines](#) (Ellucid)

## INR Guidelines for Cardiac Catheterization

Planned Access Site	INR
Femoral artery or vein	≤ 1.8
Internal jugular vein	≤ 1.8
Radial artery	≤ 2.0
Subclavian vein	≤ 1.5
Brachial or basilic vein	≤ 2.0
Pericardiocentesis	≤ 1.5

## VAD Peri-Procedural Cardiac Catheterization Guidelines

INR goal	1.8-2.5; continue warfarin
PTT goal	≤80; continue UFH pre-, intra-, & post-procedure

## Cangrelor and Antiplatelet Agents

- See ACS for switching/bridging P2Y12 inhibitors
- Generally, prasugrel is held on day -7, clopidogrel/ticagrelor on day -5, & cangrelor is started on day -3. Cangrelor is held 1-6h pre-procedure

## IR PROCEDURES

- NPO guidance:** NPO (no solid food; ok to take medications with sip of water) for 8h if will receive sedation (e.g. port placement, biopsies, tube placement) or if a patient-specific need for sedation
- Low bleeding risk procedures:** paracentesis, thoracentesis, chest tube, PleurX, PICC placement/exchange/removal, non-tunneled central catheter, transjugular liver biopsy, IVC filter placement & simple removal, non-vascular catheter/tube exchange, dialysis access interventions, superficial bx/aspiration (thyroid, LN, breast, superficial bone), embolization for bleeding control
  - AC goals:** INR <3, plt >20k; **if cirrhosis/liver disease:** INR <3, plt >20k, fibrinogen >100. **No need to hold AC**
- High bleeding risk procedures:** tunneled central access catheter placement/removal, G- or J-tube placement, nephrostomy tube placement, biliary interventions, TIPS, solid organ/deep tissue biopsies, LP/spine procedures, arterial interventions/angiography, intrathoracic venous interventions (SVC/IVC), portal vein interventions, catheter-directed lysis, complex IVC filter removal
  - AC goals:** INR <1.8, plt >50k; **if cirrhosis/liver disease:** INR <2.5, plt >30k, fibrinogen >100. **AC management per table below**

Medication	Hold Pre-Procedure**	Resume Post-Procedure
Heparin	<b>Therapeutic:</b> 4-6h; <b>Prophylactic:</b> 6h	6-8h
Enoxaparin (Lovenox)	<b>Therapeutic:</b> 24h / 2 doses; <b>Prophylactic:</b> 12h / 1 dose	12h
Dalteparin	24h / 1 dose	12h
Fondaparinux	$\text{CrCl} \geq 50: 2-3 \text{ days}$ ; $\text{CrCl} < 50: 3-5 \text{ days}$	24h
Bivalirudin	2-4h	4-6h
Argatroban	2-4h	4-6h
Warfarin	5 days or INR ≤1.8	Day after procedure; bridge if high-risk
Apixaban, edoxaban	$\text{CrCl} \geq 50: \geq 2 \text{ days} / 4 \text{ doses}$ ; $\text{CrCl} < 50: \geq 3 \text{ days} / 6 \text{ doses}$	24h
Rivaroxaban	$\text{CrCl} \geq 30: \geq 2 \text{ days} / 2 \text{ doses}$ ; $\text{CrCl} < 30: \geq 3 \text{ days} / 3 \text{ doses}$	24h
Dabigatran	$\text{CrCl} \geq 50: \geq 2 \text{ days} / 4 \text{ doses}$ ; $\text{CrCl} < 50: \geq 3-4 \text{ days} / 6-8 \text{ doses}$	24h

\*\*See [MGH Interventional Radiology Periprocedural Management](#) (Ellucid)

