TOC

Housestaff Manual

July 2020 - June 2021

Department of Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, MA

Editors
Jacqueline Henson, MD
Alexandra Wick, MD

MGH Housestaff Manual

Preface

It is an honor to present the **26th edition** of the **MGH Department of Medicine Housestaff Manual**. **"The White Book"** is a trusted resource for medical residents and other clinicians at MGH and a great tradition of the Department of Medicine Residency Program. It exemplifies the rigor, autonomy, and pride with which MGH medical residents approach their work and their training.

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

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

Cardiology: Shawn Li, Avanthi Raghavan
Pulmonology & Critical Care: Robert Arao, Anna O'Kelly
Gastroenterology: Ryan Flanagan, Sally Knooihuizen
Nephrology: Daniel Gromer, Elizabeth Kurtz
Infectious Disease: Rebecca Abelman, Hawra Al-Lawati
Hematology: Nora Abo-Sido
Oncology: Leon Pappas, Vinayak Venkataraman
Geriatrics & Palliative Care: Paige McLean
Rheumatology: Leslie Chang
Endocrinology: Max Petersen, Seth Tobolsky
Allergy & Immunology: Jessica Plager
Neurology: Jeffrey Gluckstein
Psychiatry: Alexandra Wick
Primary Care: Nate Alhalel
Consultants: Jacqueline Henson, Alexandra Wick
Radiology: Sam Cartmell
Procedures: Sean Mendez, Chitra Mosarla

We would like to thank the many faculty and fellows who assisted with this book, particularly Jonathan Dau for his work on the Rheumatology section. In addition, we are grateful for the contributions from residents in the neurology and radiology programs.

Multiple sections have had significant updates and there are some new articles including: Infectious Disease – COVID-19; Hematology – Anticoagulation Management; Allergy & Immunology – Mast Cell Disorders; Primary Care – Eye & Ear Complaints; Consultants – OB/GYN; Logistics – Peri-Procedural Anticoagulation.

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

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

And of course, none of this would be possible without the guidance and support of so many amazing people that make up the Department of Medicine. In particular, we extend special thanks to Gabby Mills, Libby Cunningham, and Paula Prout for supporting this project. In addition, we would like to thank our Chief Residents – Pierre Ankomah, Alyssa Castillo, Kelsey Hills-Evans, and Aisha James – as well as Jay Vyas and Katrina Armstrong for their undying support and endless devotion to the housestaff and our education. We will always be grateful for their unwavering leadership during the COVID-19 pandemic.

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

Jacqueline Henson, MD & Alexandra Wick, MD
Department of Medicine, Massachusetts General Hospital
June 2020

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

MGH Housestaff Manual

Table of Contents

CARDIOLOGY
ACLS: Cardiac Arrest & Cooling 1
ACLS: Bradycardia 3
ACLS: Tachycardia 4
ACLS: Defibrillation, Cardioversion, Pacing 5
EKG Interpretation 6
Narrow & Wide Complex Tachycardia 8
Atrial Fibrillation & Flutter 10
QTc Prolongation 12
Chest Pain 13
Acute Coronary Syndrome 14
MI Complications 17
Cardiac Catheterization 19
Non-Invasive Cardiac Testing 20
Echocardiography 22
Inpatient Heart Failure 23
Right Ventricular Failure 26
Pulmonary Artery Catheterization 27
Mechanical Support & Transplant 28
Cardiac Devices: PPM & ICD 29
Valvular Heart Disease 30
Pericardial Disease 32
Aortic Disease 33
Syncope 35
Hypertensive Urgency & Emergency 36
Peripheral Artery Disease / Cardio-Onc 37
Outpatient CV Health 38
Anti-Arrhythmic Medications 40

PULMONOLOGY & CRITICAL CARE
Respiratory Distress 41
Hypoxemia & Hypercarbia 42
Noninvasive Oxygenation/Ventilation 43
Asthma 44
COPD 45
Bronchiectasis & Hemoptysis 46
Interstitial Lung Disease 47
VTE 48
Pulmonary Hypertension 50
Mechanical Ventilation 51
ARDS 53
ECMO 55
Sedation 56
Shock 57
Sepsis 58
Vasopressors 60
Toxicology 61

GASTROENTEROLOGY
Upper GI Bleeding 63
Lower GI Bleeding 64
GERD & Peptic Ulcer Disease 65
Nausea & Vomiting 66
Diarrhea 67
Constipation & Colonic Disorders 69
Motility Disorders 70
Inflammatory Bowel Disease 71
Intestinal Ischemia 72
Nutrition & Feeding 73
Pancreatitis 74
Liver Chemistry Tests 75
Biliary Disease 76
Acute Liver Injury & Failure 77
Viral Hepatitis 78
Alcohol-Related Liver Disease 79
End Stage Liver Disease 80
Hepatorenal Syndrome 84
Liver Transplant 85

NEPHROLOGY
Acute Kidney Injury 86
Glomerular Disease 88
Chronic Kidney Disease 89
Dialysis & Transplant 90
Advanced Diuresis 91
Acid-Base Disorders 92
Sodium Disorders 94
Potassium Disorders 95
Magnesium & Phosphorus Disorders 96
IV Fluids & Electrolyte Repletion 97
Urinalysis 98
The Nephron 99

INFECTIOUS DISEASE
Empiric Antibiotics 100
Gram Stain Interpretation 101
Multidrug Resistant Organisms 102
Community Acquired Pneumonia 103
HAP/VAP & Aspiration Pneumonia 104
Viral Respiratory / Head & Neck Infections 105
COVID-19 106
Urinary Tract Infections 108
Skin & Soft Tissue Infections 109
Osteomyelitis 110
Bacteremia & Endocarditis 111
Meningitis & Encephalitis 112
C. Difficile Infection 113
Invasive Fungal Infections 114
Tuberculosis 115
HIV/AIDS & Opportunistic Infections 116
Transplant ID 117
STIs & Travel Medicine 118
Tick-Borne Diseases 119
Fever of Unknown Origin 120
Rare Diseases 121
Infectious Precautions 122
Vancomycin & Renal Antibiotic Dosing 123
MGH Antibiogram 124

HEMATOLOGY
Anemia & Pancytopenia 125
Thrombocytopenia 127
Eosinophilia 128
Coagulation Disorders 129
Anticoagulation Agents 130
Anticoagulation Management 131
Transfusion Medicine 132
Transfusion Reactions 134

ONCOLOGY
Acute Leukemia 135
Lymphoma 137
Plasma Cell Disorders 138
MDS & MPN 139
Stem Cell Transplantation 140
CAR T-Cell Therapy 143
Solid Organ Malignancies 144
Chemotherapy & Toxicities 146
Immune Checkpoint Inhibitors 148
Oncologic Emergencies 150
Febrile Neutropenia 151

GERIATRICS & PALLIATIVE CARE
Frailty & Polypharmacy 152
Pain Management 153
Non-Pain Symptom Management 155
Adv Care Planning & Code Status 156
End of Life & Pronouncement 158
Organ Donation 159

RHEUMATOLOGY
Approach to Rheumatologic Disease 160
Arthritis 161
Connective Tissue Diseases 163
Vasculitis 164
Miscellaneous Rheumatologic Diseases 166
Autoantibodies 167
Rheumatologic Medications 168

ENDOCRINOLOGY
Outpatient Type 2 Diabetes 169
Inpatient Diabetes Management 171
DKA/HHS 172
Adrenal Insufficiency 173
Pituitary Disorders 174
Calcium Disorders 175
Osteoporosis 176
Thyroid Disorders 177

ALLERGY & IMMUNOLOGY
Drug & Contrast Allergy 179
Angioedema & Anaphylaxis 181
Mast Cell Disorders 182
Primary Immunodeficiency 183

NEUROLOGY
Altered Mental Status 184
Delirium 185
Dementia 186
Headache & Vertigo 187
Stroke & TIA 188
CNS Emergencies 190
Seizures 191
Weakness & Neuromuscular Disorders 192
Neuroprognostication 193

PSYCHIATRY
Psychosis & Agitation 194
Consent & Capacity 195
Catatonia, NMS & Serotonin Syndrome 196
Depression & Anxiety 197
Alcohol Use Disorder & Withdrawal 198
Opioid Use Disorder & Withdrawal 200
Other Substance Use 201

PRIMARY CARE
Health Screening & Maintenance 202
Women's Health 204
LGBTQ Health 206
Immigrant & Refugee Health 207
Musculoskeletal Pain 208
Respiratory Complaints 210
Eye & Ear Complaints 211
Nodules 212

CONSULTANTS
Calling Consults 213
Perioperative Medicine 214
Dermatology 216
Surgery 219
Urology 220
ENT 221
Ophthalmology 222
OB/GYN 223

RADIOLOGY
Contact Information 224
Radiology Basics 225
Contrast 226
Protocols 227
Interpretation of Common Studies 229

PROCEDURES
Ultrasound Basics 231
Ultrasound-Guided Peripheral IV 233
Central Line 234
Arterial Line 236
Intraosseous Line 237
Paracentesis 238
Arthrocentesis 239
Lumbar Puncture 240
Thoracentesis 241
Pericardial Drain 242
Fluid Analysis 243
Tube Management 244
Exposures & Needle Sticks 247

LOGISTICS
Monitoring & Prophylaxis 248
Peri-Procedural Anticoagulation 249
Senior On Encounters 250
Post-Acute Care 251
Formulas 252
MGH Directory 254
NWH Directory 256

TOC

Cardiology

ACLS: Cardiac Arrest & Cooling

Code Tasks:
- **A**ccess (IO), **A**irway
- **B**ackboard
- **C**ode status
- **D**efibrillator, **D**rips
- **E**CMO pager <10 mins
- **F**amily (call)
- Run tele + meds

Assess for responsiveness, pulse, and spontaneous respirations (C-A-B)
No definite pulse within 10 seconds = start chest compressions (CPR)

1. Call **Code Blue** (x6-3333, blue button on the wall)
2. Call for defibrillator pads, backboard & Ambu bag for mask ventilation
3. Establish monitoring: tele, defibrillator, O2 sat probe, place BP cuff
4. **In both *witnessed AND unwitnessed* arrest, rhythm check ± defib as soon as pads are on** (Class IIa recommendation)
   2015 AHA Guidelines Update, 2018 AHA Focused Update

High Quality CPR
- **Minimize interruptions**
- **Fast**: 100-120/min
- Compress 2-2.4 in deep
- Allow complete recoil
- Change compressors every 2 mins
- 30:2 CPR:vent (mask)
- $PETCO_2$ >10, DBP>20

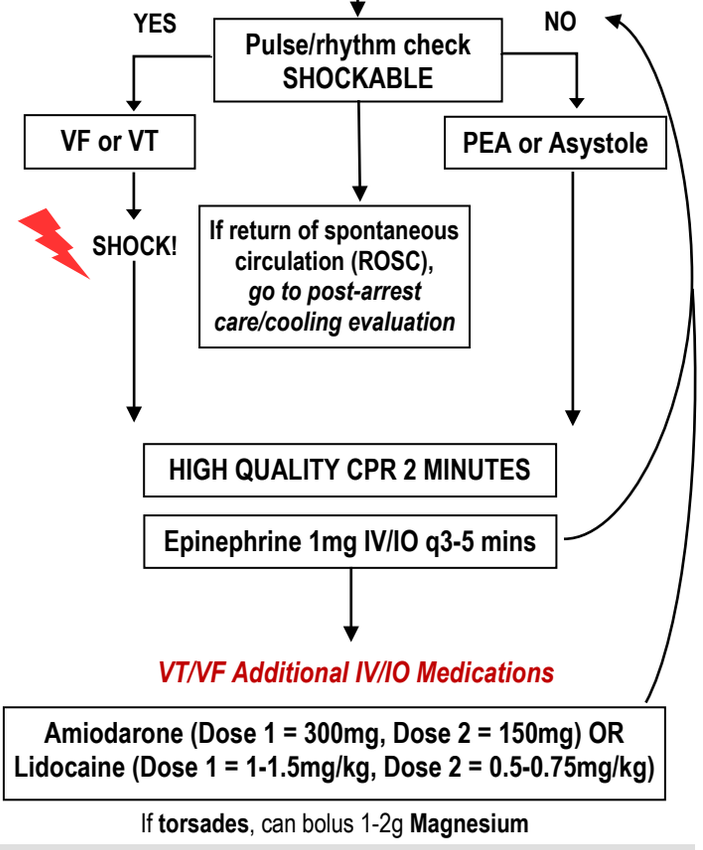
DEFIBRILLATOR
Biphasic (MGH) 120J-200J
Monophasic 360J

- If unknown, use max setting
- Repeat shocks at same or higher dose

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

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

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



If **torsades**, can bolus 1-2g **Magnesium**

Reversible Causes (H&Ts)
- **H**ypovolemia, hemorrhage
- **H**ypoxia
- **H**+ ion (acidosis)
- **H**ypo/hyperkalemia
- **H**ypothermia
- **T**hrombosis, coronary (ACS) & pulmonary (PE)
- **T**ension pneumothorax
- **T**amponade (cardiac)
- **T**oxins (drugs, accidents)

TREAT REVERSIBLE CAUSES (H&Ts)
Hyperkalemia Treatment:
Ca gluc 1-2g IV (or $CaCl_2$), Bicarb 1-2 amp IV, D50W 1-2 amp (give first) + insulin 10 units IV

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

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

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

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

ECMO in Cardiac Arrest
- Consider if possible reversible cause to arrest and ECMO a bridge to definitive treatment (Class IIb recommendation). At MGH, recommended to **contact ECMO team <10 minutes from code initiation**. STAT page "**ECMO Consult MGH**" or use "**MGH Heart**" app to call ECMO consult and for MGH ECMO guidelines (Circ 2015;132:S444; Intensive Care Med 2016;42:1922).

MGH Code Roles:
- Sr On: code leader
- Code Whisperer (consult SAR during day, units NT at night): facilitates other aspects of code
- CCU JAR: brings I/O; can help w/ tasks (e.g. run tele, recent labs – check in w/ whisperer)
- SDU JAR: hand on pulse
- Interns: compressions

Brad Petek

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

Pulse and blood pressure measurable or spontaneous arterial pressure waves on A-line tracing

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

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

Rationale: TTM decreases cerebral oxygen demand and ischemia-related inflammation

- Class I recommendation for comatose cardiac arrest patients following ROSC for in- and out-of-hospital arrest (Circ 2015;132:S465)
- Improves neurologic outcomes (NNT 6) and survival to discharge (OR 5.25) following **out-of-hospital** cardiac arrest from **VF, pulseless VT, or PEA/asystole of presumed cardiac cause**, although the benefit may be from avoidance of hyperthermia rather than from hypothermia (NEJM 2002;346:549; NEJM 2002;346:557; NEJM 2013;369:2197; Circ 2015;132;2146; NEJM 2019;381:2327)

Cooling Criteria

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

Relative Exclusion Criteria

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

Abbreviated Therapeutic Hypothermia Protocol (MGH 2019 protocol)

- **Preparation**:
  - Consult neurology Stroke/ICU consult (p20202) prior to initiation of hypothermia
  - Non-contrast head CT, baseline labs including electrolytes, PT/PTT/INR, fibrinogen, D-dimer
  - Access: A-line, central line +/- PA catheter, temperature probe (esophageal/bladder/rectal); access is challenging once patient is hypothermic
- **Temperature targets**: reach **hypothermia target** of **32-34ºC ASAP → maintain** at hypothermia target for **24h** (starting at the time from initiation of therapy) → **rewarm** at **24h** @ 0.5ºC/hr to goal temp 37ºC → upon rewarming, **maintain** at normothermia target (37ºC) for **24h**
- **Monitoring**: maintain normal Na, K, pCO2 (35-45 mmHg), MAP (>70), glucose (140-180)
  - If water temp <70ºF, pursue fever workup and consider starting antibiotics
  - Maintain sedation and paralysis to prevent pain and shivering

- **Neuro-prognostication** (Lancet Neurol 2016;15:597) (also see *Neurology: Neuroprognostication*)
  - AHA 2015 Guidelines: Recommended Markers of Poor Neurologic Outcomes (Circ 2015;132:S465)
    - **Exam**: absence of pupillary light reflexes (>72 hrs post arrest), status myoclonus (72-120 hrs post arrest)
    - **Blood markers** (should not be used alone, no cutoff established): high neuron specific enolase (NSE, 48-72 hrs)
    - **Imaging**: brain MRI (extensive restriction/diffusion, 2-6 days post arrest), head CT (reduced gray-white ratio, <2 hrs post arrest if no TTM)
    - **Neuro testing**: bilateral N20 SSEP absence (24-72 hrs post arrest), EEG with absence of reactivity, persistent burst suppression, or intractable status epilepticus (72 hrs post arrest)
  - In-hospital mortality at 72h post-rewarming (100% if **≥2 criteria present**) (Ann Neurol 2010;67:301)
    1. unreactive EEG (most helpful)
    2. bilaterally absent SSEP
    3. early myoclonus
    4. incomplete recovery of brainstem reflexes

Circ 2010;122:S729

Bradycardia with Pulse

HR<60 bpm and **symptomatic**

DDx of Sinus Bradycardia:
- Med toxicity, especially in liver/renal failure (BB, CCB, digoxin, amiodarone)
- Nocturnal
- Athletic heart
- Elderly
- SSS
- Infiltrative diseases (sarcoid)
- Ischemia/ACS
- Vasovagal
- ↑ ICP
- Hypothermia
- Hypoxemia
- Hypothyroid
- Carotid disease, recent stent
- Hypo/HyperK
- Endocarditis
- Chagas, Lyme

Assess patient, treat underlying causes

- Maintain **airway**, give supplemental O2 to maintain SpO2 >94%
- IV access
- Monitor **BP** frequently
- **12-lead ECG** and **telemetry**
- Prepare **pacing pads** if needed
- Review recent medications, hospital events
- Obtain **labs**: BMP, Mg, lactate & troponin if concern for ischemia/ACS

Unstable or inadequate perfusion?

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

If pulseless arrest develops, go to PEA/Asystole ACLS algorithm

NO

Type II second-degree AV block
or
Third-degree AV block

NO

- Observe
- Avoid nodal blockers

YES

- Call Cardiology for possible **temp wire** placement
- Use transcutaneous pacemaker or beta-adrenergic agents ***as bridge*** to transvenous pacemaker (see right side of algorithm)

YES

Place pacing pads

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

If atropine ineffective

Dopamine IV infusion 2-20 mcg/kg/min

OR

Epinephrine IV infusion 2-10 mcg/min

OR

Isoproterenol 2-10 mcg/min

OR

Transcutaneous/transvenous pacing
If transcutaneous, consider sedation with versed/fentanyl or ativan/morphine

AND/OR

Antidotes by cause

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

Cardiology ACLS: Tachycardia

Tachycardia with Pulse
HR>100 bpm and symptomatic

Circulation 2010;122:S729

If pulseless arrest develops, go to cardiac arrest ACLS algorithm

Assess patient, treat underlying causes
- Maintain **airway**, give supplemental O2 to maintain SpO2 >94%
- IV access
- Monitor **BP** frequently
- **12-lead ECG** and **telemetry**
- Prepare **defibrillation pads** if needed
- Review recent medications, hospital events
- Obtain **labs**: BMP, Mg, lactate & troponin if concern for ischemia/ACS

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

NO

Wide QRS?
≥120ms

NO

- **Vagal maneuvers**
- **Adenosine** (if regular)
- Beta blocker or calcium channel blocker
- Amiodarone

YES

Ventricular tachycardia?

Monomorphic

Preserved LVEF (>40%)
- First line:
  - **Amiodarone**
  - Procainamide
  - Lidocaine
  - Adenosine (to differentiate SVT w/ aberrancy from WCT Circ 2015;132:S444)
- Other:
  - Metoprolol
  - Sotalol *(not first line, expert consultation advised)*

Impaired LVEF (<40%)
- **Amiodarone**
- Lidocaine

Polymorphic

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

Normal baseline QTc
- **Treat myocardial ischemia**
- **Lidocaine**
- Amiodarone
- Procainamide

Prolonged baseline QTc)
(Torsades de Pointes)
- **IV Magnesium**
- ↑**HR: dopamine**, isoproterenol, overdrive pacing
- ↓**QTc**: **lidocaine**
- Avoid bradycardia: hold nodal agents and amiodarone

YES

Place defibrillation pads

If **regular narrow complex**, can give **adenosine** (see below for dosing).

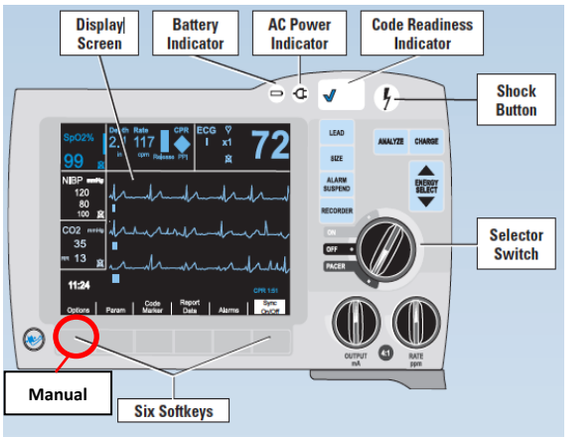
Cardioversion		
Rhythm	**Dose***	**Mode**
Narrow regular	50-100 J	Sync
Narrow irregular	120-200 J	Sync
Wide regular	100 J	Sync
Wide irregular	120-200 J	Defib
*Biphasic (MGH)		

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

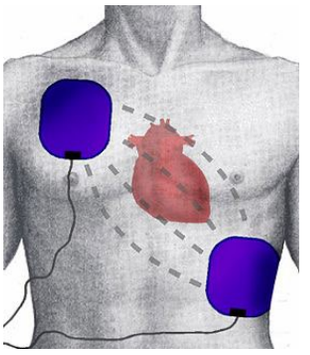
External Defibrillation/Cardioversion/Transcutaneous Pacing:

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

Display/Operation of Zoll R Series:



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

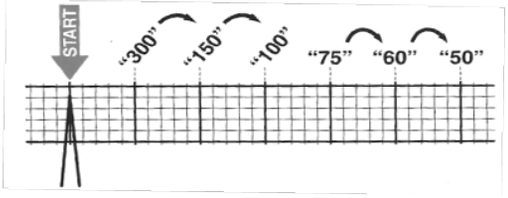


Pearls:
- CPR ok to perform while pacing, take R-sided pulses (L not reliable)
- Failure to capture? Increase output, ensure pads are in correct location, consider ddx (barrel chest, COPD, tamponade/pericardial effusion, acidosis, hyperK, obesity, MI, cardiac drug tox [dig, anti-arrhythmic])
- Failure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

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

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

Rate (atrial, ventricular)



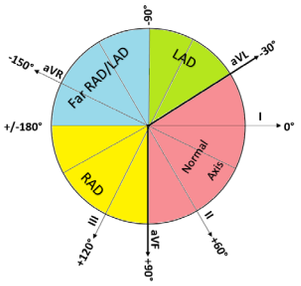
- If the rhythm is regular, use the counting method (300 / #large boxes)
- If the rhythm is irregular, count R waves in rhythm strip and multiply by 6 (EKG printout records 10 sec)
- Normal 60-100bpm; <60 = bradycardia, >100 = tachycardia

Rhythm (regular or irregular; sinus vs. non-sinus)

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

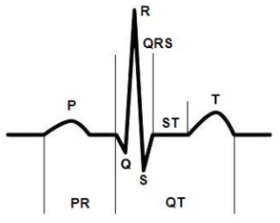
QRS Axis (use direction of QRS complex)

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



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

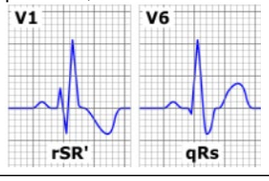
Complexes and Intervals (Circ 2009;119:e241)



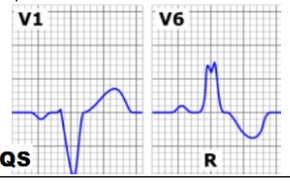
- P wave: right and left atrial depolarization. Normal duration <120ms
- PR interval: atrial depolarization, AV node and His-Purkinje conduction. Normally 140-200ms, changes with rate (shortened at faster rates, longer at lower rates d/t autonomic effects on AV nodal conduction
- QRS: ventricular depolarization.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

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

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



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



- ST segment: represents a time of electrical silence. See below.
- T wave: ventricular repolarization, with a slow upstroke and a rapid return to the isoelectric line after peaking. Usually asymmetric and in the same direction as the QRS. Should have smooth contours (bumps in T are usually buried P waves)
- U wave: occurs in the same direction as the T wave, rate-dependent (shorter at faster rates); DDx: bradycardia, hypoK/Mg/Ca, hypothermia
- QT interval: ventricular depolarization and repolarization. Excludes U wave unless fused with T wave. Rate-dependent (shortened at faster rates). Normal <450ms (M) and <470ms (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). Suggestive if R in aVL >11mm.
- RVH: R>S or R ≥7mm in V1, S ≥7mm in V5 or V6
- LAE: negative P wave in V1 >1mm wide and deep, total P wave duration >110ms
- RAE: P wave >2.5mm in II

Ischemia/Infarction (JACC 2009;53:1003)

- Analyze abnormalities along the vectors of ventricular depolarization and repolarization (QRS-ST-T)
- **T wave abnormalities**: hyperacute, symmetric T waves can be found within minutes, followed by T wave inversions (≥1mm in 2 contiguous leads). TWI not abnormal if only in aVR, V1 or III.

- TWI DDx: myocardial ischemia (symmetric), prior MI, acute PE, intracranial pathology ("cerebral T waves", asymmetric), myocarditis, pericarditis, BBB pattern, ventricular-paced, LVH with "strain", normal variant, digoxin effect
- deWinter's T waves: 2% of STEMIs present with tall, symmetric T waves + >1mm STD at J point in precordial leads + 0.5-1mm STE in aVR c/w acute LAD occlusion (NEJM 2008;359:2071)

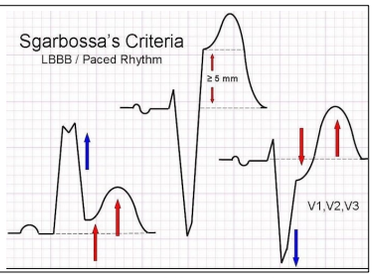
- **ST depression**: suggests subendocardial injury, ≥0.5mm below the baseline (PR segment), measured at the J point in 2 contiguous leads
  - Downsloping or horizontal = more ominous. STD do not localize to territories. (Circ Res 1998;82:957)
  - Always look for STE to rule out reciprocal STD. STD in V1-V3 can be posterior MI (check posterior leads).
- **ST elevation**: suggests transmural ischemia, ≥0.1mV, except for leads V2-V3 (≥2mm in M ≥40y and ≥1.5mm in F), use PR segment (isoelectric interval), measured at the J point.
  - **Differential Diagnosis** (NEJM 2003;349:2128, Annals 2004;141:858, NEJM 2004;351:2195)

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

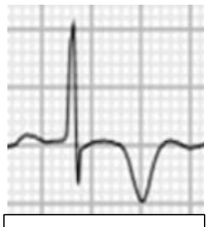
  - **Coronary Distribution**

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

Sgarbossa Criteria:
Used to diagnose acute MI in the presence of LBBB (does not apply to pacers). Score >3 is 90% Sp
- Concordant STE >1mm in any lead = 5 points
- Discordant STE >5mm in any lead = 2 points
- STD >1mm in V1-V3 = 3 points



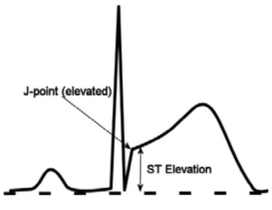
- **Q wave**: usually a marker of scar, pathologic Q waves must be deep (>1mm), 25% height of QRS, and 40ms long. More likely 2/2 prior MI if inverted T wave in same lead. Small "septal" Q physiologic in V5, V6, I, aVL.
- **Wellen's Syndrome**: sign of **critical proximal LM or LAD lesion**, 75% MI in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

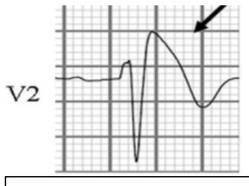


Wellens Type B

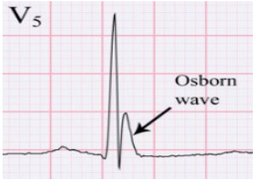
Other

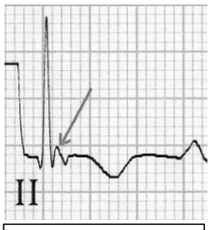
- **J-Point Elevation Syndromes**: J point is when QRS transitions to ST segment
  - Early repolarization pattern: benign STE in absence of chest pain, terminal QRS slur, or terminal QRS notch
    - Suspicious features: FH of sudden cardiac arrest or early unexplained death, eval and workup suggestive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





Brugada Syndrome: Type 1





Epsilon wave

- **Electrolyte Abnormalities**

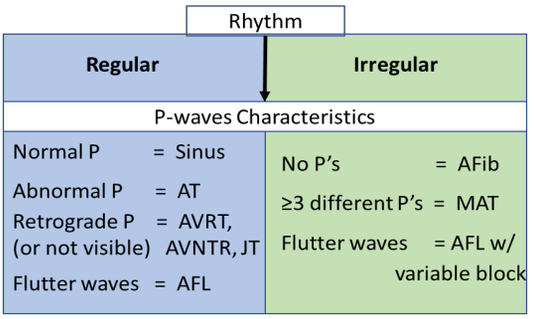
Electrolyte Derangement	Characteristic ECG Findings
Hypokalemia	Prolonged QT, ST depression, flattened T wave, prominent U wave
Hyperkalemia	Peaked, symmetric T wave, prolonged PR, flattened P and widened QRS (severe)
Hypocalcemia	Prolonged QT, unchanged T wave
Hypercalcemia	Shortened QT

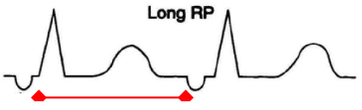
Narrow Complex Tachycardia (QRS < 120 ms)

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

Diagnostic approach & general principles:

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





Long RP Tachycardias

Sinus Tachycardia

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

Atrial Tachycardia (AT)

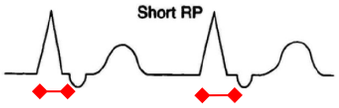
- Single P morphology, non-sinus P wave axis
- Arises from increased automaticity at single atrial focus
- Classic digoxin toxicity is AT w/ variable AVB

Multifocal Atrial Tachycardia (MAT)

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

Atrial Flutter (AFL)

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



Short RP Tachycardias

Junctional Tachycardia

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

Atrioventricular Re-entrant Tachycardia (AVRT)

- Arises from true re-entry via bypass tract
- Usually short RP, uncommonly long RP
- Ventricular activation via AV node (orthodromic, narrow QRS) more common than accessory tract (antidromic, wide QRS)
- Rates usually 150-250

Atrioventricular Nodal Re-entrant Tachycardia (AVNRT)

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

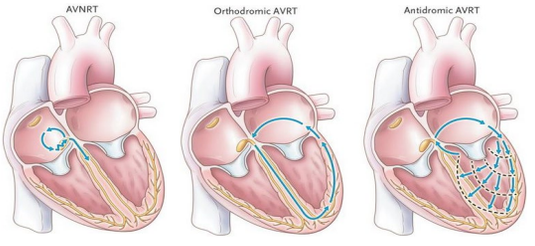
No RP Interval

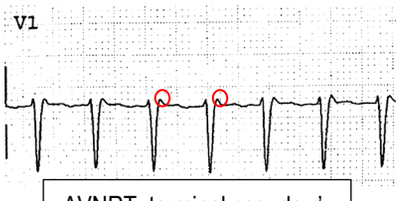
Atrial Fibrillation (AF)

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

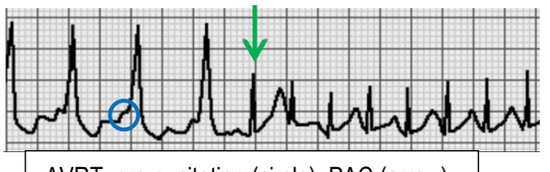
AVNRT vs AVRT

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





AVNRT: terminal pseudo-r'



AVRT: pre-excitation (circle), PAC (arrow)

Wide Complex Tachycardia (QRS ≥ 120 ms)

Etiology

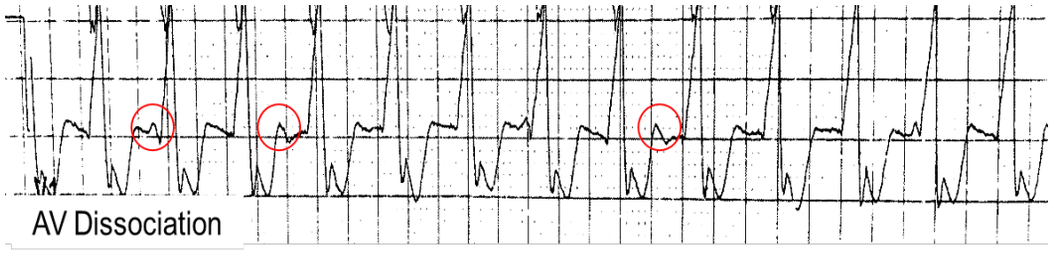
- Ddx: **VT** (90%), **SVT with aberrant conduction**, pacemaker-induced tachycardia

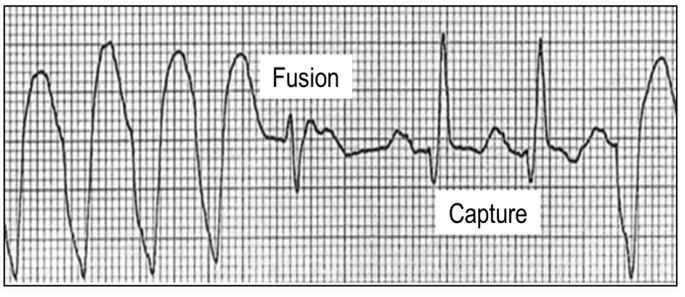
ECG Factors that Favor VT
- **Very broad QRS** (>160 ms) - **Superior** axis (II, III, aVF neg) or **northwest** axis (I, aVF neg) - **AV dissociation** (often V rate > A rate) → *diagnostic of VT* - **Concordance**: all QRS across precordium completely positive or completely negative - Partial (**fusion beat**) or complete (**capture beat**) depolarization of ventricle by underlying supraventricular rhythm - Brugada criteria (Circ 1991;83:1649) – only applicable if rhythm is regular

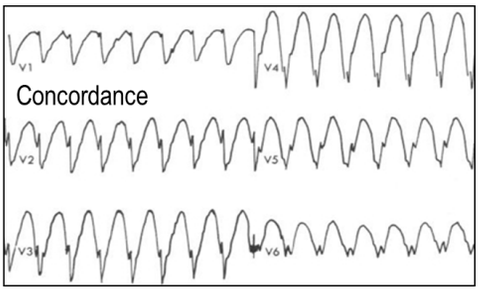
ECG Factors that Favor SVT with Aberrancy
- **Pre-existing BBB** → functional/rate-dependent BBB d/t encroachment on bundle refractory period; RBBB > LBBB - QRS with sharp initial deflection followed by broad terminal deflection - **Pre-excitation** on baseline ECG → antidromic AVRT

Other important considerations:
- Hyperkalemia, antiarrhythmic drugs (digoxin, class IA or IC, amiodarone), TCA overdose

- Pacemaker/endless loop tachycardia: retrograde VA conduction of V-paced beat misidentified as native A-beat → V-pacing





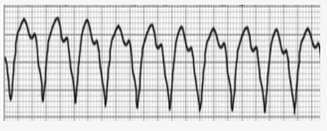


Management of VT (also see *ACLS*: *Tachycardia*)

- 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

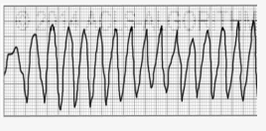
DDx: ischemia, structural heart disease, idiopathic



1. **Non-sustained VT** (>3 complexes, <30 secs) → nodal blockade (e.g. BB/CCB)
2. **Stable and sustained** (>30 seconds) → antiarrhythmic agent (e.g. amiodarone)
3. **Unstable** → synchronized cardioversion (100J) if pulse; defibrillation if pulseless

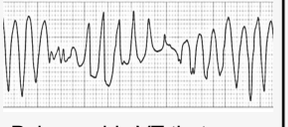
Polymorphic VT

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



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

Torsades de Pointes



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

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

- Reduction of autonomic tone: **intubation** and **sedation**
- Treatment of underlying ischemia: **revascularization**, **IABP** to improve coronary perfusion, reduce cardiac afterload
- Anti-tachycardia **pacing** (ATP): over-drive pacing at a faster rate than VT
- **Amiodarone** 150 mg IV + gtt, co-administer propranolol 60mg q6h (superior to metoprolol JACC 2018;71:1897)
- VANISH trial: 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)

Epidemiology (Heart Rhythm 2012;9:632)

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

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

Clinical Evaluation of New-Onset AF

- H&P: **presence and timing of sx**, HTN, DM, valvular disease, CHF, angina, congenital heart disease, OSA, FH of AF, acute precipitants (e.g. EtOH, thyrotoxicosis, sympathomimetic drugs, surgery, myocardial ischemia, myocarditis, PE, acute pulmonary disease, infection)
- ECG: absence of discernible p waves, irregularly irregular R-R intervals (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)

Acute Management of AF with Rapid Ventricular Response

Hemodynamically stable?

Stable (SBP >90)	**Peri-stable** (SBP 80-90)	**Unstable** (SBP<80)
1. Address **underlying etiology** of RVR (sepsis, hypovolemia, hypervolemia, etc.) 2. **Rate control** agents (IV if HR >130 or sx, follow with PO agent once rates controlled) - **Beta blocker**: metoprolol preferred in most cases - IV: bolus 2.5-5 mg over 2min, repeat as required q5min for max 15 mg total - PO: fractionated, up to 400 mg total daily dose - Caution if severe bronchospasm and w/ rapid escalation in pts w/ ADHF **- Calcium channel blocker**: diltiazem - IV: bolus 0.25 mg/kg (average adult dose 10-25 mg) over 2min, repeat as needed q10-15min - PO: fractionated, up to 360 mg total daily dose - Reduce dose with hepatic or renal impairment - Avoid in pts with LVEF<40% and in ADHF	If borderline BP, carefully attempt **low dose** BB or CCB (can try concomitant **IVF** if pulm edema not a concern) Consider BP-sparing agents: (weigh risk of pharmacologic cardioversion if not on AC) - **Amiodarone**: 150mg IV over 10 min, can repeat x1 if needed and start gtt at 1mg/min - **Digoxin**: 0.5mg IV followed by 0.25mg IV q6h x2, total load 1mg. Can lead to toxicity with renal impairment, contraindicated if accessory pathways.	Usually with HR >150, signs of shock (AMS, cool extremities), refractory pulmonary edema or angina **Synchronized cardioversion**: typically start with 150J If pressors are required, **phenylephrine** is first-line given reflex bradycardia Higher HRs (>140) are more likely to cause HoTN alone; lower HRs may cause HoTN if systolic/diastolic dysfunction or decreased preload ("loss of atrial kick")
Correct underlying causes or precipitants whenever possible once stable		

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

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

Long-Term Rate vs. Rhythm Control

- Overall, rate control is noninferior to rhythm control for AF symptoms, CV mortality, and stroke risk. (AFFIRM, RACE, PIAF, STAF, HOT CAFÉ, AF-CHF).
  - 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 and exercise performance (NEJM 2005;352:1861, JACC 2004;43:241).

- **Rate Control**
  - **BB** more successful than **CCB** in achieving rate control (70% vs. 54%), either alone or in combination with digoxin
  - **Digoxin** alone is moderately effective in controlling V-rate at rest, ineffective during exertion or high adrenergic tone
    - Long-term digoxin a/w increased mortality in AF patients (JACC 2018;71:1063)
  - **Rate Targets**: lenient rate control (resting HR <110) non-inferior to strict rate control (HR <80) with similar outcomes in CV death, stroke, bleeding, arrhythmia and hospitalization for HF (RACE II). Stricter HR (or rhythm control) may be beneficial in younger pts or pts w/ HF.
  - Contraindications/Warnings: evidence of pre-excitation on ECG (in these patients, IV procainamide is 1st line), cautious use in high-degree AVB. 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" (flecainde/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. antiarrhythmic agents in both pAF (MANTRA-PAF, RAAFT-2) and persistent AF (EHJ 2014;35:501). Ablation in pts with HF ↓ morbidity/mortality CASTLE-AF
  - **AV nodal ablation with PPM**: indicated when pharm rate/rhythm control not achievable (JACC 2014;64:2246)

Antithrombotic Therapy (Stroke 2010;41:2731)

- Treatment recommended for all pts **except** those with CHA_2DS_2-VASc 0, lone AF episode, or contraindications to therapy (AHA/ACC/HRS Guidelines: Circ 2019;140:e125)
- LA appendage is the source of at least 90% of thrombi in pts with CVA and AF.
- Subclinical AF still associated with increased stroke/systemic embolism (ASSERT)
- Patients at relatively low risk for thromboembolism may be maintained on ASA alone (see below), but no reliable data exist to guide decision between 81mg vs 325mg dose

Risk Assessment

- **CHA_2DS_2-VASc**: 1pt for **C**HF, **H**TN, **A**ge 65-74, **D**M, female **S**ex, **V**ascular disease; 2pt for **A**ge≥75, **S**troke/TIA. CHA_2DS_2-VASc > $CHADS_2$ in "truly low risk" subjects (Thromb Haemostasis 2012;107:1172).
  - Score 0 = no AC or ASA; Score 1 = no AC vs. ASA vs. oral AC based on clinical judgment → how high is risk from specified risk factor? (e.g. HTN, DM, age bring greater risk compared to female sex, vascular dz); Score ≥2 = oral AC

CHA_2DS_2-VASc Score	0	1	2	3	4	5	6	7	8	9
Adjusted stroke rate (%/yr)	0	1.3	2.2	3.2	4	6.7	9.8	9.6	6.7	15.2

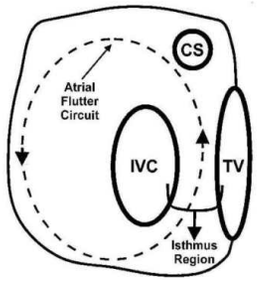
- **HAS-BLED**: risk stratification of bleeding risk w/ oral AC. HTN (SBP>160); abnml renal function (CrCl<50); liver disease (cirrhosis or Bili 2x ULN or AST/ALT/AlkPhos 3x ULN); stroke; bleeding history; labile INR (<60% in Rx range); elderly (>65y); antiplatelet meds (ASA, NSAID); alcohol (>8 drinks/wk) or other drug use. Score ≥3 suggests caution and regular follow-up.
- http://www.sparctool.com/ can aid in risk assessment and choice of anticoagulation

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

- **DOACs vs warfarin**: DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) are recommended over warfarin in all pts (except with mod-severe mitral stenosis or mechanical heart valve). DOACs have ↓ risk of stroke, mortality, and ICH but higher risk of GI bleeding compared to warfarin (Lancet 2014;383:955).
- **Dosing**: see section in *Hematology* for dosing. Dose-reduce apixaban to 2.5mg BID if Cr ≥1.5 AND age ≥ 80 OR weight ≤60kg
- **Renal impairment**: for pts w/ CrCl<15 or on dialysis, can use either warfarin or apixaban
- **Bridging AC**: see *Hematology: Anticoagulation Management*.
- **LAA closure (Watchman device):** In non-valvular AF, device placement→comparable stroke prevention to warfarin with ↓bleeding risk and improved mortality (JACC 2017;70:2964)

Atrial Flutter (less prevalent but often coexists or precedes AF)

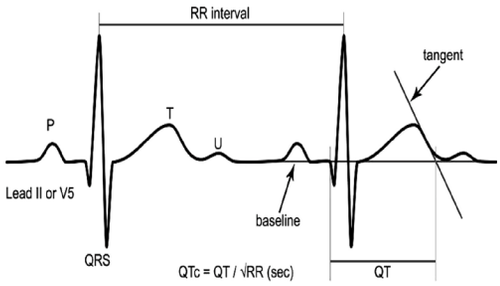
- ECG: "Sawtooth" P waves (F waves), atrial rate typically 300bpm w/ 2:1 conduction (~VR 150), though can be variable block, 3:1, or 4:1. 1:1 conduction can briefly precede VT/VF.
  - **Type 1 (typical)**: reentrant loop in RA via cavo-tricuspid isthmus
    - Counterclockwise: more common, inverted flutter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



Cardiology QTc Prolongation

Definition

- QT interval correlates with repolarization time of ventricles
- Prolonged QTc >450ms (M) or >470ms (F)
- Measure from beginning of QRS to end of T wave in a lead with T wave > 2mm (best in II, V5), define end point using tangent from peak of steepest slope to isoelectric line
- QTc is QT corrected for HR
  - Bazett = QT/√RR; overcorrects at high HR and undercorrects at low HR
  - Fridericia = QT/^{3}√RR; more accurate at high or low HR (Am J Cardiol 1993 26;72:17B)
  - Hodges = QT + 0.00175 * (60/RR – 60)



Assessment of QT with Underlying BBB (Heart Rhythm 2014;11:2273)

- Bundle branch blocks lengthen QT interval. Can obtain rough estimate using QT – (QRS-120)
  - JT Interval = JT(HR + 100)/518, with a JTI ≥ 112 identifying repolarization prolongation in all ventricular conduction defects
  - Modified QT = QTb – (0.485 x QRSb), where QTb = measured QT and QRSb = measured QRS

Congenital Long-QT Syndromes

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

Drug-Induced Prolonged QT Interval (Heart 2003;89:1363)

- Drugs inhibit I_{Kr} causing prolonged ventricular repolarization and 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 which can degenerate into VF
Longer QT increases risk for "R on T" phenomenon and development of torsades (higher risk if PVCs)

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

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

Monitoring for QT/QTc Prolongation

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

Management of Acquired LQTS

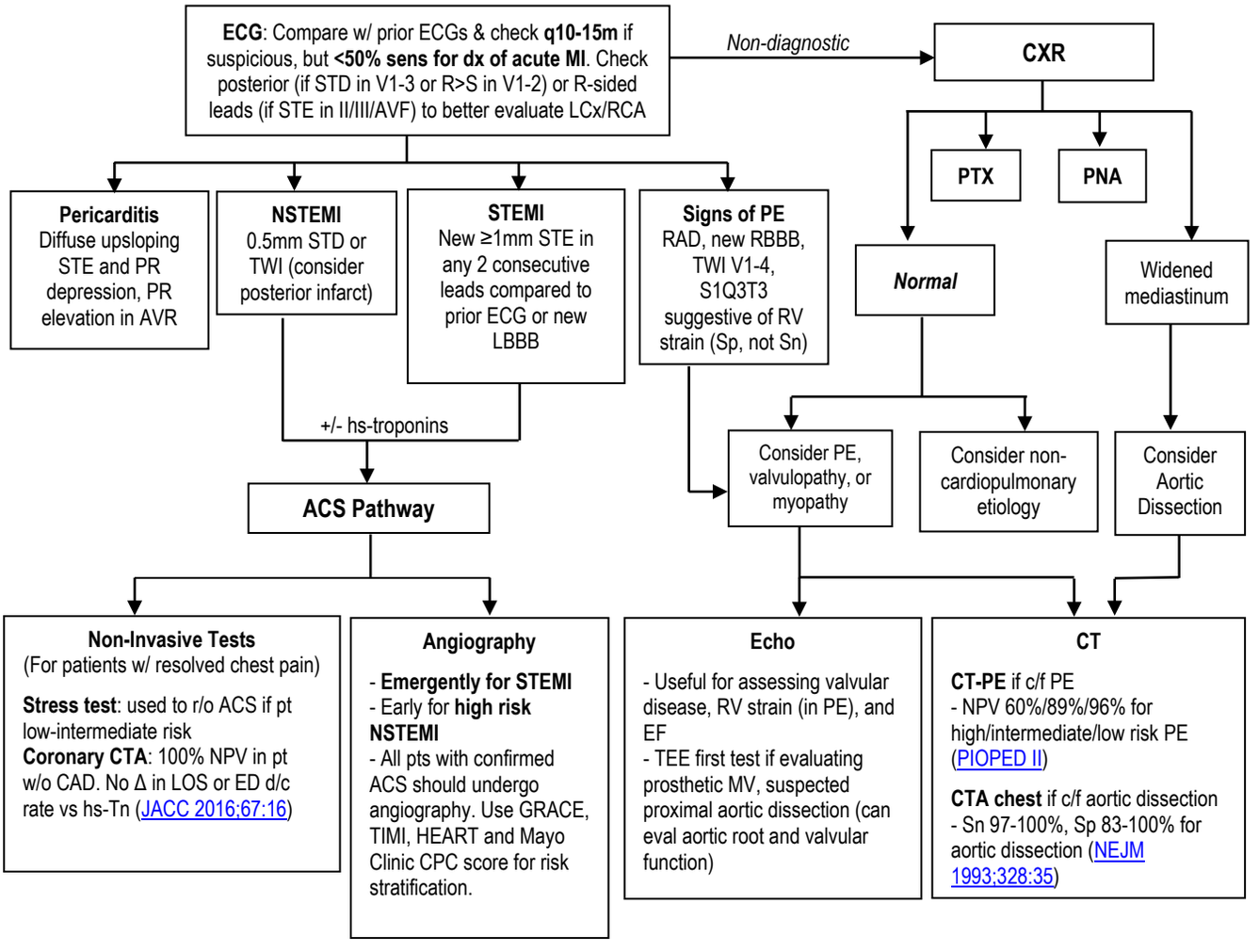
- **Stop offending drug** if **QTc >500ms** or **increase in QTc of >60ms**
- ECG should be checked for bradyarrhythmias and signs of impending TdP (R on T). Stop drugs causing bradycardia.
- Check electrolytes checked and replete (K >4, Mg >2.4). Supratherapeutic repletion of K to 4.5-5.0 can be used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

	HISTORY	PHYSICAL EXAM
Stable Angina/ACS	**CVD risk**: Use Framingham or ASCVD Risk Estimator. Women, elderly, and diabetics may have atypical presentations. Age, h/o CAD, and male sex most predictive of ACS (NEJM 2000;342:1187). **Angina** (NEJM 1979:300:1350): (1) **substernal** chest pain (2) brought on by **stress/exertion** (3) **relieved** by rest or TNG *3/3 = typical, 2/3 = atypical, 1/3 = noncardiac* **Antianginals**: nitrates - 1st SL, then IV; avoid if preload sens. (HoTN, AS); BB (avoid in ADHF, long PR, 2°/3° AV block); CCB.	• **New S4**, MR (*ischemia*) • **CHF** (rales, +S3, ↑JVP, pedal edema) • Carotid, subclavian, and abdominal bruit (indicates vascular disease) • Bilateral femoral and radial pulses (*document pre-cath*) • Frank's sign: bilateral diagonal earlobe crease (slight ↑ in likelihood of CAD) • Less likely ACS: **p**leuritic, **p**ositional, re**p**roducible by **p**alpation (LR 0.28)
Acute Aortic Syndromes	**Abrupt onset** of tearing/sharp thoracic or abdominal pain RF: known aneurysm, Marfan syndrome, HTN, M:F 2:1, 60-80yrs, cocaine use, high-intensity exertion (weightlifting)	BP variation >20 mmHg between arms, pulse deficits, new diastolic murmur, focal neurologic changes
Acute Pericarditis	Pleuritic, sharp, improves upon leaning forward. May have URI prodrome, though consider bacterial pericarditis if high fevers	Friction rub (*breath hold to distinguish from pleural rub*); tamponade (pulsus >10)
PE	Sudden onset, dyspnea/hypoxemia, pleuritic RF: hx of cancer/recent surgery/immobility, hemoptysis, calf/thigh pain/swelling	Tachycardia, tachypnea, hypoxemia, calf/thigh erythema, swelling, tenderness
Pneumothorax	Sudden onset dyspnea; RF: 20-40yrs (more likely if tall), FH or personal history, smoker, known emphysema, M > F, recent chest procedures/lines	Ipsilateral absence of breath sounds, contralateral deviation of trachea
Pneumonia/ Pneumonitis	Sharp, pleuritic CP associated with fever/leukocytosis, productive cough, recent radiation, autoimmune (SLE, RA, drug-induced lupus, collagen vascular diseases)	Bronchial breath sounds, rales, dullness
Other	**Cardiac**: HOCM, AS, vasospasm (Prinzmetal's angina, drug/toxin), Takotsubo CM; **MSK**: costochondritis, Zoster; **GI:** GERD, esophageal spasm (may be relieved by TNG), Boerhaave's, PUD, biliary colic, pancreatitis; **Psych**: panic attack	

Likelihood Ratios for ACS (JAMA 2015;314:1955)

Low Risk	
Pleuritic (0.3)	Syncope (0.5)
Intermediate Risk	
Radiation to left arm, neck, or jaw (1.3-1.5)	Diaphoresis (1.4); exertional (1.5)
Pressure / typical (1.9)	Pattern change /24h (2.0)
High Risk	
Similar to prior ischemia (2.2)	Pain radiating to both arms (2.6)
PAD (2.7)	Abnormal prior stress test (3.1)

Basic Chest Pain Algorithm



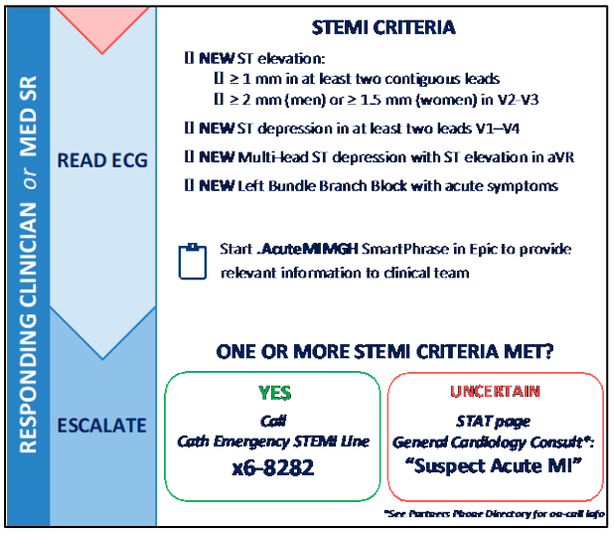
Myocardial infarction: myocardial necrosis (trop >99th percentile + Δ) w/ ischemia (4th universal def. of MI: JACC 2018;72:2231)

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

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

Evaluation of CP with hsTnT	
Emergency Department – CP onset ≥ 3h PTA	**Inpatient or Emergency – CP onset < 3h**
Check hsTNT immediately and at **1h**	Check hsTNT immediately and at **3h**
Rule in: hsTnT ≥ 52 OR Δ ≥ 5 from baseline → **consider ACS**	Rule in: hsTnT ≥ 10 (F) or ≥ 15 (M) AND Δ ≥ 7 from baseline AND sx or ECG changes or concerning imaging (CCTA, cath) → **consider ACS**
Rule out: hsTNT <10(F) or < 12(M) AND Δ <3 from baseline → **unlikely ACS**	
Intermediate: calculate HEART score, repeat hsTnT in 3h and apply inpatient criteria (right)	Rule out: no significant Δ in 3h → **unlikely ACS**

STEMI	NSTEMI	Unstable Angina
1mm STE in two contiguous leads (if V2-V3: >2.5mm in M<40, 2mm in M>40, 1.5mm in F) OR New LBBB *AND* (+) biomarkers	⊕ ECG or hx, ⊕ biomarkers	⊕ ECG or hx, ⊖ biomarkers



Clinical Evaluation & Risk Stratification:

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

ECG: (NEJM 2003;348:993)

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

Cardiac Biomarkers:

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

Risk Stratification for PCI Timing in NSTEMI/UA:

- Multiple risk models: GRACE, TIMI, PURSUIT, AMIS. 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)
  1. **Very high risk** ("immediate invasive," within 2 hrs): **refractory/recurrent angina, hemodynamic or electrical instability**
  2. **High risk** ("early invasive," within 24 hrs): temporal change in troponin, EKG changes (STD, TWI), high risk pt (GRACE>140)
     a. Conflicting results between TIMAC (NEJM 2009;360:2165) and VERDICT (Circ 2018;138:2741) trials about outcome benefit of early cath. However both show improved outcomes with early cath in patients with GRACE >140.
  3. **Intermediate risk** ("delayed invasive," within 72 hrs): none of above but risk factors at baseline (e.g. EF <40%, GFR <60)
  4. **Low risk** ("ischemia guided," no cath): no risk factors, GRACE <109, TIMI 0-1

Revascularization:

- **PCI Indications**: recommended over fibrinolysis at a PCI-capable center (1A)
  - STEMI: PCI if <12h sx onset, goal to PCI ideally <60min at PCI centers. PCI regardless of time from onset for cardiogenic shock, malignant arrhythmia, persistent STE and/or CP. Late PCI (>48h post-event) generally not indicated in stable pts (NEJM 2006;355:2395)
  - NSTEMI/UA: see Risk Stratification above
- **PCI Strategies**:
  - In pts with STEMI and no cardiogenic shock, complete revascularization strategy (culprit + non-culprit) has a ↓ risk of CV death and MI at 3yrs (COMPLETE NEJM 2019;381:1411)
  - In pts with cardiogenic shock, culprit-lesion only PCI has a ↓ risk of death/RRT (CULPRIT-SHOCK NEJM 2018;379:1699)
  - Access: radial > fem | Stent: DES > BMS (NEJM 2016;375:1242)

- **CABG**: preferred for 3VD (SYNTAX NEJM 2009;360:961, NEJM 2008;358:331), left main disease (Lancet 2016;388:2743, NEJM 2016;375:2223), 2VD with prox LAD stenosis or EF <50%, large area of viable myocardium or high risk. Consider if DM + 2VD (FREEDOM NEJM 2012;367:2375)

Adjuncts to Revascularization

1. **ASA**: established mortality benefit, give to all pts in an immediate load/maintenance strategy (325mg/81mg) (Lancet 1988;2:8607)
2. **P2Y12 Inhibitors**: (pre-cath load not done at MGH, controversial if beneficial and may delay CABG by 5-7 days)
   - Ticagrelor: ↓ mortality compared to clopidogrel w/o increasing major bleeding. Reversible with platelet transfusion. Side effect: mild dyspnea on initiation. 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 >75yr
   - Clopidogrel: ↓ death, repeat MI when load/maintenance with PCI (Lancet 2001;358:527I). Prodrug, metabolized by CYP219, less effective in those with LOF allele (NEJM 2009;360:354)
   - 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.
3. **Nitrates**: TNG SL x3, transition to gtt if refractory CP. 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 CP despite ↑ dose of TNG, indication for earlier cath.
4. **Anticoagulation**:
   - **UFH**: usually stopped after 48h if ECG changes improving and concern for ongoing ischemia resolved (BMJ 1996;313:652). Start gtt w/ bolus and use **low intensity PTT goal** (63-83). No bolus if giving lytics or if on warfarin and INR<2.
   - **LMWH**: possible reduction in death w/ minimal evidence for ↑ major bleeding, trials vs UFH largely null (BMJ 2012;344:e553)
   - **Fondaparinux**: preferred to UFH/LMWH if medically managed. Contraindicated in PCI 2/2 ↑ catheter thrombosis/complications (JAMA 2006;295:1519)
   - **IIb/IIa Inhibitors**: eptifibatide (Integrilin) used at MGH. Initiated in cath lab if PCI high-risk (extensive thrombus).
   - **Bivalirudin**: direct thrombin inhibitor, preferred for patients w/ HIT, otherwise cost does not outweigh benefit
5. **Beta Blockers**: start within 24h (1b), mortality benefit. Consider early initiation if ischemic arrhythmias present.
   - Caution in decompensated HF, ↑ risk for cardiogenic shock (>70yr, SBP<120, HR>110 or <60)
   - Contraindications: cocaine-induced MI, PR>240ms, 2nd or 3rd degree AVB, severe bronchospasm (Lancet 2005;366:1622)
6. **ACEi or ARB**: start within 24h if BP/renal function normal
   - Mortality benefit maximal if EF<40%, pulm edema, or anterior MI (Lancet 1995;345:669)
7. **Statin**: atorvastatin 80mg daily regardless of baseline LDL (NEJM 2004;350:1495)
   - Early high-dose statin within 24-96h may reduce death/adverse cardiac events if given pre-PCI (JACC 2009;54:2157, JAMA 2018;319:1331). Early inflammatory effect may stabilize plaque (JAMA 2001;285:1711, JAMA 2004;291:1071).
8. **Morphine**: consider only if unacceptable level of pain refractory to TNG, careful if suspicious for inferior MI/RVMI
9. Discontinue NSAIDs: ↑ risk of mortality, re-infarction, CHF, and myocardial rupture after ACS

Secondary Prevention:

1. **Aspirin**: 81mg w/o enteric coating indefinitely (NEJM 2010;363:930)
2. **Dual antiplatelet therapy (DAPT)**: recommend 6-12mo DAPT after DES (Circ 2016;134:e123). New evidence trending towards shorter DAPT duration (JAMA 2019;321:2428, JAMA 2019;321:2414). Based on individual pt risks. Use DAPT score to help risk stratify.
3. **Beta blockers**: start in all pts (1b) w/o contraindication indefinitely
4. **ACEi or ARB**: start in all pts (2b) but stronger recommendation (1a) in anterior STEMI, EF<40%, stable CKD, HTN, or DM
5. **Statin**: high intensity statin (atorvastatin 40-80mg or rosuvastatin 20-40mg QD) indefinitely for pts ≤75y, moderate intensity in >75y.
   - If very high risk clinical ASCVD w/ LDL>70 mg/dL, add **ezetimibe** and consider PCSK9i (JACC 2019;73:3168)
6. **Triple therapy**: P2Y12 inhibitor + DOAC > triple therapy in pts with AF + PCI. ↓ bleeding and non-inferior for ischemic events (AUGUSTUS NEJM 2019;380;1509, RE-DUAL PCI NEJM 2017;377:1513, NEJM 2016; 375:2423). See *Hematology: Anticoagulation Management* for more details.
7. **Lifestyle**: smoking cessation, BP <130/80 (start treatment if >140/90), cardiac rehab (1c), depression screening (1b)

MGH $P2Y_{12}$ Switching Guidelines (does not apply to triple therapy patients)

Acute Setting – within 30 days of index event

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

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

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

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

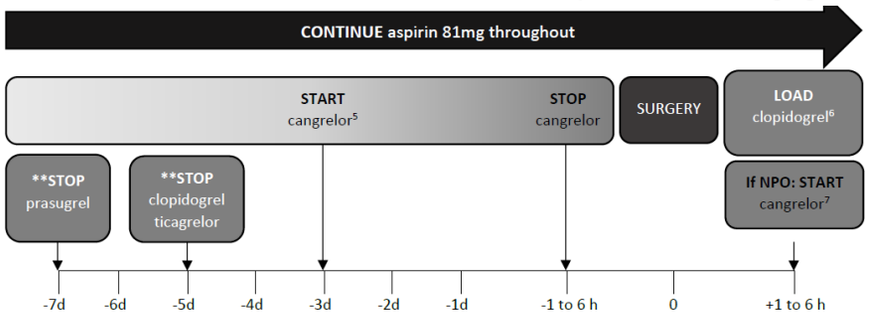
Chronic/Maintenance Setting – >30 days after index event

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

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

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

Peri-operative $P2Y_{12}$ Bridging



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

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

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

Mechanical Complications (JACC 2013;61:e78)

Complication	Prevalence / Risk Factors	Timing / Clinical Signs	Evaluation	Treatment
Early Complications (Hours – Days)				
Cardiogenic Shock (see *Inpatient HF*)	▪ STEMI ~6% ▪ NSTEMI ~3% ▪ Anterior MI, LBBB, prior MI, 3VD, age, HTN, DM, mechanical complications ▪ Accounts for 50% post-MI death	▪ STEMI: 50% develop shock w/in 6h of MI, 75% w/in 24 h ▪ NSTEMI: 72-96 h after MI ▪ New onset CP, cold/wet physiology, HoTN, tachycardia, dyspnea, JVD, rales (66%), new murmur	▪ TTE ▪ PA catheter	▪ Inotropes/pressors ▪ Emergent PCI, CABG (<75y + STEMI + shock w/in 36h of MI). (NEJM 1999;341:625) ▪ IABP and other MCS
Myocardial Free Wall Rupture (Pseudoaneurysm: LV defect contained by only pericardium/ scar, more prone to rupture than aneurysm)	▪ 0.5% in modern era ▪ Transmural MI, 1-vessel MI, 1st MI (poor collaterals), anterior and lateral MI, HTN, late thrombolysis (>14 h), fibrinolysis>>PCI, NSAIDs, female, >70 y ▪ Accounts for 10% post-MI death	▪ 40% w/in 24h, 85% w/in 1 week ▪ Tamponade in 85% ▪ Olivia's triad: pericarditis, repetitive emesis, restlessness/agitation (PPV 95% w/ 2/3). (JACC 1993;22:720) ▪ Electromechanical dissociation, aberrant T wave evolution, abrupt episodes of ↓HR/BP	▪ TTE ▪ STAT cardiac surgery consult	▪ Emergent surgery
Interventricular Septal Rupture →VSD	▪ 0.2-3% ▪ 1st MI, 1-vessel MI (esp. LAD), anterior infarct w/ inferior STE 2/2 wrap-around LAD, older age, female ▪ Accounts for 5% post-MI death	▪ Bimodal: 24 h and 3-5 days (can occur up to 2 weeks out) ▪ New, harsh holosystolic murmur (50% w/ thrill), S3, loud P2, hypotension, BiV failure (R>L)	▪ TTE w/ doppler ▪ RHC: O2 sat step-up between RA and PA >5 suggestive	▪ Emergency surgery ▪ IABP ▪ Vasodilators (use cautiously) to decrease L to R shunt (nitroprusside preferred)
Papillary Muscle Rupture →Acute MR	▪ 1% ▪ Posteromedial (supplied by PDA, a/w inf. or post. MI) >> anterolateral (dual blood supply by LAD and LCx) ▪ Accounts for 5% post-MI death	▪ No reperfusion: 2-7 d ▪ With reperfusion: median 13 h ▪ Abrupt dyspnea, pulmonary edema, hypotension ▪ Hyperdynamic LV, holosystolic murmur at apex (radiates to LSB w/ posterior pap muscle rupture) possible thrill; *NB*: murmur may be absent in severe HF	▪ TTE ▪ CXR: edema (can be asymmetric to RUL if MR jet directed at right pulm. veins) ▪ Large v wave	▪ Aggressive afterload reduction (nitroprusside) ▪ IABP ▪ Emergent surgery
Late Complications (Weeks – Months)				
LV Aneurysm (can be acute or chronic)	▪ No reperfusion: 10-30% ▪ Apical transmural > posterior-basal MIs, steroids, NSAIDs	▪ Days to weeks ▪ Acute: diffuse, displaced PMI, S3 and/or S4, MR murmur, CHF ▪ Chronic: HF, VT/VF, systemic embolization, may be asymptomatic	▪ ECG w/ persistent STE ▪ TTE	▪ Acute: management of CHF, ACEi, avoid NSAIDs/steroids, heparin (if EF<35%) ▪ Chronic: ACEi, digoxin, diuretics, warfarin (if EF<35%)
LV Thrombus	▪ Occurs in 15% of AMI pts post-PCI ▪ Usually in LV apex ▪ Large infarct size, severe apical akinesis or dyskinesis, LV aneurysm, anterior MI	▪ Can occur within 24h ▪ 90% of thrombi are formed at a maximum of 2 weeks ▪ Embolization risk persists for chronic LV thrombus for 6 mo, occurs in 3%, but most at <4 mo.	▪ TTE with contrast	▪ Warfarin (INR 2-3) ▪ When to stop anticoag unclear, check for resolution of thrombus on TTE at 3-6 mos.
Pericarditis	▪ 5% of pts in the ED w/ CP and no MI, male predominance ▪ 85-90% idiopathic (viral/post viral), infectious, post-MI, uremic, autoimmune, malignancy, XRT, meds	▪ 10% at 2-4d post-transmural MI ▪ May be focal or diffuse ▪ Dressler's syndrome: late autoimmune carditis, rare	▪ ECG ▪ TTE ▪ CMR and/or cardiac CT (If needed to confirm dx	▪ ASA + colchicine ▪ Avoid NSAIDs and steroids for fear of mechanical complications
Coronary Artery In-Stent Thrombosis	▪ Highest risk is absence of P2Y12 inhibitor ▪ 1% at 1 year. Yearly rate following one year is ~0.2/ yr	▪ Most cases occur within 30 days of PCI irrespective of stent type ▪ ACS symptomatology	▪ ECG ▪ Biomarkers (troponin/ CKMB)	▪ PCI ▪ Long term anti-platelet therapy (adherence to therapy)

Urgent Assessment of Post-MI Complication (page cardiology)

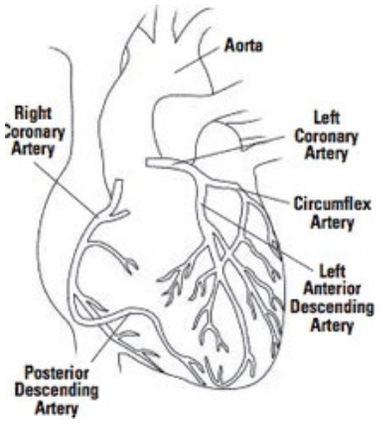
- Assess VS for hemodynamic instability and perform a focused physical exam (eval for new murmur, pericardial friction rub, elevated JVP)
- Stat labs (troponin, PT/INR, PTT, T&S, BMP, lactate) and ensure adequate vascular access (≥2 PIVs)
- Run telemetry, repeat EKG, urgent echocardiography, consider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

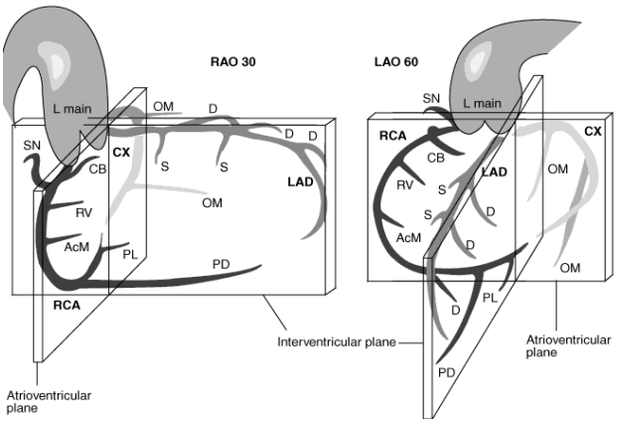
Electrical Complications

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

	Arrhythmia	Location/Mechanism	Incidence/Timing	Treatment/Outcome
Bradyarrhythmia	Sinus bradycardia	▪ Anterior or inferior MI ▪ Protective by ↓ O2 demand	▪ Up to 40% of acute MI ▪ Occurs early in STEMI	▪ Atropine, atrial pacing if sx/unstable, dopamine if also hypotensive
	First degree AV block	▪ Inferior: ↑ vagal tone *or* AV node ischemia (RCA) → narrow QRS ▪ Anterior: septal necrosis below AV node → RBBB, wide QRS	▪ More common in inferior MI	▪ If 2/2 inferior MI, transient (vagal) ▪ Usually continue CCB or BB unless PR interval is longer than 240ms.
	Second degree AV block: Mobitz Type I	▪ Usually inferoposterior MI (↑ vagal tone → narrow QRS)	▪ Usually within first 24h of MI	▪ Usually transient; observe ▪ Atropine if symptoms or HR < 45
	Second degree AV block: Mobitz Type II	▪ Usually anterior MI with infranodal conduction injury, wide QRS, HR often < 30, 33% progress to CHB	▪ Usually within first 24h of MI	▪ Consider temporary pacing ▪ In infranodal block, *atropine may paradoxically worsen AV block*
	Third degree AV block	▪ If inferior MI: intra-nodal lesion; narrower QRS escape ▪ If anterior MI: infra-nodal lesion; wide, unstable escape rhythm	▪ 3-7% acute MI ▪ Inferior: gradual, stable, more common ▪ Anterior: sudden, 12-24h after MI	▪ Recovery 3-7 days; temp pacing required ▪ Inferior: more benign, resolves on own ▪ Anterior: carries high mortality rate (80%) b/c indicates extensive necrosis
Intraventricular Conduction Blocks		▪ 50% already present on 1st ECG, may represent antecedent disease of conduction syndrome ▪ Suggests more extensive infarct	▪ 2-5% of MI	▪ Pts w/ BBB are more likely to have comorbid conditions, less likely to have received therapies, have larger area infarcts, and have high mortality
Supraventricular Arrhythmias	Sinus tachycardia	▪ Persistent sinus tach. may be compensatory for LV dysfunction, common in anterior MI	▪ 25% of acute MI	▪ Undesirable b/c decreases coronary perfusion time, increases O2 demand, and may worsen ischemia ▪ Treat underlying cause
	Atrial premature beats	▪ May reflect ↑ LA pressure		
	Atrial fibrillation	▪ Early: due to atrial ischemia ▪ Late: due to atrial stretch/HF	▪ 6-8%, may be >30% of acute MI	▪ Associated with mortality, particularly if late (>30d) AF (Circ 2011;123:2094)
Ventricular Tachyarrhythmias	Premature Ventricular Contractions	▪ Due to electrical instability and increased sympathetic tone	▪ Variable	▪ Correct electrolyte deficits. Do NOT treat with class I anti-arrhythmic → a/w ↑ mortality (NEJM 1991;324:781)
	Accelerated Idioventricular Rhythm (AIVR)	▪ 50-110bpm, higher V- vs. A-rate; in 40%, considered a reperfusion rhythm	▪ Up to 20% of STEMI ▪ Usually within 12-48 h, occurs after reperfusion	▪ Do not treat unless symptomatic or hemodynamically unstable, usually short duration and does not affect prognosis
	Ventricular Tachycardia	▪ Monomorphic VT<170bpm is unusual early after STEMI; suggests pre-existing arrhythmogenic scar (mono VT) vs recurrent ischemia (poly VT)	▪ NSVT 1-7%, sustained VT (2-3% of STEMI, <1% NSTEMI) ▪ Usually 48h post STEMI, late VT (>48h) has very poor prognosis	▪ Antiarrhythmic agents ▪ Cardioversion/defibrillation as ppx against VF and restore hemodynamic instability ▪ Correct underlying abnormalities (pH, K)
	Ventricular Fibrillation	▪ Risk factors: ↑ age, prior MI (scar), anterior MI, cardiogenic shock, ↓ LVEF, CKD ▪ VF >48h post-MI may indicate LV dysfunction	▪ 5% of STEMI ▪ 1% of NSTEMI	▪ ACLS/defibrillation ▪ Anti-arrhythmic infusion (24-48h amiodarone post-defibrillation) ▪ Maintain K>4, Mg>2

Circuit	Coronary Vessel Supply
Sinus Node	RCA in 60% of pts, LCx in 40% of pts
AV Node	Distal RCA in 90% of pts, distal LCx in 10% of pts
Bundle of His	AV nodal artery (RCA), LAD septal perforators
RBB	LAD septal perforators, collaterals from RCA/LCx
LBB LAFB LPFB	LAD LAD septal perforators, 50% w/ AV nodal collaterals Prox AV nodal arteries, distally dual supply from LAD/PDA septal perforators





Anatomy

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

Preparation for Catheterization

- NPOpMN; INR<2; monitor Cr closely, no ppx abx. Continue ASA, statin, BB, heparin gtt (hold when on call) or lovenox (hold 24h prior to cath; see *Logistics: Peri-Procedural AC*). Hold metformin (usually 1d pre-, 2d post-proc.). May need to hold/delay starting ACEi.
- Document bilateral radial, femoral, popliteal, DP pulses, and Allen's test prior to cath. Check for bruit. Note hx of HIT, PVD, Ao aneurysm/dissection.
- **Contrast allergy**: pre-treatment with steroids and benadryl if patient has documented allergy. See *Radiology* section for MGH 13h protocol. *Consult allergy service for expedited protocol if the cath is required emergently.*
- Respiratory distress: patient will need to lie flat; consider intubation if prohibitive hypoxemia/pulmonary edema
- Pre-hydration w/ crystalloids and NAC/bicarb have not been shown to prevent CIN in most patients with moderate CKD (Lancet 2017;389:1312; NEJM 2018;378:603); CIN risk calculator; diagnostic cath = 25cc contrast (CT-PE = 80-100cc)

Percutaneous Coronary Intervention Considerations

- Access: fewer bleeding/vascular complications if **radial** (vs. femoral), possible ↓death in ACS (JACC 2018;71:1167)
- BMS vs DES: ↓ **in-stent thrombosis with DES** → subsequent ↓ revascularization; however, ↑ **risk of late stent re-stenosis** → **requires longer duration of DAPT**
- Contraindications to stents: predicted DAPT non-adherence, anticipated major surgery within treatment time, elevated bleeding risk
- Antiplatelet Tx: 81 mg ASA indefinitely (Circ 2016;134:e123). P2Y12 inhibitor added after cath.
  - No high bleeding risk: for ACS, 12 mos of DAPT (DES or BMS); for stable ischemic heart disease, at least 6 mos of DAPT (DES) or 1 mo (BMS)
  - High bleeding risk: for ACS, 6 mos of DAPT (DES or BMS); for stable ischemic heart disease, at least 3 mos of DAPT (DES) or 1 mo (BMS)
  - Triple therapy: See *ACS* section

Post-Procedure Care

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

Post-Catherization Complications

- Access site complications: always inform the interventional fellow who performed the procedure, **diagnose by exam and U/S**
  - **Hematoma**: mass w/out bruit. Apply compression. If unable to control, may require Fem-Stop device to apply external pressure.
  - **Pseudoaneurysm**: presents as pulsatile mass with bruit at access site. Treat with compression; if <2 cm, may require thrombin injection or surgery if >2 cm. Urgent U/S and vascular surgery consult.
  - **AV fistula**: presents as continuous bruit with no mass. Evaluate w/ U/S. Surgical repair is usually necessary.
  - **Limb ischemia**: from thrombus, dissection, or malpositioned closure device. Evaluate pulses, limb warmth, and PVRs.
  - **Retroperitoneal bleed**: presents within **hours** post-cath, often with hemodynamic instability +/- flank pain +/- ecchymoses. STAT CT A/P if stable. Transfuse, IV fluids, discussion with attending re: stopping/reversing anticoagulation.
- 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**: peak ↑ Cr 2-5d post contrast load, risk correlated with contrast load and initial GFR
  - **Tamponade**: post-cath **hypotension** from coronary or cardiac perforation. Check pulsus paradoxus (Δ >10mmHg), STAT TTE, alert cath fellow. Give IVF.
  - **MI/CVA**: due to in-stent thrombosis (MI) or distal embolization post-cath (CVA). Discuss all CP/neuro changes with cath fellow
  - **Radiation injury**: more common in CTO cases. Occurs days to weeks after PCI. Ranges from erythema to skin ulceration.

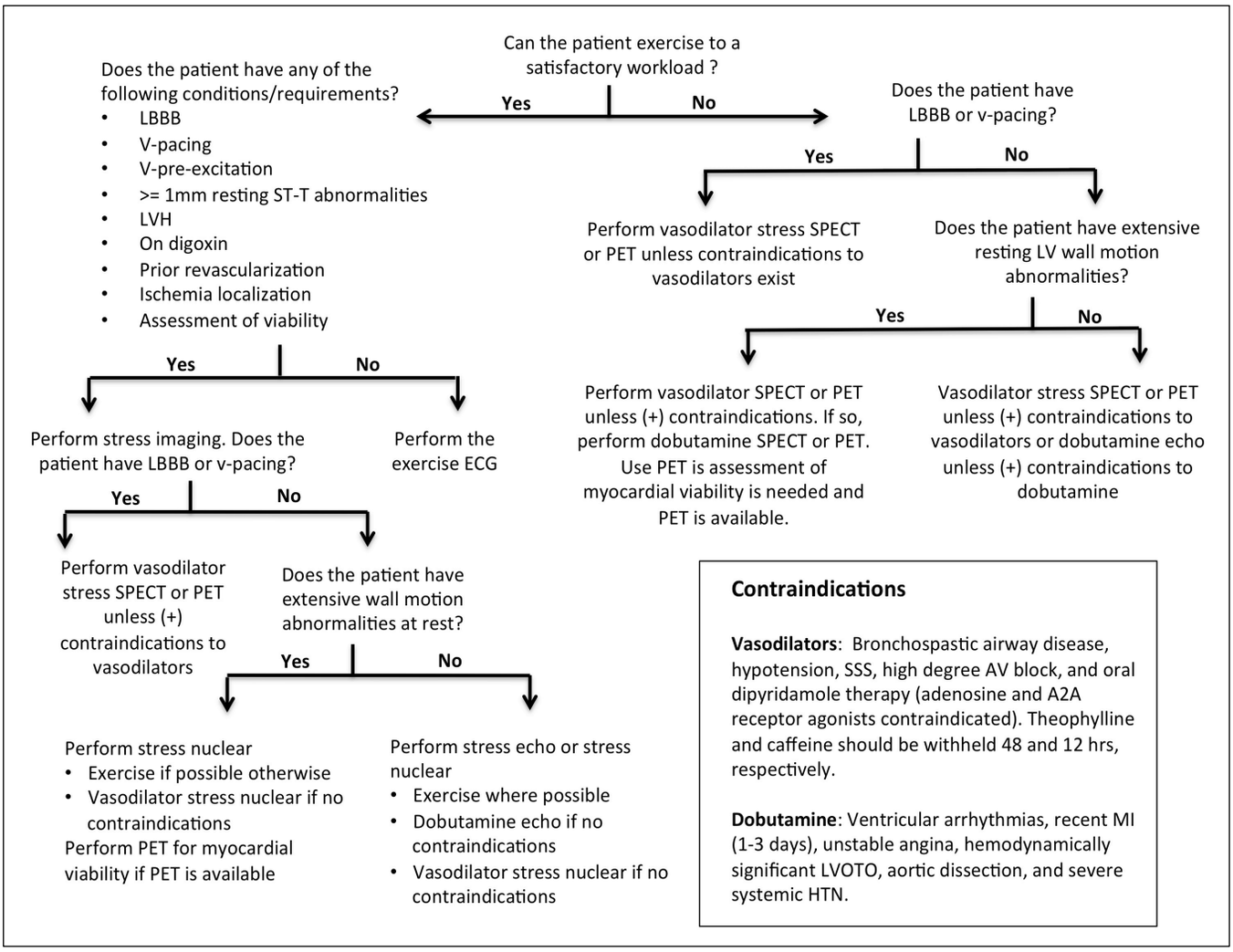
STRESS TESTING

- **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 ischemia in pts with known CAD
  - Post-revascularization: evaluate pts with angina or asymptomatic pt if incomplete revasc or >2yrs post-PCI/5yrs post-CABG
  - Pre-op risk assessment: not routinely indicated (see *Perioperative Medicine*)
  - Newly diagnosed HF or cardiomyopathy likely due to ischemia, functional capacity (for exercise prescription), viability testing, valvular disorders
- **Contraindications**: untreated ACS, MI within 2d, high risk or LM CAD, uncontrolled arrhythmia, acute CHF, severe AS or HOCM, recent DVT/PE, acute myo-/peri-/endocarditis, aortic dissection, uncontrolled HTN
- **Preparation**: NPO 3h prior, longer if imaging or adenosine. Must reverse DNR/DNI for test.
  - If the question is "*Does the patient have CAD?*" → **hold BB and nitrates**
  - If the question is "*How well are meds working in known CAD?*" → **continue BB and nitrates**
  - **Hold caffeine** >12h for adenosine. Hold BB >24h for dobutamine.

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

- **Caveats**:
  - Majority of vulnerable plaques are angiographically insignificant (<70% stenosis) → stress testing unable to identify the presence of these plaques (CTA more sensitive)
  - Angiographically significant (>70% stenosis) 3VD may produce false-negative vasodilator stress test → "**balanced ischemia**"
- **Positive test results**: optimize medical tx. Decision re: angiography/revascularization varies by pt (degree of sx, known stenosis, current meds). In recent ISCHEMIA trial, revascularization did not decrease ischemic CV events for pts with stable CAD (NEJM 2020;382:1395)

Schematic Approach to Noninvasive Cardiac Testing (adapted from UpToDate)



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

- ETT preferred over pharmacologic testing if pt is able to reach goal exertion
- Assesses exercise duration, METs, BP/HR response, HR recovery, double product (HR x SBP), Duke Treadmill Score
- Duke Treadmill Score = estimates risk of CAD in pts w/ chest pain undergoing exercise stress testing (Circ 1998;98:1622)
  - Exercise time (min. based on Bruce protocol) – (5x max ST deviation in mm) – (4x exercise angina [0 = none, 1 = non-limiting, 2 = exercise-limiting]). *Low risk*: score ≥ +5; *Moderate risk*: score from -10 to +4; *High risk*: score ≤ -11
- **Protocols**: Bruce (large changes in workload between stages), modified Bruce (for less fit pts → adds stages of lower workload)
- **Diagnostic** if >85% max-predict HR (220-age), peak double product (HRxBP) >20k, HR recovery (HR_{peak} – $HR_{1min\ post\text{-}exercise}$) >12
- Increased probability of **ischemia**: ↑ # of leads with STD, ↑ degree of max STD, ↓ METs when EKG changes occur, ventricular ectopy during recovery, increased time to recovery of EKG, failure of SBP to rise with exercise

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

1. **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 because no relative perfusion deficit exists when all 3 vessels affected equally ("balanced ischemia")
   - **Dobutamine**: workload induced by positive inotropy and chronotrophy via β-1 receptor agonism
     - Extremly high dose of dobutamine is given, dose titrated up to 40 mcg/kg/min
     - Side effects: tachyarrhythmias. *Caution* if MI<48h, hx of malignant arrhythmia, severe AS, HOCM, severe HTN, severe PAH, aortic dissection
2. **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 and high amount of radiation (SPECT > PET).
     - **PET** is more sensitive and specific than SPECT with faster image acquisition. Less widely available and most expensive.