## CODES AND RAPID RESPONSES (Consider MGH STAT App in Partners App Catalog)

### MGH CODE ROLES

- **Code leader:** Senior On
  - **Code Whisperer:**  
AM = Consult SAR  
PM = Units NT
  - **Pulse:** SDU JAR
  - **Compressions:** Interns
  - **Bring Lucas:** MICU Intern
  - **Bring IO:** nursing sups
- NON-SR ON TASKS**
- **Confirm code status**
  - Confirm/stop IV infusions
  - Run tele/print strips
  - Check labs, med list
  - Notify attending, family

### REVERSIBLE CAUSES (H&Ts)

Hypoxemia, Hypothermia, Hypovolemia, Hypoglycemia, Hemorrhage, Tamponade, Hypoxia, Tension PTX, H+ ion (acidosis), Thrombosis – MI/PE, HypoK, HyperK, Toxin/drugs

### CODE/RAPID DATA TO OBTAIN

Preceding events, code status, access, vitals, focused exam, POCT glucose, one-liner, PMH, recent procedures, last TTE, run MAR, infusions, ECG, telemetry, last labs, ABG/VBG

### SPECIFIC SCENARIOS (see linked pages for details)

#### ACS

ASA 325, heparin, statin, TNG, BB  
Serial ECGs, ensure telemetry  
Cath lab if HD unstable, refractory CP, VT; **STEMI: x6-8282**  
Discuss with interventional attending; decides on cath

#### BRADYCARDIA

Conduction disease, R-sided MI, vagal, med effect, ↑ICP, hypothyroidism, hypoxemia  
Exam: vitals, mentation, pupils, warm/cold  
Place pacing pads, establish IV access  

- **Atropine** 0.5-1mg q3-5m, max 3mg (will not help in setting of CHB and Mobitz II)
- **Dopamine** 5-20mcg/kg/min
- **Epinephrine** 2-10mcg/min
- **Isoproterenol** 2-10mcg/min
- **Transcutaneous pacing** (midaz/fentanyl or ativan/dilaudid); turn to PACER → set RATE: 100BPM at first + set OUTPUT: select 100 at first
- **Transvenous pacing** (cards consult)

#### TACHYCARDIA

Narrow: AVRT/AVNRT, AF/Aflutter, AT, MAT  
Wide: MMVT, PMVT, SVT w/ aberrancy, PPM-mediated  
**Medications**  
Narrow/reg: vagal maneuvers; adenosine; IV BB/dilt  
Narrow/irregular: IV BB/dilt, amio (rhythm), digoxin (rate)  
Wide/reg:  

- **Amio:** 150mg → 1mg/min
- **Lido:** 100mg → 50mg q5 x3 1-2 mg/min
- **Procainamide:** 20-50mg/min until hypoTN or QRS ↑50%
- Consider adenosine unless WPW

  
Wide/irregular:  

- PMVT: amio, lido; evaluate and treat for ischemia
- Torsades: Mg 2mg, ↑HR (isoproterenol, over-drive pacing)
- AF+WPW: procainamide, ibutilide (1mg)

 Call **CODE BLUE** (x6-3333, blue button on wall)

 Call for defibrillator, backboard, ambu bag

 Establish monitoring: tele, defib pads, cont O2, BP cuff

 Compress 2-2.4" deep, 100-120BPM,

 minimize interruptions & allow full recoil

 W/o ETT: 30:2 compressions to mask vent

 W/ ETT: Δ compressors q2min, breaths q6-8s, ETCO<sub>2</sub> > 10

 **Rhythm check as soon as pads are on**

 for both witnessed and unwitnessed arrest

Epi: 1mg IV/IO q3-5m **Amiodarone (VT/VF):** 300→150 mg

**Post Arrest:** Pressors: if brady→levophed, if tachy→neo, bring Epi

#### IF INTUBATING

Prior intubations, difficult airway?, hemodynamics (RV/LV), aspiration risk (last meal), **x63333 STAT RICU**

#### ECMO FOR CARDIAC ARREST

Consider if possible reversible cause to arrest and ECMO a bridge to definitive treatment; at MGH, recommend contacting ECMO team <10 minutes from code initiation. STAT page "ECMO Consult MGH."