Viability Testing

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

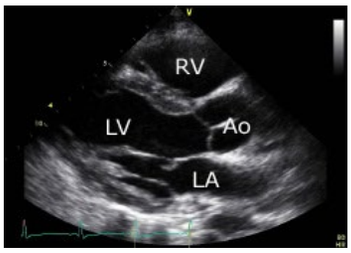
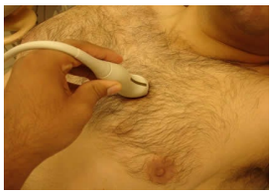
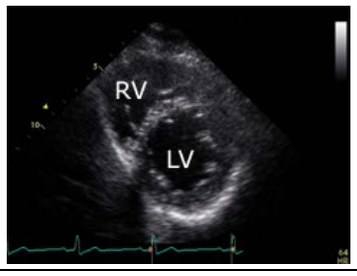
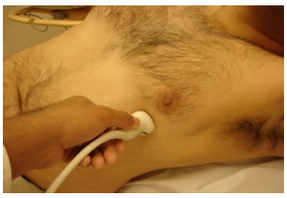
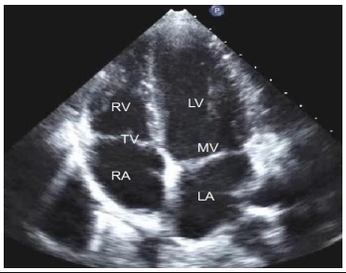
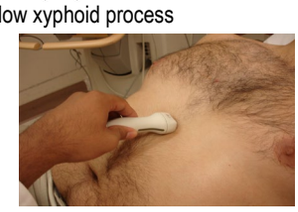
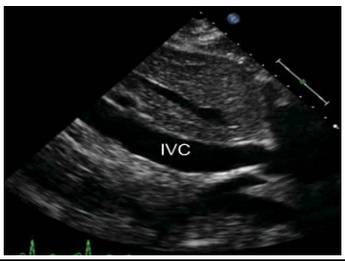
Rest Imaging

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

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

Cardiac MRI:

- Modality of choice for assessment of funtional and tissue properties of the heart than cannot be adequately assessed with 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

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

Reviewing the MGH Report: for questions or clarification of findings, call Echo Lab (**x6-8871**) or page on-call Echo Fellow

- Valvulopathy: look for stenosis/regurgitation (valve area, gradients, severity), leaflet numbers/motion, vegetations
- Structure/chamber dimensions:

AoSinus = aortic sinus	ASC AO = ascending aorta
LVIDd = LV internal diameter in diastole (range 37-52 mm)	LVIDs = LV internal diameter at end-systole (range 22-35 mm)
PWT = posterior wall thickness (↑ thickness seen in LVH, diastolic dysfxn)	IVS = intraventricular septum (if ↑ along with ↑ PWT, consider diastolic dysfunction; if isolated ↑ consider HOCM)

- 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=$4v^2$ + RAP. **RAP assumed to be 10 mmHg** (often not clinically accurate) and v = TR jet velocity.
  - Clinically, often used as surrogate marker for pHTN (present if >35; not gold standard for dx and requires euvolemia)

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

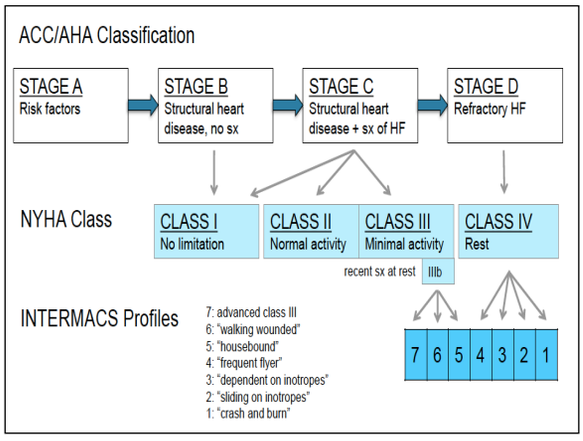
Indications for STAT Echocardiography:

- Evaluation of **hemodynamic instability** of suspected cardiac etiology (assess for biventricular dysfunction, acute valvular dysfunction, tamponade)
- Evaluation of early **MI complication** (myocardial free wall, septal, or papillary muscle rupture)
- Evaluation of acute chest pain with **suspected MI** in patients with non-diagnostic lab markers and ECG
- Identify the cause of **cardiac arrest** (i.e. PE with RV dysfunction, ACS with WMAs or EF decrement, tamponade)

Definitions: HFrEF: EF<40% **;** HFmrEF ("mid-range" EF 41-49%); HFpEF (EF>50%)

Etiologies

- **Dilated**: **ischemic** (most common cause, 50-75%), HTN/LVH, valvular (e.g. MR), myocarditis, stress-induced (Takotsubo), tachyarrhythmia, infiltrative (as below) CTD, ARVC, LVNC, HIV, cocaine/methamphetamines, EtOH, chemotherapy, nutritional deficiency, cirrhosis, sepsis, peripartum, idiopathic/genetic
- **Restrictive**: **infiltrative** (amyloid, hemochromotosis, sarcoid), Löffler's, radiation, metabolic storage disease, carcinoid
- **High-output HF**: anemia, thyroid dysfxn, liver failure, Paget's, systemic infection, AV shunts



Initial Workup: New Heart Failure Diagnosis

- Echo: TTE for all new presentations; obtain thereafter only if concern for clinical/functional change. TEE can provide better visualization of MV and AV
- Dx: **Ischemic**: EKG, TnT, stress test, coronary angiogram vs CCTA; **Non-ischemic**: CBC, BMP, LFTs, lipid panel, TSH, A1c, urine hCG, iron studies, HIV, SPEP w/ UFLC
    1. *Consider*: ANA, *T. cruzi* serologies, viral panel, antimyosin Ab, tox screen, thiamine, genetic testing, cardiac MRI, endomyocardial bx (if serologic testing neg, new onset <6 mo unexplained HF, major arrhythmias) to r/o myocarditis, ARVC, sarcoid, cardiac masses

Specific Causes of Cardiomyopathy

- **Hypertrophic Cardiomyopathy (HCM)** (Circ 2011;124:2761)
    - LV and/or RV hypertrophy of various morphologies ± LVOT dynamic obstruction (**HOCM**), diastolic dysfxn, ischemia, MR
    - Exam: SEM at LLSB/apex that augments with Valsalva or on standing (due to ↓ preload); S2 paradox split, S4
    - Dx: **EKG** (prominent voltages w/ depolarization abnormalities, large abnormal Q waves in inferior/lateral leads, LAD, giant negative T waves in V2-V4 (apical HCM variant→*"Yamaguchi's syndrome"*), **TTE** (unexplained LVH >15mm, SAM of MV, outflow tract gradient), **cMR** (late gadolinium enhancement [LGE] = fibrosis)
    - Tx: **avoid volume depletion** or high dose vasodilators (may worsen obstruction). **Phenylephrine is pressor of choice** if no response to IVF bolus for HoTN (↑ afterload, stents open LVOT). Activity restriction, meds (BB > verapamil), septal ablation or surgical myectomy for medically refractory sx, ICD (for high SCD risk)
    - Clinical **genetic testing** (mutation in ~70%) helpful for family screening; not useful for dx or risk stratification
    - Risk factors for **SCD/VT**: prior VT/SCD/unexplained syncope; FHx of SCD in 1° relative; massive LVH (>30mm); NSVT on Holter; abnormal BP response to exercise; burden of LGE on cMR
- **Stress-induced (Takotsubo)** (JACC 2018;72:1955)
    - Potential mechanisms: catecholamine surge from physical/emotional stress, coronary artery spasm, microvascular ACS
    - May present like ACS with CP (most common), SOB, shock, syncope. If in shock, urgent TTE to assess for LVOT obstruction.
    - Diagnostic criteria (**ALL** needed): (1) **transient dysfunction** (hypo-/dys-/akinesis) of LV mid-segments. Regional **WMA extend beyond a single coronary distribution**; (2) rule out ACS/obstructive coronary disease (via **cath**); (3) new **EKG** Δ (STE or TWI) OR ↑ **troponin**; (4) absence of pheo or myocarditis
    - Tx: Remove stressor. **ACEi** (may improve survival), BB, diuretic.
    - Prognosis: most recover LV function in 1-4 wks
- **Alcohol-induced**
    - Associated with >80g/day of EtOH over >5 years (toxic to myocytes via O2 free radicals + defects in protein synthesis)
    - Tx: abstinence + HF therapy
    - Prognosis: better/equivalent to idiopathic CM if able to abstain/consume <20g/day, worse w/ continued EtOH abuse
- **Restrictive Cardiomyopathy** (JACC 2010;55:1769) – *conditions below may also manifest as DCM*
    - Tx: Treat underlying disease and HF as below. For **amyloidosis**: tafamidis (↓ TTR deposition) (NEJM 2018;379:1007)

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

Inpatient Acute Decompensated Heart Failure (ADHF)

- Admission orders: tele, Na (2g) restricted diet, daily weights, strict I/Os, DVT ppx
- **Avoid**: **CCB** (esp. **non-dihydropyridines**), **NSAIDs**, **flecainide**
- Check **NT-proBNP** (and 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, HFpEF.
- Screen for and treat **iron deficiency** in all HF pts independent of Hgb (JACC HF 2019;7:36)
  1. Dx: ferritin <100 or ferritin <300 + TSat <20% (JACC 2017;70:776); though some evidence that TSat ≤ 19.8% or serum iron ≤ 13μmol/L most predictive & ferritin may be less useful (Circ Heart Fail 2018;11:e004519)
  2. 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

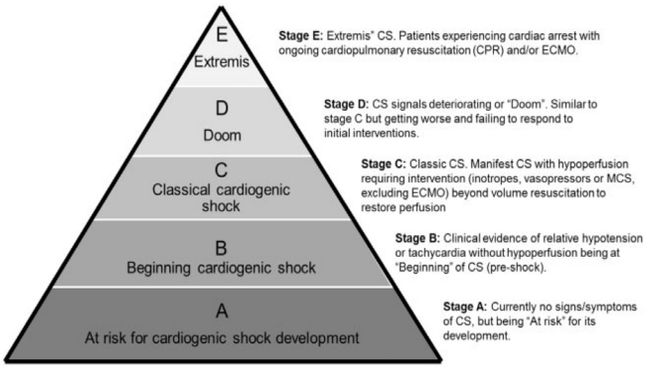
		Congestion at Rest	
		NO	**YES**
Low Perfusion at Rest	**NO**	**Warm and Dry** *Outpatient mgmt*	**Warm and Wet** *Diuresis ± Vasodilators*
	YES	**Cold and Dry** *Inotropes (ICU)*	**Cold and Wet** *Tailored Therapy (ICU)*

1. Identify **hemodynamic profile**, & triage accord. (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, rales, pleural effusions, ascites, LE edema, interstitial/alveolar edema on CXR)
   - Evaluate for signs of **pulmonary congestion on exam**. Pulm edema may be **absent on CXR** in chronic HF due to lymphatic compensation (Chest 2004;125:669)
   - ~80% of decomp HFrEF and nearly all decomp HFpEF pts will be warm and wet
2. **Identify precipitants**: dietary/med non-compliance (~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
3. **Early/Acute Management**:
   - **Diuresis**: ↓CVP, PCWP to optimize Starling curve mechanics & relieve sx (NEJM 2017;377:1964; JACC 2020;75:1178)
     - Initial tx: IV loop diuretics (furosemide, bumetanide, torsemide), start with 2x home dose (IV/PO). No difference between continuous gtt vs bolus dosing (DOSE NEJM 2011;364:797). See *Advanced Diuresis* for conversions.
     - Refractory diuresis: metolazone 2.5-5mg (or chlorothiazide 500mg IV) administered 30min before loop diuretic. May need RHC to clarify hemodynamics or inotropes to augment diuresis. May need 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 of pt still congested (Circ 2018;137:2016).
     - Endpoints: target resolution of symptoms (SOB) and signs of congestion (JVD). Daily weights and hemoconcentration are useful adjuncts.
   - If acute pulmonary edema, **NIPPV** may improve mortality and need for intubation (Annals 2010;152:590).
   - **Vasodilators**: arterial/venous dilation can relieve symptoms by ↓ afterload, ↓ PCWP and ↑ SV. Can acclerate early sx relief. Consider esp. in severe HTN, acute MR, acute AR.
     - Floor: isosorbide dinitrate, hydralazine, nitropaste, captopril; SDU/CCU: TNG, nitroprusside
   - **Guideline-Directed Medical Therapy (GDMT)**: if not in cardiogenic shock, continue ACEi/ARB and βB during ADHF (but do not newly initiate βB) (B-Convinced EHJ 2009;30:2186)
4. **Pre-Discharge Optimization**: document d/c weight and NT-proBNP, appt in HF Transitions Clinic if pt has MGH cardiologist
   - **HFrEF** (EF<40%) **GDMT**
     - **Beta blockers (1A)**: initiate, uptitrate evidence-based βB (carvedilol, metoprolol succ., bisoprolol) (COPERNICUS, MERIT-HF). Caution if recently weaned from inotropes.
     - **RAAS inhibitors (1A)**: if renal fxn stable, initiate/titrate ACEi/ARB (CONSENSUS, CHARM) or ARNI (sacubitril/valsartan) (PARADIGM-HF, PIONEER-HF). Switch to ARNI from ACEi/ARB if tolerating and NYHA II-III, needs 36hr washout period.
       - ♦ Guidance for GDMT in advanced CKD: JACC HF 2019;7:371
     - **Mineralocorticoid receptor antagonist (1A)**: initiate spironolactone or eplerenone if CrCl>30 (EMPHASIS-HF, RALES). Watch for rebound hyperK after de-escalation of diuretics (check K, Cr within 72h of discharge)
     - **Hydralazine/isosorbide dinitrate**: consider if contraindication to ACEi/ARB (unstable renal fxn) or in African Americans w/ persistent NYHA III-IV sx despite BB and ACE/ARB (A-HeFT)
     - **SGLT2i (dapaglifozin)**: if DM2 and NYHA II-IV already on standard GDMT (DAPA-HF)
   - **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 and consider adding GDMT agents for HFrEF (Curr Heart Fail Rep 2020;17:1)
   - **HFpEF** (EF >50%): prevent volume overload, treat with diuretics, treat comorbidities (DM, HTN, AF)
     - Consider **spironolactone** if normal renal fxn/K, improv. in CV death/admits in N/S Am. sites in TOPCAT (Circ 2015;131:34)
     - No proven benefit to BB (EHJ 2018;39:26), ACEi (PEP-CHF), ARNi (PARAGON-HF), ARB (CHARM-Preserved, I-PRESERVE)
   - ICD indicated if: ischemic CMP 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* and guidelines for specifics: JACC 2013;61:e6; EHJ 2016;37:2129)

Cardiogenic Shock – CCU:

- Definition: HoTN (**SBP<90** for 30 mins 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: EKG, troponin to r/o acute MI. TTE to exclude tamponade/mechanical lesions/contraindications to MCS
- Monitoring: A-line, consider **PA catheter** for inotropes/pressors and MvO2 monitoring

2019 SCAI Classification Pyramid (Cath Cardio Interv 2019;94:29)



Immediate Management:

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

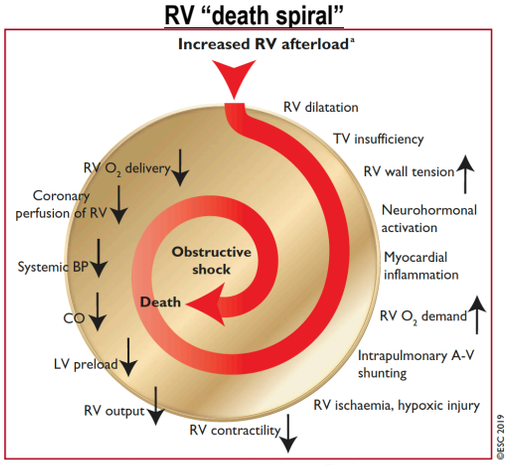
Tailored Therapy: uses invasive hemodynamic monitoring (i.e. PAC) to guide medical therapy

- **Goals**: tissue perfusion (↑ CO, MAP), decongestion (↓ CVP, PCWP), ventricular unloading (minimize myocardial O2 demand)
  1. **Preload**: LVEDV ∝ LVEDP ≈ PCWP; goal **PCWP 14-18, PAD 16-20, CVP 8-12**
     - Diuresis, UF with RRT, or TNG
  2. **Afterload**: wall stress ∝ MAP (Laplace's law); SVR = (MAP - CVP)/CO; goal **MAP >60, SVR <800-1200**
     - Vasodilators: captopril, hydralazine, nitroprusside, TNG, IABP
     - Vasopressors: ↑ afterload but sometimes necessary to stabilize MAP in mixed shock or to counteract vasodilatory effect of inodilators
  3. **Contractility**: ∝ CO for given preload/afterload; goal **CO>4, CI >2.0-2.2, MvO2 >65**
     - **Dobutamine** (inodilator): β1>β2 agonist (↑ production of cAMP)
       - Watch for tachycardia, increased ventricular response to AF, arrhythmias, ischemia, HoTN, tachyphylaxis in infusions >24-48 hrs
     - **Milrinone** (inodilator): PDE-3 inhibitor (↓ breakdown of cAMP)
       - Watch for tachycardia, arrhythmias, ischemia, HoTN. Compared to dobutamine, milrinone has longer half-life, greater pulmonary vasodilatation, slightly less chronotropy, fewer arrhythmic events.
       - Preferred in patients on βB and w/ RV failure. Is renally cleared. Often choice for home inotrope for palliative therapy
     - Epinephrine, norepinephrine, dopamine (inopressors): use if severe HoTN, unable to tolerate inodilators
       - Watch for tachycardia, arrhythmias, end-organ hypoperfusion
  4. **Advanced**: consideration of need for mechanical circulatory support or transplant
     - Goal of mechanical circulatory support: improve systemic perfusion while reducing myocardial oxygen demand (in contrast to inotropes which ↑ CO at the expense of increased oxygen demand)
     - Types of MCS at MGH: IABP, Impella, VAD, VA-ECMO (see *MCS & Transplant)* – if considering, obtain SHOCK c/s (p11511)
- **Limitations**:
  - **CO** measured via thermodilution or calculated using Fick equation: CO = VO_2/(13.4 x Hgb x [SpO2-MvO2]); CI = CO/BSA; VO_2 estimate = 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_2 (oxygen consumption) that in reality varies depending on physiologic state (e.g. infxn)

Right Ventricle Physiology
- RV has thinner myocardium compared to LV→↑ compliance compared to LV, so it does not adapt well to acute increases in pressure
- RV and LV are interdependent→failure of RV leads to failure of LV through several mechanisms: (1) decreased LV preload because RV output = LV preload and (2) septal bowing into LV, causing diastolic impairment ("Bernheim effect")

Acute Changes in RV Hemodynamics
- ↑ RV afterload (e.g. PE), ↑ RV preload (e.g. L→R shunt or TV disease), or ↓ RV contractility (e.g. MI) all lead to increased RV wall stress and resultant ischemia
- RV CO subsequently ↓ and RV dilates, precipitating RV "death spiral"
- ↓ RV CO leads to ↓ MAP (and ↑ RVP), resulting in ↓ coronary perfusion pressure (CPP_{RV} = MAP – RVP)
- ↓ CPP_{RV} leads to more RV ischemia, propagating "death spiral" further

RV "death spiral"



Eur Heart J 2020;41:543

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

Management (AHA Guidelines: Circ 2018;137:e578)
- Treat reversible causes (RVMI, PE, hypoxemia, infections)
- Preload: clinical assessment of optimal preload is challenging. Both hypo- and hypervolemia may ↓ CO.
  - Acute: judicious IVF use in pts with acute RVMI or PE in absence of marked CVP elevation (goal CVP 10-14 in RVMI)
  - Subacute/chronic: diuresis to ↓ RV filling pressures, ↓ functional TR and and improve LV CO by relieving ventricular interdependence
- Afterload:
  - Systemic: if pt hypotensive, start pressors – *do not tolerate hypoTN* as propagates RV death spiral (↓CPP); no clinical data regarding pressor of choice, but often choose **vasopressin** or **norepinephrine** (vaso affects PVR less than norepi)
  - Pulmonary: remove factors that ↑ pulm vasc tone (e.g. hypoxemia, acidemia). Consider pulm vasodilators (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 causes ↑ reduction in RV afterload but higher risk of hypotension)
- Devices: if refractory RVF, consider RV MCS (Impella RP, VA-ECMO)

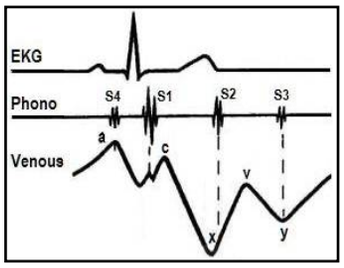
Intubation and Mechanical Ventilation (Curr Heart Fail Rep 2012;9:228)
- Intubation/NIPPV in RV failure **precipitate risk for hemodynamic collapse and cardiac arrest**
  - Drugs commonly used in intubation (BZDs, propofol, muscle relaxants) → tendency towards **vasodilation** and **negative inotropy** → decreased venous return → decreased LV preload → systemic hypoTN → propagates death spiral
  - Consider RSI (etomidate >> propofol for induction) and push dose epinephrine (10-20mcg)/vasopressin (1-2U) if emergent intubation anticipating hypotension
- Positive pressure ventilation → increased pulmonary pressures and RV afterload → increased RV dilation → "death spiral"
- Vent management: prevent hypoxemia and hypercarbia (↑ PVR), consider moderate TV (~8cc/kg), low PEEP (<12 cm H_2O), and moderate plateau pressure goal (<30 mmHg)

Right Ventricular Myocardial Infarction (ACC/AHA Guidelines: Circ 2012;127:e362)
- EKG: check R-sided EKG leads in pts with inferior STEMI (10-15% of pts with inf. STEMI have RV involvement)
  - 1mm STE in V4R → 88% Sn, 78% Sp in inferior STEMI; STE III>II suggests 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) and BB
  - If CVP >15mmHg and BP not improving w/ IVF, additional fluids may worsen RV failure/overload (Eur Heart J Acute Cardiovasc Care 2013;2:226)

Overview:

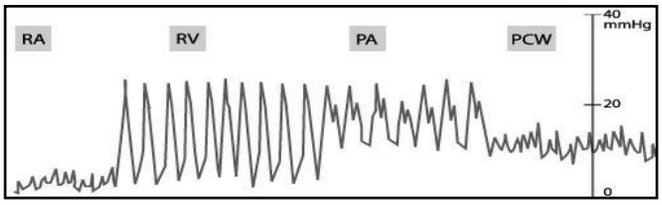
- Indications: (1) diagnose etiology of shock (e.g. cardiogenic vs. distributive); (2) diagnose cardiogenic vs. non-cardiogenic pulm edema; (3) tailored therapy; (4) diagnose PH; (5) diagnose L→ R shunting; (6) diagnose valve disease (7) diagnose pericardial disease
- Efficacy: controversial - ESCAPE trial (JAMA 2005;294:1625) showed no mortality benefit to PAC use in pts w/ ADHF, but pts on inotropes were excluded. 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**: **a**trial contraction; coincides with QRS complex (on CVP tracing)
- **c wave**: bowing of TV/MV into atrium during ventricular **c**ontraction; more visible in 1st degree AV block. Often absent on PCWP.
- **x descent**: atrial rela**x**ation (early x descent), downward mvmt. of TV/MV (late x descent)
- **v wave**: passive atrial filling (**v**enous return) when TV/MV closed; coincides with T wave
  - Prominent v waves seen in MR and TR
- **y descent**: rapid atrial empt**y**ing following opening of the TV/MV (ventricular diastole)
  - Prominent y descent + x descent seen in pericardial constriction
  - Blunted y descent seen in tamponade

Obtaining PA Line Numbers on AM Rounds:



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

Calculating Hemodynamic Parameters:

- Normal: "rule of 5s" → RA 5, RV 25/5, PA 25/10, PCWP 10, LV 125/10
- Cardiac output:
  - **Fick** = VO_2 / (13.4 * Hgb * [SpO_2 – MvO_2]) [*nml*: 4-7 L/min]
    - $VO_2 \approx$ 250 ml/min *OR* 3*wt(kg) *OR* 125*BSA
  - **Thermodilution**: temperature change (measured by thermistor in PA) is proportional to LV CO (inaccurate w/ TR, intracardiac shunt)
- Cardiac index = CO/BSA [*normal*: 2.6-4.2 L/min/m^2]
- SVR = (MAP-CVP) / CO x 80 [*normal*: 700-1200 dynes*s*cm^5]
- PVR = (mPAP-PCWP) / CO [*normal*: <2 Woods units]

Hemodynamic Profiles of Shock

Subtype	CVP [JVP]	PCWP [CXR]	CO/CI [MvO2, UOP]	SVR [cap. refill]
Hypovolemic	↓	↓ [nl]	↑ [var, ↓]	↑ [delayed]
Cardiogenic	↑	↑ [nl, wet]	↓ [↓, ↓]	↑ [delayed]
Septic	Var	Var [nl, wet]	↑ [↑, ↓]	↓ [normal]
RHF or PE	↑	N [nl, large PA]	Var [var, nl to ↓]	Var [nl to ↓]
Tamponade	↑	↑ [nl, large heart]	↓ [↓, ↓]	↑ [delayed]

Hemodynamic Considerations:

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

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 insertion if: severe PH (PAP>70mmHg), large RV, LBBB, PPM/ICD, temp wire, severe TR, prosthetic TV/PV
- Contraindications: RA/RV mass/thrombosis, mechanical TV/PV, endocarditis (TV/PV)
- Markings on PA catheter: each thin line=10cm; each thick line=50cm.
- Position: on CXR: 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
- Duration: no data defining maximum length of time; at MGH, standard is 7d; others suggest 4-5d

Mechanical Circulatory Support (MCS) – if inotrope-refractory cardiogenic shock, call SHOCK team (p11511)

Selected MCS Modalities					
Device	**Indications**	**Support Provided**	**Considerations**	**Management**	**Complications**
IABP (intra-aortic balloon bump)	- Refractory heart failure (**bridge** to durable MCS) - **Cardiogenic shock**/massive PE - Refractory malignant **arrhythmias** - Support during **high-risk procedures:** o Complex PCI o Ablation of ventricular arrhythmias o Percutaneous valve repair - Acute allograft failure	Minimal hemodynamic support (**0.5 L/min**), greater in ADHF than acute MI shock (Am J Card 2019;124:1947) - ↓ LV afterload - ↑ **Coronary perfusion** - Requires native contractility to work	- Bedside insertion - Does not require AC (when at 1:1) - No ↓ mortality in cardiogenic shock (IABP-SHOCK II, NEJM 2012;367:1287) - Prevents mobility (if femoral placement) - Least costly	- ✓**CXR** daily (tip 1-4cm below Ao notch) - ✓ **Waveform** daily - Wean by ↓ ratio (then return to 1:1, stop AC, pull)	- **Limb ischemia** - Vascular injury - Thromboemoblism - Bleeding - Infection - Balloon leak/rupture (STAT vascular surg c/s)
Impella		Partial LV support - Cath lab placement: Impella 2.5 (**2.5 L/min**), Impella CP (**3.5 L/min**) - OR placement: Impella 5.0 (**5 L/min**) or 5.5 (**6.5 L/min**) Partial RV support - Impella **RP (4 L/min**)	- Ventricular unloading - **Requires AC** (purge +/- systemic) - Allows pt **mobilization** (if axillary placement) - Longer-term support (days to weeks) - ↑ complications compared to IABP	- P1 (lowest) to P9 (highest support) - ✓ Urine color (**hemolysis**), LDH - ✓ **Suction events** (↓ preload, RV failure, position) - ✓ Ventricular arrhythmias (device migration)	- Infection - Bleeding - Limb ischemia - Thromboembolism - Thrombocytopenia - Vascular injury - **Position alarm** (reposition under fluoro/echo)
VA-ECMO		**Full bi-ventricular HD support** (**4-10 L/min**) + oxygenation & CO2 clearance	- Bedside and urgent insertion possible - Short-term support (days/weeks) - Often requires additional device for LV venting, i.e. Impella	See *ECMO* chapter	
Durable VAD	- **Bridge to transplant** - **Destination therapy** (DT) - "Bridge to decision" (on transplant or DT) - Bridge to **recovery** (LV unloading can be therapeutic)	Full LV support (**10 L/min)** - HeartMate II - HeartMate 3 - HeartWare HVAD	- **Mobility** - **Long-term support** (years)	- **BP via manual cuff w/ doppler** (goal MAP 70-80) - If hypotensive, place A-line - If unconscious, w/o hum, and MAP<50: chest compressions - TTE if any concern	- **Acquired vWF defic**. - **Hemolysis** (possible pump thrombosis) - Ventricular arrhythmias - Thromboembolism - RV failure - AR - **Driveline infections**

Heart Transplant

2018 UNOS Adult Heart Allocation Criteria:
Status 1: VA-ECMO, MCS with life-threatening vent. arrhythmia; ***Status 2:*** non-dischargeable LVAD, MCS + device malfunction, IABP; ***Status 3:*** ≥2 inotropes or single high-dose + continuous hemodynamic monitoring, dischargeable LVAD for discretionary 30 days, VA-ECMO after 7d, IABP after 14d; ***Status 4:*** re-transplant, inotropes without hemodynamic monitoring, dischargeable LVAD without discretionary 30 days; ***Status 5:*** awaiting dual organ Tx; ***Status 6:*** all others; ***Status 7:*** inactive listing

Transplant evaluation at MGH: *(orders are typically placed by transplant coordinators)*

- Labs: blood typing (2 samples on separate days), second sample for PRA (check with tissue typing x63722), BMP, LFTs, amylase, CBC+diff, INR/PTT, TFTs, lipids, PTH, 25-OH-D, 1,25-Vit-D, HIV, CMV, Toxo Igs, EBV, VZV serology, MMR, RPR, hepatitis serologies, IGRA, UA, 24h urine CrCl (and 24h urine protein if diabetic)
- Vaccines: HBV, PPSV23, Tdap
- Consults: Psychiatry (Dr. John Purcell), SW (Kathryn Tsagronis), Tx coordinators (Sally Keck, Coral Haggan, Kerry Gaj, Karen Turvey – they can all consent patient for Tx), Dental (Panorex, inpatient consult), Nutrition, Endocrine, Palliative Care
- Diagnostics: RHC (eval for presence & reversibility of pHTN with vasodilator challenge; if unsuccessful vasodilator challenge, note that PVR often declines after 24-48h of treatment [e.g. diuretics, inotropes, vasoactive agents]), +/- LHC, level 1 CPET (x4-7825), abdominal U/S, carotid U/S, TTE, ECG, CXR, DXA, ABIs +/- angiography, cancer screening up-to-date

Post-transplant immunosuppression: **steroids** (typically tapered off over 6 months, 1st line for acute rejection), calcineurin inhibitors (cyclosporine/**tacrolimus**), anti-proliferatives (azathioprine/**mycophenolate**), mTOR inhibitors (sirolimus/everolimus – most effective for coronary allograft vasculopathy; avoid in immediate post-tx phase as inhibit wound healing)
Monitoring: protocolized schedule of RV biopsies to r/o cellular/humoral rejection, RHC/LHC and TTE to assess graft function and for coronary artery vasculopathy

Permanent Pacemakers (PPM), Implantable Cardioverter-Defibrillators (ICD), & Cardiac Resynchronization Therapy (CRT):

- Types: single chamber (RA or RV lead), dual chamber (RA + RV leads), biventricular (+/- RA + RV + coronary sinus leads)
- PPM: sense/pace the RA and 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 ↓ desynchrony → LV reverse remodeling and ↑ LVEF
  - **CRT-P** = BiV +/- RA pacing; **CRT-D** = CRT-P w/ ICD functions

Hardware Overview: system consists of pulse generator + leads. Usually implanted SQ in upper chest (L>R) >> abdominal.

- Types: **traditional** (SQ pulse generator + IV leads in ventricle), **leadless** (pulse generator directly implanted into RV; no pocket complications; when battery dies, device retrieval is rare), **SQ ICD** (no IV hardware; low risk for infection but NO pacing capabilities)
- Placement: RA lead → RA appendage; RV lead → RV apex; LV lead → coronary sinus → branches of great cardiac vein
- Interrogation: page EP Technician (**PPM, p16939**) during normal business hours; EP fellow on call if after-hours/weekend.
- MRI compatibility: not all devices are MRI compatible, however even non-MRI compatible devices may be safe to scan after re-programming (NEJM 2017;376:755). Determined on case-by-case basis by radiology. Need to know device model.

NASPE/BPEG Codes for Pacing Operating Modes

Position I	Position II	Position III	Position IV
Chamber(s) Paced	Chamber(s) Sensed	Response to Sensing	Rate Modulation
O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T =Triggered	R = Rate Modulation
V = Ventricle	V = Ventricle	I = Inhibited	
D = Dual (A+V)	D = Dual (A+V)	D = Dual (A+V)	

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

PPM Indications (Class I): (JACC 2013;61:e6)

Sinus Node Dysfunction:

- **Symptomatic sinus bradycardia** (± sinus pauses) or chronotropic incompetence
- Symptomatic medication-induced bradycardia *if* medication (e.g. βB) is required for underlying medical condition

AV Block (AVB)/Conduction Disease:

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

Neurocardiogenic:

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

ICD Indications (Class I):

- Primary prevention indications only apply to pts on **optimized medical therapy** (OMT) and have a reasonable **expectation of 1-year survival**. (JACC 2013;61:e6)

Primary Prevention	Secondary Prevention
Ischemic CM: NYHA Class I: EF ≤ 30% at least 40d s/p MI NYHA Class II/III: EF ≤ 35% at least 40d s/p MI Other: EF ≤ 40% at least 40d s/p MI + NSVT + inducible VT/VF on EP study	- **Prior episode of cardiac arrest** (VF/pulseless VT) or sustained unstable VT if no reversible cause found - Structural heart disease with spontaneous sustained VT (stable or unstable)
***Non-ischemic CM**: EF ≤ 35% + NYHA Class II/III	
Other: Unexplained syncope w/ hemodynamically significant inducible VT/VF on EP study	

*DANISH demonstrated that in pts with non-ischemic CM, ICD implantation reduces risk of sudden cardiac death, but does **not** provide a mortality benefit

CRT Indications: ↓ mortality compared to OMT (ACA/AHA/HRS 2012 Guidelines, JACC 2013;61:e6)

	NYHA I	NYHA II	NYHA III / NYHA IV
Class I	None	LVEF ≤ 35%, QRS ≥ 150ms, LBBB, & sinus rhythm	LVEF ≤ 35%, QRS ≥ 150ms, LBBB, & sinus rhythm
Class IIa	None	LVEF ≤ 35%, QRS 120-149ms, LBBB, and sinus rhythm	LVEF ≤ 35%, QRS 120-149ms, LBBB, & sinus rhythm LVEF ≤ 35%, QRS ≥ 150ms, & non-LBBB
Class IIb	LVEF ≤ 30%, QRS ≥150ms, LBBB, & iCM	LVEF ≤ 35%, QRS ≥ 150ms, non-LBBB pattern, & sinus rhythm	LVEF ≤ 35%, QRS 120-149ms, non-LBBB pattern, & sinus rhythm

Aortic Stenosis

- **Etiology**: senile calcific (most common cause >70yo; a/w metabolic syndrome, CAD, CKD), bicuspid valve (most common cause <70yo), rheumatic heart disease (leaflets fuse, often with concurrent MV disease)
- **Clinical Manifestations**: most important determinant of prognosis → 50% mortality at 5y for angina, 3y for syncope, 2y for HF
  - Angina: ↑ afterload/outflow obstruction→ ↑LV pressures→ LVH→ ↑O2 demand and compression of coronary arteries
  - Syncope: exercise-induced vasodilation → inability to augment CO due to obstruction → hypotension
  - Heart failure (dyspnea): LVH → diastolic dysfunction (*systolic dysfunction is a late finding*)
  - Acquired vWF def: 20% of severe AS, can expose bleeding from GI AVMs (Heyde's syndrome) (NEJM 2012;367:1954)
- **Diagnosis**:
  - Physical exam: harsh, mid-systolic crescendo-decrescendo murmur at RUSB radiating to carotids. **If more severe**: murmur late-peaking, delayed carotid upstroke (pulsus parvus et tardus), soft S2 (Am Heart J 1999;137:298)
  - TTE: measure mean (not peak) gradient, valve area, and jet velocity; also important to assess EF (gradient can be underestimated with **reduced EF → low flow, low gradient AS**)
    - **Severe AS**: peak aortic valve velocity >4m/s, **mean** aortic valve pressure gradient **>40 mmHg**, aortic valve **area <1cm²** (AHA/ACC Guidelines: JACC 2014;63:2438)
  - EKG: LVH, LAE, LAFB, LBBB
  - Exercise stress testing: recommended in asymptomatic severe AS to assess for symptoms; do **not** perform in pts w/ sx
- **Natural History**: variable, but on average, AVA ↓ ~ 0.1 cm²/yr and mean gradient ↑8 mmHg/yr (JACC 1989;13:545)
- **Aortic Valve Replacement (AVR)** (AUC Severe Aortic Stenosis 2017): determining indication for valve replacement is based on evaluating: (1) presence of **symptoms,** (2) **severity** by TTE criteria, (3) LV function (**EF**)
  - Symptomatic, severe AS: AVR indicated
  - Asymptomatic, severe: AVR appropriate if LVEF<50% or undergoing other cardiac surgery
  - If suspect low-flow (LVEF<50%) and low-gradient (<40mmHg) w/ AVA <1cm²: **dobutamine stress TTE** to distinguish between low-flow, low-gradient AS versus "pseudosevere AS" (Circ 2011;124:e739)
    - Low-flow, low-gradient severe AS: if dobutamine stress echo results in V_{max} >4 m/s or pressure gradient >40mmHg while AVA remains <1cm², then AVR is indicated
    - Pseudosevere AS: if dobutamine stress echo results in AVA >1cm², then AVR not indicated
  - **SAVR vs TAVR**: depends on surgical risk (STS-PROM score) and/or concomitant heart/vascular disease that is amenable to surgery. TAVR is recommended for those at extreme surgical risk (compared to medical therapy, PARTNER). TAVR is noninferior to SAVR in those at high (NEJM 2011;364:2187), intermediate (PARTNER 2), and low surgical risk (PARTNER 3). Valve-in-valve TAVR may additionally be beneficial in pts with surgical bioprosthetic AV failure (JACC 2017;69:2283).
  - **TAVR Evaluation**: consult structural cardiology, cardiac surgery. Obtain TTE, TAVR-protocol CT, dental clearance (Panorex).
  - **TAVR Complications**: valve embolization, valvular regurgitation, paravalvular leak/regurgitation, cardiogenic shock, coronary occlusion, annular rupture, ventricular perforation, CHB requiring PPM, stroke (ischemic/hemorrhagic), bleeding/hemorrhage, access site complication
- **Medical Management**: *AS is a surgical disease and medical management is only utilized for sx management*
  - Treat HTN: reduce the "double load" on the ventricle. However, no optimal regimen exists because many anti-hypertensives can lead to hemodynamic issues (diuretics reduce preload which lead to decreased CO, vasodilators can reduce coronary artery perfusion, BB can reduce needed contractility). Bottom line: **start low and go slow.**
  - Control volume status: these patients operate within a narrow preload range, prone to both underfilling ("preload-dependent") and overfilling (volume overload)
- **Anticoagulation after Valve Replacement**:
  - DOACs are not approved for valve replacement and may cause harm (RE-ALIGN)
  - Bridging UFH or LMWH if AC interrupted only in mechanical MV or mechanical AV with RFs (Class I)
  - Risk factors: AF, LV dysfxn, previous VTE, hypercoagulable state, older generation mech AVR (Star-Edwards valve or disc valve other than Medtronic Hall) (Circ 2014:129:2440)
  - Bleeding risk: mechanical > bioprosthetic (likely AC related). Reoperation risk: bioprosthetic > mechanical

Prosthesis	Location	Timing and Risk Factors	INR	Class
Mechanical	Mitral	Indefinitely	**2.5-3.5 (+ ASA 81)**	I
	Aortic	Indefinitely, (+) risk factors	**2.5-3.5 (+ ASA 81)**	I
		Indefinitely, (-) risk factors	**2.0-3.0 (+ ASA 81)**	I
Bioprosthetic	Mitral	First 3 months after placement, regardless of RFs	**2.0-3.0 (+ ASA 81)**	IIa
		>3 months after placement	**ASA 81**	IIa
	Aortic	First 3 months after placement, regardless of RFs	**2.0-3.0 (+ ASA 81)**	IIb
		>3 months after placement	**ASA 81**	IIa
TAVR	Aortic	No high-level trial data. DAPT does not provide mortality benefit with available data though active research ongoing. Expert consensus recommends lifelong ASA + 3-6mo. clopidogrel for patients in sinus rhythm. AC considered for AF or other indication for long term AC. Avoid DAPT in these patients (ACC 2017 Guidelines).		

Other Valvular Disease

	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation	Tricuspid Regurgitation
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 (HTN, CTD, dissection, syphilis)	- 80% due to RHD (only 50-70% report h/o rheumatic fever), endocarditis, annular calcification (rarely significant), congenital, autoimmune valvulitis (SLE), carcinoid, endomyocardial fibroelastosis, XRT (10-20 yrs after Hodgkin's treatment)	- Dilated annulus ("functional MR"), MVP, ischemic papillary muscle dysfunction, ruptured chordae, endocarditis, RHD, CTD	- Dilated annulus, pulmonary hypertension ("functional TR"), direct valve injury, endocarditis, RHD, carcinoid, ischemic papillary muscle dysfunction, CTD, drug-induced
Pathophys.	**Acute**: diastolic regurgitant flow → *sudden* ↑LVEDP (w/o remodeling time) → ↓CO → pulm edema **Chronic**: diastolic regurgitant flow → ↑LVEDV → initial maintenance of SV/CO → progressive dilatation, eventual failure	- Elevated LAP → pulmonary HTN, **AF (47%)** - Demand for ↑ CO precipitates symptoms - Valve narrows 0.1cm^2/yr	- LA/LV volume overload → LV dysfunction, progressive enlargement of LV → dilated mitral annulus → worsening MR	- Similar to MR
Clinical	- Cardiogenic shock (acute), angina, left-sided HF - 31 eponyms for signs in chronic AI, most due to large initial SV (Int J Car 2006;107:421)	- Dyspnea (most common symptom), pulmonary edema, hemoptysis, thromboembolism even w/o AF (Annals 1998;128:885), RV failure	**Acute**: flash pulmonary edema, HTN, shock **Chronic**: DOE, orthopnea, PND, edema, AF	- Right-sided HF: hepatosplenomegaly, ascites, edema
Exam	- ↑ pulse pressure (bounding pulses, bouncing head/uvula, nail bed capillary pulse). - High-pitched, blowing diastolic decrescendo murmur along LSB - Longer = more severe/chronic. - May also hear low-pitched diastolic murmur at apex due to regurgitant jet displacing anterior leaflet	- Loud S1, high-pitched opening snap (earlier more severe, indicating higher LAP) - Low-pitched diastolic rumble heard best at apex at end-expiration	- Holosystolic murmur at apex radiating to axilla, S3, displaced PMI - Early diastolic rumble and S3 may be the only signs in acute MR	- Holosystolic murmur at left mid or lower sternal border that increases with inspiration, S3.
Treatment	**Acute**: usually needs urgent surgery. Nitroprusside to ↓ afterload; ino- and chronotropes to ↓ diastole time. - Do not use vasoconstrictors or IABP (worsens regurg) or beta-blockers (blocks compensation, ↑ diastolic regurgitant time) **Chronic**: ACE-I, nifedipine, or hydralazine/nitrates (to reduce LV afterload) - Proceed to AVR if: symptomatic, LV systolic dysfunction (EF <50%), LV end-systolic dimension >50mm, need for CABG or other valve surgery	**Medical**: warfarin if LA thrombus, AF, prior embolism (Class I) or LA > 55mm (Class IIb) - β-blocker if tachycardic or dyspneic - diuresis if pulm vasc congestion **Intervention**: need to have severe MS + symptoms to be considered for surgery (unless noted below) - Tx is *percutaneous balloon mitral commissurotomy* (PBMC) if pt has favorable valve morphology (Wilkins Score based on TTE). - Proceed to MVR if not PBMC candidate, PBMC fails, or undergoing another cardiac surgery (even if asymptomatic)	**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**: MVR if: **primary symptomatic** severe MR and EF >30% *OR* asymptomatic but EF 30-60% or significant LV dilatation (LVEDD >40mm) (NEJM 2005;352:928, Circ 2013;127:1870). - If excessive surgical risk, percutaneous MV clip/repair or CRT are also options (EVEREST II). - If severe functional MR, repair equivalent to chord-sparing replacement (NEJM 2014;370:23). - Benefit of percutaneous clip if HF and **secondary symptomatic** failing GDMT including CRT (COAPT)	**Medical**: diuresis, management of underlying cause **Intervention:** TVR if: undergoing left-sided valve surgery *AND* severe TR, tricuspid annular dilatation, or evidence of right heart failure (Circ 2017;135:e1159). - Isolated TV surgery a/w high mortality, although may be recommended for severe TR refractory to medical therapy - Numerous transcatheter therapies are potential options but still lack long-term clinical outcome/performance data (JACC 2018;71:2935)

CARDIAC TAMPONADE

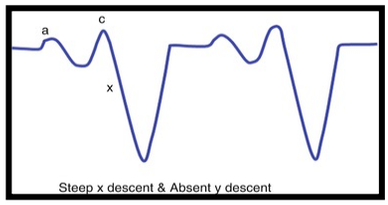
- Definition: hemodynamic insufficiency caused by impaired cardiac filling due to ↑ pericardial pressure due to effusion, leading to ↑ intracardiac chamber pressures & eventually equalization of diastolic pressure in all 4 heart chambers.
- Etiologies of pericardial effusion: idiopathic (20%), iatrogenic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

Clinical Manifestation and Diagnosis:

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

- Beck's Triad: ↓BP, ↑JVP, muffled heart sounds
- Pulsus paradoxus (PP): exaggeration of normal decrease in SBP during inspiration. (If >10mmHg, ⊕LR=3.3. If ≤10 mmHg, ⊕LR=0.03).
  - How to measure PP
    1. Slowly deflate cuff→note pressure when systolic Korotkoff sounds only heard w/ during expiration (will sound irregular) (**a**) → continue slowly deflating cuff until heard throughout (**b**). **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

CVP tracing in tamponade



- ECG: sinus tach, low QRS voltage (50%; limb ≤ 5mm, precordial ≤ 10mm), electrical alternans (20%; precordial leads).
- TTE: inspiratory leftward septal shift, diastolic collapse of cardiac chambers (R > L-sided), respirophasic changes in transvalvular velocities, IVC plethora. SIZE of effusion does NOT predict tamponade – RATE of accumulation is more important.

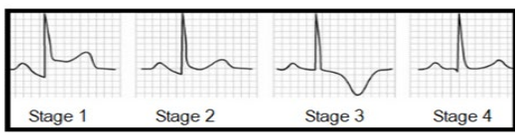
Treatment:

- **Fluid resuscitation**: administer volume urgently to increase intracardiac pressures (monitor closely as overfilling can worsen tamponade), starting w/ 250-500cc bolus
- 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 pericardiectomy (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 cc/day**, otherwise may need **pericardial window** (pleural>abdominal)

PERICARDITIS

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

ECG Evolution in Pericarditis



Clinical Manifestations and Diagnosis:

- Symptoms: sudden onset, pleuritic, retrosternal **CP relieved w/ sitting up & leaning forward** (may radiate to trapezius muscles), +/- viral prodrome if infectious etiology. Uremic or CTD pericarditis: CP may be absent.
- Exam: pericardial **friction rub** (~30% cases), best heard at LLSB w/ diaphragm of stethoscope at end-expiration w/ pt leaning forward
- ECG: 4 stages: (1) **diffuse ↑ST & ↓PR** (↑PR & ↓ST in aVR/V1); (2) ST & PR normalize; (3) diffuse TWI; (4) TW normalize. May see continual low-voltage or electrical alternans if effusion present. 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 (>2cm) (3) tamponade

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

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

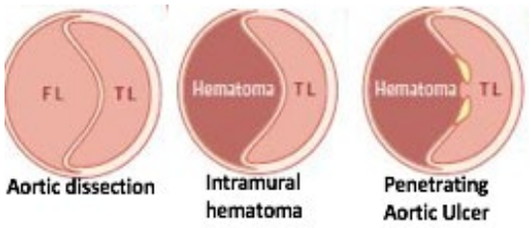
Aortic Aneurysms (JACC 2016;68:1054)

	AAA	TAA
Epidemiology	• 4-6:1 M:F ratio • 4-8% if age >65 • Most infrarenal	• 1.7:1 M:F ratio • Mostly 50s-70s • 50% ascending Ao, 40% descending Ao, 10% arch
Etiology	• Usually due to **atherosclerotic disease** • Risk factors: **smoking, male sex, age, pre-existing atherosclerosis**, obesity, HLD, HTN, FHx	• **Atherosclerotic**: majority of cases. Mostly in descending Ao. Risk factors: **smoking, HLD, HTN** • **Structural/genetic**: mostly in root and ascending aorta. Causes: CTD disease (Marfan, Ehlers-Danlos, Loeys-Dietz), Turner, bicuspid AoV, trauma • **Infectious**: 3° syphilis, mycotic aneurysm (most common org: *Staph* spp., *Salmonella* spp.) • **Inflammatory**: GCA (~10% have TAA), Takayasu, RA, psoriasis, Behcet's, Wegener's, IgG4

Screening/ Surveillance	• **ACC/AHA**: one-time abdominal U/S in all men >60 w/ FHx of AAA (IIC) and all men >65 that have ever smoked (IA)
	• **USPSTF**: one-time abdominal U/S for men age 65-75 who have ever smoked (Grade B) and selective screening for male never smokers 65-75 (Grade C). Screening women not recommended.
	• **Surveillance**:
	  ○ 3-3.4 cm: U/S q3y
	  ○ 3.5-4.4 cm: U/S or CT q12mo
	  ○ 4.5-5.4 cm: U/S or CT q6mo
		• **General population**: not recommended
		• **Indications**: at time of dx of Marfan (IC), Turner (IC), Loeys-Dietz, Takayasu or GCA. 1° relatives of pt w/ TAA, dissection, bicuspid valve (IB/IC)
		• **Surveillance**: if aneurysm only, then same as AAA. If also with dissection, image at 1, 3, 6, & 12 months then annually. Image entire aorta (CT/MRI) if multiple aneurysms (~25% TAA will have AAA; ~25% AAA will have TAA).

Imaging Modalities	• **Abdominal U/S**: screening and surveillance of infrarenal AAAs. High Sn/Sp (>90%), operator-dependent • **CT w/ contrast**: high Sn/Sp, better than U/S for suprarenal AAAs • **MRI/MRA**: good Sn/Sp, preferred for aortic root imaging and for imaging tortuous aortas • **CXR**: "enlarged aorta" nonspecific (tortuous aorta vs. aneurysm) • **TTE**: useful for root and proximal thoracic aorta; **TEE**: will visualize entire thoracic aorta but rarely used.	
Treatment	**Medical** • **Smoking cessation** (slows AAA growth by up to 25%) • **Reduce BP** in accordance with ACC/AHA standards • Meds: statins (reduce all-cause mortality in pts s/p surgery); BBs (may slow expansion; IA for perioperative use); ACEi (controversial; may prevent rupture but may speed growth); low dose ASA (may slow growth) **Surgical** • Men: **>5.5cm** *OR* **growing >0.5cm/yr** *OR* **sx** Women: **>4.5-5cm** (controversial) • Open repair (~4-6% 30 day mortality) vs. EVAR (only ~50% suitable, c/b endoleaks)	**Medical** • **Reduce BP** (<140/90 or <130/80 if DM or CKD; little actual evidence, IB) • Meds: BBs (decrease TAA growth in Marfan pts), ARBs (slow aortic root aneurysm in expansion in Marfan pts, likely via TGF-β inhibition), statins (goal LDL<70) • Smoking cessation • Avoid straining • Stress test used to guide BP management (follow SBP response to stress) **Surgical** • Root/ascending TAAs: usually concomitant aortic valve replacement • Arch/descending TAAs: mostly open graft (EVAR). Ischemic brain/spine injury most worrisome complication.
Complications	• **Rupture**: devastating mortality. AAA annual rupture rates are 4%, 7%, 20% at 5, 6, and 7cm, respectively. Risk factors: size, rate of expansion, female gender. Sx: triad of **abd/back pain** + **pulsatile abd mass** + **HoTN** → immediate OR (don't image) • **Dissection**: **pain** (chest/abdomen/back), **occlusion of aortic vessels**, **thromboembolism** • **Post-repair**: EVAR: endoleak, graft failure, thrombosis. Open: MI, embolization, AKI, ischemic colitis	

Acute Aortic Syndromes (AAS) (Nat Rev Cardiol 2015;12:103)



Definitions: three distinct processes within the aortic wall, all which have inherent risk of aortic rupture

- Aortic dissection (AD): intimal tear resulting in development of false lumen
- Intramural hematoma (IMH): rupture of vasa vasorum causing hemorrhage within aortic wall resulting in hematoma w/o tear
- Penetrating aortic ulcer (PAU): ulceration of atherosclerotic plaque that penetrates into intima of aortic wall

Classification:

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

Epidemiology:

- Prevalence: among AAS, aortic dissection most common (62-88%), followed by IMH (10-30%) and PAU (2-8%)
- Risk factors: male, HTN, age 60-70 (If <40yo, think Marfan syndrome or other CTD), atherosclerosis, prior cardiac surgery, aortic aneurysm, FHx of AAS, aortitis, trauma, pregnancy
- Aortic dissection prognosis:
  - Type A: *Medical*: 50% 2-week mortality, 90% 1-year mortality. *Surgical*: 10-35% mortality.
  - Type B: *Medical*: 9% in-hospital mortality, 16% 1-year mortality, 20% 5-year mortality.
- IMH will progress to complete dissection in 28-47% of pts. PAU will progress to aortic rupture in 42% of pts.

Diagnosis:

- Clinical features: AD, IMH, and PAU cannot be distinguished by presentation alone
  - Signs: AI murmur, pulse deficit, upper extremity BP differential (>20mmHg), CHF
  - Sx: chest or back pain most commonly reported (radiates to neck/jaw if ascending; back/abdomen if descending; may be migratory pain)
- Complications: syncope, shock, tamponade, branch artery occlusion (MI, CVA, paraplegia, cold extremity, renal failure)
- Labs: **D-dimer** <500ng/mL (96% NPV for absence of aortic dissection), **troponin** (high Sn and Sp for diagnosis of ACS, but AAS may still be present if ⊕ [extension into coronaries])
- Imaging:

CXR	- 50% of patients with AAS have normal CXR; only 1/3 will have widened mediastinum
CT	- Sn 95% / Sp 87-100%; **first-line imaging modality** in patients with high clinical probability of AAS. - Combined I+/I- (assess for IMH, mediastinum hemorrhage, or hemopericardium)
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% for AAS. Often used intra-op to confirm dx prior to surgery. - Invasive nature limits use; cannot detect pathology below the diaphragm
MRI	- Sn: 95-100% / Sp: 94-98% for AAS - Rarely used in the initial evaluation of AAS due to long acquisition time in the MRI suite

Management:

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

Overview:

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

Etiology and Diagnosis: 2017 AHA/ACC/HRS Syncope Guidelines

Etiology	Historical Features	Diagnosis	Treatment
Reflex (60%) • Vasovagal • Situational • Carotid sinus syncope	Vasovagal: prodrome of dizziness, nausea, warmth, diaphoresis, pallor; a/w intense emotion, pain, or stress. Situational: cough, sneeze, laugh, micturition, defecation CSS: neck turning/surgery/irradiation	• Vasovagal: can dx w/ tilt table test (*Class IIa*) (Sn 32-85%, Sp 90%) (JACC 1996;28:263) • Carotid sinus syncope: diagnose via carotid sinus massage (if no underlying bruits or CVA history)	• Avoid provocative stimuli • Isometric counterpressure maneuvers of the limbs (e.g. leg crossing, hand grip, Valsalva, squatting) • Meds used in select cases only (i.e. midodrine, fludrocortisone, βB). (NEJM 2005;352:1004)
Orthostasis (15%) • Autonomic failure (1° or 2°) • Drug-induced • Volume depletion	Prodrome of dizziness, nausea, warmth, diaphoresis, pallor. Risk factors for autonomic failure: - 1°: PD, Lewy body, Shy-Drager - 2°: DM, amyloid, spinal cord injury, chronic EtOH, Lyme, syphilis, B12 deficiency, meds (vasodilators, diuretics, BB, TCAs, PD meds, opiates, α-blockers)	• Orthostatic vital signs (systolic ↓ 20mmHg or diastolic ↓ 10mmHg within 3 min of standing) - ↑ HR is **NOT** part of definition • Consider: Hct, A1C, SPEP if c/f amyloid, RPR, B12	• Primary: **fludrocortisone** (0.1-0.2mg QD), **midodrine** (5-20mg TID), pyridostigmine, droxidopa (for PD-associated orthostasis) • Secondary: treat underlying etiology, replete volume, d/c culprit meds
Cardiac (15%) • Arrhythmia • Structural (AS, LVOT obs.) • Obstruction (e.g.,PE, tamponade) • Dissection	**No prodrome**, syncope while in sitting or supine position, palpitations, FHx or personal history of heart disease	• Causes of cardiac syncope in young people (+ ECG signs): 1. WPW (delta wave) 2. HOCM (LVH, apical TWI) 3. Brugada (pseudo-RBBB with coved/saddleback pattern in V1-V2) 4. Long QTc syndrome (QTc >500ms) 5. ARVC (Epsilon wave) • **Consider cardiac monitoring** on basis of frequency and nature of syncope events (inpatient telemetry, Holter, Zio patch, implantable cardiac monitor). • ONLY consider TTE if hx suggestive of cardiac cause (<1% yield if no underlying heart disease and normal ECG) • Consider PE if no other apparent cause→ identified in 17.3% of pts hospitalized with 1st syncope episode (and 25.4% of pts with no other apparent cause for syncope) (NEJM 2016;375:1524)	• Based on etiology, follow guideline-directed management and therapy
Neurologic (<10%) • Seizure • Stroke/TIA • Subclavian steal	Seizure: tongue biting, urinary/fecal incontinence, aura, postictal confusion Focal deficits: stroke, TIA Steal: syncope after arm exercise	• Seizure: EEG • Stroke: CT, MRI/MRA • Steal: UENI w/ Dopplers (specify for subclavian steal) • Carotid dopplers are of low clinical utility (changes management in <2% of patients) (JAHA 2014;3:e001063)	• Based on etiology, consider neurology consult and follow guideline-directed management and therapy

Cardiology — Hypertensive Urgency & Emergency

Definitions, Triage, and Management: See *Outpatient CV Health* for workup. (Chest 2007;131;194, NEJM 2019;381:1843, HTN 2018;71:1269)

- **Hypertensive urgency**: BP ≥180/120 **without** evidence of end-organ damage (may have mild headache)
  - **Assess adherence** to prior Rx before aggressively uptitrating regimen to avoid overcorrection of BPs and hypotension.
- **Hypertensive emergency**: BP ≥180/120 **with** evidence of end-organ damage (rate of BP rise may be more impt. than actual BP)
  - End-organ damage: *Neuro:* HTN encephalopathy (severe HA, seizure, AMS), PRES, TIA, CVA (SAH, ICH); *Retinopathy:* papilledema, hemorrhage; *Resp/CV*: pulm edema, MI, +TnT, angina, Ao dissection; *Heme*: MAHA; *Renal*: AKI, hematuria

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

Disease Process-Specific Recommendations for Hypertensive Emergency

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

Antihypertensive Dosing – ICU

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

Antihypertensive Dosing – Floor

Agent		Dosing	Onset	Duration	Specific Indications
Labetalol	**IV**	10-80mg q10min until effect seen, then use PO	5-10 min	3-6 hrs	Ao dissection, CVA; *avoid in ADHF*
	PO	Start 100mg q8-q12h (max: 2400mg/day)	20 min	8-12 hrs	
Hydralazine	**IV**	5-20mg q15-30min until see effect, then use PO	10-20 min	1-4 hrs	Eclampsia
	PO	Start 10 mg Q6H, inc by 10-25mg/dose q2-5d	20-30 min	~8 hrs	
Captopril (PO)		12.5-25mg q8h (NOT TID)	30-90 min	6-8 hrs	
Lisinopril (PO)		Initial 2.5-5 mg QD. Inc 10 mg q2 weeks to max of 40 mg QD. (Can use **ARB** if ACEi intolerance).	1 hr	24 hrs	
Amlodipine (PO)		Initial 5 mg QD. Inc 2.5 mg q7 days to max 10 mg QD. **Requires few days to take effect**.	24-48 hrs	24 hrs	
Nifedipine (PO)		10-30mg TID. **Use with caution** (may cause pronounced vasodilation, orthostasis)	20 min	6-8 hrs	
Hydrochlorothiazide (PO)		Initial 12.5 mg QD (max: 50 QD, doses >25 mg associated with ↑ electrolyte derangements)	2 hrs	6-12 hrs	
Isosorbide dinitrate (PO)		Initial 5-20mg 2-3 times/day (dose TID not q8h for nitrate holiday). **Mononitrate** = long-acting	1 hr	~8 hrs	Anti-anginal, CHF
Nitropaste (topical)		0.5-1.5 inches. Apply to chest. Need 10-12hr nitrate holiday to avoid tachyphylaxis.	15-30 mins	~12 hrs	If lacking IV/PO access

PERIPHERAL ARTERY DISEASE

Overview:

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

Clinical Presentation and Diagnosis:

- Sx: **classic claudication** - reproducible exertional pain distal to occlusion; **atypical leg pain** (most common); asymptomatic (Circ 2006;113:e463). **Critical Limb Ischemia**: **rest pain** (improved w/ hanging feet off bed or walking), ulcers at pressure points, dry gangrene, >2wks duration
- Exam: arterial bruit, **↓ peripheral pulses** (palpation, doppler), ↓ cap refill, pallor on elevation, ulcers, atrophic changes, ↓ hair growth
- ABI: doppler U/S. Ratio of DP/PT (higher of the two) SBP to brachial SBP. Abnormal: **≤0.9**. ABI ≥1.30 suggests ↓compressibility usually due to ↑ calcifications (e.g. elderly, DM, ESRD).
  - If ABI abnormal: obtain segmental ABI w/ pulse volume recordings (**PVR**) to localize disease.
- Exercise testing: if high suspicion for PAD and normal resting ABIs
- CTA (w/ distal run off), MRA, or angiography: if considering revascularization

Treatment:

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

Acute Limb Ischemia

- Sudden decrease in limb perfusion threatening viability (BMJ 2000;320:764). **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
- Etiologies: embolic (e.g. AF, endocarditis) > acute thrombosis (e.g. atherosclerosis, APS, HITT), trauma
  Precipitating factors: dehydration, HoTN, abnormal posture (i.e. kneeling), malignancy, hyperviscosity, hypercoagulability
- Presentation: (**6Ps**) **P**ain, **P**oikilothermia, **P**allor, **P**ulselessness, **P**aresthesia (unable to sense light touch), **P**aralysis
- Diagnosis: pulse (w/ doppler) + neuro checks; angiography (CTA w/ run-off or arteriography)
- Treatment: urgent vasc surgery consult; anti-coagulation ± IA lytic; endovascular repair.
  - After treatment, monitor for reperfusion acidosis, hyper-K, myoglobinemia (ATN) and compartment syndrome (BMJ 2000;320:764)

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

Overview: toxicities include HF, ischemia, HTN, myocarditis, pericardial disease, thromboembolism, QTc prolongation, arrhythmia
Chemo-induced CM = EF drop ≥10% to <55% w/o sx or decline ≥5% to <55% w sx (Eur Cardiol. 2018;13:64)
Risk factors: heart disease, DM, HLD, young or old, female, high-dose chemo
Dx: TTE (compare to baseline), EKG, TnT (↑correlates to adverse cardiac events post-chemo), MRI/PET/bx if suspect ICI myocarditis (Lancet Onc 2018;19:e447)
Prevention:

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

Monitoring:

- **TTE** surveillance schedule depends on therapy and baseline cardiac risk; ranges from Q3-Q6 months with long-term risk >10yrs
- Monitor weekly BP in first cycle, then Q2-3wks on therapy, initiate therapy when DBP >20mmHg

Treatment: *cessation of chemotherapy is a last resort*

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

Common Cardiotoxicities (Circ Res 2016;118:1008)

Anthracyclines (doxorubicin): HF, LV dysfunction (5-23% pts), based on cumulative dosage

HER2 agents (trastuzumab): 2.1% risk in reducing LV function, resolves once stopped, TTE q3mo

TKI (esp. sunitinib): HF, cardiac dysfunction

Angiogenesis inhibitors (bevacizumab, lenalidomide): HTN, 3-fold ↑ in arterial TE events

Platinum-based (cisplatin): HTN, HL, CAD, thromboembolic, in advanced testicular disease

Microtubule inhibitors (paclitaxel): arrhythmias

Anti-metabolites (5-FU, cytarabine): MI, angina, CP, EKG changes, 1-8% pts, early onset

Immune checkpoint inhibitor (ICI): fulminant lymphocytic myocarditis, HF, cardiac arrest; onset variable, risk factor = combo therapy

Radiation: CAD (up to 85%), pericardial dz (6-30%), CM (up to 10%), valvular abnormalities, PVD, arrhythmias, autonomic dysfunction, can occur 10-15 yrs later, many RF incl dosage, metabolic RF

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

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

Risk Factors:

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

ASPIRIN FOR CVD PREVENTION

- **2019 ACC/AHA primary prevention guidelines** recommend considering low-dose ASA for 1˚ prevention in select pts aged 40 to 70 yrs at higher ASCVD risk but not at increased bleeding risk. **Avoid aspirin for 1˚ prevention** in pts **age >70** (Circ 2019;140:e596)
- ASCEND (pts >40 with diabetes), ARRIVE (moderate CVD risk pts), and ASPREE (elderly pts >70) showed variable CV benefit for low-dose aspirin, at expense of increased bleeding events

OUTPATIENT BLOOD PRESSURE SCREENING AND MANAGEMENT

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

- **Method**: 2 checks > 1wk apart, sitting 5min with arm at heart level, cuff bladder 80% length & 40% width of arm circumference
- **24h ambulatory SBPs** show greater association w/ all-cause mortality than clinic BPs. Masked HTN (normal BP in clinic, ↑ outside) more strongly associated than sustained HTN (↑ in both) or white coat HTN (↑ in clinic, normal outside) (NEJM 2018; 378:1509)
- **Definition**: *Normal*: <120/(and)<80; *Elevated*: 120-129/(and)<80; *Stage 1 HTN*; 130-139/(or)80-89; *Stage 2 HTN*: >140/(or)>90

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

2˚ HTN: indications for workup include:

- Severe HTN (control w/ 4+ agents) or resistant HTN (not controlled on 3+ agents, one of which is a diuretic)
- Acute rise in blood pressure in a previously well-controlled patient, esp. diastolic BP
- Age **< 30 years** without risk factors (e.g. obesity, FHx)

Secondary Causes of HTN		
Cause	**Clinical Clues**	**Work-up**
Medications/Drugs (use or withdrawal)	NSAIDS, OTC decongestants, OCPs, sudden d/c of anti-HTN meds (i.e. clonidine)	Thorough history
OSA	Obesity, snoring, smoking	Sleep study
Renal disease	Elevated Cr, protein/blood on UA	See *AKI* and *CKD* sections
Primary aldosteronism	**Hypokalemia**, hypernatremia, adrenal incidentaloma, FHx	Plasma aldo:renin activity; ratio >30. MUST measure in the morning (~8AM), after being upright/ambulatory for >3 hrs, with both drawn at the same time
Renal artery stenosis	>50% rise in Cr after ACEi initiation Lateralizing abdominal bruit Atrophic or asymmetric kidneys	If intervention likely to be pursued, begin with Duplex Doppler US (Sn 85%, Sp 92%) → if stenosis (ARAS>50%) or ambiguous results, then angiography.
Rare: pheochromocytoma (screen w/ 24h urine fractionated metanephrines/catecholamines [Sn 98%, Sp 98%], plasma fractionated metanephrines if high suspicion), Cushing's disease, hyper/hypothyroidism, hyperparathyroidism, aortic coarctation, ADPKD		

Lifestyle Counseling (JACC 2014;63:2960)		
Exercise	40 min per day, 3-4x/week, moderate to vigorous intensity	↓ 5mmHg for aerobic exercise, unclear for resistance
Diet	Dash diet (salt intake <2g per day); ↓ sweets & red meat	↓ 8-14 mmHg (DASH); dec by 2-8 mmHg (low Na)
Caffeine	Limit to <2 cup per day	↓ 5/2.5 mmHg
Alcohol	Limit consumption (<2-3 standard drinks per day)	↓ 2-4 mmHg

Medical Management – 2017 ACC/AHA Guidelines			
When to Treat	**Stage II HTN** or **Stage I *if*:** clinical CVD, DM2, CKD, or ASCVD ≥10%		
Target BP	<130/80		
Choice of Agent	First-line: thiazides (recent data suggests that chlorthalidone may not be > HCTZ, ↑ side effects JAMA Int Med 2020;180:542), ACEi/ARB, CCB Other: βB, hydralazine, isosorbide, clonidine, α-blockers (e.g. doxazosin), minoxidil (rare)		
Compelling Indications	African-Amer: CCB, thiazide	HF: βB, ACEi/ARB, diuretic, spiro	DM2: ACEi/ARB (if proteinuria)
	CAD: βB	Pregnancy: labetalol, CCB	CKD: ACEi/ARB
Monitoring	BP check 2-4 weeks after change in medication (home readings vs. office), Labs: yearly BMP/Mg if on ACEi/ARB or diuretic		
Important Trials	SPRINT: high risk for CVD: SBP goal <120 vs 135-139 ↓ CVD events and all-cause mortality but ↑ non-orthostatic hypotension, syncope, electrolyte abnormalities, and AKI. ACCORD BP: showed no benefit for CV mortality in pts w/ DM for SBP goal of <120 vs <140.		

OUTPATIENT CHOLESTEROL SCREENING AND MANAGEMENT

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

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

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

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

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

Common Medications					
Medication	**Mechanism**	**Indication**	**% ↓ in LDL-C**	**Effect on CV outcomes**	**Adverse effects**
Statins*	HMG-CoA reductase inhibitor	1st-line therapy for 1° & 2°prevention	20-60% LDL-C reduction	For 1° & 2°prevention, ↓**CV events** (ARR 1.1%, NNT 91, HOPE-3)	Myopathy, ↑ LFTs, memory loss and 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, IMPROVE-IT)	Mild ↑ LFTs (usually w/ statin)
PCSK9 inhibitors (alirocumab, evolocumab)	Promotes degradation of LDL-R on hepatocyte surface	High risk pts w/ CVD and LDL-C >70 on statin+ezetimibe; approved for use in FH	38-72% reduction; ~60% in pts on statin therapy	Evolocumab + statin ↓**CV events** (ARR 1.5%, NNT 67 at 48 wks, FOURIER); Alirocumab + statin ↓**CV events** (ARR 1.6%, ODYSSEY)	Uncommon; mainly injection site reactions. Cost: 150k/QALY
O3FAs (e.g. Vascepa [EPA])	Incorporates into phospholipids	Severe hyperTG, CVD prevention	↓TG ≥30% with no change in LDL	EPA + statin ↓**CV events** (ARR 4.8%, NNT 21, REDUCE-IT)	Med interaction (e.g. warfarin), GI sx
Note: if patient has concomitant **severe hypertriglyceridemia (TG > 886 mg/dL)**, then also start **fenofibrate** (many formulations)					

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

***Statin Properties:**
Biggest change in LDL: rosuvastatin > atorvastatin > simvastatin
Safest in CKD: atorvastatin, fluvastatin (no renal dose adj. required)
Safest in cirrhosis: pravastatin
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

Definition: *Overweight*: BMI 25.0-29.9 kg/m^2; *Obesity*: BMI ≥ 30 kg/m^2; *Severe Obesity*: BMI ≥ 40 kg/m^2
Management:
Set goals: target initial weight loss of 5-7% body weight
Diet: diet compliance (↓ # calories) more important than macronutrient composition. No data to guide specific diet choice (JAMA 2014;312:923)

- Mediterranean: high in monounsaturated fats, fruits, vegetables, legumes, grains; moderate dairy & EtOH; low meat (↓ overall mortality, CV mortality; may ↓ DM incidence independent of weight 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:

- >30 min, 5-7 days/wk; combine aerobic + resistance training for optimal health gains (Arch Intern Med 2009;169:122)
- Not sufficient for wt loss; improves glycemic control, BP, and functioning; ↓CVD risk, predicts long-term weight mgmt

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 [theoretically]

Benefits of Weight Loss on Comorbidities	
DM or at risk	2.5-5kg wt loss over ≥2 yrs: ↓risk T2DM 30-60% 2-5% wt loss: ↓HbA1c by 0.2-0.3% in 1-4 years
HLD	5-8kg weight loss: ↓ LDL 5 mg/dL, ↑ HDL 2-3 mg/dL
HTN	5% weight loss: ↓SBP 3 mmHg & ↓DBP 2 mmHg
CVD	MI: HR 1.26 for overweight and HR 1.88 for obese

(Curr Obes Rep 2017;6:187)

Medications:

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

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

Anti-Arrhythmics					
Class	**Generic**	**Mechanism**	**Usage**	**Dosing**	**Side effects**
IA	**Procainamide** (IV)	Na^+ channel blockade; slows conduction; lengthens action potential	VT; AF, **especially in accessory bypass tracts (WPW)**	Load 20mg/min until total 17 mg/kg reached (e.g. ~1h, BP q5 min); then 1-4 mg/min (in urgent situations, up to 50 mg/min may be given for a total max dose 17 mg/kg)	HoTN, PVCs, VT, ↑QT, **drug-induced lupus**, agranulocytosis
	Disopyramide (PO)	Na^+ channel blockade; also has anticholinergic effects	**Used in HOCM** (efficacy relates to negative inotropic effect), VT, AF, A-flutter	VT: If <50kg →load 200mg x1, then 100mg q6h; if >50kg →load 200mg x1, then 150mg q6h AF conversion: 200mg q4-6h AF prevention: 400-750mg daily divided q6h	**Anticholinergic** side effects, **negative inotropy,** hypotension, ↑ QTc
IB	**Lidocaine** (IV)	Na^+ channel blockade; no effect on conduction; may shorten action potential	**VT, pulseless VT/VF**	Load: bolus **1.0-1.5 mg/kg**. May give additional 0.5-0.75 mg/kg IV push PRN q5-10 min; max total: 3 mg/kg Maintenance: **1-4 mg/min (30-50 mcg/kg/min)**	Bradycardia, junctional arrhythmia, HoTN, angina, AMS, tremor, seizure, dysarthria, paresthesias, nausea, dizziness
	Mexiletine (PO)	PO analogue of lidocaine	**VT**	Load: 400mg x1 Maintenance: 200mg q8hrs	Tremor, nausea
IC	**Flecainide** (PO)	Na^+ channel blockade	**pAF** ("pill in the pocket"), rarely ventricular arrhythmia	Pill in the pocket: 200mg (<70kg) or 300mg (>70kg). Max: once/24hrs Maintenance of sinus rhythm: 50-150mg BID	**Ventricular arrhythmia** (high risk if any structural heart disease)
	Propafenone (PO)	Na^+ channel blockade; Some β1 blockade	Same as above	Pill in the pocket: 450mg(<70kg) or 600mg (>70kg). Max: once/24hrs Maintenance of sinus rhythm: 225-425 BID	GI sx, dizziness, pro-arrhythmia
II	**Esmolol** (IV)	β1 antagonist. t 1/2 = 9 min	Acute HR/BP control in **Ao dissection**, SVT	Load: **20-30 mg IV** (500 mcg/kg) x1 min Maintenance: 2-21 mg/min IV (25-300 mcg/kg/min)	Same as other β-blockers Atenolol is renally cleared
	Atenolol (PO)	β1 antagonist; atenolol 2x more potent than metoprolol	SVT, ACS, post-MI, CAD, HTN, chronic HF	25-50mg QD (max: 100mg QD)	
	Propranolol (IV, PO)	Non-selective β-blocker	**Thyroid storm**, Ao dissection, tremor, variceal bleed ppx, pheo, anxiety	IV: 0.5-1mg load, followed by 1-3mg every several hours PO: 120-320 mg/day (based on indication)	Crosses BBB and may cause **AMS**. Less HoTN than β1 antagonists.
	Nadolol (PO)		**Variceal hemorrhage** prophylaxis	20-80mg QD (max: 240mg)	Changes in mental status. Less HoTN
III	**Amiodarone** (IV/PO)	Blocks K^+ channels, slowing repolarizaqtion. Multiple effects including class Ia, II, and IV properties. **Class II property (i.e. BB) is fastest effect.**	**SVT, VT, pulseless VT/VF**	Pulseless VT/VF: **300 mg IV** push, may repeat 150 mg IV push every 3-5 min as needed WCT: - IV: load with **150 mg IV** x1 (may repeat q10 min as needed), then **1 mg/min IV x 6h (360 mg)**, then **0.5 mg/min IV x 18h (540 mg)** - PO: total **8-10 grams** over days (200-400mg, BID-TID) - Maintenance: 100-200 mg PO QD-BID	HoTN (IV), bradycardia,↑QT. Long t1/2 (58d). Multiple systemic side effects with long-term use (lung, hepatotoxic, thyrotoxic; check baseline PFTs, LFTs, TFTs). **Do NOT use for torsades, pre-excitation**.
	Sotalol (IV, PO)	Nonselective β1/β2 antagonist, K+ channel blockade	**AF, VT**	IV: start 75mg IV q12h, may increase dose by 37.5mg/dose q3d (max: 600mg/day) PO: start 80mg PO q12h, may increase dose by 40mg/dose q3d (max: 640mg/day) - Adjust dosing interval in renal impairment	QT prolongation, typical effects of β-blockade
	Ibutilide (IV)	Blocks K+, prolongs action potential	**AF, AFlutter**	>60kg: 1mg over 10min; can repeat x1 in 10min; ≤60kg: 0.01mg/kg over 10min; can repeat x1 in 10min	QT prolongation, 1.7% TdP, HA
	Dofetilide (PO)		**AF, AFlutter**, SVT	Intial dose 500 mcg BID max Decrease dose if CrCl<60	QT prolongation, renally cleared (CI if CrCl<20)
IV	**Diltiazem** (IV, PO)	CCB→slows AV node conduction and phase II of the cardiac action potential	**AF, AFlutter**, SVT, MAT, angina	IV: 0.25 mg/kg (max 25 mg, usual **15-20 mg**) IV over 2 min; may repeat q15min as needed; gtt @ **5-15 mg/hr** PO: 120-320mg QD (max: 480/day) IV infusion: 5-10mg IV bolus over 2 min, repeat q15-30min PRN (max: 20-30mg); start gtt at 0.3mg/kg/hr if needed PO : 80-120mg TID (max : 480/day)	Contraindicated in SSS, bradycardia, 2°AVB, 3°AVB, VT, AF + WPW, hypotension, pulmonary edema, HFrEF
	Verapamil (IV, PO)				

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

- Tachypnea (go look at the patient and measure yourself. RR ≥20)
- Cyanosis (typically SpO_2 <80%)
- ↑ WOB (nose flaring, retractions, grunting, tripod-ing, diaphoresis)
- Obstruction (wheezing, stridor)

Dyspnea DDx:
- CV: MI, HF, valv. disease, arrhythmia, tamponade, PE, PHT
- AIRWAYS: asthma, COPD, mucus plugging, angioedema, anaphylaxis, foreign body
- ALVEOLI: edema, PNA, hemorrhage
- PLEURAL: large effusion, PTX
- CNS: CVA, intox (CO, ASA), met. acidosis 2/2 sepsis, DKA, etc, psych/anxiety
- OTHER: anemia, ↑abd girth, ALS/GBS/MG, spinal cord, deconditioning

APPROACH:

1) **Confirm code status**
2) **Low threshold to call Rapid Response for assistance**
3) **Assess respiratory status**
   - **Place on supplemental O_2**: NRB to start, can always wean later
   - **Red flags (CALL RICU STAT for intubation, x6-3333)**: GCS <8 (hard criteria for intubation), pooling airway secretions, hemoptysis, life-threatening hypoxemia despite supplemental O_2 (SpO_2 <80%, PaO_2 <55 mmHg), severe hypercarbia despite BiPAP, tiring out (increased work of breathing, progressive hypercarbia), RR >35
     - **Temporize**: suctioning, jaw-thrust or chin lift to open airway, AMBU bag ventilation
4) **Initial workup** (*think about* PNA, CHF, COPD, sepsis, ARDS) (J Hosp Med 2013;8:76)
   - **EKG**: ST depressions/elevations (ischemic changes), sinus tach / e/o RV strain (PE), arrhythmia (AF+RVR, SVT, VT)
   - **CXR** (order STAT and must call x**6-3050**): look for new infiltrate (aspiration, PNA), pulmonary edema, lobar collapse (consider mucus plug), PTX. Call x4-1533 for read. If normal, think about ischemia, PE, acidosis, etc.
   - **ABG**: worrisome if $PaCO_2$ >45 mmHg (*poor ventilation*), PaO_2 <60 mmHg (*poor oxygenation*), pH <7.25
   - **Labs**: VBG (and ABG if possible, helpful to correlate to VBG), hs-Trop, NT-proBNP, lactate, BMP, CBC
   - **Additional studies based on clinical suspicion**: CT-PE (if stable to travel), TTE (acute valvular disease, RH strain)
5) **Subsequent workup**: see specific pages for further guidance

TREATMENT:

- **Supplemental oxygen therapy** (see *Oxygen Delivery Therapies* section for more detail):
  - NC: for every liter increase in O2, ↑ FiO_2 0.03/L (max: 6L = 0.40 FiO2)
  - Venturi masks: pre-set FiO2 (0.24, 0.28, 0.31, 0.35, 0.40) (*flow rate decreases with increasing FiO_2*)
  - NRB: can give FiO_2 ~0.90, but in tachypneic patient, FiO_2 ~0.60 *(due to entrainment of room air)*
  - HFNC: FiO_2 0.6 to 1.0 at 10-60 L/min (humidified air); ↓90-day mortality vs. NIPPV for pts with hypoxemic respiratory failure not due to pulmonary edema or obstructive lung disease (NEJM 2015;372:2185)
- **NIPPV** (BIPAP for COPD; CPAP for CHF): RR >25-30, accessory muscle use, pH <7.35, P_aCO_2 >45mmHg
- **Intubation**: See **red flags** above

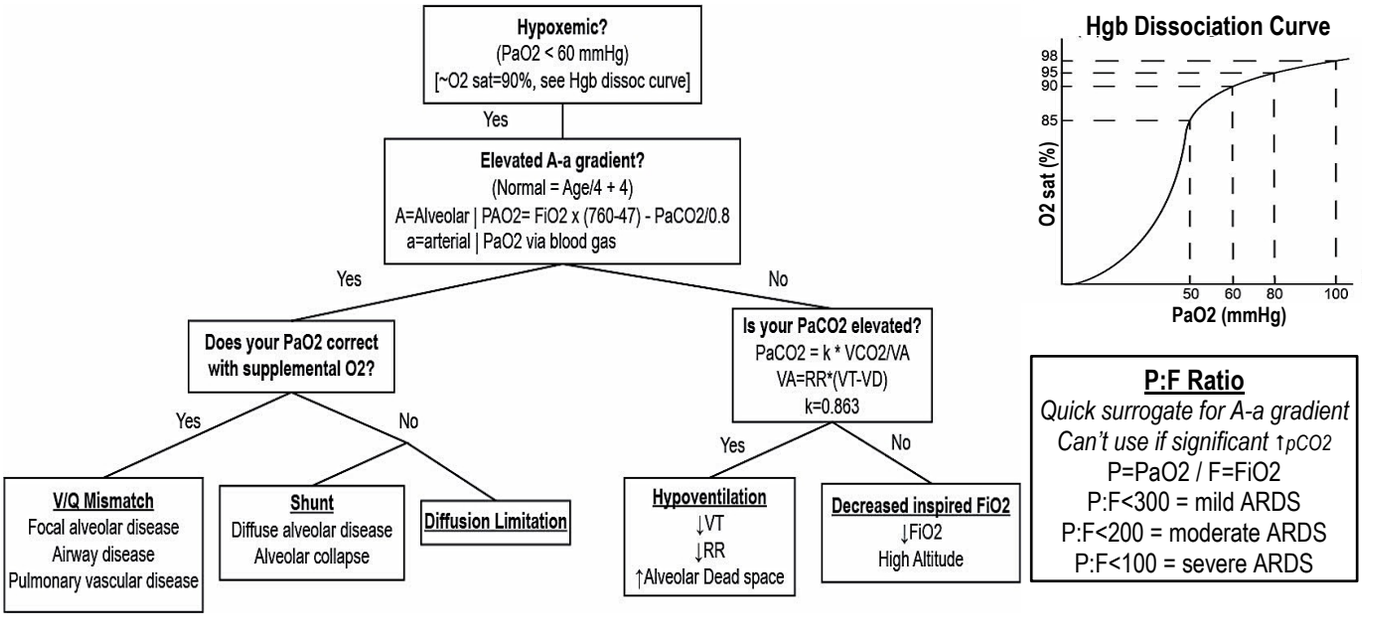
DISEASE SPECIFIC TREATMENT:

- **CHF**: CPAP, IV diuresis, nitrates *(paste or drip,* if BP room*)*, low dose morphine (1-2mg)
- **COPD**: BiPAP, nebulizers *(stacked DuoNebs x3)*, steroids (PO pred 40mg = IV methylpred 32mg); if severe exacerbation, consider methylpred 60-125mg q6h; abx if 2/3: ↑sputum volume, purulence, or dyspnea
- **PE**: if high suspicion and no contraindication, start **empiric** anticoagulation (Lovenox therapeutic faster than heparin gtt)
- **PTX**: if unstable, needle thoracostomy *(14G angiocath, 5th ICS at mid-axillary line or 2nd ICS at mid-clavicular line)*; STAT page Thoracic Surgery/IP for chest tube
- **Pleural effusion**: thoracentesis (see *Procedures*; must be performed by IP or supervised by pulm attending)
- **Opioid overdose**: Narcan 0.4-2mg IV/IM Q2 minutes, observe response; given short half-life, consider gtt if response
- **Anaphylaxis**: Epi *(1:1000)* 0.3 mL = 0.3 mg IM, methylprednisolone 125mg IV, diphenhydramine, ranitidine
- **Cardiac ischemia**: ACS treatment (*see Cardiology section)* – ASA 325, atorva 80, TNG (SL→gtt), heparin gtt, BB

Rapid Response x6-3333 (Senior On, nursing supervisor, RT, pharmacy) | **STAT page RICU x6-3333**

- **RICU communication guide:** *have information ready for RICU prior to intubation; greet RICU in patients' room*
  - ***Code status***
  - ***Hemodynamics*** *– LV, RV, valves, volume status, access*
  - ***Aspiration risk*** *– NPO status, last meal, risk factors*
  - ***Urgency/acuity of decline***
  - ***Difficult airway*** *(look for prior intubation notes)*
  - ***Allergies***
- **Have ready**: sedation (propofol/fentanyl/versed), pressor (Neo >> Levo), IV fluids w/ push line; RICU brings paralytic
- **MICU/CCU**: Resource RN will call for RICU; make sure attending/OI, fellow, RT and RN are aware of plan
- **INTUBATION IS NOT AN ACT OF WEAKNESS**: do not delay intubation in patients with impending respiratory failure

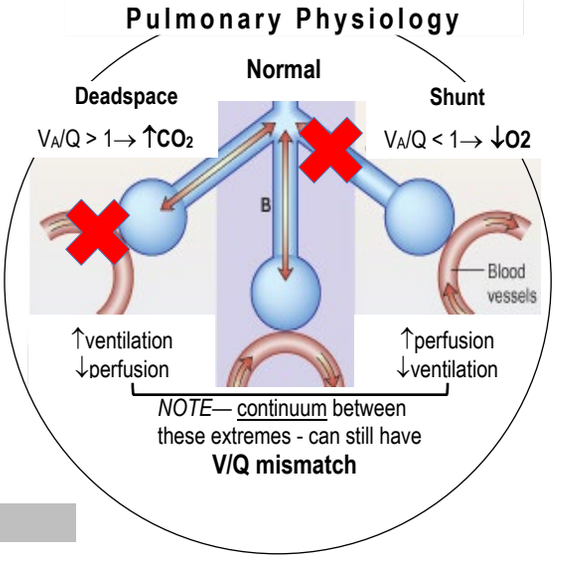
Respiratory Failure: inability to oxygenate (deliver O2) or ventilate (blow off CO2). Can be hypoxemic (PaO2 <60 mmHg), hypercarbic (PaCO2 >45 mmHg), or both. A quick algorithm can be used to determine the etiology based upon ABG results:



P:F Ratio
Quick surrogate for A-a gradient
Can't use if significant ↑pCO2
P=PaO2 / F=FiO2
P:F<300 = mild ARDS
P:F<200 = moderate ARDS
P:F<100 = severe ARDS

HYPOXEMIC RESPIRATORY FAILURE

- **Hypoventilation; low FiO2**: decreased O_2 delivery to lungs
- **V/Q mismatch**: imbalance in delivery of oxygenated air & blood flow
  1. *FOCAL* alveolar infiltrates: **PNA**, **edema**, **hemorrhage**
  2. Airway: **asthma**, **COPD**, **bronchiectasis**
  3. Vascular: **pHTN**, **PE**
  4. Iatrogenic: too much **PEEP**
- **Shunt**: flow of blood through lung without encountering oxygenated air, *"perfusion without ventilation"* (severe V/Q mismatch)
  1. *DIFFUSE* alveolar infiltrates: **above + ARDS**
  2. Alveolar collapse: **PTX, atelectasis, mucus plug**
  3. Intra-cardiac/intra-pulmonary shunt: **PFO**, **AVM** (e.g. hepatopulmonary)
- **Impaired diffusion (↓ DLCO)**: hypoxemia worse w/ exertion
  - ILD (correlates with severity on CT), pHTN, advanced COPD



HYPERCARBIC RESPIRATORY FAILURE

- **"Won't breathe" (↓RR)**: **sedatives**, **obesity hypoventilation**, central sleep apnea, **brainstem** stroke/tumor/infection (pons & medulla), hypothyroidism (myxedema coma), compensation for metabolic alkalosis (chemoreceptors)
- **"Can't breathe" (↓V_T)**: nerves/muscles/chest wall/airways
  1. ↑ Alveolar dead space (airspace which does not participate in gas exchange; *"ventilation without perfusion"*)
     - Dead space = **anatomic** (~150cc upper airway air without perfusion) + **alveolar** (~0 normally; in disease, capillaries get destroyed or compressed →↑ V_D)
     - Parenchyma: **emphysema**, **ILD**/fibrosis, **CHF, PNA, ARDS**
     - Airway: **asthma, COPD**, CF, bronchiectasis, OSA, tumor, foreign body, **high PEEP**
     - Vascular: severe **PE** (wasted ventilation due to blocked circulation; more often see ↓pCO2 2/2 hyperventilation)
  2. Chest wall/pleural constraints →↓ lung volume: effusion/fibrosis, obesity, kyphosis/scoliosis, abd distension, PTX
  3. Neuromuscular (Neurol Clin 2012;30:161): **neuropathy** (C-spine/phrenic nerve, GBS, ALS, polio), NMJ disorder (MG, botulism), myopathy (polymyositis/dermatomyositis, hypophosphatemia), critical illness. **Consider EMG**.
- **↑ CO_2 production (V_{CO2})**: ↑ **WOB, fever**, seizure, sepsis, steroids, overfeeding, thyrotoxicosis

Acid-Base Interpretation:
Hypercarbia→Respiratory acidosis (↑ pCO2)
• Acute: HCO3 ↑ by 1 (per pCO2 ↑ 10)
• Chronic: HCO3 ↑ by 3-4 (per pCO2 ↑ 10)
Hypocarbia→Respiratory alkalosis (↓ pCO2)
• Acute: HCO3 ↓ by 2 (per pCO2 ↓ 10)
• Chronic: HCO3 ↓ by 5 (per pCO2 ↓ 10)

Pulmonary & Critical Care Non-Invasive Oxygenation/Ventilation

OXYGEN DELIVERY DEVICES

Low Flow Devices

- **Nasal cannula**: FiO_2 **24-40**%. Variable flow/FiO_2 relationship (3-4%/L). Max flow 6L. Humidify if >4L
- **Simple facemask**: FiO_2 **35-50**%. Keep flow >5L to avoid rebreathing trapped CO_2 in mask. Max flow 10L.
- **Shovel mask**: FiO_2 **24-50**%. Difficult to control FiO_2 – consider in patients with stable need for O_2 who do not tolerate NC or require more humidity for comfort.

Reservoir Systems

- **Oxymizer**: FiO_2 **24-45**%. Small (20cc) reservoir stores O2 and delivers a "push" of high FiO2 oxygen with inspiration. Can deliver slightly higher FiO_2 than NC. Can decrease flow needs (esp. for outpatients) by increasing available O2.
- **Non-rebreather**: ***easily accessible – consider starting with this for the acutely hypoxemic patient***
  - Theoretically delivers **100%** FiO_2, but true delivery **60-90**% F_iO_2 due to entrainment of room air
  - Air entrainment is increased (true FiO2 lower) when patient is tachypneic or drawing large tidal volumes
  - Flow should be set >10L to adequately fill the reservoir – want bag collapse <1/3 on inspiration. Max flow 15L.

High Flow Devices

- **Venturi mask**: FiO_2 **24-50**%. Colored valve designed to permit constant flow of room air mixed with O_2 source to deliver a fixed FiO_2 independent of patient's RR and tidal volume. Total gas flow rate decreases with increasing FiO_2.
  - Color coded by FiO_2: Blue 24%, White 28%, Yellow 35%, Red 40%, Green 60%
  - Consider for patients who need careful titration of oxygen, such as a COPD patient with set SpO_2 goals. **NOT for use in acute respiratory distress.**
- **High-flow nasal cannula (HFNC)**: delivers up to **100%** FiO_2 (when mouth is closed) at flow rates 10-60 L/min and provides small amount of **PEEP** (approximately 0.7 cm H2O/L) when patient's mouth is closed
  - Consider use in **pure hypoxemic respiratory failure**
  - No Δ in intubation rates vs. NIPPV, but may ↓ 90-day mortality for pts with hypoxemic respiratory failure not due to pulmonary edema or obstructive lung disease (NEJM 2015;372:2185)
  - Mixed data in immunocomp. pts on whether ↓ intubation (Intensive Care Med 2017;43:1808, JAMA 2018;320:2099)
  - Extubation to HFNC similar to extubation to NIPPV in terms of reintubation rate (JAMA 2016;316:1565)

Caution: liberal supplemental of oxygen to improve SpO2 above 94-96% in acutely ill adults is associated with ↑mortality (Lancet 2018;391:1693)

NONINVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)

- **CPAP** (continuous positive airway pressure): provides PEEP, which prevents upper airway collapse (e.g. OSA) and lower airway collapse (e.g. atelectasis) while raising intrathoracic pressure and decreasing venous return (e.g. helpful in CHF)
  - In CHF, ↓ intubation, ↓ mortality (NEJM 2008;359:142, Cochrane Rev 2013)
- **BiPAP** (bi-level positive airway pressure): provides both inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP = PEEP)
  - Can be helpful for hypercarbic respiratory failure caused by hypoventilation as IPAP decreases respiratory fatigue/WOB, especially in obstructive lung disease and neuromuscular disease.
  - In COPD, ↓ mortality, intubation, and LOS (Cochrane Rev 2017)

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

- Cardiogenic pulmonary edema (CPAP/BiPAP)
- COPD exac. w/ acute resp. acidosis (BiPAP)
- Ppx against extubation failure in high risk pts
- Respiratory failure in immunocomp. pts

Weak Indications for NIPPV

- Hypoxemic resp. failure (other than CHF/COPD)
- Patient is DNI w/ indication for intubation
- Palliation for increased WOB, dyspnea
- Asthma exacerbation w/ acute resp. acidosis

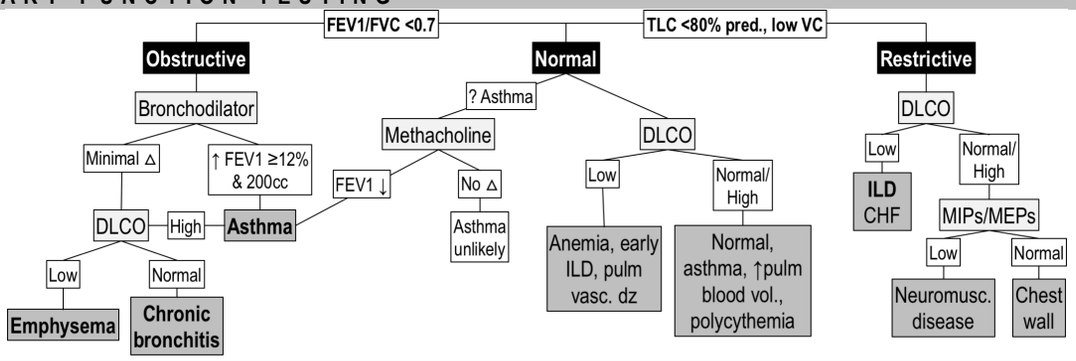
Contraindications to NIPPV

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

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

REMEMBER: BiPAP/HFNC should NOT be used to delay intubation!

PULMONARY FUNCTION TESTING



ASTHMA – DIAGNOSIS & OUTPATIENT CARE

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

DIAGNOSIS:	
Spirometry	**Obstructive**, **reverses w/ bronchodilator**, worsens w/ methacholine (can be nml before provocation)
Peak expiratory flow (PEF)	Estimates degree of control. <80% personal best c/w poor control. ♀: 300-500, ♂: 450-750 L/min
Allergy testing	If allergic component suspected (sx w/ exposure/persistent sx): ✓ IgE, CBC+diff (Eos), refer to Allergy.
New-onset adult cases unusual → should consider systemic disease (ABPA, EGPA, systemic mastocytosis), occupational asthma (10-25%; NEJM 2014;370:640), aspirin-exacerbated resp. disease (esp. if nasal polyps; J Allergy Clin Immunol 2015;135:676)	

MANAGEMENT: (GINA guidelines: ERJ 2019;53:1901046)

- **Controller + reliever**: stepwise based on severity (*see below*); step up if not controlled; step down if well controlled 3mo.
  - Note: *changes in recent guidelines to recommend that all receive ICS-containing controller*; no longer rec. SABA only tx as a/w ↑ allergic responses & airway inflammation, ↓ response when SABA needed, & overuse a/w ↑ severe exacerbations
  - In mild asthma, PRN budesonide-formoterol (Symbicort) > PRN SABA (Novel START NEJM 2019;238:2020; SYGMA1 NEJM 2018;378:1865) & non-inferior to maintenance ICS for preventing exacerbations (though ↑ sx; SYGMA2 NEJM 2018;378:1877)
  - In mild/mod., maintenance ICS-LABA + PRN ICS-LABA also > + PRN SABA (AJRCCM 2005;171:129; Chest 2006;129:246). PRN ICS w/ SABA > PRN SABA alone (TREXA Lancet 2011;377:650).
  - May be some phenotypes however w/ low eos. inflamm. (<2% in sputum) in whom ICS ↓ effective (NEJM 2019;380:2009)
- **Trigger avoidance**: e.g.: exercise, cold air, irritants (smoke, perfume), allergens, infxn, drugs (ASA, NSAIDs, β-blockers)
- **Exacerbations**: short course pred. 40-50mg x5-7d on top of controller/reliever regimen.
  - Consider 4x controller ICS for mild exacerbations (NEJM 2018;378:902)

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

ICS: inhaled corticosteroids | LABA: long-acting β-agonists (e.g. formoterol) | SABA: short-acting β-agonist | LTRA: leukotriene receptor antagonist
Biologics: anti-IL4: dupilumab; anti-IgE: omalizumab (Annals 2011;154:573); anti-IL5: mepo-, res-, benra- lizumab, tezepelumab (AJRCCM 2019;199:433)
Contraindicated to use LABA without ICS (CHEST 2006;129:15; NEJM 2010;362:1169)

ASTHMA - INPATIENT CARE

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

Floor Patient	**ICU Patient** (Thorax 2003;58:81)

- **Bronchodilators**: **albuterol** +/- ipratropium
  ○ DuoNebs in ED a/w ↓ admit (Cochrane Rev 2017) but evidence in children that no benefit after hospitalized
  ○ Can Δ to SABA alone after admit unless severe/worsening
- **Steroids**: **pred 40-60mg** or **IV methylpred** 40-60mg q12-24 (if ⃠ PO / impending arrest); total **x5-7d** (Cochrane Rev 2016)
- O2 >92% (93-95% in severe; >95 →↑pCO2; Thorax 2011;66:937)
	- **Bronchodilators**: albuterol + ipratropium
	- **Methylpred 125mg IV q6h** (Archives 1983;143:1324)
	- **BiPAP**: limited data, generally avoided in adults
	- **Rescue therapies**: continuous albuterol nebs (CAB), Heliox (lower density gas, data controversial)
	- **Mechanical ventilation**: large ET tube, high insp flow rate (80-100 L/min), low V_T (6-8 cc/kg), low RR (10-14), paralysis; **Goal:** maximize expiratory phase, permissive hypercapnia

- **If impending respiratory failure**: stacked DuoNebs (x3/hr), methylpred IV 60-125mg, Mg IV 2g / 20 min, transfer to ICU	

ASTHMA / COPD OVERLAP (ACO) (GINA Guidelines; ATS/NHLBI: AJRCCM 2017;196:375; NEJM 2015;373:1241)

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

Pulmonary & Critical Care — COPD

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

Diagnosis of COPD (GOLD Guidelines: AJRCCM 2017;195:557)

1. **Diagnosis**: spirometry w/ **FEV1/FVC <0.7** (*actual*, not predicted; no sig. Δ w/ bronchodilator)
2. Determine severity of airflow limitation: **GOLD grade** based on FEV1 →
3. Evaluate sx/risk of exacerb.: mMRC, CAT score, exacerbation hx → **GOLD ABCD group**

mMRC
0 = SOB w/ strenuous exercise
1 = SOB when hurrying or walking up slight hill
2 = walks slower d/t SOB or has to stop
3 = stops for breath after 100yds or few min.
4 = too SOB to leave house, SOB w/ dressing

	mMRC 0-1 CAT <10	mMRC ≥2 CAT ≥10
≥2 exacerbations or ≥1 admission	C	D
0 or 1 (not leading to hospital admission)	A	B

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

Management of Stable COPD (GOLD 2020 Guidelines; NEJM 2019;381:1257)

Pharmacologic interventions: based on level of sx and risk of exacerbations

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

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

Non-Rx interventions: ⦸ smoking (↓ mortality; Annals 2005;142:233), pulm. rehab (Cochrane Rev 2015), vaccines (flu, PCV13, PPSV23)

- **Lung CA screening**: annual low-dose CT (age 55-80 w/ 30 pack-year hx & active/quit <15yr) (NEJM 2011;365:395, USPSTF 2014)
- **Home O_2**: if PaO_2 ≤55 or SpO_2 ≤88% or if pulmonary HTN or polycythemia (Hct >55%) with PaO_2 ≤59 or SaO_2 ≤89%
- **Nocturnal NiPPV**: if daytime pCO2 ≥52 & nocturnal SpO2 ≤88% (despite 2L O2) or if recent exacerb. & persistent pCO2 >53 (↓ risk of readmit & mortality: JAMA 2017;317:2177)

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

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

Management:

- **SpO_2 88-92%**: hyperoxia → ↓ vent. via Haldane effect & hypoxic vasoconst., ↑V/Q mismatch; ↑mortality (BMJ 2010;341:c5462)
- **Bronchodilators**: albuterol, ipratropium, DouNebs (combo)
  - "Stacked" DuoNebs (x3 in 1 hr) initially → space to standing DuoNebs q4 w/ albuterol PRN q2 → space further as able
  - Ok to hold home inh. while on scheduled short-acting agents
- **Steroids**: pred 40mg x5d. PO ~ IV (Chest 2007;132:1741) & 5d ~ 14d (REDUCE JAMA 2013;309:2223, Cochrane Rev 2018); though some may need higher dose/longer course if severe
  - If severe: IV methylpred 60-125mg q6-q12 x72hrs
- **NPPV**: if resp acidosis, severe dyspnea w/ resp. muscle fatigue or ↑ WOB (access. muscles, thoracoabdominal paradox, etc), or persistent hypoxemia. ↓mortality, intub., LOS (Cochrane Rev 2004)
- **Antibiotics**: controversial; ↓ mortality but challenging to identify who will benefit (Chest 2008;133:756, Coch Rev 2012)
  - Indicated if: ↑ all 3 cardinal sx, 2/3 w/ ↑ sputum purulence, or require NPPV/mechanical ventilation
    - CRP may be useful in outpt (NEJM 2019;381:111)
    - PCT may be useful but ↑mortality when utilized in ICU setting (Eur Resp Rev 2017;26; ICM 208;44:428)
  - Abx choice: based on PsA risk, prior SCx, resistance
    - ⊖ PsA RFs: FLQ, CTX; outpt: amox/clav, azithro
    - ⊕ PsA RFs: FLQ, cefepime, pip/tazo
    - Duration: 5-7d inpt; 3-5 outpt (varies by drug)
    - Concurrent CAP: treat by CAP guidelines
- **Antivirals**: oseltamivir if influenza⊕, even if ≥48-72hrs.

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: may ↑ urinary retention)
Long-acting β-agonist (**LABA**)	Salmeterol, formoterol (N.B. 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)

Mitu Bhattatiry and Cody Cichowitz

BRONCHIECTASIS (CYSTIC FIBROSIS AND NON-CF)

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

Symptoms	Chronic productive cough, recurrent bronchitis/pneumonia, wheezing, dyspnea, hemoptysis	
Etiology	**Recurrent insult**: infection (PNA, MAC, TB, childhood infection, ABPA), inhalation, GERD/aspiration **Impaired immunity**: ↓ mucus clearance (CF, primary ciliary dyskinesia), immunodeficiency (e.g. ↓IgG) **Obstruction**: foreign body, tumor, COPD, tracheomalacia, CTD (Marfan's), radiation **Systemic disease**: RA, Sjogren's, SLE, IBD, A1AT **Idiopathic = ~50%**	
Workup	**Initial**: HRCT, PFTs, CBC w/ diff, Ig levels, sputum Cx (bacterial, mycobacterial, fungal) - CT: **bronchial diameter > 1.5x adj artery;** bronchi fail to taper, thickened bronchi (Thorax 2010;65:1)	**As indicated**: exclude CF w/ gene/sweat Cl^- testing, Aspergillus Ab, ANA, RF/CCP, SSA/SSB, A1AT; consider nasal NO (PCD), pneumococcal vaccine titers (often low), bronch., GI eval
Natural Hx	Exacerbations (avg 1.5/yr), progressive ↓ in FEV_1, PsA colonization → worsening disease	

Chronic Management

CF: AJRCCM 2013;187:680, AJRCCM 2009;180:802; non-CF: AJRCCM 2013;188:647, ERS Guidelines: Eur Resp J 2017;50

Principles originally arose in CF population then applied to non-CF

- **Airway clearance**: nebs (albuterol, hypertonic saline) + chest PT (acapella, vest)
  - CF: add DNase to neb bundle; not effective in non-CF
- **Antimicrobials/anti-inflammatories**:
  - Non-CF:
    - Azithro has some benefits w/ ↓ exacerb. also but c/f ↑ abx resistance (Lancet 2012;380:9842, JAMA 2013;309:1251, Coch Rev 2018, Lancet RM 2019;7:845). Ensure no NTM first.
    - Trial inhaled abx if PsA colonization & ≥3 exacerb./yr
    - Consider eradication of new PsA isolate
  - CF: azithro + inhaled tobramycin (for PsA; alt: aztreonam, colistin)
- **Disease specific treatment:**
  - Non-CF: treat underlying cause if found; consider PPI/H2 blocker
  - CF: *CFTR mut → defective Cl^-/HCO_3^- transport on airway surface)*
    - Potentiators open CFTR channel (**ivacaftor**); correctors bring CFTR to surface (**lumacaftor, tezacaftor, elexacaftor**)
    - Dual/**triple tx**→long-term FEV1 benefits (NEJM 2015;373:220, NEJM 2017;377:2013, NEJM 2018;379:1599, NEJM 2019;381:1809)
    - **Pancreatic enzyme supplementation**, vitamins ADEK

Acute Exacerbation

- **Sx**: ↑ cough/sputum/dyspnea; usually ⦸ fever
- **Obtain resp cx prior to abx**
- Micro: *PsA* + *S.aureus* > *H. flu, Moraxella, Burkholderia*; treat *Stenotrophomonas* and *Achromobacter* as pathogenic; *Aspergillus* in CF not treated
- **Abx**: use previous Cx data; **tx 14d**
  - No prior Cx data: empiric FLQ (for PsA)
  - If prior R-PsA: IV abx; 2 agents – β-lactam & either FLQ or IV tobra (dosed QD)
    - *No great evidence for double coverage of PsA though is standard of care* in CF
  - If β-lactamase⊕ *H flu* or *Moraxella*: amox/clav, doxy, macrolide, or FQ
  - Home abx: continue azithro ± inh tobra (practice varies)
- Steroids not used unless concomitant asthma or ABPA
- Continue chronic treatment (airway clearance)

HEMOPTYSIS

DEFINITION: *expectoration of blood from lower respiratory tract*

Etiology:	• **Airway**: bronchitis, bronchiectasis (incl. CF), CA (usually primary lung CA), trauma (incl. foreign body) • **Pulmonary parenchyma**: infection (PNA, abscess, TB, aspergilloma), ANCA-vasculitis (GPA), anti-GBM (Goodpasture syndrome), immune-complex vasculitis (SLE, cryo, HSP), drug-induced vasculitis (cocaine, PTU, TNFi, hydral), coagulopathy, endometriosis, inhalation injury, sarcoid, pulmonary hemosiderosis • **Pulmonary vascular**: PE, CHF (esp if on AC), mitral valve dz, bronchovascular fistula, aneurysm, AVM
Work-up:	1) Consider other sources (GI or nasopharyngeal) 2) **CXR (most important),** CBC, coags, U/A (for vasculitis, anti-GBM), sputum Cx, CT chest (if stable) 3) Consider NT-proBNP, D-dimer, ESR/CRP, C3/C4, ANA, ANCA, anti-GBM, APLAS, IGRA/AFB
Management if *non-massive*:	• If minimal & likely infectious: observe. • If active & without clear etiology or recurrent: chest CT → bronch.

MASSIVE HEMOPTYSIS (>500mL/day or >100mL/hr) is a **life-threatening emergency** with mortality rate 50-80%. Asphyxiation NOT exsanguination is mechanism of death. (CCM 2000;28:1684)

- **LIE PATIENT ON SIDE OF SUSPECTED BLEED** (preserve gas exchange in unaffected lung)
- Control airway: if very dyspneic, poor gas exchange, or rapid bleed, **STAT RICU consult** (x6-3333), largest ET-tube possible (8mm+). *Note: ensure suction (+/- IP) available upon intubation as blood can rapidly fill ET tube*
- Ensure hemodynamic stability, correct coagulopathy. Inhaled TXA may be beneficial (Chest 2018;154:1379).
- **Call IP** → bronch to localize; temporize w/ balloon tamponade, bronchial blockade, electrocautery, topical vasoconstriction
  Call IR → if stable, can CTA to localize; otherwise bronchial angiography to embolize site
  If refractory, thoracic surgery evaluation.
- Can consider pulse dose methylprednisolone if vasculitis suspected

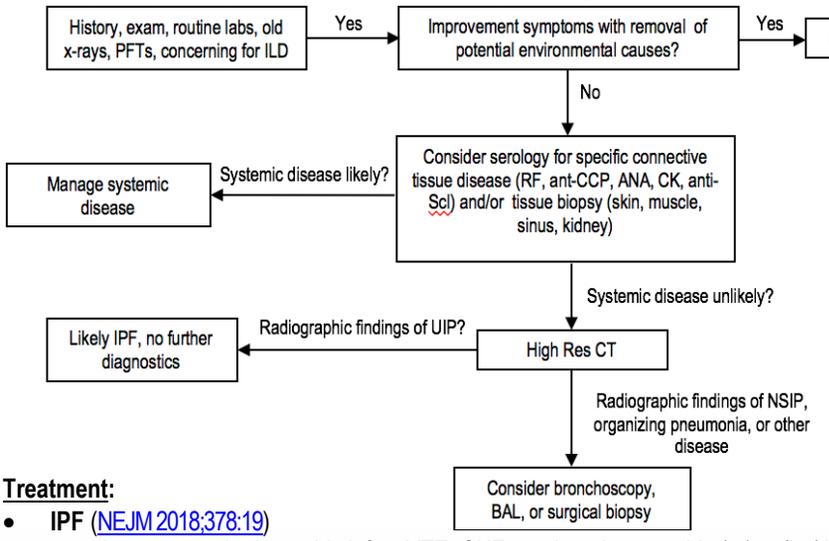
Pulmonary & Critical Care — Interstitial Lung Disease

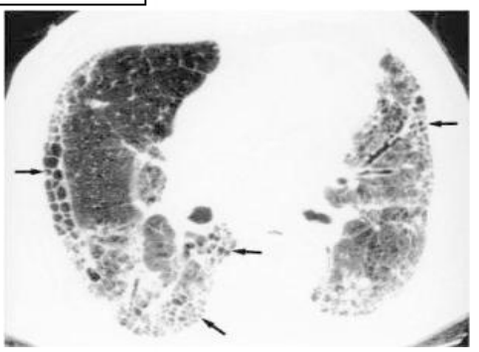
Overview: diverse group of disorders that cause scarring/fibrosis in the lungs, often leading to structural changes in the parenchyma (alveoli, interstitium, alveolar-capillary interface) → loss of lung volume/compliance
Presentation: progressive dyspnea, non-productive cough, hypoxemia (esp. w/ exercise); some (e.g. AIP, HSP, COP) often w/ systemic sx
History: tempo, hx CTD/IBD/malig., rheum ROS, meds, exposures (chemicals, dusts, barns, pets, AC, humidifier, hot tub), smoking, FH
Physical exam: "velcro-like" crackles, clubbing, e/o CTD (heliotrope rash, Gottron's papules, mechanic's hands, joint disease, muscle weakness, skin fibrosis, sicca), extrapulmonary manifestations of other systemic diseases
Etiologies: known and idiopathic causes broken down by subcategories (ATS/ERS classification: AJRCCM 2013;188:733)

<table>
<tr><th colspan="3">Idiopathic Interstitial PNAs (IIPs)</th><th colspan="5">Known Causes</th></tr>
<tr><td>Chronic</td><td>Acute/subacute</td><td>Smoking-rel.</td><td>Systemic Diseases</td><td>Connective Tissue Disease</td><td colspan="2">Exposures</td><td></td></tr>
<tr><td rowspan="2">Idiopathic pulmonary fibrosis (IPF; UIP pattern), idiopathic non-specific interstitial PNA (NSIP)</td><td rowspan="2">Acute interstitial pneumonia (AIP; DAD pattern), cryptogenic organizing pneumonia (COP)</td><td rowspan="2">Resp. bronchiolitis-ILD (RB-ILD), desquamative interstitial PNA (DIP)</td><td rowspan="2">Sarcoid, amyloid, ANCA-vasculitis, IBD, CA</td><td rowspan="2">Scleroderma, Poly/dermato-myositis, RA, SLE, Sjogren's, MCTD</td><td colspan="2">Inhalation</td><td>Drugs</td></tr>
<tr><td>Organic
Grains, molds, AC/humidifier, birds, etc.</td><td>Inorganic
Silica, asbtesos, coal, metals, etc.</td><td rowspan="2">Amiodarone, nitrofurantoin, methotrexate, nivolumab, pembrolizumab, ipilimumab, talc, radiation, etc.</td></tr>
<tr><td colspan="3"></td><td colspan="3"></td><td>Hypersensitivity pneumonitis
Pneumoconiosis</td></tr>
<tr><td colspan="8">Others: Lymphangioleiomyomatosis (LAM): seen in young ♀ with reticular opacities on CXR & thin walled cysts on CT chest. Pulmonary Langerhans cell histiocytosis (PLCH): young adults w/ upper-zone-predom. cysts (can be bizarrely shaped) & nodules. Eosinophilic PNA: acute form (AEP) w/ <1mo of sx, BAL with >25% eos; chronic (CEP) with >1 mo. of sx, periph. eos (>6%), BL periph. consol. that are "photo. negative" of pulm edema; Tx w/ steroids.</td></tr>
<tr><td colspan="8">Idiopathic PNA w/ autoimmune features (IPAF): idiopathic PNA pattern (NSIP, UIP) w/ features of autoimmune dz that do not meet criteria for CTD dx.</td></tr>
</table>

Diagnostic Evaluation:

- Labs: CBC+diff, CMP, U/A, ESR/CRP, CPK/aldolase, C3/C4, auto-antibodies (ANA, RF/anti-CCP, anti-RNP, anti-Ro/La, Scl-70, ANCA, hypersensitivity panel, myositis panel 3, anti-Jo1 [part of myositis panel but comes back faster])
- Radiology: **HRCT ILD-protocol**; upper- (HSP, smoking-rel., dusts) vs. lower-predom. (IPF, NSIP), LAD (CA, sarcoid), pleural dz?
- PFTs: restrictive defect (↓TLC, ↓FRC, ↓RV; FEV1/FVC normal to ↑); ↓DLCO can be early sign
- BAL: if acute onset or hemoptysis (eval for AEP, alveolar hemorrhage, CA, infection); if more chronic, can perform if suspect HSP, sarcoidosis, infection, or pulm. Langerhans histiocytosis. Not useful if suspect IPF except to exclude chronic HSP.
- Lung biopsy: if diagnosis unclear and will change management

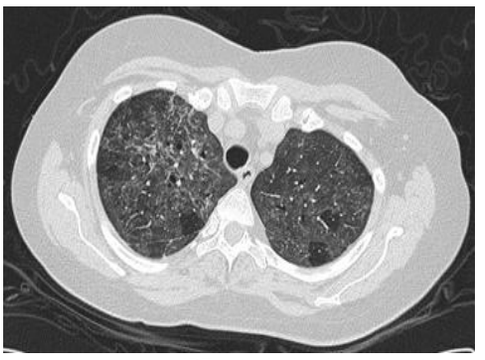




Above: Usual Interstitial Pneumonia (UIP) is the radiographic corollary of IPF
Features: basilar-predominant, *honeycombing*, traction bronchiectasis

Treatment:

- **IPF** (NEJM 2018;378:19)
  - Acute exacerbations: ddx infxn, VTE, CHF; no data, but steroids (~1mg/kg/d pred) & broad-spectrum abx (x7d) generally given (AJRCCM 2011;183:788). Can re-pulse & slow taper if tx failure during taper.
  - Chronic therapy: consideration for **pirfenidone** (antifibrotic; SE: nausea, fatigue), **nintedanib** (TK inhibitor; SE: diarrhea) (↓FVC decline but no Δ in survival) (NEJM 2014;370:2083). Azathioprine/pred/NAC w/ ↑ mortality (NEJM 2012;366:1968) & no clear benefit to NAC monotx (though minimal side effects; NEJM 2014;370:2093). GERD tx & aspiration precautions may be beneficial (Lancet RM 2013;1:369). Steroids NOT indicated. Lung txp evaluation.
- **NSIP**: remove inciting exposures, tx underlying condition (if non-idiopathic); can be steroid-responsive (pred 0.5-1mg/kg/d or pulse solumedrol if severe & requiring hospitaliz.); 2nd agent (AZA, MMF, ritux, CYC) pending response. Nintedanib may benefit non-IPF progressive fibrotic disease (NEJM 2019;381:1718, Lancet RM 2020)
- **COP**: monitor; if sx persist/progress → pred ~0.75-1mg/kg/d (pulse if fulminant)
- **AIP**: many cases of idiopathic ARDS; tx is supportive; usually not steroid-responsive, but often give high dose steroids, empiric abx as in-hospital mortality >50%



Above: many non-IPF pathologies (e.g. idiopathic, CTD, meds, some HSP) may have a *NSIP* pattern
Features: *subpleural sparing*, increased reticular markings, ground glass, mosaic attenuation due to air trapping (requires inspiratory/expiratory HRCT), HSP will be upper lobe predominant

CLINICAL MANIFESTATIONS

Signs/Symptoms

DVT

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

PE (Chest 1991;100:598; Am J Med 2007;120:871)

- Sx: **dyspnea** (73-79%), **pleuritic CP** (47-66%), **cough** (37-43%), orthopnea (36%), leg swelling/pain (26-42%), syncope (10%), hemoptysis (13%), diaphoresis (4-11%), palpitations (10%), angina (4%); many may be asymptomatic
  - *Syncope*: among pts hospitalized for syncope, PE in 2-17% (NEJM 2016;375:1524, JACC 2019;76:744)
- 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)	
- Fracture (hip/leg)	- Arthroscopic knee surgery	- CHF (JACC 2020;75:148)	- Bed rest >3 days	- Pregnancy (antepartum)
- Hip or knee replacement	- Central venous lines (PICC: Lancet 2013;382:311)	- Resp. failure	- Immobility due to sitting (e.g. airplane, car)	- CKD (J Thromb. Haemost 2014;12:1449)
- Major general surgery	- Hormone replacement tx/OCPs	- Asthma (ERJ 2014;43:801)	- Increasing age	- Smoking (mixed; Am J Hem 2008;83:97)
- Major trauma	- Pregnancy (postpartum)	- Malignancy/chemotherapy	- Laparoscopic surgery (e.g. CCY)	- Cirrhosis (Thromb Haemost 2017;117:139)
- Spinal cord injury	- Hospitalized/SNF (w/o surgery)	- Paralytic stroke	- Obesity (Circ 2008;117:93)	
	- Previous VTE	- IBD		
	- Thrombophilia	- Nephrotic syndrome		
		- Sepsis (Chest 2015;148:1224)		

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

- **Pre-test prob**: Wells' for LE DVT (NEJM 2003;349:1227), 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; if D-dimer ⊕, further eval. If **high** (or mod. PE) → imaging.

Wells' Criteria for PE		
Clinical s/sx of DVT	3 points	0-1 = low risk
PE #1 dx OR equally likely	3 points	2-6 = mod. risk
HR >100	1.5 points	>6 = high risk
Immobilization x3d or surgery ≤4wks	1.5 points	
Hemoptysis	1 point	≤4 = unlikely
Malignancy w/ tx last 6mo. or palliative	1 points	≥5 = likely

PERC Rule		
Age ≥50	Hemoptysis	If meets none of criteria to left, no further testing needed.
HR ≥100	Surgery/trauma ≤4wks	
SpO2 <95%	Prior DVT/PE	
Unilateral leg swelling	Hormone use	

Interpreting D-Dimer (Nml <500)

- **DVT**: if nml + low pretest prob, excludes DVT (NEJM 2003;349:1227, JAMA 2006;295:199)
- **PE**: if nml + low pretest prob, excludes PE (Thromb Haemost 2009; 101:886).
- **Adjusted D-dimer**: → ↓ imaging w/o ↑ in PE
  - *Age-adjusted*: if >50, use age x10 as cut off (JAMA 2014;311:1117)
  - *Prob.-adjusted*: use of <1000 cutoff w/ low prob. (NEJM 2019;381:2125)
- Ddx for ↑ D-dimer: arterial thrombus (MI, stroke, AF/intracardiac, acute limb ischemia), DIC, CA, inflammation/infection, ESLD, CHF, renal disease, ↑ age, aortic dissection, trauma, surgery

- **DVT diagnosis**: venous doppler U/S ("LENIs" = Lower Extremity Non-Invasives; "UENI" = Upper Extremity Non-Invasives)
- **PE diagnosis**:
  - PE-CT: study of choice; may also detect alt dx (PIOPED II NEJM 2006;354:2317)
  - V/Q scan: validated in PIOPED (JAMA 1990;263:2753). Performed if c/i to CT/contrast. Need nml CXR (minimize other causes of V/Q mismatch)
  - LENIs: if suspect PE & unable to CT or V/Q & ⊕, can treat; if ⊖, however, does not exclude PE (clot may have migrated or be from other 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 (↑ A-a gradient, normal in ~20%), respiratory alkalosis
- **PE risk stratification**:

High Risk (Massive)	**Intermediate Risk** (Submassive)	**Low Risk** (Nonmassive)

Hemodynamically unstable
• SBP <90 or requiring vasopressors & not due to hypovolemia, arrhythmia, etc.
• Cardiac arrest
	Right heart strain w/o hypotension
	• Biomarkers:
	  ○ ↑NT-proBNP >500; though >600 cut-off ↑Sp. (ERJ 2014;43:1669)
	  ○ ↑hs-TnT; age-adjusted cut-off of ≥14 in age <75 & ≥45 in age >75 may ↑ NPV (ERJ 2015;45:1323)
	• Echo: RV overload/dysfunction – enlarged RV, flattened IVS, mod/severe TR, McConnell's sign (RV free wall akinesis sparing apex), ↓ TAPSE
	• CT: RV/LV diameter ratio >0.9 (EHJ 2011;32:1657)
	• PE severity index (PESI): class III-V; short PESI (sPESI) ≥1
	ESC further classifies into *intermediate-high* (both ↑TnT & RV dysfunction on TTE or CT) & *int.-low* (⊕ biomarkers or TTE or neither w/ PESI III-V)
		No right heart strain or hypotension
		• Normal biomarkers
		• Low risk per PESI & sPESI

MANAGEMENT OF VTE (CHEST Guidelines for VTE: Chest 2016;149:315; ESC for PE: EHJ 2020;41:543)

Proximal DVT (popliteal, femoral, iliac vv.)	**Distal DVT** (calf: ant./post. tibial, peroneal vv.)
Anticoagulate (unless contraindications), regardless of symptoms Agent: **DOAC** > VKA > LMWH; if malig.: **DOAC** or **LMWH** > VKA *(*For dosing & more info on choosing agent see* Hematology *section)* Duration: at least 3 months for all. Extend >3mo. if: • 1st or 2nd **unprovoked** prox. DVT & **low/mod. bleeding risk.** If high bleeding risk (*see below*), stop at 3mo. Unprovoked have ↑ recurrence rate (10% <1yr off AC, 5% each subsequent yr). ○ If stop AC after 1st VTE, D-dimer at 1mo. may be useful in deciding to resume, esp. in ♀ (NEJM 2006;355:1780, Blood 2014;124:196, Annals 2015;162:27) ○ If stop AC, low-dose ASA rec'd if no contraind. (may ↓ recurrence: NEJM 2012;367:1979 & 366:1959, Circ 2014;130:1062) • **Cancer-associated** If contraindications to AC (active bleeding, recent/planned high bleeding-risk procedure, major trauma, acute ICH) → **IVC filter**	**Serial imaging vs. anticoagulation** Serial imaging: if asx, low risk for extension, or high risk for bleeding • **Repeat U/S** at 1-2wks (1/3 will extend; ↓ risk in muscular veins: soleal, gastrocnemius) Anticoagulate if: (see ← for choice/duration) • **Severe symptoms** • **Risk factors for extension**: (1) ⊕ D-dimer, (2) extensive (>5cm, mult. veins, >7mm in diam.), (3) close to prox. veins, (4) no reversible provoking factor, (5) active CA, (6) h/o VTE, (7) inpatient • On serial imaging, **extends** into proximal veins. AC also suggested if extends but remains in distal vein.
UE DVT (NEJM 2011;364:861): 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), though no data.	
Bleeding risk: low = 0 RFs (1.6%/3mo; 0.8%/yr after 3mo.); mod. = 1 (3.2%/3mo; 1.6%/yr); high = ≥2 (12.8%/3mo; ≥6.5%/yr) RFs: age >65-75, previous bleeding, CA, renal failure, liver failure, thrombocytopenia, previous CVA, DM, anemia, anti-platelet tx, poor AC control, ↓ functional capacity, recent surgery, frequent falls, EtOH use disorder, NSAID use	
Testing in unprovoked VTE: age-appropriate cancer screening (found in 1/20 within 1yr; Annals 2017;167:410) & sx-directed studies only. Do **not** perform thrombophilia testing at time of VTE event or while on AC (affects testing results & $$$). Can test after treatment for acute event if will Δ mgmt. (which it rarely does). See *Hematology: Coagulation Disorders*.	

High Risk PE (Massive)	**Intermediate Risk PE** (Submassive)	**Low Risk PE**
PERT consult (x47378)		
Resuscitation: • Limit IVF: can try 500cc if CVP low, but ↑RV distention → ↓CO • Vasopressors: NE generally preferred • O2: HFNC pref. for severe hypoxemia. *Mech vent. very high risk*: hypoTN from induction & pos. pressure → ↓venous return → ↓RV CO & ↑RV failure • Circulatory collapse/arrest: VA ECMO **Anticoagulation**: UFH (w/ bolus) **Thrombolysis**: systemic unless contraind. **Embolectomy**: if thrombolysis contraind./fails; can be catheter-directed; surgery if all options contraind./fail or if clot in transit in RA/RV, PFO	**Anticoagulation**: LMWH preferred > UFH (faster time to therapeutic range) unless impending hemodynamic collapse / thrombolysis (or CrCl <30 or severe obesity) **Thrombolytic therapy in select pts**: (AHA: Circ 2011;123:1788) • No strict guidelines, but may include: developing circulatory failure (episode of hypoTN, persistent HR > SBP) or respiratory failure, mod/severe RV dysfunction/injury on TTE (RV hypokinesis, RVSP >40) w/ major ↑ in hs-TnT/NT-proBNP (>900) • *May be observed x24hrs on AC first pending trajectory* • Routine tPA in int. risk PE → ↓ hemodynamic decomp. but no clear long-term Δ in mortality or CTEPH; ↑ major bleeding & hemorrhagic CVA (PEITHO NEJM 2014;370:1402, JACC 2017;69:1536)	**Anticoagulation**: See above (DVT) and *Hematology* section **Disposition**: if no other reasons for hospitaliz., & adequate support, can d/c home
Thrombolysis: → ↓ mortality (Am J Card 2019;123:684, JAMA 2014;311:2414) Systemic: alteplase 100mg/2hr (bolus 50mg/2min if cardiac arrest). Hold AC during infusion (but do not delay if got LMWH). No convincing evidence to support *routine* use of lower dose tPA (MOPETT Am J Card 2013;111:273) • *Absolute contraindications*: intracranial neoplasm, recent CNS surgery/trauma (<2-3mo.), h/o ICH, active bleeding, non-hemorrhagic stroke <3mo. Catheter-directed: may be preferred if high-risk for bleeding, failed systemic thrombolysis, or otherwise selected patients; can couple w/ U/S-assisted thrombolysis (EKOS) or suction thrombectomy. Studies show ↓in RVSP, ↓RV/LV ratio but no data for mortality benefit (ULTIMA Circ 2014;129:479, SEATTLE II JACC Card Interv 2015;8:1382, Am J Med 2019;132:240, Am J Card 2019;124:1470)		
Anticoagulation: if started on LMWH/UFH, transition to DOAC after has stabilized for 2-3d (unless other agent indicated).		

PERT (x47378): call if large PE w/ abnormal VS (tachycardia, hypotension), evidence of RH strain (TTE, EKG, biomarkers), central/saddle PE. Order (if not already obtained): CBC w/ diff, BMP, LFTs, lactate, D-dimer, ABG, PT/INR, PTT, T&S, NT-proBNP, hs-troponin, EKG, CT-PE protocol, LENIs, TTE.

Pulmonary Hypertension = mean PA pressure (mPAP) ≥20
mPAP = (PVR x CO) + PCWP ; PVR = (mPAP - PCWP) / CO
∴ ↑ in PVR or PCWP can → pulmonary hypertension (PH)
- *Pre-capillary PH*: ↑ PVR ≥3, nml PCWP ≤15, ↑ DPG & TPG
- *Post-capillary PH*: nml PVR <3, ↑ PCWP >15, nml DPG &TDPG
- *Mixed PH*: ↑ PVR ≥3, ↑ PCWP >15, ↑ DPG & TPG

Transpulmonary gradient (TPG) = mPAP – PCWP; nml <12
Diastolic pulm. gradient (DPG) = PA diastolic (PAd) – PCWP; nml <7

Clinical Manifestations
Sx: nonspecific; 2yr 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 (2/2 progressive RV failure)
- Rare: cough, hemoptysis, hoarseness (Ortner's syndrome)

Exam: loud P2; ↑ JVP, edema, ascites, TR murmur, R-sided gallop, parasternal heave (LSB), PA tap (L 2nd ICS), edema, hepatomegaly, ascites
Imaging: CXR w/ enlarged PA, RA, RV (↓retrosternal space on lat.), pruning of peripheral vessels; CT w/ PA/Ao diameter ≥1
EKG: normal vs. signs of RV hypertrophy/strain: RAD, R/S >1 in V1, RBBB, p pulmonale in II (RAE)
TTE: ↑ tricuspid regurg. jet velocity (≥2.9 = int. prob for PH), RVSP (ePASP) >36; IVS flattening, RVH → RV dilation, RV hypokinesis, RA dilation, TR, PR, ↑PA size, ↑IVC w/ ↓ collapse

Diagnosis (ERJ 2019;53:1801904)
- RHC: gold-standard for diagnosis (though may not be needed in all circumstances). Can also do iNO vasoreactivity testing (guides treatment in idiopathic PAH).
- Evaluation for etiology:
  - TTE: eval for left HF (& whether severity explains PH)
  - PFTs, HR-CT, 6MWT +/- PSG, CPET: chronic lung dz, OSA
  - 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)

WHO Classification (6th World Symposium on PH: ERJ 2019;53:1801913; JACC 2013;62:D34)

Pre-Capillary			Post-Capillary
Group 1: pulmonary arterial hypertension (PAH)	**Group 3: lung disease and/or hypoxemia**	**Group 4: pulmonary artery obstructions**	**Group 2: left heart disease**
- **Idiopathic** (♀>♂) - **Heritable** (e.g. *BMPR2*) - **Drug/toxin-induced**: cocaine, anorexigens, dasatanib, amphetamines - Associated with: **CTD**, **HIV**, **portal HTN**, congenital heart disease, schisto. - PAH long-term responders to CCBs - PVOD and/or pulmonary capillary hemangiomatosis - Persistent PH of newborn	Obstructive: **COPD** Restrictive: **ILD** Mixed obstructive/restrictive Chronic hypoxia w/o lung disease: **OSA** Developmental lung disorders (ERJ 2019;53:1801914)	**Chronic thromboembolic disease** (ERJ 2019;53:1801915) *NB*: only ~33-75% had known prior VTE. Occurs after ~4% of PEs (NEJM 2004;350:2257) Other PA obstructions: malignancy, arteritis without CTD, parasites, congenital PA stenosis	**HFpEF** **HFrEF** **Valvular disease** Congenital/acquired conditions (ERJ 2019;53:1801897)
Group 5: Misc.: chronic hemolytic anemia (e.g. sickle cell), myeloproliferative d/o, sarcoid, metabolic d/o, complex congenital HD			

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

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

Mechanism	Medication	Route	Indication	Side effects
Endothelin receptor antagonists	Bosentan, ambrisentan, macitentan	PO	Group 1: ↓sx, ↑ 6MWT (NEJM 2002;346:896, Circ 2008;117:3010) Macitentan: ↓morbid/mortality (NEJM 2013;369:809)	Anemia, PNA, edema, hepatotox. Macitentan: also flu, HA, UTI, bronchitis
(NO)-cGMP enhancers	PDE5 inhibitors: sildenafil, tadalafil	PO	Group 1: ↓sx, ↑ 6MWT (NEJM 2005;353:2148, NEJM 2009;361:1864)	Erythema, flushing, indigestion, HA, insomnia, epistaxis, rhinitis, retinal hemorrhage
	sGC stimulator: riociguat	PO	Group 1 & Group 4: ↓sx, ↑6MWT (NEJM 2013;369:330)	↓BP, n/v/d/constipation, GERD, anemia, dizziness, HA, hemorrhage
Prostacylin pathway agonists	Analogues: epoprostenol, treprostinil, iloprost	IV or inh.; treprostinil also SC	Group 1: ↑6MWT, ↑QOL; reserved for sickest patients (NEJM 1996;334:296) Group 5: some etiologies	CP, ↓BP, ↑HR, flushing, abd pain, anorexia, n/v/d, jaw pain, MSK pain, dizziness, HA, hemorrhage
	Receptor agonist: selexipag	PO	Group 1: ↓ hospitalization; no Δ mortality (NEJM 2015;373:2522)	Diarrhea, nausea, jaw pain, HA, anemia
CCB	Nifedipine, diltiazem	PO	Positive vasoreactivity test (↓mPAP by ≥10 mmHg & to ≤ 40 mmHg w/o ↓CO). ⦸ RV failure.	↓BP, LE edema

- Per CHEST guidelines: If WHO FC II or FC III w/o rapid progression, start w/ ambrisentan/tadalafil combo (pref. over monotx w/ ERA, PDE5i, or riociguat; NEJM 2015;373:834). If FC III w/ rapid progression or FC IV, start w/ IV prostanoid. If unacceptable clinical status, add 2nd/3rd class (Chest 2019;156:187).

Indications for Intubation:

- **Failure of NIPPV**: no clinical improvement
- **Cannot ventilate**: $PaCO_2$ >60 with severe acidemia (COPD or other obstruction, sedation, neuromuscular disease, resp. muscle fatigue, trauma)
- **Cannot oxygenate**: worsening P:F ratio (PNA, pulmonary edema, ARDS, PE)
- **Airway protection/instability**: unconsciousness, AMS (GCS <8), shock, facial/head trauma, nausea/vomiting/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, last 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)

General Principles (NEJM 2001;344:1986; Respir Care 2017;62:629)
Five main variables: (1) RR, (2) tidal volume (V_T), (3) FiO_2, (4) positive end-expiratory pressure, (PEEP) (5) mode of ventilation

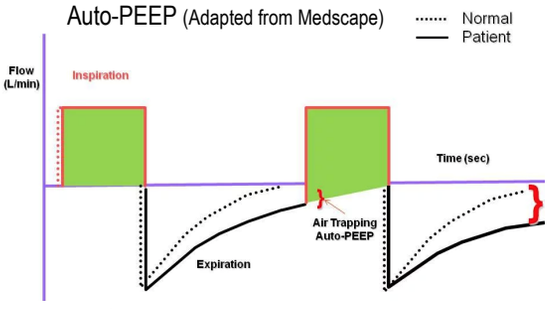
- **Ventilation** (determines CO_2): ↓ **$PaCO_2$ by increasing RR and/or V_T** (↑ minute ventilation where MV = RR x V_T)
  1) RR: often adjust this first; avoid >RR 30-35 due to risk of inadequate expiratory time → air trapping/auto-PEEP
  2) V_T (often set at ≤ 6cc/kg IBW): when ↑, ensure P_{plat} ≤30 and driving pressure ($\Delta P = P_{plat} - PEEP$) ≤15 to minimize lung injury
- **Oxygenation**: ↑ **PaO_2 by increasing PEEP and/or FiO2**
  3) FiO_2: avoid FiO_2 >0.6 for prolonged periods due to oxygen toxicity
  4) PEEP: ↑ alveolar recruitment, improves V/Q matching; if ↑PEEP → ↑PaO2/FiO2 (P/F) & Pplat stable, suggests recruitable lung; if ↑PEEP → no Δ/↓ P/F or ↑PaCO2, suggests not recruitable & instead causing ↑shunt or dead space (should ↓PEEP)

Ventilator Modes (Respir Care 2007;52:301)

MODE	SET *Indep. variables*	MEASURED *Dep. variables*	PROS/CONS	HOW TO READ
AC/VC *Assist Control/Volume Control: delivers a breath until set tidal volume is reached*	**V_T** PEEP RR FiO_2 I:E or flow	PIP & P_{plat} I:E or flow	☺: ↑ control over ventilation (fixed V_T prevents barotrauma or atelectrauma) ☹: fixed inspiratory flow regardless of effort, ↑ pt-vent dyssynchrony	"Pt is on Volume Control w/ V_T of 400 (4cc/kg), set at a rate of 16 breaths/min, PEEP of 8, and FiO_2 0.6; they are breathing at the set rate of 16 (or over) with V_T ~400 for MV of 6.4L"
AC/PC *Assist Control/Pressure Control: delivers a breath until set pressure is reached*	**P_{insp}** PEEP RR FiO_2 I:E	Flow V_T	☺: variable flow (& variable V_T) during inspiration to satisfy pt demand, ↓ dyssynchrony ☹: can cause volutrauma as compliance or pt effort changes	"Pt is on Pressure Control of 18 (P_{insp}) over 5 (PEEP), set at a rate of 16 breaths/min, and FiO_2 0.3; they are breathing V_T ~400, at the set rate of 16 (or over) for a MV of 6.4L."
PSV *Pressure Support Ventilation: delivers a set pressure triggered by patient's spontaneous breathing*	P_{insp} PEEP FiO_2 RR (backup)	I:E Flow V_T RR	☺: better tolerated, less sedation required, used as trial setting prior to extubation (i.e. SBT on 0/0 or 5/5) ☹: less control over respiratory parameters, volutrauma possible, no fixed RR (only backup)	"Pt is on Pressure Support of 10 (P_{insp}) over 5 (PEEP) with an FiO_2 0.3; they are breathing V_T of ~500 at 20 breaths/min. for a MV of 10L.

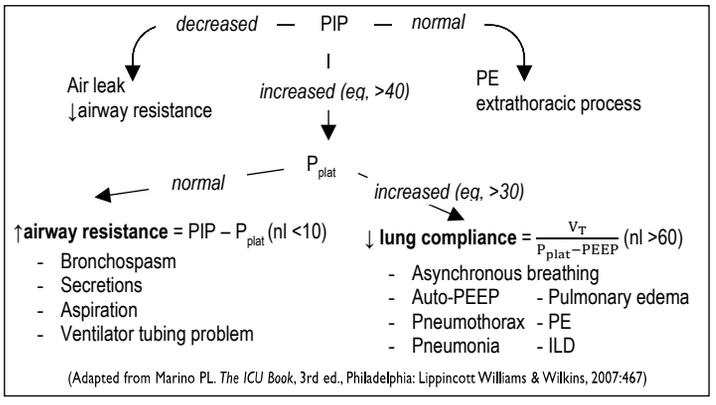
Ventilator Complications:

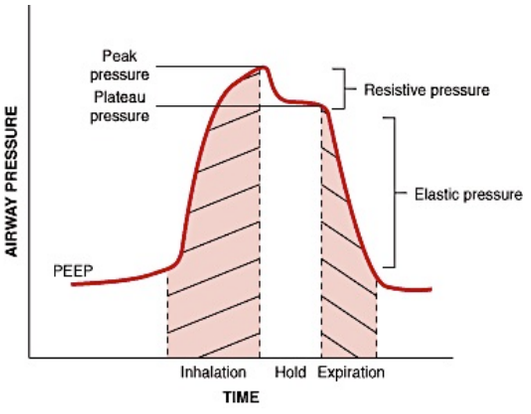
- **Dynamic hyperinflation (auto-PEEP)**: due to incomplete alveolar emptying during expiration; measured during expiratory hold
  - Diagnosis: end-expiratory flow >0 (residual pressure); see graphic
  - Risk factors: vent strategy causing hyperinflation (high RR, ↑ I:E ratio) or obstructive disease (asthma, COPD, CF)
  - Consequences: adverse hemodynamic effects (hypotension due to ↓ venous return), alveolar over-distention (→volu-/barotrauma); ↑ effort for pt to trigger ventilator-assisted breath
  - Treatment: allow longer exhalation (↓ I:E ratio, ↓RR), set exogenous PEEP to 2/3 auto-PEEP, bronchodilators for obstruction
  - If severe hemodynamic or resp. compromise, transiently **disconnect pt from ventilator** and manually bag ventilate to allow deflation



- **Ventilator-induced lung injury (VILI)**: alveolar injury →↑alveolar permeability, interstitial & alveolar edema, alveolar hemorrhage, hyaline membranes, & alveolar collapse (similar to ARDS) (NEJM 2013;369:2126). Avoid w/ lung protective ventilation (see *ARDS*).
  - **Volutrauma**: over-distension of alveoli due to high V_T; or, if there is heterogenous consolidation or atelectasis, a disproportionate volume from each breath is delivered to open alveoli
  - **Atelectrauma**: shear forces from cyclic alveolar recruitment and de-recruitment injure adjacent alveoli/airways
  - **Biotrauma**: cytokine release from lung epithelium → multi-organ dysfunction
  - **Oxytrauma**: elevated FiO2 → free radical production and lung injury
  - **Barotrauma**: injury from high Pplat (highest risk >35) → PTX, subcutaneous emphysema, pneumomediastinum
- Other complications: ventilator-associated pneumonia, laryngeal edema, tracheal stenosis

- ↑ **Peak inspiratory pressure (PIP)** = airway resistance + $P_{plat,}$; normal PIP <35cm H_2O; can be elevated due to increased airway **resistance** OR decreased airway **compliance** (higher P_{plat}). See flowchart for differential.
  - Management: consider steroids, nebulizers, or bronchoscopy to clear secretions/mucus plugs





Monitoring Mechanics

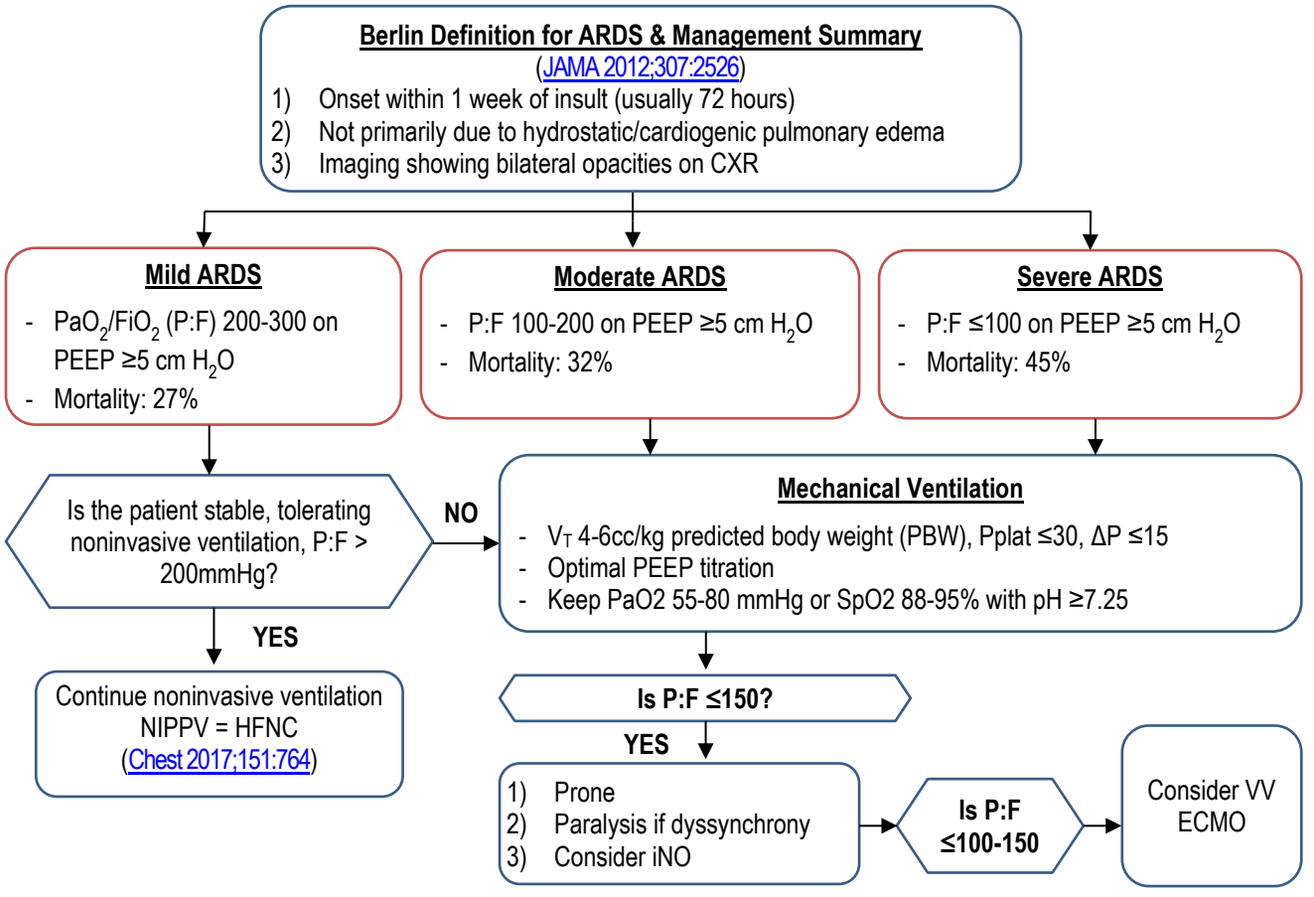
- Target values: V_T ≤6cc/kg IBW, P_{plat} ≤30; driving pressure (ΔP = Pplat-PEEP) ≤15; compliance >50; resistance <10
  - Non-ARDS: V_T 10cc/kg vs 4cc/kg → no difference in mortality or vent-free days (PReVENT JAMA 2018;320:1872)
- Ventilator maneuvers for monitoring mechanics:
  - *Expiratory hold*: end expiratory pause; measures auto-PEEP
  - *Inspiratory hold*: end inspiratory pause; measures P_{plat} and compliance
    - At end-inspiration, resistive pressure is 0 and PIP = P_{plat}

Algorithm for Respiratory Plan on MICU Rounds (REMIX)

R	Reason for intubation	ARDS, PNA, COPD, pulmonary edema, aspiration, hypoventilation, altered mental status, etc.
E	Exchange (gas exchange)	Recent ABG; how to improve PaO_2 (i.e. diuresis, pulmonary vasodilators) and/or PCO_2 (i.e. ↑RR)
M	Mechanics	Resistance (PIP) and compliance (Pplat, ΔP); chest wall/respiratory muscle strength, cuff leak
I	ID/infection (abx)	Sputum Cx data, abx day #, source control, need for bronchoscopy; assess for VAP/tracheobronchitis
X	eXtubation barriers	Daily SAT/SBT, secretion clearance, mental status, planned procedures
(S)	Sedation	Current sedation, whether changes needed (e.g. start Precedex as bridge peri-extubation)

Liberation & Extubation (ATS/CHEST: AJRCCM 2017;195:115 & Chest 2001;120:375S; NEJM 2012;367:2233; ERJ 2007;29:1033)

- **Requirements for extubation**: (1) adequately treated underlying disease process, (2) adequate oxygenation and ventilation: PaO_2/FiO_2 ≥150-200, PEEP ≤5-8, FiO_2 ≤0.4-0.5, pH >7.25, (2) ability to cough, (3) able to manage secretions, (4) hemodynamic stability. Ideally sufficient mental status (alert, following commands), but as long as protecting airway, AMS does not preclude extubation.
  - **Rapid Shallow Breathing Index (RSBI) = RR/V_T**; RSBI >105 predicts extubation failure (Sn>Sp) (NEJM 1991;324:1445)
- **Liberation protocol**:
  - Daily **Spontaneous Awakening Trial (SAT)** + **Spontaneous Breathing Trial (SBT)**
    - **SAT**: ↓ ventilator time, ICU LOS, and mortality if paired with SBT (NEJM 2000;342:1471, Lancet 2008;371:126)
    - **SBT**: ~30min (up to 2hrs) daily trials with little/no support (PEEP ≤5 on PSV; generally 0) = ↓ vent time (NEJM 1996;335:1864; NEJM 1995;332:345)
      - Ways to fail SBT: hypoxemia (SaO_2 <90%, PaO_2<60), hypercarbia ($PaCO_2$ ↑ by >10), inadequate V_T, respiratory distress (↑HR, ↑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 → ↓ post-extubation respiratory failure (Lancet 2009;374:1082, JAMA 2016;316:1565). HFNC w/ intermittent NIV post-extubation → ↓ reintubation compared to HFNC alone (JAMA 2019;322:1465).
  - Check for **absence of cuff leak** before extubation (concerning for laryngeal edema) → consider methylpred 20mg IV q4h 12hrs prior to extubation or IV methylpred 40mg x1 4hrs prior or IV dexamethasone 5mg q6h (Eur J Anaesthesiol 2010;27:534)
  - If **agitation** is limiting ability to extubate, consider dexmedetomidine → may improve odds of extubation (JAMA 2009;301:489)
- **Post-extubation respiratory failure**: usually 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 if still intubated for 14 days
  - **Early tracheostomy** (7 days) if expect intubation >14 days → ↑comfort, allows ↓ sedation, ↓ risk of tracheal stenosis, ↓ vent-free and ↓ ICU days, though no change in VAP rate (JAMA 2010;303:1483, Crit Care 2015;19:424, Br J Anaesth 2015;114:396)



Management Principles in ARDS (ATS/ESICM/SCCM Guidelines: AJRCCM 2017;195:1253)		
Treat underlying etiology: Direct lung injury: pneumonia, aspiration, inhalational injury, near drowning, pulmonary contusion; Indirect lung injury: sepsis, trauma, pancreatitis, drugs, burns, cardiopulm bypass/pump, transfusion-related acute lung injury (TRALI) ⇒ Common pathway: diffuse, immune-mediated lung injury causing pulmonary capillary and alveolar epithelial damage leading to increased vascular permeability, impaired gas exchange, and decreased lung compliance (NEJM 2017;377:562)		
Strategy (in order of decreasing level of evidence)		**Effects**
Low Tidal Volume Ventilation (LTVV) (NEJM 2007;357:1113)	• **Maintain oxygenation while preventing ventilator-induced lung injury (VILI)** • VT 4-6 cc/kg PBW w/ goal Pplat ≤30, driving pressure ≤15 (ΔP=Pplat-PEEP) ○ May allow ↑Pplat if ascites, obesity, etc. as may not accurately reflect transpulmonary pressure (see "esophageal balloon catheter" on next page) • Permissive hypercapnia: pH goal ≥7.25 allows for lower VT to minimize VILI ○ *Contraind*: ↑ICP, RV fail./PH (↑pulm. vasoconst.), TCA/ASA o/d, pregnant	↓ **Mortality** (31% vs 39.8%) and ↑ vent-free days vs. "traditional" VT (12 cc/kg, Pplat <50) (NEJM 2000;342:1301)
Prone Positioning	• **↓V/Q mismatch** by ↓compressive atelectasis from heart & diaphragm → more homogenous vent. →↑ alveolar recruit. → ↓ regional volutrauma & ↑compliance • *Contraind*.: hemodynamic instability, ↑ICP, inability to turn neck (fixed/unstable C-spine), 2/3rd tri. pregnancy, recent sternotomy	↓ **Mortality** (28d & 90d) in mod/severe ARDS (PROSEVA NEJM 2013;368:2159)
Conservative Fluid Management	• **Minimize pulmonary edema**: "dry lungs are happy lungs" • Avoid ⊕ fluid balance after reversal of shock • FACTT Trial: CVP<4 (conservative) vs. CVP ≤10-14 (liberal) (NEJM 2006;354:2564)	FACTT: ↓ICU LOS & vent-free days, **no Δ in 60d mortality** or AKI
Positive End-Expiratory Pressure (PEEP) (NEJM 2004;351:327; AJRCCM 2010;181:578)	• **Maximize recruitment, minimize trauma from cyclic atelectasis** • Higher PEEP distributes VT over more alveoli → less over-distention → improves oxygenation (via ↓V/Q mismatch and ↓ shunt fraction) & compliance • CV effects of PEEP: ↓preload, ↑RV afterload, ↓LV afterload, ↑CO but variable • Harms of PEEP: barotrauma, ↑ dead space, hemodynamic effects • See next page for more on PEEP optimization	**No clear mortality benefit.** ? benefit for ↑PEEP if P:F ≤200 (JAMA 2010;303: 865)
Neuromuscular Blockade	• **Maximize oxygenation by ↓vent dyssynchrony and chest wall compliance** • Routine early paralysis (cisatracurium) for moderate-severe ARDS (P:F <150) w/o survival benefit (ROSE NEJM 2019;380:1997); previous trial had shown possible mortality benefit (ACURASYS NEJM 2010;363:1107) • Can use as bolus/infusion to maintain vent synchrony in mod./severe ARDS	ROSE: **no Δ in 90d mortality,** ↑ CV adverse events vs. non-paralyzed

Summary of Rescue Therapies for Hypoxemia (6 P's of refractory hypoxemia):

- Pee: consider diuresis to reduce pulmonary edema (see "conservative fluid management" above)
- PEEP: optimize PEEP (see "PEEP" below)
- Prone positioning: should be implemented *early* (12-24hrs) if P:F <150 (or 200) despite optimal PEEP titration
  - Maintain prone ≥16 hours. If supinate and P:F remains >150 (or 200) and ΔP ≤15 after 2hours, can remain supine.
- Pulmonary vasodilators: start with iNO trial (40ppm; up to 80ppm) and if effective, use inhaled Epoprostenol.
  - Should see at least 20% ↑ in PaO2, otherwise do not continue therapy due to cost and risks, including hypotension
  - ↓ V/Q mismatch by selectively dilating vessels that perfuse well-ventilated lung; also ↓ PVR and ↓ RV afterload
  - No mortality benefit and ↑ risk of renal failure, but may improve oxygenation in first 24hrs and total lung capacity at 6 months (Cochrane Rev 2016, Crit Care 2012;16:R36). NB: risk of methemoglobinemia w/ iNO.
- Paralysis: can be used to maintain vent synchrony (see "neuromuscular blockade" above). Start w/ intermittent boluses & transition to infusion if persistent dyssynchrony >3 boluses/2hrs (cisatracurium/Nimbex 0.1-0.2 mg/kg q30min PRN → 0-5mg/kg/min; rocuronium 0.6-1.2**mg**/kg q30-60min PRN → 0-20**mcg**/kg/min, start at 8-12mcg/kg/min)
- Perfusion (ECMO): consider for severe, refractory hypoxemia; for details see *ECMO* section.
  - Mortality benefit, but unclear if due to ECMO vs. transfer to specialized center (CESAR Lancet 2009;374:135, JAMA 2011;306:1659)
  - Unclear if mortality benefit to upfront ECMO vs. as rescue therapy (EOLIA NEJM 2018;378:1965)
  - Call for evaluation by the **ECMO Team** (typically the HCICU/Blake 8 attending) - **p24252, 857-310-0335**

Lung Protective Ventilation: ARDSNet Ventilation

- **Initial ventilator set-up**: V_T = 6 cc/kg PBW, RR to approximate baseline MV (RR <35), moderate PEEP (8-10)
- **Adjustments**: adjust V_T & RR to achieve **Pplat ≤30** cm H_2O, **driving pressure ≤15** (ΔP=Pplat-PEEP), and **pH 7.25-7.45**
  - Oxygenation: goal **PaO2 55-80 mmHg** or **SaO2 88-94%**
    - SpO2 target <94% a/w ↓ mortality (JAMA 2016;316:1583); hyperoxia→ ↑ mortality (Crit Care 2014;18:711)
    - If persistent hypoxemia requiring high FiO2 (~0.6), should optimize PEEP (see below)
  - Mechanics: goal plateau pressure (**Pplat**) **≤30** (obtain with inspiratory pause); goal **ΔP ≤15**
    - If Pplat >30 and/or ΔP>15: ↓ V_T by 1 cc/kg PBW (minimum V_T 4 cc/kg PBW); limit on ability to ↓ is ↓MV→↑pCO2/pH
    - If Pplat <25 and V_T <6cc/kg PBW: can ↑ V_T by 1 cc/kg until Pplat >25 or V_T 6 cc/kg PBW
  - pH: **7.25-7.45** ("permissive hypercapnea" unless contraindicated – see previous page)
    - pH >7.45: ↓ RR
    - pH <7.25: ↑ RR (up to 35/min) until pH ≥7.25 or PaCO2 <25; watch for auto-PEEP development at high RR
    - pH <7.15: set RR = 35/min; ↑ V_T by 1 cc/kg until pH >7.15 (may exceed Pplat goal)

Optimal PEEP for ARDS

- **ARDSNet FiO2/PEEP scale**: http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf
  - If P:F <150 on PEEP 5 cm H_2O, assess ability to recruit lung by increasing PEEP from 5 to 15 cm H_2O
  - If improvement, use ARDSNet high PEEP/low FiO2 scale; if no improvement, use low PEEP/high FiO_2 scale
- **Best PEEP trial**: goal is to select the PEEP corresponding to best global recruitment with lowest risk for over-distention based upon **respiratory system compliance (C_{RS} = V_T / [Pplat - PEEP])**
  - Keep V_T constant and use **decremental titration of PEEP**; choose best PEEP based on balance of highest compliance, *lowest driving pressure*, acceptable oxygenation, and stable hemodynamics
  - Consider performing if persistent hypoxemia (FiO2 ≥0.6) w/ P/F <150
- **Driving pressure**: ΔP = Pplat - PEEP (goal: ≤15)
  - Represents the relationship between tidal volume and lung compliance ($\Delta P = V_T/C_{RS}$)
  - Lower ΔP associated with ↑ **survival** independent of other variables (V_T, PEEP, Pplat) (NEJM 2015;372:747)
- **Recruitment maneuvers**:
  - Used to open collapsed alveoli to ↓ tidal opening and closing (**atelectrauma**) and ↑ participation in gas exchange
  - Begin with **high PEEP** to open up alveoli, then decremental PEEP titration to optimize mechanics (JAMA 2008;299:637)
  - Outcomes are mixed w/ both ↑ (JAMA 2017;318:1335) and ↓ mortality (Cochrane Rev 2016); avoid massive PIPs (>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)
  - No effect on mortality, ventilator free days, or ICU days, despite improved oxygen and lung compliance, but ↓ risk of needing advanced rescue therapy (JAMA 2019;321:846)
  - **Consider in cases of high intra-abdominal pressure (e.g., obesity, ascites, abdominal compartment syndrome)**

Controversial Management Strategies

- Steroids: conflicting data; generally not used. Possible benefit in early mod/severe ARDS but ↑ mortality if persistent ARDS ≥14d (CHEST 2007; 131:954; NEJM 2006;354:1671). Avoided in viral pneumonia (influenza, COVID-19).
- High frequency oscillatory ventilation: no vs. ↑ mortality w/ HFOV in ARDS (OSCILLATE NEJM 2013;368:795; OSCAR NEJM 2013;368:806)

Pulmonary & Critical Care — ECMO

ECMO: MGH ECMO App; p24252, # 857-310-0335

Types of ECMO: (JACC 2014;63:2769)

1. **Venoarterial** (*VA*, **replaces heart and lungs**): treats cardiogenic shock and hypoxemic resp. failure
   - Venous blood is removed, oxygenated, CO_2 extracted, and returned to arterial system
   - Venous cannula is placed in common femoral vein (drainage from IVC or RA); arterial cannula is placed in R femoral artery
2. **Venovenous** (*VV*, **replaces lungs**): treats hypoxemic respiratory failure; relies on native hemodynamic (cardiac) support
   - Venous blood is removed, oxygenated, CO_2 extracted, and returned to venous system
   - Either two venous cannulae (common fem. vein and SVC) or a single bicaval device via R IJ (Avalon) that allows for early mobility

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

- Acute resp failure (VV): PaO_2/FIO_2 <100-150 despite optimization, unable to achieve safe inflation pressures (Pplat <30), uncomp. CO2 retention (>80) with inability to mechanically ventilate
- Cardiogenic shock (VA): refractory low cardiac output (CI<2L/min/m^2) and hypotension (SBP<90mmHg) despite adequate volume, inotropes, and intra-aortic balloon pump
- Reversible etiology (ARDS, massive PE, cardiac arrest)
- Bridge to definitive therapy (transplantation, VAD, recovery)
- Less invasive strategies have failed:
  - VV: FiO_2 1.0, paralysis, iNO/Veletri, proning, PEEP, diuresis
  - VA: volume, pressors, inotropes, IABP, mechanical support

Contraindications

- Absolute (VA or VV): non-recoverable multi-organ failure/neurological disease; unwitnessed arrest or CPR > 30 minutes w/o ROSC; active severe bleeding; contraindication to AC, recent NSGY procedure/active intracranial bleed (<10d)
- Absolute VA: BMI>40; Ao dissection; severe AI; ESLD/ESRD
- Absolute VV: severe right or left HF
- Relative: age>70; multi-organ failure; severe pHTN; unknwn neuro status; GVHD; active malignancy; significant immunosuppression; ventilated >7d (ECMO most effective if started within 7d); DIC; survival <30% based on RESP and SAVE Scores (respscore.com / save-score.com)

ECMO Variables

- **Sweep**: increasing sweep lowers P_aCO_2 in blood returning to pt; titration of sweep affects CO_2 elimination >> oxygenation
- **FiO_2**: (circuit oxygen) usually set at 1.0
  - Note: VV circuit oxygenates fraction of native CO; if native CO increases, more blood naturally flows via lungs → may allow FiO_2 settings to be decreased *if* the lungs are functioning
- **RPM**: RPM is predominant determinant of blood flow (2-5 L/min; also affected by cannula size and native CO)
- **Hgb goal**: >7.5g/dL
- **Clotting**: PTT 60-80 (q2h, check with team on goal); Plt >75K; Fibrinogen >150 (may change if bleeding). Use UFH for anticoagulation and check AT-III and anti-Xa.

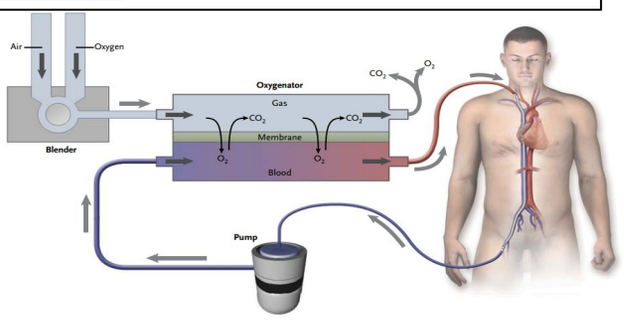


Diagram of VV ECMO (NEJM 2011;365:1905)

Complications: (Heart Lung Circ 2014;23:10)

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

Troubleshooting the Circuit:

- **Chatter**: "shaking" sound caused by high (-) pressure in the tubing; usually due to **hypovolemia**, treat w/ volume (**5% albumin**)
- **Poor oxygenation** (as measured on **patient ABG**):
  a) Recirculation: blood recirculates from the outflow (return) catheter back into the inflow (drainage) catheter, bypassing body; usually due to catheter malposition → **discordant circuit O2** and **patient O2** content (treatment: reposition cannula, ↓ RPM)
  b) Machine malfunction: hypoxemia on **post-membrane ABG** (treatment: replace membrane)
  c) Shunt: occurs if native CO > ECMO CO (large fraction of blood travels through diseased lungs rather than ECMO circuit and is poorly oxygenated) → hypoxemia on **patient ABG only** (treatment: ↑ RPM, reduce fever, reduce inotropes, +/- beta blockade)
- **Harlequin syndrome** (VA only): **hypoxia of upper extremities, heart, brain** – can occur only when femoral artery is cannulated. Cardiac recovery, but poor lung fx → native cardiac output (de-oxygenated) pushes against oxygenated ECMO blood in aortic arch leading to hypoxia of UE, brain, heart; treated by relocation of arterial cannula to R subclav or aorta (Heart Lung Ves 2015;7:320).

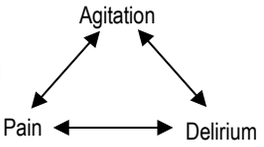
Outcomes:

- **Acute respiratory failure**: 2 major studies show ↓ mortality, though unclear if benefit from referral to ECMO center or ECMO itself
  - 75 matched pairs ARDS d/t H1N1; transfer to ECMO center ↓mort. (23% vs. 52%); 85% tx w/ ECMO (JAMA 2011;306:1659)
  - CESAR: RCT of 180 pts w/ severe ARDS randomized to referral to single ECMO center vs. conventional management. ECMO-referred group ↑ survival without disability at 6 months (63% vs. 47%) (Lancet 2009;374:135)
  - EOLIA: RCT of 249 with severe ARDS (P:F <80) to ECMO w/in 7d vs. conventional therapy; early ECMO showed more days free of renal failure (46 vs 21 days), fewer ischemic strokes (0% vs 5%), and no significant difference in 60d mortality (35% vs 46%) (NEJM 2018;378:1965) though stopped early d/t prelim results in favor of ECMO (NEJM 2018;378:2031)
- **Refractory cardiogenic shock**: 40-41% survive to discharge (all comers); ECMO implantation while under CPR was strongest predictor of death (CCM 2008;36:1404, ASAIO 2017;63:60)
- **ECPR**: ECMO as extension of CPR in pts with cardiac arrest – in-hospital cardiac arrest: improved survival (OR: 0.17) compared to conventional CPR (CCM 2011;39:1); out-of-hospital arrest: 22% with meaningful neurologic recovery (Resuscitation 2016;101:12); overall: 29% survive to discharge (ASAIO 2017;63:60). Consider calling ECMO team if 10 minutes w/o ROSC to discuss ECMO.

MGH ECMO App (download here): "Call MGH ECMO Consult", consult/transport info, ECMO guidelines

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

1. **Pain**: common, ↑ energy expenditure; analgesia alone adequate in some (Lancet 2010;375:475)
2. **Agitation**: target light sedation in intubated pts; no benefit to non-sedation approach (NEJM 2020;382:1103)
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: a/w ↑ vent-free days (21 vs. 24d over 28d study period), ↓ delirium (CCM 2014;42:1024)

A – Spontaneous awakening trial (SAT): daily interruptions of sedation → ↓ ICU LOS, vent days (NEJM 2000;342:1471), PTSD sx (AJRCCM 2003;168:1457)
B – Spontaneous breathing trial (SBT): for pts who pass SAT, assess for suitability of extubation (Lancet 2008;371:126)
C – Choice of sedation: see below
D – Delirium: assess CAM-ICU daily
E – Early mobility: ↓ pressure sores, ↑ functional status, ↓ vent days, ↓ delirium (Lancet 2009;373:1874; NEJM 2014;370:1626)

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

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

Opioids: primarily **analgesia**. **Side effects (SEs)**: resp. depression, tolerance, constipation (Rx w/ bowel reg), ileus, ↑ delirium w/ ↑ use

Agent	Notes	Clearance
Hydromorphone bolus 0.25-1mg q1hr, gtt 0.5-5mg/hr	↑ potency (compared to morphine)	May accumulate in **hepatic/renal failure** but least affected by end-organ dysfunction.
Fentanyl bolus 25-50mcg q30m, gtt 50-200 mcg/hr	t1/2 30-60m w/ bolus; ↑t1/2 with gtt (9-16h) can cause chest wall rigidity	Accumulates in adipose No renally excreted metabolites
Morphine bolus 2-4mg q1hr, gtt 2-30mg/hr	Inexpensive, generally well-tolerated but can cause pruritus, bradycardia, HoTN	Accumulates in **renal failure**

Non-benzodiazepine sedatives: primarily **anesthesia**, **amnesia**; do **NOT** provide analgesia

Agent	Notes	Clearance
Propofol 5-50mcg/kg/min (max of 83) *Mechanism unclear*	**1st line sedative**. Immediate onset/rapid awakening. ↓ ICP & seizures so also used in status epilepticus & EtOH w/d. Earlier extubation & ↓ mortality vs benzos (AJRCCM 2014;189:1383) **SEs**: HoTN, bradycardia, hypertriglyceridemia → pancreatitis (follow TGs), green urine, **propofol infusion syndrome (PRIS)** (>48 hrs): acidosis, bradycardia, renal/liver failure, rhabdo, HLD, HSM	Metabolism unaltered by renal/liver failure Accumulates in adipose
Dexmedetomidine (Precedex) 0.2-1.5mcg/kg/hr *Central α2 agonist*	Sympatholytic w/ **anxiolysis w/o resp. depression** or amnesia. No sig. analgesia A/w ↓ delirium & earlier extubation (JAMA 2016;315:1460); ↓ vent days vs. midazolam (JAMA 2012;307:1151, JAMA 2009;301:489), ↓ delirium vs. lorazepam (JAMA 2007;298:2644) and propofol (Eur J Anaesthesiol 202;37:121); nightly admin. may prevent delirium (AJRCCM 2018;197:1147). No Δ in mortality (NEJM 2019;380:2506) **SEs: bradycardia, HoTN**, withdrawal syndrome (agitation, tachycardia); can cross-titrate to clonidine (Pharmacotherapy 2015;35:251)	Dose-reduce in **renal, liver failure**
Ketamine 5-30mcg/kg/min *NMDA antagonist*	"Dissociated amnesia" & analgesia w/o resp depression; some bronchodilator effects **SEs: sympathetic stimulation** (hypertension, bronchodilation, hypersalivation), **hallucinations**, delirium upon withdrawal, falsely ↑ BIS activity	Metabolites accumulate in **renal, liver failure**

Benzodiazepines: primarily **amnesia, anxiolysis**. **SEs**: resp depression, agitation, withdrawal/tolerance

*For sedation, propofol (& dexmedetomidine) preferred > BZDs due to ↓ mortality, ↓ time to light sedation & extubation, ↓ delirium

Agent	Notes	Clearance
Midazolam bolus 0.5-4mg q2h, gtt 2-8mg/hr	CYP3A4 metab → med interactions (fluconazole, azithro, flagyl, amio) Shorter t1/2 vs. lorazepam (~2-6h vs 14h), both w/ fast onset (2-5min) Only IV BZD not in propylene glycol	Accumulates in adipose Metabolites **accumulate in hepatic/renal failure**
Lorazepam bolus 1-2mg	Propylene glycol (solvent) toxicity w/ ↑↑ dose (lactic acid, HoTN, arrhythmia). Risk of oversedation due to delayed response/accumulation.	Preferred in renal, liver failure over midazolam *but* **caution in severe liver disease**

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

Agent	Notes	Clearance
Quetiapine 50mg q12 → max 400mg/d	May ↓ time to resolution of delirium w/ haldol (CCM 2010;38:419); ↓ NMS, EPS; also treats insomnia	No dosing adjustment in renal or hepatic failure
Haloperidol 2.5-5mg q6 PRN	Does not ↓ mortality, delirium incidence, duration of ICU stay or hospitalization, vent time (JAMA 2018;319:680; NEJM 2018;379:2506)	No dosing adjustment in renal or hepatic failure

Overview: (NEJM 2013;369:1726)

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

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

MAP = RAP + CO x SVR → SVR determined by vessel diameter/length and blood viscosity

(2/3) DBP + (1/3) SBP ; HR x SV → SV determined by preload, afterload, & contractility

Lactic Acidosis (NEJM 2014;371:2309)

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

Etiologies of Shock:

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

SHOCK → **↑CO** / **↓CO**

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

	Distributive (66%)	Hypovolemic (16%)	Cardiogenic (16%)	Obstructive (2%)
Pathophys.	↓ systemic vascular resistance & altered oxygen *extraction*	↓ cardiac output → inadequate oxygen *delivery*		
Examples	Sepsis, SIRS, anaphylaxis, adrenal insufficiency, liver failure, toxins/meds, neurogenic (NEJM 2013;369:840; NEJM 2001;345:588)	**Hemorrhagic** (GI, RP, abdomen, thigh), GI losses, 3rd spacing (pancreatitis) (NEJM 2018;378:370)	**MI, HF,** myocarditis, severe valve disease, **arrhythmias**	Extra-cardiac causes: **PE, tension PTX, tamponade**
Extremities	Warm and dry	Cold and dry	Cold and wet	Cold and dry
CVP/PCWP	⇩ / normal	⇩⇩	⇧⇧	⇧ (tamponade) / normal
CO or CVO2	⇧ / normal	⇩	⇩	⇩
SVR	⇩⇩	⇧	⇧	⇧
TTE Findings	Normal chamber size, normal/↑ contractility	Small chambers, normal/↑contractility	Large chambers, poor contractility	Tamponade: pericardial effusion PE/PTX: dilated RV
Basic Management	All causes: fluids, pressors Sepsis: source control, abx Adrenal insuff: steroids (hydrocort) Anaphylaxis: epi 0.3mg IM, H1RA. H2RA, solumedrol, albuterol	**Ensure adequate access!** Most cases: fluids Hemorrhage: pRBCs, hemostasis via surgery/IR/GI	HF: diuresis, inotropes, +/- PA line Arrhythmias: electricity, anti-arrhythmics	Tamponade: acutely, fluids; pericardiocentesis PE: AC/lysis PTX: chest tube vs. needle decompression

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

- First step: **vitals:** wide vs. narrow (<25% of SBP) pulse pressure; **exam:** warm vs. cold, dry vs. wet, rashes or mottling
- Quick data points: **CVO2** (normal CvO2 = 70%), **CVP**, **TTE** (consider POCUS and/or STAT TTE)
- Consider: PA catheterization for shock differentiation. See *PA Catheterization* for full discussion, but no benefit in terms of mortality, LOS, or cost in unselected ICU or CHF pts (Cochrane Rev 2013, ESCAPE JAMA 2005;294:1625, PAC-Man Lancet 2005;366:472)

Management Considerations

- Ventilatory support: intubate if necessary (concomitant respiratory failure, unable to compensate for metabolic acidosis, marked hemodynamic instability), but have pressors available as intubation often worsens hypotension; be aware that SpO2 is often unreliable due to peripheral vasoconstriction (even on earlobe), & may require frequent ABG plus (includes SaO2)
- Antibiotics: if septic shock is on the differential, get early cultures and start broad spectrum antibiotics without delay
- Fluid resuscitation: crystalloid bolus (not infusion). Can predict **fluid responsiveness** by pulse pressure variation, passive leg raise, IVC diameter (see *Sepsis*). Good approximation = improvement in BP/UOP/lactate with fluid challenge. *Appropriate fluid challenge should raise CVP by 2.* **Be more cautious with fluids if possible cardiogenic shock.** (NEJM 2013;369:1243)
- Vasoactive agents (see *Vasopressors*): typically titrate to **MAP >65 mmHg** (if cardiogenic, MAP >60 mmHg)
- Steroids: if known adrenal insufficiency or chronic steroid use, consider stress-dose steroids such as hydrocortisone 50mg q6h or 100mg q8h x5-7 days pending clinical stability; unclear role & highly debated for septic shock (see *Sepsis*).
- Bicarbonate: if pH <7.1 or <7.2 w/ severe AKI, can temporize while fixing underlying etiology. HCO3 → CO2 that pt must ventilate off, so cautious if ↑CO2 or otherwise tenuous resp. status. No mortality benefit except in AKI (BICAR-ICU Lancet 2018;392:31)
- Specialized teams: **STEMI** (x6-8282), **PERT** (x4-7378), **SHOCK** (p11511 – IABP, Impella), **ECMO** (p24252 / 857-310-0335)

OVERVIEW

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

qSOFA
1. RR>22
2. AMS
3. SBP≤100

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

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

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

INITIAL MANAGEMENT (2016 Surviving Sepsis Guidelines: Intensive Care Med 2017;43:304)

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

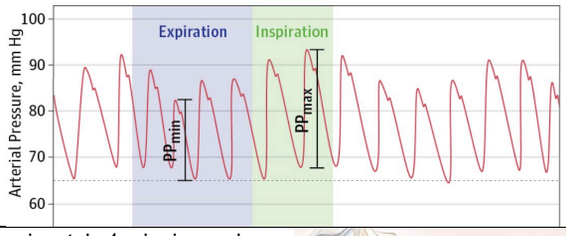
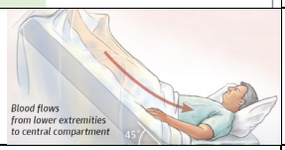
1) Antibiotics: empiric broad spectrum IV antibiotics should be administered within one hour of recognition. Order STAT.

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

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

- **Balanced crystalloids** (e.g., **LR**) with ↓ mortality and ↓ renal impairment in critically ill adults compared to **NS** (NEJM 2018;378:829); no mortality benefit to colloids > or in addition to crystalloids (NEJM 2004;350:2247, JAMA 2013;310:1809; NEJM 2014;370:1412)
- After the initial resuscitation effort, further fluid administration should be guided by dynamic measures of fluid responsiveness:

Assessing Fluid Responsiveness (JAMA 2016;316:1298)

Method	Fluid responsive if:
Pulse pressure variation: must be mechanically ventilated w/ Vt ≥8 mL/kg, not spontaneously triggering ventilator, & in NSR (Crit Care 2014;18:650) **PPV** = (PPmax- PPmin)/ PPmean 	PPV ≥12%
Passive leg raise: raise legs to 45° w/ torso horizontal x1 min. in mech. ventilated patient to provide "autotransfusion" of ~250-350cc; assess Δ in hemodynamics 	Pulse pressure ↑ ≥10% (surrogate for ↑SV if invasive measures of CO not available)
Δ in IVC diam: measure 1cm prox. to hepatic vein junction in M-mode; if mech. vent, calc. distensibility: **dIVC** = (Dmax-Dmin)/Dmin; if spont. breathing, calc. collapsibility: **cIVC**= Dmax-Dmin/Dmax	dIVC ≥15% cIVC ≥40%
Fluid challenge: bolus 250-500cc fluids; measure CVP before and immediately after and if ↑ by ≥2 then was appropriate volume challenge. If chosen parameter(s) improve, then fluid responsive. If do not, then not fluid responsive.	Improvement in BP/vasopressors, UOP, lactate; ↑ in pulse pressure ≥10%

- Resp. variation w/ vent: pos. pressure during expiration→ ↓ venous return & RV preload→ ↓ LV preload. If on ascending portion of Starling curve, sensitive to Δs in preload. Volume responsive pts will show larger variations in PP or SV during respiratory cycle.
- Lack of volume responsiveness suggests patient is on the flat part of the Frank-Starling curve; use/increase **vasopressors** instead.
- Targets of resusc.: **lactate clearance** (normalization or >20%/2hrs) (JAMA 2010;303:739); **cap. refill** (<30s) (JAMA 2019;321:654)

3) Vasopressors: target a mean arterial pressure (MAP) of >65 mm Hg (NEJM 2014;370:1583) (see *Vasopressors* page for full details)

- Norepinephrine (NE, Levophed): **first choice vasopressor**
- Vasopressin: can be added to NE to reduce dose or ↑MAP; ?vaso deficiency in septic shock (Circulation 1997;95:1122)
- Epinephrine: recommended when 2nd or 3rd agent is needed; can be used instead of vaso
- Phenylephrine (Neo): recommended primarily when: (a) NE is associated with serious arrhythmias, (b) CO is high and BP persistently low, (c) as salvage therapy when NE + vaso have failed to achieve MAP target (d) hypotension a/w AFRVR
- Dopamine: reserved for highly selective patient population with bradycardia and low risk of tachyarrhythmia; a/w ↑ risk of arrhythmias/mortality in all-comers (CCM 2012;40:725; NEJM 2010;362:779)
- Methylene blue*:* uncommonly used, pressor of last resort when NO-mediated vasoplegia is suspected
- Angiotensin II: not currently available at MGH; anticipate eventual availability given ATHOS-3 trial (NEJM 2019;377:419)

4) Source Identification and Control

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

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

OTHER ASPECTS OF MANAGEMENT

Renal Dysfunction

- 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)
- 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 showed that bicarb infusion to keep pH >7.3 (max 1L/24hrs) a/w ↓ mortality (Lancet 2018;392:31)
- Bicarbonate administration: **1 amp** = 50mEq / 50mL (or 8.4%); or **infusion** of solution of 150 mEq (3 amps) in 1L of D5W
  - **Caution**: HCO3 → pCO2 that must be ventilated off, so must have sufficient resp. drive / be intubated. Also → ↓ iCa.

Transfusions

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

CONTROVERSIAL MANAGEMENT STRATEGIES

Corticosteroids

- Rationale: critical illness affects HPA axis, may cause relative adrenal insufficiency (i.e. inadequate cortisol for total body demands) / "critical illness-related corticosteroid insufficiency" (CIRCI)
- Diagnosis: cortisol levels/stim. have not reliably predicted pts who will benefit from steroids, but random AM cortisol ≤10 or Δ in baseline cortisol of ≤9 after 250mg cosyntropin stim. are indicators of likely adrenal insufficiency (*NB*: etomidate can interfere w/ stim.)
- Controversy: initial study ("Annane / French trial") w/ mortality benefit w/ IV hydrocort 50mg q6 + fludricort 50mcg/d x7d in pts w/ septic shock w/ abnormal cort stim (Δ ≤9) (JAMA 2002;288:862). Similar results by same group in more recent study (APROCCHSS NEJM 2018), but mortality benefit not seen in other trials (CORTICUS NEJM 2008, HYPRESS JAMA 2016, & ADRENAL NEJM 2018).
- Conclusion: if **refractory septic shock** (esp. if e/o CIRCI), consider IV **hydrocort 50mg q6 or 100mg q8** (max 400mg/d) ± fludricort (hydrocort likely has sufficient mineralcorticoid 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: single study by Marik et al. (Chest 2017;151:1229) showed ↓ mortality w/ combination of high-dose **Vit C** (1.5g q6 x4d), **hydrocort** (50mg q6 x7d), & IV **thiamine** (200mg q12 x7d) but was small, single-center cohort (not RTC) and has not been validated. No benefit to vitamin C alone in meta-analysis (CCM 2019;47:774) or in sepsis w/ ARDS (JAMA 2019;322:1261). Also no benefit to Vit C/thiamine in addition to hydrocort (VITAMINS JAMA 2020).
- Conclusion: **no proven benefit** to Vitamin C, either alone or in combination w/ thiamine & hydrocortisone.

Esmolol

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

Pulmonary & Critical Care — Vasopressors

Category	Name	α	β_1	β_2	D	PVR	SVR	CO
Inoconstrictors	Norepinephrine	4+	2+	(+)	0	1+	⇧	⇧
	Dopamine (low)	0	1+	0	2+	±	-/⇧	⇧
	Dopamine (med)	1+	2+	0	2+	±	⇧	⇧
	Dopamine (high)	2+	2+	0	2+	±	⇧	⇧
	Epinephrine	4+	3+	2+	0	1-	-/⇧	⇧
Inodilators	Dobutamine	(+)	3+	2+	0	1-	⇩	⇧
	Milrinone	PDE inhibitor				2-	⇩	⇧
Vasoconstrictors	Phenylephrine	5+	0	0	0	2+	⇧	⇩
	Vasopressin	V_1				±	⇧	-/⇩
Chronotrope	Isoproterenol	0	3+	3+	0	0	⇩	⇧

α_1: vasoconstriction, ↑ duration of heart contraction
α_2: sedation/analgesia, vasoconstriction (if peripheral) vs. vasodilation (if central, e.g., clonidine)
β_1: ↑ inotropy, ↑chronotropy
β_2: ↑ vasodilation
D: renal/splanchnic/coronary/cerebral vasodilation
V_1: vasoconstriction (especially splanchnic)

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

VASOPRESSORS & INOTROPES (Circulation 2008;118:1047)

	Name	Mechanism	Uses	Side effects	Dosing
VASOPRESSORS	Norepinephrine *Levophed* **"Levo"**	$\alpha_1 > \beta_1$ agonist: ↑↑ **SVR** , ↑ **CO** *Reflex brady from vasodilation can negate ↑HR from chronotropy*	Septic shock (1st) Cardiogenic shock (1st) Hypovolemic shock (1st)	Arrhythmia Digital ischemia ↑ FSBG	Initial: 5-12 mcg/min (0.1-0.15 mcg/kg/min) Max: 35-100 mcg/min (0.75 mcg/kg/min)
	Phenylephrine *Neosynephrine* **"Neo"**	Pure vasopressor α_1 agonist: ↑↑ **SVR**	Septic shock if ↑↑ HR from NE *or* ↑CO w/ ↓↓ BP *or* 3rd agent needed AFRVR, HOCM, AS, RV failure	**Reflex bradycardia** ↓ CO, ↑ PAP, ↑ SVR Digital ischemia	Initial: 100-180 mcg/min (0.5-2 mcg/kg/min) Max: 360-1000 mcg/min (6 mcg/kg/min) *PIV: <250 mcg/min*
	Vasopressin *Pitressin* **"Vaso"**	V_1 agonist: ↑ **SVR** V_2 agonist: ↑ renal H_2O reabsorption	Septic shock (2nd) (↓ mortality w/ NE vs. NE alone) (VASST NEJM 2008;358:877) Anaphylaxis (2nd) Pulmonary HTN/RV failure Hepatorenal syndrome	Coronary ischemia Mesenteric ischemia ↓ Na	Usual: 0.04 U/min Max: 0.08 U/min (only as salvage therapy)
	Epinephrine *Adrenalin* **"Epi"**	Low: $\beta_1 > \beta_2 > \alpha_1$: ↑ **CO**, neutral **SVR** High: $\alpha_1 > \beta_1 > \beta_2$: ↑ **CO**, ↑ **SVR**	ACLS (1st) Anaphylaxis (1st) Symptomatic bradycardia (2nd) Septic shock Bronchospasm	↑ HR, arrhythmias Myocardial ischemia ↑ lactate ↑ splanchnic SVR ↑ FSBG	Low: 1-4 mcg/min High: 5-35 mcg/min
	Dopamine *Intropin* **"Dopa"**	Low: $D_1 > \beta_1$: ↑ **CO**, ↑ **UOP** Med: $\beta_1 > D_1$: ↑ **CO**, ↑ **SVR** High: $\alpha_1 > \beta_1 > D_1$: ↑ **SVR**	Symptomatic bradycardia Septic shock w/ bradycardia ↑ **mortality vs. levophed** in septic (CCM 2017;45:486) & cardiogenic shock (SOAP-II NEJM 2010;362:779)	Tachyarrythmia Myocardial ischemia ↓ BP (low dose) ↑ PCWP, pulm shunt ↑ FSBG	Low: 1-2 mcg/kg/min Med: 5-10 mcg/kg/min High: 10-50 mcg/kg/min
	Methylene blue	↓ NO and cGMP → ↑ Sm musc tone: ↑ **SVR**	Refractory vasoplegia due to sepsis/anaphylaxis Post-cardiopulm bypass Amlodipine overdose Metformin overdose Methemoglobinemia	Falsely ↓ SpO_2 Arrhythmias ↑ PVR Rash, hemolysis, serotonin syndrome Contraindicated in G6PD	Initial: 1-2 mg/kg Max: 5 mg/kg
	Angiotensin II	ANG-II agon.: ↑ **SVR**	Refractory septic shock (*NB*: not avail at MGH)	Peripheral ischemia	10-20ng/kg/min; max 40
INOTROPES	Dobutamine *Dobutrex* **"Dobuta"**	$\beta_1, \beta_2 > \alpha_1$ agonist: ↑ **CO**, ↓ **SVR**	Cardiogenic shock Sepsis + ↓LV EF (added to NE)	↓ **BP**, ↑ **HR** Arrhythmias Myocardial ischemia Tachyphylaxis	Initial: 0.5-1 mcg/kg/min (2.5 if more severe) Max: 20-40 mcg/kg/min
	Milrinone *Primacor*	PDE inhibitor (↑cAMP) → ↑ inotropy, vasodilation: ↑ **CO**, ↓ **PVR/SVR**	Cardiogenic shock RV failure (↓PVR, ↓LVEDV)	**Hypotension** Arrhythmias Myocardial ischemia	Initial: 0.125 mcg/kg/min Max: 0.75 mcg/kg/min
	Isoproterenol *Isuprel*	$\beta_1 = \beta_2$ agonist: ↑ **HR**, ↓ **SVR**	Symptomatic bradycardia Mg-refractory Torsades	↓ BP, ↑ HR Arrhythmias Myocardial ischemia Flushing, anxiety	2-10 mcg (can bolus 2-6mcg first) 30 mcg/min

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

Drug/Toxin	Presenting Symptoms	Diagnostic Workup	Management
Acetaminophen	See *Acute Liver Injury & Failure*		
Salicylates	Tinnitus, fever, vertigo, N/V/D, tachypnea, pulmonary edema, AMS (can have neuroglycopenia w/ normal serum glucose), respiratory alkalosis (early), metabolic acidosis (late)	ABG (mixed respiratory alkalosis / metabolic acidosis), BMP, CXR, salicylate level (>30-50 mg/dL toxic, though a clinical dx).Repeat levels and ABG Q2H until improving.	Avoid intubation (if required, hyperventilate to avoid acidemia), IVF, charcoal (1 g/kg), glucose (100 mL D50), bicarb, alkalinize urine to pH 7.5-8, avoid acetazolamide. Consider HD.
Opioids	↓RR and tidal volume, CNS depression, ↓bowel sounds, miosis	EKG, core temp, glucose, CPK	IV or intranasal naloxone (0.4-2 mg). Repeat PRN. Naloxone ½-life shorter than most opioids → repeated dosing or gtt, esp if long-acting opioids (2/3 effective bolus dose per hr).
Benzodiazepines	Depressed MS, ataxia, slurred speech, hyporeflexia, ↓RR, coma	Hx, urine tox can give qualitative result	Supportive; avoid flumazenil as it precipitates withdrawal + seizures.
Anticholinergics Atropine, Benztropine, Scopolamine, Diphenhydramine	Mydriasis, hyperthermia, decreased sweating, flushing agitated delirium, urinary retention, ileus, tachycardia, HTN	Hx, EKG, CPK	Supportive, cooling for hyperthermia; charcoal (1 g/kg) if <1hr, benzos for agitation & seizure, physostigmine if severe (ICU, atropine at bedside; not for TCA ODs).
CCBs	N/V, HoTN, CHF, brady, AV block, stupor, cardiac arrest, hyperglycemia	Hx, EKG (brady, long PR), blood levels slow & correlate poorly. Extended release preps dangerous. High glucose = poor prognosis.	Calcium (2-3 g), pressors, glucagon, HIGH DOSE-insulin (1 U/kg bolus, then 0.5-1U/kg/hr gtt, adjust to cardiac response), IVF; consider pacing, atropine, ECMO.
B-Blockers	HoTN, bradycardia, AV block, long QTc (sotalol), CHF, bronchospasm, hypoglycemia, stupor, hyperkalemia, seizure (propranolol), miosis	Hx, EKG, blood levels slow and correlate poorly; propranolol highest mortality.	Pressors, calcium, glucagon (0.05-0.15mg/kg bolus q3-5min or gtt), high-dose insulin (see above), IVF; atropine, pacing, ECMO.
Digoxin	Bradycardia, AV block, N/V/abd pain, hyperkalemia, AMS, xanthopsia (yellow-green halo), bidirectional VT, "regularization of AF"	EKG, digoxin level (nl 0.9-2.0 ng/mL; may not be accurate if drawn within 6h of last dose, also tests for bound Fab fragments, may need send out "free" dig level after treatment), lytes, BUN/Cr, UOP.	Digoxin-specific Fab fragments (if K>5.5, severe end-organ dysfxn, or life-threatening arrhythmia), magnesium, AVOID hypokalemia.
TCAs	Prolonged QRS, arrhythmia, hypotension, anticholinergic toxicity, myoclonus, hyperthermia, AMS, coma, seizure	Tox screen, EKG (↑ QRS duration, terminal R wave >3mm in aVR, QRS >100ms correlates w/ 26% seizure risk; >160ms correlates w/ 50% risk. Monitor for ventricular arrhythmia, CPK.	IV bicarbonate (for the Na not the alkalization) if QRS >100ms or hypotensive. Benzos for seizure. Salvage Rx: hypertonic (3%) saline, lipid emulsion
Lithium	N/V/D, tremor, hyperreflexia, clonus, ataxia, AMS, seizure, hyper/hypothyroidism, AV block, sinus brady, long QT, nephrogenic diabetes insipidus if chronic	BUN/Cr, serial Li levels (nl 0.5-1.5 mmol/L), EKG Toxicity common with AKI from NSAIDs, ACEi, diuretics	Frequent neuro checks; IVF (NS preferred), maintain UOP, HD if encephalopathy, renal dysfunction.
Serotonin Syndrome Antidepressants, Linezolid, Tramadol	AMS, hyperreflexia (LE predominant), hyperthermia, mydriasis, ↑ HR, HTN, diarrhea, diaphoresis, clonus, rigidity	Search for causative agent. CBC, CPK, BMP, coags, LFTs, UA, CXR.	Benzos for agitation (avoid antipsychotics); supportive care for altered VS (esmolol, nitroprusside for ↑HR and HTN, cooling). If all else fails, consider cyproheptadine.
Neuroleptic Malignant Syndrome (NMS)	AMS, "lead pipe" rigidity, sialorrhea, hyperthermia, dysautonomia, diaphoresis. Typically no N/V/D or hyperreflexia	Search for causative agent. CPK (often very high), CBC (leukocytosis), LDH, LFTs, BMP, serum iron (often low); consider brain imaging, LP, EEG.	D/c causative agent (restart dopamine if d/c-ed), IVF, cooling blanket, nitroprusside for HTN, BZD for agitation. Dantrolene, bromocriptine, amantadine.
EtOH	Disinhibition, stupor, nystagmus, memory loss, discoordination, ↓RR, coma	EtOH level, methanol and ethylene glycol if + osmol gap. BMP, LFTs.	Thiamine (before glucose), folate, MVI, IVF w/ dextrose. Calculate discriminant fxn if EtOH hepatitis.
Ethylene glycol Antifreeze	Inebriation, AMS; flank pain, hematuria, reversible kidney injury, calcium oxalate crystals in urine	AG metabolic acidosis (severe), osmol gap, oxalate crystalluria, renal failure, hypocalcemia, lactate elevation	Fomepizole (15 mg/kg bolus over 30min then 10mg/kg Q12H), bicarb if pH<7.3, leucovorin 50mg IV, consider HD
Methanol Windshield fluid, "moonshine"	Inebriation, retinal injury (visual blurring, papilledema, blindness)	AG metabolic acidosis (severe), osmol gap, visual acuity testing	As above, fomepizole (or ethanol), bicarb, or HD.

Cocaine	Agitation, psychosis, seizure, HTN, ↑HR, vasospasm/MI, arrhythmia, stroke, vasculitis, lung injury, rhabdomyolysis	Serum, urine tox (metabolites detectable for 2-5d), ECG, cardiac biomarkers if chest pain, CPK, UA.	Hyperthermia treatment (cooling, benzos), treat chest pain with ASA, CCB, nitrates, labetalol (no pure BB).
Sympathomimetics Amphetamines, MDMA, cathinones "bath salts"	Agitation, mydriasis, hallucinations, paranoia, tachycardia, HTN, diaphoresis, hyperthermia, piloerection, seizure	EKG, chem 7, lactate, CPK, LFTs, coag.	IV benzos, atypical antipsych. if refractory agitation, avoid succinylcholine and ketamine.
Carbon Monoxide	Minor sx: headache, N/V Major sx: confusion, LOC, seizure, coma, cardiac ischemia, arrhythmias	History (house fires, winter w/ indoor space heaters), carboxyhemoglobin level, cyanide level, CO-oximetry b/c pulse ox (SpO2) invalid, AG acidosis, EKG, troponin.	100% O_2 (t½ 6h→60 min); Hyperbaric O_2 (t½ 6h→20 min); watch for delayed neuropsychiatric sequelae.
Cholinergics Organophosphates, carbamate insecticides, nicotine	"DUMBBELLS": Diaphoresis/Diarrhea, Urination, Miosis/Muscle spasm, Bronchoconstriction/Bronchorrhea, Bradycardia, Emesis, Lacrimation, Lethargy, Salivation/Seizure	ABG, ECG, Chem 7, CPK, lactate. Can monitor RBC AChE inhibitor if available.	100% O_2, atropine (2-5 mg IV, redose to effect q3-5 min, no effect on muscular symptoms); Pralidoxime (30mg/kg over 30 min→8-20mg/kg/hr. Only for organophosphate toxicity).
Cyanide	HA, nausea, AMS, seizure, coma, shock. Suspect in structural fires, prolonged nitroprusside infusion.	Cyanide level, lactate, anion gap metabolic acidosis, carboxyhemoglobin level.	Hydroxocobalamin (5g over 15 min) and sodium thiosulfate (use amyl nitrate if hydroxo unavailable).
Gamma-hydroxy-butarate (GHB)	Agitation, coma (sudden onset/resolution), bradycardia, ↓RR, low BP, co-intoxicants common	Not detected on routine toxicology screen, need 100mL urine and 10-30 mL blood for send-out. EKG, r/o other causes, B-hCG.	Supportive; benzodiazepines for withdrawal. *Note*: OD at low dose if on protease inhibitors.
Synthetic Cannabinoids Spice, K2	Anxiety, paranoia, sedation, memory impairment, hallucinations, psychosis, seizure, tachycardia, HTN, N/V, AKI	Not detected on routine toxicology screen, can send blood and urine sample for send-out.	Supportive care. Benzos for agitation and seizure. Antipsychotics for agitation.

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

Anion and Osmol Gaps:

Anion Gap	Osmolal Gap
Methanol	***With normal AG:***
Uremia (CKD)	EtOH, isopropyl-OH
Ketoacidosis	Ether
INH	glycine/sorbitol/mannitol
Iron	hyperproteinemia
Lactic Acidosis	hyperlipidemia
Ethylene/propylene glycol	***With elevated AG:***
Salicylates	Ethylene/propylene glycol
CO	Methanol
Cyanide	Ketoacidosis
Sympathomimetics	Lactic Acidosis

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

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

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

Decontamination Therapies:

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

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

Dialyzable Toxins
EtOH, methanol, isopropyl alcohol
Glycols
Acetone
Lithium
Salicylates
Barbiturates
INH
Atenolol, sotalol

Acid Diuresis (→give Vitamin C)	Alkaline Diuresis (→give $NaHCO_3$)
Quinine	Phenobarbital
PCP	Salicylates
	Methotrexate
	TCAs

MGH GI Taskforce Protocol for Acute Upper GI Bleed Management

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

Urgent Assessment & Management of GI Bleeding

- *Assess & reassess V/S for hemodynamic stability*
- Attempt to quantify **amount & rate** of blood loss
- **≥ 2 PIV** (18G or larger) – rarely done by IV nurse; look at their arms (green = 18; pink = 20; blue = 22)
- **Type & screen** (type & cross if plan to transfuse), **IVF** (and blood if indicated): liberal transfusion if active bleed or unstable VS. Hct drop lags 24-72h from onset of bleeding.
- **Correct coagulopathy**: IV vit K, FFP, Plt, PCC. If severe/life-threatening, consider reversal agent. If uremic, consider ddAVP (0.3 mcg/kg); if ESLD, consider amicar, avoid FFP (volume).
- **Transfusion goals**: **Hb >7** (avoid overtransfusion if EVs), Plt >50k, INR <2 (unless ESLD), PTT <50, Fibrinogen >100
  - See *Transfusion Medicine* for **Massive Transfusion**; generally, give FFP/plts after 4U
- **GI consult** for EGD and/or colonoscopy
- **Surgery or IR consult** if hemodynamic instability or difficult endoscopic correction
- **Intubation**: if high volume hematemesis, AMS, variceal bleeding requiring balloon tamponade

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

- **Ulcers** (~50%): PUD: H. pylori, NSAID, ZE, EtOH
- **Varices** (~5%): EVB (esophageal) > gastric
- **Esophagitis or gastritis** (~30%): GERD, pill, ASA, NSAIDs, clopidogrel, EtOH, infectious
- **Vascular lesions** (~5-10%): Dieulafoy's, AVM, GAVE, HHT, XRT, aortoenteric fistulae
- **Traumatic** (~5%): Mallory-Weiss, foreign body, Boerhaave's
- **Neoplastic** (~5%): primary > metastatic
- **Post-procedural** (varies): polypectomy, sphincterotomy

High Risk Features in UGIB

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

Acute Upper GI Bleeding (International Guidelines: Annals 2019;171:805; NEJM 2016;374:2367)

- **Definition**: bleeding proximal to ligament of Treitz
- **S/Sx**: hematemesis, melena (+LR 25); brisk UGIB can p/w hematochezia, orthostasis; BUN/Cr >30 (⊕ LR 7.5; JAMA 2012;307:1072), especially >35 (100% Sp; J Clin Gastro 1990;12:500).
- **Risk stratification** (30d mortality): Glasgow-Blatchford Score recommended over AIMS65 (Annals 2019;171:805, BMJ 2017;356:6432); Machine Learning Scoring System with > specificity (100%) than both (Gastro 2020;158:160)
- **Management**: EGD generally within 24hrs (debated), but no Δ in outcomes if between 0-6hrs vs. 6-24hrs (NEJM 2020;382:1299)

Pre-EGD	Post-EGD
- **Transfusion**: **Hb >7** (NEJM 2013;368:11). Consider higher threshold if CVD (Annals 2019;171:805). *Avoid overtransfusion in variceal bleed – can ↑ portal pressures and worsen bleeding.* - **IV PPI**: ↓ high-risk lesions requiring endoscopic therapy, but unclear clinical impact pre-EGD (Cochrane Rev. 2010) - **IV erythromycin or azithromycin**: 250mg 30m prior to EGD ↑ gut motility & visualization (AJG 2006;101:1211) - If cirrhosis: **IV octreotide**: **50 mcg x1 → 50 mcg/hr** + **IV CTX 1g q24hr x7 days** for ppx against bacterial infections (Gastro 2006;131:1049; APT 2011;34:509); *stop β-blockers* - If continues to bleed, consider **amicar** (5 g bolus followed by 1 g/hr, max ~24g in 24h), **ddAVP** (if uremia)	- **If high risk PUD, intensive PPI x72 hr →↓** re-bleeds & need for repeat EGD: **pantoprazole 40mg IV BID** (intermittent dosing non-inferior to bolus+gtt; JAMA Intern Med. 2014;174:1755). **Oral PPI** may replace **IV PPI** if good PO intake. - Treat ***H. pylori*** if positive - **If variceal bleed**: continue octreotide x 3-5d, consider TIPS or BRTO if refractory to EGD - **If angiodysplasia**: consider long-term octreotide (AJG 2007;102:254), bevacizumab or thalidone w/ GI help - **If re-bleed**: repeat EGD, consider angiography, surgical/IR consult. If variceal, consider balloon tamponade, TIPS, BRTO

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

Warfarin: **hold** during bleed; **resume** after hemostasis (w/ UFH bridge at ~48hrs if indicated; see *Hematology* section); ↓ risk of thrombosis, death in AF if resumed w/in 7d (Am J Cardiol 2014;113:662)
DOAC: **hold** during bleed; no data to guide, but generally **resume** 48-72hr after hemostasis
ASA: **hold** during bleed (unless recent PCI/ACS – see below); **resume** in pts w/ CAD (2° prev.) after hemostasis, best if w/in 1-7d; ↑risk of 30d mortality if not resumed (Annals 2010;152:1); if PUD, add PPI to ↓ risk of bleeding
DAPT for PCI/ACS: d/w cardiologist though generally if very recent (<30d PCI, <90d ACS) continue both unless life-threatening; if more distant, continue ASA but less risk in holding P2Y2i. Resume w/in 1-7d if able, esp if low rebleed risk.
In general, restarting AC/AP sooner → ↓ risk of vasc. events, though ↑ risk of bleeding (APT 2019;50:8)

- **Prognosis:**
  - PUD rebleeding w/o med management: 90% if active bleed, 50% if visible vessel, 30% if clot, 20% if oozing, else < 10%
  - Esoph variceal bleed: 50% resolve spontaneously; 30% mortality → 70% if continued bleeding; 60% risk re-bleeding overall

Acute Lower GI Bleed (NEJM 2017;376:1054)

- **Definition**: hematochezia from colon or rectum; classic def.: distal to lig. of Treitz
- **Sx**: hematochezia (maroon stools, bright red blood, or blood clots); less commonly melena (dark, sticky; requires that blood spend 14hr in GI tract)
  - *Stool appearance is a poor indicator of bleeding source*; hematochezia can also be seen with brisk UGIB (suspect if pt is hemodyn. unstable)
  - Anorectal/L colon: bright red blood
  - R colon: maroon-colored stools, melena possible if slow transit

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

- **Diagnosis**:
  - Exonerate UGIB first with EGD if brisk bleed/hemodynamic instability (10-15% of patients with severe hematochezia)
  - Consider NGT placement if there is moderate suspicion for UGIB (not done often at MGH)
    - Coffee-ground material, bright red blood → EGD
    - No blood or bile seen: indicates indeterminate source → consider EGD before colonoscopy
    - Bilious fluid: no active UGIB source → colonoscopy
  - Colonoscopy is mainstay of diagnostic therapy; imaging can also be used to help localize active bleed
    - CT angiography: (bleeding rate 0.3-0.5mL/min); available, fast, minimally invasive; first line (ACR Approp. Criteria)
    - IR angiography: (>0.5 mL/min); allows for intervention (e.g. embolization) but risk of bowel ischemia, vascular injury
    - Tagged RBC scan: (>0.1 mL/min); most sensitive, but time-consuming, poor localization
- **Risk stratification**:
  - Several risk-factor models have been developed. Overall limited ability to predict which patients will have poor outcomes.
    - NOBLADS score: NSAID use, no diarrhea, no abdominal tenderness, SBP <100 mmHg, antiplatelet agent, albumin <3.0 g/dL, ≥2 comorbidities, syncope (CGH 2016;14:1562)
    - HR >100 bpm, SBP <115 mmHg, syncope, non-tender abodomen, bleeding in <4 hr of eval, ASA use, >2 comorbidities (AJG 2005;100:1821)
    - Patients with coexisting cardiopulmonary, renal or hepatic conditions have worse outcomes (Colorectal Dis 2011;14:8)
- **Management**: (ACG Guidelines: AJG 2016;111:459)
  - Transfusion goals: Hgb >7 (consider >9 in active CAD), Plt >50k, INR <1.5 (INR 1.5-2.5 ok to perform endoscopic hemostasis before reversing; INR >2.5 consider using reversal agent)
  - Initial labs: CBC, CMP, coags, T&S; trend Hgb Q2-8 hrs depending on severity of bleed
  - **IF HEMODYNAMICALLY STABLE:** prep for colonoscopy (after discussion with GI); need 8 hrs w/o solid food prior
    - If ongoing bleeding or high-risk, perform colonoscopy within 24hr; use order set for colonoscopy prep
    - OK to place NG tube for high-risk patients with ongoing bleeding who are intolerant of prep (if no known h/o varices)
    - Some evidence that performing colonoscopy at 24-36 hours is a safe approach in most stable patients (Gastro 2020:158:1); however, remains controversial, as may reduce identification of stigmata of recent hemorrhage, ↑LOS
    - For refractory angioectasias, can treat with thalidomide and bevacuzimab
  - **IF HEMODYNAMICALLY UNSTABLE:** EGD to r/o UGIB causing brisk hematochezia followed by urgent colonoscopy, IR (embolization), surgical consult (subtotal colectomy if cannot locate colonic bleed), massive transfusion
  - Diverticular hemorrhage, angioectasia, post-polyp. bleed, hemorrhoids, rectal varices amenable to endoscopic treatment
  - Anticoagulation/antiplatelet management: generally extrapolated from UGIB data
    - ASA for 1° prev. should be stopped & generally not resumed. ASA for 2° prev. should not be held; if it is, should be resumed soon after bleed resolves (Gastro 2016;151:271). If on DAPT for recent PCI/ACS (<30d PCI, <90d ACS), should continue unless life-threatening bleed. If less recent, can likely hold P2Y12i for 1-7d though d/w cardiologist.