#### PHONE NUMBERS

ICU resource RN (x6-6718), Cardiac Access RN (x4-2677), MICU Intensivist (p26955), HCICU Intensivist (p29151), RRT/Code x6-3333

#### HYPOTENSION

**Cardiogenic:** MI, ADHF, BB/CCB tox, acute myocarditis, valvular dz (AS)

**Distributive:** sepsis, anaphylaxis, liver dz, toxin, adrenal insuff, spinal

shock, sleeping

**Hypovolemic:** bleed, trauma, diuresis, removal w/ HD, insensible losses

**Obstructive:** PE, tamponade, tension PTX

#### PULMONARY EMBOLISM

**Intermediate-High risk:** PE w/ abnl VS (↑HR, ↓BP), evidence of R heart strain (TTE, ECG, or +biomarkers), central or saddle PE → PERT **x4-7378**

**Order:** TTE, ECG, CBC, coags, lactate, D-dimer, trop, NT-proBNP, T&S

**tPA:** Pulseless → 50mg/2m, 50mg in 30m | **Pulse** → 100mg/2h | follow w/ heparin gtt

C/I: prior ICH, isch. CVA <3mo., active bleed, CNS surg./trauma (<2-3mo)

#### ACUTE HYPOXEMIA

aspiration, mucus plug, PNA, pulm. edema, PE, PTX, pleural effusion

#### GASTROINTESTINAL BLEED

2 large-bore IV, T&S, IVF, pRBC, IV PPI 40mg. Octreotide 50mcg + CTX if portal HTN. Correct coagulopathy. RICU if hematemesis

#### HYPERCARBIA

↓RR: sedatives, central sleep apnea, OHS, brainstem stroke, tumor, infection, hypothyroidism

↓V<sub>T</sub>: OSA, pleural effusion/fibrosis, obesity, kyphosis/scoliosis, abd dist, PTX, neuropathy, NMJ disorder, myopathy

↑V<sub>D</sub> and/or ↓V<sub>T</sub>: COPD, asthma, OSA, ILD, CHF, PNA, PE

#### ALTERED MENTAL STATUS

**CNS:** CVA, ICH, sz, infxn, PRES

**Metabolic toxins:** NH3, CO2, BUN, Na, glucose

**Exogenous toxins:** meds, drugs, w/d

**Vitals:** HTN/HoTN, hypoglycemia, hypoxemia

**Misc:** TTP, AI, hypothyroid

**For seizure:** lorazepam

2-4mg IV x2, diazepam

20mg PR, or keppra

20mg/kg

#### ANAPHYLAXIS

**Epi 0.3-0.5 IM** (1:1000; 1mg/mL); or 0.1-0.3mg IV (1:10,000; 0.1mg/mL), repeat q3-15min; other agents: benadryl 50mg, methylpred 12mg, albuterol

# Logistics

# Post-Acute Care

## POST-ACUTE CARE: post-hospital care of patients

- Largest source of Medicare regional variation. High cost growth ([NEJM 2014;370:689](#)) & risk of readmission ([Health Aff 2010;29:57](#))
- Risk factors for use: living alone, impaired mobility, depression, comorbidity ([JAMA Intern Med 2015;175:296](#))
- Note: do not have capability for rapid diagnostics (CT), procedures, or significant acute issues (hypoxemia, hypotension)
- Rely on Case Management, PT, & OT to help determine who qualifies for each of the below post-discharge destinations