Unidentified Source after EGD/Colonoscopy: ~75% small bowel, 25% missed UGIB/LGIB (ACG Guidelines: AJG 2015;110:1265)

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

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

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

- Alarm symptoms: dysphagia/odynophagia, wt loss, GIB, Fe def. anemia, persistent vomiting, anorexia, new onset age ≥60

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

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

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

Management: (Gastro 2018;154:302)

- Lifestyle Δs: weight loss, HOB elevation, tobacco cessation, reduce food triggers, no meals 2-3hrs before bed
- 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 (controversial): *probable association*: Mg wasting (↑QTc), AIN; *possible association*: ↑ risk of osteoporosis, dementia, CKD, C. diff/other enteric infxn (Gastro 2017;152:706)
- H2RAs (ranitidine, famotidine): can be given for nighttime sx PRN w/ PPI, tachyphylaxis common after wks
- Others: PRN antacids, sodium alginate (APT 2013;38:1059; APT 2014;39:595), baclofen (as adjunct)

Severe/Refractory Symptoms:

- If no sx relief after 8w on high-dose BID PPI, refer for EGD & consider alternative dx such as functional dyspepsia (need symptoms >6mo; NEJM 2015; 373:1853), EoE, or rumination syndrome (effortless regurgitation)
  - EoE: dysphagia, GERD sx, food impaction; a/w allergic conditions. Eos on bx. PPI, topical steroids (Gastro 2020;158:1776)
- Gastric fundoplication may be superior to medical treatment for refractory heartburn (NEJM 2019;381:1513)

Complications:

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

PEPTIC ULCER DISEASE (PUD) (BMJ 2019;367:l5495)

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

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

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

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

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

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

H. pylori treatment: (ACG Guidelines: Gastro 2017:112:2)

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

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

Complications and Management: ulcer consider *complicated* if any of the following are present:

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

General approach to patient with nausea/vomiting (Gastro 2001;120:1)
(1) Seek out etiology. Make sure to consider chronicity & comorbidities
(2) Treat underlying cause if possible; symptom management based on underlying etiology
(3) Anticipate and address complications of N&V (aspiration, volume depletion, hyperchloremic metabolic alkalosis, hypokalemia, MW tear)

Evaluation	Etiologies (VOMITING mnemonic)		Receptor	Targeted treatment
History - Acute <1mo. or chronic (AJG 2018;113:5) - Relation to time of day - **Triggers**: relation to POs, recent foods/meds, sick contacts, headache, head trauma, last BM - Hematemesis, melena - Abd pain, heartburn - Prior abd surgery - CP, SOB, diaphoresis - Vertigo, uncontrolled DM **Labs to consider** - Chem 10, LFTs, amylase/lipase - hCG, UTox, VPAIN - UA, ABG, lactate - Cort stim - Troponin **Studies to consider** - KUB/upright - EKG - CT abdomen (I+/O+) - Barium swallow or EGD - Gastric emptying study - CT head **Can't-miss diagnoses** - SBO, mesenteric ischemia - Cardiac ischemia - Pancreatitis, pyelo, cholecystitis - Pregnancy - AI, DKA - ↑ ICP	**V**estibular & **V**ertigo	Acute/gait instability; Labyrinthitis, BPPV, vestibular neuritis, Meniere's disease	ACh H_1	Scopolamine, dimenhydrinate, diphenhydramine, meclizine, Dix-Hallpike → Epley maneuver
	Obstruction	Adhesions, hernia, volvulus, constipation, gastric outlet obstruction	Multiple	Prochlorperazine, ondansetron, bowel rest, NGT, IVFs, surgery consult, serial exams/KUBs, NO metoclopramide (risks perf)
	Operative	Post-op nausea/vomiting (PONV; risk factors: female, nonsmoker, post-op opioids, hx of PONV, type of surgery) 1/3rd cases	Multiple	Serotonin antagonist, aprepitant, dexamethasone (use 2 in combo as ppx if 3+ risk factors present), gabapentin
	Motility	Gastroparesis (common in uncontrolled DM), autonomic dysfunction, cyclic vomiting syndrome, chronic idiopathic nausea (See Motility Disorders)	D_2 (periph)	Low fat & insoluble fiber diet, metoclopramide, erythromycin (tachyphylaxis after 4 wks; motilin agonist),diphenhydramin, cannabis abstinence, TCAs, gabapentin, olanzapine, benzos, SSRI/SNRI
	Meds (drugs & withdrawal)	Antibiotics, anti-epileptics, chemo, opioids, illicits (cannabis hyperemesis), anti-arrhythmics	D_2 (central)	Stop offending medication if possible, prochlorperazine, haloperidol
	Inflammation/ **I**nfection/ **I**schemia	Chemo, XRT, bowel ischemia, gastroenteritis, PUD, hepatitis, pancreatitis, cholecystitis, pyelonephritis	$5\text{-}HT_3$ NK1	Ondansetron, prochlorperazine, dexamethasone, olanzapine & aprepitant (chemo), treat underlying disorder (antibiotics, surgery, etc)
	Toxins	Uremia, ketoacidosis, hypercalcemia, food poisoning, hypo/hyperglycemia	D_2 (central)	Prochlorperazine, haloperidol, treat underlying disorder
	Intracranial	Elevated ICP, migraine, meningeal irritation, acute glaucoma	ACh H_1 $5\text{-}HT_3$	Dexamethasone (if ↑ICP), treat underlying disorder
	Nerves	Anxiety, depression, anticipatory nausea, pain	Multiple	Lorazepam (anticipatory N/V), dexamethasone, pain control
	Gums/mouth	Mucositis thrush, oral HSV	Multiple	Treat cause; magic mouthwash

Management	Receptor	Med	Dose	Side effects
Address underlying cause while treating symptoms with targeted agents • Non-pharm options: Acupuncture/acupressure to anterior wrist (P6), meditation, ginger root • Chemo PPX: dex ± lorazepam ± ondansetron ± aprepitant ± olanzapine (NEJM 2016;375:134) • Adhesive SBO (prior GI surg): conserv. mgmt x 48h (NGT, NPO) → undiluted therapeutic gastrografin (100cc) per NGT ↓ surgery by 74% (BJS 2010;97:470)	$5HT_3$	**Ondansetron (Zofran)**	4-8 mg PO/IV q8h	↑QTc, **constipation**, HA
		Palonosetron (Aloxi)	0.075-0.25mg IV x1	No ↑in QTc, more potent
	D_2	**Metoclopramide (Reglan)**	10-20 mg PO/IV q6-8h	EPS (black box), dystonia (peripheral), promotility agent
		Prochlorperazine (Compazine)	5-10 mg PO/IV/PR q6h	↑QTc, EPS, **sedation**
		Haloperidol (Haldol)	0.5-4 mg PO/IV q6h	↑QTc, EPS, **sedation**
	Cortical	**Dexamethasone (Decadron)**	4-8mg PO q4-6h	**Psychosis**, CHF, ↑appetite
		Lorazepam (Ativan)	0.5-2 mg PO/IV q6h	**Delirium**, sedation
	NK_1	**Aprepitant (Emend)**	125mg day 1, 80mg days 2-3	CYP3A4 inhib, GI upset
	CB_1	**Dronabinol (Marinol)**	2.5-10 mg q4-6h	Dysphoria, asthenia, ↑appetite
	$5HT_{2A},D_2$	**Olanzapine (Zyprexa)**	5-10mg PO QD	Metabolic (wt gain, ↑lipids), QTc; ↑ mortality in dementia (blackbox)
	H_1,ACh,D2	**Promethazine (Phenergan)**	12.5-25 mg PO/IV/PR q4-6h	EPS, **sedation**
	ACh,H_1	**Scopolamine**	0.3-0.6 mg q24h	**Delirium**, **sedation**, 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	

Acute Diarrhea: ≥3 loose stools/d for <14 days (ACG: AJG 2016;111:602; IDSA: CID 2017;65:e45; NEJM 2014;370:1532)

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

Chronic Diarrhea: ≥3 loose stools/d for >4wk. 5 types: *secretory, osmotic, functional, malabsorptive, and inflammatory.* ***See table below.***
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, surg hx (CCY, resection, bariatric, vagotomy), travel, immunocompromised, meds, radiation
- Labs: CBC, BMP, ESR/CRP, LFTs; TSH; stool lytes (Na, K, pH), fecal WBC/calprotectin, fecal fat (24-48h coll.), FOBT
- **Stool osmotic gap for watery diarrhea**: 290 – 2*(stool [Na] + [K]); Normal 50-100 mOsm/kg

Disease Process	Physical Exam Findings
Dehydration, neuropathy	Orthostasis, hoTN
Hyperthyroidism	Tremor, lid lag
Addison's disease	Hyperpigmentation
Carcinoid	Flushing, murmur, wheezing
Amyloidosis	Hepatomegaly, macroglossia
HIV, lymphoma, CA	Lympadenopathy
Glucagonoma	Migratory nec. erythema
Celiac disease	Dermatitis herpetiformis

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

Celiac Disease (NEJM 2012;367:2419): abnormal immune response to gluten → diarrhea, wt loss, abd pain, Fe def anemia, vit D def
Diagnosis: ✓ **tTG-IgA (**Sn >95%, Sp >95%) **+ total IgA**. If IgA def, ✓ DGP- & TTG-IgG. If any ⊕, EGD w/ biopsies. If gluten-free & ⊖ serologies, ✓HLA-DQ2/DQ8. If ⊖, dx excluded. If ⊕, should challenge w/ gluten x2-8w and then ✓ serologies and EGD w/ bx. Bx: ↑ intraepithelial lymphs, elongation of crypts, villous atrophy. If Bx & serologies discordant, ✓HLA. (ACG: AJG 2013;108:656)

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

CONSTIPATION

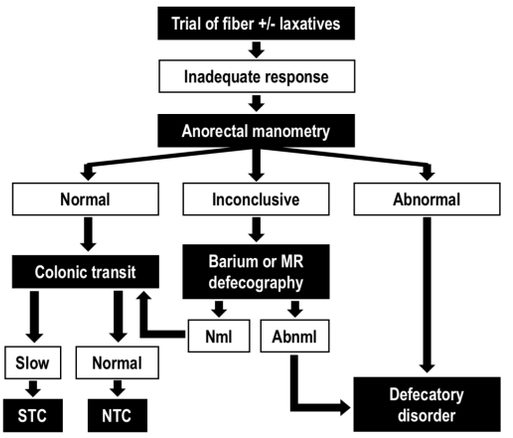
Definition: dissatisfaction with defecation; Rome IV criteria: at least 2 of: straining during defecation, lumpy/hard stool, sensation of incomplete defecation, manual facilitation of BM, <3 BMs per week

Etiologies (AGA guidelines: Gastro 2013;144:211 Gastro 2013;144:218, JAMA 2016;315:185)

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

Diagnosis/Treatment (AGA guidelines: Gastro 2013;144:211, Gastro 2013;144:218, JAMA 2016;315:185)

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



Hospital Constipation Prophylaxis and Bowel Regimens

- Risk factors: >60 yo, prolonged immobility, decreased fluid intake, preexisting constipation, meds (see above)
- 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**
- Step-wise approach: **senna → miralax → lactulose → mag citrate/MOM → bisacodyl PR → enemas → disimpaction** (*NB*: disimpaction can cause vasovagal syncope; all rectal procedures are contraindicated in neutropenic pts)
- Avoid Mg and Phos containing products in renal insufficiency (MOM, Mg citrate, Fleets enema) → can cause nephrocalcinosis

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

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

Contact GI team if not clear (completely see-through) in the AM, as the procedure will need to be rescheduled. Rx additional Nulytely (ex. 2L) or magnesium citrate to continue with prep in this case (avoid mag citrate in cases of IBD, dehydration)

DIVERTICULOSIS

- Definition: herniation of colonic mucosa into muscularis propria, where vasa recta penetrate
- Risk factors: low fiber diet ± chronic constipation, obesity, ↑ age (**present in 50% of patients >60yo;** common incidental finding on imaging), smoking, NSAIDs, red meat consumption, ♀ = ♂. No data for avoidance of seeds or popcorn.
- Location: 90% L-sided (primarily sigmoid) in "Western" populations; 75-85% R-sided in Asia.
- Bleeding: **painless** bleeding of *vasa recta* within the diverticuli. 75% are self-limited & resolve with bowel rest. Recurrence is common. Tx if bleeding does not stop: 1) endoscopic, 2) angio (IR embolization), 3) surgery. See *Lower GI Bleed*.
- Diverticulitis: develops in 4% of pts with diverticulosis; see next page

DIVERTICULITIS

- Diverticulitis: infection of diverticuli: micro-perforation 2/2 erosion of the diverticular wall by increased intraluminal pressure
- **Uncomplicated** (75%): abdominal pain (LLQ), fever, leukocytosis, anorexia, Δ in BMs (diarrhea or constipation)
- **Complicated** (25%): bowel obstruction, abscess, fistula (potentially with bladder, vagina, skin or peritoneum), or perforation
- Diagnosis: characteristic s/sx + imaging findings (diverticula, bowel wall >4mm, inflammation w/in pericolic fat +/- abscess/fistula)
- Management: (AGA Guidelines: Gastro 2015;149:1944, Gastro 2015;149:1950)
  - **Uncomplicated (medical)**: PO abx x7d (Cipro/Flagyl, Bactrim/Flagyl, or Augmentin), bowel rest. Per AGA, *use of abx should be selective* (immunosupp., pregnant, significant comorbid disease, chronic steroid use, SIRS/sepsis) & if mild disease, may not benefit from abx (Gastro 2015;149:1650) – based off RTCs in Europe (Br J Surg 2012;99:532; Br J Surg 2017;104:52). Others, however, still recommend routine abx for uncomplicated diverticulitis.
  - **Complicated (surgical)**: IV abx (GNR + anaerobe coverage), bowel rest, and surgical evaluation (peritonitis typically present; evaluation for abscess drainage or colonic resection).
- Follow-up: colonoscopy 6w after acute diverticulitis to evaluate for malignancy (if no colonoscopy within prior year)

SEGMENTAL COLITIS ASSOCIATED WITH DIVERTICULOSIS (SCAD) (WJG 2016;22:8067, CGH 2007;5:27)

- Sx: chronic diarrhea, cramping abd pain (LLQ), or intermittent hematochezia. Ddx: diverticulitis, IBD, infxn, med-assoc., XRT.
- Dx: WBC usually nml; fecal calprotectin may be ↑ if severe; endoscopy shows **inflammation of the interdiverticular mucosa** (diverticular orifices uninvolved), spares rectum.
- Tx: no direct evidence; can consider Cipro/Flagyl; if no response to abx, add mesalamine; if fail abx + mesalamine, consider prednisone 40mg x1wk → slow taper.

SYMPTOMATIC UNCOMPLICATED DIVERTICULAR DISEASE (SUDD) (Dig Dis Sci 2016;61:673)

- Definition: persistent abdominal sx (pain, discomfort, bloating, constipation, diarrhea) attributed to diverticulae in the absence of macroscopically overt colitis or diverticulitis.

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

Type	Agent	Dose	Notes
Bulk agents	**Psyllium** (Metamucil), **Methylcellulose** (Citrucel)	1tsp up to TID (for psyllium: up to 30g/d)	In some (esp. STC), can increase bloating & distention in large amounts. Should start low & ↑.
Surfactants	**Docusate** (Colace)	50-360mg QD	Less effective than other laxatives; may be inferior to psyllium. *See data in hospitalized patients above*.
Stimulants	**Senna**	1-4 tabs QD or BID	↑ colonic secretions and stimulates motility. Can cause cramping.
	Bisacodyl (Dulcolax)	5-15 mg up to 3x/w	↑ colonic motility. Can cause cramping. Can be given PO (best QHS) or PR (AM).
Non-absorbed substances (osmotic)	**Polyethylene glycol** Miralax (PEG alone) GoLytely, NuLytely (PEG + salts)	17 g QD; max 34g/d	Modestly more effective and better tolerated (less bloating) than lactulose (Cochrane Rev 2010). Dose PEG daily.
	Lactulose, sorbitol	15-30 ml QD or BID	↑ flatulence/bloating. Less effective than PEG.
	Milk of magnesia (MOM)	15-30 mL QD or BID	Benefit of simultaneous neutralization of gastric acidity and water retention in stool. Avoid if renal failure (Mg).
	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 (Mg).
Enemas	**Tap water, soapsuds mineral oil, fleets** (sodium phos.), **milk & molasses**	Varies	All work via lubrication. Soapsuds also stimulates peristalsis. Fleets is hypertonic and also has osmotic effect. Avoid Fleets in elderly or renal failure (phos).
Secretory drugs	**Lubiprostone** (Amitiza)	24μg BID for STC/NTC; 8μg BID for IBS-C	Binds Cl- channel & increases secretion, ↑ small bowel & colon transit. Most common side-effect is nausea.
	Linaclotide (Linzess), **plecanitide** (Trulance)	*Linaclotide*: 145μg QD for STC/NTC; 290μg QD for IBS-C *Plecanatide*: 3g daily	Agonists of guanylate cyclase-C; ↑ Cl, HCO3 secretion & colonic transit.
Peripheral opioid receptor antagonists	**Methylnaltrexone**, **naloxegol** (pegylated naloxone), **alvimopan**	*Methylnaltrexone*: 1 dose SQ QOD PRN - 38-62kg: 8mg - 62-114kg: 12 mg - <38, >114kg: 0.15mg/kg - CrCl <30: 1/2 dose	At MGH, methylnaltrexone approved only if on stable dose of opioids ≥ 2 weeks x3d w/o BM *AND* failed multiple other laxatives. Contraindicated in obstruction, small risk of perforation. See AGA Guidelines for opioid-induced constipation: Gastro 2019;156:218 & Gastro 2019;156:229.

		Oropharyngeal Dysphagia	Esophageal Dysphagia
Symptoms		Difficulty initiating swallowing; drooling, coughing, aspir.	Difficulty seconds after initiation, food stuck in esophagus
Etiologies	**Neuro-muscular** (solids + liq.)	Central: tumor, stroke, PD, ALS, MS, polio Peripheral: neuropathy, myasthenia gravis Muscular: polymyositis, muscular dystrophy	1°: achalasia, esophageal motility disorders (e.g. distal esophageal spasm, hypercontractile "Jackhammer" esoph.) 2°: diabetes, scleroderma, amyloid, Chagas (Chicago classification: Neurogastro Motil 2015;27:160)
	Structural (solids > liquids)	Intrinsic: tumor, XRT, trauma/surgical resection, Zenker's Extrinsic: anterior mediastinal mass, goiter, cervical spondylosis	Intrinsic: tumor, stricture, infxn, EoE, rings, webs (e.g. Plummer-Vinson), pills (NSAIDs, doxy, tetracyc., bisphosph) Extrinsic: vascular rings (e.g. dysphagia lusoria), Ao. enlarge., LA compression, mediastinal, substernal thyroid, LAD
Work-up		History: sx onset & duration, solid/liq & localization of dysphagia, +/- odynophagia, underlying conditions (e.g. CNS, malignancy, thyroid, DM, scleroderma), use of **offending meds** (pill esophagitis), immunocompromise (Cand., CMV, HSV infectious esophagitis or lymphoma in HIV), radiation, etc. Dysphagia in older adults, is **not** normal aging. PE: gen appearance (?systemic disease or CNS issue), HEENT exam (?evidence of LAD, tumor, asymmetry), FOBT Labs (consider): CBC, TFTs, ANA, α-Scl-70, α -centromere, α -RNP, α -Jo, HgbA1C, iron studies, HIV, AChR-Ab	
Diagnostics		1) Modified barium swallow, ENT and neuro evals, +/- EGD to identify obstructive structural problem 2) Consider chest/neck CT to dx extrinsic compression	1) EGD is the most useful test +/- barium swallow (mucosal pathology or structural abnormality) 2) if normal → esoph. manometry to diagnose motility d/o 3) Consider chest/neck CT to dx extrinsic compression
Selected Conditions		**Zenker's diverticulum**: p/w halitosis, regurgitation of food/aspiration, cough. Tx w/ endoscopic surgery (rigid vs. flexible).	
		Strictures & rings: if lumen <13mm, dysphagia common. Tx PPI, dilation, intralesion steroid inj, stent	
		Distal esophageal spasm: uncoordinated peristalsis a/w intermittent chest pain & regurgitation; barium swallow: corkscrew (vs. nml). **Hypercontractile esophagus**: similar sx; nml barium swall. Tx (both): PPI, nitrates/CCB/PDEi,TCA.	
		Infectious esophagitis: odynophagia; often immunosuppressed – Candida, HSV, CMV	
		Eosinophilic esophagitis (EoE): dysphagia, refractory GERD sx. EGD w/ stacked rings, strict. Bx >15 eos/hpf. Tx PPI, diet Δs (dairy, wheat > soy, eggs, nuts, fish), topical steroids (MDI/neb/liq.); consider dilation. (AGA: Gastro 2020;158:1776)	
		Achalasia: **progressive** dysphagia solids/liquids, + **regurgitation**; barium swallow with bird's beak appearance of distal esophagus; manometry: absent distal peristalsis, incomplete LES relaxation; EGD to r/o pseudo-achalasia (2/2 CA); tx w/ pneumatic dilation, Heller myotomy, POEM, botox, CCBs. (AGA Guidelines: AJG 2013;108:1238; JAMA 2015;313:18)	

Gastroparesis

Definition: decreased gastric motility w/o obstruction
Sx: **n/v, early satiety**, postprandial fullness, bloating +/- abd pain
Etiologies: **diabetes** (vagus nerve damage 2/2 hyperglycemia), post-surgical (e.g. vagus nerve injury post-bariatric surgery), **post-viral**, systemic disease (thyroid, critical illness, Parkinson's, connective tissue d/o), **meds** (opiates, CCB, anti-cholinergics)
Exam: +/- TTP in epig, succussion splash (sloshing on abd ausc)
Dx: exclude mech obstruction w/ EGD, CTE/MRE/SBFT → gastric emptying nuc. study (hold motility meds 48 hrs prior)
Labs: TSH, ANA, A1c, tot protein, alb, CBC w/ diff.
Treatment: small meals w/ low fat & non-digestible fiber, prokinetic agents before meals (metoclopramide or erythromycin; give drug holidays due to tachyphylaxis / to assess benefit), antiemetics; venting G-tube if refractory sx, J-tube for nutrition if wt loss. (ACG Guidelines: AJG 2013;108:18)

Ileus

Definition: slow motility of the gut w/o obstruction, often post-op
Sx: nausea/vomiting, ↓BMs and ↓flatus, abd distention
Studies: KUB/CT w/ colonic dilatation w/o mechan. obstruction
Paralytic ileus: s/p intra-abdominal surgery or a/w peritonitis, ischemia, meds (opioids, anti-cholinergics); worsened by hypoK
Tx: bowel rest, decompression via NGT if mod/severe/ongoing sx, avoid opiates, replete lytes. Methylnaltrexone PRN if opioids.
Acute colonic pseudo-obstruction (Ogilvie's): typically in elderly, hospitalized, ill pts. A/w severe illness (e.g. sepsis, pancreatitis, peritonitis), systemic disease (thyroid dis., DM, renal or liver failure), neuro (spinal cord compression or trauma, Parkinson's, MS), meds (opiates, CCB, anticholinergics).
Tx: conservative (NPO, IVF, NGT/rectal tube), neostigmine if cecal diam. >12 or if fail conserv tx. Colonic decomp. if fails.
(ASGE Guidelines: Gastro Endosc 2020;91:228)

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

Functional dysphagia	Sense of dysphagia w/o structural d/o, abnl motility, GERD or EoE. Sx ≥ 1x/wk. Tx: CCB, TCA
Functional dyspepsia	Early satiety, epigastric pain. Must r/o structural/organic cause. Tx: PPI/H2RA, TCA, metoclopramide
Globus sensation	Sensation of obstruction in the throat when there is none, Tx: PPI, antidepressants, CBT
Cyclical vomiting syndrome	Episodic, stereotyped. Kids>adults. Often trigger and prodrome. May be better w/ hot shower. Tx: anti-emetics (Zofran), benzos to sedate, triptans may abort, TCAs may ppx; overall limited evidence
Cannabis hyperemesis syndrome	Frequent cannabis, n/v (temp. relieved by MJ), relieved by hot shower. Tx: topical capsaicin; ⦸ MJ
Sphincter of Oddi dysfunction	Biliary pain, +/- pancreatitis 2/2 inability to relax, often post-CCY. Tx: trial CCB/nitrate; ERCP

Irritable Bowel Syndrome (IBS):
Definition (per Rome IV Criteria): recurrent abd discomfort ≥ 1x/wk on average for 3 months a/w 2+ of the following: (1) related to defecation, (2) change in stool frequency, (3) change in stool form. No nocturnal pain, weight loss, bleeding, or ↑calprotect/lactoferrin.
Types: IBS-C (constipation-predominant), IBS-D (diarrhea-predominant), IBS-M (mixed), IBS-U (unclassified), by Bristol Stool Score
Epidemiology: ↑ risk w/ younger age, ♀ > ♂, psychosocial stressors, low QoL, hypochondriasis; gastroenteritis may be trigger.
Treatment: **all**: exercise, diet Δ (low FODMAP), fiber (psyllium), rifaximin (esp. non IBS-C), anti-spasmodics (dicyclomine), peppermint oil, TCAs, CBT. **IBS-C**: laxatives (linaclotide, plecanatide, lubiprostone); **IBS-D**: eluxadoline, loperamide, alosetron (♀) (ACG: AJG 2018;113:1)

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

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

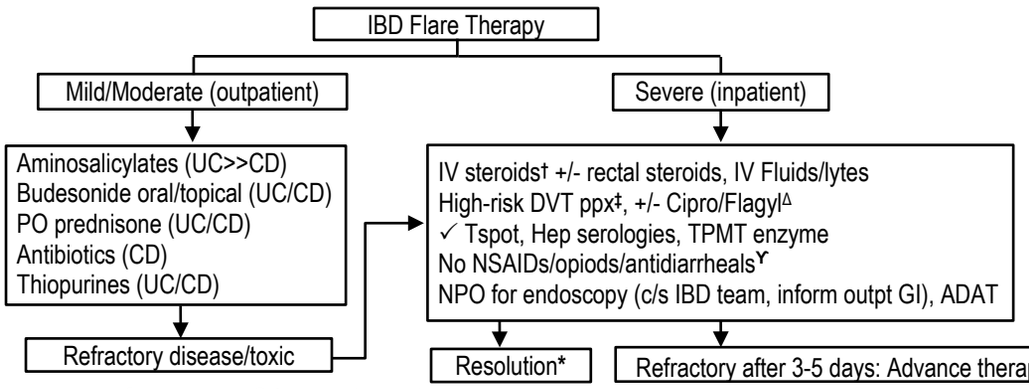
Inpatient Work-up and Management:

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

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

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

Severity	**UC (True-Love Witts)**	**CD (CD Activity Index)**
Mild	<4 stools (bloody or not), afebrile, nml ESR	Ambulatory, tolerates PO/no dehydration, no pain/toxicity
Moderate	4-6 BM, bloody BM, low fever, ↑pain, mild anemia	Failed 1st line tx, low fever, N/V, wt loss, pain, anemia
Severe	>6 BMs, Hb <10.5, fever, HR>90, wt loss, ESR >30	Failed advanced tx, toxic, abscess, obstruction, peritonitis, cachexia



† Methylpred 20mg q8h IV
‡ ↑risk of DVT/PE in IBD pts
^Δ In pts w/ fistula, abscess, peritonitis, pouchitis, perforation, high fever, leukocytosis, bandemia
^ϒ ↑risk of tox meg in UC
* Bridge to maintenance tx
^σ Anti-TNF, anti-integrin, etc.

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

Management guidelines: *CD*: ACG: AJG 2018;113:481, AGA: Gastro 2017;152:271; *UC*: ACG: AJG 2019;114:384, AGA: Gastro 2019;156:748 & 2020;158:1450

Class	**Drug***	**Use**	**Notes & Adverse Effects (AE)**
Steroids	Budesonide (PO/PR), Pred (PO), Methylpred (IV)	Induction	**PO budesonide** 1st-line in mild CD, 2nd-line to ASA for mild UC, but can be 1st-line for mod AE: osteoporosis, infection, AVN, AI, weight gain, mood lability, delirium
Amino-salicylates (UC>>CD)	Sulfasalazine Mesalamine (PO: Pentasa, Ascol, Lialda, Apriso. PR: Canasa, Rowasa)	Induction + Maintenance for mild-moderate disease	**Sulfasalazine**: pro-drug with more AEs, also systemic effects **Mesalamine** forms differ in gut penetration: Pentasa (ileum, R>L colon), Ascol (R>L colon), Lialda & Apriso (pancolon), Canasa & Rowasa (distal). AE: HA, fever, rash, diarrhea, pancreatitis, ↓sperm count, kidney injury
Thiopurines	Azathioprine (pro-drug) 6-MP	Induction + Maintenance	Typically as combination therapy for induction; can be monotherapy for maintenance AE: n/v, hepatitis, BM suppression, pancreatitis, NHL, skin cancer
Anti-TNF	Infliximab (Remicade) Adalimumab (Humira) Certolizumab (Cimzia)-CD Golimumab (Simponi)- UC	Induction + Maintenance for mod-severe	Contraindicated if toxic megacolon, pyogenic infections. **If flare during maintenance**: measure trough (24hrs prior to dose) and antidrug Ab levels, determine if dose escalation or new drug is required. If pt non-responsive despite adequate levels, switch to another class AE: site rxn, infxn, TB/HBV reactiv., demyelinating dz, HF, malignancy
Anti-integrin	Vedolizumab[1,2] (Entyvio)	Induction + Maintenance for mod-severe	VARSITY[3]- In mod-severe UC, achieved ↑ clinical remission at 52wks vs. adalimumab, but w/ greater steroid use AE: infusion reactions, nasopharyngitis
IL-12, -23 inhibitor	Uztekinumab[4,5] (Stelara)	Induction + Maintenance	AE: infection, HA, nasopharyngitis, nausea, abdominal pain, arthralgias
JAK inhibitor	Tofacitinib[6] (Xeljanz)	Induction + Maintenance	Consider if previously failed anti-TNFs AE: infection, herpes zoster, HA, nasopharyngitis, arthralgias
Calcineurin inhib (IV)	Cyclosporine	Induction *only for severe UC*	C/i in s/o toxic megacolon. Labs: troughs (q2-3d) Cr, Mg, lipids, LFTs AE: renal injury, ↑K, infxn, neurotox/seizures (esp. if ↓Mg or cholesterol)

*For UC and CD unless otherwise noted

1. NEJM 2013;369:699, 2. NEJM 2013;369:711, 3. NEJM 2019 381:13, 4. NEJM 2016;375:1946, 5. NEJM 2019;381:13, 6. NEJM 2017;376:1723

Overview

- Acute or chronic insufficiency of blood flow to GI tract; due to systemic hypoperfusion, arterial/venous occlusion, or arterial vasospasm
- Can present in a variety of ways (see below); often in elderly pts or young pts with cardiovascular disease, vasoconstrictive meds (digoxin, α-adrenergic agonists – e.g. phenylephrine, cocaine), or vasculitis
- Must consider intestinal ischemia in patient with **abdominal pain + lactic acidosis** (or unexplained elevated lactate)
- Risk factors: CAD, AF, Valvular disease, CHF, PAD/PVD, vasculitis (SLE/PAN), CKD, HD, hypercoagulable states, prior embolism/DVT, intraabdominal pathology (adhesions, hernias, intussusception, volvulus), intraabdominal infxn/sepsis, aortic surgery

	Ischemic Colitis	Acute Mesenteric Ischemia	Chronic Mesenteric Ischemia
Reference	ACG Guidelines: AJG 2015;110:18	NEJM 2016;374:959	NEJM 2016;374:959
Signs/ Symptoms	- **Cramping pain** (mostly LLQ) → mild/mod **hematochezia** - Often not critically ill, but can present w/ gangrenous bowel or fulminant colitis	- Arterial: **sudden severe abd pain out of proportion to exam**; hx ASCVD (CHF, MI, AFib) - Venous: often insidious onset, waxing/waning abd distention, **N/V**, diarrhea +/- occult blood	- **Recurrent, post-prandial pain ("intestinal angina")**; dull, crampy, starts 10-30m after PO & lasts 1-3 hr - n/v, early satiety, BM Δs - Wt loss, fear of eating
Blood Supply	- SMA & IMA	- SMA (prox. duodenum by GDA)	- SMA (prox. duodenum by GDA), IMA, celiac artery
Pathophys.	**Non-occlusive**: (95%) - Watershed areas (splenic flexure, rectosigmoid) most susceptible; 25% R-sided - Predisposing factors: general risk factors above as well as cardiopulmonary bypass surgery (low flow state), and extreme exercise (shunting of blood flow away from splanchnic circulation + dehydration)	**SMA occlusion**: (~75%) - Embolic (40-50%): SMA has narrow take-off angle; AF / endocarditis / aortic plaque ↑ risk of total occlusion - Thrombotic (20-35%): acute-on-chronic in s/o underlying ASCVD - Dissection / inflammation (<5%) **Non-occlusive**: (5-15%) - Splanchnic arterial hypoperfusion/vasospasm, typically after CV event/surgery, cocaine, vasopressin, vasculitis (SLE, PAN) **Mesenteric vein thrombosis**: (5-15%) - Hypercoag due to thrombophilia (JAK2, PNH), trauma, local inflammatory Δs (pancreatitis, diverticulitis, biliary infxn/inflammation, surgery); stasis due to cirrhosis/portal HTN; malignancy	- Due to progressive atherosclerotic narrowing at origins of visceral vessels - Assoc. w/ ASCVD risk factors: tobacco, HTN, DM, HLD - ↑ risk > 60 yo, female - Less common risk factors: dissection, vasculitis, fibromuscular dysplasia, radiation - If pain becomes constant, consider acute thrombosis (see Acute Mesenteric Ischemia to left)
Diagnosis	**Labs**: ↑lactate, ↑WBC, LDH, CK, & amylase if advanced - Stool guaiac ⊕ in ~50% - ✓ Stool Cx, O+P, C. diff **Imaging**: - Abd CT (I+/O+): wall thickening, edema, thumbprinting, pneumatosis (late), **no vessel occlusion** - Colonoscopy (to confirm/assess extent): petechial blood, pale mucosa, segmental edema/ulceration, rectal sparing	**Labs**: nonspecific, most abnormalities arise after ischemia progressed to necrosis: ↓pH, ↑lactate, AGMA (in 50%), WBC >15K (75%), stool guaiac ⊕ in ~50%; normal D-dimer may help exclude **Imaging**: - KUB: Ileus, colonic dilatation, pneumatosis intestinalis; free air → immediate surgery - Abd CT (ideally CTA**; no oral contrast**): wall thickening, pericolonic fat stranding, pneumatosis, ± arterial occlusion, portomesenteric venous gas - Angiography: consider if CTA non-diagnostic but suspicion remains high, or in cases of vasculitis affecting small-medium size vessels; can stent/tPA	**Imaging**: - CTA (preferred; alt. = MRA): ⊕ if stenosis of ≥ 2/3 major vessels (celiac, SMA, IMA). 91% with 2 vessels, 55% with all 3 vessels - Doppler U/S to measure mesenteric blood flow (and r/o median arcuate ligament syndrome) - Gastric tonometry exercise testing - Angiography (see left)
Treatment	- Bowel rest - IVF resuscitation - D/C vasoconstrictive meds - GNR/anaerobic abx if mod./severe disease (no data) - If suspicion for bowel necrosis, gangrene, or perforation, call surgery	**For occlusive disease**: - NGT/NPO, IVF/blood product resuscitation - broad-spectrum **abx** - Anti-coagulation if not bleeding (**heparin** +/- tPA) - If infarction/peritonitis/perforation → **surgical emergency** - If SMA occlusion: thrombectomy/embolectomy vs. intra-arterial vasodilators vs. thrombolysis **Non-occlusive**: treat underlying cause **Mesenteric vein thrombosis**: anticoag x3-6 mo	- Elective revascularization (if sx): open (aortomesenteric grafting) vs. endovascular (angio ± stenting) - Nutrition/TPN support - AC if acute-on-chronic mesenteric ischemia - In absence of sx, no role of prophylactic intervention
Prognosis	- Favorable prognosis: 85% spontaneous resolution in 2 wk (rarely life-threatening) - 5% have recurrence	- Mortality 50%, but can be 70-90% if delay in diagnosis leading to intestinal gangrene	- Periop mortality 0-16% - Restenosis is common (7% for open revasc; 34% for endovascular)

GENERAL APPROACH

1) Assess nutritional status (Clin Nutr ESPEN 2018;26:13-20)
   - **History/Exam**: dietary intake/tolerance, n/v/d, muscle and fat wasting, weight loss (% over time), myalgias, dermatitis, loose skin/clothes, edema, functional capacity (grip strength, ADLs)
   - **Weight loss as indicator of malnutrition**: >2% in 1 wk, >5% in 1 month, >7.5% in 3 months, >10% in 6 months, >20% in 1 yr
   - **Labs:** albumin, pre-albumin, transferrin, retinol binding protein (RBP) to assess synthetic function. Note that all are negative acute phase reactants and will *decrease* during inflammation. INR prolongation may be indicator of malnutrition. Consider checking vitamin levels if history/exam is suggestive (i.e. if dermatitis ✓Vitamin C level, if encephalopathy ✓ thiamine, etc.)
   - **24-hr calorie count; nutrition consult** if c/f malnutrition (**screen** with NRS-2002 or the NUTRIC Score in hospitalized pts)
2) Determine dietary route (oral > enteral [EN] > parenteral [PN]):
   - **Oral**: aspiration risk, dysphagia, odynophagia? Consider SLP c/s for dietary modifications (e.g. pureed, thick liquids etc.)
   - **Enteral**: if pt unable to tolerate oral diet safely, or unable to meet caloric needs through oral diet alone may need NGT. Place tube **post-pyloric** if gastroparesis, obstruction, intractable nausea/vomiting, or high risk for aspiration
   - **Parenteral**: TPN (central access) or PPN (peripheral). Used when GI tract non-functional.
3) Determine nutritional needs: healthy: ~25 kcal/kg/d; increased needs: (e.g. lung disease, IBD, burn): increase by 1.2-2x
4) Initiate diet: nutrition/TPN consult for specifics, may need to test pre-albumin, CRP at 2-3 d**.** Watch for refeeding (see below)

For reference, see **ACG 2016 Nutrition Guidelines** for hospitalized patients: AJG 2016;111:315

ARTIFICAL NUTRITION

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

Tube Feed Formulas:

ISOTONIC FORMULAS	
Osmolite 1.0	Normal absorptive capacity
Jevity 1.5	Long-term TF Prevent constipation (high fiber)
Promote	Wound healing (high protein) ICU patients (on propofol)
Vital (semi-elemental)	IBD, pancreatitis Post-abdominal surgery

HYPERTONIC FORMULAS	
Osmolite 1.5	Respiratory failure/ARDS Volume overload (high protein)
Nepro	Renal or liver failure (low Na/K/phos)
Beneprotein/ProSource Liq Protein (modular protein)	Wound healing
TwoCal HN (normal protein, no fiber)	Max fluid restriction

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

- Monitor for complications of TPN (if applicable):
  - **Metabolic effects**: hyperglycemia (2x >enteral), serum electrolyte alterations, refeeding syndrome (see below), Wernicke's encephalopathy, hepatic dysfunction, biliary sludge/gallstones. **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) can be given as PPN
- **To stop TPN,** coordinate careful transition to EN w/ nutrition; stop when EN provides >60% energy needs (AJG 2016;111:315)

REFEEDING SYNDROME

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

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

SPECIAL CONSIDERATIONS

- **IBD flares, pancreatitis**: early enteral feeding (ideally within 24-72 hrs of admission)
- **Critical care**: enteral feeding should start within 48 hrs of ICU stay (superior to TPN if GI tract functional); contraindications include significant GI pathology (e.g. GI bleed or obstruction) for which patient should be NPO (Clin Nutr ESPEN 2019;38:48)
- **Bariatric surgery** (e.g. RYGB, Gastric Sleeve): high risk of micronutrient deficiency from poor intake + malabsorption
  - Post-op micronutrient screening: generally q3-6mo during first year (labs and ROS), then annually; includes Vit A, D, iron, folate, B12, Ca, Cu, Zn, lipids; Vit E+K, thiamine (in select pts); see Table 2 in AMBS guidelines: Surg Obes Relat Dis. 2017;13:727
  - Management: ensure patient taking chewable/liquid MVI with minerals/iron (2 pills if RYGB), Ca^{2+}/Vit D, B12
  - Dumping syndrome: nutrients rapidly enter duodenum leading to pain, diarrhea, flushing, tachycardia, syncope (<30min after meal), hypoglycemia (1-3hr later). Tx w/ low carb, high protein/fat diet and frequent small meals
- **Dementia**: avoid dietary restrictions, use nutritional supplements as needed; lack of evidence to support tube feeding; guidelines recommend against TFs in advanced dementia (a/w higher mortality) (Nutr Clin Pract. 2014;29:829, Clin Nutr 2015;34:1052)

ETIOLOGY (CGH 2007;5:648)

- **Gallstones/sludge** (40-75%): #1 in women
- **Alcohol** (30%): #1 in men
- **Hypertriglyceridemia** (10%): #3; suspect if TG>1000
- **Anatomic**: ampullary diverticula/stenosis, duodenal stricture, tumor, divisum, parasites, foreign body
- **Post-ERCP** (3-5%): in high-risk pts, **rectal NSAIDs** ↓ rate of pancreatitis (NEJM 2012;366:1414)
- **Autoimmune**: ↑ IgG4, +ANA (rare)
- **Hypercalcemia**: Ca activates pancreatic enzymes
- **Genetic**
- **Trauma**: blunt, especially s/p MVA
- **Drugs** (<5%): Class Ia: ACEi, dapsone, lasix, flagyl, pentamidine, statins, sulfa, tetracycline, valproate, mesalamine; Class Ib: amiodarone, azathioprine/6-MP, dexamethasone; Class II: didanosine, estrogen, propofol, tamoxifen, hydrochlorothiazide
- **Toxins**: organophosphates, scorpion venom, methanol, **smoking**
- **Infections**: viral (Coxsackie, EBV, CMV, HIV, Mumps, VZV, HAV, HBV, HSV), bacterial (Mycoplasma, Legionella, Salmonella), fungal (Aspergillus), parasitic (Toxoplasma, Crypto, Ascaris)
- **Ischemia**: vasculitis (SLE, PAN), hypoTN/shock, cholesterol emboli
- **Tropical**: pt from low SES in SE Asia, first bout as child
- **Idiopathic** (10-25%)

DIAGNOSIS / SEVERITY / PROGNOSIS (Revised Atlanta Classification: Gut 2013; 62:102, Pancreatology 2014; 14:324)

- **Presentation**: abd pain (90%) (band-like pain to back is specific but only 50%), n/v (90%), ileus, jaundice, flank/umbilical ecchymoses
- **Diagnosis – need 2/3**: 1) consistent clinical presentation, 2) lipase >3x ULN, 3) characteristic imaging
- **Severity**: mild: absence of organ failure and local or systemic complications; moderate: organ failure that resolved within 48 hours or local/systemic complication; severe: organ failure >48 hours (22% mortality)
- **Prognosis**: many scoring systems; BISAP is quick. SIRS ↑ mortality. Ranson, APACHE II, & other organ failure scores less practical.

WORKUP

- **History**: prior episodes, EtOH/smoking, prior GI procedures (e.g. CCY, ERCP), meds, infx sx, autoimmune hx, FH
- **Labs**: ✓ lipase (↑Sn vs. amylase; *no need to trend*; false + in CKD, DKA, others), CBC (often ↑Hct), BMP w/ Ca, LFTs (↑ ALT >3.5ULN w/ 95% PPV for gallstone pancreatitis: AJG 1994; 89:1863), lipids (TGs)
- **Imaging**: CT if need to establish dx or to eval. for complications; RUQUS to r/o gallstones. MRI/MRCP can detect necrosis, stones.

MANAGEMENT (AGA Guidelines: Gastro 2018;154:1096)

- **IV fluids**: aggressive in first 24hrs: boluses + infusion 150-250/hr. **LR>NS** (↓SIRS, ↓CRP; but avoid if ↑Ca: CGH 2011;9:710). Goal-directed: ↓HR, ↓Hct, ↓BUN (Δ BUN a/w ↓mortality: Gastro 2009;137:129), UOP 0.5-1cc/kg/hr. Generally ⦸ aggressive resuscitation after 24-48hr. Overresuscitation → ↑ risk for abdominal compartment syndrome, need for intubation.
- **Pain control**: IV opioids | **Abx**: no role for prophylactic abx
- **Nutrition**: start PO (low fat) immediately once no n/v or abd pain. 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 (Cochrane Rev 2010)
- **Reverse precipitants**: treat ↑Ca or ↑TG (see below), 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 (AJG 2004;99:2417)
  - **HyperTG**: insulin gtt (0.1-0.3U/kg/hr) + D5, q1h FSBG (initially), q12h TG. Goal TG <500 (may take several days). No good evidence for apheresis so typically not done at MGH. Once can take PO, fibrates are first line. DC: lifestyle Δs, lipid clinic referral.

COMPLICATIONS (AGA Guidelines: Gastro 2020;158:67; NEJM 2016;375:1972)

<table>
<tr><th colspan="3">Local</th><th>Vascular</th><th>Systemic</th></tr>
<tr><th></th><th>< 4 weeks</th><th>> 4 weeks</th><td rowspan="4">Thromboses: splenic, portal, SMV; AC if → portal vein or bowel ischemia

Pseudoanuerysm: erosion of GDA/splenic artery → bleeding into pseudocyst. Suspect if ↓Hgb, expansion of fluid collection, unexplained GIB. Dx: arterial phase CT. Tx: IR embo. prior to drainage of fluid collection.</td><td rowspan="4">Abd. compartment syndrome: intra-abd pressure >20 w/ new organ failure. ✓ bladder pressure if in ICU.

ARDS: via phospholipase degradation of surfactant

Metabolic: ↓Ca, ↑Glc, ↑TG

GIB: via pseudoaneurysm

AKI

DIC</td></tr>
<tr><td>Interstitial edematous pancreatitis</td><td>Acute peripancreatic fluid collection: w/o features of pseudocyst; resolve spontaneously w/o drainage</td><td>Pancreatic pseudocyst: fluid collection w/ well-defined wall. If dx unclear, EUS w/ FNA (↑amylase). Drain if sx, rapidly ↑, infxn. (endo vs. perc/surg)</td></tr>
<tr><td rowspan="2">Necrotizing pancreatitis</td><td>Acute necrotic fluid collection: intra- or extrapancreatic collection of fluid & necrosis</td><td>Walled off necrosis: encapsulated collection of necrosis. Drainage if sx or infected (endo vs. perc)</td></tr>
<tr><td colspan="2">Infected necrosis: initially sterile but 1/3 become infected, usually later in course; abx: (cefepime or cipro) + flagyl vs. pip/tazo vs. carbapenem in critically ill. Necrosectomy – can delay 4wks if stable.</td></tr>
</table>

- **Chronic pancreatitis** (ACG Guidelines: AJG 2020;115:322): repeat acute attacks (esp EtOH & smoking; AJG 2019; 114:656) → fibrosis & loss of glandular tissue → chronic abd pain, exocrine insufficiency (→ steatorrhea, weight loss), endocrine insufficiency (→ brittle DM). Lipase/amylase may be ↑ early but nml/low as more tissue lost. ⊕ Fecal fat, ↓ stool elastase. CT/MRI pref. for dx: calcifications, ductal dilation. Tx: pancreatic enzyme replacement (Creon), ensure vit ADEK replete, pain control. ↑ risk of pancreatic CA.

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

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

Gastroenterology — Liver Chemistry Tests

Upper Limit of Normal (ULN): ALT (IU/L): 33 (males), 25 (females); ALK-P: 115 (males), 100 (females)

Patterns of Liver Chemistry Test Elevation:
Hepatocellular: ALT and AST ↑
Cholestatic: ALK-P ↑+ direct hyperbilirubinemia
Infiltrative: ALK-P ↑ w/o significant bilirubin or AST/ALT elevation
Non-hepatic: e.g. indirect hyperbili, non-hepatic alk phos ↑, non-hepatic AST ↑

*Calculate the De Ritis "*R ratio*"*:
R ratio = (ALT/ULN) ÷ (Alk Phos/ULN)
Hepatocellular: R ratio > 5
Cholestatic: R ratio < 2
Mixed: R ratio between 2-5

Causes of hepatocellular injury: ↑AST/ALT; R ratio >5. *Always consider relevant history (meds, OTCs, herbals) and clinical picture*

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

Extreme AST/ALT elevation >1000: **acute processes**
- Ischemia: shock, cardiac arrest, Budd-Chiari
  - Natural history: ↑ in ALT/AST (often >50xULN) then ↑ bilis (lag behind) and peak 1wk later
  - ALT:LDH ratio <1.5 favors dx of ischemia > viral hepatitis (Sn 94%/Sp 84%) (JCG 1994;19:118)
- Meds/toxins: esp. APAP
- Acute viral infection: hepatitis A-E, HSV, VZV, EBV, CMV, consider HBV reactivation if immunosuppressed
- Autoimmune hepatitis (acute)
- Acute biliary obstruction
- Acute Wilson's (very rare if >40)
- Malignant infiltration

Workup and Management

- Stop potentially offending medications/toxins
- Viral hepatitis serologies
- RUQUS: steatosis (NAFLD vs. EtOH), cirrhosis → Fibroscan
- AIH: ANA, ASMA, LKM-1, IgG
- Wilson's: ceruloplasmin (↓), urinary Cu (↑)
- Hemochromatosis: iron studies: ♂: Fe/TIBC ≥45% & ferritin >200; ♀ Fe/TIBC ≥40% & ferritin >150 → HFE testing
- *See* ESLD *for further reccomendations*

- ✓ INR, assess for HE (acute liver injury vs. failure)
- Stop offending meds/toxins, send tox screen
- Viral hepatitis serologies, including HSV, EBV, CMV
- RUQUS with doppler
- *See* Acute Liver Injury & Failure *for further diagnostic/treatment reccomendations*

Commonly used drugs that can cause hepatocellular injury: acetaminophen, allopurinol, amoxicillin-clavulanate **(Augmentin)**, amiodarone, aspirin, carbamazepine, clindamycin, fluconazole/ketoconazole, fluoxetine, glyburide, heparin, hydral, INH, labetalol, lisinopril, losartan, methotrexate, niacin, nitrofurantoin, NSAIDs (some), phenytoin, protease inhibitors, statins, sulfa drugs, trazodone, valproic acid
Illicit drugs: anabolic steroids, cocaine, ecstacy, PCP. *See* livertox.nih.gov *for full list.* (APT 2007;25:1135, NEJM 2019;381:264)

Workup and Management

Causes of cholestatic injury pattern: ↑ **ALK-P and bili; R ratio<2**
- Biliary obstruction: choledocholithiasis, malignancy (cholangio, pancreatic, ampullary), primary sclerosing cholangitis (PSC), chronic pancreatitis with strictures
- Intrahepatic cholestasis: meds (anabolic steroids, **Augmentin**, PCN / **cephalosporins**, captopril, macrolides, estrogens, Bactrim; see livertox.nih.gov) TPN, sepsis, primary biliary cholangitis (PBC)
- Biliary epithelial damage: hepatitis, cirrhosis

→
- Stop offending meds/toxins
- RUQUS for biliary obstruction
- May need MRCP or ERCP
- ✓ AMA if persists
- If chronic, consider liver bx

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

→
- ✓ GGT and/or fractionated ALK-P to confirm liver origin
- Imaging: RUQUS or CT; MRCP if negative
- Consider SPEP + IgG4
- If chronic, consider liver bx

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

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

(AGA guidelines: Gastro 2002;123:1367; ACG Guidelines: AJG 2017:112:18)

GALLSTONE DISEASES (J Hep 2016;65:146)

Cholelithiasis: presence of stones in **GB** (6% of ♂, 9% of ♀)	**Choledocholithiasis**: stones in **common bile duct**
- Sx: asx vs. **biliary colic** (dull RUQ/epigastric pain, 30m-6 hrs, caused by GB contracting around sludge/stone, often postprandial & w/ n/v) - Labs: normal - Dx: **RUQUS** (Sn 84%, Sp 99%) > CT (Sn 55-80%); EUS if ⊖ - Stone types: *cholesterol* (most common) → 5 Fs: fat, female, forty, fertile (multiparous), fair (Caucasian); *pigment*: Crohn's/ileal disease, extravasc. hemolysis, TPN - Tx: *asymptomatic*: observe; CCY only if at ↑ risk for GB CA (stone >3cm, porcelain GB, GB adenoma); *symptomatic*: elective CCY - Complications: cholecystitis, choledocholithiasis, pancreatitis, GB CA, gallstone ileus, Mirizzi syndrome (compression of CBD/CHD)	- Sx: RUQ pain, n/v, jaundice; may be asx - Labs: ↑ALP, ↑Bilis +/- ↑AST/ALT - Dx: **RUQUS** to look for CBD dilation >7mm (poor Sn for visualizing stones themselves); **MRCP** or EUS if equivocal - Tx: ERCP w/ stone removal; interval CCY - Complications: ascending cholangitis, acute pancreatitis *NB*: can occur in pts s/p CCY if de novo formation in CBD
Cholecystitis: stone in **cystic duct** → inflammation of GB ± infxn	**Cholangitis**: ascending biliary infxn 2/2 **obstruction in CBD**
- Sx: RUQ pain (w/ radiation to back/shoulder), Murphy's sign, n/v, fever - Labs: ↑WBC; may have mild ↑ALP, Bili; but if ↑↑, c/f CBD obstruction - Acalculous cholecystitis: GB stasis/ischemia w/o obstruction. Unexplained fever, ↑WBC, in ICU pt. *Risk factors*: trauma, burns, TPN, severe illness, fasting, sepsis, immunosuppression (CGH 2010;8:15) - Dx: **RUQUS** (GB wall thickening, pericholecystic fluid, *sonographic Murphy's*) → **HIDA** scan if ⊖; pre-tx w/ 2mg IV morphine ↑Sn (given by nuclear rads at MGH) (AJR 2016; 207:865). Tokyo Guidelines for dx & severity (based on deg. of organ dysfunction) (J Hep Panc Sci 2018;25:41) - Tx: **abx** (Zosyn or CTX/Flagyl). **Early (<7d) CCY** during hospitalization →↓ morbidity (Br J Surg 2015;102:1302). If critically ill or high surgical risk & fails to improve after 1-3d abx, **perc. cholecystostomy**. Stop abx 24hrs post-CCY unless septic/perc chole: 4-7d. (JAMA Surg 2019;154:873) - Complications: gangrenous cholecystitis, emphysematous cholecystitis (gas-forming org.), perforation, enteric fistula, gallstone ileus	- Etiologies: stone, stricture (malig., PSC, AIDS), liver fluke - Sx: *Charcot's triad:* RUQ pain, fever, jaundice; *Reynold's pentad*: + shock and AMS - Labs: ↑WBC, ↑ALP, ↑Bili, +/- ↑AST/ALT (can be ↑↑) - Dx: **RUQUS** (ductal dilation), **MRCP**/ERCP. Tokyo Guidelines for dx & severity (J Hep Panc Sci 2018;25:17) - Tx: broad spectrum **abx** (Zosyn or CTX/flagyl; carbapenem if life-threatening) x7d; urgent **ERCP** w/ decompression (<24-48hrs) if severe (associated organ dysfunction/shock) or if fails to improve on abx x24hrs. Perc drainage if ERCP not feasible. Interval **CCY** if due to gallstones.

AUTOIMMUNE BILIARY DISEASES

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

MALIGNANT DISEASE OF THE BILIARY TRACT

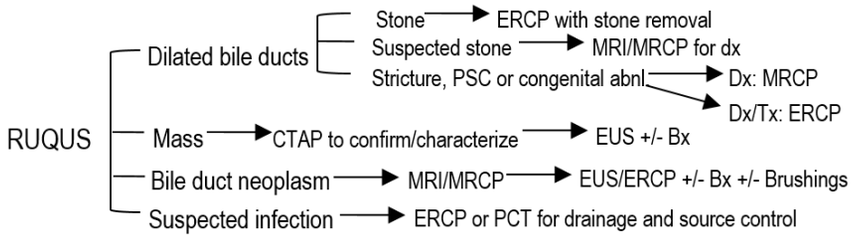
Gallbladder carcinoma: risk factors: gallstone disease (34x more likely to develop CA), porcelain GB, GB polyps, PSC, chronic infxn

- Clinical manifestations: usually asymptomatic; sx may include n/v, weight loss, biliary colic, jaundice (if obstruction)
- Diagnosis: LFTs usually normal, ↑CA19-9/CEA; RUQUS best screening test, then CT/MRI/MRCP

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

- Clinical manifestations: cholestasis (jaundice, pruritus, acholic stool, dark urine), RUQ pain, n/v, weight loss, fever
- Diagnosis: ↑ALP, Bili, CA19-9/CEA +/- ↑AST/ALT depending on deg. of obstruction; RUQUS best screening test, then ERCP/MRCP/EUS (depending on location)

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



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

Presentation: non-specific fatigue, lethargy, anorexia, n/v, RUQ pain, pruritis, +/- jaundice → confusion in ALF (and may → coma).

Initial diagnostics: CBC, CMP, PT/INR, T&S, lactate, ABG, arterial NH3, FSBG, hCG, HIV, APAP, tox screen, viral serologies (see below), HIV-1 & -2 Ab, autoimmune serologies (see below), amylase/lipase, RUQUS w/ doppler

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

General 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 (grade 3-4 ASAP).
- Disposition/monitoring: ICU if HE grade ≥2; ✓ freq. INR, CBC, ABG, Glc, Na, K, Cr, Mg, Phos; freq. exams to assess for signs of worsening HE or ↑ICP (esp. grade 3-4), e.g. Cushing's triad
- Hemodynamics: IVF (NS) and/or pressors (norepi ± vaso); goal MAP ≥75 for cerebral perfusion.
- N-Acetylcysteine (NAC): tx of APAP toxicity, but may benefit non-APAP ALF w/ grade 1-2 HE (Gastro 2009;137:856); given initially in all/most cases: 150mg/kg over 15min → 100mg/kg over 16hr
- **Encephalopathy**: intubation for HE gr. ≥3; ↑**cerebral edema** in HE gr. 3 (25-35%) & 4 (65-75%).
  - Lactulose in ALF controversial: no Δ outcomes, ↑ bowel distent. Rifaximin's role uncertain.
  - If **high risk** for cerebral edema (grade 3-4, NH3 >150, ARF, pressors), **prevent** w/ 3% saline for Na 145-155 (Hep 2004;39:464), HOB 30, ↓ stimulation, avoid overhydration & high PEEP.
  - **Treat** cerebral edema w/ IV mannitol (0.5-1g/kg bolus x1-3); if impending herniation, hyperventilate to PaCO2 ~25-30 (temporary; concern that may worsen edema by → ischemia). Pentobarbital/thiopental coma if other measures fail (though may cause hoTN which → ↓ CPP)
- Seizures: treat w/ phenytoin; benzos if refractory. Consider routine EEGs for subclinical SZ.
- Infection: high risk for bacterial (Staph, Strep, GNRs) & fungal. ✓ serial BCx, UCx, SCx, CXR. May not fever, ↑ WBC, or have localizing s/sx, 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 but routine FFP not recommended. In ICU, ppx w/ PPI.

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 (esp. if NH3 >200, grade 3-4 HE)
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 8hrs. Rumack-Matthew Algorithm
- HBV → OLT. Possible role for antivirals.
- HCV → OLT.
- 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.
- Alcoholic Hepatitis → see *Alcohol-Related Liver Disease*

Prognosis: MELD score >30.5 = poor prognosis; consider liver transplant. King's College Criteria also used for prognosis – more specific but less sensitive vs. MELD. Poor prognosis for ALF due to HBV, Wilson's, Budd-Chiari, autoimmune, drug injury.

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

HEPATITIS A (J Hep 2018;68:167)

Fecal-oral transmission from person-person contact or contam. food/water, international travel. Sx: abrupt-onset n/v, anorexia, malaise, fever, jaundice, RUQ/abd pain, ↑ALT>AST (often >1000), ↑ bilirubin, ALP. 70% of adults w/ sx, last 2-8 weeks, jaundice peaks after 2 weeks. Dx: ⊕ anti-HAV IgM (persists 3-6 months after infxn). Anti-HAV IgG forms at 2-3 weeks; persists for life and confers immunity. Tx: supportive unless ALF (rare) → transplant. Vaccinate if: MSM, IVDU, chronic liver disease, travel, etc.

HEPATITIS B (AASLD Guidelines: Hepatology 2018; 67:1560)

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

sAg	sAb	cAb	Interpretation	Next Steps
⊕	-	⊕	Hepatitis B infected (acute or chronic)	✓ IgM anti-HBc (acute vs. chronic), HBV DNA, HBeAg
-	⊕	⊕	Past infection (resolved)	None; ↑ risk of reactivation w/ chemo / immunosuppression
-	-	⊕	(1) Recovery from remote acute infxn (w/ sAb titers that have waned), (2) chronic infxn (& low level sAg), (3) acute HBV in window period, (4) false ⊕ anti-HBc *or* false ⊖ sAg	Differentiate possibilities w/ IgM anti-HBc (acute infxn vs. others), anti-HBe, HBV DNA, repeat anti-HBc (later). *NB*: "occult HBV" = DNA⊕ w/ sAg⊖ +/- cAb⊕. Low risk reactivation but ↑ if chemo/immunosuppression.
-	⊕	-	HBV-immune from prior vaccination	None
-	-	-	Uninfected, non-immune	Vaccinate

HBV reactivation: indicated by: (1) ↑ in HBV DNA vs. baseline or (2) reverse seroconversion from sAg-/anti-HBc+ to sAg+

- **High risk therapies**: rituximab, anti-TNF, high dose steroids (>20mg pred/d x4w), HSCT, chemotherapy, anti-rejection therapy
- Greatest risk if sAg+: should receive ppx before immunosuppressive/cytotoxic tx. Lower risk if sAg-/anti-HBc+ but still at risk (even if sAb+) – in some situations, can be monitored for reactivation; in others (HSCT, rituximab, other B-cell agents) should receive ppx.

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

HBeAg ⊕			HBeAg ⊖		
ALT ≤ULN‡	**ALT 1-2x ULN**	**ALT ≥2x ULN**	**ALT ≤ULN**	**ALT 1-2x ULN**	**≥2x ULN**
ALT q3-6mo HBeAg q6-12mo.	DNA >20K: - Exclude other causes ↑ALT - If ≥ F2 fibrosis*, tx. - If ↑ALT persists, tx. DNA <20K: - monitor q1-3mo.; if >2k for 6mo, tx.	DNA >20K: tx DNA <20K: - monitor q1-3mo.; if >2k for 6mo, tx.	DNA >2K: - ALT & DNA q3mo x1yr, then q6mo. DNA <2K†: - ALT & DNA q3-6mo., HBsAg q1yr	- Exclude other causes ↑ALT - If ≥ F2 fibrosis*, tx. - If DNA >2k & ↑ALT persists, tx.	DNA >2K: tx DNA <2K: - Exclude other causes ↑ALT - If ≥ F2 fibrosis*, tx - If DNA becomes >2k & ↑ALT persists, tx.

NB: ALT ULN > 35 for ♂ and >25 for ♀ (not local reference values). *Fibrosis stage determined with Fibroscan & FIB-4. If indeterminate → liver Bx. ‡HBeAg+ w/ DNA ≥10k but nml ALT = "immune-tolerant" – consider liver bx if age >40. †HBeAg-, anti-HBe+ w/ DNA <2k, nml ALT = "inactive"; monitor for spont. sAg clearance → "functional cure" (NB: still ↑HCC risk).

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

Screening	HCV Ab: *all* ≥18 x1 (CDC: MMWR Rec Rep 2020;69:1; USPSTF: JAMA 2020;323:970). Annual if IVDU or MSM w/ HIV.
Risk Factors	Blood products before 1992 or from infected individual, MSM, HIV, IVDU, chronic HD, incarceration, immigration from high prevalence area, birth to HCV infected mother, sex with HCV partner.
Diagnosis	If ⊕Ab, ✓RNA. If ⊕RNA, ✓HCV genotype and tx. If RNA-, spontaneously cleared (*NB*: can still get reinfected).
Natural History	Acute HCV: 75% subclinical. If sx, develop 2-26w after exposure, last 2-12w. Fulminant rare (<1%). Chronic HCV: 80% → chronic; if younger, ♀, genotype-1, IL28B, jaundice, ↑ALT more likely to clear spontaneously. 20% → cirrhosis (↑ risk if ♂, EtOH, obesity, HIV, immunosupp.). HCC risk 1-13%/yr.
Extrahepatic	Mixed cryo., porphyria cutanea tarda, lichen planus, LCV, thyroiditis, Sjogrens, renal dz (e.g. MPGN), NHL
Treatment	Varies based on fibrosis/cirrhosis (stage w/ FIB-4, Fibroscan, FibroTest), genotype (1-6), comorbidities (cirrhosis, CKD, HIV), prior tx regimens. DAAs x8-12 weeks. ✓HCV RNA 12 weeks after therapy to assess SVR. See hcvguidelines.org. If acute HCV, can tx w/o waiting to see if clears, esp. if risk of loss to f/u, behaviors that could result in transmission. *NB*: if cirrhosis, still ↑ risk HCC s/p HCV tx & need ongoing surveillance.

HEPATITIS D (Gastro 2019;156:461)

Coinfection or superinfection with HBV. Coinfection similar to HBV but more severe, ↑ risk ALF; often biphasic ALT course w/ 2 peaks. Superinfection most severe, highest risk ALF & chronic infxn (90%) → cirrhosis in 80% in 5-10y. 3x ↑ risk HCC vs. HBV mono-infection.

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 are asx & resolve spontaneously. Extra-hepatic: neuro (e.g. GBS), renal, arthritis, anemia, pancreatitis. ↑ Risk of acute hepatic failure/mortality in pregnant women (Annals 2007;147:28). Rarely chronic HEV in transplant recipients. Rx with supportive care in immunocompetent pts.

Alcohol-Related Liver Disease (ALD): (AASLD Guidelines: Hepatology 2020;71:308; ACG Guidelines: AJG 2018;113:175)
Risk factors: sex (F>M), pattern (↑ daily, ± ↑binge), obesity, genetics (e.g. PNPLA3), smoking, comorbid HCV/NAFLD/etc.; coffee ↓ risk
Pathophysiology: EtOH → fat accumulation; EtOH → ↑ gut permeability → ↑ innate immune response, liver cell inflammation, injury, necrosis, fibrosis; may be important role for gut microbiota (Nature 2019; 575:505)
Disease spectrum:

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

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.

Diagnosis: onset of jaundice w/in prior 8wks, ongoing heavy EtOH (F >40 g/d, M >60 g/d) for >6mo. with <60d abstinence before onset of jaundice, AST moderate ↑ (50-400) w/ AST/ALT >1.5, Tbili >3 (Consensus Dx: Gastro 2016;150:785). Often ↑WBC (<20k, ↑ PMNs), ↑ INR.

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

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

Tool	Use	Components	Stratification
Maddrey Discriminant Function (MDF)	Initiation of steroids, prognosis	PT, PT control (14.5 at MGH), Tbili	≥32 = severe → 1mo. mortality 30-50%; start steroids (Gastro 1978:75:193)
MELD	Prognosis, consider initiation of steroids	Tbili, INR, Cr, Na	>20 = 3mo. mortality 20%; consider steroids (Hepatology 2005;41:353)
Lille	Day 7 continuation or cessation of steroids	Day 0: Age, Albumin, PT, Cr Day 0 & Day 7: Tbili	≥0.45: Nonresponse → stop steroids <0.45: Response → continue steroids (Hepatology 2007;45:1348)

Treatment of Alcohol-Related Hepatitis
Corticosteroids: see algorithm. NAC may benefit, no harm (though is large vol. load)

- No MDF ceiling but if very severe (e.g. MDF >90, MELD >30), need to closely assess for occult infxn or other contraindications. Single study w/ MDF >54 a/w ↑mortality has not been replicated (Alc Clin Exp Res 1995;19:635)
- Prednisolone used as no hepatic metabolism (methylpred 32mg is IV alternative): 40mg x 28d w/ 2-4w taper (e.g. ↓ 10mg q4d until 10mg then ↓5mg q3d)
- STOPAH trial: ↓ 28d mortality but not 90d, & ↑ infxn (NEJM 2015;372:1619); recent meta-analysis also w/ ↓ 28d mortality (Gastro 2018;155:458)

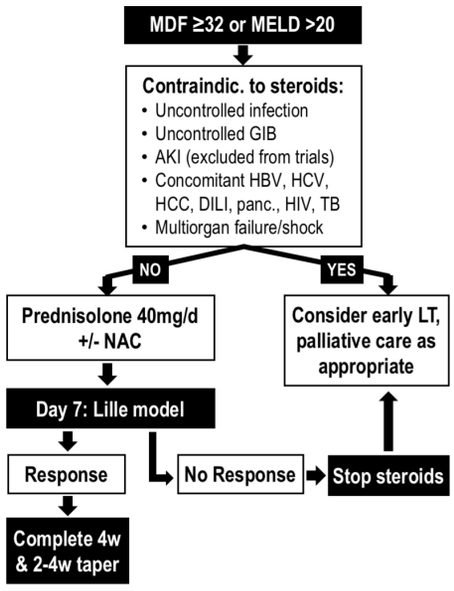
Supportive therapy: monitor for infxn, HRS; hold βB if MDF ≥32 as ↑ incidence of AKI
Nutrition: ensure adequate kcal, protein; supplement w/ MVI w/ thiamine, folate, B6, & consider Zn. Low kcal in severe AH a/w ↑ infxn & ↑ 6mo. mortality (Gastro 2016;150:903)
Abstinence: can result in rapid improvement in outcomes w/in 3 mo.

- Acamprosate 666mg TID, naltrexone 50mg QD (↓ dose in cirrhosis), baclofen 5-10mg TID (Lancet 2007;370:1915), gabapentin 600mg TID (JAMA 2014;174:70), topiramate 75-400mg/d

Liver Transplantation: definitive therapy for ALD. Traditionally required 6mo. abstinence but recent European and US studies showing that early LT in appropriately selected pts → ↑ 6mo. survival with low risk of alcohol relapse and low impact on donor pool (NEJM 2011;365:1790, Am J Transplant 2016;16:841)

- ***MGH pilot program*** offers early LT eval. prior to abstinence for pts with 1) 1st alcohol-related decompensating event (i.e. no prior knowledge of alcohol-related liver disease or alcohol-related legal issues), 2) MDF ≥32, 3) not responsive to steroids, 4) not grade 3-4 HE (to allow for psych eval), 5) strong social support, 6) absence of severe psychiatric co-morbidities, and 7) no other substance use disorder. Consult hepatology for candidacy.

Alcohol Liver Evaluation Team **p26299**: will evaluate inpts with known ALD or AUD without known ALD. If hepatology team following, they will coordinate w/ them.



Other therapies with potential efficacy:

- **NAC**: w/ steroids x5d, a/w ↓mortality at 1mo, but not 3 or 6mo. (NEJM 2011;365:1781, Gastro 2015;149:958)
- Pentoxifylline: consider if steroids contraind. No convincing data on mortality benefit though ↓AKI/HRS (Gastro 2000;119:1637, APT 2013;37:845)
- G-CSF: currently only in clinical trials (Hepatology 2019;70:802, AJG 2014;109:1417)

Definitions
- Cirrhosis: advanced state of fibrosis and regenerative nodules that distorts hepatic architecture and vasculature
- Decompensated cirrhosis: development of ascites, hepatic encephalopathy, jaundice, or variceal hemorrhage in patient w/ cirrhosis
- End-stage liver disease (ESLD): accompanying pathophysiologic state of impaired liver function

Clinical Manifestations and Diagnosis (JAMA 2012;307:832)
- **Symptoms**: fatigue/weakness, jaundice, pruritus, nausea, anorexia, abdominal distention, GIB, confusion, muscle cramps
- **Exam**: ↓BP, splenomegaly, caput medusae, ascites, jaundice, spider angiomata (>3), gynecomastia, testicular atrophy, palmar erythema, asterixis, nail Δs, Dupuytren's contracture
- **Labs**: ↑TBili, ↑INR, ↓Alb, ↓Na, ↓platelets, +/- ↓Hgb/Hct, ↓WBC; AST, ALT, alk phos, and GGT may be elevated or normal
- **Diagnostics**: viral hepatitis panel, iron studies, ANA, ASMA, AMA, α1AT, ceruloplasmin, SPEP
- **Imaging**: RUQUS (with doppler) to assess echogenicity/morphology of liver, ascites, vascular patency, biliary tree, HCC
- **Non-invasive fibrosis assessment**: goal: stratify as low, indeterminate, or high risk for adv. fibrosis; ideally combine multiple tests
  - **Radiographic**: transient elastography best in HBV/HCV, is affected by obesity; MRE better in NAFLD (Gastro 2017;152:1536)
  - **Serum tests**: APRI best studied in HCV & ALD (Hepatology 2011;53:726); FIB-4 index in HCV & NAFLD (Liver Int 2010;30:546); NAFLD fibrosis score in NAFLD (Hepatology 2007;45:846); FibroSure (6 biomarkers) in HCV & HBV
- **Biopsy**: gold standard but now performed less often. Main indications are dx uncertainty or indeterminate fibrosis severity (NEJM 2017;377:756). Perc. (cannot do through ascites, massive obesity) or transjugular (allows HVPG measurement; pref. if coagulopathy).

Etiologies
- **Most common**: alcohol, viral (HCV, HBV), non-alcoholic fatty liver disease (NAFLD), hemochromatosis
- Genetic disorders: hemochromatosis, Wilson's, α1AT deficiency (NEJM 2020;382:1443), CF, inherited disorders of glucose metabolism
- Immune-related: autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosis cholangitis (PSC), celiac disease
- Vascular: post-hepatic portal HTN (right heart failure, Budd-Chiari syndrome, veno-occlusive disease)
- Other: infection (i.e. schistosomiasis), meds (e.g. MTX, isoniazid, amiodarone; see livertox.nlm.nih.gov), cryptogenic/idiopathic

Complications of Cirrhosis
- Portal hypertension: esophageal varices, portal hypertensive gastropathy, hypersplenism (→cytopenias), ascites, SBP, hepatorenal syndrome, hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension, cirrhotic cardiomyopathy
- Hepatic encephalopathy: ↑mucosal & luminal NH_3, ↓clearance of NH_3 & endogenous BDZ-like compounds (NEJM 2016;375:17)
- Immune dysfunction: increased risk of infection; bacterial and fungal infections are major causes of morbidity & mortality
- Endocrinopathies: hypoglycemia, thyroid dysfunction, hypogonadism, hyperestrinism (palmar erythema, spider angiomata)
- Coagulopathy: ↓ in both pro- (II,V, VII, IX, X, XI) AND anti-coagulant factors (protein C/S, ATIII, plasminogen). Coags do not reflect risk of bleeding or thrombosis & patients are not auto-anticoagulated (NEJM 2011;365:147).
- Portal vein thrombosis: ↑ risk due unbalanced hemostasis & slowing of portal flow. Start AC for acute PVT w/ LMWH (unless high bleeding risk); transition to VKA/DOAC once stable & continue 6mo. (AASLD: Hepatology 2009; 49:1729; AGA: Gastro 2019;157:33)
- Hepatocellular carcinoma: 1-8% risk per year. May be asymptomatic, lead to decompensation, and/or have sx related to mass effect (pain, early satiety, palpable mass). Screen with US/MRI +/- AFP q6 months (AASLD guidelines: Hepatology 2018;68:723).

VIBES: a systematic approach to the management of cirrhosis

For all patients: etiology of cirrhosis, complications, compensated or decompensated & etiology of decompensation (infection [including new/reactivation of HBV/HCV], SBP, GIB, EtOH, HCC, PVT, LVP, dehydration, meds, surgery, etc.), current MELD score

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

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

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

Encephalopathy (portosystemic encephalopathy)
- Prior history, precipitant, and treatment
- Current severity, trend, precipitant, goal #BM on lactulose/rifaximin (e.g. goal 4 BM/d, 500cc stool, or mental status improvement)

Screening/Surgery (transplant)
- Vaccinations: HAV, HBV, Influenza, Pneumovax, Prevnar (and up-to-date on all other vaccines), should see Transplant ID
- Maintenance: alcohol abstinence, avoid NSAIDs
- Malignancy: HCC screening with q6 mo. RUQUS/MRI + AFP
- Transplant status: listed or not listed, MELD score, Milan criteria if HCC, classically requires 6 months sobriety

COMPLICATIONS OF CIRRHOSIS

ASCITES (AASLD Guidelines: Hepatology 2013;57:1651)

- Most common complication of cirrhosis (50% in 10 years); development of ascites → 15% 1-yr mortality, 44% 5-yr mortality
- Pathophysiology: portal hypertension → ↑NO, prostaglandins → splanchnic vasodilation → ↓EABV → ↑RAAS, ADH → Na & water retention. Severity of hypoNa (from ADH secretion) correlates with worsening survival.
- Diagnosis: **dx para** indicated for all new-onset or worsening ascites & pts w/ ascites w/ acutely decomp. cirrhosis or hospitalized
  - Studies: **cell count w/ diff, albumin, total protein, GS/Cx** +/- glucose, LDH, amylase, cytology (malignancy), AFB Cx/ADA (TB)
  - DDx: **portal HTN** vs. non-portal HTN. **SAAG** differentiates 97% of time (Annals 1992;117:215).
    - Can confirm portal HTN with measurement of **hepatic venous pressure gradient** (HVPG): gradient b/w portal vein (estimated by wedged hepatic venous pressure) and IVC (measured free hepatic venous pressure)
    - Normal HVPG <5mmHg; Portal HTN ≥6; Clinically-significant portal HTN: ≥10; Risk of EV bleed: ≥12
    - Limitation: may be normal in pre-sinusoidal portal HTN (e.g. PVT) as will generally not increase pressure in sinusoids

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

- Management of ascites:
  - **1st line:** <2g Na, ⃠EtOH, ⃠NSAIDs, diuretics (see below), avoid ACEi/ARB; fluid restrict 1.5L if Na <120
    - *Initiating therapy:* **100mg/d spironolactone + 40mg/d furosemide is usual starting dose (5:2 ratio).** Combo maintains normokalemia & mobilizes fluid faster. May start lower if older. Consider spironolactone alone for mild first ascites if outpt.
    - *Ongoing therapy:* ↑dose q3-5 days if inadequate diuresis (5:2 ratio, though can adjust PRN if abnormal K). Max doses: 400mg spironolactone and 160mg furosemide. Δ to amiloride 10-40mg qd if painful gynecomastia w/ spironolactone.
    - *If unsuccessful:* Check U_{Na}/U_K ratio if pt gaining weight/requiring LVPs on diuretics. Value >1 suggests >2g Na dietary intake (i.e. >2g UNa excretion). Value <1 suggests ineffective diuretic dose or resistance.
  - **Weight loss goals: 0.5 kg/d** (TBB -500) if no peripheral edema (AKI risk if too fast); if edema, 1kg/d or -1L ok. Avoid IV diuretics. Ascites mobilizes fluid slower than other compartments (Gastro 1986;90:1827)
  - **Therapeutic LVP**: indicated for tense or refractory ascites (see below) or inability to use diuretics; **if >5L, transfuse 6-8g albumin for every L ascites removed (~30-40g or 2-3 bottles of 25% albumin)**
  - Albumin: long term administration may offer survival benefit for cirrhotic patients with ascites (Lancet 2018;391:2417).
- Refractory ascites:
  - Defined as: (1) unresponsive to Na-restricted diet and high-dose diuretics or (2) rapid reaccumulation after LVP
  - Management: consider d/c βBs (↑mortality in refractory ascites; Hepatology 2010;52:1017), avoid ACEi/ARB as above (↓renal perfusion), midodrine TID (J Hepatol 2012;348), serial LVPs (usually ~q2w), TIPS as bridge to OLT

SPONTANEOUS BACTERIAL PERITONITIS (SBP) (AASLD Guidelines: Hepatology 2013;57:1651)

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

	⊕ Ascites culture	⊖ Ascites culture
PMN ≥250/μL	Spontaneous bacterial peritonitis (SBP) (secondary peritonitis → polymicrobial)	Culture negative neutrocytic ascites (CNNA)
PMN <250/μL	Non-neutrocytic bacterascites (NNBA)	Normal
Hemorrhagic ascites: RBC >50,000/mm^3, often due to traumatic tap → correct PMN count by subtracting 1 PMN for every 250 RBCs		

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

HEPATORENAL SYNDROME (HRS): See *Hepatorenal Syndrome* page.

ESOPHAGEAL VARICES (AASLD Guidelines: Hepatology 2017;65:310)

- Screening: baseline EGD at diagnosis unless liver stiffness <20kPa (by transient elastography) & platelets >150 (very low probability)
  - Repeat EGD q2yrs (if ongoing injury/condition), q3yrs (if injury quiescent), or if decompensation event & previously no/small EVs

1° PPX	EVs identified→ **ppx if high risk of bleeding**: (1) medium/large size (>5mm) (2) small (<5mm) w/ red wale signs (3) decompensated cirrhosis w/ small varices	- Medium/large: non-sel. βB (see below), carvedilol (6.25mg QD for 3 days → ↑ to 6.25mg BID), OR serial endoscopic variceal ligation (EVL) q2-8wk until eradication - Small: non-selective βB
2° PPX	Episode of variceal bleeding→ **ppx to prevent recurrence** w/ combination of non-selective βB + EVL	- **Non-selective βB**: *nadolol* 20-40mg QD or *propranolol* 20-40mg BID; adjust to goal HR 55-60, SBP>90; max dose in patients with/without ascites: propranolol 160mg/320mg QD or nadolol 80mg/160mg QD - **Serial EVL**: q1-4 wks until obliteration; repeat EGD 3-6mo. after & then q6-12mo.

- **Acute bleeding**: IV access, IVF, pRBC, PPI, octreotide, CTX, EGD. May need intubation, Blakemore as a bridge (GI), TIPS (IR), surgery, Amicar (if ↓fibrinogen). Conservative transfusion: goal Hgb 7-9 (NEJM 2013;368:11). See *Upper GI Bleeding*.
- **Indications for TIPS**: early "preemptive" TIPS (<72hrs) in pts with high risk of treatment failure or rebleeding (NEJM 2010;362:2370; Hepatology 2019;69:282); "rescue" TIPS if uncontrolled bleeding or if recurs despite max medical & endoscopic therapy
- Gastric varices: generally managed similar to EVs w/ βBs for ppx, similar mgmt. of acute bleed; BRTO is an option for fundal GVs
- Stop βB if: SBP, refractory ascites, HRS, low BP, sepsis; "window hypothesis" (J Hepatol 2014;60:643; Gastro 2014;146:1597)

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

- Pathophysiology: ↑NH_3 → neurotoxic effects, abnl neurotransmission, ↑GABA- & BDZ-like neurotransmitters & altered glutaminergic inputs → ↓excitatory transmission. In ALF, acute ↑NH_3 → cerebral edema.
- Diagnosis: clinical. Serum NH_3 should not be used to screen for HE. **↑NH_3 does not add diagnostic, staging, or prognostic value** in chronic liver disease. Only helpful in ALF (predicts mortality). Trend by regularly assessing for asterixis and/or concentration.
- Asterixis: "flapping tremor" is negative myoclonus w/ loss of postural tone; alternative is hand grip: oscillates b/w tight and loose (APT 2010;31:537)
- Precipitants: infection, dehydration/overdiuresis, GIB, hypoK or alkalosis (↑renal NH3), constipation, sedatives/BZD, new HCC, new clot, TIPS
- Treatment: ↓ GI NH_3 absorption, avoid/correct precipitating factors
  - **Lactulose**: Δs gut microbiome, has laxative effect; 30mL q2h until BM → titrate to 3-4 soft BM/day (PO, PR or NG)
  - **Lactulose + rifaximin 550 mg BID > lactulose alone** for HE reversal (NNT = 3) & all-cause mortality (NNT = 4) (AJG 2013;108:1458); prevents recurrence of HE (NEJM 2010;362:1071). Add rifaximin if refractory HE or after second episode of overt HE.
  - If refractory, consider non-standard therapies: oral branched-chain AAs (Cochrane Reviews 2017;5), IV L-ornithine L-aspartate (Hepatology 2018;67:700), neomycin, Flagyl, metabolic NH3 scavengers, probiotics (Cochrane Rev 2017), zinc, PEG (JAMA Int Med 2014;174:1727)
  - FMT may have role (Hepatology 2017;66:1727; Gastro 2019;156:1921)

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

HEPATOCELLULAR CARCINOMA (HCC) (AASLD Guidelines: Hepatology 2018;68:723 and Hepatology 2018;67:358)

- Screening indicated in:
  - **Cirrhosis due to *any* etiology**: HCV (including after cure w/ DAA treatment), HBV, NAFLD, EtOH, others
  - HBV carriers without cirrhosis if: Asian M >40, Asian F >50, African/African-American, or FHx HCC
  - Screening *not* recommended in patients with Child's class C cirrhosis unless on the transplant list
- Screen with: **RUQUS +/- AFP q6 months** (MGH practice to include AFP); if U/S inadequate, can use multiphase CT or MRI.
  - If nodule <1cm, repeat US in 3-6 months
  - If nodule ≥1cm or AFP ≥20, obtain multiphase CT or MRI & proceed according to LI-RADS class
- Staging: Barcelona stage; incorporates size, # of nodules, LN & portal vein involvement, mets, Child-Pugh score, performance status
- Management: surgical resection (1st line if CPS A & T1-T2 nodule), OLT (non-resectable but within Milan criteria), ablation (RFA), TACE (chemoembolization), TARE (radioembolization), SBRT, systemic chemotherapy (sorafenib)
  - Within Milan criteria → local-regional tx (LRT) as bridge to OLT. Outside Milan → LRT to downstage to w/in Milan → OLT.
  - Not OLT candidate (and non-resectable) → LRT and/or systemic chemotherapy (if advanced).

HEPATIC HYDROTHORAX (AASLD Guidelines: Hepatology 2013;57:1651)

- Transudative effusion due to **shift of ascites into pleural space** (due to neg. intrathoracic pressure) via small diaphragmatic defects. Can be seen without significant ascites. Usually unilateral: R- (~75%) > L-sided (~15%) > bilateral (~10%) (Medicine 2014;93:135).
- Diagnosis: exclude other causes of transudative effusion; can visualize w/ radioisotope injection into ascites if dx unclear
- Treatment: same as for ascites (diuretics, <2g Na). Therapeutic thora for dyspnea. TIPS if refractory. **Chest tube not recommended.**
- **Spontaneous bacterial empyema**: can become infected (~15%) due to translocation of bacteria from abd. cavity, even in the absence of SBP (~40%) (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 **intrapulm. shunting through intrapulm. 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, PaO_2 ↓ by 4 mmHg or ≥5%), clubbing, cyanosis, diffuse telangiectasias, hypoxemia (↓PaO2 <70-80).
- Diagnosis: **TTE with late bubbles** (3-6 cardiac cycles after RA), ↑A-a gradient ≥15 (or ≥20 if age >64)
  - ^{99m}Tc MAA scan is alternative to TTE but more invasive, less sensitive. May be useful in quantifying shunting if severe hypoxemia and coexistent intrinsic lung disease
  - Pulmonary angiography performed if severe hypoxemia poorly responsive to 100% O2 & areas amenable to embolization
  - PFTs can be performed to evaluate for intrinsic lung disease; ↓DLCO in HPS
- Risk stratification: *mild*: PaO2 ≥80, *moderate*: PaO2 60-79, *severe*: PaO2 50-59, *very severe*: PaO2 <50
- Management: O2; no effective medical therapies; OLT can significantly improve (and reverse) HPS – MELD exception points if severe

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

- Rare cause of **group 1 pulmonary hypertension** in setting of portal HTN
- Pathogenesis: unknown; possibly 2/2 humoral substances (ex. serotonin, interleukin-1, endothelin-1, normally cleared by liver) that reach pulmonary circulation through portosystemic collaterals
- Presentation: **DOE**, chest pain, fatigue, palpitations, syncope, hemoptysis, orthopnea; often w/ TR murmur, EKG w/ RVH, RAB, RBBB
- Diagnosis: RHC w/ PAH (mPAP >20 mmHg, PCWP <15 mmHg, PVR ≥3) in pt with established portal hypertension in absence of other etiology of PAH or venous hypertension.
- Risk stratification: *mild*: mPAP <35, *moderate*: mPAP 35-44, *severe*: mPAP ≥45
- Management: may benefit from advanced therapies (epoprostenol, bosentan, sildenafil, iloprost); OLT can improve/normalize the PAH (MELD exception points given if moderate); βB and TIPS may be harmful and should be avoided.
- Transplant: increased risk of morbidity/mortality with mPAP ≥35; mPAP ≥45 is a contraindication

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

- Definition: chronic cardiac dysfunction in cirrhotic patients with no known cardiac disease; characterized by 1) impaired cardiac contractility in response to stress, 2) altered diastolic relaxation, 3) electrophysiological abnormalities such as prolonged QTc
- Prevalence: up to 50% of patients undergoing liver transplantation have signs of cardiac dysfunction
- Diagnosis: echocardiography with dynamic stress testing w/ pharmacologics or exercise
- Pathophysiology: myocardial dysfunction 2/2 systemic inflammation; shear stress from portal hypertension → mechanical force on myocardial fibers; other possible mechanisms involve collagen configuration, sodium retention and activation of RAAS
- Treatment: same as HF management in non-cirrhotic patients
- Prognosis: largely subclinical and asymptomatic; however poses risk in the presence of stress such as infection, TIPS, or OLT; thus detailed cardiac assessment required prior to interventions

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

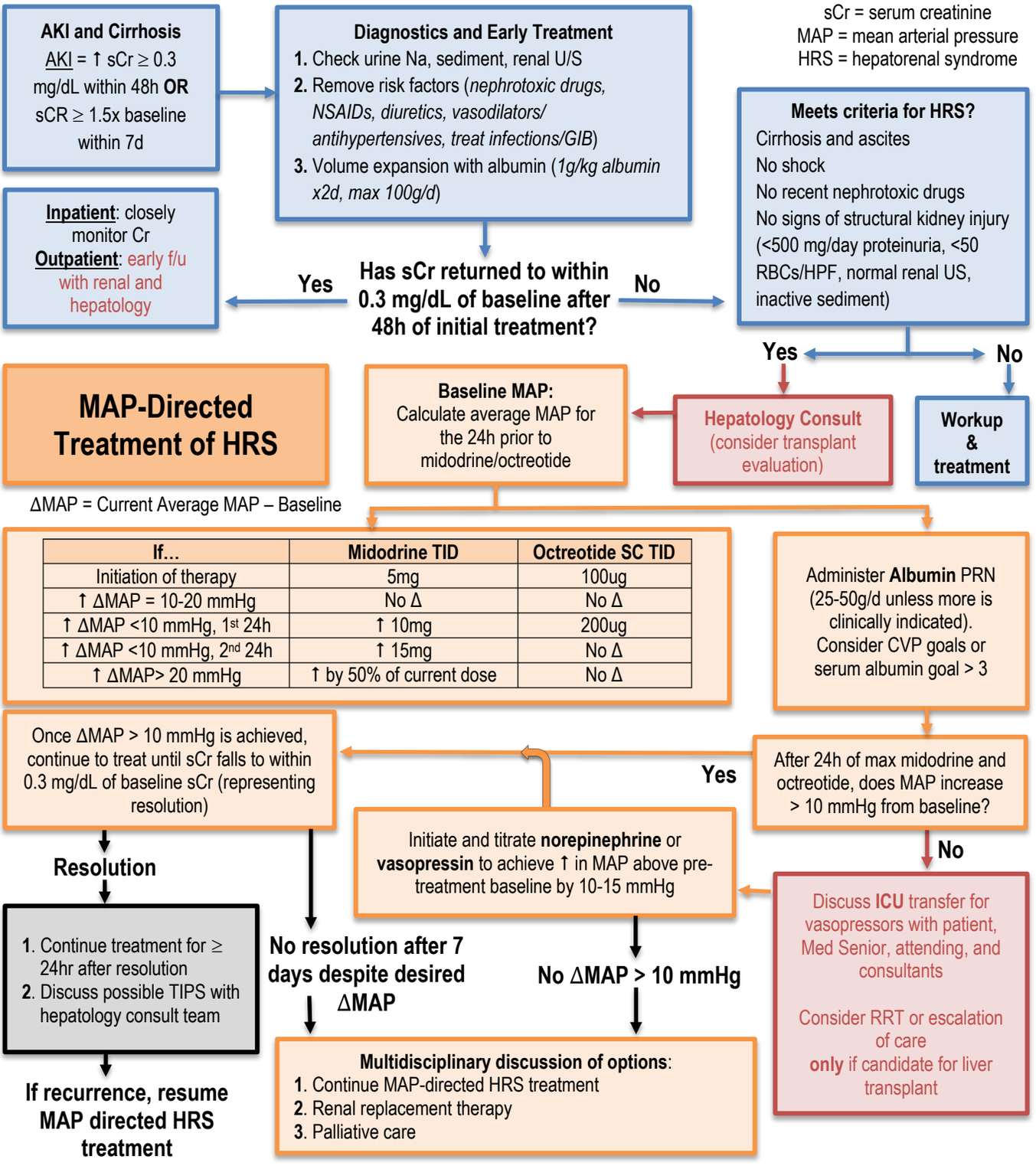
- Cytopenias: multifactorial; **thrombocytopenia** (splenomegaly, ↓TPO), **leukopenia** (splenomegaly), **anemia** (bleeding, spur cell anemia); also may have BM suppression by EtOH/infection, nutritional deficiencies (e.g. folate), direct effect of HCV/HBV
- Coagulation abnormalities: ↓ **coagulation 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 PT and PT/INR do **NOT** correlate with risk of bleeding or clotting
- **Anticoagulation**: (J Hepatol 2017;66:1313, JACC 2018;71:2162, Gastro 2019;157:33)
  - VTE ppx: should not be withheld unless high risk of bleeding or plts<50
  - Systemic AC: ok unless decompensated CPS C or high risk of bleeding. EGD for EVs prior to starting. VKA, LMWH, or DOAC all options. VKA dosing can be c/b ↑baseline PT/INR; LMWH can be c/b ↓ATIII levels; DOACs relatively safe in stable pts though all have some degree of hepatic metabolism – can use all except rivaroxaban w/ caution in CPS B, avoid all in CPS C
- **Bleeding**: consider role of coagulation factor deficiency, dysfibrinogenemia, hyperfibrinolysis, thrombocytopenia
  - If suspect vitamin K deficiency, give **vitamin K** 10mg x3 days to correct nutritional component
  - Transfuse **pRBCs** Hgb <7, **platelets** <50k, **cryo** for fibrinogen <100-120 (or if c/f dysfibrinogenemia)
  - Persistent bleeding despite cryo or requiring many pRBCs → can give FFP (though large volume → ↑ portal pressures)
  - Delayed bleeding or oozing from mucocutaneous sites → c/f hyperfibrinolysis → topical and/or systemic **Amicar** (3g PO QID or 4-5g IV over 1hr→ 1g/hr) or TXA (1g IV q6hr)
- **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 ↑plts (NEJM 2012;367:716; Gastro 2018;155:705).
  - PT/INR: **NO** benefit to giving FFP pre-procedure to "correct" INR. ↑ volume can ↑ bleeding risk by ↑ portal pressures.

Hepatorenal Syndrome (HRS) (NEJM 2009;361:1279; Clin Gastro Hep 2018;16:162)

- 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 albumin x2d, max 100g/d; use 25% albumin; goal is ↑ oncotic pressure, not volume expansion) (Gut 2015;64:531)
- Type I: ↑Cr 2x baseline and >2.5 mg/dL in <2wk + multiorgan dysfunction; Type II: slower decline, often have refractory ascites
- Precipitants: infection (SBP > other), GI bleed, fluid shifts after LVP, alcohol-related hepatitis
- Management: *see below.* Use albumin + octreotide + midodrine or levophed to increase MAP & albumin levels. No diuretics, βB, & or other vasodilators or nephrotoxins. RRT if management ineffective and a candidate for OLT. OLT is definitive treatment.

MGH Algorithm for the Diagnosis and Treatment of Hepatorenal Syndrome

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



INDICATIONS FOR LIVER TRANSPLANT (AASLD Guidelines: Hepatology 2014;59:1144)

- Acute liver failure: onset of severe acute liver injury w/ HE and coagulopathy w/in 26wks in pt w/o known cirrhosis or liver disease (see *Acute Liver Injury & Failure*)
- Cirrhosis with MELD ≥15 or complication (e.g. ascites, HE, EV bleed, HRS). Survival benefit of OLT > risk at MELD ≥15 (AJT 2005;5:307).
- HCC: if within Milan Criteria (NEJM 1996:334:693); can be "down-staged" to within Milan with treatment (see *End-Stage Liver Disease*)
- Liver-based metabolic disorders w/ systemic manifestations: A1AT deficiency, familial amyloidosis, Wilson's, hemochromatosis, glycogen storage disease, primary oxaluria
- Condition qualifying for exception (see below under "Prioritization")

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

TRANSPLANT EVALUATION PROCESS (AASLD guidelines: Hepatology 2014;59:1144)

- 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-1/2, EBV, CMV, VZV, HSV, RPR, toxo, measles/mumps/rubella titers, TB spot, 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 (I^+) (eval. for HCC), age-appropriate cancer screening (colonoscopy, mammogram, pap smear), bone density (outpt), cardiopulmonary eval. as below
- Immunizations: HAV, HBV, Prevnar13, influenza, Tdap
- Consults: transplant surgery, psychiatry, social work (address psychosocial issues, adequacy of support, financial screening, insurance counseling), nutrition
- Cardiopulmonary eval.: TTE w/ bubble ± PFTs. Dobutamine stress echo may be indicated (typically if >40 or CAD RFs). Optimal CV risk assessment strategy debated – AASLD: stress testing in all candidates (Hepatology 2014;59:1144); AHA/ACC: if multiple CAD risk factors (JACC 2012;60:434).
- ID eval.: eval. for latent TB 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 if needed.
- Combined kidney transplant: eligible if CKD w/ GFR ≤30 / ESRD on HD; sustained AKI w/ dialysis ≥6wk or GFR ≤25 for ≥6wk; or metabolic disease (e.g. hyperoxaluria) (UNOS/OPTN policy: AJT 2016;16:758)
- Living Donor Transplant (LDLT): recipients should fulfill same minimal listing criteria as for deceased donor

PRIORITIZATION FOR LIVER TRANSPLANT (AASLD guidelines: Hepatology 2014;59:1144)

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

CONTRAINDICATIONS TO LIVER TRANSPLANT (AASLD guidelines: Hepatology 2014;59:1144)

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

DEFINING AKI (KDIGO 2012 Guidelines)

AKIN Stage	Serum Creatinine	Urine Output	Work-up and management
1	↑ ≥ **0.3 mg/dl within 48h** or ↑ **1.5-1.9x** baseline	< 0.5 ml/kg/hr for ≥ 6 hours	(1) H&P, (2) monitor Cr & UOP, (3) UA and sediment (4) urine electrolytes, (5) renal U/S and other tests (below)
2	↑ **2-3x** baseline	< 0.5 ml/kg/hr for ≥ 12 hours	Above + (1) renally dose meds, (2) eval need for RRT, (3) consider ICU admission for CVVH, pressors for renal perfusion, (4) avoid subclavian catheters and PICC
3	↑ **3x** baseline, Cr ≥ 4, ↓ eGFR to < 35 (<18 yo), or RRT	< 0.3 ml/kg/h for ≥ 24 h, or anuria ≥ 12 h	

Diagnostic Tips

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

STEPWISE WORKUP

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

2) Urinalysis (UA): See *Urinalysis* page

3) Urine chemistries:

- FENa: FENa< 1% c/w pre-renal AKI, >2% c/w ATN. Note this is **ONLY** verified in oliguric AKI; overall limited use except to rule out HRS with elevated FeNa (J Hosp Med 2016;11:77)
- FEUrea: if on diuretics, FENa unreliable. Calculate FEUrea as above, <35% consistent with pre-renal (Kid Int 2002;62:2223)
- Urine Osm: >500 is consistent with a pre-renal etiology. Patients with ATN are only rarely able to concentrate to this degree.
- Urine protein: if proteinuria on UA, send serum albumin, urine total protein, urine microalbumin and urine Cr. Urine albumin/protein ratio(APR) > 0.4 suggests glomerular > tubulointerstitial process (Sn 88% / Sp 99%) (Nephro Dial Trans 2012;27:1534)

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

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

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

7) Monitor Cr: what is the response to empiric treatment of presumed cause?

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

DIFFERENTIAL DIAGNOSIS (Kid Int 1996;50:811)

PRE-RENAL *(21%)*	INTRINSIC			POST-RENAL *(10%)*
Absolute ↓ volume - Bleeding - GI or skin loss - Diuretics - Osmotic diuresis - Cerebral salt wasting **Effective ↓ volume** - CHF / cardiorenal - Cirrhosis/hepatorenal - Nephrotic syndrome - Sepsis / third-spacing **Δ renal dynamics** - NSAIDs / COX-2s - ACEi / ARBs - Abd compart. syndr. **Relative hypotension**	GLOMERULAR *(<4%)* **Anti-GBM** **ANCA +** - Microscopic polyangitis - Granulomatosis with polyangiitis (GPA) - Eosinophilic GPA - Drug-induced ANCA **Immune complex** *Low complement:* - PSGN, SLE, cryo, MPGN, MGRS *Normal complement:* - IgA nephropathy/HSP - Fibrillary/immunotactoid	TUBULO-INTERSTITIAL **ATN** *(45%)* - Ischemia, sepsis, toxic - Contrast, rhabdo, aminoglycosides **AIN** *(2%)* 1) Meds (see below) 2) Infectious: CMV, lepto, legionella 3) Autoimmune / infiltrative: TINU, IgG4 disease, sarcoid **Crystals** - TLS, acyclovir, ethylene glycol **Proteins** - MM, amyloid, Ig deposition	VASCULAR **Microvascular** *(<4%)* - TTP/HUS - APLAS - HELLP/Eclampsia - Scleroderma - Meds (calcineurin inhib/CIN, gemcitabine) **Macrovascular** *(1%)* - RAS (athero, FMD) - Dissection - Renal artery/vein thrombosis	**Urinary retention** - BPH, meds, neurogenic - Foley dysfunction **Urinary obstruction** (bilateral) - Stones (single kidney/transplant) - Malignancy - Retroperitoneal fibrosis
Common medications related to AKI (not comprehensive): **AIN**: β-lactams, NSAIDs, PPIs (delayed effect), rifampin, cimetidine, mesalamine, ciprofloxacin, allopurinol, sulfa drugs **Direct tubular injury**: NSAIDs, calcineurin Inhibitors, ACEi/ARB, methotrexate, acyclovir (IV>>PO), protease inhibitors, amphotericin, tenofovir (prox tub), vancomycin (esp in combo w/ Zosyn) (CID 2017;64:116)				

MANAGEMENT

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

1. **Optimize hemodynamics, avoid nephrotoxins**: Correct volume status - IVF if hypovolemic, diuretics if overload. Stop NSAIDs/ACEi/ARBs, spironolactone, diuretics (if prerenal). Avoid ↑ glucose and contrast. No evidence of benefit for empiric diuretics in oliguria (JAMA 2002;288:2547).
2. **Renally dose meds**: Abx, narcotics, LMWH → UFH, Keppra. Pre-hydrate if GFR<30 for contrast (MGH protocol).
3. **Manage complications**:
   - HyperK: calcium gluconate, insulin/dextrose → patiromer, bowel reg, furosemide
   - Hyperphos: sevelamer vs. phoslo depending on calcium
   - Metabolic acidosis: sodium bicarb PO/IV
   - Bleeding with concern for uremic platelets: DDAVP 0.3 mcg/kg IV, onset 1hr, lasts 4-8hr
4. **Indications for HD (AEIOU)**: **A**cidosis (esp. pH<7.0), **E**lectrolytes (refractory hyperK+), **I**ntoxication (lithium, ethylene glycol, metformin, salicylates, theophylline), refractory Volume **O**verload, **U**remia (encephalopathy, neuropathy, pericarditis)

RENAL EMERGENCIES (when to page the renal fellow overnight)

- **Acidosis**: severe metabolic acidosis, unstable patient, usually in the ICU with pH < 7.0. Temporize with NaHCO3 pushes and isotonic bicarb gtt, intubation and hyperventilation if unable to compensate by breathing off CO2. May need RRT. CVVH does not remove lactic acid and is similar in correction rate to bicarbonate infusion.
- **Hyperkalemia**: marked hyperkalemia leading to ECG changes or arrhythmia (K>6.5). Temporize with Ca gluconate, Lasix, Insulin/D50, etc. Note HD much faster at clearing K than CVVH.
- **Hyponatremia**: call if severely symptomatic (AMS with low GCS, seizures, etc) requiring bolus hypertonic saline.
- **Ingestions**: ethylene glycol, methanol (elevated osmolar gap) with end organ damage (i.e. renal failure, vision loss).
- **RPGN**: when clinically suspected, urgent Nephrology consultation to consider pulse dose steroids +/- plasmapheresis. See *Glomerular Disease*.

SPECIFIC MANAGEMENT BY CAUSE

- **Acute interstitial nephritis (AIN)**: stop offending agent, consider prednisone 40-60mg QD for 1-2wk if biopsy-confirmed or high pre-test prob 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 which impact the heart and kidneys with various causal relationships. Type 1 is HF resulting in AKI.
  - Pathophysiology: decreased renal perfusion from ↑ venous congestion +/- ↓ CO lead to a low trans-renal perfusion pressure. More of a problem with "underdraining" (congestion) than with "underfilling" (perfusion).
  - Treatment: relief of renal venous congestion. Trend Cr against TBB to test hypothesis but expect a lag effect.
    - Loop diuretics are first line for type 1 +/- addition of thiazide (metolazone/diuril).
    - No benefit of low dose dopamine or nesiritide to improve forward flow - ROSE trial
    - In CARESS-HF trial, ultrafiltration showed similar outcomes in regard to weight loss and decompensated CHF symptoms, but worsened renal function compared to pharmacologic therapy with loop/thiazide diuretics.
- **Contrast-Induced nephropathy (CIN)**: (Circ 2012;122:2451)
  - Definition: ↑Cr ≥ 0.5 or 25% within 48-72h of contrast without other causes.
  - Clinical syndrome: starts 24-48hr**, peaks 3-5d**, resolves 10d; Usually non-oliguric.
  - Controversy: pathogenesis unknown - vasospasm vs acute tubular injury due to osmotic injury. Recent studies: unclear risk of AKI following contrast, likely lower than previously estimated (Ann Em Med 2017;69:577). Exclude other causes.
  - Risk factors include higher contrast load, hyperosmolar contrast, intra-arterial injection, DM, proteinuria, concomitant AKI.
  - Prophylaxis: See *Contrast* in Radiology section for MGH protocol. Only prehydrate if GFR<30. For high risk pts receiving arterial or IV contrast, consider IV NS at 100mL/h for 6-12h pre, 4-12h post. If treating volume overload, hold diuretics day of contrast with no additional IVF. No added benefit for IV bicarb or NAC (NEJM 2018;378:603), or pre/post/intra HD (Am J Med 2012;125:66).
- **Crystalline nephropathy**: discontinue drug; fomepizole/HD if ethylene glycol toxicity; rasburicase if TLS
- **HRS**: See *Hepatorenal Syndrome* in GI section.
- **Myeloma kidney (Cast Nephropathy)**:
  - Dx: TP/Cr, SPEP/UPEP, SFLC, kidney bx if dx unclear.
  - Tx: IV hydration to target UOP >3L/day to minimize precipitation (volume overload can be treated with diuretics), initiation of bortezomib based 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 perc nephrostomy tube needed
- **Rhabdomyolysis**: AKI unlikely unless CK >2k-5k; aggressive IVF for UOP >250cc/hr with NS. Consider isotonic sodium bicarb if marked acidosis (NEJM 2009;361:62), but no convincing evidence that HCO3 is superior to NS. Monitor for electrolyte abnormalities: hyperK, hypoCa. Continue aggressive IVF until CK < 5000; continue IVF and add diuresis if volume overload.
- **Scleroderma renal crisis**: ACEi (captopril) at maximum tolerated dose. Avoid steroids.

NEPHROTIC SYNDROME (NS)

Etiology: ↓ podocyte integrity (foot process effacement)
→ Triad: **proteinuria > 3.5g/day** (albuminuria), **Alb < 3.0g/dL**, **edema** (periorbital, peripheral)
Associated sequelae: HLD + premature atherosclerosis, foamy urine, hypercoagulability (10-40% VTE risk 2/2 loss of antithrombin & plasminogen), Vit D deficiency (loss of binding protein), infectious risk (↓IgG/opsonins, esp. strep pneumo), protein malnutrition
Workup: Basic: UA/sed, spot urine P/C (if abnl, send 24h urine protein). First send HbA1c (most proteinuria 2/2 DM) to r/o DM. Advanced: ANA, anti-dsDNA, anti-PLA2R, SPEP, SFLC, HBV, HCV, HIV, C3/C4, nephrology c/s for possible renal biopsy.
Labs: 3+ protein (dip detects albumin) or spot urine P/C > 3000 mg/g, fatty casts or oval fat bodies = epithelial cells w/ engulfed lipid (Maltese crosses when polarized), Cr normal or ↑, may have mild nephritic features (hematuria, HTN more common in primary dz)

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

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

GLOMERULONEPHRITIS (GN)

Etiology: immune-mediated inflammation of the glomerulus leading to endothelial and podocyte injury → hematuria w/ *active sediment* (dysmorphic RBC; specific but less sensitive), RBC casts (rare but very specific), subnephrotic proteinuria (<3.5g/d, but 10-30% >3g/d).
Clinical presentation: AKI, HTN, edema, proteinuria, and hematuria. If systemic vasculitis, often fatigue, fever, weight loss, small-vessel involvement of other organ systems (palpable purpura, DAH, mononeuritis multiplex).

1) Asymptomatic urinary abnormalities: subnephrotic proteinuira, +/- 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: CP or MPA ± rituximab ± plasma exchange.
3) Chronic GN: persistent proteinuria, +/- hematuria, slow progression

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

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

ANCA Vasc: Tx: Induction: Steroids + RTX or CYC (NEJM 2010;363:221). Maintenance: RTX > AZA (NEJM 2014;371:1771). Induction w/o plasma exchange and w/ lower-dose steroids appears non-inferior and lowers infx risk in PEXIVAS trial
Anti-GBM: RPGN, DAH (=Goodpasture), linear IgG along BM. **Alport's**: mutant COL4A (renal, hearing, eye dx). EM w/ split GBM.

OVERVIEW

- CKD definition: GFR <60 ml/min OR presence of kidney damage (typically albuminuria ≥ 30mg/d) for ≥ 3 months (JAMA 2015;313:837)
  - Estimating GFR: **CKD-EPI** preferred (Cr-Cystatin C); Cockcroft-Gault overestimates, MDRD underestimates.
  - Albuminuria is an independent predictor of all-cause mortality, CV mortality, and progression of CKD at all stages. Note: UA detects albumin but not other proteins; if UA with + protein → check TP:Cr to quantify
- Etiologies: **DM (47%), HTN/nephrosclerosis (29%)**, GN (7%), cystic kidney (3%), unknown (14%) (USRDS 2017)
- Epidemiology: 15% US adults: White (60%), Black (30%), Hispanic (17%), Asian (5%) (Natl Kidney Fndn 2016)

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

GFR categories (ml/min/ 1.73m²) Description and range			Persistent albuminuria categories Description and range			
			A1	A2	A3	
			Normal to mildly increased	Moderately increased	Severely increased	
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol	
G1	Normal or high	≥90	55.6	1.9	0.4	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

- Staging/Action: G1-G3a: risk factor reduction, dx and tx, slow progression. G3a-G3b: evaluate and treat complications. G4: nephrology referral, preparation for RRT +/- transplant. G5: RRT if uremia or other indication, consider transplant

MANAGEMENT

- BP control: reduce to goal <130/80 if proteinuria (Alb/Cr>30) (NEJM 2015;373:2103)
  - *If proteinuria*: ACEi, then non-dihydropyridine CCB; *if edema*: loop diuretic if eGFR <30, thiazide for eGFR > 30
- Proteinuria: reduce to goal <300mg/d with RAAS blockade (ACEi or ARB, but not both simultaneously) (NEJM 2013;369:1892)
- Glycemic control: use oral agents or insulin to achieve HgbA1c < 7%. Decreased rate of CKD progression with SGLT2i (NEJM 2019;380:2295) and GLP-1 agonist (NEJM 2017;377:839).
- HCV: Tx to slow progression (Kidney Int 2020;97:193)
- CVD risk reduction: risk 2-4x general population. ASA 1° prev if high ASCVD risk (ACC/AHA 2019), statin, exercise, ⃠ smoking
- Avoid nephrotoxins: NSAIDs, herbals w/ aristocholic acid, aminoglycosides, acyclovir, contrast (iodinated, gadolinium), baclofen (stage G4/5)
- Renally dose meds: esp. abx/antivirals, atenolol, colchicine, fluconazole, gabapentin, glyburide, levetiracetam, metoclopramide, opioids
- Nutrition: nephrocaps (B-complex + C), Na <2 g/d, K/phos/fluid restriction as needed. Protein 0.6-0.8 gm/kg/d only if GFR <60 and nephrotic syndrome is not present. Very low protein diet not clearly shown to be beneficial (AJKD 2009;53:208).
- Monitoring: q1-3mo Cr & electrolytes, annual UAlb/Cr & UProt/Cr ratios, PTH, 25-vitD, CBC, Fe studies. Renal U/S at time of dx.
- Nephrology referral: GFR approaching 30, sudden decline in GFR, severe proteinuria, active urinary sediment with decrease in GFR, resistant HTN
- Prognosis: based on 1) cause of CKD, 2) GFR category, 3) albuminuria category, 4) other risk factor/comorbidity; use Tangri risk score to assess 2 and 5 year risk of requiring HD (JAMA 2016;315:164)

COMPLICATIONS

GFR threshold: hyperPTH (50), anemia (44), acidosis (40), hyperK (39), hyperPhos (37) JASN 2009;20:164.

- **Hyperparathyroidism**:

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

- Mineral and bone disorder: check Ca, PO_4, ALP, 25-OH vit D (1,25-OH vit D level will fluctuate) (KDIGO Guideline Update 2017)
  - PTH rising/persistently above goal (non-HD <3.5, HD 3.5-5.5): restrict dietary phos, non-Ca phos binders (sevalemer preferred, w/ meals), goal phos <5.5 mg/dl, calcium/Vit D supplements if low 25-OH Vitamin D.
  - Severe/refractory PTH > 1000: calcitriol vs calcium mimetic vs parathyroidectomy if non-responsive to medical therapy
- Anemia: q3-6m for goal Hb 10-11.5 (NEJM 2006;355:2071). Hb >13 with ESA increases risk of CVA
  - Iron repletion (PO or IV) when Tsat <30% and ferritin <500 ng/mL, hold if ferritin >500-800
  - Erythropoiesis stimulating agents (ESA) ↓ transfusions, risk of Fe overload, Ab formation; contraindicated in cancer, SBP>160, HF, stroke (NEJM 2009;361:2019)
- Metabolic acidosis: $NaHCO_3$ 650-1300mg up to TID for goal HCO_3 >22; decreases progression of CKD and improves bone health (CJASN 2019;14:1011)
- Uremic bleeding: no need to treat unless pre-preprocedure with DDAVP
- Preparation for HD access: avoid BP measurements and venipuncture in non-dominant arm, avoid subclavian/PICC lines due to risk of central stenosis (precludes future AVF placement), prefer small bore tunneled IJ placed by IR

OVERVIEW (NEJM 2012;367:2505)

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

Emergent Indications for RRT (AEIOU)

- **A**cidosis: pH <7.2
- **E**lectrolytes: refractory K+ > 6.0 mEq/L or rapidly rising K+
- Ingestions: dialyzable toxins (eg: Li, ASA, methanol, ethylene glycol, metformin, phenobarbital, dabigatran)
- **O**verload: diuretic-refractory volume overload
- **U**remia: encephalopathy, pericarditis, coagulopathy with uremic bleeding

Important Considerations

- Timing: controversial - ELAIN RCT: early RRT (within 8h) ↑ renal recovery, ↓ RRT duration, ↓ mechanical ventilation duration, ↓ LOS, ↓ 90d mortality; IDEAL-ICU: multi-center RCT showed no significant difference for early RRT in patients w/ septic shock and severe AKI
- Access: dialysis lines can only be accessed by dialysis/ICU RNs (except in codes); contact dialysis unit (6-3700) to request new access
- PICCs: HD pts or future HD candidates cannot receive PICCs unless first cleared by Renal (to preserve options for vascular access)
- Abx: be sure to dose abx based on IHD vs. CRRT vs. PD and w/ pharmacy; communicate directly w/ dialysis fellow to give during HD

INTERMITTENT HEMODIALYSIS (IHD) (NEJM 2010;363:1833; consider in critically ill pts Lancet 2006;368:379)

- Mechanism: Cr, Urea, K^+ move from blood to dialysate; Ca^{2+} and HCO_3^- move from dialysate to blood (down concentration gradients)
- Volume removal: occurs via UF; HD can rapidly remove solute and volume; usually three 4h sessions weekly (MWF or TTSa)
- Access: double-lumen central catheter (tunneled or temporary, ↑ infection); AV graft (↓ maturation time but ↑ thrombosis & long-term complications); AV fistula (↓ infection, ↓ overall mortality vs. catheters/AVG, but 6+ week maturation time + 50% primary failure rates)
- Intradialytic medications: erythropoietin, iron, vitamin D analogues, antibiotics
- Complications: HoTN, cramps, dialyzer rxn (SOB, urticaria, diffuse pain), HIT, hemolysis, EtOH withdrawal (rapid clearance of EtOH)

PERITONEAL DIALYSIS (PD) - call **PD RN (617-720-1317)** on call 24/7 for any inpatient on PD

- Mechanism: peritoneum acts as membrane; infusion of fluid rich in osmotic agent (e.g. dextrose) → solute removal via diffusion and osmotic gradients → similar survival to pts on IHD (Arch Int Med 2011;171:110).
- Benefits: preserves residual GFR better than IHD, better medium weight molecule clearance, no access complications, independence
- Modalities: continuous ambulatory PD (**CAPD**): manual exchanges occurring both day and night. All inpatients receive CAPD. Automated PD (APD): multiple automated exchanges overnight
- Complications: **peritonitis**, encapsulating peritoneal sclerosis, hernia, pleural effusion, hyperglycemia, HLD, hyperNa, catheter leaks

CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

- Principles: depends on high UF rate to achieve clearance → replacement fluid must be added back to restore volume, acid base balance + electrolytes. Solute clearance + volume removal are slow and not effective in toxin removal or significant volume overload
  - **CVVH**: continuous veno-venous HF, removes solute via convection; **AVVH**: intermediate CVVH circuit setting w ↑ flow rates / 12h
  - **CVVHD**: continuous veno-venous HD, removes solute by diffusion; **CVVHDF**: combines convection and diffusion to remove solute
  - **SCUF**: slow continuous ultrafiltration, removes plasma water via hydrostatic pressure applied across hemofilter (NO dialysate)
- Indications: **hemodynamic instability**; continuous large volume IV fluid in pt who cannot undergo intermittent HD; increased ICP. Not ideal for hyperK or toxins. Not ideal for acidosis given slow rate of correction with bicarbonate replacement fluid.
- Volume management: run negative (up to -250cc/hr), even, or slightly positive. Replacement fluid w/ bicarb, lactate acetate or citrate
- Anticoagulation: used to ↓risk of circuit clotting, use heparin + bicarbonate OR citrate, citrate achieves regional AC by Ca chelation → follow iCa levels (will see ↑ total Ca but ↓ iCa), metabolized in liver → ↑AG = possible citrate toxicity (avoid in liver failure)
- Complications: HoTN, arrhythmias, hypothermia, ↓ iCa/ K/PO_4, bleeding, thrombocytopenia (mechanical destruction in circuit), HIT
- Drug dosing: drugs can bind to circuit resulting in ↑ V_D → work with pharmacy to re-dose all meds based on flow rate

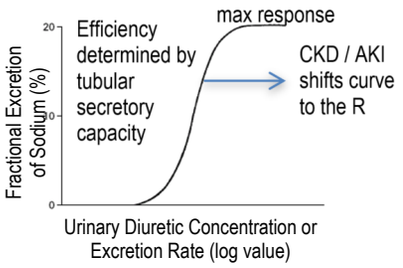
RENAL TRANSPLANT

- Listing: refer EARLY, pts can be listed when GFR <20; pt and graft survival are improved if transplant occurs PRIOR to starting HD
- Contraindications: short life expectancy, active malignancy, SUD, nonadherence; age/HIV/psych comorbidities NOT contraindications
- Allograft dysfunction: **delayed graft function**: <1wk (prerenal, ATN, thrombus, obstruction), **early**: 1-12 wks (prerenal, CNI tox, infxn [BK virus, CMV], acute rejection), **late acute**: > 3mo (prerenal, CNI tox, noncompliance), **late chronic**: yrs (HTN, CNI toxicity, BK virus, recurrence of original renal pathology, chronic allograft nephropathy

IMMUNOSUPPRESSION			
Class	**Examples**	**Mechanism of Action**	**Adverse Events**
Calcineurin inhibitor	Cyclosporine Tacrolimus (FK506)	Inhibits calcineurin-mediated activation of NFAT → blocks T-cell cytokine production	Nephrotoxicity (long-term fibrosis), HTN, tremor, insomnia, hirsutism (CsA only)
mTOR inhibitor	Sirolimus (Rapamycin)	Inhibits mTOR → blocks IL-2 production	Pulmonary edema, ↓ wound healing, hyperTG
Antimetabolite	Mycophenolate (Cellcept, Myfortic)	Inhibits de-novo purine synthesis	N/V/D
	Azathioprine	Purine analogue	BM suppression, N/V/D, hepatitis

GENERAL PRINCIPLES

- Obtain daily standing weights, Na^+ restriction 2g/day, consider fluid restriction
- Loop diuretics have a sigmoidal dose-response curve so double dose until adequate response is achieved
- Transient increases in serum Cr are common in diuresis. No association between worsening renal function during diuresis and biomarkers of kidney tubule injury; increased survival in HF (Circ 2018;137:2016)



	Loop Diuretics			Thiazide Diuretics
	Furosemide	**Torsemide**	**Bumetanide**	**Chlorthalidone, HCTZ, metolazone, chlorothiazide (IV/PO)**
Mechanism of Action	Inhibit Na-K-2Cl transporter in ascending limb of loop of Henle to ↓ Na reabsorption and "break" medullary concentrating gradient (unable to concentrate urine)			Inhibit NaCl channel in DCT to ↓ Na reabsorption and prevent urinary dilution (avoid if SIADH); no effect on medullary concentrating gradient
PO Bioavailability	20-50%	80-90%	80%	Variable
Duration	~6 hours	6-8 hours	4-6 hours	Variable
Dosing considerations	1 Bumetanide IV/PO = 20 Torsemide PO = 40 Furosemide IV = 80 Furosemide PO			Administer **30 min before loop diuretic** to "disable" DCT (PO metolazone, IV chlorothiazide)
Side effects	↓ K^+, ↓ Mg^{2+}, ↓ Ca^{2+}, ↑ urate, ↑ HCO_3^-, ototoxicity, allergy			↓ Na^+, ↓ K^+, ↓ Mg^{2+}, ↑ Ca^{2+}, ↑ urate, HLD, pancreatitis
Other	Consider dosing BID-QID to avoid anti-natriuresis seen in QD dosing			Try metolazone 2.5-10mg PO before chlorothiazide 500-1000mg IV ($$$)

Other Diuretics

- Carbonic anhydrase inhibitors: acetazolamide 250-1000mg PO QD, can do TID x1d vs QD x3d for metabolic alkalosis (pH > 7.6)
- Aldosterone antagonists: spironolactone 25-200mg QD-BID, eplerenone 25-50mg QD-BID
  - ↑ K, gynecomastia (10%, only spironolactone); eplerenone has ↑ aldosterone receptor selectivity but more expensive

DISEASE-SPECIFIC CONSIDERATIONS

Condition	Mechanism	Treatment
Renal Insufficiency	- ↓ GFR so ↓ delivery of diuretic to nephron so higher doses needed in patients with CKD - Organic acids accumulate and compete w/ diuretics	- High-dose loop ± thiazide augmentation
Chronic Diuretic Use	- Compensatory DCT hypertrophy	- Add metolazone or chlorothiazide
CHF	- GI edema leads to ↓ absorption of PO furosemide - ↓ GFR in ADHF is driven by renal venous HTN (↑ CVP, ↑ PCWP) more so than low perfusion (↓CI) - High sympathetic tone → ↑ RAAS, Na^+ reabsorption	- DOSE trial: in ADHF, no difference in sx or renal function for pts receiving low vs high dose diuretics and continuous gtt vs bolus dosing of diuretics - No benefit of RRT over stepwise diuresis - Consider sequential nephron blockade
Hypoalbuminemia	- Loop diuretic (binds to albumin) leaks out of vasculature (↑ V_D) resulting in ↓ delivery to nephron	- Consider bumetanide (lower albumin-binding) - No evidence for benefit of albumin + loop diuretic
Cirrhosis	- Decreased delivery to nephron in setting of hypoalbuminemia - Splanchnic vasodilation → ↓ EABV → ↓ renal hypoperfusion (pre-renal azotemia) - SNS and RAAS → ↑ Na reabsorption	- **Avoid IV diuretics** unless respiratory distress - Spironolactone alone if hypokalemia - Can do spironolactone:furosemide 5:2 (optimal K balance), uptitrate q3-5d up to 400mg:160mg - If gaining weight, measure urine Na and K; if K > Na (ineffective diuresis), uptitrate meds; if Na > K (effective diuresis) enforce Na restriction
Nephrotic Syndrome	- Decreased delivery to nephron due to low albumin - Urinary albumin binds drug → loss of diuretic in urine	- Use 2-3x normal dose of diuretic

Stepwise Approach in Heart Failure (NEJM 2017;377:1964)

1. **IV loop diuretic**. Starting dose: 2.5x home dose as IV furosemide (CHF) (e.g. if home 80mg PO, give ~80-100mg IV) vs Cr×30 as IV furosemide (e.g. if Cr=4, use lasix 120mg IV); if unknown, start with furosemide 20-40mg IV
2. **Reassess in 1-2 hrs** and double dose Q1H until response achieved. An adequate dose should cause brisk diuresis.
3. Consider loop diuretic **bolus + gtt** (should bolus when initiating gtt and re-bolus every time gtt increased)
4. If refractory edema, consider adding a **thiazide** (metolazone PO or chlorothiazide IV) to achieve sequential nephron blockade
   - This counteracts natural ↑ in DCT Na reabsorption from loop diuretics; **monitor closely ↓K^+, ↓Mg^{2+}, ↓bicarb**
5. Nephrology consult for consideration of short term UF/RRT as a bridge to advanced therapies (e.g. MCS, OHT)

OVERVIEW

- **ABG vs VBG**: pH VBG~0.04 lower), HCO_3 (VBG~2mEq lower; calculated on blood gas so BMP more accurate), CO_2 (VBG~8 ± 17 mmHg higher). VBG can screen for hypercarbia w/ pCO2 cutoff ≥ 45 mmHg (100% Sn) but does **NOT** accurately assess degree of hypercarbia. **When in doubt → check ABG** (AJEM 2012;30:896)
- Severe acidemia (pH < 7.2) → **vasodilation**, ↓ inotropy / SVR / MAP, ↓response catechols, arrhythmia, ↑K, insulin resistance, AMS
- Severe alkalemia (pH >7.6) → **vasoconstriction**, ↓cor/cerebral perfusion, SVT/VT, ↓K/Ca/Mg/P, AMS, seizure, hypoventilation

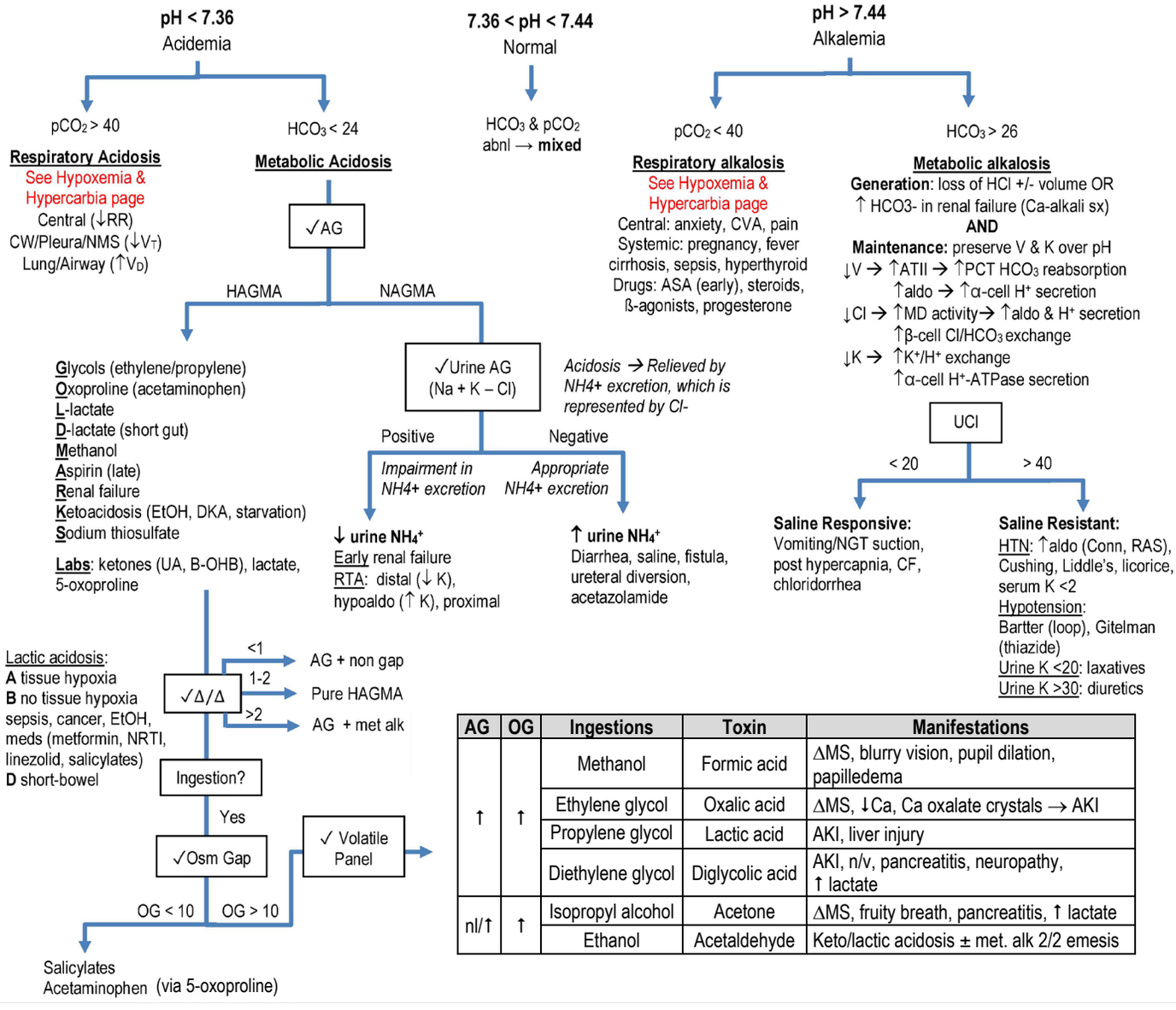
STEP-WISE APPROACH (NEJM 1998;338:26, NEJM 2014;371:1434)

1. Is there acidemia (pH < 7.36) or alkalemia (pH > 7.44)?
2. Is primary disorder metabolic (parallels pH Δ) or respiratory (opposite pH Δ)?
3. Is pt compensating? (respiratory takes min-hrs, renal 3-5 days)
4. Is there an anion gap? Regardless of pH or HCO_3
   AG = Na – (Cl + HCO_3) = unmeasured anions – unmeasured cations
   Correct AG for albumin: AG_c = AG + 2.5(4 – albumin)
   Negative AG: ↑↑Na, lipids (interfere w/ chloride), bromide intox
5. If there is ↑ AG, calculate "**delta-ratio**"
   Δ/Δ = Δ AG /Δ HCO_3 = AG – (albumin x 2.5) / (24 – HCO_3)
6. Consider Osm gap = 2x (Na + K) + Urea/2.8 + glucose/18 – serum Osm

EXPECTED COMPENSATION (JASN 2010;21:920)

Metabolic acidosis: 2-24 hr
Winter's formula: pCO_2 = 1.5 x HCO_3 + 8 ± 2
Metabolic alkalosis: start 30 min, complete 24 hrs
$PaCO_2$ = 0.7 x (HCO_3 -24) + 40 ± 2 = HCO_3 + 15
Δ HCO_3 ↑ 1 → expect Δ pCO_2 ↑ 0.7
Respiratory acidosis:
Acute: Δ pCO_2 ↑ 10 → Δ HCO_3 ↑ 1 or ↓ pH 0.08
Chronic: Δ pCO_2 ↑ 10 → Δ HCO_3 ↑ 4 or ↓ pH 0.03
Respiratory alkalosis:
Acute: Δ pCO_2 ↓10 → Δ HCO_3 ↓ 2 or ↑pH 0.08
Chronic: Δ pCO_2 ↓10 → Δ HCO_3 ↓ 4 or ↑pH 0.03

ALGORITHMIC APPROACH



AG	OG	Ingestions	Toxin	Manifestations
↑	↑	Methanol	Formic acid	ΔMS, blurry vision, pupil dilation, papilledema
		Ethylene glycol	Oxalic acid	ΔMS, ↓Ca, Ca oxalate crystals → AKI
		Propylene glycol	Lactic acid	AKI, liver injury
		Diethylene glycol	Diglycolic acid	AKI, n/v, pancreatitis, neuropathy, ↑ lactate
nl/↑	↑	Isopropyl alcohol	Acetone	ΔMS, fruity breath, pancreatitis, ↑ lactate
		Ethanol	Acetaldehyde	Keto/lactic acidosis ± met. alk 2/2 emesis

MANAGEMENT OF ACID-BASE DISORDERS: treat the underlying cause

- **Metabolic acidosis**:
  - Acute:
    - In the BICAR-ICU trial pts with metabolic acidosis (pH < 7.2) treated with IV HCO3 for goal pH > 7.3 had no change in overall mortality but ↓ RRT initiation. A subset of pts with AKIN stages 2-3 had improved mortality at 28d.
    - If pH < 7.1 or $HCO3^-$ < 6: if HDS, can start **isotonic HCO3 gtt**. Monitor VBG/ABG+ q1h. Bolus admin is controversial due to possible intracellular acidification in s/o CO2 accumulation and a pH-dependent ↓ in levels of iCa → hypercarbia, hypernatremia, hypocalcemia, hypertonicity, hypervolemia, overshoot alkalosis.
    - For bicarb to have full effect on serum pH, pt must be able to increase minute ventilation to ventilate off CO_2
  - Special considerations:
    - Toxic alcohols: Tx with HCO3, **fomepizole**, or HD (If vision Δ, AKI, methanol >50 mg/dL, ethylene glycol >300 mg/dL).
    - Salicylate poisoning: sodium HCO3 to urine pH >6.5 or HD (if level >80 mg/dL, coma, AKI, hypervolemia)
  - Chronic: in CKD, replete with PO sodium HCO3 for goal HCO_3 >22. See *CKD*.
- **Metabolic alkalosis**: replete volume, K, and Cl
  - Treat both (1) underlying cause of metabolic alkalosis and (2) cause of renal retention of HCO_3
  - If saline responsive: **NS w/ KCl** until urine pH >7. For pts with CHF/cirrhosis and alkalosis 2/2 diuresis, consider K^+-sparing diuretic
  - If saline resistant: for mineralocorticoid excess → use K^+-sparing diuretic (**amiloride**) and consider surgical removal of adenoma
  - If pH >7.6 and persistently volume overloaded, give **acetazolamide** vs KCl + loop diuretic with close K^+ monitoring
- **Respiratory acidosis**: $NaHCO_3$ unlikely to be helpful, theoretically harmful if unable to blow off CO_2 produced by conservation of mass ($CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows HCO_3 + H^+$). For every 100mEq HCO_3 administered, 2.2 L CO_2 must be exhaled (~10 min of nml body production)
- **Respiratory alkalosis**: address underlying cause (correct hypoxemia, treat pain/anxiety/fever); adjust vent settings if intubated

RENAL TUBULAR ACIDOSIS (RTA) (Int J Clin Pract 2011;65:350)

Consider in any patient with non-AG or hyperchloremic metabolic acidosis or hyperK (Type IV). R/o GI losses & excessive Cl use first!

Pathophysiology: inappropriate net retention of acid or inadequate excretion of bicarb

- In acidemia, kidney should ↑ NH4+Cl- excretion; urine pH should be < 5.3; this process is defective in RTAs
- Caveat: CKD of any etiology is associated with ↓ $NH4^+$ production and acidosis

Etiologies:

- Proximal RTA (Type II): new ↓ setpoint for proximal tubule $HCO3^-$ reabsorption so more HCO3 spills into urine
  - Primary (rare): Na-HCO3 cotransporter defect
  - Acquired: **amyloidosis, MM**, post-renal transplant, heavy metals (Pb, Cd, Hg, Cu), ↓ Vit D, Wilson's disease, PNH
  - Meds: acetazolamide, cisplatin, tenofovir, aminoglycosides, topiramate
  - Often a/w Fanconi Syndrome: glycosuria (w/ serum gluc <180), hypouricemia, aminoaciduria
- Distal RTA (Type I): inability to secrete H+ in distal tubule
  - Primary: genetic loss of H^+ or HCO3 transporters in intercalated cells
  - Acquired: **autoimmune disease** (RA, SLE, SS); **hypercalciuria** (any cause); obstructive nephropathy; SCD, MM, amyloid, cryoglobulinemia, tubulointerstitial injury, renal transplant rejection, cirrhosis, glue sniffing (toluene)
  - Meds: amphotericin B, Li^+, ifosfamide
- Type IV: effective hypoaldosteronism: ↓ aldo secretion OR tubular resistance → ↑ K → ↓ NH_3 synthesis → ↓ $NH4^+$ excretion
  - Acidosis due to inhibition of ammonia-genesis by hyperkalemia of any cause
  - Hyporeninemic hypoaldosteronism (most common): diabetic nephropathy, CIN, NSAIDs, calcineurin inhibitor, HIV
  - ↓ Aldo production: ACEi/ARB > heparin >, adrenal insufficiency, severe illness
  - Aldosterone resistance: (ENaC inhibition) K-sparing diuretic, trimethoprim, pentamidine

Workup: clinical history (PMH – autoimmune or malignancy, med review, stones), response to HCO3 supplementation

- ABG/VBG, BMP (AG, HCO_3, K), UA (pH). Consider urine Ca/Cr to differentiate proximal vs distal RTA
- Estimate of Urine NH_4^+: UAG = Na + K - Cl (less useful when ↑urine anions or UNa < 25)

	PROXIMAL RTA (TYPE II)	DISTAL RTA (TYPE I)	TYPE IV RTA
Defect	**Proximal HCO_3^- resorption**	**Distal H^+ secretion**	**Hyperkalemia**
Serum HCO_3^-	12 – 20	< 10	> 17
Serum K	↓ or normal	↓ or normal	↑
Urine pH during acidemia	Varies, but > 5.5 after HCO_3^-	> 5.5	< 5.5, but can't buffer w/ $NH4^+$
Urine AG = Na + K – CL	⊖	⊕	⊕
Additional dx testing	Urine Ca/Cr nml	Urine Ca/Cr elevated	Renin, aldosterone, cortisol
Complications	Rickets, osteomalacia	CaPO4 urinary stones	Hyperkalemia
Tx (Goal HCO3 22-24)	**Challenging**. NaHCO3 (10-20 mEq/kg) or KCitrate. K supplement	NaHCO3 (1-4 mEq/kg)	Treat hyperK: loop, low K diet If hypoaldo then can give fludricort

HYPONATREMIA: free water excess relative to serum sodium (NEJM 2015;372:55)

Symptoms: often asymptomatic; AMS, HA, vertigo, N/V, weakness, falls, seizures

Step-wise approach:

1. History and exam, volume status
2. Check **SOsm** to confirm hypotonic hyponatremia
3. Determine if ADH is present (**UOsm** >100). Can approx UOsm from UA: last 2 digits of SG x30 (e.g. SG 1.010 ≈ UOsm 300)
4. If ADH is present, check **UNa** to determine if ↑ ADH is appropriate. UNa unreliable if on diuretics.
   - UNa < 30 suggests ↓ EABV state; UNa > 30 suggests the kidney is not retaining Na
   - Fractional excretion of **uric acid** can distinguish ↓ EABV (FEUA < 12%) from SIADH/renal cause (> 12%), 100% PPV (J Clin Endo Metab 2008;93:2991). Serum uric acid <4 is almost always SIADH (Clin Nephro 1994;42:102).
   - Consider TSH, AM cortisol, urine K

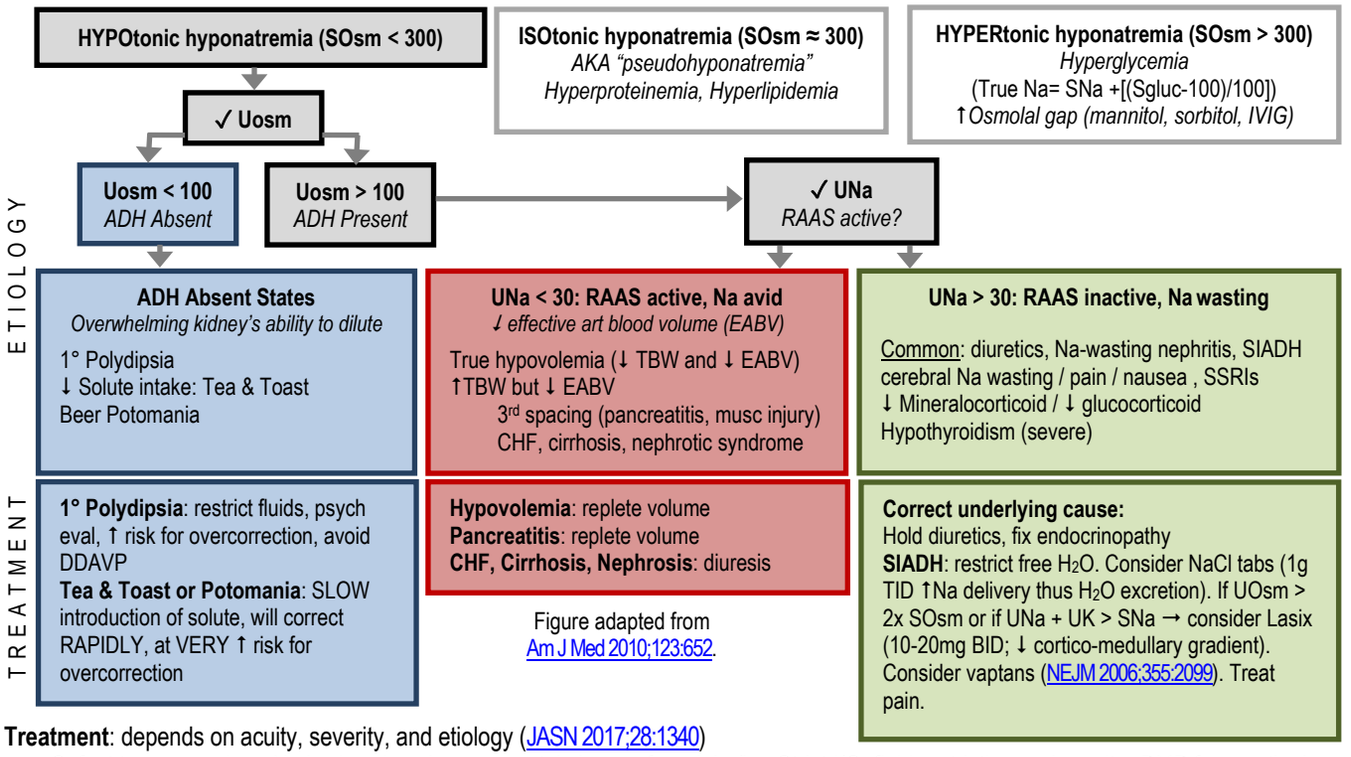


Figure adapted from Am J Med 2010;123:652.

Treatment: depends on acuity, severity, and etiology (JASN 2017;28:1340)

- Safest to assume hypoNa is chronic unless accurately known from labs/hx. Strict I/O, fluid restriction and monitor BMP frequently. In general, do not give isotonic saline. **Consult renal** if starting hypertonic saline.
- **Severe symptomatic hypoNa** (seizures, AMS): 3% NaCl bolus (100mL up to 3x over 10min until sx resolve or Na ↑ 4-6 mEq/L)
- **Severe asymptomatic hypoNa** (Na<120): Goal Na ↑ 6 mEq/L in first 24h. 3% NaCl with rate based on Sodium Correction Rate, usually 15-30mL/hr. Stop 3% NaCl when Na>125 or if correcting too fast. Consider DDAVP clamp (below).
- **Mild/mod hypoNa** (Na≥120): if not hypovolemic in etiology, fluid restriction <1.5L, +/- salt tablets 1g TID
- **Overcorrection**: ADH ↓ once euvolemic → free water diuresis and ↑ rate of correction. Increased risk of **osmotic demyelination syndrome** if **Na ≤ 105, hypovolemic** hypoNa, tea/toast, beer potomania, low K, EtOH, ESLD, malnourished
  - Definition: Na ↑ > 8 mq/L in 24h or ≥ 18 mEq/L in 48h. If overcorrecting or UOP rises > 300cc/hr x 2h, consider **DDAVP "clamp"**: 2mcg IV or SC q8h for 24-48h or until Na > 125; **plus 3% NaCl** based on Sodium Correction Rate. Augment with D5W and 3% NaCl PRN to achieve above goal. (Am J Kidney Dis 2013;61:571)
- Concurrent hypokalemia: K and Na freely exchanged, giving 1 mEq of K = giving 1 mEq of Na; be aware of overcorrection

HYPERNATREMIA: free water loss in excess of NaCl loss (Crit Care 2013;17:206, NEJM 2015;372:55)

Etiologies: impaired access to free water or impaired thirst, ↓ urinary concentrating ability or DI (↓ production or efficacy of ADH)

- Renal losses: Uosm <700–800; either ADH not released or kidney unable to respond: post ATN diuresis, osmotic diuresis, DI, rarely loop diuretic; elderly (↓ max concentrating ability)
- Extrarenal losses: Uosm >700–800; GI loss from NGT, vomiting, diarrhea, insensible losses, hypodipsia

Acute HyperNa (<48h, rare → salt poisoning, acute DI crisis). BMP q2-4h.

- Goal: correct to normal Na within 24H with D5W IV at 3-6ml/kg/hr until Na 145, then reduce D5W to 1ml/kg/hr until Na 140.

Chronic HyperNa (>48h, most common). BMP q12-24h. Strict I/O, UOP.

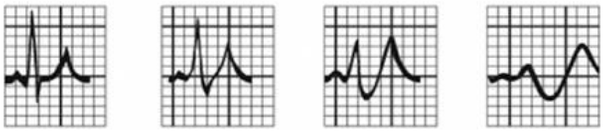
- Goal: correct at rate of 10-12mEq/L/day to prevent cerebral edema, though risk is low (CJASN 2019;14:656).
  1. Calculate free water deficit. Shortcut FWD = (Current Na – Goal Na)/3. Target Na should be 24h goal based on correction rate (i.e. <10-12mEq/L/day). Obese patients will have decreased %TBW.
  2. Account for ongoing losses: insensible losses (600-800cc/day), UOP, stool output, burn patients to avoid undercorrection
  3. Calculate hourly rate of free water replacement, adding ongoing losses and provide as PO free water, enteric tube free water boluses (e.g. 200-400mL Q6-8h) or IV D5W. If DI, may need DDAVP (See *Pituitary Disorders* in Endocrine section).

NORMAL POTASSIUM HANDLING / HOMEOSTASIS (NEJM 2015;373:60)

- Ingested K^+ absorbed in intestines → taken up primarily by liver/muscle cells via insulin & β2 receptors → ↑Na-K ATPase activity
- 98% of K^+ is intracellular; remaining extracellular levels trigger aldosterone secretion → principal cell K^+ secretion→ excretion in urine

HYPERKALEMIA

- Signs and symptoms: muscle cramps, paralysis, conduction delays (e.g. CHB, BBB, sinus arrest) and arrhythmia (VT/VF, asystole, idioventricular rhythms) (CCM 2008;36:3246)
- Dx: confirm true ↑ K^+ and not d/t hemolyzed sample, Plt > 500K, WBC > 120, or infusion of K^+-containing IVF; consider ABG/VBG+
- Low utility in checking transtubular potassium gradient



- EKG: peaked T waves → flat P → ↑ PR interval ± AVB → wide QRS ± BBB → sine wave pattern → PEA / asystole / VF
  - *ECG does not correlate w/ K^+ level* (Clin J Am Soc Nephrol 2008;3:324)
- Etiologies: **A**cidosis, ↓aldosterone; **B**-blocker, blood; **C**ell lysis / turnover; **D**rugs, DM, decreased GFR
  - **Redistribution**: cell lysis (hemolysis, rhabdo, TLS, RBCs, crush injury), acidosis, ↓ insulin (DM, octreotide), hyperosm, meds (digoxin, β-blockers, succ, calcineurin inhib [CNI], minoxidil), hyperK periodic paralysis, post-hypothermia
    - Usually transient unless impaired K^+ excretion
  - ↓ **Renal K excretion**: required for persistent hyperK^+
    - ↓ Aldo production / action: ACEIs/ARBs, NSAIDs, K^+-sparing diuretics, CNI, pentamidine, TMP, type IV RTA
    - Impaired Na delivery to distal nephron: CHF, cirrhosis
    - AKI/CKD (esp. if oliguric): usually GFR <15
    - Other: ureterojejunostomy – urine K^+ reabsorbed
- Management: *acute changes are most dangerous* → **STAT ECG.** Treat if EKG changes, K^+ > 6.5, rapid rise, or symptomatic
  - Key is **elimination**, other measures are temporizing. Address reversible factors (optimize volume status, low K^+ diet, meds)

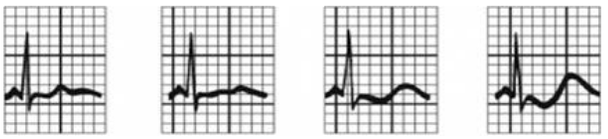
HYPERKALEMIA TREATMENT

Strategy	Treatment	Onset	Duration	Notes
Stabilize	**Calcium**: calcium gluconate or $CaCl_2$ (central line) 1-2 g IV, can repeat after 5 min PRN	1-3m	30-60m	1st line if **any ECG Δs**. Stabilizes cardiac membrane. **Avoid if on dig**
Redistribute	**Bicarb** (sodium bicarbonate 1-2 amps IV vs gtt)	5-10m	1-2h	Drives K^+ into cells. **Only if ↓↓ pH**
	Insulin (10U IV; 5U if ESRD) + **D50** 25g (if BS<250)	10-30m	4-6h	Drives K^+ into cells. ↓ K^+ 0.5-1.5 mEq/L
	Albuterol (10-20mg neb preferred over IV)	15-30m	15-90m	
Eliminate	**Furosemide** ≥40mg IV; can approx. as 30x Cr if K >6.	30m	Variable	Urinary K^+ excretion
	Patiromer (8.4 g/d PO) favored over **Kayexalate*** (15-30g PO/PR)	7h	24h	Swaps K^+ for Ca^{++} or Na^+ in gut
	Hemodialysis lowers K immediately (faster than CVVH)	N/A	3h	Removes K^+, may rebound d/t shifts

*GI ischemia/necrosis reported w/ Kayexalate, contraindicated post-op, ileus, bowel obstruction, colitis (JAMA Intern Med 2019; 179:1023)

HYPOKALEMIA

- Signs and symptoms: usually with K^+ < 2.5 → cramps, ileus, weakness (LEs > trunk/UEs > respiratory muscle paralysis), rhabdo (Annals 2009;150:619)
- ECG: flat T waves, ST dep, U waves, ↑ QT, atrial or ventricular ectopy → VT, VF (esp if K^+ <3, susceptible pts, or on digoxin)



- Etiologies:
  - **Lab artifact** (pseudo-hypokalemia): WBC >100 → WBC absorb K if sample sits out (check K on ABG+)
  - **Inadequate intake** unlikely to be 1° cause, usually combined with another etiology
  - **Redistribution**: ↑ pH, ↑ insulin, hypoK/thyrotox periodic paralysis, ↑ blood cell prod (e.g. s/p G-CSF), hypothermia, ↑ β-adrenergic activity (e.g. albuterol, epi), refeeding syndrome, toxins (cesium, barium, chloroquine)
  - **Extrarenal losses**: diarrhea (esp. if chronic, VIPoma, villous adenoma, laxatives), insensible losses, vomiting/NGT
  - **Renal losses** (*w/o HTN*): ↑urine flow (psych polydipsia, excess IVF), ↓ Mg^{++}, meds (ampho B, ifosphamide, cisplatin, gent)
    - Acidemia: DKA, RTA (proximal and some distal)
    - Alkalemia: diuretics, UGI losses (2° hyperaldo), Bartter's (~loop diuretic), Gitelman's (~thiazide)
    - Other: ↑ urine excretion of anions (β-OH-butyrate in DKA, bicarb [e.g. UGI losses], toluene + PCN metabolites)
  - **Renal losses** (*with HTN*):
    - 1° hyperaldo: ↑ aldo. ↓ renin (e.g. adrenal adenoma); 2°: ↑ a, ↑r (e.g. renin-secreting tumor, renal art. stenosis)
    - Other: ↑ glucocorticoid or ↑ ENaC activity (e.g. Cushing's, Liddle's syndrome, black licorice)
- Management: 10mEq raises K^+ by 0.1 mmol/L; caution if ↑Cr or if due to transcellular shifts
  - Oral KCl (ER = pill, IR = powder) preferred for tx as SAFER, quick acting, ↑ retention of K^+, and many pts are Cl depleted
  - IV formulation KCl if unable to take PO or if severe / symptomatic → max 10mEq/hr (floor), 20mEq/hr (ICU)
  - Always replete Mg^{++}, otherwise K^+ repletion ineffective (JASN 2007;18:2649)
  - Avoid dextrose-containing solutions → can acutely worsen hypoK (dextrose ↑ insulin secretion → K^+ shifts into cell)

HYPOMAGNESEMIA (Med Sci (Basel) 2019;7:E56)

- Signs/symptoms: other electrolyte disturbances (↓ K, ↓ Ca), weakness, anorexia, confusion, hyperreflexia, tetany, ↑ PR, ↑ QRS, ↑ **QTc**, peaked/inverted T waves, U waves, VT/torsades de pointes, accentuation of digitalis toxicity
- Etiologies:
  - ↓ **GI absorption**: ↓ intake (EtOH, malnutrition), ↑ loss (diarrhea, pancreatitis, malabsorption, small bowel resection, PPIs)
  - ↑ **renal loss**: diuretics (thiazide, loop), Gitelman's, amphoB, aminoglycosides, foscarnet, cyclosporine A, cisplatin, pentamidine
  - Distinguish GI vs renal with **FeMg** (>3% suggests renal wasting)
- Treatment: oral (slow) vs. IV (fast, typically used inpatient) (Am J Health Syst Pharm 2012;69:1212)
  - IV: $MgSO_4$ 1-2g over 15 min, max 1-2g/h; can give 4-8g over 12-24h; ½ dose if eGFR <30
  - PO: MgCl2 6-8 tabs/day causes less diarrhea than Mg oxide 800-1600mg/day, **always use in divided doses**
  - If hypoMg due to thiazide or loop diuretic, add K-sparing diuretic to decrease Mg excretion

HYPERMAGNESEMIA (rarely pathologic)

- Signs/symptoms: (typically only if Mg >6): neuromuscular (hyporeflexia [first sign], areflexia, lethargy, weakness/paralysis, resp failure), CV (hypotension, bradycardia, conduction defects [↑PR, ↑QRS, ↑QTc, CHB, cardiac arrest]), hypocalcemia (hyperMg can suppress PTH)
- Etiologies: Mg intake/repletion > renal clearance (only method of excretion)
  - Medication overdose (Epsom salts, laxatives, Maalox, Mg enemas) → avoid these agents in ESRD
  - Increased Mg absorption with gastritis/PUD/colitis
  - Mild hyperMg may be seen in DKA, hypercatabolic states (TLS), lithium, adrenal insufficiency
- Treatment: (symptomatic only): Ca gluconate 1g IV over 10 min vs gtt to counteract resp depression/hypotension. IVF, loop diuretics to enhance renal excretion. If oliguric/anuric ESRD, requires HD for removal.

HYPOPHOSPHATEMIA

- Signs/symptoms: (typically only if phos <1.0 mg/dL, esp. if acute), ↓ intracellular ATP → AMS/encephalopathy, seizures, CHF, hemolysis, respiratory depression, proximal myopathy, rhabdomyolysis, dysphagia/ileus, mineral Δ (bone pain, hypercalciuria, rickets/osteomalacia) (JASN 2007;18:1999)
- Etiologies:
  - **Redistribution (into cells)**: ↑ insulin (DKA, HHNK, **refeeding**), acute respiratory alkalosis (↑pH →↑glycolysis), hungry bone syndrome (deposition of Ca and phos in bone immediately following parathyroidectomy)
  - ↓ **GI absorption**: poor PO, chronic diarrhea, antacid use (aluminum, Mg), ↓ vit D (steatorrhea, chronic diarrhea), overuse of phos binders
  - ↑ **renal excretion**: ↑ PTH (1° or 2° hyperPTH), Fanconi syndrome (multiple myeloma, meds), ↑ FGF-23 (genetic/paraneoplastic), meds (acetazolamide, tenofovir, metolazone, IV iron) (QJM 2010;103:449), osmotic diuresis (glucosuria), proximally acting diuretics (acetazolamide, metolazone), CVVH (esp at high bicarb dose)
  - Distinguish GI/redistribution vs renal with FePhos (>5% suggests renal wasting)
- Treatment:
  - **Severe** (<1 mg/dL) **or symptomatic**:
    - Na or K phos 30mmol q4-6h with frequent levels (can give 15, 30, or 45mmol doses at MGH). Change to PO once >1.5mg/dL. Give ½ dose in CKD/ESRD
    - Aggressive IV tx can cause Ca precipitation, hypotension (often due to hypocalcemia), AKI, arrhythmia
  - **Asymptomatic** (<2 mg/dL): Na or K phos 1mmol/kg/d PO in 3-4 divided doses (total 40-80mmol)
    - NeutraPhos: 1 packet = 250mg phos (8mmol), 7.1mEq K, 6.9mEq Na; *preferred if also need K or if want lower Na*
    - K-Phos Neutral: 1 tablet = 250mg phos (8mmol), 1.1mEq K, 13 mEq Na; *preferred if do not need K*
    - If poorly tolerated (causes diarrhea), can give scheduled skim milk (8oz = 8mmol phos)

ACUTE HYPERPHOSPHATEMIA (for chronic hyperphosphatemia, see *CKD*)

- Signs/symptoms: result from effects of hypocalcemia (muscle cramps, tetany, tingling, perioral numbness)
- Etiologies:
  - **Acute phos load** (TLS, rhabdo, exogenous/phosphate-containing laxatives)
  - **Acute extracellular shift** (DKA, lactic acidosis, severe hyperglycemia)
  - **Acute kidney injury** due to decreased clearance (including acute phosphate nephropathy)
  - **Increased tubular reabsorption** (vit D toxicity)
  - **Pseudohyperphosphatemia** (hyperglobulinemia, hyperlipidemia, hyperbilirubinemia, hemolysis)
- Treatment: normal saline (though can worsen hypocalcemia), dialysis

IV FLUIDS

- Types: **crystalloid** (e.g. NS or LR), **free water** (e.g. D5W), and **colloid** (e.g. albumin, blood products)
  - Crystalloid can be isotonic (NS, LR), hypotonic (1/2 NS, 1/4 NS), or hypertonic (3% saline)
- **Bolus fluids** = volume expansion in shock, sepsis (30 ml/kg up to fluid responsiveness though debated: J Anes 2016;116:339), hemorrhage (initial resuscitation), GI losses, burns
  - Rate: ~500cc-1L over 30 min-2 hr. If concerned about volume overload, start w/ smaller volume (250-500cc)
  - NS in large volumes can cause hyperchloremic non-AG metabolic acidosis and ↑ need for RRT
  - LR or PlasmaLyte associated with better renal outcomes compared with NS though still debated (NEJM 2018;378:829, NEJM 2018;378:718)
  - Colloid is not superior to crystalloid for volume resuscitation in shock (JAMA 2013;310:1809)
- **Maintenance fluids** = replace daily losses (~1.6L per day in adults w/ normal renal function and perspiration). Also used at higher rates in conditions such as pancreatitis and rhabdomyolysis (NEJM 2015;373:1350)
  - *If patient is taking PO, there is no need for maintenance IV fluids.* **Always order with time limit.**
  - D5-1/2 NS is typical maintenance fluid for NPO patients. Insufficient calories to replace a diet (~170 kcal/L).
  - Maintenance rate: 60 ml/hr + 1 ml/kg/hr for every kg above 20 kg → ex. 60 kg adult = 100 ml/hr

Fluid	pH	Osm	[Na+]	[Cl-]	[K+]	[Ca^{2+}]	Dextrose	Other
Human plasma	**7.35-7.45**	**275-295 mOsm/L**	**135-145 mEq/L**	**94-111 mEq/L**	**3.5-5.0 mEq/L**	**2.2-2.6 mg/dL**	**60-100 mg/dL**	**1-2 mEq/L lactate**
Normal Saline	4.5-7	308	154	154				
Lactated Ringers	6-7.5	280	130	109	4	1.35		29 mEq/L lactate
1/2 NS	5	154	77	77				
D5-1/2 NS	3.5-6.5	406	77	77			5 g/dL	
D5W	3.5-6.5	252					5 g/dL	Used in hyperNa (see *Sodium Disorders*)

MGH Albumin Policy (Ellucid): put in place to prevent non-evidence-based overuse (ASA Choosing Wisely)
Albumin 25% = 12.5g albumin in 50ml solution; *Albumin 5%* = 12.5g albumin in 250ml solution
Use to replace serum oncotic pressure. If you need volume, give crystalloid.

- **SBP**: improves renal outcomes. Dosing: albumin 25% at 1.5g/kg IV within 6hrs arrival, decrease to 1g/kg on Day 3.
- **Large volume paracentesis in cirrhosis**: only if >5L removed. Dosing: Albumin 25% at 6-8g/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 IV q8h for 3 doses (requires attending approval; sop once alb >2.5. MAX 3 days).
- **Hepatorenal syndrome**: diagnosis and/or treatment by protocol. See *Hepatorenal Syndrome* in GI section.
- **Other**: chatter in ECMO/VADs, burns, nephrotic syndrome

ELECTROLYTE REPLETION – see *Potassium Disorders*, *Magnesium & Phosphorus Disorders,* and *Calcium Disorders* (Endocrinology) for more specific guidelines

	Potassium	Magnesium	Phosphorus	Calcium
Goal	- CAD/arrhythmia: ≥4 - Everyone else: ≥3.5 - Do not replete if on HD unless <3.0	- CAD/arrhythmia: ≥2 - Everyone else ≥1.7	- Replete if sx or phos <1 - At risk for refeeding: >2	- Replete if sx, long QTc, Ca <7.5, iCal <1.15mmol/L
PO or IV?	PO > IV	IV > PO	PO > IV	IV if severe, PO if mild
PO repletion	- KCl IR (powder): q4-6 hr - KCl ER (pills): giant pills - If K <3.5, ≥20 mEq KCl IR	- Mg oxide 400mg (240 mg elemental Mg) TID x1 day	- K-Phos: 1 packet QID - Neutra-Phos: 1 packet QID	- Ca carbonate 1250 mg PO BID
IV repletion	- Peripheral: 10 mEq/hr - Central: 20 mEq/hr w/ telemetry monitoring	- Mg sulfate 2g IV	- Give 15-45 mmol Phos at a time - K-Phos (1.5 mEq K/mmol Phos) - Na-Phos (1.3 mEq Na/mmol Phos)	- Ca gluconate 1-2gm IV; - CaCl2 used in codes, 0.5-1g q2-5 min
Comments	- 10 mEq K ↑ serum K by 0.1 - Max 80 mEq → re-check K - Correct hypoMg	- 2g will ↑ serum Mg by 0.5 - ↓Mg can cause ↓K and ↓Ca	- IV Phosphate can precipitate Ca → causing hypocalcemia	- Correct for low Alb and hyperphos first - 1g Ca gluconate ↑ serum Ca by 0.5

URINE DIPSTICK – urine should be analyzed within 2-4 hr

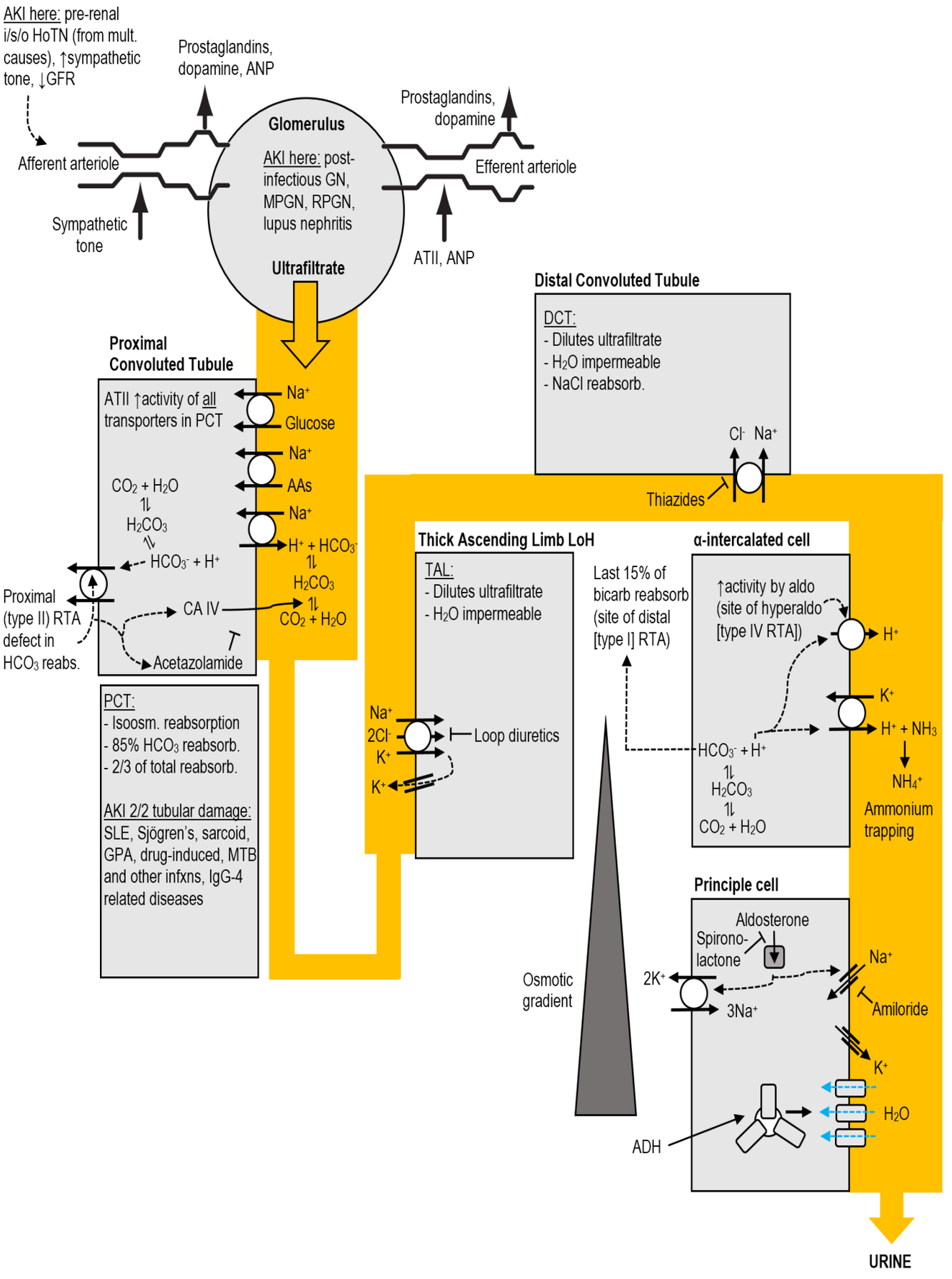
Specific Gravity	Can help approximate urine osm: decimal of SG x 30 (e.g. SG 1.020 → 20 x 30 → ~ 600mosms) SG < 1.010: post-ATN (concentrating defect), diuretics, DI, polydipsia, hypovolemic hypoNa *after resuscitation* SG 1.010 – 1.025: normal SG >1.025: prerenal, contrast (esp >1.030), ↓EABV, glycosuria (DM), proteinuria, SIADH
pH	Normal 4.5 - 8, but strongly depends on serum pH and dietary intake If normal urine pH + metabolic acidosis, suspect distal RTA (kidney not secreting NH_4^+) If pH ≥7, suspect urease-producing organisms (Proteus, PsA), strict vegetarians (low protein diet), type I RTA
LE	Released from lysed PMNs; **FP**: ↓ pH or ↓ SG (lyses WBCs); **FN**: proteinuria, glucosuria. For UTI, **Sn 80% / Sp low**
Nitrite	Indicates nitrate-reducing GNR (E. coli, Klebsiella, Proteus, PsA – NOT Enterococcus). For UTI, **Sn 60% / Sp>90%**
WBC	UTI; if sterile pyuria, consider AIN, GN, Chlamydia, Ureaplasma, urethritis, TB, foreign body, exercise, steroid use, cyclophosphamide
Blood	Detects heme (glomerular, renal, or urologic); **FP**: hemoglobinuria (hemolysis), myoglobinuria (rhabdo), semen, drugs (rifampin, chloroquine, iodine), peroxidase producing bacteria
Protein	Detects albumin when excretion >300mg/d: glomerular, tubular, and overflow causes; does NOT detect light chains Semiquantitative categories (trace, 1+, 2+, and 3+) are not reliable, vary with SG Falsely elevated by high SG, heavy hematuria (heme protein), and iodinated contrast (w/in 24h)
Ketones	Detects only acetoacetate, NOT β-hydroxybutyrate; yield decreases as collected urine sits
Glucose	Reflects glomerular overflow (serum glucose >180mg/dl or SGLT-inhibitor/mutation) OR PCT failure (glucosuria 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. Ask a Nephrology fellow or attending from the offices/HD unit nearby (day) or Security (night) to let you in.
  1. Obtain 10cc of **fresh urine**
  2. Dipstick
  3. **Centrifuge** using a balance @ 3000 RPM x 3-5 min
  4. **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.
  5. Standard or 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, increase power as needed to examine formed elements.
  6. Phase contrast microscopy: maximizes contrast and definition and allows better visualization of casts and cells. Raise condenser up high and turn light source to maximum brightness. Rotate the condenser annulus to 40 and the objective to 40 (objective and condenser annulus should always match). Analyze for dysmorphic RBCs or casts by focusing up and down, through the casts.
  7. Please use the urine sediment guide adjacent to microscope to guide analysis. Keep in mind: there is no polarized filter on our microscope

Findings	Description
RBCs	Glomerular (dysmorphic RBCs "mickey mouse ears") vs non-glomerular: trauma, exercise, infection, tumors, stones, sickle cell disease
WBCs	UTI/cystitis, pyelonephritis, AIN, atheroembolic, glomerular injury, renal/bladder TB, nephrolithiasis
Epithelial Cells	Tubular (ATN), transitional (proximal urethra to renal pelvis), squamous (contamination by genital secretions)
Casts	Viewed best w phase contrast: Hyaline, RBC, WBC, Muddy brown, Granular, Waxy, Fatty
Crystals	Viewed best w phase contrast: Acyclovir ("needles"), Tenofovir, Struvite (NH4·Mg·PO4), ethylene glycol (oxalate)

CONDITION	UA	CELLS	CASTS / CRYSTALS	COMMENTS
Pre-renal azotemia	SG > 1.010		Hyaline, granular	↓ FENa, ↓ FEUrea
CIN	SG >1.010; +Pro	Tubular cells	Granular, muddy brown	↓ UNa, ↓ FENa, **FP**: proteinuria
Nephrotic syndrome	3+ Pro		Oval fat bodies, hyaline	
Glomerulonephritis	3+ heme	Dysmorphic RBCs	RBC casts, WBC, granular	
ATN	SG ~ 1.010	Tubular cells	Granular, muddy brown	
Rhabdomyolysis, hemolysis	3+ heme w/o RBCs	NO cells	Acellular hyaline casts with red or brown pigmentation	↓ FENa, red/brown urine
AIN		WBCs; +/- eos	WBC casts, granular	Urine eos NOT Sens or Spec
Renal infarct	Sterile pyuria; +Pro	+Eos, RBCs, WBCs		↑ urine LDH (↑ serum LDH)
Cholesterol emboli	Sterile pyuria	+Eos	Cholesterol	
Myeloma kidney		Bland	Bland	Proteinuria NOT detected by UA
Ethylene glycol			Ca oxalate	
CKD			Waxy	+/- impaired ability to concentrate



For an additional schematic, see the nephron schematic at this Columbia Nephrology link.

Principles of Antibiotic Selection (Empiric Therapy from MGH, IDSA Guidelines, *Sanford Guide*, *Johns Hopkins Abx Guide)*

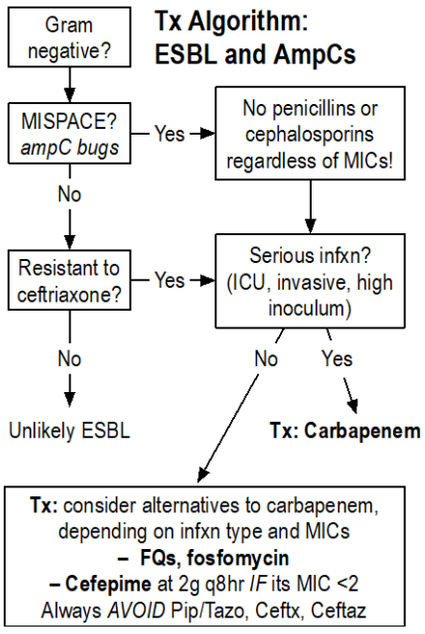
- **HOST**: presence of foreign bodies (eg. drains), structural organ disease (eg. CF, bronchiectasis, IBD), prior surgeries; when immune clearance is poor (i.e. neutropenia, endocarditis, meningitis, etc.), cidal antibiotics are preferred to static antibiotics
- **PATHOGENS**: prior micro data; risk factors for MDRO, especially IV antibiotic use within 90d
- **ANTIBIOGRAM**: identify local susceptibility and resistance patterns for likely pathogens
- **SOURCE CONTROL**: remove infected lines/hardware, evaluate for and drain abscesses/effusions

****CULTURES BEFORE ANTIBIOTICS** **TIME TO ABX CORRELLATES WITH MORTALITY IN SEPSIS****
*****More nuanced discussions on antibiotic choices can be found on topic-specific pages*****
*****See the Antibiotic Stewardship Program Page: http://intranet.massgeneral.org/id/asp/ for further information if needed*****

Suspected Process	Microbiology	Empiric Antimicrobial Therapy	Additional Info
Meningitis (IDSA: CID 2004;39:1267; CID 2017;64:e34)	-Viral, HSV, S. pneumo > N. meningitis -If >50yo, immunocompromised, EtOH use: Listeria -If hardware or nosocomial: Staph, PsA; P. acnes if VP shunt	-Vanc AND CTX 2g Q12 -If concern for Listeria: add Amp or TMP/SMX (if severe PCN allergy) -If concern for HSV: add Acyclovir -CNS abx penetration: Clin Micro Rev 2010; 23:858	-Dex 10 mg PO/IV q6h x 4 days w/ initial abx dose if S. pneumo -If healthcare-assoc / hardware / VP shunt / IVDU: Cefepime or Ceftaz or Meropenem in place of CTX
Community Acquired Pneumonia (CAP) (IDSA/ATS: AJRCCM 2019;200:e45)	-Viral (most common), S. pneumo, H. flu, Moraxella, S. aureus, Legionella, Mycoplasma, Chlamydia, Klebsiella, (EtOH)	-Healthy outpt: Amox or doxy +Comorbid: (amox/clav or cephalo) AND macrolide OR levofloxacin -Inpt w/o MRSA/PsA RFs (below): β-lact. AND azithro OR levofloxacin -Prior respiratory isolation of MRSA/PsA OR [recent hosp AND IV abx in past 90d]: vanc + cefepime + azithro	-Consider flu testing + Oseltamivir -If post-flu/cavitation/empyema: add Vanc for MRSA -If structural lung dz: Levo>Azithro -If Legionella: Levo>Azithro
Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP) (IDSA/ATS: CID 2016;63:e61)	-CAP organisms + S. aureus + GNRs including PsA	-Vanc + Cefepime (NB: double GNR coverage usually not necessary, but consider if ICU + shock)	-See HAP / VAP for more nuanced discussion; consider local MDRO and MRSA prevalence
Endocarditis (IDSA/AHA: Circulation 2015;132:1435)	-Native: S. aureus, Strep, Enterococcus, few GNRs, HACEK <5% -Prosthetic: S. aureus, S.epi	-Native: Vanc + CTX -Prosthetic: Vanc + Gent (or Vanc + CTX if prosthetic valve >1 year)	-*ID c/s improves mortality!* -MSSA: β-lactam >> Vanc -Check Rx list for rif interactions -Consider GNRs if subacute
Cholecystitis/Ascend. Cholangitis (IDSA: CID 2010;50:133)	-E. coli, Klebs; less likely Enterococcus, anaerobes. Often polymicrobial; broad abx for 48h even if BCx growing 1 org	-[CTX +/- MNZ] or Pip/Tazo -If nosocomial: consider cefepime	-Source control with ERCP vs. perc cholecystostomy
Other Intra-abdominal (IDSA: CID 2010;50:133)	-Abscess: GNRs, anaerobes, Enterococ, Candida; S. aureus, Strep rare -Diverticultis: Polymicrobial, enteric GNR, anerobes, role of Enterococcus unclear	-[CTX or Cipro] AND MNZ -If nosocomial/severe: cover PsA, add Vanc if recent instrumentation	-Need CT/US-guided drainage -Severe: Pip/Tazo or Mero or Imi -Surgical indication: peritonitis, perf, fistula, recurrent diverticulitis
Spontaneous Bacterial Peritonitis (AASLD: Hep 2013;57:1651)	-Enteric GNR, includ Enterobacter, Strep, Enterococcus; rarely anaerobes	-CTX	-Cipro reserved for patients w/ β-lactam allergies and for ppx
UTI (requiring hospitalization, non-pregnant) (IDSA: CID 2011;52:e103)	Uncomplicated: E.coli, Klebsiella, S.saprophyticus, Proteus Complicated (i.e. w/ s/sx of systemic infxn; includes Pyelonephritis): above + Enterococcus, PsA, Serratia, Providencia	Uncomp: NFT or Fosfomycin or Bactrim Comp: CTX or Cefepime (if c/f PsA), penem if ESBL, add Vanc if c/f GPC	-Comp: If afeb x48h, transition to PO FQ; can consider Bactrim or cefpodoxime but need longer course
Catheter-Associated UTI (CAUTI) (IDSA: CID 2010;50:625)	-GNR's, Enterococcus -Prior cx data useful	-CTX AND Vanc; consider PsA if risk MDRO, hosp. acquired	**-Tx only if sx**; repeat UA/UCx 48 hrs after removal or replacement (pyuria ≠ Infection)
Osteomyelitis (IDSA: CID 2012;54:e132; CID 2015;61:e26)	-Hematogenous source: S aureus -Direct inoculation/vascular (e.g. DM ulcer): S aureus > Strep, PsA (diabetic), GNR, Enterococ, Eikenella (human bites), Pasteurella (animal bites)	**-No abx until after bone bx+cx unless HD unstable/ severe neuro symp** -Vanc; ADD CTX or Cefepime if DM/PVD/Ulcer or direct innoculation	-Dx: MRI, ESR/CRP, bone bx -Debride (ortho/vasc surg/plastics) w/ bone bx+cx -Bite: Amp/Sulbact 1.5-3g IV q6h
Septic Arthritis (Curr Opin Rheumatol 2008;20:457)	-Staph, Strep, N. gonorrhea (sex. active), E. coli; Salmonella (sickle cell); PsA (IVDU); Lyme, viruses (poly-articular)	**-Blood + joint aspirate cx prior to abx** -Vanc AND CTX (consider Cefepime if IVDU, other risk factor for PsA)	-GC: CTX AND Azithro -PCN allergy: Vanc + FQ -Consult ortho for joint washout
Skin/Soft Tissue (SSTI) (IDSA: CID 2014;59:e10)	-Impetigo: S. aureus > Strep -Cellulitis/Erysipelas: Strep > Staph -Nec Fasc: Strep, C. perfringens, MRSA	-Purulent: Vanc; Non-purulent: cefazolin -Nec Fasc: Vanc AND [Pip/Tazo or Mero] AND Clinda	-DM/PV ulcer: Vanc AND [CTX or Cefepime] -If abscess: I&D is 1° therapy
Septic shock, no source (Intensive Care Med 2017;43:304)	-GNRs, S. aureus, Strep, PsA, anerobes. Consider toxic shock syndrome (TSS)	-Vanc AND [CTX or Cefepime or Ceftaz or Pip/Tazo] ± MNZ (if c/f anaerobes and not on Pip/Tazo)	-If TSS: add Clinda 900 IV q8h -MDRO: Meropenem/Imipenem -Critical illness/immuno-compromised: consider adding Aminoglycoside

Gram Positive	**Cocci**	Clusters or tetrads (never chains > 4)	Coagulase ⊕		*Staphylococcus aureus*
			Coagulase ⊖	Novobiocin sensitive	*Staphylococcus lugdunensis, S. epidermidis*
				Novobiocin resistant	*Staphylococcus saprophyticus*
		Long chains > 6 (never in tetrads)	α-hemolytic		Viridans group (optochin resistant)
			β-hemolytic		*Streptococcus pyogenes* (GAS)
		Pairs and short chains < 6	α-hemolytic (partial, green hemolysis)		*Streptococcus pneumoniae* (optochin sensitive)
					Enterococci (GDS) (also γ-hemolytic)
					Gemella (facultative anaerobe, variable hemolysis)
			β-hemolytic (complete hemolysis)		*Streptococcus agalactiae* (GBS)
			γ-hemolytic (no hemolysis)		*Streptococcus bovis* (GDS, variable hemolysis)
		Anaerobic	γ-hemolytic		*Peptostreptococcus*
	Rods	Large (and spore forming)	Aerobic		*Bacillus*
			Anaerobic		*Clostridium*
		Short	Aerobe		*Gardnerella*
			Facultative anaerobe		*Listeria, Erisypelothrix*
			Anaerobe		*Lactobacillus*
		Irregular/Pleomorphic	Aerobe ("club" shaped)		*Corynebacterium*
			Anaerobe		*Propionibacterium*
		Filamentous	Aerobe		*Nocardia, Tropheryma*
			Anaerobe		*Actinomyces*
Gram Negative	**Cocci**	CSF or genital	Facultative intracellular		*Neisseria*
		Lower respiratory	Aerobe		*Moraxella*
	Coccobacilli and Pleomorphic	Aerobic	Respiratory and Oropharyngeal		*Acinetobacter*
					Bordetella
					Haemophilus (*H. parainfluenzae* = HACEK)
					Cardiobacterium hominis (HACEK)
					Kingella kingae (HACEK)
			Zoonoses		*Brucella, Francisella, Bartonella*
		Facultative Anaerobe	Respiratory and Oropharyngeal		Aggregatibacter actinomycetemcomitans (HACEK)
		Anaerobic			*Eikenella corrodens* (HACEK)
	Curved Rods	Microaerophilic			*Campylobacter*
					Helicobacter
		Halophilic			*Vibrio*
	Straight Rods	Obligate Aerobes (*all lactose non-fermenters*)	Oxidase ⊖		*Stenotrophomonas*
			Oxidase Variable		*Burkholderia*
			Oxidase ⊕		*Pseudomonas, Alcaligenes*
		Aerobes	Respiratory		*Legionella*
			Enteric Gram Negative Rods: Lactose Fermenting (Coliforms)		*Escherichia, Enterobacter, Klebsiella*
					Citrobacter, Serratia (slow fermenters)
			Enteric Gram Negative Rods: Non-Lactose Fermenting		*Proteus*
					Salmonella
					Shigella
			Zoonoses		*Pasteurella, Yersinia*
		Anaerobes			*Bacteroides, Fusobacterium, Prevotella*
Acid Fast					Mycobacteria
Spirochetes					*Borrelia, Leptospira, Treponema*
Obligate Intracellular	Cell wall present		Tick borne		*Anaplasma, Ehrlichia, Rickettsia*
			Respiratory		*Chlamydophila, Coxiella*
	No cell wall				*Mycoplasma, Ureaplasma*
Fungi	**Yeast** (unicellular)	Budding, pseudohyphae			*Candida*
		Encapsulated, ⊕ India Ink, budding			*Cryptococcus*
		Trophozoite, sporozoite, cyst forms			*Pneumocystis*
	Dimorphic	Lives part of life cycle as yeast and part of cycle as a mold			*Blastomyces, Histoplasma, Coccidioides, Sporothrix*
	Mold (multicellular)	Branching, septated hyphae			*Aspergillus*
		Irregular aseptate hyphae, sporangia			*Mucor, Rhizopus* (zygomycetes)

EXTENDED-SPECTRUM BETA LACTAMASES (ESBL)



- **Definition**: plasmid-mediated enzymes exclusively seen in GN organisms conferring resistance to PCNs, most cephalosporins, and aztreonam
  - MGH Lab definition of *potential ESBL*: GNR resistant to **Ceftriaxone**
  - Two specific subtypes include **AmpC producers**, **CRE** (see below)
- **Pathogens**: Klebsiella (#1), E. coli (#2), Proteus mirabilis (#3), other GNs
- **Risk factors**: abx within past 6mo, long inpt hosp., nursing home, >65yo, lines/cath/tubes/vent, TPN, HD, travel to Asia
- **Treatment**: **AVOID** penicillins, cephalosporins (cefepime ok under specific conditions), & pip/tazo *even* if listed as susceptible (JAMA 2018;320:984).
  - *See algorithm to right*. For non-AmpC GNR, if CTX-R w/ cefepime MIC ≤2 and pip/tazo MIC ≤4, ok to tx with cefepime 2g q8 (CID 2014; 58:1554).
  - **If critically ill** and prior ESBL ⊕BCx, can tx empirically with meropenem (1g q8) while awaiting sensitivities.
  - **If not critically ill**, can use non-β-lactam alternatives if susceptible (e.g. FQ, fosfomycin, TMP/SMX, doxy, nitrofurantoin) (CID 2017;64:972). If isolated UTI, pip/tazo may be ok.

AmpC Beta-Lactamases (Cephalosporinases)

- Neutralize 3rd gen ceph., pip/tazo. AmpC expression can be constitutive or inducible (can appear S to CTX in vitro)
- Inducible AmpC producers include **MISPACE** (aka SPICE, SPACE-M) **organisms**: **M**organella, **I**ndole-positive Proteus (non-mirabilis species), **S**erratia, **P**rovidencia, **A**cinetobacter, **C**itrobacter, **E**nterobacter
- **Treatment**: do *not* treat these organisms with 3rd gen. cephalosporin (i.e. CTX) or pip/tazo, regardless of susceptibilities.
  - **If critically ill**, tx with meropenem (1g q8) or cefepime if MIC ≤2.
  - **If not critically ill**, can use non-β-lactam alternatives (e.g. FQ, TMP/SMX, doxy, or nitrofurantoin) if susceptible.

Carbapenem Resistant Enterobacteriaceae

- **Mechanisms**: 1) Carbapenemase or 2) AmpC/ESBL (some hydrolyze penems) + Porin loss (limits penem entry)
- **Risk factors**: cephalosporin/carbapenem use in past 3mo. (*penem exposure not req*), medical care in India/Pakistan
- **Laboratory detection**: suspicious when MIC >2 for imi-, mero-, or ertapenem
- **Treatment**: limited options; may include aminoglycosides, ceftaz-avibactim, colistin/polymixin B, Tigecycline, etc. **C/s ID**.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

- **Community-associated MRSA**: no healthcare exposure
  - Skin & soft tissue infections in young & healthy
  - Risk factors: HIV, IVDU, prior abx use; outbreaks: incarceration, military, sports, sharing needles/razors
- **Healthcare-associated MRSA**: occurs >48hrs following hospitalization or w/in 12mo. of healthcare exposure
  - Risk factors: recent hospitalization/surgery, HD, LTC facility residence
  - Nasal swab: high NPV for *pneumonia* (up to 96.5%), not as well studied for other MRSA infections. Therefore more useful if ⊖ swab → consider discontinuing MRSA coverage in pneumonia (CID 2018;18:67)
- **Treatment**: check the Vanc MIC!
  - Vancomycin-intermediate and resistant (VISA/VRSA): MIC ≤2 mcg/mL = vanc-susceptible (though ↑ tx failure and mortality when MIC=2). Intermediate (VISA) when 4 ≤ MIC ≤ 8. Resistant (VRSA) if MIC ≥16.
  - Serious infections (i.e. bacteremia): **vanc** (w/ full loading dose) and ID c/s. If persistent bacteremia or MIC ≥2, consider **dapto** (*NOT* in PNA [inactivated by surfactant] or meningitis [doesn't cross BBB]) *OR* add ceftaroline
  - Mild infections (e.g., PNA, SSTI): Bactrim, doxycycline >> clindamycin (less sensitive); linezolid

VANCOMYCIN RESISTANT ENTEROCOCCI (VRE)

- Low virulence, colonizer. *E. faecium*: often resistant & generally less virulent. *E. FaecaLIS* is *facile*: i.e. *less* resistance.
- **Risks**: multiple prior abx, urinary catheters & indwelling lines; proximity to other VRE infected/colonized patients; long hospitalization or nursing home residence; transplant / HIV / DM / ESRD or HD.
- **Clinical sites of infection**: UTI (*NB*: more commonly asymptomatic bacteriuria and rarely causes UTI in normal host; if pt not critically ill, pull catheter first if possible and retest urine); bacteremia (2nd most common CLABSI); intra-abdominal and pelvic infections; endocarditis (esp. if prosthetic valve); meningitis (rare unless immunocompromised or VP shunt)
- **Treatment**:
  - **Invasive infection** (e.g. bacteremia, endocarditis): dapto 8-12mg/kg q24 (+ amp or CTX or ceftaroline) *OR* linezolid 600mg q12
  - **Uncomplicated UTI**: fosfomycin 300mg x1 (consider repeat dose on days 4 and 7) *OR* nitrofurantoin 100mg q6

COMMUNITY ACQUIRED PNEUMONIA (CAP)

- **Definition**: PNA acquired in the community, including patients from nursing homes, dialysis, or with outpatient clinic exposure
- **Diagnosis**: new CXR consolidation (required) AND signs/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; lobar consolidation can be viral
  - If CXR ⊖ but clinical suspicion is high → treat and repeat CXR in 24hrs (PNA may "blossom" after fluid resuscitation and/or time); if still negative → consider chest CT or other dx
- **Triage**: CURB-65 (Confusion, BUN>20, RR>30, BP<90/60, age>65) → outpatient if Score 0-1, inpatient if 2, consider ICU if 3-5. Pneumonia Severity Index (PSI) more comprehensive → outpatient if <70, inpatient if >90.
- **Severe CAP**: **1 Major** (pressors or mech vent) OR **3 Minor** (RR>30, P:F<250, multilobar infiltrates, confusion, BUN>20, WBC<4K [*not due to chemo], Plt<100K, T<36C, HoTN requiring aggressive fluid resuscitation) (CID 2007;44:S27)
- **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.
    - Not recommended routinely. Obtain if: severe CAP, empirically tx for w/ MRSA/PsA, prev. MRSA/PsA, hosp. w/ IV abx ≤90d
  - **Blood cultures**: controversial benefit, positive <20% of inpt PNA, 2/3rd of positive Cx are S. pneumoniae.
    - Not recommended routinely. Obtain if: severe CAP, empirically tx for w/ MRSA/PsA, prev. MRSA/PsA, hosp. w/ IV abx ≤90d
  - **Procalcitonin (PCT)**: should NOT replace clinical judgment for dx of CAP / use of abx (also has slow turnaround at MGH).
    - ↑ in acute resp. infxns from bacterial causes but unclear cut-off to distinguish from viral. Not validated in immunocomp. pts.
  - **S. pneumo urine Ag** (Sn 70% / Sp 96%); only ⊕ in 44% of S. pneumo PNA. ✓ if severe CAP.
  - **Legionella urine Ag** (Sn 70% / Sp 99%); detects only serogroup 1 (80-90% in US). ✓ if severe CAP or recent exposure/travel. Clinical predictors include HypoNa, fever, diarrhea, and recent travel (CID 2019;68:2026)
  - **MRSA nasal swab**: high NPV (~98%). Neg test can be used to de-escalate MRSA coverage (CID 2018;67:1)
  - **Influenza**: test seasonally. **Tx**: oseltamivir regardless of duration of illness (though best if initiated <48h).
- **IDSA/ATS CAP Empiric Treatment** (NOTE: additional considerations for travelers, immunocompromised) (AJRCCM 2019;200:e45)

Outpatient	Preferred	Alternative/Other info
No Comorbidities or MRSA/PsA RFs	Amox 1g TID OR Doxy 100mg BID OR Macrolide (Azithro OR Clarithro) (if resist. <25%)	**NOTE: U.S. has high rates of macrolide- and doxy-resistant S. pneumo**
Comorbidities°	[Amox/Clav 2g BID *AND* Azithro] OR Levofloxacin 750mg QD monotherapy	Cefpodox or cefurox. can replace Amox/Clav, Doxy can replace Azithro, Moxiflox./Gemiflox. can replace Levoflox.
Inpatient	**Preferred**	**Alternative/Other info**
Non-Severe	(β-lactam (CTX) *AND* Macrolide [Azithro]) *OR* Levofloxacin monotherapy**	Amp/sulb can replace CTX, Clarithro can replace Azithro, Moxifloxacin can replace Levofloxacin
Severe/ICU	β-lactam (CTX 1-2g QD) *AND* (Azithro OR Levofloxacin)	**In ICU, azithro >> levofloxacin (anti-inflamm. effect)**; consider addt'l agents for drug-resistance (see below)
MRSA/PsA RFs#	Vancomycin *AND* Cefepime	Obtain Cx and nasal MRSA swab to inform de-escalation.

° Chronic heart, lung, liver, or renal disease; DM; AUD; malignancy; or asplenia. **CAP START showed β-lactam monotherapy noninferior to combo β-lactam/macrolide or fluoroquinolone alone, however trial was conducted in areas with lower rates of atypical organisms (NEJM 2015;372:1312). # Prior respiratory isolation of MRSA/PsA or recent hospitalization w/ IV abx (≤90d)

- **Risk factors for drug-resistant pathogens in CAP**:
  - General: hospitalization & IV abx in past 90d; prior respiratory isolation of MRSA, PsA or other resistant organisms
  - PsA: GNR on gram stain, h/o PsA, bronchiectasis, COPD w/ freq exacerbations req abx/steroids. **Tx**: *(for normal renal function)* Cefepime 2g q8h, Ceftazidime 2g q8h, Pip/tazo 4.5 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 **Tx**: **ampicillin-sulbactam** (or amox/clav if not severely ill); *alternative*: (CTX + flagyl) *OR* clindamycin (AJRCCM 2019;200:e45)
- **Steroids**: some data for benefit in severe CAP but routine use not rec. by IDSA/ATS unless o/w indicated for refractory septic shock or COPD/other comorbidity (Cochrane Rev 2017). **AVOID** in INFLUENZA as might ↑ mortality (Cochrane Rev 2016).
- **Duration**: **5d** assuming clinical stability (afebrile x48h + ≤1 sign of CAP instability: HR >100, RR >24, O2>90%, AMS, no PO intake); if have not achieved clinical stability, extend course & eval. for resist. pathogen, complication (empyema, abscess), alt. source of infxn
  - Convert IV → PO when clinically improving; no need to observe x24h on PO
  - Can utilize procalcitonin to help guide discontinuation of therapy: repeat PCT every other day and stop abx when PCT<0.25 or decreases by >80% from peak if initial PCT>5 ng/mL, though this does not supersede clinical judgment (JAMA 2009;302:1059)
  - Excessive abx duration (>5d) is associated with increased adverse effects w/o clinical benefit (Annals 2019;171:153)
- **Response to therapy**: tachycardia resolves by 2-3d; fever resolves by 2-4d; hypoxemia resolves by 3-6d
  - CXR clears by 1mo in 50% (delayed up to 12wks in older pts, pts with lung disease); do not repeat CXR for f/u if clinical improvement (CID 2007; 45:983)
  - If no response to therapy after 72h: consider chest CT (+/- BAL) to evaluate for empyema, abscess, fungal infxn

HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA (IDSA/ATS Guidelines: CID 2016;63:e61)

- **Definitions**:

Hospital-acquired pneumonia (HAP)	Pneumonia that develops ≥48 hrs after admission
Ventilator-associated pneumonia (VAP)	Pneumonia that develops ≥48 hrs after endotracheal intubation
Dx criteria: new/progressive infiltrates on CXR + 2/3 of fever, leukocytosis, purulent tracheal secretions	

- **Common microbiology**: enteric GNRs (*Klebsiella*, *E. coli*), MRSA/MSSA, *PsA*, *Acinetobacter*
- **Workup**: CXR, SCx, BCx, MRSA swab; consider induced sputum, bronch with BAL
- **Antibiotic choices and empiric treatment**:
  - **MDRO risk factors**: **IV abx use** within **90 days** preceding onset (most important); high local prevalence (>10%) of MDR GNRs & MRSA; structural lung disease (CF, bronchiectasis)
    - MDR VAP risk factors: septic shock/ICU, ARDS, onset ≥5 days in hospital, or RRT preceding onset
  - HAP/VAP with **MDRO risk:** 1 anti-PsA (**β-lactam** pref.) AND 1 anti-MRSA agent (typically **Vancomycin**)
    - Consider empiric double PsA coverage if: septic shock, rapid progression of PNA/requires mech. ventilation, hx of MDR PsA

Antipseudomonal β-lactams	Antipseudomonal non-β-lactams	Anti-MRSA agents
- Cefepime 2g IV q8H - Ceftazidime 2g IV q8H - Pip/Tazo 4.5g IV q6H - Meropenem 1g IV q8H - Aztreonam 2g IV q8H (only if severe PCN allergy: https://id.partners.org/allergy/) **Adjust dosing above as needed for renal function*	- Levofloxacin 750mg IV qday (*PsA susceptibility only 70% at MGH) - Ciprofloxacin 400mg IV Q8H - Tobramycin 5-7mg/kg IV x1, then dose by level - Polymyxin B (call ID)	- Vancomycin IV (trough 15-20) - Linezolid 600mg IV q12H

- **Tailoring therapy**:
  - If improvement after 48h or pathogen identification → narrow abx and discontinue MRSA + PsA coverage if possible. Neg MRSA swab w/ 96% NPV for MRSA infection (CID 2018;18:67; CID 2019). In VAP, if neg. tracheal aspirate, consider d/c abx after 72 hours (NPV 94% for VAP).
  - If no improvement after 48h → broaden to cover MDROs (if not currently covering), consider other sites of infection/abscess, non-infectious causes of clinical syndrome
- **Duration**: **7d** for both HAP/VAP. Can consider serial procalcitonin levels (though long turnaround at MGH) → discontinue abx when <0.25ng/mL (ERJ 2009;34:1364)

ASPIRATION PNEUMONIA

- **Definition**: pneumonia caused by the excessive entry of secretions, particulate matter, or fluid into airways. Micro-aspirations are common and the definition of aspiration pneumonia as a distinct clinical entity remains unclear.
- **Predisposing factors**: ↓ consciousness (seizure/overdose), esophageal dysmotility, post-bronchial obstruction, gum disease / poor dentition
- **Microbiology**: most common organisms are **GNRs and standard CAP/HAP organisms** (AJRCCM 2003;167:1650). Role of anaerobes is likely overstated in conventional wisdom with large studies demonstrating minimal recovery of anaerobic pathogens from bronchial samples (Chest 1999;115:178).
- **Characteristics**: indolent, putrid sputum, pulmonary necrosis w/ cavitation/abscess/empyema
- **Workup**: CXR, SCx (anaerobic respiratory culture not performed at MGH due to low utility)
- **Empiric treatment**: same as CAP/HAP empiric treatment
  - **Anaerobic coverage**: per 2019 IDSA guidelines, anaerobic coverage only routinely recommended in pts w/ **suspected lung abscess** or **empyema** (AJRCCM 2019;200:e45)
  - First line: **ampicillin-sulbactam** (or amox/clavulanate if not severely ill); *alternative*: (CTX + flagyl) *OR* clindamycin
- **Duration**: **7d** unless complicated by cavitation/abscess/empyema

ASPIRATION PNEUMONITIS

- **Definition**: aspiration of chemical substances into the airways *without* bacterial infection
- **Clinical manifestations**: abrupt onset (2hr), low-grade fever, ↑ WBC, hypoxemia, CXR consolidation (RML/RLL upright, RUL supine) → *often indistinguishable from pneumonia in the acute setting!*
- **Treatment**: if concern for aspiration pneumonia (i.e., bacterial infection), **cover with abx for 48hrs** → d/c if no consolidation develops on CXR *OR* if signs/sx/consolidation resolve rapidly (less likely to be PNA)

VIRAL RESPIRATORY INFECTIONS (for bacterial pharyngitis see *Respiratory Complaints*)

- **Epidemiology**
  - URI: rhinovirus (30-50%), coronavirus (10-15%), influenza (5-15%), parainfluenza (5%), RSV (5%)
  - LRTI (bronchitis, bronchiolitis, PNA): influenza, RSV, parainfluenza, adenovirus (Lancet 2011;377:1264)
  - In immunocompromised hosts consider reactivating latent viruses (HSV, CMV, adenovirus)
- **Presentation**
  - Risk factors: extremes of age, chronic illness, immunosuppression, malnutrition, tobacco use
  - Transmission: hand contact, droplet, peak viral shedding at 2-3 days, lasts 2 weeks
  - Symptoms: nasal congestion, dry throat, cough, wheeze, fever, malaise, headache, ear and face pain (for significant systemic illness consider influenza, measles, SARS, Hantavirus)
  - Complications: viral PNA; secondary bacterial PNA (initial improvement followed by worsening after ~7days → micro: S. pneumo [1st], S. aureus [2nd]), asthma / COPD exacerbation, acute otitis media, ARDS
- **Diagnosis**
  - Resp. viral panel: nasopharyngeal swab PCR for adenovirus, parainfluenza, metapneumovirus; can rapidly detect viral agent and help avoid unnecessary antibiotics; should be collected within 5 days of symptom onset, though approx. 15% healthy persons harbor respiratory tract viruses (Pediatr Infect Dis J 2008;27:1103)
  - Influenza testing: (IDSA guidelines: CID 2019;68:47)
    - RT PCR is most sensitive and specific; can differentiate A,B and subtypes (1-8 hours)
    - Rapid molecular assays is 92% sensitive, 96% specific, can differentiate A, B (15-30 min)
    - Rapid antigen testing is 62% sensitive, 98% specific (<15 min); during season negative test does not exclude influenza and is not sufficient to stop treatment (when in season)
- **Influenza Post-Exposure Prophylaxis**
  - Indication: severely immunocompromised persons who are unvaccinated and their unvaccinated household contacts, residents of LTCF during outbreak
  - Dosing: oseltamivir 75mg daily x7 days after last day of exposure, ideally no later than 48 hours after exposure (if symptoms arise, test for influenza, then transition to treatment dose) (CID 2019;68:47)
- **Influenza Treatment**
  - When indicated, treatment should **not** be withheld while awaiting results of diagnostic testing
  - Indications: severe disease (hospitalized or LRTI) or high risk population (>65, LTCF, pregnant / 2 wks post-partum, immunosuppressed, cirrhosis, DM, CHF/CAD, CKD, COPD, SCD, asthma, BMI>40, neuro disease)
  - Treatment: oseltamivir 75mg BID x5d; dose reduce for CKD; no data to support double dose if severe/ICU (BMJ 2013;346:3039); ideally initiate within 48h of sx but >48h OK if severe disease or hospitalized pt

HEAD AND NECK INFECTIONS (Principles of Crit Care. Chow AW. 4th edition. McGraw-Hill, NY 2015)

- Epidemiology: typically from odontogenic, otogenic or sinogenic infection with contiguous spread
- Organisms: streptococci, H flu, oral anaerobes. PSA in otogenic source. MRSA in sinogenic source and IVDU.
- Diagnostics: blood cultures, Panorex, **CT Neck**, MRI (evaluate for osteo), IR or ENT for tissue or abscess culture
- Treatment: β-lactam + anaerobic agent or β-lact. inhibitor. Early involvement of ENT for drainage and airway monitoring
- Clinical subtypes:
  - **Submandibular space** (Ludwig's angina): arising from a periodontal infection presenting with mouth pain, tongue swelling, neck stiffness, can progress to airway compromise, most commonly due to strep viridans
  - **Internal jugular septic thrombophlebitis** (Lemierre's syndrome): presents with pharyngitis and septic embolic phenomenon. Most commonly due to *fusobacterium*. Treat with abx and anticoagulation.
  - **Deep neck space**: involving retropharyngeal, danger and paravertebral spaces. Presents with neck pain and systemic toxicity. Can progress to carotid sheath abscess, mediastinitis, vertebral osteo, paravertebral abscess.