Setting (most to least intensive)	Description	Patients / Diagnoses	Avg LOS	MD	Therapy / Ancillary Services
<b>Long Term Acute Care Hospital (LTACH)</b>	High intensity hospital-level care	- Tracheostomy - Chemotherapy - ≥3d ICU stay required	20+ days	Daily MD visits	- RT - PT/OT PRN - HD
<b>Inpatient Rehabilitation Facility (IRF, "acute rehab")</b>	Intensive therapy for recovery of function	- Post-stroke - Spinal cord injury - Specific dx codes required	7-21 days	2-4x/week MD visits; PM&R presence	- 3+h of therapy/d (pt must be able to participate)
<b>Skilled Nursing Facility (SNF)</b>	"Sub-acute" rehabilitation; looks/feels like nursing home; must have 3-night hospital stay to qualify under Medicare	- CHF, PNA, UTI - Generally older patients with functional decline / unsafe at home	3-21 days	~1x/week MD visits; very limited capacity for management changes	- 1-2h of therapy/d (pt must be able to progress)
<b>Home Health</b>	Home-based services post-hospitalization or via PCP referral	- Wound care - IV antibiotics - Post-hospital functional decline - Home safety eval	N/A	Managed by PCP or prescribing outpatient clinician	- 4-8 PT/OT visits - RN visits as needed

## SPECIAL CASES

- **Hospice:** see *Comfort Focused Care & Hospice*
  - Criteria: pt must have a terminal illness with prognosis of ≤6mo as certified by a physician. Depending on the hospice agency, pt may need to forego curative treatments (i.e., chemo, expensive antibiotics, etc.)
  - Home hospice: fully funded by Medicare. RNs visit, but patients need full-time caregiver support in the home, which can be a barrier to home hospice discharge
  - Inpatient hospice (SNF or dedicated inpatient hospice facility): room & board (~\$400 per day) only covered by MassHealth, but not other insurers
  - GIP (in-hospital hospice care): fully funded by Medicare, patient must qualify
- **Long-term care:**
  - Patients residing in nursing homes with stably poor functional status and who require assistance with ADLs/IADLs, but do not require post-acute level care
  - Private pay or covered by MassHealth, but not funded by Medicare
- **Alternative programs:** if patient is in Partners ACO, discuss additional home-based care options with case manager

# Logistics Microaggressions/Bias, Patient-Directed Discharge, ICE

## MANAGING MICROAGGRESSIONS & BIAS

**Microaggression:** a brief & common indignity (statement, action, or incident) that communicates hostile, derogatory, or negative slights to target a person or group. **Despite the name, “micro” does not speak to the severity of the impact on the target**

**Bias:** an attitude projecting favorable/unfavorable dispositions towards people. Bias/microaggressions can be implicit or explicit

**Common examples in medicine:** questioning of credentials/abilities, assumption of non-physician status, requests to change providers, belittling comments, inquiries into racial/ethnic background, inquiries into relationship status/sexual orientation/gender identity, inquiries into family/pregnancy status, comments on appearance, assumptions of religious affiliation

**Upstander:** a person who chooses to intervene when witnessing bias/microaggressions

**Responding to microaggressions OR bias from patients ([JGME 2019;11:371](#)):**

### 1) Prepare before the encounter:

Within your team, talk explicitly about how leadership should address the situation. For example, team leader: “In our two weeks together, we may encounter a patient who discriminates against one of our team members. It can sometimes feel safer to have the JAR/attending address the behavior, but I want to empower you all to act if you feel comfortable. What do you think?”

### 2) During the encounter:

- 1) Ensure the patient is stable and assess decision making capacity: if unstable, call for help to provide care. If lacks capacity (see *Consent & Capacity*), consider redirection. If stable and has capacity, proceed
- 2) Check your emotions and psychological safety: if you’re not in a space to respond, it is OK to step out, process, ask for support
- 3) If you respond, address the aggression explicitly: “I’m surprised to hear you say \_\_\_\_.” “I’m disappointed you’d say that.” “What do you mean by that?” “That’s frustrating to hear from a patient.”
- 4) Align with the patient: “Our team is here to focus on your health.” “We are all here to treat your \_\_\_\_.”
- 5) Align with your team: “Our team is doing our best to respect you. We ask that you respect Dr. \_\_\_\_/me as well.”
- 6) Set boundaries: varies by aggression. “I’d ask that you refrain from commenting on \_\_\_\_.” “Please call them/me Dr. \_\_\_\_.” “Let’s keep the focus on you.” “We do not accommodate staff changes based on [race/ethnicity/religion/etc], Dr. \_\_\_\_/I will be in charge of your care today.” “Our institution does not tolerate that behavior/language/etc.”
- 7) Give space: if patient or team member is unable to continue the encounter, leave the situation with a defined time to come back. “We are going to give you space for 30 minutes and when we come back, we can focus on your health.”