ORBITAL AND PRESEPTAL CELLULITIS (Surv Opthalmol 2018;63:505)

Preseptal

- Epidemiology: local trauma
- Organisms: staph, strep
- Symptoms: eyelid pain and edema
- Diagnosis: clinical though CT orbit and sinus can distinguish preseptal from orbital cellulitis
- Treatment: PO TMP-SMX or clindamycin and amoxacillin

Orbital

- Epidemiology: bacterial sinusitis
- Organism: staph, strep; mucor and aspergillus in immunocompromised
- Symptoms: pain with eye movement, proptosis, vision changes, pupil and extraocular muscle deficits
- Diagnosis: blood cultures, CT of orbit and sinus
- Treatment: Vanc and CTX (add anaerobic coverage if concern for CNS involvement); ophthalmology consult for daily vision checks and possible surgical debridement
- Complications: subperiosteal abscess, orbital abscess, CNS spread, cavernous sinus thrombophlebitis

Virology/Epidemiology
Clinical Illness: Coronavirus Disease 2019, COVID-19
Virus: SARS-CoV-2, 2019 Novel Coronavirus, 2019-nCoV

- 4 genera of coronavirus exist, some cause common cold (or viral PNA in pts w/comorbidities). Genus Betacoronavirus includes SARS-CoV, MERS-CoV, and SARS-CoV-2
- Source: zoonotic, reservoir unknown (Nature Med 2020;26:450), original association with live animal market in Wuhan, China
- Host entry: Viral S spike binds ACE2 receptor (Cell 2020;181:271) on type 2 alveolar cells & intestinal epithelia (same as SARS). ACE2 also in olfactory epithelium, liver, kidney, endothelium, & myocardium (Cardiovasc Res 2020;116:1097)
- Epidemiology:
  - R_0 estimate 2-4; decrease to 1 with control measures (Lancet ID 2020;20:553)
  - Symptomatic CFR 1-2%, though varies with age and comorbidities; Incubation 4-24d (median 5.1d, 1/100 develop sxs after 14d; Annals 2020;172:577)
  - True # cases may be much higher than reported (Science 2020;368:489)

Symptoms (NEJM 2020;382:1708)

- No universal symptom; can vary widely
- Constitutional: fatigue (23-70%), myalgia (15-35%), anorexia (40-78%). **Fever**: 80%-96% throughout the course, but not always present on admission. May be low grade (i.e. 99.5F/37.5C)
- Respiratory: dry cough: (41-79%), sputum production (10-45%), dyspnea (11-80%), rhinorrhea (5-15%), sore throat, anosmia and ageusia
- GI: (e.g. n/v/d): 10-50% (Gastro 2020)
- Skin: localized or widespread urticaria, petechial rash

Transmission
Main Route:

- Person to person via (large) respiratory droplets + direct contact; aerosolization thought to only occur with specific procedures
- Median duration of viral shedding 20 days. Resp. viral shedding highest early in course; evidence for pre-symptomatic transmission (JAMA 2020;323:1406); may persist after sx resolution depending on illness severity. No good evidence for late transmission. Peak infectiousness around 1 day before symptoms

Extra-pulmonary transmission:

- *Fomites*: droplet → lives hours to days on surfaces (NEJM 2020;382:1564)
- Viral RNA also detected in *stool* in pts with GI sxs (NEJM 2020;382:929; no known fecal-oral transmission, but could have direct contact transmission since ACE2 receptors in oropharynx), *conjunctiva* (Acta Ophth 2020), *serum* (Emerg Microbes ID 2020;9:469; more common in critically ill pts), and very rarely *urine*.
- *Vertical transmission*: recent evidence of IgM in newborns is suggestive (JAMA 2020;323:1848 & 1846), no viral shedding in breast milk. Placental infxn may cause miscarriage (JAMA 2020)

Prevention:

- Social distancing; CDC Patient Guidance
- Hand washing soap > alcohol; don't touch face; wipe surfaces w/alcohol, bleach, EPA-approved disinfectant

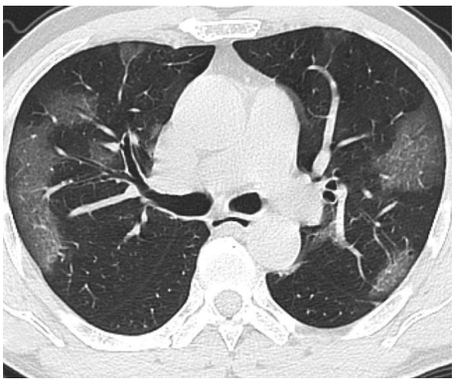
Laboratory Findings: for frequency and indications for testing, refer to MGH guidelines

Labs	Findings/Notes
Basic labs: CBC w/ diff, BMP, LFTs	Leukopenia & lymphopenia (60-80%), AKI in ~3-9% (more common later in course), ↑AST/ALT/Tbili (Lancet RM 2020;8:475)
Inflammatory markers and acute phase reactants: CK, ferritin, CRP, ESR, LDH	All may be elevated
Coagulation studies: PT/PTT, fibrinogen, D-dimer	↑D-dimer (associated with mortality), fibrinogen can be ↑ or ↓
Viral serologies: HBsAg, HBsAb, HBcAb, HCV Ab, HIV)	20% of COVID-19 cases have abnormal LFTs, want to r/o other causes, may influence treatment choice (esp. remdesivir and lopinavir/ritonavir)
Bacterial infection studies: BCx, procalcitonin, Strep pneumo + legionella urinary Ag	Only if c/f bacterial infection (note: rate of co-infection with bacterial PNA thought to be low. Procal initially low in COVID-19 but may rise after ~10 days of infxn, even w/o superimposed bacterial infxn)
Extended infectious studies: Tspot, sputum AFB/fungal Cx, pneumocystis DFA, 1,3-BDG, IgG	Please refer to MGH guidelines for testing indications. DO NOT obtain induced sputum due to risk of aerosolization
Troponin	↑ troponin in some cases (see *Complications* below)
β-hCG	Women of childbearing age
UA + spot urine protein:Cr	If AKI
IL-6	If category 2 or 3 risk factors

Risk Factors (for severe COVID-19)

- **Category 1 – epidemiological**: age>65, BMI >30, underlying pulmonary disease, CKD, DM with A1c>7.6, HTN, CVD, immunosuppression (s/p transplant or on biologics), HIV with CD4 count <200 or unknown CD4 count.
- **Category 2 – vital signs**: RR >24, HR>125, SpO2 ≤93% on RA, P:F<300
- **Category 3 – labs**: D-dimer>1000, CPK> 2x ULN, CRP >100, LDH >245, elevated troponin, admission absolute lymphocyte count <0.8, ferritin >500

Imaging

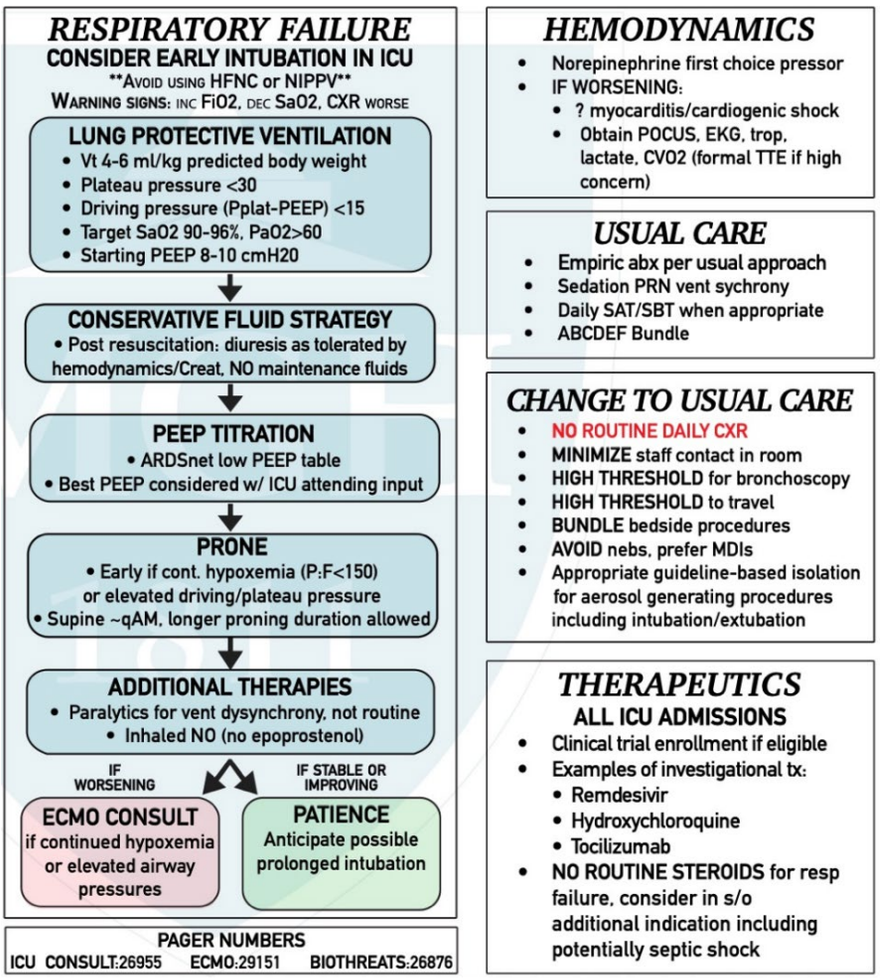


- EKG (COVID-19 can cause cardiomyopathy, some tx meds prolong QTc)
- CXR on admission; may be unremarkable early. NO clear diagnostic pattern, but often hazy **bilateral**, **peripheral** opacities (JAMA 2020). Avoid daily CXR, only obtain when indicated.
- Higher threshold to obtain CT given limited dx utility & infxn risk. May show peripheral GGOs, crazy paving, consol.; rarely unilateral (AJR 2020). CT abn. can precede or lag behind +viral PCR (Rad 2020, J ID 2020;11:1770)
- POCUS: many B-lines, pleural line thickening, consolidations w/ air bronchograms

Testing/Diagnosis/Treatment and Precautions: refer to MGH guidelines

Complications and Critical Care Management (see MGH Critical Care Guidelines; NEJM 2020)

- Suspect 5-15% of hospitalized COVID-19 patients will develop critical illness; low threshold to call Sr On if concerned
  - Sr On will work with ICU Triage intensivist to decide whether needs ICU transfer
  - Note: RICU needs ~10min to don PPE for intubation. Can call RICU attending (via x63333 – STAT vs. non-STAT) to discuss concerning pts (generally >4LNC or rapidly ↑ O2 requirement ≥1L NC/hr). Confirm Code Status before calling.
- ARDS may develop ~8-9 days after initial sx.
  - *Warning signs for deterioration*: worsening hypoxemia (P:F < 300, room air O_2 saturation <93%), progressive lymphopenia, increasing lactate and CRP, worsening CXR
  - Consider proning (MGH protocol) as a rescue therapy for floor pts requiring supplemental O2 (esp. escalating levels)
  - Note: early intubation is for **lung protection** from barotrauma (due to large spontaneous tidal volumes/transpleural pressures; avoiding HFNC/NIPPV is NOT just about aerosol generation)
- Septic shock less common. If shock worsens, consider myocarditis or cardiomyopathy → cardiogenic shock (JAMA 2020;323:1612)
- Cardiac injury: elevated troponin associated with increased risk of death (HR 4.26; JAMA 2020)
- Coagulopathy: MGH Heme Guidelines
  - *Clotting*: venous: PE/DVT seen in 7-27% of pts; arterial: reports of large vessel strokes (NEJM 2020); microvascular: lung, kidney, and liver (rates of clotting are higher in critically ill patients)
  - *Bleeding*: 2-5%
  - As many as 21% of pts with severe COVID may meet criteria for DIC (JTH 2020;18:1094)
- Causes of death: 53% respiratory, 33% combined respiratory/cardiac, 7% cardiac, 7% unattributed (ICM 2020;46:846)



Disclaimer: this page is updated in real time as more data emerge – for the most recent version, please refer to the White Book App (https://mghwhitebook.app/). The management guidelines are also actively evolving, so these are linked within this page.

ASYMPTOMATIC BACTERIURIA

Definition: bacteriuria (≥ 10^5 CFU/mL) without symptoms, irrespective of pyruria (>20% of ♀ age >80; 6-15% of ♂ age >75)

- **Treatment**: Bacteriuria or pyuria should NOT be treated in the absence of sx (*exceptions*: pregnant woman, s/p renal transplant in past 1mo., prophylaxis for invasive urologic procedures) (IDSA Guidelines: CID 2019; 68:1611)

CYSTITIS (UTI)

Clinical features: frequency, urgency, dysuria (premenopausal); malaise, incontinence, nocturia, suprapubic tenderness (Infect Dis Clin NA 2014;28:1)

↓

Fever, other s/sx of systemic illness e.g., chills/rigors, flank pain, CVA tenderness, pelvic or perineal pain (men)?

No ↓

Uncomplicated UTI (JAMA 2014; 312:1677)

- **Diagnosis**: clinical; U/A can be used to confirm; pyuria (>10 WBC) has NPV>PPV, sensitivity (nearly 100%) >> specificity
  - Women: if dysuria and ↑ frequency without vaginal discharge/irritation, >90% likelihood of UTI. In outpatient, U/A unnecessary unless immunocompromised or w/ risk factors for complicated UTI
  - In outpatient, get UCx only if male, atypical sx, persist 48-72 hr after abx initiated, or recur w/in 3 mo. of tx
  - Nitrites: only positive with Enterobacteriaceae (convert urinary nitrate to nitrite)
  - Only test for pyuria if dipstick shows +LE
- **Differential diagnosis**: vaginitis, urethritis, structural abnormality, PID, nephrolithiasis
- **Microbiology**: *E. coli*, *Klebs, Proteus, S. Saprophyticus.* ***Enterococcus rarely causes true infection***.
- **Treatment**: **NFT** 100mg BID x5d OR **T/S DS** BID x 3d OR **fosfomycin** 3g x1; alternatives: oral β-lactam (e.g. Augmentin 500mg BID, Cefpodoxime 100mg BID) x7d
  - Avoid NFT if CrCl < 30
  - Avoid empiric T/S if resistance >20% (*E. Coli* resistance 28% at MGH)

Yes ↓

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 UTI plus *Serratia*, *Morganella*, *Providencia*, *Pseudomonas, Citrobacter.* Gram-positives still 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 x 5-7d OR **T/S DS** BID x 7-10d. Can give 1x IV CTX prior to oral tx. Inpt: **CTX** OR **CEFE** OR **P/T**; CBPN if c/f ESBL. Narrow to oral agent if improving. Add **Vanc** / **Linezolid** if GPC on urine G/stain. Duration for inpt: depends on clinical course & oral agent chosen (5-7d for FQ; 7-10d for T/S; 10-14d for β-lactam).
  - Avoid **NFT** & **fosfomycin** (poor soft tissue penetration)
  - Remove/replace coated urologic devices
  - Prostatitis: **FQN** preferred for better penetration; tx duration up to 6 weeks

CATHETER-ASSOCIATED UTI (CAUTI) (IDSA Guidelines: 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 >2d) *OR* midstream voided specimen from patient whose catheter was removed w/in previous 48hrs
  - In pts w/ neurogenic bladder and ↓ sensation, other signs of UTI include new onset incontinence, autonomic hyperreflexia, malaise, lethargy, bladder pain (Urology 2015;6:321)
- **Prevention**: restrict catheters to pts w/ appropriate indications; remove catheters ASAP; consider short-term straight cath
- **Dx**: don't screen asx patients; pyuria, turbidity, odor cannot differentiate asymptomatic bacteriuria from CAUTI. Ideally remove catheter & collect midstream; if not possible, obtain from port in drainage system. Do not use Cx from bag to guide tx.
  - Purple urine bag syndrome: occurs due to byproducts from bacterial enzymes in urine; benign and ≠ UTI
- **Micro**: same as complicated UTI, with addition of *Candida* (see below); can be polymicrobial
- **Treatment**: same abx as uncomp./complicated UTI as approp., taking into account RFs for resistant infection. If recent catheterization/instrumentation, h/o MRSA in urine, add Vanc. Use Cx to narrow. Duration: 7d if improving; 10-14d otherwise.
  - **Remove** catheter ASAP, obtain repeat UA/UCx from new catheter PRIOR to abx

FUNGURIA (IDSA Guidelines for Candidiasis: CID 2016;62:e1)

- Asymptomatic colonization common; only treat if symptoms present OR neutropenic OR before urologic procedure
- Tx: **Fluc** 200-400mg (pyelo) PO QD 14d *OR* for resistant *C.glabrata or* krusei, **AmB** 0.3-0.6 mg/kg QD x1-7d

RECURRENT UTI

- Abx ppx (usually ↓dosed T/S or NFT) may be used in some ♀ w/ recurrent simple cystitis (≥2 UTI/yr) if behavior Δs ineffective. Either post-coital or continuous (Cochrane Rev 2004: 6-12mo continuous abx ppx ↓ rate of UTI in non-pregnant women).
- In pts w/ recurrent admission for complicated UTI, review prior micro data & consider resistant orgs. Consider involvement of ID +/- urology. Abx ppx not indicated in these pts.

KEY: NFT–nitrofurantoin; T/S–TMP/SMX; CTX–ceftriaxone; FQ–fluoroquinolone; P/T–piperacillin/tazobactam; CEFE–cefepime; CBPN–carbapenem; AMG–aminoglycoside; CPO–ciprofloxacin; LVO–levofloxacin; FLUC–fluconazole; AmB–amphotericin B; R–resistance

CELLULITIS (IDSA Guidelines: CID 2014;59:147; JAMA 2016;316:325)

- **Clinical features**: erythema, warmth, tenderness, edema, induration +/- purulence; smooth, poorly demarcated (vs. erysipelas which is well demarcated). May have lymphangitis, LAD, vesicles/bullae, fever (20-77%), leukocytosis (34-50%).
- **Risk fx**: edema (esp. lymphedema), venous stasis, PVD, DM, obesity, IVDU, tinea pedis, ulcer, trauma/bite, eczema, XRT
- **Differential diagnosis**: (*NB*: if "bilateral cellulitis," strongly consider alternative diagnosis)
  - Non-infectious: *inflammatory* (contact dermatitis, drug rxn, angioedema, Sweet syndrome, gout, bursitis, erythema nodosum, pyoderma gangrenosum, eosinophilic cellulitis, sarcoidosis, GVHD); *vascular* (stasis dermatitis, lymphedema, DVT, superifical thrombophlebitis, calciphylaxis), *neoplastic* (leukemia, lymphoma, breast CA, extramammary Paget's)
  - Infectious: abscess (may coexist), necrotizing fasciitis/gas gangrene, septic joint, osteo, zoster, HSV, erythema migrans
- **Diagnosis**:
  - **CLINICAL.** Can use ALT-70 score (shown to reduce abx use) (J Am Acad Derm 2017;76:618; JAMA Derm 2018;154:529). Consider ultrasound to assess for presence of abscess.
  - BCx & wound Cx are *NOT* recommended for typical cellulitis. Obtain if: systemic toxicity, extensive skin involvement, immunosuppression, special exposures (bites, water), recurrent/persistent cellulitis.
- **Treatment**: based on **1) purulence** and **2) severity**. Duration: 5 days; up to 14 days *if* delayed signs of improvement.

Severity	Purulent (abscess or fluctuance)	Non-purulent †
	MRSA (67%) > MSSA (17%) > Strep (5%)	Strep >> *S. aureus* > aerobic GNRs
Mild	I&D only	PO: cephalex., diclox., pen VK, amox/clav
Moderate: systemic signs of infxn‡ OR abcess >2cm	I&D + culture + TMP-SMX *OR* doxycycline	IV: cefazolin, ceftriaxone, pen G
Severe: systemic signs of infxn‡ *AND* HoTN, immunocomp., rapid evolution, deeper infection, or failed PO tx	I&D + culture + IV Vanc *OR* Dapto *OR* Linezolid. In TSS add clinda for toxin inhibition.	Vanc + Pip-tazo *OR* Vanc + imi/meropenem. In TSS add clinda for toxin inhibition.
† If non-purulent w/ **MRSA risk factors** (prev. MRSA infx/colonization, hosp./surgery/abx in prev 8wks, IVDU, penetrating trauma, hemodialysis, HIV, athletes, prisoners, military, LTC facility residents): add empiric PO/IV MRSA coverage (T/S or doxy) ‡ Systemic signs of infection include: T >38C or <36C, tachycardia (HR >90), tachypnea (RR >24), WBC >12 or <4		

NB: erythema may worsen initially; should improve w/ 72h of abx. Take pictures and draw margin lines to track progress.

- **Additional coverage**: *anaerobes* (if necrosis, putrid smell, crepitus, certain diabetic infections [see below], animal bite); *GNRs* (cirrhosis w/ severe infection, immunocomp, certain diabetic infections [as below]); *PsA* (neutropenic, trauma, post-op)
- **Specific associations**: gas gangrene (myonecrosis) → *C. perfringens;* dog/cat bite → *Capnocytophaga*, *Pasteurella*; human bite/IVDU → *Eikenella*; water exposure → *Aeromonas* (freshwater); saltwater → *Vibrio vulnificus* (esp. in cirrhosis)
- **IVDU**: discuss safe injection practices with patient. Links to printable patient resources: (CDC 1, CDC 2, HRC)
- Emerging data on long-acting injectables: **oritavancin, dalbavancin, & telavancin** (OFID 2018;5;S118; DIC 2018;7;1)

NECROTIZING FASCIITIS (NEJM 2017;377:2253)

- **Microbiology**: *Type I*: polymicrobial (mixed aerobes/anaerobes), risk factors include DM, immunosuppression, PVD; *Type II*: monomicrobial (usually GAS, less often other *Strep* or *Staph*, *Vibrio*, *Aeromonas*), associated with TSS; *myonecrosis* (i.e., gas gangrene); caused by *C. perfringens*, presents with gas in tissues, severe pain, toxin-mediated shock
- **Risk factors**: immunosupp., DM (esp. Fournier's), cirrhosis, neutropenia, EtOH, trauma (even minor), skin/mucosal breach
- **Clinical manifestations**: pain out of proportion to exam, bullae, induration (risk of compartment syndrome), tissue anesthesia, rapid skin changes (purple-red → blue-grey), crepitus (suggestive of myonecrosis); systemic toxicity, ↑CK, lactate, Cr, WBC
- **Diagnosis**: early suspicion and involvement of a **surgeon for surgical exploration** and ID is critical
  - LRINEC score ≥ 6 raises high suspicion for nec fasc; 90% Sn / 95% Sp (CCM 2004;32:1535)
- **Treatment**: urgent surgical debridement + Abx: (**vanc** or linezolid) + (**pip/tazo** or penem) + **clinda** for toxin inhibition

DIABETIC FOOT INFECTIONS (DFI) (IDSA Guidelines: CID 2016;63:944)

- **Severity**: *mild* (superficial ulcer, no involvement of deeper structures, erythema <2 cm); *moderate* (ulcer with involvement of deeper structures *or* erythema >2 cm); *severe* (moderate + systemic signs of infxn)
- **Initial evaluation**: cleanse, debride, probe, culture. Check pulses/sensation, ABIs (40% will have PAD), consider XR/MRI
- **Diagnosis**: wound culture. Most polymicrobial w/ GPCs>GNRs, anaerobes. For *mod-severe* infxn: add blood Cx + ESR/CRP
  - Osteomyelitis: ↑ risk if: visible bone/probe to bone (Sn 87%/Sp 83%), ulcer >2 cm^2, ulcer >1-2 weeks, ESR >70mm/h (JAMA 2008;299:806, CID 2008;47:519)
  - If suspicious for osteo, obtain plain films ± MRI ± surgical consult for bone/tissue biopsy ± ID consult
- **Treatment**: definitive tx based on deep cx obtained **PRIOR** to the initiation of abx. Appropriate wound care is critical.
  - Mild: oral → target GPCs (cephalexin, amox/clav, diclox, levoflox); TMP-SMX or doxy for MRSA; 1-2 weeks tx
  - Moderate/severe: IV → target GPCs, GNRs, ± anaerobes: (CTX or FQ) + flagyl; or amp/sulb. MRSA coverage w/ vanc, linezolid, or dapto if: severe infxn, prior MRSA infxn/colonization, other RFs (see above). PsA coverage w/ cefepime or pip/tazo if: severe infxn, immunocomp, neutropenic, water exposure, burn/puncture, nosocomial.
  - If improved, may de-escalate IV to highly bioavailable PO regimen to complete course

Clinical Manifestations:

- **Acute**: days to weeks; dull pain, local tenderness/warmth/erythema/swelling, can have systemic sx (fevers, rigors)
- **Chronic**: months to years; pain (absent if neuropathy), erythema, swelling; poorly healing ulcers; draining sinus tract is pathognomonic, sequestra (pieces of necrotic bone) often present. Unusual to have fevers.
- **Etiologies**: hematogenous seeding (usually monomicrobial) from bacteremia (↑ risk if endocarditis or indwelling device) or contiguous spread (polymicrobial) via direct inoculation after surgery/trauma.
  - Hip, vertebra, pelvis: often have fewer symptoms, can present as septic arthritis
  - Vertebral: pt tenderness, unremitting, >50yo (except IVDU), +/- 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 +/- mediastinitis (33% mortality: J Thor. Card Surg 2006;132:537).
  - Mandibular: usually contiguous spread of oral flora/odontogenic infxn; often w/ anaerobes

Diagnostic Approach: (JAMA 2008;299:806)

Risk Factors	Likelihood Ratio
Ulcer area > 2 cm	7.2 (1.1-49)
Probe-to-bone	6.4 (3.6-11)
ESR >70 mm/h	11 (1.6-79)
Abnormal plain X-ray	2.3 (1.6-3.3)
MRI c/w osteo	3.8 (2.5-5.8)
Normal MRI	0.14 (0.08-0.26)

- Physical exam: probing to bone sufficient for dx in patients w/ DM (83% Sp, 90% PPV) w/o need for further imaging (CID 2016; 63:944)
- Blood Cx: often ⊕ with hematogenous infxn involving vertebra, clavicle, pelvis (**always obtain BCxs before starting antibiotics**)
- Labs: ESR/CRP (if high can use for monitoring response), leukocytosis
- Imaging:
  - If >2 weeks of sx, obtain plain XR 1st. If <2 weeks of sx, suspected vertebral osteo, or pt w/ DM, start w/ advanced imaging (MRI). If XR non-diagnostic and story concerning, obtain advanced imaging (MRI)
  - MRI: Sn 90%, Sp 82% w/ high NPV (Arch Intern Med 2007;167:125); best in DM or if c/f vertebral osteo (CID 2015;61:e26)
  - CT: if MRI not available; can demonstrate periosteal reaction and cortical and medullary destruction
    - CT & MRI very sens. but non-spec; false⊕ if contiguous focus with periosteal reaction, Charcot changes
  - Radionuclide bone scan: very sens, but non-spec (false⊕ if soft-tissue inflamm.); option if hardware prevents MRI
- **Bone biopsy**: **gold standard diagnostic test**
  - C/s Ortho vs. IR; Ortho > IR if concern for overlying cellulitis to mitigate risk of seeding. Open Bx preferred to percutaneous. (CID 2009;48:888). If perc. Bx ⊖ and suspicion high, repeat vs. open biopsy.
  - Bone Cx may be ⊕ even on abx; need 2 specimens: GS/Cx (aerobic, anaerobic, mycobacterial, fungal) + histopath
  - If evidence of osteo on imaging or positive probe to bone, bone biopsy positive up to 86% of cases (CID 2006;42:57). Biopsy not required if ⊕ blood Cx and clinical/radiographic findings of osteomyelitis.

Treatment:

Empiric Tx	
Vancomycin + GNR coverage (typically ceftriaxone 2g q24). Include PsA coverage (cefepime) for IVDU	
Organism-Specific Tx	
MSSA	Nafcillin 2g IV q4h; cefazolin 2g IV q8h (not if a/w CNS infxn).
MRSA or CoNS	Vancomycin; daptomycin
PCN-S Strep	Pen G 4 mill U IV q4h; Ampicillin 2g q4; CTX 2g q24; Vanc.
Enterococci	Pen G 4 mill U IV q4h; Ampicillin 2g q4 +/- CTX 2g q24; Vanc; Dapto.
GNR	CTX 2g q24h; Cipro 750 PO BID; Levoflox. 750mg PO/IV q24; Cefepime 2g IV q12h, q8h if PsA

- **Antibiotics** (tx based on culture data, see table)
  - **Delay empiric tx until Bx** if pt HD stable, no neurologic compromise or epidural abscess
  - Common organisms: MSSA/MRSA, coag-neg staph, strep, enterococci, aerobic GNRs. Other: Brucella, Mycobacteria, Fungal.
  - Can consider adding rifampin if Staph + hardware (for biofilm) (Arch Intern Med 2008;168:805)
  - Duration: usually **≥4-6 wks**, PO may be adequate but discuss w/ ID (OVIVA trial). If using PO, FQ + rifampin most commonly used (NEJM 2019;380:425)
  - If no residual infected bone (i.e. amputation), short course abx 2-5d → up to 10-14 if associated soft tissue infection.
  - Consider rechecking ESR/CRP; if elevated at end of abx course, consider further w/u (*NB*: routine repeat MRI NOT done b/c MRI findings take weeks to months to resolve)
- **Surgical debridement**: indicated if failure to respond to medical therapies, chronic osteomyelitis, complications of pyogenic vertebral osteo (e.g., early signs of cord compression, spinal instability, epidural abscess), or infected prosthesis

BACTEREMIA

Evaluation (JAMA 2012;308;502)

- Signs: fevers/chills, poor food intake (J Hosp Med 2017;12:510), SIRS (high Sn, low Sp); *severity of "chills" correlates w/ risk of* bacteremia: ⊕ LR of 4.7 for **rigors** ("shaking chills") (Amer J Med 2005;118:1417.e1; Diagn Microbiol Infect Dis 2012;73;168)
- Sources: lines, procedures, endocarditis, PNA, UTI, osteomyelitis/septic arthritis, soft tissue infection, abscesses, meningitis
- Blood Cx: obtain prior to initiation of abx; **2 sets** minimum, ideally 3 diff. periph. venipunctures over 1hr (NOT from port or IV cath. at time of insertion); 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). Daily surveillance BCx until 48h neg Cx. Not necessary for GNRs (CID 2017;65:1776).
- TTE/TEE for *Staph aureus* and *Staph lugdunensis*. Consider TTE for high grade *Strep* spp. No need for routine echo for GNRs.

Empiric Management

- GPCs: **Vancomycin**. Staph: ID consult. Adding β-lactam (cefazolin/nafcillin) before final Cx known *may* improve outcomes (CID 2013;57;1760). MSSA: vanc inferior to β-lactam for long-term tx (CID 2015;61;361). See MGH PCN allergy pathway if allergic.
- GPRs: diverse resistance patterns; **Call ID on call**. Empiric regimen will depend on Gram stain and rod forms.
  - More likely true infection in immunocomp. hosts, multiple bottles, indwelling catheters or assoc. with other GPR infections (e.g., Erysipelothrix [SSTI], Actinomyces [H+N infxn], neutropenia/GVHD [Clostridia spp.])
- GNRs: **CTX** (community-acquired) or **cefepime** (HCA, comorbidities); consider **mero** if prior MDRO/ESBL
- Other considerations: *anaerobes* (intra-abdominal, empyema, obstruction, cavitation) → add **metronidazole** or substitute **pip/tazo**; *Candida* → **micafungin** + ID c/s; catheter-assoc. → generally remove line except in long-term lines; c/s ID (IDSA: CID 2009;49:1).

ENDOCARDITIS (AHA/IDSA Guidelines: Circ 2015;132:1435)

- Etiology: point of entry = cutaneous (40%), oral (29%), GI (23%)
- Clinical manifestations: bacteremia (f/c, anorexia, wt loss, fatigue), valv. complic. (HF, conduction abnorm.), septic emboli (CVA/CNS, pulm/PE, MI, kidneys, spleen, joints), immune-complex (arthritis, GN)
- Diagnosis: **Duke criteria** → 2 major OR 1 major + 3 minor OR 5 minor
  - TTE in all; TEE if: ⊖ TTE w/ high susp.; prosth. valve; intracardiac device; suspected complications (AHA/ACC: JACC 2014;63:e57)
- Monitoring: **repeat BCx** q24h until sterile x48hrs; serial ECGs for signs of perivalvular ext. (i.e. new AVB: PPV 88% for abscess but only 45% Sn)
- Microbiology: **Native Valve**: Strep, Staph, CoNS/Enterococcus (esp. >60yo)/Cx neg; **Prosthetic Valve (<12mo.)**: CoNS, Staph, Enterococc./ GNR/Fungal; **Prosthetic Valve (>12mo.)**: similar to NVE (w/ more CoNS)
- Indications for surgical consideration: valve dysfunction w/ HF (*emergent indication*), L-sided S. aureus/fungal/MDRO, HB/annular or aortic abscess/destructive penetrating lesion, persistent infection 5-7d after approp abx, PVE w/ relapsing infxn, large vegetations (>10mm on L, >20mm on R) and embolic phenomena despite abx (AATS Guidelines: JTCS 2017;153:1241; differ slightly from AHA)
- Anticoag./antiplatelet: controversial; generally ok to continue but no indication to initiate; if CVA/ICH, hold x2 weeks.

Modified Duke Criteria for Infective Endocarditis
MAJOR CRITERIA
⊕ **BCx (likely organism in 2 cultures 12 hrs apart or 3 Cx 1 hr apart) or *C. burnetii* IgG titer 1:800**
Endocardial involvement: vegetation, abscess, dehiscence, or new regurgitation
MINOR CRITERIA
Risk factors: valve disease, IVDU, prior infxn, indwelling line, prosthetic material
Temperature > 38C or 100.4F
Vascular phenomena: septic arterial or pulm emboli, mycotic aneurysm, ICH, conjunctival hemorrhages, Janeway lesions
Immunologic phenomena: GN, Osler, Roth spots, ⊕RF
⊕ **BCx not meeting major criteria**

Endocarditis Antibiotic Regimens (IDSA/AHA: Circulation 2015;132:1435; ESC: EHJ 2015;36:3075)

Empiric: NVE or PVE >12 mo. post-op: Vanc AND CTX 2g q24h; PVE w/in 12 mo. post-op: Vanc AND CTX 2g q24h AND Gent if normal GFR
PO option: POET RCT showed partial PO non-inferior to IV in L-sided IE. However no MRSA cases, only 1% IVDU included (NEJM 2019;380:415)

Organism	Native Valve (NVE)	Prosthetic Valve (PVE)	Notes
Streptococcus such as *VGS (e.g., mitis, mutans, anginosus, etc.); S. bovis (a/w colon cancer)*; *Gemella* spp.*; Abiotrophia* (treat as ↑ MIC)	PCN MIC ≤0.12: **PCN** OR **CTX** x4w -Option for 2w combo regimen w/ gent. PCN MIC 0.12-0.5: **PCN** OR **CTX** x4w *AND* **Gent** x2w PCN MIC ≥0.5: **PCN** OR **Amp** OR **CTX** x4w *AND* **Gent** x4w	PCN MIC≤0.12: **PCN** OR **CTX** OR **AMP x6w** +/- **Gent** x2w PCN MIC 0.12-0.5: **PCN** OR **CTX** x6w *AND* **Gent** x6w PCN MIC ≥0.5: **PCN** OR **Amp** *AND* **Gent** x6w	**Dosing**: PCN 12-18MU/d (div. q4) for NVE & MIC <0.12; otherwise 24MU/d; CTX 2g q24; Amp 2g q4; Vanc trough 10-15; Gent 1mg/kg q8, target peak 3-4, trough <1 **Vanc** monotherapy is alt. regimen but inferior to β-lactams –attempt desens.
Staphylococcus (*S. aureus*, CoNS – often methicillin-resistant); *S. lugdunensis* is virulent and should be treated like *S. aureus*	MSSA: **Nafcillin** OR **Cefazolin** x6wks MRSA: **Vanc** OR **Dapto** x6w *Note*: If R-sided (85% of IVDU), can do **Naf** x2w, **Dapto** x2w, or **Vanc** x4w	**Early surgical consult** MSSA: **Naf** OR **Cefazolin** *AND* **Rifampin** x6w + **Gent** x2w MRSA: **Vanc** *AND* **Rifampin** x6w *AND* **Gent** x2w	**Dosing**: Naf 2g q4; Cefazolin 2g q8; Vanc trough 15-20; Dapto 8-12mg/kg q24; Gent 1mg/kg q8, target peak 3-4, trough <1 -Do not use cefazolin for CNS involvement due to ↓ penetration
Enterococcus (*E. faecalis*, *E. faecium*)	**PCN** OR **Amp** OR **Vanc** (if PCN-R or allergic) *AND* **Gent** OR **Streptomyin** (if Gent-R) x4-6w Alternative: **Amp** AND **CTX** x6w VRE: Dapto + Amp. OR Linezolid	**Early surgical consult** -Same as for NVE; 6w tx	**Dosing**: as above; higher dose PCN, Vanc trough 15-20 -4w Amp+Gent sufficient if NVE and <3 mo. sx; 6w if >3 mo. or PVE
Gram-neg (HACEKs mostly, PsA, other GNRs possible)	HACEK: **CTX** OR **Amp** OR **Cipro** x4w GNRs: β-lactam + (Aminogly or FQ) x6w	**Early surgical consult** -Same as for NVE; 6w tx	-Rare etiology, minimal data to firmly direct treatment modalities
Fungi (*Candida*, *Aspergillus*)	Candida: **Ampho B** 3-5 mg/kg/d (± **flucytosine**) OR **Micafungin** 150mg q24 Aspergillus: **Voriconazole** or **Ampho B**	**Early surgical consult** -Same as for NVE; lifelong suppressive tx if no removal	-Risk factors: TPN, lines, PPM / ICD, prosthesis, IVDU -Ophtho c/s for candidemia

- IVDU assoc IE: refer to MGH Drug Use Endocarditis Team (DUET) includes CT surgery, ID & ACT (refer: epic phrase: .MGHDUET)

BACTERIAL MENINGITIS

Clinical Features

- History: 95% have ≥2 of: fever, nuchal rigidity, AMS, and HA (NEJM 2004;351:1849). Lethargy, hypothermia may be common in elderly. Abdominal pain, peritonitis can be seen in those with VP shunts (CID 2017;64:701)
- Exam: most findings more specific than sensitive, e.g., nuchal rigidity (30% Sn / 68% Sp); Kernig's sign (5% Sn / 95% Sp); Brudzinski's sign (5% Sn, 95% Sp) (CID 2002;35:46); jolt sign (worsening headache with horizontal rotation of the head) (64% Sn / 43% Sp) (Am J Emerg Med 2013; 31:1601). Meningococcemia associated with petechial rash, palpable purpura.

Diagnosis (CID 2004;39:1267)

- Blood cultures STAT; draw blood cultures BEFORE antibiotics, but DO NOT delay antibiotics for LP or imaging
- Lumbar puncture ASAP
  - Head CT prior to LP *only* indicated if: immunocompromised, known CNS disease (mass lesion, CVA, focal infection), new seizure, papilledema, ↓ level of consciousness, focal neurological deficit
  - Obtain opening pressure with simple column manometer (nml 200mm H_2O; mean 350mm H_2O in bacterial meningitis)
  - For a list of what studies to send and CSF analysis/interpretation, see *Procedures: Lumbar Puncture*
  - Repeat LP if no clinical improvement after 48 hours of appropriate antibiotics

Microbiology (NEJM 2011;364:2016; NEJM 2010; 362:146)

Community			**Nosocomial** (intracranial procedure, >48hrs 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%) P. acnes (takes 10 days to grow!)

Empiric Treatment (Lancet 2012;380:1693)

Adults < 50	Adults > 50	Immunocompromised	Nosocomial	SEVERE β-lactam allergy
Vanc (trough 15-20) + **CTX** 2g q12h (consider acyclovir)	**Vanc** (trough 15-20) + **CTX** 2g q12h + **Ampicillin** 2g q4h (consider acyclovir)	**Vanc** (trough 15-20) + [**Cefepime** 2g q8h OR Meropenem 2g q8h] + **Ampicillin** 2g q4h (not needed if on Mero) (consider fungal & viral)	**Vanc** (trough 15-20) + [**Cefepime** 2g q8h OR Ceftazidime 2g q8h OR Meropenem 2g q8h]	**Vanc** (trough 15-20) + **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 (2-4 wks if immunocompetent; 4-8 wks if immunocompromised)
- Dexamethasone: greatest benefit in suspected or confirmed pneumococcal meningitis w/ GCS 8-11 (↓ mortality, hearing loss, and short-term neuro sequelae in high-income countries). 0.15 mg/kg q6h x 4d; start prior to or w/ 1st dose of abx, but do not delay abx.
- CSF shunts: consult Neurosurgery for assistance with mgmt and/or shunt removal (CID 2017;64:701)

ASEPTIC MENINGITIS: meningeal inflammation with negative bacterial cultures

- Clinical presentation: similar to bacterial, usually less toxic. *LP*: lymphocytic pleocytosis
- Etiology: *Infectious*: **partially treated** endocarditis (most common cause), enteroviruses, HACEK orgs (*NB*: usually **NOT** culture negative!), HSV, VZV, partially tx'd bacterial meningitis (usually days-wks of tx), any stage of syphilis, Lyme, leptospirosis, mumps, Nocardia, TB, HIV (primary infection), LCMV, fungal (e.g. Cryptococcus, Coccidioides – see below), brain abscess; *Non-infectious*: autoimmune (Behcets, sarcoid, SLE, SJS), neoplastic (leukemia, lymphoma), drugs (NSAIDs, antimicrobials, IVIG)
- Treatment: if concern for encephalitis (HSV, VZV) → acyclovir 10 mg/kg IV q8h; otherwise tx is supportive. If suspect TB, call ID for consideration of quadruple therapy with INH, RIF, PZA and 4th agent (FQ or Aminoglycoside) + steroids (Tuberculosis 2010;90:279)

Fungal Meningitis

- Causes: *Primary (immunocompetent pts)*: Cryptococcus, Blastomyces, Histoplasma, Coccidioides, and other dimorphic fungi; *Secondary (immunocompromised pts)*: Candida, Aspergillus, other molds
- Diagnosis: submit CSF for acid-fast stain, India ink preparation, & cryptococcal antigen. Obtain large volumes (40-50 mL) for Cx.
- Cryptococcal meningitis treatment: ampho B IV 3-4 mg/kg qd + flucytosine PO 25mg/kg q6h (CID 2010;50:291)

ENCEPHALITIS (IDSA Guidelines: CID 2008;47:303)

- Presentation: AMS w/ focal neuro deficits or seizures. Abnormal brain function (vs. normal cerebral function in meningitis).
- Etiology: *Infectious*: **HSV,** VZV, arbo (**West Nile**, WEE/EEE, St Louis, Japanese), enteroviruses, HIV, CMV (extremely rare), JC, echo, adeno, influenza, Powassan virus; *Non-infectious*: post-infectious demyelination (ADEM), autoimmune, paraneoplastic (anti-Hu [(SCLC)], anti-Ma2 [testicular], anti-CRMP5 [SCLC/thymoma], anti-NMDA receptor [ovarian teratoma, idiopathic])
- Diagnosis: send CSF for HSV and VZV PCR; other viruses less common, only send if clinical suspicion high (West Nile IgM, JC, CMV/EBV [extremely rare]); consider MRI (HSV=temporal lobe enhancement, W. Nile=basal ganglia/thalamic foci); EEG
- If Sx recur s/p Tx, consider viral relapse vs. autoimmune enceph. – high rates of autoimm. dz wks later (Lancet Neurol 2018:17:760)
- Treatment: HSV, VZV → acyclovir 10 mg/kg IV q8h; otherwise supportive care

Overview (IDSA Guidelines: CID 2018;66:987; ACG Guidelines: AJG 2013;108:478)

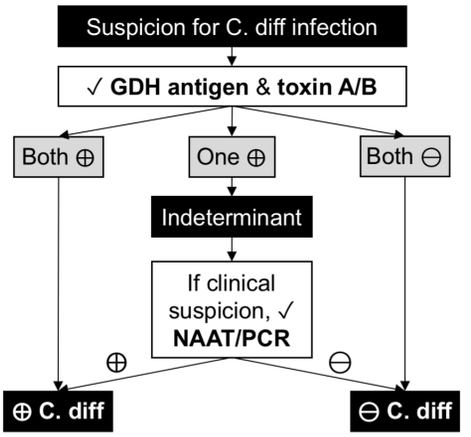
- Risk factors: **abx** w/in last 3 months (all abx, including 3rd/4th gen ceph. FQ, carbapenems, clinda), ↑age, ↑hosp. days, IBD, chemo/immunocomp., GI sugery, tube feeding ± PPI/H2RA. Receipt of abx by prev. pt in bed also weakly assoc.
- Pathogenesis: fecal-oral, colonized host; most often infection requires both acquisition of *C. diff* plus loss of gut microbial abundance/diversity (i.e., due to abx). Symptoms are toxin-mediated: toxin A (enterotoxic) & toxin B (cytotoxic).
- Community-acquired CDI: ~1/3 new cases; p/w diarrhea w/o traditional RFs. *Sources*: contam. food, H_2O, pets, asx colonization in family, babies, outpt visits. ↓ mortality vs. nosocomial (AJG 2012;107:89; JAMA Int Med 2013;173:1359).

Clinical Manifestations

- Features: **watery diarrhea** (≥3 loose stools in 24/hrs) +/- mucus/occult blood; fever, abd pain, isolated ↑WBC (CID 2002;34:1585); ileus in severe infection
- Ddx: non-C. diff abx-associated diarrhea, infectious diarrhea, postinfectious 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, or toxic megacolon & has high mortality

Diagnosis

- **MGH protocol**: see algorithm to right. *NB*: indeterminant results can be 2/2 asymptomatic (non-toxin-producing) colonization.
  - GDH: enzyme produced by all C. diff strains; assay sensitive but cannot distinguish toxigenic & non-toxigenic strains
  - Toxin A/B: assay detects toxin production; high Sp. but poor Sn.
  - NAAT/PCR toxin gene: high Sn. but can be ⊕ 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" (stool assays may remain ⊕ for up to 6w in pt w/ resolution of 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 (MGH ID Recs, IDSA Guidelines: CID 2018;66:987)

Category	Criteria	Treatment
Non-severe	WBC <15 AND Cr <1.5	-**Vanc 125 mg PO q6h or Fidaxomicin* 200 BID** -Alternative: **Metronidazole** 500mg q8 (*no longer first-line* due to ↑resistance) -D/c antiperistaltics & all non-essential abx. D/c cholestyramine (binds vanc).
Severe	WBC >15 OR Cr >1.5	-**Vanc 125 mg PO q6h or Fidaxomicin* 200 BID**
Fulminant	Hypotension/shock, ileus, megacolon	-**Vanc 500 mg PO q6h** *AND* **metronidazole 500 mg IV q8h** -If ileus: can add **Vanc PR** 500mg in 100cc NS as retention enema Q6H -Surgery consultation
Duration: **10d** for non-fulminant; if concurrent abx, continue through abx course and 7-14d after (no clear data on this)		

***Fidaxomicin**: bactericidal, ↓ recurrence vs. Vanc, some data for ↑rates of cure but $$$ (NEJM 2011;364:422, CID 2011;53:440, Lancet ID 2012;12:281, Cochrane Rev 2017)

Recurrence: up to 25% within 30d; often due to relapse as opposed to reinfection

- **1st recurrence**: pulse-tapered PO Vanc x6-8wks *OR* fidaxomicin 200mg BID x10d (unless was used for initial episode)
- **2nd recurrence**: pulse-tapered PO vanc x6-8wks *OR* 125mg PO Vanc q6 x10d followed by rifaximin 400mg TID x20d *OR* fidaxomicin 200mg BID x10d (unless used for prior episode)
- **3rd recurrence**: evaluate for **fecal microbiota transplant** (**FMT**); more effective than vancomycin or fidaxocomycin alone (NEJM 2013;368:407, APT 2015;41:835, Gastro 2019;156:1324). At MGH, consult ID (Dr. Libby Hohmann) for evaluation.

Other Considerations

- **Prophylaxis**: mixed data but secondary ppx w/ PO vanc (standard or reduced dose 125-250mg BID) may ↓ recurrence in pts w/ prior CDI receiving systemic abx (AJG 2016;111:1834, CID 2016;63:651, ICHE 2019;40:662). May also be effective as primary ppx in high-risk patients (older, recent systemic abx) w/ 125mg daily dosing (CID 2019).
- **Probiotics**: insufficient evidence & therefore not in guidelines; some evidence however does support use w/ abx to reduce abx-associated diarrhea (JAMA 2012;307:1959) and potentially prevent CDI (Gastro 2017;152:1889)

Risk Factors: heme malignancy, HSCT >> solid organ transplant >> patients on biologic Tx

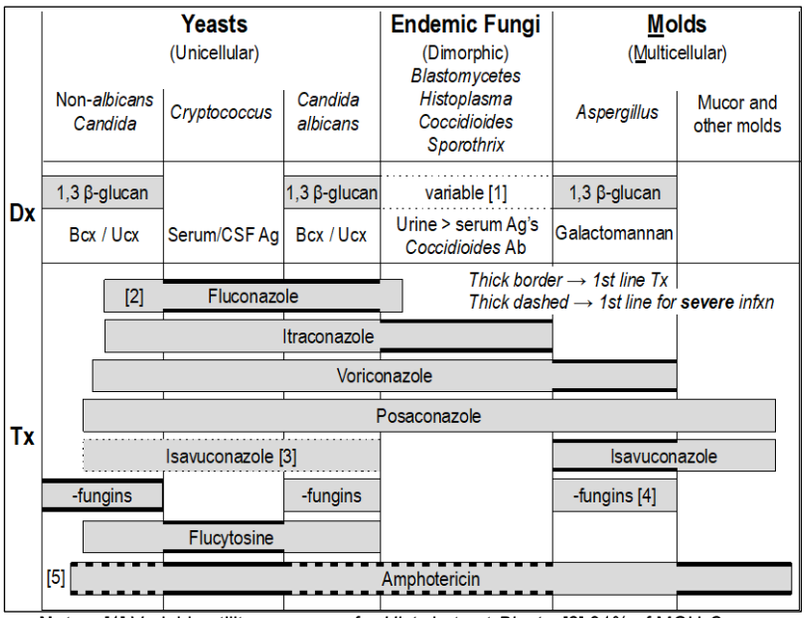
Diagnostic Testing

Fungal markers:

- **1,3-β-D Glucan (BDG)** (CID 2011;52:750): cell wall polysaccharide, detects ***Candida***, ***Aspergillus***, ***Pneumocystis* (PCP/PJP)**, ***Fusarium, Trichosporon, Histo, Coccidio***; CANNOT detect Mucor, Rhizopus, Blasto, Crypto; Sn 77%, Sp 86% w/ cut-off of 80
  - **False** ⊕ w/ IVIG, albumin, HD, meds (cefepime)
- **Galactomannan (GM)** (Cochrane Rev 2015): detects ***Aspergillus*** cell wall component; Sn 65-80% for serum test (BAL 90-95%), Sp 88%. Can be used to monitor tx.
  - **False** ⊕ w/ some TPN formulations
- **Histo urine/serum Ag**: UAg Sn 90% if disseminated (vs. serum Ag 80%); Sp limited by cross-reactivity
- **Crypto Ag**: serum Ag Sn & Sp > 90% if disseminated, less so for pulm. disease only
- **Blastomycoses**: urine > serum Ag; high Sn, but modest Sp due to cross-reactivity

Culture: *Candida* grows in blood/urine Cx but ↓Sn if deep tissue infxn; if high concern for *Coccidio*, alert lab (biohazard)

Antibody detection: clinically most useful if testing for *Coccidio*



Notes: [1] Variable utility, e.g., sens for *Histo* but not *Blasto*. [2] 91% of MGH *C. glabrata* is fluc-S. [3] Only approved for invasive aspergillosis/mucor. [4] In aspergillosis vori + mica not superior to vori alone. [5] Covers all invasive fungi w/ rare exceptions, e.g., *C. lusitaniae*. Always order AmphoB w/ **pre & post hydration** *AND* **BMP, Mg** BID.

Adapted from JA Freed and AJ Hale, IDModules.com

Pathogen-Specific Information

Invasive Opportunistic Fungi		
YEAST	**Candida**	Risk factors: neutropenia, immunocompromised, TPN, IVDU, CVC, prior abdominal surgery Spectrum of illness: sepsis (25% mortality), macronodular skin lesions (10%), endophthalmitis, endocarditis, osteo Diagnostics: **blood cultures** (Candidemia **never a contaminant** in blood); obtain **ophtho exam & ID consult** Treatment: **micafungin 1st line/empiric**, transition to fluc if *albicans*, high dose fluc/vori if *glabrata/krusei* (or AmphoB for resistant strains); Duration: 2 weeks after 1st neg Cx and no dissemination in candidemia, longer for deep-seated infxn Source: *non-neutropenic*: lines most likely source (remove early); *neutropenic*: GI most likely source Prophylaxis: fluconazole, posaconazole or micafungin (for SOT, SCT, neutropenic)
YEAST	**Cryptococcus**	Risk factors: immunocompromised, liver disease, HIV, but can occur in immunocompetent (IDSA guidelines: CID 2010;50:291) Spectrum of illness: meningitis, pulmonary, cutaneous nodules, liver abscesses Diagnostics: **serum/CSF CrAg**, LP/CSF: OP >20, ↓glucose, ↑TP, lymphs, **+India ink** Treatment: **amphoB + flucytosine (x2 wks), followed by fluconazole (≥8 wks),** serial LPs if OP>25 or symptoms of ↑ICP Prophylaxis: typically not recommended
YEAST	**Pneumocystis**	Risk factors: HIV with CD4 <200, steroids equiv. to pred 20mg x4 wks Spectrum of illness: pulm symptom onset over days/weeks, PTX, hypoxemia out of proportion to CXR (BL diffuse GGO) Diagnostics: **LDH >500** (Sn not Sp), **BAL > induced sputum** for silver stain, **1,3-BDG** (Eur J Clin Microbiol Infect Dis 2014;33:1173) Treatment: **TMP/SMX** w/ **steroids (if A-a >35, PaO2 <70)**; Alternatives: atovaquone or pentamidine; Duration: 21 days Prophylaxis: TMP/SMX (1 SS qD or 1 DS MWF), atovaquone or dapsone; Indications: pred 20mg ≥4wk, SCT, and others
MOLD	**Aspergillus**	Risk factors: immunocompromised esp. neutropenia/steroids/transplant, COPD with prolonged ICU stay Spectrum of illness: invasive pulm w/ hemoptysis, PTX, aspergilloma, sinusitis, CNS, endophthalmitis Diagnostics: CT **with halo sign**, **BAL**/sputum culture, **1,3-BDG** (not Sp), **GM** (Sp; can trend in tx, BAL > sputum) Treatment: **vori** (requires monitoring of drug levels and drug-drug int) or **isavuconazole**; Duration: 6-12 weeks min. for pulm disease Prophylaxis: consider posaconazole in grade III-IV GVHD (NEJM 2007;356:348), vori in lung transplant w/ h/o aspergillus.
MOLD	**Mucor**	Risk factors: DKA, iron overload, heme malig, prolonged neutropenia, immunocomp. (Semin Respir Crit Care Med 2015;36:692) Spectrum of illness: rhino/orbital/cerebral invasion, pulmonary, GI, renal; black eschars over ulcers, rapidly progressive Diagnostics: culture, wet prep (**non-septating hyphae** with **wide-angle branches**), **CT with reverse halo sign** Treatment: **DEBRIDEMENT**, **AmphoB**, consider posaconazole or isavuconazole (for salvage therapy or if renal disease)
Endemic Fungi		
Histoplasmosis		Endemic areas: Houston, OH/MS river valleys, Central America, Asia, Africa (CID 2007;45:807) Spectrum of illness: PNA, meningitis, mediastinal disease, disseminated disease Diagnostics: Ag from urine/serum/BAL, Cx; *NB*: chest imaging may appear similar to sarcoid Treatment: **itraconazole** (mild-mod) or **ampho B** (severe), followed by **itraconazole**; Duration: 6-12 weeks Prophylaxis: for both Histo and Blasto (below), consider itraconazole ppx for HIV+ with CD4 <150 in hyperendemic areas
Blastomycosis		Endemic areas: OH/MS river valleys) Spectrum of illness: fever, PNA, ARDS in severe, ulcerated skin lesions, prostatitis, CNS Diagnostics: wet prep (broad-based, budding yeast), culture, urine > serum Ag, **never a colonizer** Treatment: **itraconazole** (mild-mod) or **ampho B** (severe), followed by **itraconazole**; Duration: 6-12 mos
Coccidiomycosis		Endemic areas: SW and S US Spectrum of illness: fever, cough, rash, HA, eosinophilia, meningitis, osteo. Diagnostics: serologies, cx, spherules on bx/aspirate Treatment: **fluconazole** or **itraconazole**, consider **amphoB** if severe; Duration: 3-12 mos Prophylaxis: fluconazole for 1° ppx ONLY for transplant recipients in endemic areas, not in HIV; use fluconazole for 2° ppx

Epidemiology: world: 1 in 4 infected; US: incidence 2.8/100,000, with 5.6% HIV coinfection and 1% MDR (CDC MMWR TB US 2017)

Risk Factors: acquisition: travel hx to/from high-prevalence area, homelessness or incarceration, PWID, health care work, racial/ethnic minority; reactivation: risk is 5% in first 2 years and 5%-10% over lifetime, but higher if pt has ≥1 of the following: HIV+, immunosupp, CKD (esp. HD), DM, CA, txp, TNFα inhib., silicosis, malabsorption malnutrition, tobacco, EtOH (NEJM 2011;364:1441)

Screening for Latent TB: test based on likelihood of exposure + progression to active disease. IGRA preferred (Quant-GOLD test of choice at MGH); TST acceptable (NB: only 60% spec in pts who received BCG vaccine). Both IGRA and TST are 80-90% sens and >95% spec in immunocompetent, ↓ sens in immunocomprom. Neither test rules in/out active TB and they can be discordant ~30% of the time. If ⊕ test but no risk factors, repeat either IGRA or TST prior to treatment. If ⊕ test in high risk pt, proceed to treatment. (ATS/CDC/IDSA Guidelines: Clin Infect Dis 2017;64:111 [Figures 1+2 especially!]; CDC Risk Assessment Tool; TST/IGRA Interpreter)

TST Size at 48-72 Hrs	Patient Population
≥5 mm	HIV, prior TB hx, CXR c/w prior TB, silicosis, immunosuppression
≥10 mm	Diabetes, CKD, IVDU
≥15 mm	No risk factors
NB: size reflects skin induration, NOT erythema	

Clinical Manifestations:

- Primary TB: fever, chest pain, cough, arthralgias. CXR often normal or ⊕ hilar LAD
- Reactivation TB: fever, cough, hemoptysis, night sweats, weight loss; CXR often involves posterior/apical upper lobe or superior aspect of lower lobe, or cavitation (seen in 1/3 of pts, a/w ↑ org. burden → ↑ infectious, AFB⊕); more common than primary TB!

Diagnostics for Active Pulmonary and Extrapulmonary TB (J Clin Microbiol 2007:45:4064; Lancet 2007;369:9578)

Site of Infection		Diagnostic Tests
Lungs	Sputum	Expectorated or induced, AFB smear and culture x3 ≥8hrs apart, add NAAT/PCR to one of the specimens; smear may be ⊖ if burden is low (~20% if HIV-, ~60% if HIV+)
Lungs	Bronch	Send brushings, washings, BAL, sputum for AFB smear, NAAT/PCR (Xpert) and culture; +/- transbronchial biopsy. Obtain post-bronch induced sputum to increase yield.
Ascites or pleural fluid		Adenosine deaminase (ADA): if >39 units/L → high Sn/Sp; free IFN-gamma (if elevated, high Sn/Sp); AFB smear, NAAT/PCR (Xpert), & culture (poor sensitivity, helpful if positive)
CSF		At least 3 large vol (10-15cc) serial LPs if possible (↑ dx yield). Cell counts w/ ↓ glucose, ↑ protein, lymphocyte predominance; ↑ ADA useful adjunct. Send smear, Cx, and NAAT/PCR (Xpert)
Wound/Tissue		AFB-positive staining and caseating granulomas; if cytopenic, consider bone marrow biopsy
Urine		UA shows "sterile" pyuria; send first AM void (large vol -50cc) for culture x3 days
Blood		Can send mycobacterial cultures (isolators) for AFB

Patient Isolation: clinical decision based on likelihood of active TB

- When: cough, dyspnea, or hemoptysis + ≥1 risk factor (HIV+, foreign born, substance use disorder, homeless, recent incarceration, prior TB or exposure). First obtain CXR; if CXR normal (and HIV- or CD4>200), TB less likely. If CXR abnormal/equivocal (or HIV+ and CD4<200), maintain isolation and obtain 3 sputum samples for AFB smear and mycobacterial culture as above. Consider ID c/s.
- Discontinue: if alt dx ***OR*** AFB smear neg x3 w/ very low suspicion ***OR*** on TB tx x2wks + AFB smear neg x3 + clinical improv.

Approach to Treatment (ATS/CDC/IDSA Guidelines: Clin Infect Dis 2016;63:e147; NEJM 2015;373:2149)

- **Prior to starting treatment**:
  - General: check baseline LFTs/Cr, visual acuity/color discrimination, screen for HIV, Hep A/B/C, DM, EtOH use, pregnancy
  - Before treating latent TB: need to rule out active TB (obtain relevant history, CXR)
  - Before treating active TB: **obtain ID consult**, send TB for drug sensitivity testing
- **Treatment regimens**:
  - Active TB: isoniazid (INH) + rifampin (RIF) + pyrazinamide (PZA) + ethambutol (EMB) x2mo., followed by INH+RIF x4mo.
  - Latent TB: INH+rifapentine (RPT) qweek x12 (DOT no longer required) ***OR*** RIF x4mo. ***OR*** INH+B6 x6-9mo (less preferred) (CDC Tx Table; CDC Tx Specifics; NEJM 2011;365;11; NEJM 2011;365;2155)
  - Quinolones: 1st line w/ MDR-TB, **avoid in bacterial PNA** if suspicious for active TB (↓ dx yield & ↑risk of resistance)
- Drug-resistant TB: **suspect if previously treated**, treatment failure, from prevalent area (India, China, Russia, S. Africa), or known exposure. Treatment regimen depends on drug susceptibility profile; usually for 12-24 month tx course. 80% mortality
- HIV co-infection: if CD4<50 or CD4>50 with severe clinical disease but not meningitis, start ART within 2 weeks after starting TB therapy. Discuss with ID.
- Extrapulmonary TB: highly variable presentation/therapy, duration depends on site of infection & response. For meningitis, glucocorticoids confer 25% short term RR 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)

Definition and Clinical Manifestations:

- Acute HIV: mono-like syndrome → rash, LAD, fever, oral ulcers, pharyngitis, myalgias, diarrhea; **presents 3-6 wks after infection**
- AIDS: HIV+ with: CD4 count<200 *or* CD4 T-cell <14% of total lymphs *or* AIDS-defining illness

HIV Screening and Diagnostics:

- **Screen** all 13-64yrs **once,** every **pregnancy**, if another STI, IVDU (annually), commercial sex workers (CSW), MSM >1 partner since last test, partners of all high-risk pts. In MA: opt out verbal consent *("We'll be conducting a number of tests, including for HIV")*
- 4th gen combined HIV 1/2 Ab/p24 Ag assay: mean detection limit @ **18d (5d sooner than 3rd gen.)** (STD 2017;44:739)
- HIV RNA PCR/viral load (VL): mean **12d**, high Sn/Sp but slow, expensive; used for: 1) concern for **acute HIV** (Ab/Ag testing are negative early in disease course); 2) confirmation of HIV diagnosis; 3) viral load

Prophylaxis

- **PrEP (Pre-Exp)**: pts w/ high risk of HIV (sero-discordant couples, STI in last 6mos, inconsistent condom use in MSM, IVDU, high risk sex, CSW, transgender pts). If partner of pt is HIV+ but has undetectable VL, risk of HIV transmission is near 0! (JAMA 2016;316:171)
  - Regimen: **TDF/FTC (Truvada) QD ↓ risk** (40-75%, >95% w/excellent adherence), **d/c** when risk is no longer present.
  - Event-driven PrEP ("2-1-1") is also option: double dose 2-24h before sex, then 1 dose each day after. Prior to initiation HBV/HCV; STI, Cr, pregnancy **q3mos**. **TAF/FTC (Descovy)** FDA-approved, but not for women w/ receptive vaginal intercourse.
- **nPEP (Non-Occupational Post-Exp)**: persons presenting at ≤72hrs after non-occupational high-risk exposure from HIV+ source; case-by-case decision if HIV status of source unknown; test w/ HIV Ab/Ag at baseline & test for STIs, HBV, HCV.
  - Regimen: **TDF/FTC (Truvada) + [raltegravir or dolutegravir] x28d**; if ≥1 course nPEP in last year, consider PrEP

Basic Evaluation for Newly Diagnosed HIV/AIDS Patients:

- CD4 count, VL, genotype/resistance testing, CBC w/diff, BMP, U/A, LFTs, lipase, lipids, Hep A/B/C, hCG, cervical and/or anal pap, RPR, GC/CT, PPD or IGRA; CMV, VZV, toxo, mycobacterial BCx if CD4 < 100, dilated eye exam if CD4<50
- **Initiate ART early** through referral (p36222) at all CD4 levels to decrease mortality (NEJM 2015;373:795). In many cases, ART can be initiated on site, even prior to genotype return, even in high-risk patients (AIDS 2018;32:17) Make sure ID is involved in this decision.
- Treatment as Prevention (TasP): ART initiation has public health benefit to prevent HIV transmission (NEJM 2016;375:830)

Treatment for ARV-Naïve Patients: many options, choose based on indiv. pt factors, drug-drug interactions, resistance testing

- 1st line: 2 NRTI "backbone" (typically TAF/FTC or TDF/FTC [Truvada]) + 1 from diff. class, typically integrase inhibitor

Hospital Management of HIV/AIDS Patients:

- **If patient is on ART**: determine regimen & adherence; typically **continue ARVs** (interruptions can ↑ disease progression)
  - If must hold ARVs because of significant non-adherence or recent severe adverse reaction, hold **all** ARVs and consult ID
  - Beware of drug-drug interactions, particularly with boosted PIs (e.g. PPIs, check https://www.hiv-druginteractions.org/)
- **If patient not yet on ART**: prioritize OI tx, ppx, consult ID for help on early inpt vs outpt initiation of ART
- **IRIS**: worsening sx of underlying infxn (TB, MAC, CMV, others) 1-3 mos post-ART initiation, high risk if low CD4 count
  - Early ARV initiation safe after OI dx, **except** in crypto meningitis (PLoS ONE 2009;4:e5575)

Opportunistic Infections Prophylaxis Summary Recommendations for HIV in the US (JAMA 2018;320:379)

CD4	Opportunistic Infection	Prophylaxis	Criteria for D/C
All	Influenza, HAV, HBV, HPV, VZV, *S. pneumo*, TB	Vax: Flu; HAV, HBV, HPV, PCV 13, PPSV23 after 8 wks; no live vax w/ CD4<200; latent TB: INH/B6 x 9mo	None
<200	*Pneumocystis jirovecii* (or hx of thrush)	TMP-SMX DS QD (preferred) or 1 SS QD *or* dapsone 100mg QD *or* atovaquone 1500mg QD	CD4 >200 x 3mo
<150	*Histo* (only if endemic; not in MA)	Itraconazole 200 mg PO QD	CD4 >150 x 6 mo
<100	*Toxoplasma*	TMP-SMX DS QD *or* dapsone 50mg QD + pyrimethamine 50mg qWk + leucovorin 25 qWk	CD4 >200 x 3mo
<50	*Mycobacterium avium* complex (MAC)	Ppx no longer recommended if ARVs started	CD4>100 x3mo

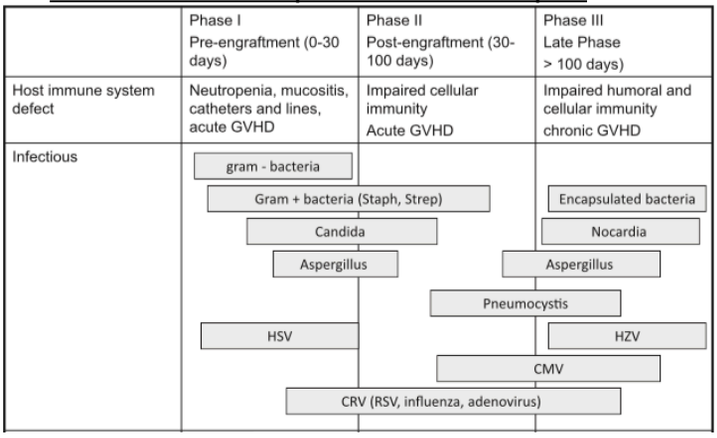
Treatment of OIs in Adults with HIV/AIDS (also see *Invasive Fungal Infections*)

Pathogen	Diagnosis	1st Line Treatment
MAC	Cx (blood/sputum/bronch/marrow/tissue), AFB stain	(Azithro 600mg qday *or* clarithro 500mg BID) + ethambutol 15mg/kg QD
Pneumocystis jirovecii	Typically induced sputum (Sn 50-90%) or BAL wash (Sn >90%) for dx; Cx not reliable	TMP-SMX (15-20 mg/kg/day of TMP IV) x 21d, +/- **steroids** if PaO2 < 70 or A-a >35
Toxoplasma gondii	CT/MRI: ring-enhancing; most pts have IgG+ but not IgM+, brain Bx if Rx fails (r/o CNS lymphoma)	Pyrimeth 200mg x1; then by weight + sulfadiazine + leucovorin x6wks
Herpes Simplex Virus (HSV)	Oral/genital: DFA, PCR, viral cx CNS: LP + CSF PCR	Acycl. 400 PO q8h *or* valacycl. 1g PO q12h x5-10d; CNS: acycl. 10mg/kg IV q8h x3wk
Cytomegalovirus (CMV)	Retinitis: exam; Colitis/esophagitis: bx; PNA: bronch; Neuro: LP with PCR, brain Bx, Blood: PCR	In general: ganciclovir or foscarnet IV, switch to PO w/improvement
PML	MRI: non-enhancing lesions; LP with JCV PCR	Only disease-modifying tx is ARVs
Cryptococcus (rare in US pts)	Serum and CSF CrAg, serum and/or CSF culture, ↑ CSF opening pressure	Ambisome + flucytosine x 2wk→ then high-dose fluc x 8wk→ then low-dose x1yr
Mucocutaneous candidiasis (esophageal/oral)	Clinical dx. White plaque removed w/tongue depressor, +KOH; EGD + Bx	Oral: fluc 100mg PO x7-14d vs nystatin S&S; Eso: fluc 100-400mg PO/IV x14-21d)

General Principles (Am J Transplant 2017;17:856)

- **Early infections**: *donor-derived*, *nosocomial*/reactivation early, followed by OIs as immune suppression peaks
- **Late infections**: *community-acquired* infections, fungal infections
- **Pre-transplant evaluation**: ✓ mumps IgG, measles IgG, rubella IgG, VZV IgG, HAV IgG, HBV (sAb, sAg, cAb), HCV, HIV, syphilis, CMV IgG, EBV IgG. *Consider*: T. Spot, redemic fungi, T. cruzi, Strongy Ab. Goal is to immunize or treat prior to solid organ transplant.

Infections After Hematopoietic Stem Cell Transplant



Infections After Solid Organ Transplant

	<4wk.	1-12mo.	>12mo.
Virus	Donor-derived	Adeno, BK	
		EBV, HCV, **HBV**	
		HSV	
		HHV 6,7	HPV, JC/PML, **PTLD**
		VZV	
		CMV, community-acquired	
Fungus		**Aspergillus**	**Aspergillus**
	Candida	Endemic fungi	Crypto
		Mucor	**PCP** Mucor
Bact.	Surg.-related	**Listeria, Nocardia**	
		TB, non-TB mycobacteria	
Para.		**Toxo**, leishmaniasis	
		Strongy, T. cruzi	

Adapted from Am J Transplant 2017;17:856

HSCT Prophylaxis (J NCCN 2016;14:882)

- **Candida**: fluconazole 400mg PO (d0-365 at MGH)
- **HSV/VZV**: famciclovir 250mg PO BID or acyclovir (d0-365)
- **PJP**: TMP/SMX SS QD or DS TIW; also covers *Toxo, Nocardia*, *Listeria*; alternative: atovaquone, dapsone (d0-180 or 365)
- **High-risk HBV reactivation**: entecavir, tenofovir, or lamivudine (duration varies)
- **CMV**: **pre-emptive monitoring** of VL in high-risk pts & initiate tx (valganciclovir or ganciclovir) when ↑ vs. **ppx** in high-risk pts. Letermovir (CMV-specific; no activity against HSV) can be considered for ppx in select cases (NEJM 2017;377:2433)

Select Transplant-Associated Infections

Pathogen	Clinical Syndrome	Diagnosis/Treatment	Additional comments
CMV	P/w fever, leukopenia, +/- hepatitis, colitis/esophagitis, pancreatitis, retinitis, meningoencephalitis	**Dx**: serum PCR +/- bx involved organ (GI bx, BAL, CSF). Serum PCR may be ⊖ in colitis (15%). **Tx**: c/s ID. PO valganciclovir vs. IV ganciclovir. Consider resistance testing if not improving (UL97, UL57). Alt Tx: foscarnet or cidofovir	Most common infxn s/p solid tx. *Highest risk*: D+/R- in SOT and D-/R+ in HSCT. May ↑ rejection and susceptibility to OIs. Repeat VL testing should be at least 7d apart ($t_{1/2}$ of CMV). VL not comparable between labs.
PJP	Subacute dyspnea, hypoxemia, fevers.	**Dx**: BAL PJP stain/PCR +/- TBBx, LDH, 1-3-β-D-Glucan **Tx**: TMP-SMX (15-20 mg/kg/day of TMP IV in divided doses q6h)	In contrast to HIV, there is limited data to support the routine use of glucocorticoids
BK Virus	Nephritis w/ AKI, ureteral stenosis, hemorrhagic cystitis.	**Dx**: BK PCR +/- biopsy **Tx**: ↓ immunosuppression	Mainly in renal tx and HSCT pts
Strongyloides	*Hyperinfection syndrome*: fever, n/v/d, cough / wheeze / hemoptysis, no eos with hyperinfection; 2° polymicrobial bacteremia (e.g., GNRs)	Ivermectin 200 ug/kg/day until stool ⊖ x2 weeks	Identify at-risk individuals and treat pre-transplant

Symptom-Driven Diagnostics

SOB	CXR, CT chest w/ contrast, induced sputum (GS/Cx, consider AFB stain, MB Cx, PJP stain), legionella urine Ag (Sn 70-90% / Sp 100%), viral resp panel. **If cavitating or nodular lesions**: β-D-glucan/galactomannan, crypto Ag, urine/serum histo Ag, early bronch w/ BAL. *NB*: engraftment syndrome, cryptogenic organizing PNA also on DDx
Diarrhea	Stool Cx, O+P (consider micro add-on for: *Cryptosporidium, Isopora, Cyclospora, Microsporidia*), C. diff, CMV PCR. If high suspicion for viral colitis (e.g., CMV, adeno), c/s GI re: colo w/ Bx. In HSCT, consider typhlitis and GVHD.
AMS/HA	CT head, LP (OP, GS/Cx, glucose, TP, HSV PCR, crypto Ag, save extra for additional tests). *NB*: fludarabine, cytarabine and calcineurin inhibitors (via PRES) can also lead to encephalopathy
Rash	GVHD, medication allergy, HSV, cellulitis, fungal infection
Leukopenia	CMV PCR, EBV PCR, consider tick-borne illnesses during the correct season or if frequent blood transfusions
Hepatitis	If post-HSCT, consider viral (HAV, HBV, HCV, EBV, CMV, adenovirus + more rarely enterovirus and HHV6), *Candida*, and non-infectious (GVHD, iron tox., meds, hepatic sinusoidal occlusion syndrome)
AKI	UA/UCx, renal U/S, BK PCR if renal transplant. Consider med toxicity and check levels (tacro, cyclosporine)

SEXUALLY-TRANSMITTED INFECTIONS

Routine STI testing in asymptomatic adults: HIV, syphilis, GC, chlamydia

	Lesions	Symptoms	Diagnosis	Treatment
Painless	Syphilis (*T pallidum*)	**1°**: painless, firm, round ulcer **2°**: fever, condyloma lata of skin/mucus membranes, LAD, uveitis **3°**: aortitis/aneurysm, disseminated gummas, CN palsies, tabes dorsalis (impaired gait, sensation, reflexes) *Latent* = asymptomatic - Early latent <1yr; Late >1yr/unknown	**1st step**: **treponemal testing** (Sn 96% / Sp 98%); detect IgG specific to *T pallidum*; ⊕ for life. **2nd step**: **confirm w VDRL/RPR titers** (Sn 86% / Sp ~90%) to track response to tx; detect anti-cardiolipin Ab; nonspecific. CSF titres if concern for neurosyphilis (IJSTD AIDS. 2006;17)	1°/2°/early latent: PCN G benzathine 2.4 million units IM x1 3°/late latent: PCN G benzathine 2.4 million units IM qweek x3 Neuro: **IV** PCN G 3-4 million units q4 hours/continuous infusion x10-14d. (CID 2011;53:S110)
	LGV (*C trachomatis*)	**1°**: transient, painless anogenital lesion **2°**: 2-6w later, painful inguinal LAD **3°**: "Genitoanorectal syndrome" pelvic & abd LAD +inflamm diarrhea/abscess	Positive IgG/complement fixation + clinical diagnosis; NAAT in pipeline	Doxy 100mg bid x21d + aspiration of buboes
	GI (*K granulomatis*)	Painless progressive beefy red ulcerative genital lesions in tropics	Presence of Donovan bodies in phagocytes on bx specimen	Azithro 1g qwk/ 500mg qd x3 weeks, until healed (MMWR 2015;64)
Painful	Genital herpes (HSV2>1)	Prodrome → painful vesicles → ulcers 1° infection: possible systemic sxs +/- LAD	Confirm clinical dx with PCR or viral Cx	Acyclovir/Valacyclovir. Episodic tx vs. chronic suppressive tx (if 6 outbreaks/yr)
	Chancroid (*H ducreyi*)	Painful genitals/perianal ulcer 5-7d post-exposure w/ inguinal LAD +/- drainage in tropics	Usually clinical with negative syphilis/HSV; also gram stain, Cx, PCR in some labs	Azithro 1g or CTX 250mg IV; PCN often also given empirically for syphilis; evaluate partners as well

Discharge	Symptoms	Diagnosis	Treatment
Gonorrhea (*N gonorrhoeae*), Chlamydia (*C trachomatis*)	♀: mucopurulent cervicitis, urethritis, PID (abd pain, adnexal/cervical tenderness, +/- fever), frequently asx ♂: dysuria + purulent discharge, epididymitis All: pharyngitis	♀: vaginal swab NAAT (Sn >65%) > urine NAAT (Sn >57%) ♂: dirty catch urine NAAT All: consider pharyngeal/anal swab based on hx (pts can self-swab) (BMJ Open 2019;9)	Ceftriaxone 250mg IM + azithromycin 1g PO *NB:* consider Cx to test for resistance- Asia (EID 2018; 24:381); Doxy not alternative to azithro but used in PID to treat *C trachomatis*
Mycoplasma genitalium	*Suspect in pts who fail tx for GC/CT* ♀: cervicitis, PID, often asymptomatic ♂: dysuria + purulent discharge, proctitis	Testing unavailable in USA, but: ♀: vaginal swab NAAT ♂: urine NAAT	If failed tx for GC/CT & trich: moxifloxacin 400mg x7d (CID 2015;60)
Trichomoniasis (*T vaginalis*)	♀: purulent malodorous discharge, pruritus, dysuria, frequency, dyspareunia ♂: usually asymptomatic	Wet mount → vaginal swab NAAT	Metronidazole 2g PO or tinidazole 2g PO +/- GC/CT tx; treat partner

TRAVEL MEDICINE

Pre-Travel Evaluation

- Patient: medical conditions (immunosuppressed?), allergies (esp. vaccines), pregnant/planning to get pregnant, immunization hx, prior travel history (experience with malaria prophylaxis/prior travel related illlnesses), med list
- Trip: place, duration, season, purpose of a trip, itinerary (urban vs. rural, cruise ship, exposure to animals, cave / water exposure)
- Counsel re: safety: sunscreen (SPF 50+), seatbelt/helmet, sexual practices etc. Provide patient with CDC Travel Tips.

Immunizations

- Ensure routine vaccinations are up to date then use MGH developed "Pre Travel PREP" or CDC site to get country-specific recs
- Common travel vaccines: Yellow Fever, HAV, Typhoid, Japanese Encephalitis, pre-exposure rabies, Cholera

Malaria Prophylaxis (typically South/Southeast Asia, Africa, Central/South America)

- Vector avoidance: DEET, permethrin, mosquito nets, cover exposed skin
- Rx per CDC tool based on resistance pattern. Start ~1 week before travel and up to 4 weeks after. Daily Rx: atovaquone-proguanil (Malarone), doxy, primaquine. Weekly meds: mefloquine, chloroquine

Traveler's Diarrhea

- Common pathogens: ETEC > C. Jejuni, Shigella & Salmonella spp, Giardia, E. histolytica, Strongyloides
- Tx: *mild / moderate*: loperamide/bismuth; *severe* (fever, interference w/ activity, dysentery): azithro 1g x1 > FQ (CDC Yellow Book)

Infections in a Returning Traveler

- Assess if life threatening illness or if transmissable via respiratory droplets, contact, etc (isolate pts)
- Broad ddx, consider geography, exposure risk, pt vulnerability, incubation periods. Common culprits: Malaria, dengue, TB, STIs, tick-borne, typhoid fever, regular infections (CAP/UTI etc.) (NEJM 2017;376:548)

LYME DISEASE (IDSA Guidelines: CID 2006;43:1089; Lancet 2012;379:461; NEJM 2014;370:1724)

- Etiology: *Borrelia burgdorferi*, transmitted by *Ixodes scapularis* (deer tick). Endemic regions: NE/Midwest US & Europe in summer.
- Western blot interpretation: IgM considered positive if 3 particular bands present; IgG positive if any 5 of 10 total bands present
- NB: *always* consider possible co-infection w/ other tick-borne illnesses (see below)

Disease Stage	Presentation	Diagnosis	Treatment
Early localized (within 1 month)	- **Erythema migrans** (spreading red patch +/- central clearing) - Fever, fatigue, myalg./arthralgia	Clinical dx only (serologic conversion >1wk after EM appears)	If EM: doxycycline 100mg PO BID x 14d (amoxicillin 500mg TID x 14d if pregnant) If no EM: consider serology in 2 weeks
Early disseminated (days to months)	- Multiple EM lesions - **Neuro** (CN palsies, meningitis, mononeuritis, radiculopathy) - **Cardiac** (heart block, myopericarditis)	2-Tier Testing: 1. Screening ELISA IgM/IgG 2. Western blot if serology **positive** or **equivocal** IgG becomes positive after 6-8wks; if *only* IgM positive on ELISA/Western blot after 6-8wks = **false positive**	Abx: CTX 2g IV QD *OR* doxycycline 100mg PO BID Duration: 14-28 days depending on indication and severity (IV abx for encephalitis or severe cardiac involvement)
Late disseminated (months to yrs)	- **Arthritis** (mono- or polyarthritis of large joints, esp. knee) - **Neuro** (mild encephalopathy, peripheral neuropathy)		

- Recurrent symptoms after completion of treatment course are likely **re-infection, NOT relapse** (NEJM 2012;367:1883)
- Chronic Lyme disease: ***not a scientific entity***; while post-infectious syndromes (fatigue, depression) are reported in up to 20% of pts after treatment for Lyme disease, these are NOT due to persistent Lyme infection → abx NOT indicated (NEJM 2007;357:1422)
- Prophylaxis: doxy 200mg PO x1 **IF** Ixodes tick attached & engorged ≥36h in endemic area *AND* pt presents <72h after tick removed

OTHER TICK-BORNE ILLNESSES (CDC Guide: includes maps)

Disease	Vector / Geography	Presentation	Diagnosis	Treatment
Anaplasmosis (HGA)	*I. scapularis* tick NE, MW, Atlantic	Common: fever, myalgias, HA Uncommon: rash rare in HGA, 36% in HME Labs: **leukopenia**, thrombocytopenia, ↑ALT/AST, ↑CK	- PCR - Morulae seen in 20-80% of *neutrophils* on smear	Doxy 100mg BID x 10d
Ehrlichiosis (HME)	*A. americanum* (Lone-star tick) South, MW, Atlantic		- PCR - Morulae seen in 0-20% of *monocytes* on smear	
Babesiosis (NEJM 2012;366:2397)	*I. scapularis* tick Endemic to the regions surrounding Cape Cod, Southern NE, NY, north central MW	Mild-to-moderate: **viral-like sx** (fever, fatigue, chills, sweats), less commonly arthralgias, myalgias, HA, n/v, cough Severe: immunosupp/HIV+, (functionally) asplenic, rituximab, >50 y/o; can p/w **severe hemolysis**, DIC, ARDS, multiorgan failure *Labs*: DAT-negative **hemolytic anemia**, thrombocytopenia, ↑ALT/AST	- Blood smear: ring forms within RBC: Maltese cross rare; malaria appears similar. *NB*: parasitemia determined by % infected RBCs on smear - PCR: Sn & Sp but $$; not routine at MGH	Pref: atovaquone + azithromycin (dose varies with severity) Alt: clinda + quinine Exchange transfusion if severe hemolysis, parasitemia ≥10%, or end-organ failure
Borrelia miyamotoi (NEJM 2013;368:2910)	*I. scapularis* tick Same regions as Lyme disease	Fever, HA, chills; leukopenia, thrombocytopenia, ↑ALT/AST (**mimics anaplasmosis**); rash usually absent	- PCR > serology *NB*: EIA cross-reacts w/ *B. burgdorferi*	Doxy 100mg BID x 14d
Powassan virus (CID 2016;62:707)	*I. scapularis* tick Summer in NE, MN, WI, NY	Fever, **encephalopathy** MRI: T2/FLAIR hyperintensities (esp. basal ganglia enhancement) CSF: lymphocytic pleocytosis (can also be neutrophilic)	- Serum/CSF serology (send-out test to state lab) - Consider WNV	Supportive; consider steroids, IVIG
Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)	*Dermacentor* tick Canada, Mexico, Central/South America, OK, TN, AR, MD, VA, NC, SC; peaks spring & summer	Early (3d): non-specific (fever, myalgia, HA, conjunctivitis, N/V/abd pain) Late (2 wks): **fever/HA/rash triad** in ~60%; rash (90%) progresses from wrist/ankle (palms/soles) → trunk; rash macular (3d) → petechial (6d) Severe: shock, DIC, organ failure; 20% mortality if untreated; 5% if treated. Labs: leukocytosis or leukopenia, thrombocytopenia, hypoNa, AKI, ↑LFTs	- Clinical dx initially; start empiric tx - Serology: undetectable until 7-10d after sx onset; need to repeat at convalescence (14-21d after sxs onset) to confirm dx - Skin biopsy: 70-90% Sn / 100% Sp	Doxy 100 mg BID x 5-7d and at least 3 days after afebrile (*still give doxy to kids & pregnant women*) Chloramphenicol is the only alternative, if available

Definition (CCM 2008;36:1330, Medicine 1961;60:1)

- Clasically defined as: temp >38.3C, assessed on multiple occasions, for ≥3 weeks without an obvious cause or etiology
- FUO is far more often caused by an atypical presentation of a more common disease than by a very rare disease.

Workup

- **Ddx**: most commonly **ID** vs. **cancer** vs. **rheumatologic** vs. **meds** (see box)
  - In 25-50% of cases, no source is identified (Medicine 2007;86:26)
- **History**: verify fever trend/pattern, past medical history including dental history and history of immunocompromise, travel, animal/tick/mosquito/ environmental/food exposures, h/o blood product transfusions, sick contacts, sexual history, illicits, occupation, TB history, meds, vaccines, family history, valve disorders, recent procedure/hospitalization, changes in weight/anorexia
- **Exam**: assess for dental caries/thrush, sinus and temporal artery tenderness, thyromegaly, CV murmur, abd tenderness, HSM; inspect eyes, fundi; perform complete lymph node, skin/nails, rectal, and joint exam

Diagnostic Testing

- **Initial**: CBC w/ diff, BMP, LFTs, ESR/CRP, UA/UCx, BCx x3 (diff. sites), CXR (AJM 2015:128;1138e1)
- **Inflammatory markers**:
  - ESR: measure of chronic inflammation. Falsely elevated in ESRD (can be very high), paraproteinemia, anemia, obesity, and advanced age. ***Correct for age → (age / 2) for males and (age / 2) + 10 for females.***
  - CRP: rises more acutely than ESR; may be falsely low in cirrhosis
- **Other labs to consider**: IGRA, HIV Ab/Ag/PCR, RPR, LDH, TFTs, SPEP/SFL, 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 (19% Sn / 71% Sp), LENIs, TTE, FDG-PET/CT (Sn 50-100% / Sp 46-90%), tagged WBC scan (Sn 60-75% / Sp 82-92%), maxillofacial CT
- **Tissue diagnosis**: biopsies of LN, liver biopsy (14-17% yield), BM (low yield at 0-2%), temporal artery biopsy (GCA), kidney (RPGN), consider LP in patients with CNS findings

Etiologies of FUO	
Infectious	Abscess (abdomen/pelvis, perianal, brain, dental), HIV, EBV, CMV, HHV6-8, HBV/ HCV, endocarditis (fastidious/HACEK, nutrionally variant *Strep*), nosocomial infection, vascular graft infection, osteomyelitis, septic arthritis, sinusitis, prostatitis, **TB (miliary)**, tick-borne infections**,** endemic fungi (e.g. cocci/histo/paracocci), malaria, cat-scratch disease, toxoplasmosis, **Q fever** (*Coxiella*), **brucellosis**, *Bartonella*, salmonella, typhus, mellioidosis, schistosomiasis, visceral leishmaniasis, Whipple's disease, lymphogranuloma venereum
Malig.	**Lymphoma**, leukemia, MM, myeloproliferative disorders, **RCC**, HCC, pancreatic, cervical, mets, myxoma
Rheum.	Cryo, PMR/**GCA/TA**, RA, **Adult Still's (JRA)**/MAS, SLE, dermato/polymyositis, sarcoid, HSP, PAN, Kikuchi's, Takayasu's, Behcet's, GPA/MPA/EGPA
Other	**Drug fever**, serotonin syndrome, NMS, DVT/PE/hematoma, hypothalamic dysfunction, pheo, thyroiditis, alcoholic hepatitis, **cirrhosis**, IBD, factitious, HLH, familial periodic fever syndromes (FMF, Hyper-IgD Syndrome, Schnitzler's, TRAPS)
***bold** = common causes (AJM 2015;128:1138e1)	

Treatment

- **Try to avoid empiric antibiotics** and observe (unless hemodynamic instability or immunocompromised)
- Discontinue possible offending medications
- If high suspicion for GCA/vasculitis, strongly consider empiric steroids (prior to biopsy) to prevent vision loss / end-organ damage
- If extensive workup is negative, prognosis is usually good and most cases defervesce (AJM 2015:128;1138e1)

Etiologies by Patient Population

Patient Population	Etiologies
General (Am J Med Sci 2012;344:307)	Infection 16-35%, rheumatic 13-36%, malignancy 3-10%; undiagnosed 16-51%
Elderly patients (Am Geriatr Soc 1993;41:1187)	Infection 35% (abscess 12%), rheum 28% (most common GCA/PMR), malignancy 19% (heme 10%, solid 9%)
Uncontrolled HIV* (CID 1999;28:341)	Infection 88% (dMAC 21%, PJP 13%, CMV 11%, histo 7%, other viral 7%), malignancy 8% (lymphoma 7%)
Neutropenic (refractory to abx) (NEJM 2002;346:222)	Fungal infections 45%, bacterial infections 10% (resistant, biofilms), GVHD 10%, Viral 5%, Misc 25%

*Mean CD4 count 53/mm^3

Select Causes of FUO

- **Drug fever**: diagnosis of exclusion that broadly refers to any febrile response to medication. Can occur at anytime while taking drug, with resolution ~2-3 days post-cessation (can take up to 1 week)
  - Fevers can be in excess of >102F. Rarely, have accompanying signs (e.g., morbilliform rash, LFT elevations, eosinophilia)
  - Mechanisms of drug fever include: hypersensitivity reaction (including SJS/TEN), dysfunctional thermoregulation, aseptic meningtitis, Jarisch-Herxheimer reaction, NMS/serotonin Syndrome, G6PD deficiency
  - Medications commonly assoc. with drug fever: antimicrobials (β-lactams, sulfa, macrolides), AEDs, dexmedetomidine, chemo
- **VTE**: DVT, PE, and thromboplebitis may cause fever. Likely 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)

Organism/Syndrome	Epi & Transmission	Symptoms	Labs	Diagnostic Tests	Treatment
Malaria (*Plasmodium* spp)	Africa, Latin Am, Asia, MidEast, Eastern Europe *Anopheles* spp. (nocturnal)	12-35d incub. (up to yrs if *P. vivax*); fever, HSM, AMS, jaundice, petechiae	Anemia, ↓plt, AKI, ↑LFTs, ↓**glucose**, acidemia	**BinaxNOW** (RDT) + thick/thin blood smear w/ Giemsa	Variable, **d/w ID**
Mosquito-borne viruses: Dengue, Chikungunya, and Zika are often indistinguishable clinically/epidemiologically; consider testing for all 3 if concerned					
Dengue fever (DENV serotypes 1-4; *Flavivirus*)	India, Asia/Pac, Africa, Lat Am *A. aegypti* and *A. albopictus* (diurnal feeders)	Fever, retro-orbital HA, arthralgia "**break bone fever**", petechiae, shock	Lymphopenia, thrombocytopenia, ↑**Hct**	Serum RNA early → IgG/IgM (cross-rxn w/ Zika); tourniquet test	Rest, fluid; **avoid NSAIDs** due to ↑ hemorrhagic sx
Chikungunya fever (*Alphavirus*) **Zika virus** (*Flavivirus*)	Africa, Asia/Pac, **Caribbean**, Lat Am, S USA *A aegypti* and *A albopictus* (diurnal feeders); sexually-transmitted (Zika)	1-14d incubation; fever (>102 in chik), HA, polyarthrlagia, rash, conjunctivitis, GBS + fetal microcephaly (Zika)	Chik: lymphopenia, thrombocytopenia, ↑LFTs, AKI Zika: labs freq. nml	Chik: PCR if <7d sxs; serology if ≥7d. Zika: serum/urine PCR if <14d sxs → serology/plaque reduct.; serology if ≥14d of sxs	Rest, fluid; avoid NSAIDs unless definitely not dengue
West Nile virus (*Flavivirus*)	Africa/MEast, Europe, Americas *Culex* spp. (nocturnal feeders)	Asx; fever, HA, myalg., 1% meningitis	CSF pleocytosis (lymphs)	**Serum + CSF Abs >** PCR	Rest, fluid
Leishmaniasis, cutaneous/visceral (*Leishmania* spp)	C/S America, S Europe, Mid East, E Africa, S Asia *Lutzomyia*/*Phlebotomus* sandfly	CL: painless ulcer(s), regional lymphaden. VL: fever, HSM, ↓wt	VL: cytopenias, ↑LFTs	Clinical dx, tissue smear/cx; rarely Ab	Varable, call ID; abx if superinfected lesions
Bacterial Zoonoses: *Coxiella*, *Bartonella quintana*, and *Brucella* are important causes of **culture-negative endocarditis**					
Cat scratch disease (*Bartonella henslae*)	Worldwide Cat bite/scratch, fleas	Fever, LAD 1-3 wks, neuro, ocular	↑ESR/CRP,↑LFT	PCR 1-3d; Ab 1-2wks; histology	Regimens vary
Leptospirosis (*Leptospira* spp.)	Worldwide; tropics > temperate Water contaminated by animal urine/sewage, esp. after floods	Fever, HA, myalgia, jaundice, conjuc. suffusion	**AKI, ALF, rhabdo**, anemia, hypoNa,	Serology if 3-5d sxs	Outpt: doxy 100 bid x7d; inpt: PCN G, doxy, or CTX
Q fever (*Coxiella burnetii*)	Worldwide (not New Zealand) Aerosolized ungulate fluid	Fever, HA, myalgia, PNA, **endocarditis**	↑AST/ALT, ↑Bili, ↓Plt, ↑CK	PCR if <7d sxs, serology if ≥7d	Doxy 100 bid x14d
Brucellosis (*Brucella* spp)	Worldwide Dairy products, ungulate contact, lab exposure	Fever, arthritis (SI/spine), endocarditis	↑AST/ALT, ↓WBC with relative ↑lymph	Serology if 7-1d sxs	Doxy 100 bid x6 wks + gent/rifampin
Tularemia (*Francisella tularensis*)	N America, Europe > Asia Arthropod bite, animal contact (rabbit), food/water, airborne	**Regional LAD**; 6 syndromes: PNA, glandular, etc.	Nonspecific; ↑ESR/CRP; nl WBC, LFTs, Cr; ↓Plt	Serology if sxs ≥2wks; Cx cysteine+ media; gram stain	Streptomycin 7-10d; cipro or doxy 10-21d if mild dz
Rickettsia: in general, rickettsial diseases with eschars are scrub typhus, African tick-bite fever, RMSF, Mediterranean spotted fever, and rickettsialpox					
Murine typhus (*Rickettsia typhi*)	SE Asia, N Africa, N America Feces of infected rat fleas	Fever, **centrifugal rash**, HA, myalgia	↓Plt, ↑AST/ALT	Serology performed 2wks apart	Doxy 100 bid x7d
Scrub typhus (*Orientia tsutsugamushi*)	India → E Asia; Pacific, Chile Bites from infected mite larvae (AKA chiggers)	**Eschar**, fever, lymphadenopathy, centrifugal rash, HA	↓Plt, ↑AST/ALT, ↑Bili, AKI, WBC usually wnl	Serology performed 2wks apart; consider eschar bx	Doxy 100 bid x7d; azithromycin if tetracycline-resist.
Helminths: if concerned about intestinal worms, albendazole is an effective and safe medication to give empirically while awaiting lab results					
Schistosomiasis (*Schistosoma* spp)	Africa, Brazil, MidEast, Asia Fresh water with free cercariae from infected snails	Acute (3-8wks): fever, urticaria, HA Chronic: HSM, portal HTN, hematuria	↑**Eos** (30-60%) in acute, ↓Plt; LFTs usually nml	Serology at 6-12wks; stool/urine microscopy for speciation	Acute: pred 20-40 x5d + praziquantel Chronic: 40-60 x1 of praziquantel
Trichinellosis (*Trichinella* spp)	Worldwide, esp. Europe Undercooked meat, esp. pork	Abd pain, n/v, diarrhea → myalgia, weakness, +/- fever	↑**Eos**, ↑WBC, ↑CK, ↑LDH	Serology 2-8d; muscle biopsy	Albendazole 400 bid + pred 30-60 qd x8-14d
Strongyloidiasis (*Strongyloides stercoralis*)	Rural tropics/subtropics; Appalachia, SE USA Skin contact with soil contaminated w/ human feces, fecal-oral, autoinfection	Skin rxn, epigastric pain, diarrhea, resp. sxs; fever, n/v, sepsis or shock if hyperinfection	↑**Eos**, ↑WBC; in immunosupp. pts → hyperinfection & disseminated dz (normal eos)	Serology more Sn stool but less Sp. ✓ BCx, may have GN bacteremia (gut translocation)	Ivermectin 200 mcg/kg/day x2d; treat for x5-7d if disseminated dz
Other Infections					
Typhoid fever (*Salmonella enterica* serotype Typhi)	India, SE Asia, Africa Fecal oral; asymptomatic carriers	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 (mero-penem if Pakistan)
Melioidosis (*Burkholderia pseudomallei*)	India → SE Asia; N Australia Soil; aspiration, inhalation, percutaneous inoculation	Fever, PNA, skin abscess, community-acquired sepsis, GU	↑WBC; other nonspecific values c/w organ failure	Blood Cx on Ashdown's agar, gram stain	Abscess I&D + IV mero/ceftaz x2wks → TMP-SMX x3mo
Hantavirus (Sin nombre, Andes)	SW USA, Lat Am, Europe, Asia Aerosolized rodent excreta	Hemorrhagic fever, renal failure, ARDS	↑PTT, ↓Plt, AKI, **proteinuria**	Serology via state department of health	Supportive care
Toxoplasmosis (*Toxoplasma gondii*)	Worldwide Cats; contaminated meat/water	Mono-like symptoms	Atypical lymphs, ↑AST/ALT	Serology 1-7d; CSF 2-5d	Tx if CNS, preg, or chorioretinitis

Multiple: NEJM 2017;376:548, NEJM 2018;379:557, NEJM 2007;357:1018, NEJM 2015;372:954, JAMA 2002;287:2391; Malaria: JAMA 2010;304:2048; Dengue: NEJM 2012;366:1423; Zika: NEJM 2016;374:1552; Chikungunya: NEJM 2015;372:1231; West Nile: JAMA 2013;310:308; Brucellosis: NEJM 2005;352:2325; Schistosomiasis: NEJM 2002;346:1212; Typhoid: NEJM 2002;347:1770; Melioidosis: NEJM 2012;367:1035

Resources: visit Ellucid (EPIC -> Resources -> Handbook -> Manuals-> MGH Infection Control Manual & Policies) for the most up to date MGH policies and list of disease/ conditions requiring isolation. For additional support work with unit specific nursing supervisors and contact Infection Control (x62036).