### 3) After the encounter:

- 1) Attend to emotion: if you were the target of the aggression, seek support, debrief however feels right to you. If you were a bystander, explicitly acknowledge what you witnessed, offer to support your colleague. Support can range from listening to holding their pager so they can step off the floor to decompress. Ask what they need from you
- 2) Discuss the encounter: once emotions have been attended to, if the target is willing, discuss as a team how the interaction went. What went well? What didn’t? What would you do differently next time? Practice future phrasing together
- 3) Involve others: ensure attending, other providers, and unit-based leadership are aware
- 4) If the behavior continues: reconvene to discuss next steps as a team (attending, residents, other colleagues)

## PATIENT-DIRECTED DISCHARGE (HISTORICALLY KNOWN AS AMA)

All patients have the right to discharge from treatment when they have capacity. It is the duty of the physician to obtain informed consent of discharge after discussing the risks and benefits to discharging from care. Common reasons why patients request discharge include: financial concerns, communication issues, insufficient management of pain/cravings/withdrawal, family obligations

**Approach to a safe patient-directed discharge ([JGIM 2013;28:1657](#)):**

- 1) Is the patient on section 12a or under guardianship? If yes, these patients cannot choose to leave. Involve psychiatry and security as needed to help the patient stay safely and place on medical hold. See *Psychiatry: Agitation*. If no, proceed
- 2) Perform a capacity evaluation: see *Consent & Capacity*. If patient has capacity, proceed
- 3) Determine why the patient is motivated to leave: acknowledge their reasons for leaving, validate their emotions. Use a harm reduction lens, negotiate to meet their needs as able. If time allows, involve SW and CM to help brainstorm solutions
- 4) Discuss risk and benefits of leaving: ask them what they believe are the risks and benefits. Explain your recommendation. Discuss not only the immediate medical impact of their options, but the impact on their longer-term values/goals
- 5) Offer alternatives: if the primary recommendation of staying is rejected, offer other reasonable options. Acknowledge this may require sub-optimal care, for example, admission for IV antibiotics vs PO antibiotics with outpatient follow up or a home visit
- 6) Summarize recommendations, confirm understanding: Example language: “I understand you’d like to leave the hospital today to \_\_\_\_\_. As we have discussed, remaining in the hospital will \_\_\_\_\_. That is my primary recommendation for you. Another potential option we discussed is \_\_\_\_\_. While it is not ideal medically, it is a reasonable option and care should align with your goals.”
- 7) Confirm contact information and give return precautions: coordinate follow up, remind the pt they are always welcome back for care
- 8) Complete paperwork: avoid documenting “AMA” → stigmatizing and has no medicolegal benefit ([JHM 2017;12:843](#))

## INFORMATION ON IMMIGRATION AND ICE/DHS

**When should a patient's immigrant status be documented in the EHR?**

NEVER. EHR can be accessed by law enforcement/immigration officials and used as evidence

**What to do if ICE/DHS inquires about a patient?**

If an Immigration and Customs Enforcement (ICE) or Department of Homeland Security (DHS) Agent asks for a patient or patient information, **do not provide any information about the patient. Immediately contact your attending and the Partners Office of General Counsel** (available 24/7; during normal business hours, call 857-282-2020. During off hours, call MGH Page Operator)