Standard Precautions: apply to *all* patients

- ***Hand hygiene***: disinfect with an alcohol-based hand rub before AND after gloving, contact in room or with patient. If hands are visibly soiled, wash hands with soap and water, dry hands, and apply an alcohol-based hand rub.
  - Gloves/gowns for contact w/blood, bodily fluids (e.g., wound), secretions, excretions, mucous membranes, broken skin
  - Mask + 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 equipment (e.g., personal stethoscope, U/S) using correct wipes after patient use
- ***Cough etiquette***: cover mouth/nose, mask coughing person, prompt disposal of used tissues, hand hygiene, spatial separation (>3ft)
- ***Safe injection practices***: use sterile, single-use, disposable needle/syringe and single-dose vials whenever possible

Transmission-Based Precautions (in addition to standard precautions above):

Isolation	Pt Population & Transmission	Description	Examples
Contact	Transmitted by direct or indirect contact with patient or his/her environment	- Hand hygiene + nonsterile gloves + isolation gowns - **Do not touch phones, beepers, notes while in room** - Remove gown and gloves *together* with only touching inside of PPE with bare hands, dispose of in the room - Dedicate the use of equipment (stethoscope, BP cuff) to avoid sharing with other patients. All equipment residing within the Contact Isolation room is presumed contaminated. - Disinfect using correct wipes for pathogen of concern	MRSA† VRE† MDROs† CRE Lice / Scabies Uncontained drainage (abscesses)
Contact PLUS	Patients with known/suspected spore forming or alcohol-resistant organisms transmitted by indirect/direct contact	- Contact instructions as above - After doffing; wash hands with soap and water for 15-20 seconds, dry, then use CalStat; Bleach wipes for equipment - **Isolate patient empirically while awaiting results of tests for *C. diff* and Noro**	*C. diff* Norovirus *C. auris* Cutaneous anthrax
Droplet	Patients with organisms transmitted by large respiratory droplets (coughing, sneezing, talking)	- Disposable surgical mask must be worn when entering the room. Discard upon exit. - Patient travel: surgical mask - **Isolate patient empirically while awaiting results for bacterial meningitis, influenza, pertussis**	*N. meningitidis* (1st 24 hrs of effective antimicrobial therapy) Influenza (*N95 for aerosol-generating proc.) Pertussis
Enhanced Respiratory Isolation	COVID-19	- Contact + Eye Protection + N95 - Isolation; no need for ⊕ press. unless aerosolizing proced. - Patient travel: surgical mask	COVID-19
Airborne	Transmitted by droplet nuclei that can remain suspended in the air and disperse widely	- Isolation in negative pressure room with door closed - N95 respirator (fit-tested) to enter the room; retest if weight +/- 20lbs; PAPR for facial hair or if not fit-tested - Patient travel: surgical mask - Visitors are asked to wear N95 respirator, no fit testing required, but should be shown how to wear it correctly	Pulmonary TB Measles Varicella Disseminated herpes zoster
Enhanced Isolation	Required for patients with Cystic Fibrosis	- Contact + private room limitations on use of shared spaces	
Strict Isolation	Patients w/ highly pathogenic organisms	Airborne + Contact + Eye Protection If suspected, isolate and contact Biothreats Pager (26876)	SARS / MERS Avian Influenza
† Pts will be identified in the Infection Status banner in EPIC, removal of precautions discussed below			

Immunocompromised Hosts: BMT, lung transplant and neutropenic patients.

- Generally standard precautions + positive pressure room + N95 maks for patient during travel + dietary precautions
- BMT: gloves and surgical mask for healthcare workers
- Lung transplant: gown, glove and surgical mask for healthcare workers
- See Immunocompromised Host Policy on Ellucid for details

When to Remove Precautions:

For questions regarding screening for resolution of infection status for patients with histories of MRSA, VRE, and MDROs call the Infection Control Unit (x6-2036). Discontinuation of isolation should be discussed with Infection Control directly.

- TB: 3 negative sputum specimens (via cough or induction at least 8h apart or 24h if known) is not sufficient for rule out; TB must be excluded entirely from the differential. Please consult Infection Control to discuss discontinuation of isolation.
- Influenza: 7d after onset *or* until 24h after resolution of fever and non-cough symptoms (whichever is longer); although in some patients shedding may be prolonged; discuss with Infection Control

Drug (By Class)	Usual Dosing	CrCl 50-25	CrCl 25-10	CrCl<10	HD
PENICILLINS					
Ampicillin IV (bacteremia)	2g q6h	CrCl 50-10: 2g q8-12h		CrCl <10: 2g q12h	2g q8-12h*
Ampicillin IV (endocarditis, meningitis)	2g q4h	CrCl 50-10: 2g q6-8h		CrCl <10: 2g q12h	2g q8-12h*
Ampicillin-sulbactam IV (blood, intra-abd, PID)	3g q6-8h	CrCl 30-15: 3g q8-12h	CrCl<15: 3g q12h		3g q12h*
Piperacillin-tazobactam IV (non-*Pseudomonas*)	3.375g q6h	CrCl 20-40: 2.25g q6h		CrCl <20: 2.25g q8h	2.25g q8h
Piperacillin-tazobactam IV (*Pseudomonas*)	4.5g q6h	CrCl 40-20: 3.375g q6h	CrCl<20: 2.25g q6h		2.25g q8h
CEPHALOSPORINS					
Cefazolin IV	2g q8h	CrCl 50-10: 2g q12h		CrCl <10: 2g q24h	1gm daily q24 OR 2g post-HD
Ceftriaxone IV	1–2 g q24h	No change with renal function; meningitis dosing is 2g q12h to max 4g/day; on HD days, give post-HD			
Ceftazidime IV (most except UTI, meningitis)	2g q8h	CrCl 50-31: 2g q12h	CrCl 30-16: 2g q24h	CrCl 15-5: 1g q24h; CrCl<5: 1g q48h	2g x1 → 1g daily* OR 2g post-HD
Cefepime IV (febrile neutropenia, PNA)	2g q8h	CrCl 59-30: 2g q12h	CrCl 29-10: 2g q24h	CrCl<10: 1g q24h	1g q24h* OR 2g post-HD
Cefepime IV (others)	1-2g q8-12h	CrCl 59-30: 1g q12h	CrCl 29-10: 1g q24h	CrCl<10: 1g q24h	1g q24h* OR 2g post-HD
FLUOROQUINOLONES					
Ciprofloxacin IV (if critically ill or PNA, q8 dosing)	400 mg q8-12h	CrCl<30: 400mg q24h			400 mg q24h*
Levofloxacin IV/PO (CAP, complicated infx)	750mg q24h	CrCl 49-20: 750mg q48h	CrCl<20: 750mg x1 → 500mg q48h		750mg x1 → 500mg q48h
CARBAPENEMS					
Meropenem IV (most except meningitis, CF, in which case double dose)	1g q8h	CrCl 50-26: 1g q12h	CrCl 25-10: 500mg q12h	CrCl<10: 500mg q24h	1g q24h*
OTHER ANTI-INFECTIVES					
Acyclovir IV (most; higher dose for CNS/systemic)	5-10mg/kg q8h	CrCl 49-26: 5-10mg/kg q12h	CrCl 25-10: 5-10mg/kg q24h	CrCl <10: 2.5-5mg/kg q24h	2.5-5mg/kg q24h*
Clindamycin IV	600-900mg q8h	Usual dose since Clindamycin not renally eliminated; max 2,700mg/day			
Fluconazole IV/PO	12mg/kg x1 → 6mg/kg q24h OR 800mg x1 → 400mg q24h	CrCl <50: 6mg/kg x1 → 3mg/kg q24h OR 400mg x1 → 200mg q24			6mg/kg x1 → 3mg/kg q24h* *OR* 400-800mg x1 → 200mg q24 (or 400 post-HD)
Metronidazole IV/PO	500mg q8h	Usual dose. Can use q6h dosing interval for CNS dosing			

***Dialysis dosing**: if drug dosed multiple times/day, administer 1 of the doses after HD. If drug dosed QD, administer after HD on HD days
Adapted from MGH/Partners antibiotic dosing guidelines: http://handbook.partners.org/content/pdf/AntimicrobialRenalDosingGuidelines.pdf. For more information on renal dosing for other antimicrobials (including **CVVH dosing**): see http://handbook.partners.org/pages/3805

VANCOMYCIN DOSING (https://hospitalpolicies.ellucid.com/documents/view/1719l; **HD/CVVH dosing**: https://hospitalpolicies.ellucid.com/documents/view/13031)

- Typical dosing regimen: **20mg/kg** LOAD (max 2g) → **15mg/kg q8** maintenance; adjustments for renal function per table below:

Weight (kg)	Loading Dose (per ACTUAL BODY WEIGHT, *max 2,000mg*)	Maintenance Dose (actual OR adjusted body weight (if ≥120% of IBW), age, & CrCl)					
		Age ≤65 y/o *AND* CrCl ≥80	CrCl 40-79 *OR* Age >65 y/o	CrCl 30-39	CrCl 20-29	CrCl <20, AKI *OR* Labile Renal Function	CRRT *OR* iHD[4]
40-45	1000mg	500-750mg q8h	750mg q12h	750mg q24h	750 mg q24-48h	Load followed by dose by level	Load followed by Renal Replacement Protocol
46-50	1000mg	750mg q8h	750mg q12h	750mg q24h	750 mg q24-48h		
51-55	1000-1250mg	750mg q8h	750-1000mg q12h	750-1000mg q24h	750-1000 mg q24-48h		
56-60	1250mg	750-1000mg q8h	1000mg q12h	1000mg q24h	1000 mg q24-48h		
61-65	1250mg	1000mg q8h	1000mg q12h	1000mg q24h	1000 mg q24-48h		
66-70	1250-1500mg	1000mg q8h	1000mg q12h	1000mg q24h	1000 mg q24-48h		
71-75	1500mg	1000-1250mg q8h	1250mg q12h	1250mg q24h	1250 mg q24-48h		
76-80	1500-1750mg	1250mg q8h	1250mg q12h	1250mg q24h	1250 mg q24-48h		
81-85	1500-1750mg	1250mg q8h	1250mg q12h	1250mg q24h	1250 mg q24-48h		
86-90	1750mg	1250-1500mg q8h	1250-1500mg q12h	1250-1500mg q24h	1250-1500 mg q24-48h		
91-100	1750-2000mg	1250-1500mg q8h	1500mg q12h	1500mg q24h	1250-1500 mg q24-48h		
101-110	2000mg	1500mg q8h	1500-1750mg q12h	500-1750mg q24h	1500-1750 mg q24-48h		
>110	2000mg	1500mg q8h	1750-2000mg q12h	1750-2000mg q24h	1750-2000 mg q24-48h		

- **Dose monitoring**: check trough **1hr prior to 4th dose** (goal typically 15-20; 10-15 for simple skin/soft tissue infection); if fluctuating renal function, check 24hr level (or random level, depending on the circumstances) and discuss dosing with pharmacy
- **Subtherapeutic level**: if first trough ≤10% from target (e.g. 13.5, w/ goal 15-20), continue same dose; if first trough <5mcg lower than target (e.g. 12 w/ goal 15-20), ↑ each dose by 250mg (e.g. 1000mg → 1250mg); if if first trough >5mcg lower than target, shorten dosing interval (e.g. q12 → q8).
- **Supratherapeutic level**: if 21-25, hold next dose and reinitiate at 250mg less (e.g. 1000mg from 1250mg) when expected to be within target range; if 26-30, hold next dose and adjust dosing to next longer interval (e.g. q12 from q8); if >30, hold until random level falls w/in target range

Bacterium	No. of Strains	Penicillin	Ampicillin	Oxacillin	Cephalothin	Ceftriaxone	Vancomycin	Clindamycin	Erythromycin	Doxycycline	TMP-SMX	Levofloxacin	Linezolid	Daptomycin	Rifampin	Nitrofurantoin[a]
Staphylococcus aureus	3621	—	—	70	70[b]	—	100	70	49	97	95	78	99	99	99	99
Coagulase-negative staphylococci	1895	—	—	50	50[b]	—	100	60	39	87	66	63	100	99	97	100
Staphylococcus lugdunensis	410	—	—	97	97[b]	—	100	82	82	99	99	99	100	100	100	100
Staphylococcus saprophyticus	187	—	—	—	—	—	100	—	—	97	96	99	100	—	100	99
Streptococcus pneumoniae (non-meningitis)	162	97	—	—	—	99	100	85	64	63[c]	80	99	—	0	—	—
Streptococcus pneumoniae (meningitis)		75	—			91										
β-hemolytic streptococci (group A)	172	100	—	—	100[d]	100	100	76	75	75[c]	0	99	—	—	—	—
β-hemolytic streptococci (group B)	1286	100	—	—	100[d]	100	100	63	54	18[c]	—	98	—	—	—	—
β-hemolytic streptococci (group C, G)	106	100	—	—	100[d]	100	100	66	66	64[c]	—	100	—	—	—	—
α-hemolytic streptococci[e]	286	69	—	—	—	95	100	87	53	59[c]	—	92	—	—	—	—
Streptococcus anginosus (*milleri*) group	358	99	—	—	—	100	100	80	77	68[c]	—	99	—	—	—	—
Enterococcus faecalis	2305	—	100	0	0	0	96	0	9	28	0	83	98	100	—	99
Enterococcus faecium	604	—	17	0	0	0	34	0	3	31	0	14	96	97[f]	—	18

[a] Urine isolates only.
[b] For staphylococci, cephalothin is predicted from oxacillin.
[c] For streptococci, rates are tetracycline susceptibility rates.
[d] For streptococci, cephalothin is predicted from penicillin.
[e] Includes alpha-hemolytic streptococci, *S. bovis, S. canis, S. mitis, S. mutans, S. oralis, S. parasanguinis, S. salivarius, S. sanguinis, S. vestibularis.*
[f] Fewer than 150 isolates tested. See "Antimicrobial Costs" table for information about the need for higher daptomycin dosing in *E. faecium* infections.
(-) Drug not tested or insufficient data available.

Bacterium	No. of Strains	Ampicillin	Piperacillin-Tazobactam	Cefazolin	Ceftriaxone	Cefepime	Aztreonam	Ertapenem	Meropenem	Gentamicin	Amikacin	Ciprofloxacin	Levofloxacin	TMP – SMX	Tetracycline	Nitrofurantoin[a]
Achromobacter spp.[b]	110	—	92	—	—	13	0	—	89	0	0	22	60	84	—	—
Acinetobacter baumannii complex[c]	155	0	71	0	0	74	0	0	85	89	—	76	78	83	73	—
Aeromonas spp.	28	0	96	0	100	100	100	85	96	100	100	89	—	74	—	—
Burkholderia cepacia complex[d]	39	0	0	0	—	—	0	0	86	0	0	46	56	68	—	0
Citrobacter freundii complex	298	0	85	0	81	98	83	99	99	98	100	95	94	89	85	96
Citrobacter koseri (diversus)	193	0	98	96	98	99	98	99	100	99	100	98	98	98	98	90
Enterobacter aerogenes	239	0	84	0	84	98	86	99	99	100	100	98	98	97	91	15
Enterobacter cloacae complex	631	0	79	0	75	95	79	90	99	97	100	95	95	88	89	39
Escherichia coli	8297	51	94	82	90	96	93	99	99	91	100	79	79	73	71	95
Haemophilus influenzae	70	70	—	—	100	—	—	—	100	—	—	—	100	59	—	—
Klebsiella oxytoca	360	0	94	49	94	99	95	99	99	97	100	97	97	94	93	82
Klebsiella pneumoniae	2006	0	91	85	88	95	90	98	99	94	99	90	92	83	79	36
Morganella morganii	234	0	97	0	88	95	92	99	100	88	100	87	89	81	61	0
Proteus mirabilis	826	72	99	71	98	99	97	88	100	88	100	79	82	75	0	0
Proteus vulgaris	51	0	100	0	90	96	98	88	100	100	100	100	100	92	0	0
Providencia spp.	73	0	88	0	91	96	97	75	99	49	97	66	66	92	0	0
Pseudomonas aeruginosa[e]	1482	0	82	0	0	86	69[f]	0	84	84	90	76	70	0	0	0
Raoultella spp.	76	0	95	89	91	97	91	100	100	93	100	96	97	89	80	95
Salmonella spp.	65	85	98	—	91	100	94	100	100	—	—	72	72	92	82	—
Serratia marcescens	282	0	—	0	95	99	98	97	100	98	100	93	93	98	23	0
Shigella spp.	21	67	100	—	100	100	100	100	100	—	—	86	—	10	19	—
Stenotrophomonas maltophilia[g]	337	0	—	0	0	0	0	0	0	0	0	36	79	98	—	0

[a] Urine isolates only.
[b] For *Achromobacter* spp., 81% are susceptible to ceftazidime.
[c] For *A. baumannii* complex, 89% are susceptible to ampicillin-sulbactam.
[d] For *B. cepacia* complex, 74% are susceptible to ceftazidime.
[e] For *P. aeruginosa*, 86% are susceptible to ceftazidime.
[f] 443 isolates (predominantly from cystic fibrosis patients) tested.
[g] For *S. maltophilia*, 35% are susceptible to ceftazidime.
(-) Drug not tested or insufficient date available.

YEAST	No. of strains	Fluconazole (% susceptible)
Candida albicans	341	94
Candida glabrata	155	89
Candida parapsilosis	64	94
Candida tropicalis	32	88
Candida krusei: intrinsically resistant to fluconazole		

ANEMIA

GENERAL APPROACH (Williams Hematology 2018)

- **S/Sx**: ↓O2 delivery (fatigue, lightheadedness, DOE, pallor, angina, claudication, retinal hemorrhage), nonspecific sx (cramps, abd pain, n/v), compensatory mechanisms (↑RR, ↑HR, palpitations, orthostasis, ↑pulsation, flow murmur, bruit)
- **Other findings**: jaundice (hemolysis), glossitis (folate / B12 / Fe def.), motor / sensory deficits (B12 def), PICA / koilonychias / angular cheilitis (Fe def), splenomegaly (cirrhosis, infxn, thalassemia, malig., chronic hemolysis), constipation / bone pain (myeloma), melena (GIB, CRC), Mediterranean / Asian / Black (thal/SS), unusual thromboses (PNH), petechiae / purpura (coagulopathy, pancytopenia)
- Initial labs (draw/add on labs prior to transfusion!): **CBC w/ diff** (Δs in other cell lines, **MCV**, RDW), **retic count**, **special slide, T&S**
- Calculate **reticulocyte index** **(RI)** to determine if adequate BM response: **hypo- (RI <2%) vs hyper-proliferative (RI >2%)**
  - Very **low RI (<0.1%)** indicative of **aplastic anemia or red cell aplasia**
- Additional labs depend on **retic index** and clinical history:
  - RI <2% -"**Anemia labs**": **Fe/TIBC/ferritin**, **folate / B12** (in last 6 mo.)**, BMP**, **LFTs, TSH, CRP**
    - If unrevealing / otherwise indicated by history: +/- SPEP/SFLC, Hb electrophoresis, AM testosterone, Epo, BMBx
  - RI >2% - "**Hemolysis labs**": **LDH**, **bilirubin**, **haptoglobin**, **DAT** (Coombs), **Coags, UA**

CLASSIFICATION OF ANEMIA (NEJM 2014;371:1324, Lancet 2018;391:155, Williams Hematology 2018)

UNDERPRODUCTION (RI <2%)		
Microcytic (MCV < 80 μm³)	**Normocytic** (MCV 80-99 μm³)	**Macrocytic** (MCV ≥ 100 μm³)
Iron deficiency anemia (IDA) • ↓ Fe, ↑ TIBC, ↓ ferritin (<30 high Sp.; <15=⦸Fe in BM), Fe/TIBC <16%, ↑ RDW **Anemia of chronic inflammation** • ↓ Fe, ↓/nl TIBC, ↑ ferritin (<100 if ACI+IDA or <200 in ESRD), Fe/TIBC ↓/nl (>18%) **Thalassemias** • Fe studies nml, MCV ↓↓ (often <70), MCV/RBC <13 (Mentzer index; high Sp.); ✓ Hb electrophoresis **Sideroblastic anemia** • ↑ ferritin, Fe/TIBC nml, basophilic stippling (Pb), ringed sideroblasts (BM)	**Inflammation & variant**: • Early anemia of inflammation • Early IDA • Mixed IDA & ↓ folate/B12 (dimorphic: nml MCV w/ ↑RDW) **Organ-specific**: • **Renal** (CKD/ESRD): ↓Epo (should ↑10x per 10% Hct drop) • **Endocrine** (thyroid, pituitary, adrenal, parathyroid, testosterone; ↓metab. rate→↓O2 demand): ↓Epo • **Marrow** (red cell aplasia, AA, MDS, myelofibrosis, myelophthisis, PNH, MM): ✓ SPEP, serum FLC, BMBx	**Megaloblastic**: *smear shows hyper-seg PMNs and macro-ovalocytes*; MCV >110 • ↓ **Folate**: ↑ homocysteine, nl MMA • ↓ **B12**: ↑ homocysteine, ↑ MMA (↑ anti-IF Ab, ↑ gastrin if pernicious anemia; falsely nml B12 possible) • **Early myeloproliferative d/o** **Non-megaloblastic**: MCV usually <110 • **Cirrhosis, EtOH** • **Reticulocytosis**: lysis or bleed • **Hypothyroidism** • **MDS** (refractory anemia) **& MM** **Meds**: HAART, 5FU, AraC, Hydrea

↑ DESTRUCTION / LOSS (RI >2%)	
Extrinsic (transfused RBC has shortened life span)	**Intrinsic** (transfused RBC has normal life span)
MAHA (-DAT, +schisto): see *Thrombocytopenia* • Smear (≥2 schisto/HPF), PLT ~25K, ↑ LDH, ↑ indir bili, ↓ hapto **Immune (+DAT, +spherocytosis)**: Ab- and/or complement-mediated • **Warm autoimmune** (CLL, HIV, lymphoma, SLE): +DAT anti-IgG/C3 • **Cold autoimmune** (EBV, lymphoid malig., Mycoplasma): +DAT anti-C3 • **Drugs** (PCN, cephalosporins)**, alloimmune** (hemolytic transfusion rxn) **Non-immune (-DAT, +/- RBC inclusion)**: • **Infection**: babesia, malaria, bartonella, C. perfringens, H. flu (type B) • **Toxin**: lead, copper, insect / spider / snake bites, hypotonic infusion • **Hypersplenism**: many; massive SM usually 2/2 heme malignancy	**Hereditary**: • **Hb** disease (SS, HbC, thal): Hb electrophoresis • **Enzyme deficiency** (G6PD, PK): *G6PD levels often nml in attack*; check 4wk later & repeat in 3mo if neg. • **Membrane defect:** spherocytosis, elliptocytosis **Acquired (new onset)**: • **PNH** (paroxysmal nocturnal hemoglobinuria): flow cytometry +/- FLAER for GPI anchor, smear nml, UA (hgb/hemosiderin), thrombosis (intra-abd/cerebral) **Acute blood loss**: GI blood loss, hematoma
Intravascular: ↑↑LDH, ↓↓hapto, hemoglobinemia & -uria; **Extravascular**: ↑indir bili ± ↑LDH ± ↓hapto (if free Hb escapes spleen), SM	

IRON DEFICIENCY ANEMIA (NEJM 2015;372:1832; Blood 2019;133:30)

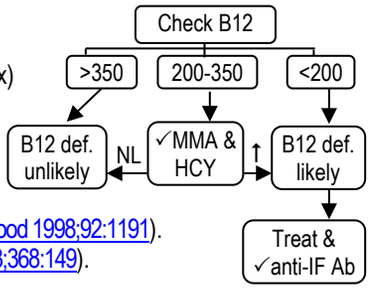
- **Etiology**: ↑loss due to chronic bleeding (PUD/UGIB [↑BUN w/o ↑Cr], LGIB/CRC, menses, parasites, intravascular hemolysis), ↑demand (Epo, pregnancy, blood donation), ↓intake (malnutrition) or ↓absorption (Crohn's, ↑pH [e.g. PPI], post-gastrectomy, celiac)
- **Evaluation**: GI bleed eval, H. pylori; consider celiac (esp. if not responsive to PO iron).
- **Treatment**: **PO 325 mg $FeSO_4$ x1-3 QD or QOD** (↑ absorp. w/ QOD: Lancet Haematology 2017;4:e524).~6wk to correct anemia, ~3-6mo to replete stores. Absorp. ↑ on empty stomach, w/ VitC, ↓ w/ Ca foods, antacids. GI SE: constipation, epigastric pain, N/V.
  - IV iron if excessive SEs, CKD, malabsorption, IBD, intolerant to PO, or CHF (FAIR-HF NEJM 2009;361:2436-48). Typical dose: **iron sucrose 200mg QOD x5 or 300mg QOD x3**. SE: n/v, pruritus, flushing, myalgia/arthralgia, CP; ⦸ by 48h. Anaphylaxis rare.

ANEMIA OF CHRONIC INFLAMMATION (NEJM 2019;381:1148-57, Blood 2019;133:40)

- **Etiology**: autoimmune, infection, malignancy, chronic disease (HF, CKD); inflammatory cytokines (IL-1, IL-6 & TNFα) →↑ hepcidin → ↑ ferroportin degradation/internalization → ↓ intestinal Fe absorption, ↓ Fe recycling by macrophage & hepatic Fe mobilization
- **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%, ferritin <100 (<200 in ESRD+IDA), or no response to EPO; can ✓*soluble transferrin receptor/ferritin index* to distinguish pure ACI vs. ACI+IDA but typically hx & Fe studies sufficient.
  - **Erythropoiesis stimulating agents (ESA)**: FDA-approved for anemia a/w CKD & HIV on HAART. Controversial in cancer pts, but there are specific indications for it (ASCO/ASH Guidelines: JCO 2019;37:1336). Evidence against use in CHF (RED-HF NEJM 2013;368:1210). Maintain Tsat ≥20%, ferritin ≥100 for EPO therapy.

MEGALOBLASTIC ANEMIA: ↑RBC size due to abnml cell division in BM; macrocytosis = RBC MCV >100 & can be non-megaloblastic

- ↓ **Folate**: *foliage*, **3mo.** stores; ↓intake (EtOH, elderly), ↓absorption (celiac, jejunal processes), ↑demand (pregnancy, hemolysis, malig.), meds (MTX, TMP, AEDs); severe form a/w hemolytic anemia, pancytopenia; ↑homocysteine, MMA nml; **Tx**: 1-5 mg PO QD (NB must ✓ B12 before tx)
- ↓ **B12**: *beef*, **3yr.** stores; ↓intake (EtOH, vegan), pernicious anemia (Ab to IF, gastric parietal cells), ↓absorption (gastrectomy, celiac, Crohn's, PPI, chronic pancreatitis), ↑competition (bacterial overgrowth, tapeworm); severe form a/w pancytopenia & subacute combined degeneration (dorsal columns, corticospinal tract) w/ dementia, ataxia, paresthesia, ↑homocysteine, ↑MMA. **Tx:** 1-2 mg PO B12 QD (*as effective as IM if not 2/2 malabsorption*) (Blood 1998;92:1191). For pernicious anemia, typically given IM. Post-tx, neuro sx start to improve 3mo-1yr (NEJM 2013;368:149).



AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) (NEJM 2019;381:647-654)

- **Mechanism**: antibody-mediated (warm) or complement-mediated (cold) hemolysis. DAT detects IgG / C3 bound to RBCs.
- **Warm AIHA** (idiopathic, CLL/lymphoma, SLE/autoimmune disease, HIV, Babesia, meds): +DAT anti-IgG +/- C3, extravascular hemolysis in spleen; Tx: transfuse if Hb <6 & treat w/ **steroids**: prednisone 1-2 mg/kg/d for up to 3 weeks with slow taper when Hb >10 (effective 50–90% of cases), 2nd line: rituximab, immunosuppressants, IVIG, splenectomy. **Notify Blood Bank** if rapid hemolysis.
- **Cold AIHA**: most often cold agglutinin disease (lymphoid malignancies, EBV, Mycoplasma), rarely cold IgG; +DAT anti-C3 at room temp. (can ✓ thermal amplitude, consider titer), intravascular hemolysis; Tx: avoid cold; if sx/transfusion-dependent, plasmapheresis/IVIG as temporizing, rituximab; NO steroids or splenectomy
- **Drugs**: both Ab & non-Ab-mediated; abx (PCN, cephalosporins, sulfa); NSAIDs; CV (methyldopa, procainamide); rasburicase (G6PD)
  - If +DAT but no hemolysis, think **Drugs**, ↑↑ **IgG** (IVIG/Rhlg/myeloma), **CTD** (e.g. controlled SLE)

SICKLE CELL ANEMIA (NEJM 2017; 376:1561, JAMA 2014;312:1033)

- **Manifestations**: HbS → sickling when ↓O_2 → hemolysis (chronic anemia: Hb ~8-10, normocytic unless +thalassemia or IDA, reticulocytosis ~3-15%, ↑LDH, ↓hapto) + microvascular occlusion (acute chest, CVA, pain crises, splenic sequest., hand-foot synd., renal pap. necrosis, priapism); ↑ risk of encapsulated infxn (⊗ spleen), osteomyelitis (infarct. bone), aplastic anemia w/ parvo B19
- **Inpatient**: ✓CXR (r/o acute chest), CBCd, retic, LDH, CMP, T&S; Mgmt in all: VTE ppx, adequate hydration, incent. spirometry
- **Pain crises**: pain ctrl: opioids +/- NSAIDs; check for Acute Care Plan. If unknown prior dose: IV **morphine 0.1-0.15mg/kg** (max 10mg) **or Dilaudid 0.02-0.05mg/kg** (max 1.5mg) → PCA; O2 if <92%, IVF if hypovol.; incent. spir. (↓acute chest: NEJM 1995;333:699)
- **Acute chest syndrome**: fever, ↑WBC, pulm. infiltrate; r/o PE, ACS, PNA; Tx: O2 if <92%, *transfusions* (goal Hb >10; simple vs. exchange if severe), *pain ctrl* (see above), *abx* (CTX/azithro or FQ), bronchodilators. *NB*: 50% preceded by/assoc. w/ pain crisis.
- **Hyperhemolytic crisis**: rare complication (1%); presentation: pain, fever, worsening anemia w/in 7-15 days of transfusion, dropping reticulocyte count, DAT may be negative. Tx: notify blood bank, hydration +/- steroids, IVIG, rituximab, eculizumab.
- **Transfusions**: indicated in acute stroke, multiorgan failure, acute chest syndrome, sequestration, and peri-op. Goal Hb >10. Exchange > simple due to risk of hyperviscosity. Transfusions should be judicious; ASH guidelines: Blood Adv 2020;4:327.
- **Outpatient treatment**: **hydroxyurea** (↑ HbF; continue as inpt), folate & MVI, **vaccines** for encapsulated bacteria (Mening, HiB, Pneumo), HepB & Flu. Consider L-glutamine (NEJM 2018;379:226), voxelotor (NEJM 2019;381:509), crizanlizumab (NEJM 2017;376:429).

PANCYTOPENIA

Etiologies	
BM	↓**cellular** (aplastic, myelofibrosis, chemo, PNH, mets), **nml cellular** (MDS, PNH), ↑**cellular** (leukemia, lymphoma, MM)
Systemic	↑**spleen** (cirrhosis), **toxin** (EtOH, cocaine), **nutrition** (↓B12/folate, Cu), **CTD** (SLE, RA), **sepsis, HLH/MAS**
Meds	NSAIDs, PPIs, sulfas, antihistamine, chemo, anticonvulsants, antiprotozoals, heavy metals, **many others**
Infxn	**viral** (HIV, HBV/HCV, CMV/EBV, parvo), **bacterial** (Brucella, TB), **fungal** (Histo), **parasitic** (leish, malaria, schisto)
Work-up	
Initial/Mild	✓ **meds, CBC w/ diff**, **retics**, **smear**, LFTs, TSH, B12, folate, PT/PTT, fibrinogen, HIV, HBV, HCV
Severe	✓ HcY/MMA, Cu, Zn, LDH, DAT, ANA, RF/CCP, ESR/CRP, SPEP, CMV, EBV, Parvo, Tox, Abd US+Doppler
Heme	✓ **BMBx** (strongly consider if pancytopenic w/o obvious systemic causes), flow cytometry (if c/f PNH)

- **HLH**: infxn/malig./rheum dz (MAS)/CART/checkpoint inhib.→hyperinflamm.→ in some, cytokine storm. **Dx**: 5/8 of **fever**, ↑**spleen**, 2/3 **cytopenias**, ↑TG /↓fibrinog., ferritin ≥500 (NB usually >7-10k), ↑sIL-2R, hemophagocytosis in BM, low/no NK activity. Usually ↑LFTs, hepatomegaly, ↑LDH, ↑D-dimer. H-score for probability. **Tx**: depends on etiology (ASH guidelines: Blood 2019; 133:2465)

APPROACH TO THE PERIPHERAL BLOOD SMEAR (NEJM 2005;353:498)

- Low power (200x): scan slide for WBC distribution. Identify the "thick" edge and the "feathered" or thin edge.
- Med power (400x): examine feathered edge for rouleaux, parasites, abnormal WBC, platelet aggregation / microsatellites.
- Oil Immersion (1000x): assess the size, shape, and morphology of major cell lineages:
  - **RBC**: examine where RBCs are close but not touching, compare to lymphocyte nucleus size for scale
  - **WBC**: concentrate on edges and thin end of film, normal WBC include PMN, eos, basos, lymphocytes, monocytes

RBCs	Hypochromia / microcytes (↓Fe, thal); spherocytes (AIHA, HS); schistocytes (valve, MAHA); target cells (thal, Hb dz, liver disease, asplenia); tear drops / nRBCs (myelofibrosis, myelophthisis, thal.); bite cells / Heinz bodies (G6PD); basophilic stippling (thal, Pb, sideroblastic); acanthocytes / echinocytes (liver/renal disease); Howell-Jolly bodies (sickle cell, asplenia)
WBCs	HypOsegmented PMNs (MDS); hypERsegmented PMNs (folate/B12); toxic granulation (sepsis); myeloid vs. lymphoid precursors (left shift, myelocytes, blasts, Auer rods), basophils (MPD)
Platelets	Clumping (pseudothrombocytopenia); large platelets (↑ production, ITP, or congenital disease)

THROMBOCYTOPENIA (Hematology 2012;2012:191)
Definition: platelet count < 150k. **Risks**: **<50k** w/ surgery, **<20k** spont. bleed (less so in ITP), **<10k** severe bleed

↓ PRODUCTION	↑ DESTRUCTION	SEQUESTRATION / POOLING / DILUTIONAL
- Infxn: late HIV/HCV, parvo, sepsis - Nutrition: ↓B12/folate/Cu, EtOH - Drugs: see list in margin - Malignancy: leukemia, MDS, PMF, aplastic anemia, infiltrate - Congenital: Bernard Soulier, vWD (specific types), other rare causes	- Infxn: early HIV/HCV, H. pylori > HSV/VZV/CMV/EBV, tick-borne illness - Immune: ITP (+AIHA=Evan's), SLE/APS, RA, CLL, CVID, post-transfusion - Drugs: immune (see list; NEJM 2007;357:580) - MAHA: DIC, TTP/HUS, mHTN, HELLP - Shearing/aggregation: CVVH, CPB, IABP; vasculitis, hemangioma (Kasabach-Merritt)	- Splenomegaly (e.g. cirrhosis & portal HTN): may sequester 90% of circulating platelets - Massive transfusion → 10U pRBC ↓ plt by 50% - Hypothermia - Gestational

Workup: initial labs: CBC w/ diff (Δ other cell lines), review special slide (schistos, other), HIV, HCV (if not ✓ recently)

- If c/f **hemolytic anemia** (↓Hgb & ↓Plts) → also ✓ LDH / hapto / bili, DAT (AIHA), retic count
- If **schistocytes** on slide → also ✓ coags, D-dimer, fibrinogen (eval for DIC vs. TTP/HUS), consider heme consult
- Consider **ANA** (SLE), ACL/LA (APLS) if appropriate based on other clinical signs/symptoms
- If **>60 yo, splenomegaly,** or **systemic sx** → consider BMBx to r/o MDS, AA, leukemia, infiltrate
- Rule out **pseudo-thrombocytopenia** → platelet clumping 2/2 EDTA (can order Platelet Count, Citrated)

PRIMARY IMMUNE THROMBOCYTOPENIA (ITP) (ASH: Hem 2018;2018:568, Blood 2017;129:2829, NEJM 2019;381:945)
Pathophys: thrombocytopenia d/t auto Ab-mediated megakaryocyte destruction and ↓ plt production
Presentation/Dx: p/w mucocutaneous bleeding (or asx); defined by isolated plt <100k, dx of exclusion; 10% have ITP + AIHA = Evans Syndrome. BMBx only done if atypical; anti-plt Ab not useful. Screen for H. pylori (tx may ↑plts in ITP)
Management: treat if <30k, but 20-30k w/ no/mild bleeding (i.e. skin only) can be observed; response = >30k & ↑2x

- **Severe bleeding**: plts, IVIG, methylpred 1g/d IV x3d (or dexamethasone 40mg/d x4d), consider romiplostim.
  - If no response in plts, consider *Amicar* (0.1g/kg/30min→0.5-1g/hr) / tranexamic acid / activated FVII
- **1st line**: dexamethasone 40 mg/d x4d (or prednisone 1 mg/kg/d PO x2-3wk → taper) +/- IVIG 1 g/kg/d IV x 2d
- **No response/recurrence**: romiplostim (Nplate) / eltrombopag / avatrombopag, rituximab, splenectomy (after 6mo-1y)

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) (Blood Adv 2018;2:3360, Blood 2017;129:2864, NEJM 2015;373:252)
Pathophys: anti-PF4-heparin complex Ab→ binds & activates plts, ↑ thrombin → hypercoag. state, ↓ plts
Presentation: 5-10d after exposure, ↓plt >50%, nadir 40-80K, thrombosis in 30-50% (skin necrosis, DVT/PE, arterial)

- ↑ risk w/ UFH; major surgery restarts the clock; consider rapid-onset HIT if <24hrs with prior exposure <1-3mo.; delayed-onset can present up to 3wks after heparin is discontinued

Diagnosis: calculate **4Ts Score**. If ≥4, D/C heparin and ✓**anti-PF4**. If high prob 4T w/ any degree of ⊕PF4 or int. prob 4T w/ mod/strong ⊕PF4, ✓ **serotonin release assay**. Otherwise, if neg PF4 or int. prob 4T w/ only weakly ⊕PRA, HIT unlikely, ok to resume heparin. 4T of ≤3 has high NPV (99%).
Management: D/C all heparin products & add to allergy list. C/s heme, start alternative AC (NEJM 2013;368:737). Do NOT transfuse platelets unless severe hemorrhage. Needs AC until plt >150k if ⊖ thrombosis, ≥3mo. if ⊕.

- **Fondaparinux** (synthetic, IV or subQ): for stable non-surgical patients, contraindicated if GFR <30, irreversible
- **Argatroban** (DTI, IV): monitor w/ chromogenic Xa (goal 20-40%), preferred in renal failure & surgical pts
- **Bivalirudin** (DTI, IV): only approved for HIT undergoing PCI, preferred in liver failure
- **DOACS for non-urgent AC**: apixaban, edoxaban, rivaroxaban, dabigatran
- **VKA**: not until plt >150K for 2 consecutive days

THROMBOTIC MICROANGIOPATHIES (TMAs) (NEJM 2014;371:654)
Pathophys: small-vessel irregularities → microthrombi → **MAHA** (↓Hb, ↑LDH, ↓haptoglobin, +schistos, -DAT), **↓plt** (aggregation, consumption), **ischemic end-organ injury** (vascular occlusion)
Diagnosis: special slide, CBC w/ diff, coags, D-dimer, fibrinogen, LDH, haptoglobin, retics, Cr, LFTs
Secondary etiologies: DIC, infxn, malignancy, SLE, APLAS, HELLP syndrome, scleroderma, severe HTN, post-HSCT
Primary etiologies: in addition to below, also metabolism-mediated (B12 metab. d/o) & coag.-mediated; rare & typically present in infants

- **TTP** (plt <30K): inherited/acquired *ADAMTS13 def.* → vWF multimers. S/Sx: fatigue, purpura, GI sx, neuro sx in 60%; fever uncommon, AKI rare, pentad rare. Dx: PLASMIC score → if mod/high prob., ✓ADAMTS13 (<10% = TTP). Tx: **plasma exchange,** steroids, ritux. Caplacizumab may be option (NEJM 2019;380:335). **No plts** unless bleeding. (Blood 2017;129:2836, NEJM 2019;381:1662)
- **HUS** (plt >30K): Shiga-toxin-mediated bloody diarrhea w/ abd pain (O157:H7 *E. coli*, *Shigella*). S/Sx: severe AKI; severe neuro sx (SZ, coma, hemiparesis) rare. Dx: stool⊕ for organism or toxin; Tx: supportive, often w/ HD, unclear role for Abx (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; Blood 2017;129:2847)
- **Drug-induced**: 1) Immune-mediated (gemcitabine, oxaliplatin, quetiapine, quinine) → acute f/c, abd pain, n/v/d, AKI
  2) Dose-dependent (gemcitabine + other chemo; tacrolimus, CSA + other IS; cocaine) → subacute fatigue, HTN

Anti-infectives:
TMP/SMX
Vancomycin
Penicillin
Ampicillin
Piperacillin
Ceftriaxone
Rifampin
Ethambutol
Quinine
(in tonic water, bitter lemon)
Quinidine

Anti-epileptics:
Cabamazepine
Phenytoin
Valproic acid

Anti-platelets:
Abciximab
Eptifibatide
Tirofiban

Others:
Heparin (HIT)
Ranitidine
Simvastatin
Haloperidol
Amiodarone
Oxaliplatin
Irinotecan
Acetaminophen
Naproxen
Ibuprofen
Furosemide
OTC/herbal

Direct ↓ BM:
Linezolid
Thiazide
Chemo/XRT
EtOH

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.
- Either primary and due to clonal expansion (HES/leukemia) or secondary (reactive) due to infection, atopy, meds, rheum dz, etc.

Infections	**Helminth**: Strongyloides, toxocariasis, shistosomiasis, ascaris, filariasis, trichinellosis. **Fungal:** Aspergillus (ABPA), coccidiomycosis, histoplasmosis. **Protozoal**: isospora. **Viral**: HIV, HTLV1/2.
Malignancy	Primary HES (PDGFRA-assoc.), eosinophilic leukemia, CML, NHL, HL, mastocytosis; less common with solid tumors
Autoimmune	EGPA (see *Vasculitis*), PAN, eosinophilic fasciitis, RA, IBD, IgG4, sarcoidosis, GVHD, blistering disease
Allergic	Drugs, DRESS Syndrome, asthma/atopy, ABPA, hyper IgE syndrome, AIN, episodic angioedema (Gleich syndrome)
Misc	Adrenal insufficiency, cholesterol emboli syndrome, acute arterial thrombosis.

WORKUP (Br J Haematol 2017;176:553, J Allergy Clin Immunol Pract 2018;6:1446, Hematology 2015;2015:92)

- **Hx**: meds/supplements (<6 wks), diet, travel, occupational exposures, atopy, infxn, malignancy, rheumatic dz, full ROS
- **Exam**: assess for rashes, cardiac/pulmonary abnormalities, nasal/sinus involvement, LAD, hepatosplenomegaly, neuropathy
- **Initial diagnostics**: CBC w/ 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 obtain B12, tryptase, serum Ig levels
- **Additional diagnostics** (as clinically indicated): Strongyloides serology & stool O&P, other serologies if potential exposure; ANCA if ?EGPA; ANA, RF, CCP if ?rheum dz; IgE levels + allergy testing if ?allergic; imaging/bronch, serologies (e.g. aspergillus IgE) if ?pulm. dz; imaging/endoscopy if ?GI dz; TTE/CMR if ?cardiac dz; periph. flow +/- BMBx if ?MPD or >1500 & no obvious 2° cause

TREATMENT (Hematology 2015;2015:92)

- Urgent Tx: if cardiac, neuro, or thromboembolic complications, AEC >100,000/rapidly rising, or s/sx of leukostasis → 1mg/kg to 1g solumedrol (+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

DRUGS: can be isolated ↑Eos or accompanied by systemic illness (DRESS, hepatitis, AIN, etc). In hospital, PCNs/cephalosporins common culprits. Suspect DRESS if new drug 2-6w prior, fever, rash, facial edema, LAD, abnml LFTS, ± organ involvement, atyp. lymphs.

ORGAN-SPECIFIC PATHOLOGY

Cardiac: (JACC 2017;70:2363, Immunol Allergy Clin North Am 2007;27:457)

- 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 (≥1mg/kg pred) & remove culprit med (if hypersensivity), treat underlying disorder (parasite, HES)
- Eosinophilic coronary arteritis: rare complication of EGPA; may mimic ACS

Pulmonary: (Clin Microbiol Rev 2012;25:649, Chest 2014;145:883, J Allergy Clin Practice 2014;2:703)

- Acute eosinophilic PNA: <7d fever, cough, SOB; a/w smoking; ↑periph. Eos often absent at presentation; Dx: BAL Eos ≥25%
- Chronic eosinophilic PNA: subacute fever, cough, SOB, wt loss; a/w asthma; Dx: BL periph/pleural infil, UL-predom; BAL Eos≥25%
- Allergic bronchopulmonary aspergillosis (ABPA): asthma/CF c/b *recurrent exacerbations* w/ fever, malaise, brown mucus plugs; Dx: ↑Eos, ↑total IgE, ↑Aspergillus IgE & IgG, imaging w/ central bronchiectasis, UL/ML consolidations; Tx: steroids + itraconazole

Loeffler syndrome: transient/migratory pulm. opacities, ↑Eos 2/2 helminth larvae; Dx: larvae in resp secretion (stool usually ⊖)

GI: (AGA EoE: Gastro 2020;158:1776; NEJM 2015;373:1640; Clin Rev Allergy Immunol 2016;50:175)

- Eosinophilic esophagitis (EoE): dysphagia, food impaction, GERD-like sx/refractory GERD, assoc w/ allergic conditions; Dx: EGD w/ bx, exclude other causes (GERD, motility d/o, Crohn's, infxn, CTD, etc.); Tx: dietary Δs, PPI, topical steroids (MDI/neb, PO liquid)
- Eosinophilic gastroenteritis (EGE): stomach/duod. +/- esoph., colon; Sx: n/v/d, abd. pain, ascites; Tx: dietary Δs, PO steroids

Others: neuro (peripheral neuropathy, encephalopathy, CVA/TIA from thromboemboli), thrombotic complications, skin Δs

PRIMARY HYPEREOSINOPHILIC SYNDROMES (HES) (Am J Hematol 2017;92:1243, Hematology 2015;2015:92)

- **Myeloproliferative HES** (~20% of HES in US): acute/chronic eosinophilic leukemia, PDGFRA-associated MPN → clonal expansion of Eos; 80% pts have *FIP1L1-PDGFRA* fusion gene; remainder have PDGFRA, FGFR1, JAK2 rearrangements
  - Dx: anemia, thrombocytopenia, ↑ tryptase, ↑ B12, special slide (dysplastic eosinophils), flow cytometry (PDGFRA, BCR-ABL1, JAK2, FGFR1, KIT), BM Bx (fibrosis, hypercellularity)
  - Tx: if PDGDR+, imatinib; if JAK2+, JAK2 inhibitor; if FGFR1+, chemo; 2nd line or no rearrangment: hydroxyurea, IFN-α, other TKI/empiric imatinib
- **Lymphocytic HES**: clonal T-cell expansion →↑IL-5 → ↑Eos. Often p/w skin/soft tissue involv., polyclonal hyper-IgG, ↑IgE. Episodic angioedema (Gleich syndrome) is very rare subset of L-HES. Up to 25% risk of progression to lymphoma.
  - Dx: flow cytometry for CD3, CD4 (clonal IL-5-secreting $CD3^-$ $CD4^+$ T-cells)
  - Tx: steroids; 2nd line: IFN-α, hydroxyurea, mepolizumab (anti-IL-5; NEJM 2008;358:1215), alemtuzumab
- **Idiopathic HES**: eosinophilia without identified cause and evidence of end-organ damage → consider ANCA-neg EGPA (50% cases)
  - Tx: steroids; 2nd line: hydroxyurea, IFN-α, imatinib, mepolizumab, alemtuzumab

HYPERCOAGULABLE STATES (NEJM 2017;377:1177)

WORKUP OF FIRST VTE			
Presentation	**Provoked by strong trigger**: - Major surgery/trauma - Immobility ≥3d - CA, pregnancy/OCP, SLE, IBD, nephrotic sx, HIT - Paget-Schroetter, May-Thurner	**Unprovoked / provoked by weak trigger &**: - Recurrent thrombosis - Young (<45 y/o) - Strong FH	**Unusual site**: - Arterial thrombosis - Portal, hepatic, splenic, renal, mesenteric, or cerebral venous thrombosis
Workup	- No role for hypercoag. testing - Consider age-appropriate cancer screen	- *May* benefit from testing from inherited conditions if will alter mgmt (e.g. OCP use, AC duration, s/p pregnancy loss) - APLAS if young or recurrent events	- Arterial: test for APLAS - Cerebral veins: inherited + APLAS - Splanchnic veins: inherited conditions + APLAS + JAK2 + PNH

Hypercoag testing: no evidence that improves outcomes, rarely changes mgmt (inherited thrombophilic abnormality does not sig. ↑ risk of recurrent VTE [JAMA 2005;293,2352]), $$$. Do **NOT** perform at time of event (affected by VTE & AC); **wait** until 2 wks after AC d/c'ed.

- Panel includes: APC resistance (reflexes to FVL), protein C/S (reflexes to FVIII/fibrinogen), ATIII, LA, prothrombin G20210A (PTG), anti-cardiolipin. Does NOT include anti-β2 glycoprotein. Only FVL, PTG, aPL Ab are reliable in acute VTE or on AC.

See *VTE Management* & *Anticoagulation Management* pages for guidance on AC agents / duration of treatment.

CONDITION	CLINICAL PEARLS	TESTING
Inherited Conditions		
Factor V Leiden/ APC resistance	- Most common inherited cause of hypercoagulability	- APC resistance assay → reflex FVL genetic test
Prothrombin gene mutation	- 2nd most common cause of hypercoagulability - ↑ prothrombin (FII)	- PCR for PTG G20210A mutation (most common)
Protein C/S deficiency	- Activated protein C/S inactivate FVa and FVIIIa; ↓ level (more common) or function leads to hypercoagulability - A/w warfarin-induced skin necrosis (screen if hx)	- Free protein C/S functional assays - ↓ by acute thrombosis, Vit K antagonists, liver dz, nephrotic syndrome, DIC, pregnancy (S only), chemo - ↑ by DOACs
Antithrombin III deficiency	- ↓ level or function - *NB*: heparin works via ATIII to inactivate FIIa and FXa; if ATIII defic., will be heparin-resistant & require ↑↑↑ doses	- ATIII functional assay assessing FXa inhibition - ↓ by acute thrombosis, UFH/LMWH - ↑ by VitK antagonists, DOACs
Others	- ↑ FVIII, dysfibrinogenemia, hyperhomocysteinemia	- FVIII & fibrinogen ↑ by inflamm. (acute phase rxn)
Acquired Conditions		
APLAS	- **Sapporo criteria** = 1 clinical + 1 lab criterion - Clinical criteria: venous/**arterial** thrombosis, pregnancy complications - **Catastrophic APS:** ⊕aPL w/ ≥3 organ thromboses in <1 wk, mortality ~50% (Autoimm. Rev 2010;10:74) Tx: LMWH acutely → warfarin +/- ASA (if arterial)	- Lab criteria: ⊕ LA, anti-cardiolipin, or anti-β2 glycoprotein >2x ULN, **12 weeks apart** - LA unreliable on AC; anti-CL and β2GP not affected - *NB*: ⊕ aPL Ab can be seen in infxn, rheum dz, malig, meds w/o clinical APLAS; unclear significance - False ⊕VDRL (NEJM 2018;378:2010)
Other	- Hyperhomocysteinemia (also inherited), HIT; *NB:* Hyperhcy/HIT/APLAS are the d/o freq. a/w arterial thrombosis	

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)
- 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 (or partial) correction: supports **presence of inhibitor** (confirm w/ inhibitor specific assays)
    - Types: drugs (e.g. heparin), acquired factor inhibitor (VIII, V>>IX, XI; autoimmune d/o, malig.), nonspecific inhib. (e.g. LA)
  - If work-up is unrevealing, think VWD, platelets, can check FXIII (most commonly presents w/ delayed surgical bleeding)
- Tx: replace missing factor, eliminate inhibitor (immunosuppressants), treat underlying condition

Coagulation Defect	Normal aPTT	Prolonged aPTT
Normal PT	**Platelet dysfunction** (VWD, other platelet disorders) ↓ Factor XIII	**Intrinsic pathway:** ↓ Factor VIII, IX (hemophilias), or XI (Ashkenazi) VWD (↓ factor VIII in severe cases)
Prolonged PT	**Extrinsic pathway:** ↓ Factor VII inhibitor or early systemic defect (liver, DIC, Vit K deficiency, warfarin); FVII has shortest t1/2	**Common pathway:** Liver disease, DIC, Vit K deficiency, warfarin Rarely common pathway deficiency/inhibitor

DIC: massive activation of coag cascade → consumption of coag. factors (→**bleeding**), microvascular **thrombosis** (→MAHA, organ ischemia). 2/2 various inflamm. etiologies (sepsis, CA, trauma, pancreatitis). Dx: **↑PT/PTT, ↑D-dimer, ↓fibrinogen, ↓plts, +schistos, ↑LDH, ↓hapto**. NB: often normal coags in chronic DIC. Can differentiate DIC from liver dz w/ ↓FVIII (in endothelium, not liver). DIC score. Tx: underlying cause, transfuse plts if <10k (or serious bleeding <50k), cryo if fibrinogen <100, FFP if INR >2. Amicar generally contraind.

ORAL AGENTS (ASH Guidelines: Blood Adv 2018;2:3257; CHEST Guidelines: Chest 2012;141:e152S, Chest 2012;141:e44S)

Agent	Dosing	Bridging/Switching/Reversal
Warfarin (Coumadin) - Vitamin K antagonist: inhibits vitamin K-dependent gamma-carboxylation of F II, VII, IX, X, Protein C, S - $t_{1/2}$ 40h (variable)	- Initiation: 5mg QD x2d; if frail, HF, kidney/liver dz: consider 2.5mg; If BMI >40: consider 7.5mg - Adjust by INR, which lags 48h behind dose Δ Monitoring: (UW Dosing Nomogram) - INR <2: ↑ up to 10-20%/wk - INR 2–3: no change - INR 3–4: ↓ 10%/wk - INR >4: hold until INR 2-3, restart ↓ 5-15%/wk - If overlap w/ direct thrombin inhibitor, check chromogenic FXa: goal 20-40%	Bridging: - To parenteral A/C: start IV w/o bolus when INR <2 - From parenteral A/C: see below Reversal: IV vitamin K faster > PO at 6h, ~ at 24h - Active bleeding: • IV vit K 10mg + FFP (10mL/kg; 1U = 200-250mL) • Kcentra (4-factor PCC) 50U/kg if life-threatening (Circ 2013;128:1234; Transfusion 2016;56:799) - No active bleeding • INR >10 → PO vitamin K 2.5-5 mg OR IV 1-2.5 mg • INR <10 → hold warfarin, no need for reversal
Dabigatran (Pradaxa) - Direct thrombin (IIa) inhibitor - $t_{1/2}$ 12-17 h - 80% renal clearance - P-gp substrate - Other: ↑ dyspepsia, ? ↑coronary events vs. VKA?	- **Non-valvular AF**: 150mg PO BID if GFR >30, 75 mg PO BID if GFR 15-30 (RE-LY NEJM 2009;361:1139); some use 100mg PO BID dose if high bleeding risk - **VTE**: 150mg PO BID *after 5d UFH/ LMWH* (RE-COVER NEJM 2009;361:2342) - **PPX**: 110mg x1 then 220mg PO QD (RE-NOVATE II Thromb Haemost 2011;106:721)	Bridging/switching: - To parenteral A/C: start 12h after last dose - From parenteral A/C: start <2h before next dose/gtt ⦸ - To warfarin: start 3d before dabigatran ⦸ if CrCl ≥50; 2d if CrCl 31-50, 1d if GFR 15-30; bridge PRN - From warfarin: hold warfarin, start when INR <2 Reversal if life threat.: (NB can be dialyzed, lipophilic) - Idarucizumab 5g (REVERSE NEJM 2017;377:431)
Rivaroxaban (Xarelto) - Direct Xa inhibitor - $t_{1/2}$ 5-9h; 11-13 in elderly - 66% renal clear. - interacts w/ CYP-3A4 & P-gp inhib.	- **NV AF**: 20mg PO QD if GFR >50, 15mg if GFR 15-50 (ROCKET-AF NEJM 2011;365:883) - **VTE**: 15mg PO BID x21d, then 20mg QD. After 6mo. ↓ to 10mg QD if no absolute indication for indef. tx (EINSTEIN-DVT, PE, & CHOICE: NEJM 2010;363:2499, 2012;366:1287, & 2017;376:1211) - **PPX**: 10mg PO QD (MAGELLAN NEJM 2013;368:513)	Bridging/switching: (J Thromb Thrombolysis 2016;41:206) - To parenteral A/C: start when next DOAC dose due - From LMWH/fonda: start w/in 0-2h of next sched. dose - From UFH: start immediately after ⦸ gtt (for **edoxaban,** start 4h after stopping UFH) - From warfarin: • Start **rivaroxaban** when INR <3 • Start **apixaban** when INR <2 • Start **edoxaban** when INR ≤2.5 - To warfarin: (NB all ↑ INR; ✓ just before dose if able) • **Rivaroxaban/apixaban:** coadminister until INR ≥2 • **Edoxaban:** cut edoxaban dose by ½ and begin warfarin, ⦸ edoxaban once INR ≥2 - DOAC to DOAC: start when next dose due Reversal if life-threat.: (NB not dialyzed off, protein-bound) - Andexanet alfa (recombinant FXa): low or high-dose bolus depending on dose/timing → 2h gtt (ANNEXA-R & -4: NEJM 2015;373:2413 & 2019;380:1326)
Apixaban (Eliquis) - Direct Xa inhibitor - $t_{1/2}$ 12h - ~25% renal clear. (*Can use in ESRD*) - interacts w/ CYP-3A4 & P-gp inhib.	- **NV AF**: 5mg PO BID, 2.5 mg BID if 2/3: Cr ≥1.5, Wt ≤60kg, age ≥80; some use 2.5mg BID if CrCl 15-29 (ARISTOTLE NEJM 2011;365:981) - **VTE**: 10mg BID x7d, then 5mg BID x6mo; after 6mo. ↓ to 2.5mg BID if no absolute indication for indef. tx (AMPLIFY & AMPLIFY-EXT: NEJM 2013;369:799 & 368:699) - **PPX**: 2.5 mg BID (NEJM 2009;361:594)	
Edoxaban (Savaysa) - Direct Xa inhibitor - $t_{1/2}$ 10-14 h - 50% renal clearance - P-gp substrate	- **NV AF**: 60mg PO QD; 30mg if CrCl 15-50 or wt ≤60kg; do not use if CrCl>95 (ENGAGE-AF NEJM 2013;369:2093) - **VTE**: 60mg QD *after 5d UFH/ LMWH*, 30mg QD if CrCl 15-50, ≤60kg, or taking P-gp inhib. (NEJM 2013;369:1406) - **PPX**: not FDA-approved (15-30mg PO QD)	

PARENTERAL AGENTS

Agent	Dosing/Monitoring	Bridging/Switching	Reversal	Other
Heparin (UFH) - Binds & activates ATIII→ inactivates Xa & IIa - $t_{1/2}$ 60-90min	- **ACS**: 60U/kg → 12U/kg/hr; PTT 63-83 - **VTE**: 80U/kg → 18U/kg/hr; PTT 70-100 - **PPX**: 5,000U SC q8-12h - Monitoring: PTT; anti-Xa (goal 0.3-0.7) if baseline ↑ PTT or high doses; ACT if ↑↑↑	- To LMWH: give LMWH & ⦸ UFH at same time - To warfarin: ⦸ UFH once therapeutic ≥2d	- Protamine: 1 mg per 100U heparin or 1mg LMWH (max 50mg). 60% reversal for LMWH, most effective if last dose within 8 hr - Do NOT give FFP (has ATIII, which potentiates A/C effect)	- Preferred in renal failure (CrCl <30), peri-procedure, poor absorption, pregnancy
Enoxaparin (LMWH, Lovenox) - Binds & activates ATIII→inact. Xa>>IIa - $t_{1/2}$ 4.5-7hrs	- **ACS/VTE**: 1mg/kg BID; QD if GFR <30 - **PPX**: 40mg SC QD; 30mg BID if ↑↑risk; ↑30% if BMI ≥40; 30mg QD if GFR <30 - Monitoring: not routine; can ✓anti-Xa 4h after 4th dose, goal 0.5-1.0	- To UFH: ⦸ LMWH & start UFH w/o bolus 1-2h before LMWH dose due - To warfarin: ⦸ LMWH once therapeutic INR ≥2d		- Acute VTE: LMWH > UFH (Cochrane Rev 2017) - Prolonged $t_{1/2}$ in renal failure
Fondaparinux (Arixtra) - Binds & activates ATIII→inact. Xa only - $t_{1/2}$ 17-21 hrs	- **VTE**: <50kg → 5mg QD | 50-100kg → 7.5mg QD | >100kg → 10mg QD - **PPX**: 2.5mg SC QD - CrCl <30: contraindicated - Monitoring: not routine; can ✓4hr anti-Xa	- To warfarin: ⦸ fonda. once therapeutic INR ≥2d - To UFH: start UFH (no bolus) 1-2hrs before due - From UFH: start 1hr after UFH ⦸	- No reversal agent	- ↑ aPTT at therapeutic doses - If CrCl 30-50, consider Δ to different agent
Argatroban - Direct IIa (thrombin) inhibitor - $t_{1/2}$ 45min	- **HIT**: 1-2mcg/kg/min - Monitoring: PTT, goal 1.5-3x baseline PTT - Caution in critically ill, cardiac dysfunction, liver disease	- To warfarin: ⦸ once chromogenic factor Xa is 20-40% (argatroban ↑INR)	- No reversal agent	- Only dabigatran (PO) has antidote (idarucizumab)

CHOOSING AN ANTICOAGULATION AGENT

Guidelines: CHEST for VTE: Chest 2016;149:315, ASH for VTE: Blood Adv 2018;2:3257, ASCO for VTE in CA: JCO 2020:38;496; ACC/AHA/HRS for AF: JACC 2019;74:104, CHEST for AF: Chest 2018;154:1121; AHA/ACC for Valvular HD: JACC 2017;70:252

VTE	**All Others**	**DOACs** > warfarin > LMWH
	Active Malignancy	**Apixaban** (CARAVAGGIO NEJM 2020;382:1599), **edoxaban** (NEJM 2018;378:615), **rivaroxaban** (JCO 2018;36:2017), **LMWH** > warfarin (CLOT NEJM 2003;349:146). Both edoxaban & rivaroxaban w/ ↑ bleeding risk vs. LMWH, so avoided in GI/GU CA w/ intralum. lesions. Effect not seen w/ apixaban. NB*: use of apixaban in CA population not yet in published guidelines*. DOAC ppx a/w ↓ VTE in high-risk outpts: consider if Khorana ≥2 (AVERT NEJM 2019;380:711; CASSINI NEJM 2019;380:720).
	Obesity	**Avoid DOACs** if BMI ≥40 or wt ≥120kg, though rivarox. may be ok. If use, ✓peak/trough level (ISTH: JTH 2016;14:1308)
	Recurrent	**If on non-LMWH**: switch to LMWH. **If on LMWH**: increase LMWH dose.
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) vs. **triple therapy** (+ ASA): dual w/ ↓ bleeding, likely no ↑ events (Annals 2020; EHJ 2019;40:3757)
		Dual therapy: **DOAC + clopidogrel** x12mo. Rivaroxaban 15mg QD (some use 20mg) (PIONEER AF NEJM 2016;375:2423) & dabigatran 150mg BID (RE-DUAL PCI NEJM 2017;377:1513) in guidelines, but now also data for apixaban (5mg BID unless 2.5mg indicated) (AUGUSTUS NEJM 2019;380:1509) & edoxaban 60mg QD (*though edox. w/o ↓ bleeding vs. VKA) (ENTRUST-AF PCI Lancet 2019;394:1335). Warfarin + clopi or ticag also option (WOEST Lancet 2013;381:1107). Ticag may be used in-hospital or if very high thrombotic risk. After 12mo., can likely Δ to OAC alone (AFIRE NEJM 2019;381:1103).
		If triple therapy chosen due to high thrombotic/low bleed risk, typically d/c ASA & transition to dual therapy at 4-6 weeks.
Valve	**Mechanical**	**Warfarin** + **ASA**. Warf. > dabigatran (RE-ALIGN NEJM 2013;369:1206). INR for AVR 2.5 (3 if +AF, VTE, etc.); MV & TV = 3.
	Bioprosthetic	Surg: **Warfarin** (INR 2.5) + **ASA** 3-6mo→**ASA**. TAVR: **ASA/clopi** 3-6mo→**ASA**. If AF/VTE, OAC+clopi→OAC. (Evolving)
APLS		**Warfarin**. Warfarin > rivaroxaban in high-risk APLS (TRAPS Blood 2018;132:1365)
CAD	**ACS** (⦸ PCI)	Very low dose rivaroxaban (2.5mg BID) added to ASA/clopidogrel→↓CV mortality but ↑major bleeding (NEJM 2012;366:9)
	2° prevention	Very lose dose rivaroxaban (2.5mg BID) + ASA → ↓ MACE vs. ASA alone; ↑ major bleeding but no Δ in ICH or fatal bleeding (COMPASS NEJM 2017;377:1319). Can consider if high risk for events & low bleeding risk.

ANTICOAGULATION BRIDGING

Guidelines: ACC: JACC 2017;69:871; ASH: Blood Adv 2018;2:3257; CHEST: Chest 2012;141:e419s

Indication	AF		VTE		Mechanical Valve	
Thrombotic Risk	**Risk Factors**	**Bridge?**	**Risk Factors**	**Bridge?**	**Risk Factors**	**Bridge?**
High	- CHA_2DS_2-VASc ≥7 (or CHADS2 5-6) - CVA/TIA, or systemic embolism <3mo. - Rheumatic valv. HD	Bridge unless major bleed/ICH <3mo.	- VTE <3 mo. - Severe thrombophilia: protein C/S or ATIII def, APLAS, multiple abnormalities	Bridge	- Any mechanical MV - Caged ball/tilt disc AVR - Any mechanical valve w/ CVA/TIA <6mo.	Yes
Moderate	- CHA_2DS_2-VASc 5-6 (or CHADS2 3-4) - CVA/TIA or systemic embolism >3mo.	Likely bridge if prior CVA/TIA and if not ↑ risk of bleeding	- VTE 3-12mo. - Recurrent VTE - Active malignancy - Non-severe thrombophilia: heterozygous factor V Leiden, PTG mutation	No bridge	- Bileaflet AVR w/ ≥1 CVA risk factor: age >75, AF, prior CVA/TIA, HTN, DM2, CHF	Consider based on risk of bleeding in patient/from procedure
Low	- CHA_2DS_2-VASc ≤4 (or CHADS2 0-2) - No prior CVA/TIA or systemic embolism	No bridge	- VTE >1yr & no other risk factors	No	- Bileaflet AVR w/o AF or CVA	No

- **BRIDGE** trial (NEJM 2015;373:823) demonstrated ↑ risk of bleeding w/ bridging in pts with AF undergoing invasive procedure requiring interruption of VKA (*NB*: excluded pts w/ mech. valves, stroke/TIA <12wk, major bleeding <6wk, CrCl <30, Plt <100k)
- Bridging VKA w/ UFH or LMWH:
  - Stop VKA 5d prior to procedure if therapeutic INR. Start UFH or LMWH when INR <2.
  - Stop UFH 4-6h prior to surgery and LMWH 12 or 24hrs prior to surgery (depending on dosing interval).
  - Restart UFH/LMWH at 24hrs postop. if low postprocedural bleeding risk or 48-72hrs if high risk. ⦸ when INR >2.
  - Resume VKA w/in 24hrs postop if no bleeding complications (will not ↑ early bleeding risk because effect takes 24-72hrs).
- DOACs: no bridging required; most can be stopped 24-72h prior to surgery, depending on procedural bleeding risk & renal function:

	High Bleed Risk		Low Bleed Risk	
	CrCl >50	**CrCl <50**	**CrCl >50**	**CrCl <50**
Dabigatran	≥48hrs (4 doses)	≥96hrs (8 doses)	≥24hrs (2 doses)	≥48hrs (4 doses)
Rivaroxaban	≥48hrs (2 doses)	≥48hrs (2 doses)	≥24hrs (1 dose)	≥24hrs (1 dose)
Apixaban	≥48hrs (4 doses)	≥48hrs (4 doses)	≥24hrs (2 doses)	≥24hrs (2 doses)
Edoxaban	≥48hrs (2 doses)	≥48hrs (2 doses)	≥24hrs (1 dose)	≥24hrs (1 dose)

  - If low bleeding risk, can resume 24hrs after procedure. If high bleeding risk, wait 48-72hrs. If unable to take PO for prolonged period or second procedure is anticipated, start UFH/LMWH at the above time points instead.

See *Peri-Procedural Anticoagulation* for MGH-specific peri-procedural guidance for cardiac cath. lab & IR procedures.

TRANSFUSION MEDICINE TERMINOLOGY (http://handbook.partners.org → Clinical Topics → Transfusion Medicine)

- **ABO typing**: front type: **A/B antigens** (pt's RBC + reagent anti-A or B); back: anti-A or B in plasma (pt's plasma + reagent RBCs)
- **Rh(D) typing**: tests for **D antigen** on RBC (pt's RBC + reagent anti-D) – *NB: anti-D is not a naturally occurring antibody*
- **Screening** (T&S): tests for **unexpected antibodies** in pt's plasma (pt's plasma + **screening** RBC + Coomb's reagent), "active" **x3d**
- **Crossmatching** (T&C): final confirmation test by mixing pt's plasma & **donor** RBC; performed just prior to transfusion
- **Direct antiglobulin test** (DAT/Coomb's Test): tests for Ab or complement on RBCs (RBCs + Coomb's reagents [anti-IgG, anti-C3])

BLOOD PRODUCTS

Product	Description	Indications	Notes
Red Blood Cells	1U = 330cc = $895 Processing 1. Leukocyte reduction 2. Irradiation 3. Washing (rarely)	- Hgb <7 (NEJM 2014;371:1381, NEJM 2013;368:11) - Hgb <8 if CAD/ACS, ortho/cardiac surgery - AIHA and MDS (no specific Hgb threshold) - Sickle cell disease (see *Anemia*: Sickle Cell Disease)	- Response: **1U ↑Hgb ~1** - Hct ~55%
Platelets	1U = 6pk = 300cc = $3400 Types 1. Apheresis platelets derived from 1 donor 2. Pooled platelets from multiple donors Processing 1. Leukocyte reduction 2. Irradiation	**Low platelets *or* functionally abnormal platelets** - <10k: PPX spont bleeding. Consider antifibrinolytics in refractory thrombocytopenia in CA (NEJM 1997;337:1870) - <50k: major bleed, intra- or post-op surgical bleed, ppx prior to invasive operative procedures (no data) - <100k: post-bypass bleed, ICH/ophthalmic (no data) - ITP: only if life-threatening CNS/GI/GU bleed (often preceded by wet purpura, mucus membrane bleeding) - HIT/TTP: avoid PLTs unless bleeding	- Response at 30-60m: **1U ↑ PLT ~ 30K.** - No evidence that apheresis > pooled plts. - No evidence that platelets reverse anti-platelet agents (PATCH Lancet 2016;387:2605)
Fresh Frozen Plasma	1U = 250cc = $460 1 Dose ~ 10-20 cc/kg Non-cellular portion of blood containing all coag factors; separated and frozen after collection.	- Active bleed d/t deficiency in multi coag. factors *or* isolated coag factors for which concentrate is not available - Cirrhosis: **consider anti-fibrinolytics instead**. Treating INR w/ FFP can ↑ bleeding due to ↑ portal pressures. - ALF: consider for ↓ Plt or ↑ INR only if bleed or pre-op - VKA reversal: IV Vitamin K first. PCC if life-threatening. - Trauma, DIC in presence of bleeding, congenital TTP	- Response: **1U ↑ coag activity ~ 10%** - Max correction **INR 1.7** - Effect < 6H due to short $t_{1/2}$ of FVII - Potentiates effect of heparin by providing ATIII
Cryoprecipitate	10U = 150cc = $2850 Contains factor VIII, factor XIII, VWF, and fibrinogen	- Fibrinogen <100: 50-100mg/dL, give 10U; <50, give 20U - Massive transfusion w/ ↓ fibrinogen or abnl ROTEM/TEG - Complex cardiac surgery (JAMA 2017;217:738) - Postpartum hemorrhage (Br J Anaesth 2015; 114:623) - FVIII deficiency, VWD - Cirrhosis: also consider antifibrinolytics	- Fibrinogen replacement: 0.2 bag/kg → 100 mg/dL fibrinogen w/ $t_{1/2}$ 3-5d - FVIII or vWF replacement: cryo is last resort therapy
Coagulation Factors	1-factor: VIII, IX, rF VIIa (NovoSeven), ATIII 3-factor (II, IX, X; Profilnine) 4-factor PCC (II, VII, IX, X; Kcentra) FEIBA (anti-inhib. complx) vWF/FVIII (Humate-P)	- Coagulation factor deficiency / inhibitor - Von Willebrand's disease (Humate-P, NovoSeven) - Life-threatening bleed due to VKA (PCC > FFP)	- Blood Transfusion Service approval required - S/E: allergic rxn, thrombosis
Antifibrinolytics	Contain Lysine derivatives that bind to plasminogen to ↓ fibrinolysis and ↑ hemostasis Types (topical, PO, IV) 1. Aminocaproic acid (Amicar) 2. Tranexamic acid (TXA)	- Trauma (CRASH-2 Health Tech 2013;17:1) - Postpartum hemorrhage (WOMAN Lancet 2017;389:2105) - Cardiac surgery (NEJM 2017;376:136; ATACAS J Thor C Surg 2019;157:644), ECMO - Cirrhosis: see *End Stage Liver Disease* - Major orthopedic surgery, platelet refractoriness due to HLA alloimmunization, fibrinolysis of serosal surface and closed space bleeding, coagulation factor inhibitor patients	- Amicar: load 4-5g over 1hr → 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	Types ~$40/bottle 1. 5% (iso-oncotic) 2. 25% (hyper-oncotic) Both contain 12.5g albumin & 154 mEq Na (isotonic)	**5% if hypovol/intravasc depl., 25% if fluid/Na restricted** - Cirrhosis: HRS, SBP, LVP (see *End Stage Liver Disease*) - Shock: 4% albumin similar to 0.9% NS for IVF resuscitation (when alb. >2) (SAFE NEJM 2004;350:2247) - ARDS: 25% albumin (25g) q8h x3d + lasix gtt x3d → ↑O2, neg. TBB (when alb. <2) (Crit Care 2005;33:1681)	- C/I: traumatic brain injury (SAFE trial subgroup) (Also see *IV Fluids and Electrolyte Repletion*)
IVIG	Types ($280/g) Polyclonal IgG and trace plasma contaminants Dose adjust for obesity	- Immunodeficiency: hypogammaglobulinemia IgG <400: 0.3-0.5 g/kg q mo. - Immunosuppression in autoimmune disease (e.g. ITP, AIHA, Kawasaki disease, acquired VWS) - Certain infections	- SE: hemolysis (in A-type), aseptic meningitis, hyperosm renal tubular injury, allergic reaction, thrombosis

TRANSFUSION MODIFICATIONS

- **Leukoreduction (LR)**: filters leukocytes to (1) ↓ HLA sensitization in chronically transfused pts / **heme malignancies**, bone marrow / kidney / heart / lung **transplant candidates** (not liver transplant) (2) ↓ CMV risk & (3) ↓ febrile non-hemolytic transfusion reaction
- **Irradiation**: prevents proliferation of donor lymphocytes from attacking the recipient (transfusion-associated-GVHD in 1st degree directed donors); indications: **heme malignancy** & BMT to prevent GVHD; not indications: solid tumor, solid organ transplant, HIV+
- **Saline-washing**: removes anti-IgA Ab & plasma proteins; indications: severe anaphylaxis to blood products (w/ or w/out 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 15-30 mins after transfusion if clinically indicated

MASSIVE TRANSFUSION: call **Blood Bank (x63623)** and physically run down 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
- 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; combat trauma studies confounded by survival bias (JAMA 2015;313:471)
  - Excessive FFP a/w higher ARDS in pts not requiring massive transfusion
- Correct coagulopathy → IV vit K, FFP 15cc/kg; platelet dysfunction (ASA, plavix, uremia) → PLTs, DDAVP 0.3 mcg/kg
- Consider IV amicar @ 5g bolus over 1h, then 1g/hr gtt x 8h or IV TXA @ 1g bolus over 10min, then 1g over 8h
- **Complications**: dilutional coagulopathy, hypothermia, hypocalcemia (citrate), metabolic alkalosis (citrate metabolized to bicarb)

PLATELET REFRACTORINESS: failure to achieve acceptable ↑ platelet count following transfusion. Normal $t_{1/2}$ of 3 days.

- **Causes**:
  - Alloimmune: **Ab to class-I HLA antigens** (e.g. +PRA) or PLT-specific antigens. Risk factors: multiple pregnancies, prior transfusions with non-leukoreduced blood products, and organ transplants (NEJM 1997;337:1861)
  - Non-alloimmune: **non-HLA Ab-mediated**; 2/3 of cases; Ddx: sepsis/DIC, HIT, TTP, CVVH/CPB/IABP, splenomegaly, HSCT, viral infection (HIV/HCV) & meds (sulfa, vanc, linezolid, piperacillin, rifampin, amphotericin, heparin, thiazide, anti-GpIIb/IIIa)
- **Evaluation**: check plt post-transfusion on 2 occasions and assess plt recovery (15min-1hr later) & plt survival (18-24hr 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: test for alloreactivity against HLA antigens. Normal is 0%, range 0-100%.
    To order: HLA Lab, MGH (choose: Blood > Platelet Refractory > Platelet Refractory Workup, HLA class I Ab screen). Test is only run on Tuesdays and Fridays.
  - **If platelets required urgently** (i.e. actively bleeding), notify Blood Bank and ask for send out to Red Cross
- **Management**: with each platelet transfusion, **must** check a post-transfusion CBC within 15-60 minutes of completion
  - 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 costs approximately $3000 and has a shelf life ~3 days.
  - Consider Amicar if bleeding (contraindicated in thrombotic DIC); correct coagulopathy with DDAVP if e/o uremia

MANAGEMENT OF ANEMIA IN JEHOVAH'S WITNESSES (Am J Hematol 2017; 92:1370)

- Discuss management with patients on a case-by-case basis
- **Acceptable products**: hematinics (iron, folate, B12, recombinant human EPO), non-blood volume expanders (NS, LR, hydroxyethyl starches), hemostatic agents (amicar, tranexamic acid, DDAVP, albumin-free clotting factors)
- **Acceptable to some**: autotransfusion, HD/apheresis/CBP/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); erythrocytopheresis 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)

INITIAL EVALUATION: Blood Bank (**x63623**, **p21829**)

- Sx: fever / chills, hives / flushing / jaundice, infusion site pain, shock / oliguria, wheezing / rales, DIC

1. STOP transfusion, ABCs, VS q15min, clerical check
2. If only urticarial sx → treat symptomatically, resume transfusion once Sx resolve
3. If suspected rxns → Purple Top (10cc EDTA tube for hemoglobinemia, DAT, repeat ABO/Rh), UA (for hemoglobinuria)
   - High suspicion for hemolysis: bilis, LDH, hapto, crossmatch, smear
   - High suspicion for sepsis: GS/BCx of both pt & blood product
   - High suspicion for TRALI/TACO: JVP, BNP, ABG, portable CXR

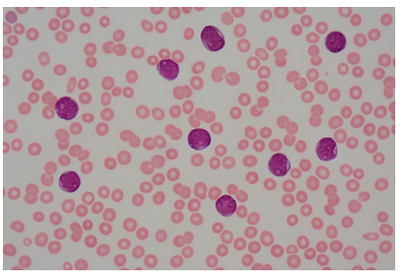
	Acute	Delayed
Immune-mediated	AHTR FNHTR Urticaria/hives Anaphylactic TRALI	DHTR TA-GVHD Post-tx purpura
Non-immune mediated	Cold toxicity Citrate toxicity Sepsis TACO	Iron overload Viral infection

Reaction / Incidence	Presentation / Diagnosis	Pathophysiology	Treatment / Prevention
ACUTE TRANSFUSION REACTIONS (<24 HRS)			
Acute Hemolytic (AHTR) 76,000-137,000	**Sx**: first 15 min; fever / chills, back / flank pain, bleeding / DIC **Dx**: +Hb (blood / urine), +DAT, +DBili / IBili / LDH, +smear (spherocytes)	- ABO / Kidd incompatibility (preformed Abs) → intravascular hemolysis (IgM), cytokine / complement activation - Rh / Kell / Duffy incompatibility → less severe extravascular hemolysis	**Tx**: NS (+/- lasix) for goal UOP > 100 cc/hr x 24h - Monitoring: HoTN, AKI, DIC, mortality ∝ volume transfused **PPX**: vigilance
Febrile Non-Hemolytic (FNHTR) 200-2,500 (RBC) 50-1,600 (PLTs)	**Sx**: 1-6h; low-grade fever, chills, HA, flushing **Dx**: hemolysis workup negative	- Donor WBCs produce TNFα, IL1, IL6 - RBC: donor WBCs activated by recipient anti-HLA Abs - PLT: donor WBCs make cytokines before transfusion	**Tx**: APAP +/- meperidine **PPX**: leukoreduction, little evidence for pre-medication
Sepsis (Bacterial Contamination) 75,000 (PLTs)	**Sx**: 15-60 min; high fever, rigors, abd sx, HoTN / shock **Dx**: GS / BCx of both pt & bag	- Bacteria >> Viruses in donor blood - RBC: Yersinia, PsA (endotox-GNRs) - PLTs: Staph epi (GPCs)	**Tx**: antibiotics, quarantine all other similar products **PPX**: routine screening
Urticaria / Hives 33-100	**Sx**: anytime during / after transfusion; localized or diffuse hives & redness **Dx**: no work-up necessary	- IgE-mediated hypersensitivity to donor plasma proteins	**Tx**: pause → diphenhydramine → resume if urticaria resolves **PPX**: washed products, no evidence for pre-medication
Anaphylactic Anaphylactoid 20,000-50,000	**Sx**: within min; acute HoTN, angioedema, urticaria, wheezing, abd pain **Dx**: clinical; consider IgA deficiency	- IgE-mediated hypersensitivity in recipient lacking IgA or haptoglobin - Bradykinin-mediated flushing/HoTN in pt taking ACEi or neg charged filters (e.g. TPE w/ albumin)	**Tx**: ABCs, O2, IVF +/- pressors, epi IM Q15min, methylprednisolone 125 mg, diphenhydramine 25-50 mg **PPX**: washed products
Transfusion-Related Acute Lung Injury (TRALI) 5,000 (FFP > PLT > RBC)	**Sx**: 1-6h; hypoxemia 2/2 noncardiogenic edema (ARDS); +/- fever **Dx**: BNP nml, bilateral CXR infiltrates w/o CHF	- Pre-transfusion stress activates lung endothelial cells & primes PMNs - Donor anti-HLA Abs/bioactive factors attack primed PMNs of recipient	**Tx**: ABCs, O2, intubation **PPX**: male donor plasma (fewer anti-HLA, anti-PMN Abs); defer donors w/ prior assoc. TRALI cases
Transfusion-Assoc. Circulatory Overload (TACO) 350-5,000	**Sx**: 1-6h cardiogenic pulm. edema 2/2 vol. overload **Dx**: elevated BNP, CXR	- Highest risk in elderly, HF, CKD, chronic anemias	**Tx**: O2, IV diuretics, ± nitrates, NiPPV **PPX**: slower rate (1cc/kg/hr)
IVIG Transfusion Reactions 5-15% of infusions	- Inflammatory rxn: fever, chills, flushing, myalgias - Anaphylactoid rxn: urticaria, flushing, chest pain, N/V, HTN	- Inflammatory rxn: Ab/Ag interaction i/s/o concurrent infxn - Anaphylactoid rxn: unknown, potentially kinin-mediated, rare	**Tx:** IVF, sx mgmt **PPX**: slow, space out infusions
DELAYED TRANSFUSION REACTIONS (>24 HRS, <28 DAYS)			
Delayed Hemolytic (DHTR) 2,000	**Sx**: ~3d; fever, anemia, jaundice, flu-like illness **Dx**: +DAT, +DBili / LDH, +smear w/ spherocytes	- Anamnestic IgG against previously exposed antigen (Kidd / Duffy / Kell) → extravascular hemolysis	**Tx**: none *NB*: delayed serologic transfusion reaction is the same except w/o hemolysis
TA-GVHD Rare (typically immunosuppressed)	**Sx**: 2-30d; fever, rash, mucositis, diarrhea, hepatitis, pancytopenia	- Donor T cells attack non-HLA matched recipient organs in s/o immunosuppression or 1st degree relative donor	**PPX**: irradiation
Post-Transfusion Purpura (PTP) Rare (women>>>men)	**Sx**: 3-14d; purpura, mucocutaneous bleed **Dx**: plt < 10,000, anti-HPA-1A	- HPA-1A neg women develop anti-HPA-1A Abs, which is common in donor PLTs	**Tx**: 1st line: IVIG | 2nd: PLEX **PPX**: HPA-1A negative PLTs

General Admission Approach

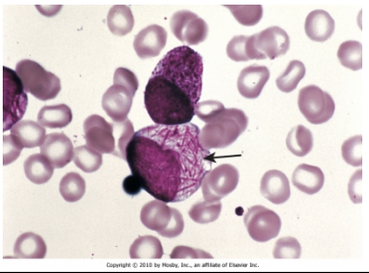
- **History**: note sibling status (for donor search), and if pre/peri menopausal, obtain date of last LMP, full ROS
- **Laboratory workup**:
  - **Peripheral smear**: anemia, thrombocytopenia, variable WBC, circulating **blasts**, Auer rods (*indicates myeloid origin*)
  - **Peripheral flow cytometry**: **do not delay ordering**, even overnight. Collect and send in yellow top tube, then hand-carry specimen to the Warren 506 flow lab and inform them this is RUSH for New Leukemia. On Epic: Orders → Flow cytometry (not bone marrow flow); must fill in flow cytometry clinical history and check "Flow Cytometry CBC and differential, Special Slide Box, Leukemia Panel;" Inpatient Leukemia Attending manages results, but CC outpt Oncologist; ***Rush* samples**.
  - **Screening labs**: CBC w/ diff, BMP, LFTs, coags, UA, bHCG, HBV/HCV, CMV IgG, T&S
  - **DIC labs**: CBC, PT/PTT/INR, fibrinogen, D-dimer (esp if concern for APL)
  - **TLS labs**: BMP, LDH, uric acid, Ca, Mg, Phos; diagnosis requires 2 lab (↑uric acid, ↑K, ↑PO4, ↓Ca) + 1 clinical (AKI, arrhythmia, seizure) criteria
- **BM Bx**: **>20% blasts**, flow cytometry, cytogenetics (karyotype, FISH), molecular testing (FLT3 ITD/TKD, NPM1, IDH1/2)
- **Studies**: **EKG**, **CXR**, **TTE** (needed prior to induction due to cardiotoxic chemotherapies), +/- **CT head** (if CNS sx)
- **Access**: double-lumen **Hickman** vs. triple-lumen **PICC** in anticipation of chemotherapy. Coordinate central access with attending.
- **LP +/- intrathecal chemo**: indications for LP include all ALL; AML w/ CNS or ocular symptoms; APL with systemic relapse
  - **CT or MRI before LP**: AMS, focal neurologic signs, papilledema, seizure within the last week
- **HLA-typing**, **HSCT work-up** (if ≤80 yo): collect in 2 yellow top tubes, send to American Red Cross; siblings>parent/children as donor
  - On Epic: Orders → HLA Lab → Specimen Type: Blood → Pt: Recipient → Type: Bone Marrow/HSC → Test: Allotransplant, if HLA, to AmRedCross → if Panel-Reactive Antibody (PRA), Class I/II Ab screen
- **Utiilize the Leukemia Admission Order Set**: includes Neutropenic precautions, BMT diet, PRNs, among others.
  - TLS ppx: allopurinol 300mg QD
  - GI ppx: omeprazole 20mg QD
  - VZV reactivation ppx: Famvir 500 mg QD
  - Hibiclens daily and Peridex mouthwash BID
  - No VTE ppx (thrombocytopenia)

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)



- Epi: bimodal. Peak incidence in 3-5 y/o, another peak in >45 yo (68% 5-year survival), Most common cancer in children.
- S/sx: pancytopenia sx, bone pain (if acute disease), masses (LAD, HSM, anterior mediastinal mass in T-ALL), CNS sx (CN palsy, n/v, HA), TLS, DIC
- Smear: lymphoblasts with scant cytoplasm, large nuclei containing nucleoli
- Subtypes: precursor B-cell ALL, mature B-cell ALL, mature T-cell ALL
- Risk stratification:
  - Precursor B-cell ALL (cytogenetics >> WBC/age effect on risk)
    - **Favorable**: WBC < 30k, age < 35 years; hyperdiploidy (trisomy 4, 10, or 17 most favorable), t(12;21)(p13;q22): *ETV6-RUNX1*; rapid response to treatment (<0.01% minimal residual dz on Day 29 BM)
    - **Unfavorable**: WBC ≥ 30k, age ≥ 35 years, hypodiploidy, *KMT2A* rearrangement, t(9;22)(q34;q11.2): *BCR-ABL1*, BCR-ABL1-like (Ph-like) ALL, *iAMP21*, t(v;14q32)/IgH, complex karyotype (≥5 chromosomal abnormalities), CNS or testicular involvement; slow response to treatment (>0.01% minimal residual dz on Day 29 BM)
  - Mature T-cell ALL: poorer prognosis than precursor B cell, associated with t(8;14)
  - Mature B-cell ALL: poor prognosis, generally in elderly and with elevated WBC
- Treatment (NEJM 2006;354:166, JCO 2011;29:532)
  - *General*: no single superior regimen, many regimens. Involves 1) induction, 2) consolidation (can be multiple rounds), 3) intensification (if needed), 4) CNS therapy (if needed), 5) maintenance, 6) allo-HSCT (high risk disease)
    - *AYA versus adult*: if pt is AYA (age 15-39), pediatric-inspired regimen are often used
  - *CNS ppx*: **intrathecal** MTX/cytarabine vs. **systemic** high-dose MTX w/ leucovorin rescue
  - *Maintenance*: weekly **MTX/6-MP** + monthly **Vinc/Pred** x2-3 yrs; ↑ **prognosis** if young, WBC < 30K, T-cell type, early CR
  - For refractory/relapsed ALL, **blinatumombab** (Blincyto) (B-ALL) and **anti-CD19 CAR-T** cell therapy

ACUTE PROMYELOCYTIC LEUKEMIA (APML)



- Subtype of AML with distinct biology and excellent prognosis (NEJM 2013;369:111)
- S/sx: pancytopenia sx (fatigue, anemia, ecchymoses, infections). Especially high risk for DIC and bleeding
- Smear: **atypical promyelocytes** (large, "dirty" granular, bilobed nuclei, **+Auer rods**)
- Cytogenetics: **t(15;17) → PML-RARα (>97%)**, rarely t(11;17), t(5;17)
- Treatment: **EARLY Tx** w/ **ATRA CRITICAL** given high early mortality 2/2 to coagulopathy; should start ATRA if there is even mild suspicion for APL as there is low drug toxicity and high mortality with delayed treatment
  - *Induction*
    - Low-risk (WBC≤10K): ATRA (all-trans retinoic acid) + ATO (arsenic trioxide) (JCO 2017;35:583)
    - High-risk (WBC>10K): ATRA + idarubicin or daunarubicin/cytarabine

- *Consolidation*
  - ATRA + (daunorubicin vs. ATO), may depend on induction therapy
  - After completion, check for remission; goal **molecular complete remission** (absence of PML-RARα on RT-PCR)
- Complications of ATRA therapy:
  - **Differentiation syndrome**: SIRS, hypoxemia, edema, pulmonary infiltrates, AKI → high-dose steroids (dexamethasone 10mg q12h), consider temporary cessation of ATRA
  - **Hyperleukocytosis**: see *Oncologic Emergencies*
  - **Idiopathic intracranial hypertension**: headache, vision loss, papilledema → hold ATRA, pain control +/- steroids/acetazolamide

ACUTE MYELOID LEUKEMIA (AML)

- Epi: most common leukemia in adults (80%). Median age of dx: 68yo.
- S/sx: **pancytopenia** (fatigue, petechiae, ecchymoses, infections), myeloid sarcoma (i.e. chloroma), **leukemia cutis** (non-tender red/brown papules/nodules), **neutrophilic dermatosis** (i.e. Sweet syndrome: tender red/violet papules/plaques), gingival hypertrophy (due to leuk. infiltration), joint swelling (leuk. infiltration, gout), **leukostasis** (WBC >50K; SOB, HA, blurry vision, stroke)
- Subtypes: t-AML (therapy-related from chemo, radiation), s-AML (secondary from preceding heme disorder, e.g. MDS, MPN, PNH)
- Risk stratification: based on cytogenetics, mutations, performance status (Karnofsky/ECOG). Worse if t-AML or s-AML.
- Treatment: (NEJM 2009;361:1249)

Risk Category	Genetic Abnormality (NCCN 2019 AML Guidelines)
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogen. abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated *RUNX1*; Mutated *ASXL1*; Mutated *TP53*

1) Day 1 Induction Chemotherapy: standard regimen for "medically fit" pts: **"7+3"**, cytarabine continuous infusion x 7d + ida/daunorubicin (bolus/short infusion) days 1-3. Older pts (≥60 yrs) receive lower-intensity therapy. Regimen will kill leukemia & healthy BM cells but will not ablate the marrow. The goal is for healthy BM cells to recover more quickly and restore normal marrow function. Additional/alternative targeted agents for pts with certain cytogenetic abnormalities:

- Midostaurin (tyrosine kinase inhibitor) added to 7+3 in AML with FLT3 mutations (NEJM 2017;377:454)
- Liposomal cytarabine/daunorubicin (Vyxeos): improved survival in therapy- and MDS-related AML compared w/ standard 7+3 (JCO 2018;36:2684)
- Gemtuzumab ozogamicin added to 7+3 in CD33-positive AML (Blood 2017;130:2373)

↓

2) Day 14 Bone Marrow: check for residual leukemia

→ **3a) Residual Leukemia**: if residual leukemia cells, re-induction chemo (e.g. **7+3**, **5+2, Vyxeos**) may be given.

3b) No Residual Leukemia: if BM is ablated (i.e. sufficiently acellular without evidence of residual leukemia), check for complete remission (CR) at day 28.

↓

4) Day 21-25 Count Recovery: expect count recovery (may be delayed w/ addition of experimental therapies).

← **5) Day 28 BM Biopsy**: check for CR (<5% blasts, nl CBC) 70-80% if < 60 yo; 40-50% if >60

↓

6) Consolidation Therapy: initiated soon after remission is achieved. Goal to eradicate residual disease & sustain lasting remission. Options include chemo or allogeneic stem cell transplant (allo-SCT), depending on pt- and disease-specific factors. In general, allo-SCT is preferred in higher-risk disease and if pt medically able to tolerate it. Chemo in lower-risk disease & in pts who are not allo-SCT candidates. **Risk stratification** (Blood 2017;129:424):

- Favorable risk: **HiDAC (high dose AraC)** x 3-4 cycles vs. standard dose AraC
- Intermediate risk: chemo vs. allo-HSCT
- Unfavorable risk: **allo-HSCT** vs. clinical trial
- Older pts with high-risk dz can be treated with intermed-dose cytarabine or hydroxyurea

→ **7) Surveillance**: CBC every 1-3 months for 2 years, then every 3-6 months up to 5 years.