Main Number	
617-726-2000 (MGH prefix: -724, -726, -643)	
Emergency Numbers	
Senior On (Med Sr)/Bauer Room	3-1388, p22337
ED Triage Sr (ED Sr)	3-1388, p28786 Voalte: DOM ED
Med Consult Pager (Code Backup)	p13480
RICU Team (intubation), Code Stroke	6-3333
ECMO Consult	857-310-0335, p24252 / p29151
SHOCK Consult	p11511
STEMI Team (CCL activation)	6-8282
PERT (massive PE)	4-7378
IV Nurse (urgent access)	6-3631, p26571
ED Radiology (STAT imaging)	6-3050
RT (on call)	p24225
ICU Nursing Supervisor	6-6718, p25213
Poison Control (ingestion)	617-232-2120
Pharmacy	
Outpatient pharmacy (fax: 6-3789)	4-3100
Outpatient pharmacy (private line)	6-2354
Laboratories	
General lab info	4-LABS
Chemistry/Hematology (Core Lab)/Toxicology	6-2345
STAT Chemistry/Hematology	4-7617
Serology	4-7645
Special coagulation	4-2969
Blood gas / STAT lab – Bigelow 5	6-3856
Blood bank – Bigelow 2	6-3623
Blood bank – Lunder	8-5280
Microbiology – Bigelow 5	6-3613
Micro after hours (blood culture room)	6-7919
Parasitology	6-3861
Virology	6-3820
Surgical Pathology – Blake 3	4-1449
Immunopath (Flow, ANCA, EM)	6-8487
Cytology / Cytopathology – Warren 1	6-3980
Cardiology Studies	
Cath Lab	6-7400
Echo Lab	6-8871
Stress Lab	4-3600
Holter Lab	6-7737
EP Lab	6-5036
Pulmonary Studies	
PFTs – Cox 2	6-1200/3-9680
Sleep Study (inpatient/outpatient)	4-7426
GI Studies	
Endoscopy Lab – Blake 4	6-3732
Neurology Studies	
EEG – Blake 12	6-3640
EMG/NCS – Blake 12	6-3644
Subspecialties	
Anticoagulation (AMS)	6-2768
Boston Healthcare for the Homeless	781-221-6565
Brace Shop (White 10)	6-3248
Mass Eye and Ear Infirmary	
Page Operator	617-523-7900, 0
11 <sup>th</sup> floor (Inpatient)	Above plus x2480
MEEI ED (for ENT transfers)	617-573-3431
Interpreter Services	
In Person	6-6966, p27403
Phone (Pin 1050)	617-643-3344

## RADIOLOGY

- **Life Images**

- Upload images to Lifelimage and Epic: Partners Applications → Utilities → MGH Upload Image to Radiology (Lifelimage) → Access Lifelimage → find exam on CD/DVD → Upload images
- Send images to MGH PACS: upload to MGH → request read
- Retrieve images from The Cloud: <ISDrequests.partners.org> → file urgent ticket or request changes to existing ticket
- Additional information:
  - Urgent reads: contact ISD (**p34188, x30003**)
  - Multiple body parts: interpretations only given for selected body parts
  - Multiple Lifelimages of the same body part: upload all images → request a read only on the most recent
  - Exams will not be read if: requisition was for a different body part than the uploaded images; study >6 months old; a more recent Lifelimage is available; US, fluoroscopy, or mammography

## Radiology Reading Rooms

Dodd Reception	44212
Cardiac CT	47132
Cardiac MRI	66947
Chest CT	33899
CXR Inpatient	42051
CXR Outpatient	62197
ED	41533
GI CT	65162
GI Fluoro/KUB	32605
GI MR	49919
IR (GI & VIR)	34723
Mammography	40228
MSK	40516
Neuroradiology	41931
Nuclear Cardiology	43600
Nuclear Medicine	61404
PET	66737
Vascular	47115

## Technologists

CT Blake 2	48518
CT ED	66760
ED Radiology	63050
GI Fluoro	44295
Mammography	63092
MRI ED	49867
MRI Inpatient	85692
Nuclear Medicine	68350
PET	64209
Scheduling	4XRAY
US White 2	53074