- Complications: (1) **DIC** (if present→strong suspicion for APL, see below); (2) **febrile neutropenia**; (3) **TLS** → allopurinol, fluids, consider rasburicase if uric acid >10; (4) **leukostasis** → hydroxyurea, fluids, consider leukapheresis

Lymphadenopathy (LAD) Evaluation (Am Fam Phys 2016;94:896)

- Generalized LAD DDx: HIV, EBV, mycobacteria (TB), SLE, medications (e.g. phenytoin), sarcoid, lymphoma/malignancy
- Localized LAD DDx: cervical (EBV, CMV, toxo, TB, lymphoma), supraclav (malignancy), axillary (infxn, breast CA), inguinal (STDs)
- Hx: exposures, travel, meds, B Sx (fevers/drenching night sweats, >10% unintentional wt loss in 6 mo), other s/sxs of infxn or malig
- Exam: localization (think about area of nodal drainage), size (abnormal >1 cm), consistency, fixation, tenderness (inflammation)
- Labs: CBC, HIV (RNA if acute), LDH, HBV/HCV, PPD/TSpot, RPR, ANA, heterophile Ab; consider HTLV and EBV serologies
- Imaging: CT C/A/P (I+), PET (can define node size and distribution, more helpful for monitoring of disease treatment/progression)
- Biopsy: consider if large node (>2cm), persistence 4-6 wks, or increase in size, with immunophenotyping and cytogenetics
  - Excisional (open) biopsy: reveals abnormal cells and nodal architecture (THIS IS THE PREFERED METHOD)
  - Core needle biopsy: tissue for molecular studies, alternative to open if node inaccessible; ask IR to use large-bore needle
  - FNA: can be used as initial screening test for LAD, *not* diagnosis; no info on tissue architecture, high false neg rate

General Lymphoma Staging: for Hodgkin lymphoma (HL), add "B" if presence of B symptoms

Stage I: ≥ 1 LN in a single LN group, or single extralymphatic organ
Stage II: ≥ 2 LN groups on same side of diaphragm
Stage III: LN groups above and below diaphragm
Stage IV: disseminated ≥ 1 extralymphatic organs

BM biopsy, PET (except in HL stage IA/IIA w/ favorable features, CLL by flow cytometry), labs above, HBV serologies if Rituximab needed

Hodgkin Lymphoma: Reed-Sternberg cells (**CD15+ CD30+** CD20-) in inflammatory background; bimodal age distribution (Lancet 2012;380:836)

- WHO classification (classical HL, separate from NLPHL):
  - Nodular Sclerosis (70%): mediastinal mass, good prognosis
  - Mixed Cellularity (25%): periph LAD, HIV/EBV, poor resource areas
  - Lymphocyte Rich (5%): periph LAD, good prognosis
  - Lymphocyte Depleted (<1%): worst prognosis (late stage @ pres)
- Treatment: *note risk of late effects – cardiotox, 2° malignancy, pulm tox*
  - Stage I-II: **ABVD** + **XRT** (curative intent)
  - Stage III-IV: **ABVD** x 6 cycles vs. escalated **BEACOPP** ± XRT
  - Refractory/relapsed: salvage chemo + auto-SCT, followed by maintenance Brentuximab; PD1/PD-L1 blockade (JCO 2018; 36:1428)

Hodgkin Lymphoma International Prognostic Score (IPS)
1 point per factor (JCO 2012;30:3383)

	Points	5y PFS
Age >45	0	88%
Male	1	84%
Stage IV	2	80%
Albumin <4	3	74%
Hb <10.5	4	67%
WBC ≥15,000	≥5	62%
Lymphocytes <600 or <8%		

Non-Hodgkin Lymphoma (NHL): a/w immunosupp (e.g. HIV, txp), autoimmune disease (e.g. Sjogren), infection (e.g. H. pylori, HCV, HTLV1, EBV) (Lancet 2012;380:848)

- **Indolent**: incurable but better prognosis, follicular lymphoma international prognostic index (**FLIPI**) (Blood 2004;104:1258)
- **Aggressive**: higher chance of cure but worse prognosis, aggressive NHL revised international prognostic index (**IPI**) (Blood 2007;109:1857)

Diagnosis	Age	Prevalence	Clinical Features	Treatment
DLBCL	70	25-35%	Aggressive, rapidly growing, nodal / extranodal site; BCL-2, BCL-6 or MYC translocations common ***Double-hit lymphoma (DHL)**: more aggressive subtype w/ both MYC and BCL-2 or 6 translocations	- Stage I-II: R-CHOP + RT - Stage III-IV: R-CHOP +/- targeted tx (lenalidomide, ibrutinib, bortezomib-based on subtype, CD47 Ab (NEJM 2018;379:1711); CAR-T in relapsed/refractory disease *DHL treated with aggressive tx similar to Burkitt (ie R-EPOCH, R-hyperCVAD, R-CODOX-M/IVAC)
Follicular	60	20-25%	Indolent, painless LAD **t(14:18) BCL2+**	- Stage I/contiguous II: RT preferred - Stage II-IV: anti-CD20 +/- bendamustine, lenalidomide, CHOP, or CVP (in III-IV observe to progression first)
SLL/CLL	65	<5%	Indolent, painless LAD **IgM paraprotein**	- SLL Lugano Stage I: RT preferred - CLL or SLL Lugano Stage II-IV: Ibrutinib, acalaburtinib + obinutuzumab (anti-CD20) or venetoclax + obinutuzumab
Mantle Cell	60-70s	<5%	Aggressive, splenogemaly **t(11;14) cyclin D1+**	- Stage I/non-bulk II: BR, VR-CAP, R-CHOP, or LR + R maint - Stage II-IV: RDHA and platinum, R-CHOP/R-DHAP, NORDIC regimen, or HyperCVAD + auto-HSCT + R maint
MALT	65	<5%	**Good prognosis**, mucosal sites (GI) associated with **H. pylori**	- Gastric: triple therapy if H. Pylori+ - Non-gastric: similar to follicular
Splenic MZL	70s	<5%	Indolent, splenomegaly associated with **HCV**	- HCV treatment can lead to regression - If HCV negative, tx with R (preferred) or splenectomy
Adult Burkitt	45	<1%	Aggressive, rapidly growing, extranodal sites (jaw-African, abdomen-American) **t(8:14), cMYC+**, a/w **EBV & HIV**	- R-CODOX-M, R-EPOCH or R-HyperCVAD - Diff doses for Low (single site, <10cm, nl LDH) vs. High Risk

ABVD = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
BEACOPP = Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
CHOP = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CODOX-M/IVAC = Cyclophosphamide, Vincristine, Doxorubicin, HD-Methotrexate, Ifosfamide, Etoposide, HD-Cytarabine
BR = Bendamustine, Rituximab, LR = Lenalidomide, Rituximab
CVP = Cyclophosphamide, Vincristine, Prednisolone
EPOCH = Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
HyperCVAD = Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone
VR-CAP = Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone
RDHA and platinum = Rituximab, Dexamethasone, Cytarabine and Carboplatin, Cisplatin, or Oxaliplatin
NORDIC regimen = dose-intensified Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (maxi-CHOP) alternating with Rituximab + high dose Cytarabine

EVALUATION OF PLASMA CELL DISORDERS (Am Fam Phys 2005;71:105, Leukemia 2009;23:215)

Evaluation	Utility	When to Send
Ig Levels	**Quantify** immunoglobulins (Ig): IgG, IgM, IgA, IgD, IgE. Will not discern clonal vs. polyclonal	If suspect a 1° (e.g. B cell deficiency) or 2° humoral immunodeficiency (e.g. immunosupp, marrow crowding). IgG/A/M included in SPEP order set.
SPEP	**Detect/quantify** M-protein (monoclonal protein, paraprotein; typically, immunoglobulin from an abnormally expanded B/plasma cell = monoclonal gammopathy). Appears as "M-spike"	If suspect a monoclonal B cell or plasma cell process, send SPEP/SFLC. SFLC adds sensitivity. ("SPEP panel" order in Epic contains quantitative IgG, IgA, and IgM, total protein, SPEP, and reflexive IF (if M-spike detected). SFLC assay needs separate order.)
Serum IF	**Identify** the type of M-protein (intact Ig [G, M, A, D, E], light chain only [LC: κ or λ], or heavy chain only [HC])	
SFLC Assay	More sensitive than IF for **identifying** abnormal LC abundance (i.e. outside normal κ/λ ratio of 0.26-1.65). Normal ratio w/: ↓ LC = immunosupp/def., ↑LC = infxn/inflammation (i.e. polyclonal activation; includes some autoimm dz) or ↓LC renal clearance**.	
UPEP	**Detect/quantify** Bence Jones Protein (BJP) (= urine monoclonal protein, typically κ or λ LC). Dipstick will miss BJP.	Generally after serum M-protein confirmed, to assess for nephrotoxic FLC/BJP. Use 24h urine to quantify.
Urine IF	**Identify** the type of BJP (κ or λ)	If UPEP positive for BJP.

Ig = immunoglobulin = antibody ≈ gammaglobulin (i.e in the gamma region on an electrophoresis gel; thus, "gammopathy"). SPEP = serum protein electrophoresis. SFLC = serum free light chain. UPEP = urine protein electrophoresis. IF = immunofixation.
**ESRD can ↑ serum LCs and skew ratio up to 3. Get UPEP + urine IF to rule out urine Bence Jones Protein.
Note, some therapeutic antibodies may show up in above assays as false positives (e.g. daratumumab).

CLASSIFYING PLASMA CELL DISORDERS (Lancet Oncol 2014;15:e358)

CRAB symptoms: **C**a^{++} (>11 mg/dL) or **R**enal dz (Cr >2) or **A**nemia (Hgb <10) or **B**one lesions (≥1 focal lesion on survey, CT, or PET).
All those with M-protein ≥1.5 g/dL, IgA M-protein of any size, abnormal SFLC assay, or CRAB sx need BM biopsy.

	MGUS	Smoldering MM	Multiple Myeloma (MM)	Waldenstrom's (WM)	AL Amyloidosis
BM Involvement (%)	< 10	10-60	≥ 10 (or plasmacytoma)	≥ 10	< 10
Serum M-protein (g/dL)	< 3	≥ 3 [IgG or IgA]	Present	Present (IgM)	< 3
Clinical Signs	Absent	Absent	CRAB	LAD/HSM or hyperviscosity	Present

- **Monoclonal Gammopathy of Undetermined Significance (MGUS)**: premalignant clonal plasma or lymphoplasmacytic cells. ↑incidence w/ age (50+: 3%, 85+: 7.5%). Classified as non-IgM, IgM, or LC. IgG>M>A>D. κ>λ. BJP in 20%. Risk of progression to MM (or AL amyloid, LC deposition disease [LCDD], other lymphoproliferative dx). Risk of WM if IgM. ↑MM risk if IgD. Abnl SFLC ratio predicts prog to MM (~1%/yr). Generally, can omit BM biopsy if IgG M-protein <1.5 g/dL, normal SFLC ratio, and no CRAB symptoms.
- **Smoldering Multiple Myeloma (MM)**: M-protein ≥3 g/dL or 10-60% BM clonal cells and no CRAB.
- **MM**: ≥10% BM clonal cells & CRAB. If ≥60% BM, SFLC ratio ≥100, or ≥1 focal bone lesion, meets criteria even w/o CRAB.
- **Smoldering Waldenstrom's Macroglobulinemia (WM)**: IgM MGUS ≥3 or ≥10% BM involved but no below symptoms.
- **WM**: lymphoplasmacytic lymphoma in BM, IgM MGUS in blood, and symptoms: LAD/HSM, hyperviscosity (IgM = large pentameter; HA, vertigo, vision Δ), anemia, constitutional. Measure viscosity.
- **AL amyloidosis**: monoclonal LC-derived fibrils form β-pleated sheets (amyloid) and deposit in tissues. Bind Congo red (apple-green birefringent) and thioflavine T (yellow-green). Sx: cardiomyopathy, purpura, nephrotic syndr, neuropathy, orthostasis, HSM, macroglossia.
- **Light chain deposition disease**: like AL amyloid but deposition of globular monoclonal LC often in kidney.
- **POEMS syndrome**: (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes), a/w ↑VEGF, sclerotic bone lesions, and Castleman's disease. Polyneuropathy and MGUS required for dx. Almost always λ MGUS.

MULTIPLE MYELOMA WORKUP AND MANAGEMENT (Nat Rev Dis Primers 2017;3:17046; NCCN 2020 MM Guidelines)

- **Lab findings/workup**: ↓AG, ↑globulin, ↑ESR, peripheral smear (rouleaux RBCs), ↑LDH, ↑β2M, SPEP/IF/SFLC, whole body low-dose CT +/- PET (more sensitive than skeletal survey), BM biopsy (IHC, flow, cytogenetics, FISH)
- **Prognosis**: depends on age, performance status, comorbidities, R-ISS staging (incorporates cytogenetics, LDH, β2M, albumin)
- **Treatment agents**: most common induction regimens combine a proteasome inhibitor, immunomodulator and steroids:
  - Proteasome inhibitors: bortezomib (Velcade – V, Bor), carfilzomib (Cz), ixazomib (Ix)
  - Immunomodulatory agents (IMiDs): lenalidomide (Revlimid - R), pomalidomide (Pom), thalidomide (T),
  - Steroids, chemo: dexamethasone (D), prednisone (P), melphalan (M), cyclophosphamide (Cy), doxorubicin (dox)
  - Monoclonal Abs: daratumumab (anti-CD38, Dara; NEJM 2018;378:518); elotuzumab (anti-SLAMF7, Elo)
- **Induction & consolidation**: NOT curative
  - Induction: triplet therapy with VRd most common, other combos also seen; CyBorD used if renal failure at presentation.
  - If candidate for autologous SCT → consolidation w/ auto-SCT; consider early SCT if > standard risk
    - Well-established PFS benefit with auto-SCT; improved OS also seen in most RCTs (NEJM 2017;376:1311)
    - Early (SCT directly after SC collection) vs. delayed SCT (at time of relapse): better PFS, but no clear OS benefit
  - Maintenance therapy (e.g. single agent **R** or **V**) following SCT or if not SCT candidate
  - Relapsed/refractory: combinations of above agents or repeat auto-SCT; CAR-T under investigation (NEJM 2019;380:1726)
- Other Tx: aimed at reducing skeletal lesions/fractures (bisphosphonates, denosumab, XRT), hyperCa^{++}, renal damage, hyperviscosity, infection (PCP, HSV, fungal, VZV; depending on therapy), VTE (immunomodulator-induced higher risk), anemia (EPO).

MYELODYSPLASTIC SYNDROME (MDS): clonal stem cell mutation → ineffective/dysmorphic hematopoiesis → risk of AML

- Presentation: age > 50, cytopenia sxs (fatigue, bleed, infxns), most are asymptomatic with unexplained cytopenias (~90% anemia)
- Risk factors: male, exposure (benzene, tobacco), tx-related (alkylating agents, XRT), genetic (Down, Li-Fraumeni, Diamond-Blackfan)
- Diagnosis: **smear**: hypogranulated PMNs, pseudo-Pelger-Huet (hypolobated PMNs), ovalomacrocytosis, blasts (<20%). **BM Bx**: usually hypercellular w/ single- or multi- lineage dysplasia, +/- blasts <20%, +/- ring sideroblasts, +/- fibrosis
  - Exclude other reasons for cytopenias: ANA, HIV/HCV, EBV/CMV/Parvo, EtOH, ↓B12/folate/copper, ↑Zinc, TSH, Fe/TIBC/ferritin, DAT, SPEP/SFLC, CD55/59 flow (PNH), erythropoietin, review meds (e.g. MTX, mycophenolate mofetil, cyclophosphamide)
- Prognosis: based on IPSS-R; median survival ranges from 0.7 yr in "very high" risk, to 8.8 yrs in "very low" risk
  - IPSS-R is based on blast %, cytogenetics, cytopenias. Correlates w/ survival & progression to AML
- Treatment: based on IPSS-R, performance status & age; see NCCN 2020 MDS Guidelines
  - *Low risk*: observation and supportive care. Anemia: Epo (if serum epo < 500), pRBC (watch for Fe overload). Neutropenia: abx ppx +/- G-CSF (if infxn). Thrombocytopenia: if suspect ITP, TPO agonist +/- steroids
  - *Intermediate/high risk*: hypomethylating agent (decitabine, azacitidine) to prolong time to transplant or if poor SCT candidate
    - If good PS: allogeneic HSCT (only curative tx, though with high up-front toxicity)
  - *Special variants*: del(5q) = lenalidomide; hypoplastic MDS with PNH+ cells, HLA-DR15 or age <60 = ATG + cyclosporine

MYELOPROLIFERATIVE NEOPLASMS (MPN): clonal expansion of one or more myeloid lineages

Most common: CML, polycythemia vera (PV), essential thrombocythemia (ET), & primary myelofibrosis (PMF). Sequelae vary depending on lineage; PV & ET can progress to 2° MF; all can transform to AML. Goals of Tx: improve sx, prevent thrombosis, prevent transformation to AML; only potentially curative therapy for any MPN is allogeneic HCT. (NCCN 3.2019 MPN Guidelines, NCCN 3.2020 CML Guideline)

	PV (↑Hgb ↑WBC ↑Plt)	ET (↑Plt)	Primary MF (↓Hgb ↓WBC ↓Plt)	CML (↓Hgb ↑WBC ↑Plt)
Sx	Hyperviscosity (HA, dizziness, Δ vision, abdominal pain, ruddy complexion), thrombosis (VTE, stroke, Budd-Chiari), aquagenic pruritus, erythromelalgia	Up to 50% asx at dx. Similar to PV (erythromelalgia), bleeding (2/2 acquired vWF disorder, consider if plt > 1 million)	Fatigue, night sweats, weight loss, abd pain, satiety, hepatosplenomegaly, anemia, thrombotic/hemorrhagic events	Often asymptomatic; fatigue, night sweats, bleeding, abd pain, weight loss, splenomegaly (most common physical exam finding)
Dx	**Major WHO criteria**: - Hgb >16.5 (♂), Hgb >16 (♀) - BMBx showing trilineage proliferation - Mutations: JAK2 V617F or JAK2 exon 12 mutation **Minor WHO criteria**: - Low Epo (below reference)	**Major WHO criteria**: - PLT >450k - BM Bx shows enlarged megakaryocytes with hyperlobulated nuclei - Mutations: JAK2 50%, CALR 30%, MPL 5% **Minor WHO criteria**: - Other clonal markers	**Major WHO criteria**: - BM Bx w/ "dry" tap showing reticulin or collagen fibrosis - Mutations: JAK2 50%, CALR 40%, MPL 5% **Minor WHO criteria**: - Leukoerythroblastic smear (left-shift, nucleated and teardrop RBCs), ↑LDH, anemia, splenomegaly	**Mutation**: **BCR-ABL** (by FISH, RT-PCR) CBC with ↑ granulocytes of all maturities (myelo, metamyelo, bands), basophilia, eosinophilia Can be chronic, accelerated, or blast phase. In blast phase, can convert to AML (80%) / ALL (20%)
Tx	**All**: phlebotomy (goal HCT < 45), ASA 81 (*if no bleeding), allopurinol, antihistamine **If >60, ↑risk thrombosis**: hydroxyurea (but risk AML transformation) > interferon-α **2nd line**: ruxolitinib (NEJM 2015;372:426)	**All**: ASA 81 (unless vWF disorder) **If age>60 or ↑risk thrombosis**: hydroxyurea > interferon-α > anagrelide (NEJM 2005;353:33)	Allo-HSCT (only cure), transfusion, hydroxyurea, ruxolitinib (JAK2 inhibitor, primary benefit is symptom reduction) (NEJM 2012;366:787)	**BCR-ABL inhibitors**: imatinib, nilotinib, dasatinib. Allo-HSCT if resistant or in accelerated/blast phase.
DDx	↑**Epo**: hypoxia-induced (heart/lung dz, carboxy-Hb, smoking) vs. **Epo-producing tumor**. ↓Epo: activating epo receptor mutation (rare)	Infection, inflammation, iron deficiency, splenectomy, neoplasm	Other MPNs (especially ET); MDS; hairy cell leukemia; other marrow-infiltrating malignancies	Leukemoid rxn (↑LAP), drugs (steroids, GCSF, ATRA), infection (C. diff, mono), severe hemorrhage, splenectomy, DKA, organ necrosis.

OTHER MDS/MPN TYPES:

- **Chronic myelomonocytic leukemia (CMML)**: MDS/MPN overlap syndrome w/ monocytosis >1000 & splenomegaly
- **Systemic mastocytosis**: rare, mast cells and precursors (CD34+); Dx: skin bx (cutaneous), BMBx (systemic), ↑ tryptase, KIT D816V mutation, ↑urinary histamine; Sx: flushing, pruritus, anaphylaxis, ↑Eos; *Darier Sign*: erythema/urticaria when rubbing skin. Tx: no cure, treat sx; hydroxyurea, interferon-α; c-kit inhibitor Masitinib. Epi available for anaphylaxis. H1- and H2-block for systemic sx.
- **Hypereosinophilic syndrome**: eosinophilia (>1500) w/o other etiology; Tx: steroids, imatinib if FIP1L1–PDGFRA fusion gene, mepolizumab, HSCT. See *Hematology: Eosinophilia*.
- **Hemophagocytic lymphohistiocytosis (HLH)**: "cytokine storm" syndrome, 1° or 2° (infectious, inflammatory, neoplastic – esp. lymphoma); Dx: pathologic mutation or 5+: fever, cytopenia, splenomegaly, ↑TG, ↑ferritin, ↓NK cells, ↑CD25, hemophagocytosis in BM/Spleen/LNs. H-score for prob. Sx: fever, HSM, rash, sepsis; Tx: depends on etiology. HLH-94 protocol (dexamethasone/etoposide then Cyclosporine A +/- IT MTX if CNS involvement), survival ~2 mo w/o therapy. Also see: *Anemia & Pancytopenia*.

TERMINOLOGY

- One-liners include: underlying malignancy; **day since transplant** (transplant day = day 0**,** day before = day -1, day after = day +1); **conditioning regimen** (myeloablative vs reduced-intensity/non-myeloablative); **autologous** vs. **allogeneic** transplant; **donor type** (matched related/unrelated, haploidentical) and **source** (bone marrow, peripheral blood stem cells, cord blood); **GVHD prophylaxis** regimen, and include day 0
- Example one-liner: "35M w/ AML (FLT3-mutated) who is now day +4 from his **myeloablative** (flu/mel) matched related donor (**MRD**) peripheral blood stem-cell transplant (**PBSCT**) with tacrolimus/methotrexate GVHD prophylaxis (day 0 = 1/1/19)."

	Allogeneic Transplant	Autologous Transplant
Definition	Transplant of **non-self (donor)** stem cells	Transplant of **self (patient)** stem cells
Goals	**Reconstitute hematopoiesis after high-dose chemo** *and* **graft-versus-tumor (GVT) effect** to kill high-risk disease or treat profound marrow failure. *Always* curative intent	**Reconstitute hematopoesis after high-dose chemo** to kill all cells in BM (tumor/normal). Intent is mostly curative except for myeloma (goal deep remission)
Indications	High-risk **AML** (40-60% 5YS), **ALL** (40-50% 5YS), **MDS** (45% 5YS), high-risk **myelofibrosis**, TKI-resistant **CML**, **indolent relapsed lymphomas**, **aplastic anemia,** thalassemia, sickle cell dz, primary immunodeficiency (SCID), inborn errors of metab.	**1st relapsed lymphomas** (40-50% 5YS), **myeloma** (35% 5YS); relapsed **Waldenström**, **AL amyloidosis**, select solid tumors (germ cell, neuroblastoma, Ewing sarcoma, breast), autoimmune dz (MS, SS, Crohn, SLE)
Source of cells	Traditionally **BM**, now more commonly **PBSC**. Umbilical cord blood also used (delays engraftment)	Usually peripheral blood stem cells **(PBSC)** – less invasive, more rapid engraftment than BM
Timeline overview (see below for details)	Donor HLA matching → **mobilize and harvest** donor cells → **conditioning** with chemo ± RT to eradicate disease → **transplant** → **engraftment** (count recovery) → monitor for infectious, transplant, and graft-versus-host (**GVHD**) complications	**Mobilize and harvest** cells from **self** → **conditioning** with chemo ± RT to eradicate disease → **transplant** → **engraftment** (count recovery) → monitor for infectious & transplant-related complications
Time to engraftment	14-28 days (time for CB > BM > PBSC)	7-10 days
Graft-versus-host disease (GVHD)	**Yes**, skin, liver, GI most commonly affected. ***Acute*** (w/in 6 mo, peri-transplant mortality) ***Chronic*** (>3 mo, morbidity/mortality mo/yrs later)	No
Graft-versus-tumor (GVT) effect	**Yes** (*therapeutic mechanism* – goal for donor T cells to engraft and attack host tumor cells)	No
Immunosupression	**Yes** (sometimes for 1-2 years)	No

TIMELINE (NEJM 2006;354:1813)

(1) Mobilization and harvest of stem cells: few weeks prior to transplant admission
- Stem cells mobilized using G-CSF ± chemotherapy ± plerixafor (CXCR4 inhibitor)

(2) Conditioning: day **-8 to -3**; varies based on conditioning regimen and donor type (Blood 2014;124:344)
- **Goal**: (i) eradicate/debulk tumor (ii) produce adequate immunosuppression to allow donor cell engraftment
- **Types**: myeloablative, reduced-intensity/nonmyelablative regimens of chemotherapy / radiation

(3) Transplantation: day **0**, *infusion of stem cells*

(4) Engraftment (count recovery): day **+7** to **+28** varies based on stem cell source
- Defined as persistent ANC > 500 & Plt > 100k after nadir (nadir occurs 3-6d after conditioning)
- **G-CSF** (neupogen/filgrastim) accelerates neutrophil engraftment by a few days: **10 mcg/kg/d** (Day +1 until ANC > 500)
- Transfusions (irradiated & leukoreduced), **Hct>25, Plt>10K** (>50K if bleeding), attending-dependent
  - Check post-transfusion CBC in 15-60 min

ALLOGENEIC STEM CELL TRANSPLANT: SPECIAL CONSIDERATIONS

- **Donor types**: matched to pt by HLA typing to **minimize GVHD**; matching at alleles **A, B, C, DR, DQ**
  - **Matched-related donor (MRD)**: preferred, compatible siblings, matched at 10/10 HLA alleles
  - **Matched-unrelated donor (MUD)**: common, NMDP database, matched at 8-9/10 HLA alleles
  - **Haploidentical**: any parent/sibling/child, match at 5/10 HLA alleles, ↑ GVHD (Blood Rev 2015;29:63)

Stem Cell Source	Harvest	Engraft	GVHD Risk	Notes
Bone marrow (BM)	Aspirated from iliac crest	18-21d	Reference	No longer favored despite lower GvHD risk, due to higher graft failure rate than PBSC
Peripheral blood stem cells (PBSC)	Mobilization and peripheral aphersis	12-15d	Higher risk	Preferred source due to faster engraftment and improved graft versus tumor effect
Cord blood (CB) (Blood 2013;122:491)	Immature SC from umbilical cord at delivery	28d (most variable)	Lower risk	↑ txp-mortality compared to MUD (similar DFS/OS) Allows for more HLA disparity

- **Conditioning (preparative) regimens**: determined by underlying condition, disease status, performance status/comorbidity
  - **Agents**: chemo (ex. alkylating agents - busulfan, cyclophosphamide, melphalan) ± total body irradiation ± mAb
  - **Myeloablative conditioning**: complete disease eradication & ablation of host BM/immune cells
    - Used for young healthy patients, with **MRD** or **no CR**; ↑ toxicity, ↑ immunosuppr, ↑ txp-mortality, ↓ relapse
  - **Reduced intensity conditioning** (**RIC**): tumor debulking & immunosuppress enough to allow engraftment
    - Permits transplant in elderly w/ co-morbidities; ↓ toxicity, ↓ txp-mortality, ↑ relapse, ↓ GVHD
    - Result is mixed chimerism: host and donor hematopoiesis coexists – rely on **Graft vs. Tumor** effect for cure
- **GVHD PPX**: day **-3 to indefinite (tapered after months to years)**, *goal is to prevent graft rejection & acute/chronic GVHD*
  - **Immunosuppression regimens**: combined Tacrolimus/Methotrexate or Tacrolimus/Sirolimus most common
  - **T-cell depletion regimens**: (ATG, decreased T-cell dose) no longer favored; ↓ chronic GVHD but no effect on OS

Immunosuppressant	Mechanism	Dosing	Toxicities
Tacrolimus (FK506)	Calcineurin inhibitor	Trough goal: 5-10 ug/L	AKI, ↑K, ↓Mg, ↑LFTs, N/V, TMA, tremor, ↑DM risk
Sirolimus (Rapamycin)	mTOR inhibitor	Trough goal: 3-12 ug/L	AKI, Sinusoidal obstruction syndrome (SOS), leukopenia, TMA, HLD, cytopenias
Methorexate (MTX)	Anti-metabolite (inhibits thymidine)	Given on day +1,3,6,11 w cyclosporine or tacrolimus	**Mucositis**, myelosuppression, hepatotoxicity, AKI
Mycophenolate (MMF/Cellcept)	Anti-metabolite (inhibits purines)	N/A	Myelosuppression, N/V/D
Post-transplant cyclophosphamide (PTCy)	Kills early alloreactive T-cells	Given days +3 and +4, particularly for haploidentical	

INFECTIOUS COMPLICATIONS: 2/2 chemo-related pancytopenia & immunosuppression (ASBMT/IDSA Recommendations)

- **Infectious PPX**: *items with asterisks have well-established benefit and are employed at all institutions*
  - **Bacterial**: cipro 500 BID or levofloxacin 500 QD (Day -1 to ANC > 500)
  - **Viral (HSV/VZV)***: **acyclovir 400 TID/800 BID** or famciclovir 500 BID (Day -1 to +365 [auto]; 2 yrs min & until off IS [allo])
  - **Fungal***: **fluconazole 400 QD** or vori 200 BID or posaconazole 200 TID (Day -1 to ANC>500 [auto], until 3-6 mo [allo])
  - **PCP/Toxo***: **Bactrim DS QD** (start after engraftment as outpatient for 6 months [auto], >1 year or off IS [allo])
  - **CMV***: no ppx, if CMV+ pre-emptive treatment with IV ganciclovir or PO valganciclovir (Day -1 to +100)
    - **Letermovir** is a novel anti-CMV drug approved for use in high-risk allo-HCT patients
- **Timeline**:

	Day 0-30 Pre-Engraftment	Day 30-90 Early Post-Engraftment	Day 90+ Late Post-Engraftment
Immune Defect	Neutropenic, mucositis, lines Acute GvHD	Poor cellular immunity Acute GvHD	Poor cellular and humoral immunity Chronic GvHD
Bacterial	GPCs & **GNRs** (F&N) Neutropenic enterocolitis (**typhlitis**)	GPCs & GNRs	**Encapsulated bacteria** (SHiN) Nocardia
Viral	Resp/enteral (adeno, flu, RSV, para) HSV	Resp/enteral (adeno, flu, RSV, para) EBV (risk of PTLD), CMV HHV6 (screen for in cord blood tx)	Resp/enteral (adeno, flu, RSV, para), EBV (PTLD), VZV, BK (hemorrhagic cystitis), **JC** (PML)
Fungal	Aspergillus, candida	Aspergillus, candida, **PCP**	**Aspergillus, PCP**
Parasitic	-	**Toxo**	Toxo (can mimic PCP PNA)

- **Neutropenic enterocolitis** (**typhlitis**): polymicrobial infxn leading to necrotizing enterocolitis, most often involving cecum
  - Sx: fever, ANC < 500, abdominal pain (often RLQ), n/v, watery/bloody diarrhea
  - Micro: polymicrobial (GPC/GNR/anaerobes/fungal), clostridium septicum a/w fulminant course & high mortality rate
  - Dx: CT (I+/O+) w/ bowel wall thickening, mesenteric stranding, bowel dilatation, mucosal enhancement, pneumatosis
  - Tx: pip/tazo vs. -penem vs. cefepime/flagyl + ***surgery c/s*** + add fungal coverage if persistently febrile > 72h

NON-INFECTIOUS COMPLICATIONS: immune-mediated organ damage, toxic effects of chemo, or immunosuppression

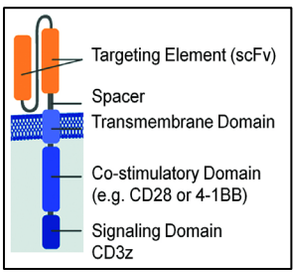
- Non-infectious PPX:
  - *Tumor lysis syndrome*: **allopurinol** 300 QD (admit to Day -1, but much lower risk in SCT than with induction chemo)
  - *Hepatic sinusoidal obstruction syndrome* (SOS): **ursodiol** 300 TID (admit to Day +30)
- Day 0-30: common to have mucositis, nausea/vomiting, alopecia, rash, diarrhea
  - **Nausea/vomiting**: optimal management varies based on timing relative to chemo initiation
    - Immediate (day 0-1): 5-HT_3 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): Ativan, steroids, Marinol (more helpful in younger pts, marijuana users)
  - **Mucositis**: most HSCT patients get some degree of mucositis; duration and severity are worse in allogeneic HSCT. Treatment is focused on pain and caloric intake.

  - Pain: topical/IV opiates; low threshold for PCA
  - Nutrition: TPN initiated if PO intake impaired by mucositis, and expected to continue for ≥1 week
  - Palifermin (recombinant keratinocyte growth factor): can reduce duration, severity of mucositis
- **Liver – sinusoidal obstruction syndrome (SOS)** (previously **veno-occlusive disease**):
  - Cause: direct cytotoxic injury to hepatic venules leading to hypercoaguable state and microthrombi
  - Sx: **RUQ pain**, **jaundice**, ascites/edema; ↑ALT/AST/**TBili**, ↑INR/Cr (if acute liver failure or HRS)
  - Dx: **doppler U/S** 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** 300 TID
  - Tx: defibrotide
- **Pulm – idiopathic interstitial pneumonitis/diffuse alveolar hemorrhage (DAH)**:
  - Cause: direct cytotoxic injury to alveoli
  - 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
- **Heme – graft failure**:
  - Primary: persistent neutropenia without engraftment
  - Secondary: delayed pancytopenia after initial engraftment (immune or infectious)
- **Engraftment syndrome**: sudden PMN recovery causing cytokine storm and vascular leak
  - Sx: **fever**, **rash**, **weight gain**, **bone pain**; if severe – pulmonary edema, ↑ LFTs, AKI, seizures
  - DDx: infection, drug reaction, acute GVHD (dx of exclusion)
  - Tx: high-dose IV **steroids** (*discuss with attending prior to initiation of steroids!)

- Day 30+
  - **Acute GVHD**: ~40% in MRD, ~60% in MUD (cellular immune response, T_H1 cell-mediated) (NEJM 2017;377:2167)
    - Risk factors: ↑ HLA mismatch, ↑ age, female donor/male recipient, TBI-myeloablation, PBSC > BM > CB
    - Cause: donor T-cell recognizes and attacks recipient native cells (usually **day 0 to +100**, but can be later)
    - S/Sx: **skin** (rash, graded by biopsy findings, % body surface, desquamation), **liver** (cholestatic injury, graded by bilirubin), **GI** (diarrhea, graded by volume of diarrhea/day)
    - DDx: skin (viral, drug, engraftment), liver (viral, drug, SOS, TPN), GI (C. diff, CMV, adeno, GNR, typhlitis, drug)
    - Tx: Grade I (topical), II-IV (**IV methylpred 1-2 mg/kg x 5d**; if severe or steroid-refractory: MMF, etanercept, ruxolitinib (Jakafi; NEJM 2020;382:1800), antithymocyte globulin (ATG); many other agents proposed. Consider trial enrollment.
  - **Chronic GVHD**: 30-70% of patients s/p allo-HSCT (humoral immune response, T_H2 cell-mediated) (NEJM 2017;377:2565)
    - Cause: both donor T-cell & B-cell mediated attacks on recipient **after day +100**
    - Risk factors: **prior acute GVHD**, HLA mismatch, ↑ age, PBSC > BM
    - Sx: resembles **scleroderma** (sicca, dysphagia, arthritis, skin tightening, malar rash), lung (obliterative bronchiolitis), liver (cholestasis), cytopenias/immunodeficiency; any organ system can be affected
    - Tx: **steroid** +/- broad immunosuppression, **photopheresis** (ECP) for skin; novel agents including ruxolitinib (Jakafi), ibrutinib, rituximab have been shown to be effective in steroid-resistant disease
  - **PTLD** (post-transplant lymphoproliferative disease): ~1% in allo-SCT; median **day +70-90** (NEJM 2018;378:549)
    - Cause: IS leads to EBV reactivation (dormant in B cells) & clonal B cell proliferation (usually donor-derived)
    - Risk factors: T-cell depleted donor graft, treatment with ATG, HLA-mismatch, cord blood transplant
    - Dx: plasma EBV DNA monitoring can raise suspicion for PTLD (thousands of copies/microL compared with hundreds); biopsy with immunophenotyping for true dx
    - Tx: **reduce IS**, anti-viral, rituximab-based chemo (if systemic) vs. surgery/RT (if localized)

QUICK REFERENCE (Day -8 conditioning to Day +30 engraftment)			
Monitor S/Sx:	**DDx fever:**	**DDx abdominal pain/ascites:**	**DDx dyspnea/hypoxia:**
• **Chemo toxicity**: mucositis, N/V/D, S/Sx of infection • **GVHD**: rash, jaundice, diarrhea (24h volume) • **SOS**: RUQ pain, jaundice, ascites, edema • **Engraftment syndrome**: fever, dyspnea, edema	• Infection (bacterial, viral, fungal, parasitic) • Drug rxn • Engraftment (d7-9 for auto, d14-21 for allo) • Tumor (initial lysis & cytokine release) • Immobility (Atelectasis, aspiration, DVT/PE) • GVHD	• Neutropenic enterocolitis • Colitis: C. Diff, CMV • SOS • GVHD • Obstruction/ileus/ constipation	• Existing dz: CHF, COPD, asthma • PNA: bacterial, fungal, aspiration • Volume (often on mIVF with chemo) • Drug: chemo-induced lung injury or cardiotoxicity • Engraftment (pulmonary edema from capillary leak) • Pneumonitis • Alveolar hemorrhage • PE, TRALI, GVHD

MECHANISM OF ACTION (NEJM 2018;379:64)



- **Chimeric antigen receptor T cells (CAR-T cells)**: type of autologous therapy; T lymphocytes collected from the patient, genetically modified with a gene encoding a chimeric antigen receptor (CAR) that directs the T-cells against a selected antigen on the patient's tumor
- **CAR**: transmembrane engineered protein consisting of extracellular immunoglobulin (antibody)-derived domains (ScFv), which target and bind a tumor antigen (i.e. CD19), fused to an intracellular T-cell receptor domain (CD3z) and a costimulatory domain that signal for T-cell activation (see figure)

FDA-APPROVED THERAPIES: anti-CD19 cell-based therapies

- **Yescarta** (axicabtagene ciloleucel; aka axi-cel)
  - Aggressive, refractory adult B-cell lymphoma: ZUMA-1, Phase II trial, 54% complete response (NEJM 2017;377:2531)
- **Kymriah** (tisagenleucel)
  - Relapsed/refractory B-ALL age <25y: ELIANA, Phase II: NEJM 2018;378:439. Adult phase I long-term f/u: NEJM 2018;378:449
  - Adults with relapsed/refractory DLBCL: JULIET- Phase II, 52% OR (40% CR), 65% w/o relapse at 1y (NEJM 2019;380:45)
- Other CAR-Ts for hematologic malignancies (CD19, CD123, etc.) and other antigen/solid malignancies under investigation: BCMA/multiple myeloma (NEJM 2019;380:1726), IL13Rα2/GBM (NEJM 2016;375:2561), others (Front Immunol 2019;10:128)
- Also under investigation: combination of immune checkpoint blockade (anti-PD, anti-PD-L1) with CAR-T (Cancer Cell 2019;36:471)

TOXICITIES (NCCN 1.2020 Guidelines; Nat Rev Clin Oncol 2018;15:47)

- **Cytokine-release syndrome (CRS)**
  - Most common toxicity. Typically 2-3d post-infusion, lasts 7-8d. Fulminant cytokine release (IL-2, sIL2R, IFNγ, IL-6, GM-CSF) triggered by CAR-T engagement of antigen and T cell proliferation. ↑risk in bulky disease and specific constructs.
  - **Signs/Sx**: fever, ↓BP, ↑HR, ↓pO_2, malaise, anorexia, myalgia. Can affect any organ (CV, lung, GI/liver, renal, CNS) w/ arrhythmia, ARF, capillary leak, HLH/MAS.
  - **Diagnosis**: monitor for 14 days post infusion (inpt or possibly close outpt); vitals, basic labs, ferritin, coags, CRP, TLS labs. When suspect: admit, tele, r/o infection.
  - **Therapy**: if plan to treat CRS with steroids or anti-IL6, **first get clear approval by the treating attending**
    - Broad-spectrum abx if fever or neutropenic until r/o infxn
    - MGH: *tocilizumab* (anti-IL6R) 8 mg/kg IV over 1h (max 800 mg); siltuximab (anti-IL6) also exists; 2nd line: steroids

	CRS Grade	Therapy
1	Fever	If >3 days, consider tx as in grade 2.
2	Fever w/: hypotension not requiring pressors or hypoxemia on NC	Tocilizumab q8h PRN up to x4. Add steroids per below if still ↓BP after 1-2 doses. Fluids.
3	Fever w/: ↓BP requiring pressors or ↓pO_2 requiring HFNC / face mask / Venturi / NRB	Tocilizumab as above. Dexamethasone 10 mg IV q6h (or equiv.).
4	Fever w/: ↓BP requiring multiple pressors or ↓pO_2 requiring NIPPV / MV	Tocilizumab + dex as above. If refractory, consider methylpred 1g/d IV x 3d w/ taper

- **CAR-T-cell-related encephalopathy syndrome (CRES)**
  - Etiology is unclear; passive cytokine diffusion into brain (IL-6, IL-15 a/w neurotoxicity) vs. CAR-T trafficking into CNS
  - **Timing**: typical onset 4-10d post-infusion, duration 14-17d, variable. Can be concurrent w/ CRS or after (more severe)
  - **S/Sx**: toxic encephalopathy. See ICE tool and ICANS grade.
  - **Diagnosis**: neuro consult, ICANS (or CARTOX-10) score. If ≥ grade 3: MRI brain w/wo contrast + EEG ± LP. Funduscopic exam.
  - **Therapy**: *Ppx*: if CAR-T known to cause neurotoxicity, start seizure ppx on day of infusion (levetiracetam 500-750 mg q12h for 30d). Tx per chart.
  - **Prognosis**: generally reversible, rare fatal cases

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool	
Max score: 10	AAOx3 (4 pts), naming x3 (3 pts), follows commands (1 pt), writes sentence (1 pt), serial 10s from 100 (1 pt)

ASBMT Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grade		Treatment (if CRS, add tocilizumab)
Grade 1	ICE = 7-9	Supportive
Grade 2	ICE= 3-6, or does not awaken spontaneously	Dex 10 mg IV x1. If worsens, advance.
Grade 3	ICE = 0-2, or awakens only to tactile stimulus, or focal edema on neuroimaging	Dex 10 mg IV q6h PRN or methylpred 1 mg/kg IV q12h.
Grade 4	ICE = 0, difficult to arouse, prolonged seizure >5m or w/o return to b/l, or deep focal motor weakness (e.g. paresis), or diffuse cerebral edema or ↑ICP	Methylprednisolone IV 1g/d x 3d or equivalent w/ taper.

- **CAR-T-cell-related hemophagocytic lymphohistiocytosis (HLH) / macrophage activation syndrome (MAS)**
  - Profound systemic inflammatory state characterized by cytotoxic T cell hyperactivation (IFNγ) → macrophage activation (IL-6), lymphohistiocytic tissue infiltration, and multiorgan failure; develops in ~1% of patients treated with CAR-T. S/Sx: fever, cytopenias, multiorgan dysfunction
  - **Criteria for considering**: rapidly rising ferritin >5K with cytopenias in context of CRS, especially if any: oliguria or ↑Cr >4 or 3x b/l, or pulmonary edema, or ↑AST or ALT 5x ULN, or ↑Tbili 1.5x ULN; hemophagocytosis in bone marrow or other organs.
  - **Dx**: labs resemble HLH. CBC w/ diff, ferritin, sIL2R, LDH, fibrinogen, TGs, LFTs, Cr. BMBx rarely critical (low Sn/Sp).
  - **Tx**: high mortality, do not delay diagnosis, escalate therapy aggressively. Manage as per CRS with addition of steroids. If no improvement in 48h, consider etoposide or intrathecal cytarabine for neurotoxicity.
    See Anemia & Pancytopenia *for further details on HLH.*

Organ	Risk factors/screening	Staging/diagnostics	Treatment
Prostate ▪ Adenocarcinoma (95%) ▪ Transitional, basal cell, intraductal carcinomas; neuroendocrine, carcinosarcoma, lymphoma, stromal sarcoma (~5%) Androgen deprivation therapy (ADT): ▪ *Orchiectomy* ▪ *LHRH agonist*: goserelin, histrelin, leuprolide, triptorelin ▪ *LHRH antagonist*: degarelix ▪ *Androgen R blocker* (+ LHRH agonist): enzalutamide, darolutamide, flutamide ▪ *Androgen synthesis inhib*: abiraterone (+ prednisone)	**Risk factors**: ▪ Age, AA race, genetic factors (BRCA1/2 and family history), smoking **Screening with PSA** (JAMA 2018;319:1901): ▪ 55-69: individualized risk-benefit discussion ▪ 70 and above: no testing	**Staging**: ▪ AJCC Stages I- IV: TNM, PSA and Grade Group ▪ Grade Group: Gleason Score (GS) and Pattern ▪ NCCN risk: PSA, grade, TNM, Biopsy. Use with life expectancy to guide treatment. **After diagnosis**: ▪ TRUS, MRI, biomarkers, evaluate for metastases (CT, radio-nucleotide bone scan) **Germline testing**: ▪ High/very high NCCN risk ▪ Any risk level if positive FHx or intraductal histology	**Low risk** (T1c/T1-T2a + Gleason score ≤6 + PSA ≤10) (JCO 2015;33:3379, NEJM 2016;375:1415): active surveillance (PSA, DRE +/- Bx) vs. external beam radiation therapy (EBRT) +/- brachytherapy (BT) vs. radical prostatectomy (RP) +/- EBRT +/- ADT **Intermediate risk** (≥1 risk factor: T2b-T2c, PSA 10-20, GS 7) (JNCCN 2019;17:479): ▪ **Favorable** (1 RF, <50% Bx cores positive): above + RP +/- pelvic LND +/- EBRT +/- ADT ▪ **Unfavorable** (≥1 RF or >50% cores +): EBRT & ADT or EBRT & BT +/- ADT, RP +/- pelvic lymph node dissection (PLND) +/- EBRT +/- ADT **High risk** (T3a/T3b-T4b or GS 8-10 or PSA >20): EBRT & ADT, ERBT & brachy & ADT, or RP with extended PLND +/- EBRT +/- ADT **Metastatic/recurrent** (Lancet 2016;387:1163, NEJM 2015;373:737, NEJM 2010;363:411): ▪ Castration-sensitive: ADT +/- abiraterone/ pred vs docetaxel vs apalutamide v. enzalut. v. EBRT ▪ Castration-resistant: ADT (goal testo <50ng/dL) and doxcetaxel (chemo naïve) or cabazitaxel (dox exposed) v. mitoxantrone + pred v. abiraterone/pred v. enzalut. vs sipuleucel-T. Bone mets: radium-223 or denosumab/zoledronic acid. MSI-H/dMMR: pembrolizumab. (NCCN Guidelines v. 4.2019)
Breast ▪ Infiltr. ductal (76%) ▪ Invas. lobular (8%) ▪ Ductal/lobular (7%) ▪ Mucinous (2%) ▪ Tubular (1.5%) ▪ Medullary (1%) ▪ Papillary (1%) ▪ TCH(P): docetaxel, carboplatin, trastuzumab +/- pertuzumab ▪ AC-TH(P): doxorubicin/ cyclophosphamide → weekly paclitaxel + trastuz +/- pertuz ▪ Aromatase inh (AI): anastrozole, letrozole,exemestane	**Risk factors**: ▪ Age, genetics (BRCA1/2), FHx, obesity after menopause, menopause >55, chest RT, 1st birth >30, nulliparity, HRT, menarche <13y, ETOH, benign breast disease, tobacco **Screening**: ▪ USPTF: q2y mam 50-74 ▪ NCCN: q1y mam > 40 or 10y before earliest FHx if > 30 or 10y after RT if > 30 ▪ ACOG: q1-2y mam; offer 40-50, recommend 50-75	**Staging**: ▪ AJCC Stage I-IV: *pathologic stage* (TNM) + *clinical stage*: ER/PR, Her2; Recurrence score (RS): OncotypeDx gene panel for Her2(-), HR+, LN-, >0.5cm **Diagnostics**: ▪ Dx mam (Bi-RADS), US, FNA or core Bx (> excisional), breast MRI if young or to assess extent (good Sn, but Sp 72%)	**Early stage** (I, IIA, IIB through T2N1): ▪ Breast Conserving Surgery + RT vs mastectomy +/- RT & HR tx & HER2 tx (≥1cm) & chemo if high risk **Locally advanced** (Stage IIB T3N0, IIA-IIIC): ▪ Surg + RT w/ neoadj +/- adj chemo & HR/HER2 Tx **(Neo)adjuvant therapy**: ▪ **ER/PR+, HER2-** (NEJM 2015;372:436, Lancet 2013:301;805): tamoxifen or AI (no AI in premenopausal) +/- ovarian suppression (OS) if high risk x2-5 yrs f/b 5 yrs endo rx. Chemo: AC-T or TC (give for most LN+ & LN- if RS>16, <50yo) ▪ **HER2+**: TCH(P) or ACTH(P) + ER/PR rx if HR+ ▪ **Triple Neg** (NEJM 2017:372;2147): adjuvant cape **Metastatic/recurrent** (Stage IV): ▪ **ER+**: As above +/- fulvestrant (ER antagonist) +/- CDK4/6 inhib or everolimus (mTOR inhib) ▪ **HER2+**: THP (1st line). Or: T-DM1 (trastuzumab-drug conjugate), trastuzumab+lapatinib ▪ **BRCA mutation** (NEJM 2017;377:523, NEJM 2018;379:753): olaparib or talazoparib, platinum-based chemo ▪ **Triple neg** (NEJM 2018;379:2108): atezolizumab + nab-paclitaxel. (NCCN Guidelines v.3.2020)
Pancreas ▪ Exocr./adeno (94%) ▪ Endocrine (6%) ▪ FOLFIRINOX: leucovorin, 5-FU, irinotecan, oxaliplatin ▪ ChemoRT: capecitabine or CI 5-FU + RT	**Risk factors**: ▪ Tobacco, EtOH, obesity, DM, chronic pancreatitis, age, male, FHx, HNPCC, BRCA1/2	**Staging**: ▪ AJC Stage I-IV: TNM system **Diagnostics**: ▪ CT C/A/P pancreas, EUS+Bx, MRCP +/- ERCP, CA19-9, germline testing +tumor gene profile ▪ Bx b/f neoadj tx & locally adv dz. Bx met site in metastatic dx.	▪ **Resectable**: surgery +/- neoadj (FOLFIRINOX vs. gem/abraxane) + adj (FOLFIRINOX vs. gem/cape) +/- chemoRT. Resect depending on vasc. involv. ▪ **Borderline**: surg + neoadj +/- adj +/- chemoRT ▪ **Locally advanced**: FOLFIRINOX v. gem/abraxane v. chemoRT v. stereotactic body radiation (SBRT) ▪ **Metastatic** (NEJM 2011;364:1817): 1st line: FOLFIRINOX v. gemcitabine/abraxane. 2nd line: FOLFIRI v. FOLFOX v. Gem v. Cape +/- pall RT ▪ **BRCA**: FOLFIRINOX or gemcitabine/cisplatin (only for BRCA) +/- chemoRT. Consider olaparib. ▪ **NTRK fusions**: larotrectinib, entrectinib ▪ **MSI-H/dMMR** (NEJM 2015;372:2509): consider pembrolizumab (NCCN Guidelines v.1.2020)

Colon and rectum ▪ Adenoca (98%) ▪ Neuroendocrine ▪ Lymphoma ▪ FOLFOX: oxaliplatin, leucovorin, 5-FU ▪ CAPEOX: capecitabine, oxaliplatin ▪ FOLFIRI: irinotecan, leucovorin, 5-FU ▪ FOLFOXIRI: irinotecan, oxaliplatin, leucovorin, fluorouracil ▪ EGFR inhibitor: cetuximab, panitumumab	**Risk factors** (JAMA Oncol 2018;4:e173695): ▪ Obesity, inactivity, tobacco, red/processed meat, ETOH, adenom. polyps, IBD, FHx, genetic (FAP, HNPCC), age, AA ▪ Increased death w/ R-sided (BRAF/KRAS mut) **Protective factors**: ▪ ASA for 50-59 yo and ≥10% CVD risk (Annals 2016;164:814) ▪ VitD data inconclusive **Screening**: ▪ Colo, flex sig, CT colo, FIT, FOEBT for 50-75yo. Per ACS: 45-75yo.	**Staging**: ▪ AJCC stage I-IV: TNM system **Diagnostics**: ▪ Colonoscopy, CT C/A/P, CEA ▪ Pelvic MRI or endorectal US for rectal CA ▪ Genetic testing: MSI/MMR status in all, K/N-RAS, BRAF status in metastatic	**Colon**: **I**: surgery + observation **II**: surgery +/- adj 5-FU/leucovorin v capecitabine. Add oxali if T4 or high-risk. Neoadj for T4b. No adj for MSI-H/dMMR (Ann Surg Onc 2011;22:630) **III**: surg + FOLFOX/CAPEOX. Neoadj if bulky nodal **IV**: liver/lung met resection* (+/- neoadj) + FOLFOX v CAPEOX v FOLFIRI v FOLFOXIRI +/- bevacizumab ▪ **KRAS/NRAS/BRAF Wt + left-sided tumors (IV)**: FOLFOX/FOLFIRI + EGFR inhibitor ▪ **BRAF V600E**: encorafenib + EGFR inhibitor ▪ **MSI-H/dMMR** (NEJM 2015;372:2509): immunotherapy (pembrolizumab, nivolumab or nivolumab + ipilimumab) **Rectal**: **(I)**: low anterior (LAR) v abdominoperineal resection (APR) +/- neo v adj chemoRT. Chemo as in colon cancer. **(II-III)**: resect + neo +/- adj chemoRT (NCCN Guidelines v.2.2020) *limited mets only
Lung ▪ NSCLC (84%): adeno, large>SCC ▪ SCLC (13%) ▪ ChemoRT: cisplatin/ etoposide, cisplatin/ vinblastine, carboplatin/ pemetrexed, cisplatin/pemetrexed, paclitaxel/carboplatin ▪ EGFR inhibitors: osimertinib (1st line), erlotinib, afatinib, gefitinib, dacomitinib *T790MΔ assoc w/ TKI resistance. ▪ ALK/ROS1 inhibitors: alectinib (1st line), crizotinib, ceritinib, brigatinib, lorlatinib ▪ BRAF/MEK inhibitors: dabrafenib/trametinib ▪ NTRK inhibitors: larotrectinib, entrectinib	**Risk factors** (Nat Rev Ca 2007;10:778): ▪ Tobacco, asbestos, occup. exposures, lung fibrosis, age, male, AA, SE status ▪ 25% lung cancer worldwide not due to smoking (50% of women with NSCLC are never smokers, 60-80% in Asian populations are women)→ more likely single mutation (ALK, EGFR, ROS1) **Screening** (Annals 2014;160:330): ▪ Annual low dose CT chest for pts 55-80yo with ≥30 pack-yr hx and smoking within last 15 yrs	**Staging**: ▪ NSCLC stage I-IV: TNM system ▪ SCLC staged with TNM system as limited (St I-III) vs. extensive (St IV and T3-T4 with extensive nodules). Limited can be tx with RT. **Diagnostics**: ▪ CT chest/upper abd, PET/CT, brain MRI ▪ Evaluate pathologic LNs with biopsy (EUS, EBUS, mediastinotomy, mediastinoscopy, thoracoscopy) ▪ Molecular testing for NSCLC (EGFR, ALK, ROS1, PD-L1) before starting systemic therapy	**NSCLC**: (NCCN Guidelines 1.2020) ▪ **IA**: surgery vs. definitive RT ▪ **IB-IIIA**: surgery if able +/- adjuv chemoRT. ▪ **IIB/IIIA unresectable, IIIB**: definitive chemoRT + adjuvant Durvalumab (NEJM 2018;379:2342) ▪ **IV**: targeted, immunotx, and systemic tx ▪ **Targeted inhibitors**: EGFR (EGFR sensitizing mut); ALK/ROS1 (ALK v ROS1 rearrangement), BRAF/MEK (BRAF V600E), TRK (NTRK fusion) ▪ **Immunotherapy (if no driver mutation)** (Lancet 2016;387:1540, NEJM 2018;378:2078): pembrolizumab (≥50% PD-L1). Pembro + chemo (1st line *regardless of tumor PD-L1 level*). Alternative: ipi/nivo, atezolizumab+platinum+taxane ▪ **Initial**: non SCC: pembro/platinum agent/ pemetrexed. SCC: pembro/carbo/paclitaxel. If immunothx c/i: cisplatin v carboplatin + docetaxel v pemetrexed v gemcitabine v etoposide **SCLC**: (NCCN Guidelines v.3.2020) ▪ **Limited**: surgery + chemo +/- mediastinal RT ▪ **Extensive** (NEJM 2018;379;2220): chemo & atezolizumab vs durvalumab +/- RT for lobar obstruction, SVC synd, bone/brain mets ▪ **Chemo**: platinum agents, etoposide, irinotecan
Melanoma ▪ Superficial spreading (75%) ▪ Nodular (15-30%) ▪ Lentigo maligna (10-15%) ▪ Acral lentiginous (<5%) ▪ Amelanotic (2-10%) ▪ Ocular (5%) BRAF/MEK inhibs: dabrafenib & trametinib, vemurafenib & cobimetinib, encorafenib & binimetinib (approved 6/2018)	**Risk factors**: ▪ Sun exposure (UVB > UVA), atypical nevi, high nevi count, family or personal hx, immuno-suppression ▪ Genes mutated in familial melanoma: CDKN2A, CKD4, POT1. Most common somatic mutations are: BRAF 40-50%, NRAS 15-20%, cKit 10-15% (acral). Genetic testing recommended for St III-IV disease.	**Staging**: ▪ AJCC Stage I-IV: TNM system ▪ For classification of primary tumor (T) AJCC 8th ed. uses Breslow thickness and ulceration but no longer mitotic rate. M stages subdivided by met site and presence/absence of LDH elevation. ▪ Serum LDH is an important prognostic factor used in active surveillance and treatment	**Surgical excision**: ▪ Margins (0.5-2cm) based on tumor thickness +/- sentinel LN bx vs. complete regional LN dissection **Adjuvant treatment or for metastatic disease**: ▪ **Immunotherapy** (NEJM 2015;373:23, NEJM 2015;372:2521): anti-PD-1 (pembrolizumab or nivolumab); ipilimumab if prior anti-PD1; nivolumab + ipilimumab (NEJM 2019;381:1535) ▪ **Targeted tx** (NEJM 2014;371:1867): BRAF/MEK inhibitor combination (*BRAF* V600 activating mutations), binimetinib for NRAS mutated after prior ICI, KIT inhibitor imatinib (*KIT*-mutant tumors) ▪ **Radiation**: considered with symptomatic localized disease (e.g. brain mets) ▪ **Regional tx**: isolated lib perfusion with melphalan ▪ **Talimogene laherparepvec (T-VEC)** (JCO 2015;33:2780): intralesional injection of HSV→ tumor cell lysis & GM-CSF expression (NCCN Guidelines v.1.2020)

Common Chemotherapy Toxicities

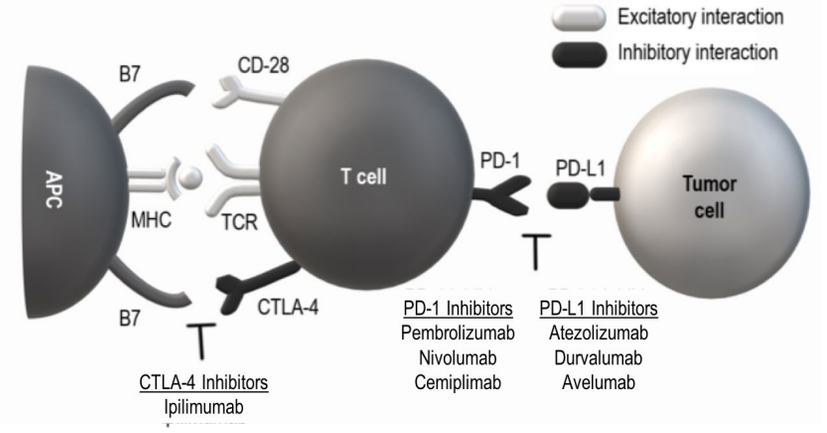
- Severe n/v: any AC combinations (doxo/epi/ida/daunorubicin+ifos/cyclophosphamide), carmustine, dacarbazine, cisplatin, mechlorethamine, streptozocin; HiDAC (AraC), aldesleukin/IFNα, amifostine > 300, ATO, azacitidine, bendamustine, busulfan, clofarabine, dactinomycin, irinotecan, melphalan, methotrexate > 250, temozolomide; refer to NCCN Guidelines for management (NCCN Guidelines v.1.2020)
- Severe BM↓: busulfan, carmustine, cyclophosphamide, dacarbazine, ifosfamide, 5-FU, methotrexate, doxorubicin (daunorobicin), taxotere, taxol, carboplatin, melphalan, fludarabine

Drug	Indications	Toxicities
Anti-Metabolites		
5-Fluorouracil	Breast, colorectal, pancreatic, gastric, esophageal, H&N	**Coronary vasospasm, acute cerebellar ataxia, hand-foot syndrome**, stomatitis, hemorrhage, GI ulcers/bleeding, hiccups, diarrhea, **BM↓**
Capecitabine	Breast, colorectal	**Monitor INR** (if on warfarin), hand-foot syndrome, SJS-TEN, n/v/d, cytopenias (worse with stage IV breast CA), hepatotoxicity
Cytarabine (HiDAC)	AML, ALL, CLL, meningeal leukemia	**Acute cerebellar ataxia,** PRES, BM↓, **chemical conjunctivitis** (Rx dexamethasone eye drops), ↑LFTs, cutaneous tox, hand-foot syndrome
Gemcitabine	Breast, ovarian, NSCLC, pancreas, bladder	**Capillary leak syndrome, PRES, TMA/HUS**, **ARDS**, ↑LFTs, n/v, hematuria
Mercaptopurine	ALL (w MTX), CML	**Biliary cholestasis & hepatocellular necrosis**, BM↓ (consider TPMT SNP testing if severe BM↓), n/v/d
Fludarabine	CLL, NHL, AML	**BM↓,** IS, **autoimmune hemolytic anemia, neurotoxicity**, **fatal pulm toxicity** (when used w/ pentostatin for CLL)
Hydroxyurea	CML, cervical, sickle cell, H&N	**BM↓,** cutaneous tox, n/v/d, ↑LFTs, ↑Cr, ↑BUN
Anti-Folates		
Methotrexate	ALL, breast, H&N, CTCL, SCLC, NSCLC, NHL, osteosarcoma	**BM↓, aplastic anemia**, AKI, ↑LFTs, hepatic fibrosis/cirrhosis, cutaneous tox, IS (PCP), pneumonitis/PF, teratogenic, ulcerative stomatitis/diarrhea, IF
Pemetrexed	Mesothelioma, NSCLC	**BM↓,** desquamating rash, pneumonitis, renal tox
Alkylating Agents (all cause BM↓, infertility & increased risk of MDS/AML)		
Busulfan	HSCT conditioning, CML	**BM↓, sinusoidal obstruction/VOD**, tamponade, ILD, **seizures**, renal tox
Ifosfamide	Testicular, breast, lung, HL, NHL, bone	**Hemorrhagic cystitis**, **encephalopathy**, renal/pulmonary/cardiac tox
Melphalan	MM, ovarian	**BM↓, hypersensitivity, amnesia**, pulmonary fibrosis, mucositis, rash, IF
Carmustine	CNS tumors, HL, NHL, MM	**BM↓, pulm tox** (dose-related), ↑LFTs, renal tox, ocular sx
Cyclophos-phamide	Leukemia, MM, breast, NHL, ovarian, retinoblastoma	**Hemorrhagic cystitis**, renal/cardio tox, **pulm fibrosis, IF,** sinusoidal obstruction/VOD, IS, hypoNa
Dacarbazine	HL, melanoma	**Hepatic necrosis, teratogenic**, hepatic vein thrombosis, ↑↑n/v, BM↓
Cisplatin	Bladder, ovarian, testicular, H&N	**N/v, renal tox, ototoxicity**, neurotoxicity, BM↓, ↑uric acid
Carboplatin	Ovarian, lung, H&N, CNS tumors	N/v, ototoxicity, neurotoxicity, **BM↓** (less nephrotoxic than cisplatin)
Oxaliplatin	Colorectal, pancreatic	N/v, renal/pulm/liver tox, **neurotoxicity**, BM↓, rhabdo, ↑QT, PRES
Antibiotics		
Bleomycin	HL/NHL, testicular, ovarian, H/N	**Late pulm fibrosis**, dermatographia, hyperpigmentation, **Raynaud's**
Mitomycin	Gastric, esoph, anal, bladder, pancreas	**BM↓,** renal/cardiac tox, HUS, interstitial pneumonitis/ARDS, bladder fibrosis
Hormonal Therapy		
Tamoxifen Raloxifene	ER+ breast	**Menopausal sx** (hot flashes, vaginal atrophy/pruritus /bleeding), **VTE** (DVT/PE), **endometrial cancer** (tamoxifen only)
Anas-/Letrozole Exemestane	ER+ breast (post-menopausal)	Sexual dysfunction, bone/joint pain, osteoporosis, premature menopause
Fulvestrant	ER+ breast (post-menopausal)	Sexual dysfunction, bone/joint pain, osteoporosis, injection site reactions
Megestrol	Breast, endometrial	**Teratogenic, ↑weight**, hypogonad, VTE, hot flashes, adrenal suppression
Leuprolide Goserelin	Prostate, breast (goserelin)	**Hypogonadism**, edema, depression, **bone pain**, osteoporosis, transient worsening of prostate CA sx 2/2 **brief testost. surge** (ppx w/ AR inhibitors), seizure, ↑CVD risk
Flutamide Nilutamide	Prostate	**Hot flashes**, **gynecomastia**, ↓libido, n/v/d, muscle atrophy/pain, hepatotoxicity (> w/ F), interstitial pneumonitis, visual changes (N), osteoporosis
Bicaludamide	Prostate	**Hypogonadism**, sexual disfunction, depression, fatigue, **hepatotoxicity**, ILD
Topoisomerase Inhibitors		
Anthracyclines (Dauno/Epi/ Doxorubicin)	Breast, ALL, AML, MM, lung, bladder	**Cardiotoxicity** (DCM, myopericarditis); BM↓, IS, 2nd malignancies, **local tissue necrosis in setting of extravasation**, liver/renal tox, typhlitis, "chemo brain"
Mitoxantrone	Breast, ALL, AML, breast	**Cardiotoxicity** (DCM, myopericarditis); BM↓, IS, n/v
Irinotecan (I) Topotecan(T)	Colorectal (I), SCLC (I,T), cervical (T), ovarian (T)	**BM↓, diarrhea**, late ILD, thrombosis, typhlitis
Etoposide	SCLC, testicular, KS, glioblastoma	BM↓, acute infusion reaction (HoTN), **metallic food taste**, SJS/TEN
Mitotic Inhibitors		
Paclitaxel	Breast, ovarian, NSCLC, KS, H&N	**BM↓, hypersensitivity**, acute infusion reactions, peripheral neuropathy
Docetaxel	Breast, NSCLC, prostate, gastric, H&N	Hepatotoxicity, BM↓, hypersensitivity, fluid retention
Vinblastine	Lymphoma, mycosis fungoides, testicular, KS, Histiocytosis X	**Extravasation**, BM↓, neuropathy, bronchospasm, stomatitis
Vincristine	ALL, CNS, HL, NHL	**Neurotoxic** (deaf, blind, ataxia, **peripheral neuropathy**, areflexia, ileus), MI, SIADH, extravasation, bronchospasm
Monoclonal Antibodies		
Trastuzumab Pertuzumab	Anti-HER2: HER2+ breast cancer	**Cardiotoxicity (↓EF), hypersensitivity, pulm tox,** headaches, diarrhea, URI sxs, extremity pain, teratogenic

Rituximab	Anti-CD20: NHL, CLL	**Hypersensitivity,** cytokine release syndrome, HBV reactivation, PML, renal toxicity
Bevacizumab	Anti-VEGF: cervical, colorectal, GBM, ovarian, RCC, NSCLC	**Perforations** (septal, **GI**), wound dehiscence, nec. fasc., hemorrhage, HTN, eye infection 2/2 endophthalmitis
Cetuximab	Anti-EGFR: colorectal (KRAS wt), H&N	Cardiopulmonary arrest, **hypersensitivity**, angioedema, ILD
Panitumumab	Anti-EGFR: colorectal (KRAS wt)	**Rash, photosensitivity**, n/v/d, hypoMg, ocular sxs, ILD/pulm fibrosis
Immunomodulators		
Aldesleukin Denileukin	Aldesleukin: melanoma, RCC; Denileukin: CTCL	**Capillary leak syndrome, sepsis** (↓PMN chemotaxis), cardiopulmonary disease, CNS toxicity, hypersensitivity, renal insufficiency, autoimmune diseases, **vision loss (denileukin)**
Lena/poma/ thalidomide	MM, MDS (lena)	**Teratogenicity, neutropenia/thrombocytopenia, DVT/PE, MI, stroke,** rash, SJS (lena), hepatotoxicity, peripheral neuropathy, ?2° malignancy
IFN-alpha	Hairy cell leukemia, KS, CML	**Flu-like sx**, ↑LFTs, **fatigue, depression,** HLD, anorexia, cytopenias
ATRA	APL	**Differentiation syndrome**, **hemorrhage, ↑ICP**, xerosis, DIC, teratogenicity
Arsenic	APL	Differentiation Syndrome, **↑QTc,** confusion, n/v/d, respiratory sx
Azacytidine	MDS	**BM↓,** constipation, n/v, renal/liver tox
Decitabine	AML, CML, MDS	**BM↓,** constipation, n/v/d, hyperglycemia, MSK pain, respiratory sx
Tyrosine Kinase Inhibitors (TKIs)		
Imatinib (I), Dasatinib (D)	**BCR-ABL**: Ph+ CML/ALL (I,D), GIST (I,D) , MDS (I), HES/CEL (I)	**Renal toxicity (I) hepatotoxicity, CHF,** edema, DRESS/SJS (I), n/v/d, BM↓, hemorrhage, pleural/pericardial effusion, PAH (D), **↑QTc** (D)
Nilotinib (N) Bosutinib Ponatinib (P)	**BCR-ABL**: Ph+ CML/ALL	**↑QTc**, hepatotoxicity**,** edema, n/v/d, BM↓, hemorrhage, MI (N), **arterial occlusions and VTE** (P), CHF/arrhythmias (P)
Gilteritinib	**FLT3**: FLT3+ AML	**Myalgia/arthralgia**, ↑LFTs, n/v/d, rash, stomatitis, **differentiation syndrome**, FN
Midostaurin	**FLT3:** FLT3+ AML (combination tx), syst mastocytosis, mast-cell leukemia	N/v/d, edema, BM↓, mucositis, ↑LFTs, renal insufficiency, **↑QTc**, pyrexia, fatigue, URI, hyperglycemia, hyperuricemia
Ibrutinib	**BTK:** CLL, B cell lymphomas (marginal, mantle), Waldenstrom's, cGVHD	**Afib,** edema, diarrhea, URIs, **bruising/ bleeding** including SDH/ICH (may want to avoid if on DAPT), fatigue, HTN
Osimertinib Dacomitinib Gefitinib Erlotinib (E)	**EGFR**: met EGFR+ NSCLC, pancreas (E)	**Acneiform rash** (predictive of response), late ILD, ↑LFTs, pneumonitis, ocular tox from keratitis/conjunctivitis to corneal perf/ulceration (E), n/v/d, risk of MI (E), GI perf (E), liver failure and HRS (E)
Lapatinib	**EGFR:** breast (EGFR & HER2)	**ILD/pneumonitis**, hepatotoxicity, n/v/d, rash
Crizotinib Brigatinib Ceritinib (Ce)	**ALK:** NSCLC (ALK+)	**↑QTc,** bradycardia, pneumonitis, n/v/d, edema, ↑LFTs, **visual disturb** (blurred vision, diplopia, ↓acuity), neuropathy, ↓K, ↓phos, BM↓, hyperglycemia (Ce)
Lorlatinib	**ALK, ROS1:** NSCLC	**HLD,** edema, hyperglycemia, neuropathy, BM↓, ↑LFTs, ↓alb, n/v/d, myalgia
Vemurafenib + Cobimetinib	**BRAF/MEK:** melanoma (BRAFV600E)	**N/v/d**, **central serous retinopathy, skin SCC (vemurafenib monotherapy),** keratoacanthomas, **photosensitivity**, **arthralgia, rash,** hand-foot syndrome, ↑QT, **↓EF**, hepatotoxicity, pyrexia
Dabrafenib + Trametinib, Encorafenib + Binimetinib (E+B)	**BRAF/MEK:** melanoma (BRAFV600E/K), NSCLC (D+T)	**HA**, **pyrexia (often tx-limiting, less w/ E+B)**, **n/v/d**, **rash**, hyperkeratosis, skin SCC, hand-foot syndrome, photosensitivity, central serous retinopathy, HTN, CHF, edema, arthralgia
Vandetanib	**VEGF**: medullary thyroid	N/v/d, rash, **↑QTc,** dry mouth, cerebrovascular ischemia
Neratinib	**Pan-HER:** breast	N/v/d, stomatitis, rash, hepatotoxicity, muscle spasm
Sorafenib (So) Sunitinib (Su) Regorafenib (R), Lenvatinib (L)	**VEGF:** RCC (So, Su, L), HCC (So, R, L), GIST (Su, R), thyroid (So), pNET (Su), CRC (R), Endometrial (L), thyroid (L)	**Hemorrhage**, HTN, renal tox, hand-foot skin reaction (So, Su, R?), palmar-plantar erythrodysesthesia (L), CHF/MI (So), neuropathy, ↓K, ↓phos, ↓Ca, ↑LFTs, **liver failure (Su,R),** GI perf, **↑QT, ↓EF** (Su), mucositis (Su), thyroid impairment (So), ONJ (Su), TLS, arthralgia/myalgia (L), **fistula/GI perf (L),** arterial thrombosis (L)
Cabozantinib	**VEGF:** medullary thyroid, RCC, HCC, NSCLC (ROS1)	Fistula, GI perf, hemorrhage, osteonecrosis, ↑LFTs, cytopenias, hand-foot syndrome, HTN, ↑triglycerides, abnormal electrolytes, PRES
Axitinib (A) Pazopanib (P)	**VEGF:** RCC (A, P), soft-tissue sarcoma (P)	**Hepatotoxicity** (P), ↑QT (P), **↓EF** (P), n/v/d, HTN, hemorrhage, hypothyroidism, **dysphonia (A)**, BM↓ (P), perf/fistula (P), arterial thrombosis (A)
Bortezomib	**Proteasome**: MM, mantle lymphoma	Neuropathy, PRES, PML, ARDS, BM↓, AIN, n/v/d, HoTN, ↑shingles, **↓EF**
Larotrectinib	**NTRK** fusion inhibitor (tissue agnostic)	N/v/d, ↑LFTs , fevers, BM↓, neurotox (dizziness, dysarthria, delirium, enceph.)
Temsirolimus	**mTOR**: RCC	N/v/d, edema, mouth sores, anemia, increased thirst/hunger, **pneumonitis**, metabolic effects (HLD, hyperglycemia), proteinuria, renal failure, fever
PARP Inhibitors		
Olaparib	BRCA-mutant ovarian (3rd line), breast	**N/v**, fatigue, somnolence, pneumonitis, BM↓
Rucaparib	BRCA-mutant ovarian (2nd line)	N/v/d, constipation, fatigue/asthenia, BM↓
Niraparib	Ovarian, peritoneal	BM↓ (usually mild), n/v, constipation, HTN
Cyclin-Dependent Kinase (CDK) 4,6 inhibitors		
Palbo/ribociclib,	HR+ metastatic breast	Leukopenia, anemia, thrombocytopenia, fatigue
Abemaciclib	HR+ metastatic breast	Diarrhea, leukopenia, thrombocytopenia

***Key:** BM↓= myelosuppression, IS=immunosuppression, IF=infertility, DHFR=dihydrofolate reductase, HES (hypereosinophilic syndrome), ONJ= osteonecrosis of the jaw. **Table does not include all off-label clinical indications. ***See "Immune Checkpoint Inhibitors" for immunotherapy toxicities.

IMMUNE CHECKPOINT INHIBITORS (ICIs)

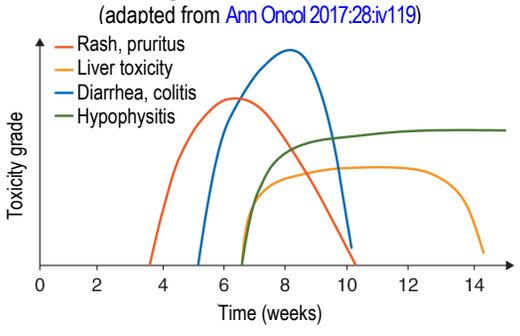


- **Mechanism of action**: ICIs increase antitumor immune response by ***blocking down-regulators*** of T cell activation. These down-regulators include *cytotoxic T-lymphocyte antigen 4* (CTLA-4), *programmed cell death 1* (PD-1), or its ligand, *programmed cell death ligand 1* (PD-L1) (Nat Rev Clin Oncol 2016;13:473, NEJM 2018; 378:158, NEJM 2016;375:1767). ICIs with alternative modes of action (CD137, LAG-3, TIM-3) are in development.
- **Indications**: melanoma, NSCLC, RCC, urothelial, gastric, colorectal, HCC, H&N, HL, cutaneous SCC (cemiplimuab), triple negative breast, cervical, numerous other indications are under investigation. PD-1 inhibitors are FDA-approved for ***any*** microsatellite instability-high (MSI-H) or mismatch-repair deficient cancers (dMMR) (NEJM 2017;377:1345, NEJM 2018;378:1277)
  - Pre-existing autoimmune disease is NOT an absolute contraindication to the use of ICIs. Can be associated with flare but rarely treatment-limiting (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 or inflammatory events due to immune system activation by ICIs
- **Risk factors**:
  - Combination immunotherapy (anti-CTLA-4 + anti-PD-1): associated w/ earlier, higher incidence, and ↑ severity; significantly less with anti-PD1 compared with anti-CTLA-4
  - No predictors of who will develop irAEs. Patients with pre-existing autoimmune disease can flare (see above).
- **Timing**: highly variable based on organ system involved, drug target, monotherapy vs combination. Can present over weeks to years.
- **Clinical presentation**: dermatologic toxicity (rash, vitiligo), hepatitis, thyroiditis, colitis, myocarditis, pneumonitis, DM1, neurotoxicity (aseptic meningitis, encephalitis, transverse myelitis, neuropathy/mononeuritis, GBS, myasthenia), arthralgias>arthritis, Sicca syndrome. See below for organ-specific details.
- **Tx**: absence of prospective data, treatment recommendations based on expert consensus, see ASCO guidelines (J Oncol Pract 2018;14:247). First line immunosuppressant is prednisone. Treatment-refractory cases: infliximab [except hepatitis], MMF, tacrolimus, MTX, ATG, IVIG/plasmapheresis in autoAb-mediated/neurologic irAEs

Timing of irAE after ipilimumab
(adapted from Ann Oncol 2017;28:iv119)



IRAE Grading (ASCO Guidelines: JCO 2018;36:1714; NCCN Guidelines v.1.2020)

IRAE	Features	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
Colitis	• More common with anti-CTLA-4 • Grade 3/4 colitis higher with ipilimumab (<10%) than with anti-PD-1 agents (1-2%). • Median onset 6-8 wks after treatment initiation	≤4 stools/ day, above baseline	4-6 stools/day above baseline	>7 stools/ day above baseline	Life-threatening, requiring urgent intervention
Hepatitis	• Median onset 6-14 wks after treatment initiation	Bili: 1-1.5x ULN AST/ALT: 1-3x ULN	Bili: 1.5-3x ULN AST/ALT: 3-5x ULN	Bili: 3-10x ULN AST/ALT: 5-20x ULN	Bili: >10x ULN AST/ALT: >20x ULN
Pneumonitis	• Dyspnea, cough • Onset highly variable, later than other irAEs • More common with anti-PD-1 • Higher risk with combination therapy	Asymptomatic radiographic changes, confined to one lobe of lung or <25% parenchyma	Symptomatic, 25-50% parenchyma or >1 lobe involved, limits ADLs	Severe symptoms, hospitalization required, involves all lobes of >50% parenchyma	Life-threatening respiratory compromise, intubation required
Endocrinopathies	Hypo-/Hyperthyroidism, adrenalitis, hypophysitis, DMI	Asymptomatic/ mild symptoms	Moderate symptoms, may require thyroid replacement	Severe, requiring hospitalization, may need insulin or hormone replacement	Life-threatening, requiring urgent intervention

Additional reading: hepatitis Oncologist 2018;23:991; pneumonitis: Chest 2017;152:271, JCO 2017;35:709

irAE Severity	Management
Grade 1	• Continue checkpoint inhibitor • Increased monitoring • Supportive care
Grade 2	• Delay checkpoint inhibitor • Oral corticosteroids (0.5-1 mg/kg) as outpatient, taper over 2-4 wks • Re-challenge with ICI if returned to grade 1 toxicity • Increased monitoring
Grade 3	• Delay checkpoint inhibitor, consider rechallenge if benefits outweigh risks • Oral corticosteroids (1-2 mg/kg) as outpatient, IV if symptoms persist 48-72 hours, taper over 4-6 wks • Consider organ specialist consultation (GI, pulm, etc.)
Grade 4	• Discontinue checkpoint inhibitor (except for endocrinopathies managed with hormone replacement) • Hospitalize for IV steroids • Consider additional immunosuppressive agents if no response to IV steroids • Consult organ specialist

Adapted from Curr Oncol 2018; 5:342

Skin toxicity: typically manifests as rash, pruritis, rarely SJS/TEN. Common, up to 30-40% of patients (higher with CTLA-4 than PD-1/L1 blockade). Vitiligo seen only in melanoma, associated w/ response to tx (JAMA Dermatol 2016;152:45)

- **Timing**: early, within the first few weeks of treatment initiation
- **S/Sx**: four types of skin reactions
  1) Inflammatory: psoriasiform or lichenoid reactions
  2) Immunobullous: dermatitis herpetiformis or bullous pemphigoid
  3) Keratinocyte alteration: acantholytic dyskeratosis
  4) Immune reaction mediated by alteration of melanocytes (regression of nevi, tumoral melanosis, vitiligo)
- **Dx**: exam; r/o other etiologies (i.e. infection, DRESS, TEN/SJS); grade based on BSA (<10% Gr 1, 10-30% Gr 2, >30% Gr 3)
- **Tx**: topical steroids, oral antihistamines for inflammatory/pururitic reaction. If severe, consider systemic steroids and derm consult. Often does not require treatment interruption.

Hypophysitis (JAMA Oncol 2018;4:173): primarily w/ anti-CTLA-4, est. prev. 3.2%. Rarely w/ anti-PD-1/PD-L1 (0.5%). Mechanistically distinct from other irAEs; ?mediated by direct binding of ipi. to CTLA-4 on normal cells of ant. pituitary (Sci Transl Med 2014;6:230)

- **Timing**: median onset is 8 weeks
- **S/Sx**: HA most common (can be severe); fatigue, n/v, dizziness, weight loss, hot flashes, cold intolerance, hyponatremia (anterior hypopituitarism); no central diabetes insipidus (posterior pituitary spared)
- **Dx**: MRI brain/pituitary shows transient diffuse pituitary enlargement (generally resolved by 2 months); test hormonal axes: 8AM serum cortisol + ACTH and/or cort stim; TSH w/ fT4/T4/T3; PRL; LH/FSH, serum testosterone/SHBG (in men); IGF-1.
- **Tx**: symptoms resolve with appropriate hormone substitution; hormone deficiencies tend to persist
  - **Hypocortisolism**: physiologic glucocorticoid replacement (prednisone 3-5mg daily equivalent; increase x2-3 with infection/illness), high-dose glucocorticoids do not improve outcomes (may be associated with reduced survival); counsel about adrenal crisis; obtain medical bracelet (Cancer 2018;124:3706, Oncologist 2016;21:804)
  - **Central hypothyroidism**: hormone replacement with levothyroxine (hyperthyroidism can also occur, but rare)
  - **Hypogonadism**: consider testosterone replacement if persists
  - **GH deficiency**: GH theoretically contraindicated due to active malignancy, although no evidence

Myocarditis (JACC 2018;71:1755): rare, but serious AE of ICI a/w high mortality (46% in severe myocarditis); risk higher with combo tx

- **Timing**: generally within 3 months (Oncologist 2018;23:874, Lancet 2018;391:933)
- **S/Sx**: sx of heart failure (SOB, LE edema), chest pain, palpitations, arrhythmia
- **Dx**: EKG/tele; **troponin**, CK-MB, NT-proBNP, ESR/CRP; TTE; consider myocardial bx; CPK/aldolase; EMG/muscle bx
- **Tx**: pulse-dose steroids (1g IV x3d, then PO pred 1mg/kg); 2nd-line consider ATG/IVIG (if unstable), or infliximab/MMF/tacro (if stable) (Oncologist 2018;23:879); βB, ACEi/ARB (if EF low)

Pneumonitis: more common w/ anti-PD-1, but serious toxicity rare. Combination therapy confers significantly higher risk. (Chest 2017;152:271, JCO 2017;35:709); risk also increased in combination with targeted therapy for lung CA

- **Timing**: highly variable onset, later than other irAEs
- **S/Sx**: dyspnea (53%), cough (35%); AIP/ARDS; 1/3 asymptomatic (JCO 2017;35:709, Clin Cancer Res 2016;22:6051)
- **Dx**: VBG, influenza/RSV/RVP, BCx, SCx/smear, PCP if at-risk, consider BAL; NT-proBNP, troponin, TTE, CT-PE/LENIs. CT/HRCT (CXR often unhelpful). Findings non-specific: GGOs, NSIP-like, COP-like, HP-like.
- **Tx**: oxygen, glucocorticoids (pred 1-2 mg/kg/d or methylpred 1mg/kg) prolonged taper, consider empiric abx, diuresis

Colitis: more commonly seen with anti-CTLA-4; grade 3/4 colitis is higher with ipilimumab (<10%) than with anti-PD-1 agents (1-2%)

- **Timing**: 6-8 weeks (median) after initiation of therapy
- **Dx**: CBC, BMP, CRP, ANCA, consider lactoferrin/calprotectin; rule out alternative etiologies: C diff., bacterial or viral pathogens (stool Cx, O&P, CMV PCR, cryptosporidia); CT A/P can show mild diffuse bowel thickening or segmental colitis associated with diverticulosis; GI c/s for EGD/flex sig/colo (can affect upper/lower) for grade 2 sxs (4-6 BM/d >baseline); path: active acute colitis
- **Tx**: antidiarrheal agents after exclusion of infection; Grade 1/2 (<3/4-6 BM >baseline): antidiarrheal; budesonide 9 mg PO or prednisone PO if fails to improve (G1>14d; G2>3d); Grade 3/4 (>6 BM over baseline): systemic steroids (prednisone 1-2 mg/kg or methylprednisolone 1-2 mg/kg IV) with taper; infliximab in refractory cases

TUMOR LYSIS SYNDROME (NEJM 2011;364:1844, JCO 2008;26:2767)

- **Pathophys**: tumor lysis (in s/o cytotoxic tx initiation; rarely spontaneous in NHL and acute leukemia) → release of intracellular components (nucleic acids → uric acid, K+, PO4+); **clinical effects (can be deadly)**: renal failure (↑uric acid precipitates in renal tubules); seizure/Ca-phos crystal deposition (↑phos → ↓Ca); arrhythmias (↑K); **timing:** 1-2d after tx (can occur w/in hrs)
- **Presentation**: n/v/d, constipation, ↓UOP, weakness/cramps, seizure, arrhythmia
- **Risk factors**: high risk: ALL/AML (WBC ≥100k), CLL (on venetoclax & ↑uric acid), stage 3/4 Burkitt's/lymphoblastic NHL, bulky DLBCL; intermediate risk: ALL (WBC <100k), AML (WBC 25-100k or <25k & ↑LDH), Burkitt's, DLBCL, CLL (chemo-specific & ↑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), ionized Ca, Mg, phos (calculate Ca-phos product), uric acid, CBC w/ diff, ECG
- **Diagnosis (Cairo-Bishop criteria)**:
  - Laboratory diagnosis: ≥2 criteria within 3d before or 7d after cytoxic therapy: uric acid ≥8 mg/dL, K ≥6 mEq/L, phos ≥4.5mg/dL, or Ca ≤7mg/dL. Criteria also satisfied if 25% change from baseline.
  - Clinical diagnosis: laboratory dx & ≥1 clinical criteria: Cr 1.5x ULN, arrhythmia, seizure, death (not attributable to chemo agent)
- **Prophylaxis and treatment**: while treating, labs should be checked Q2-Q4H & pt should be on telemetry given electrolyte abn
  - **Hydration**: 2-3 L/m^2 per day. Maintain UOP ≥100 cc/hr for optimal excretion of uric acid and phos; can use diuretics PRN
    - Use bicarb only with marked acidosis, as ↑urine pH will ↓uric acid crystals but ↑Ca-phos crystals
  - **Electrolyte abnormalities:** ↑K (hyperK tx), ↑phos (binders), ↓Ca (avoid correction until Phos nml or sx of ↓Ca)
  - **Allopurinol**: 100mg/m^2 PO q8h or 200-400mg/m^2 IV, administer 24-48 hr before chemo, continue until hyperuricemia resolved
    - Renally dose; note reduced clearance of other meds (e.g. cyclophosphamide, MTX, 6-MP, azathioprine, ampicillin)
  - **Rasburicase** (discuss with attending): 0.2 mg/kg IV, administer if high risk or baseline uric acid ≥8 mg/dL
    - Risk of anaphylaxis, hemolysis, methemoglobinemia. **Contraindicated in G6PD deficiency** (risk of hemolysis)
  - **Renal replacement therapy**: indicated if Ca-phos product ≥70 mg^2/dL^2

HYPERVISCOSITY SYNDROME/LEUKOSTASIS (Blood 2012;119:2205, Blood 2018;132:1379)

- **Etiology**: 1) *hyperproteinemia* from monoclonal gammopathies (mostly commonly Waldenström's macroglobulinemia [IgM], uncommonly myeloma) 2) *hyperleukocytosis/leukostasis* seen in **AML** with blasts >50k (uncommon in ALL/CLL unless very high counts); 3) *other diseases* such as rheumatoid disease, polycythemia, sickle cell, spherocytosis
- **Symptoms**: most common: pulmonary (SOB) and CNS (blurry vision 2/2 retinal venous engorgement, headache, dizziness, ataxia, confusion, coma), fever → **if concerned, page hematology fellow on call and clinical pathology resident** for EMERGENCY VISCOSITY STUDY, p21828, (notify attending ASAP as pheresis will involve attending-level decision)
- **Diagnosis**: ↑ Ostwald tube serum viscosity, light chains, SPEP, **WBC (often >100k, but can be lower in blast crisis)**
  - Lab artifacts from hyperleukocytosis: **spurious ↑K** (use ABG K), **falsely low arterial pO_2** (use oximeter)
- **Treatment**: always start with plasma volume expansion with **IV NS**
  - *Hyperproteinemia:* **plasmapheresis** (aiming for resolution of symptoms); reduces viscosity by 20-30% per session
  - *Leukostasis*: **leukapheresis**; cytoreduce (**hydroxyurea**); **induction chemo**; **avoid RBC & plt transfusion** (↑viscosity)

METASTATIC EPIDURAL SPINAL CORD COMPRESSION (Seminars in Neurology 2010;30:245, Lancet Neurology 2008;7:459)

- **Primary CA**: lung > prostate & breast > non-Hodgkin's lymphoma, renal cell, multiple myeloma, lymphoma
- **Location**: T (60%) > L (25%) > C (15%); multiple sites in 20-35%; ESCC score for spinal level (JNCCN 2016;14:70)
- **Symptoms**: back pain (usually 1st sx; radicular, localized, worse at night/recumbent/valsalva) → weakness, gait instability → sensory deficits (saddle anesthesia in cauda equina lesions), bowel/bladder dysfunction
- **Exam**: pain precedes other sx by ~7 wks, weakness/ataxia, paresthesia, ↑ reflexes, ⊕ Babinski, ↓ anal sphincter tone
- **Diagnosis**: STAT vs. urgent FULL spine MRI with cord compression/metastasis protocol, alternative is CT myelography
- **Treatment**: call Spine Surgery & Radiation Oncology ASAP → more effective than chemo (except for heme, germ cell malignancies)
  - Severe deficits: **dexamethasone 96mg x1**, then 24mg IV q6hr x3d, then taper x10d
  - Minimal deficits: **dexamethasone 10mg IV x1**, then 4mg IV q6hr

BRAIN METASTASES WITH INCREASED INTRACRANIAL PRESSURE (Ann Palliat Med 2015;4:225, JCO 2015;33:3475)

- Intracranial tumors present in ~10-30% of patients with metastatic disease; call Neurosurgery & Radiation Oncology
- **Primary CA**: lung (48%), breast (18%), melanoma, RCC, osteosarcoma, head and neck, thyroid, colorectal
- **Symptoms**: headaches (40-50%; "tension", worse w/ Valsalva, n/v), focal neuro deficits (20-40%, hemiparesis most common), cognitive dysfunction (30-35%), new onset seizures (10-20%), stroke (5-10%)
- **Diagnosis**: contrast MRI w/ ↑ sensitivity > non-enhanced MRI or CT with contrast
- **Treatment**: control vasogenic edema (**dexamethasone 10mg IV x1, then 8mg BID**), consider AED (usually not recommended for 1° ppx); avoid AC if concern for active hemorrhage; definitive treatment will ↓ local recurrence: stereotactic radiosurgery > whole-brain XRT (↑ neurocognitive impairment; hippocampal sparing helpful) > surgery

SUPERIOR VENA CAVA SYNDROME (SVC SYNDROME) (NEJM 2007;356:1862, Mayo CP 2017;92:609)

- **Etiology**: external compression of SVC from a mediastinal mass (commonly lung CA or NHL) causing ↑ upper body venous pressure
- **Symptoms**: cerebral edema (HA, confusion, herniation), narrowing of larynx/pharynx (dyspnea, stridor, cough, dysphagia, hoarsness), head/neck swelling (visually striking, often not clinically significant), hemodynamic instability (↓ venous return)
- **Diagnosis**: **venography,** CT chest w/ contrast, **obtain/ensure tissue diagnosis to guide tx (extremely important!)**
- **Treatment**: secure airway, RT/chemo, intravascular stent (emergent/refractory), steroids (stridor/resp distress only, clear with onc)

DEFINITIONS AND ETIOLOGY (J Oncol Pract 2019;15:19, NCCN Prevention and Treatment Guidelines)

- **Fever**: single temperature ≥101°F (38.3°C) orally or ≥100.4°F (38°C) >1h
- **Neutropenia**: defined as ANC <500 or <1000 and predicted nadir ≤500 within 48h
  - Functional neutropenia: defective PMNs, common in leukemia (↓ neutrophil function despite ANC>500)
- **Microbiology**:
  - Only 40-50% have infectious source identified; others attributed to translocation of intestinal bacteria
  - 25% organism identified: 40% GNRs (E. coli, Klebs > PsA); 60% GPCs (CoNS > MSSA/MRSA, strep, enterococcus/VRE) esp w/ indwelling lines or mucositis; fungal (Candida, Aspergillus) more likely w/ prolonged ↓ ANC, broad-spectrum abx use, or TPN

EVALUATION

- **H&P**: prior micro data, time since last chemo, recent antibiotic therapy/ppx, major comorbid illness, use of devices
- **Exam**: mouth (mucositis), emphasis on skin, perineum/rectal (visual inspection, **avoid DRE**), indwelling lines (erythema)
- **Studies**: BCx x2 sites (≥1 periph, 1 per CVC lumen), UA/UCx, CBC, BMP, LFTs, CXR, sputum Cx/GS, viral panel, CMV PCR (SCT)
- **Further site-specific studies to consider**:
  - Diarrhea: stool culture, O&P, C. diff; abdominal pain: CT A/P (may not have abdominal pain, consider imaging)
  - Pulmonary symptoms: influenza/RSV PCR, CXR/CT chest, +/- bronch/BAL (especially if prolonged F&N)
  - HA/sinus pain: CT face/sinus
  - Fungal markers: LDH, β-D-glucan; galactomannan if high risk for *Aspergillus* (SCT, GVHD, neutropenia >10-14d)
- **Risk stratification**: (J Oncol Pract 2019;15:19, NCCN Prevention and Treatment Guidelines)
  - **MASCC Risk Index score** (JCO 2000;18:3038): identifies cancer patients with febrile neutropenia at *low* risk of complication
  - **High risk**: anticipated ANC ≤100 for ≥7d, inpt status, MASCC<21, co-morbidities/infections (renal/hepatic impairment, PNA, central line infxn), allogeneic HSCT, mucositis grade 3-4, alemtuzumab use within past 2 months → inpatient management
  - **Low risk** (JCO 2018;36:1443): anticipated ANC ≤100 for <7d, no co-morbidities, good performance status (ECOG 0-1), strong home social support, MASCC ≥21, → treated with PO antibiotics after brief inpatient stay versus strictly outpatient

TREATMENT/PROPHYLAXIS (NCCN Prevention and Treatment Guidelines)

- **Empiric abx**: within 1hr; up to 70% mortality if delayed abx (Antimicrob Agents Chemother 2014;58:3799)
  - **Gram-negatives (PsA dosing)**: broad gram negative coverage (including PsA) within 60 min of presentation
    - Cefepime 2g q8h (or ceftazidime 2g q8h), pip/tazo 4.5g q6h, or meropenem 1g q8h
    - PCN allergy: confirm allergy; use Penicillin Hypersensitivity Pathway and test-dose cefepime or meropenem; consider allergy consult. If true allergy, use aztreonam (avoid in ceftazidime allergy) + levofloxacin
    - High-risk ESBL: meropenem 1g q8h (2g q8h if meningitis)
    - Low risk: PO regimen; cipro/levofloxacin + amox-clav vs. clinda (if PCN allergy); avoid if prior FQ ppx
  - **Gram-positives**:
    - First line: Vanc; VISA/VRSA or VRE: daptomycin (unless pulmonary process, poor lung penetration) or linezolid
    - Indications: hypoTN/severe sepsis, GPC bacteremia, catheter-related infxn (rigors with infusion), SSTI, PNA on imaging, MRSA colonization (esp in HSCT), severe mucositis + prior FQ ppx + GNR coverage with ceftaz
    - *Vancomycin NOT part of FN empiric regimen* (JAC 2005;55:436); indwelling lines, mucositis alone, FQ ppx, & persistent fever despite GN coverage are NOT indications
  - **Anaerobes**:
    - Indications: intra-abd source, C. diff, oral ulcer/periodontal infxn, post-obstructive PNA, necrotizing ulceration
  - **Fungal (invasive molds)**:
    - Indications: **F&N >4-7d** despite abx, ⊕ fungal biomarkers, ⊕ CT chest (circumscribed, air crescent, cavity), ⊕ BAL Cx
    - Micafungin 100mg q24h or Amphotericin 3mg/kg (admin after 500cc NS)
- **Modification/duration**: refer to NCCN guidelines for additional modifications
  - **Resolution of fever**:
    - Documented infxn: narrow abx and tx for recommended course, then switch to FQ ppx until ANC >500
    - Culture negative: continue empiric treatment until afebrile & ANC >500 vs. narrow to FQ ppx if afebrile x4-5d
  - **Fever continues >4-7d**:
    - Clinically stable: do not broaden abx or add vanc, consider other causes (e.g. engraftment, differentiation, GVHD, TLS, drug fever, thrombophlebitis, hematoma, hepatosplenic candidiasis)
    - Clinically worsening: broaden abx +/- fungal coverage, consider CT chest +/- bronch to evaluate for fungal infxn
  - **Catheter-associated infection**:
    - Coag-negative staph, non-VRE Enterococcus: can keep line if IV abx + abx lock x2 wks
    - Staph aureus, PsA, fungi: must remove line. For gram negative, d/w attending; line removal vs. lock therapy.
    - Complicated infxn (endocarditis, septic thrombosis, bacteremia/fungemia >72 h): remove line, abx x4-6 wks
- **Prophylaxis**
  - **Anti-microbial ppx**: refer to NCCN guidelines for more specific indications
    - Antibacterial (FLQs): high-risk pts (heme malignancy) and attending discretion for intermediate-risk pts
    - Antifungal (azole vs echinocandin): heme malignancies during neutropenia and 75 days post-allo HSCT
    - PCP (TMP-SMX): if ≥20 mg prednisone daily for ≥1 month, purine analog (Azathioprine) use, and allo/auto HSCT
    - HSV/VZV (acyclovir vs. famciclovir): sero+ undergoing tx while neutropenic, or 1 yr post-auto and 2 yrs post-allo HSCT
  - **G-CSF**: recommended if risk of F&N >20% → shortens duration of F&N, but does NOT decrease mortality (JCO 2006;24:3187)

FRAILTY

Screening: consider for all admissions >70 years old, or admissions for **"failure to thrive"**

- Reframe "failure to thrive" as frailty, which has evidence-based assessment criteria and diagnostic approach
- Definition: "medical syndrome with multiple causes and contributors characterized by **diminished strength, endurance,** and **reduced physiologic function** that **increases an individual's vulnerability** for developing increased dependency and/or death" (JAMDA 2013;14:392). Older age is a risk factor but is not necessary or sufficient for the diagnosis
- Most cited tool is Phenotype of Frailty (J Geront 2001;56:M146; BMC Geriatr 2013;13:64) but can use quick screen below
- **FRAIL screen**: **frail** = 3 or more positive answers; **pre-frail** = 1-2 positive answers (J Nutr Health Aging 2012;16:601)
  - Fatigue: "In the past four weeks, do you feel tired all or most of the time?"
  - Resistance: "By yourself, do you have any difficulty walking up 10 steps without resting?"
  - Ambulation: "By yourself, do you have any difficulty walking a city block?"
  - Illnesses: Does patient have more than 4 comorbidities?
  - Loss of weight: Greater than 5% weight loss over past year?

Inpatient frailty assessment: **find the root cause!**

- Thorough H&P and workup to evaluate for new/progressive illness and reversible causes
- Ddx: anemia, cancer, CHF, COPD, cirrhosis, CKD, DM, PMR, thyroid dz, nutritional deficiencies (incl vit D), depression
- Physical functioning: goal is to identify ADL/IADL deficits for targeted intervention
  - Katz ADL Scale ("Does anyone help you with: walking, feeding, dressing, bathing, grooming, toileting?")
  - Instrumental ADLs ("Does anyone help you with: cooking, cleaning, shopping, driving, medications, finances?")
- Cognition and mental health:
  - Evaluate for delirium with Confusion Assessment Method (see *Psychiatry*: *Mental Status Exam*)
  - If negative, proceed to Mini-Cog evaluation to screen for dementia; if any deficits, refer for outpatient evaluation
  - Always screen for depression with PHQ-2 (see *Primary Care*: *Health Screening & Maintenance*)
- Social functioning: how much social support does the patient require? Address advanced directives/HCP/Code Status

Interventions for frailty (Age Ageing 2017;46:383)

- Establish **patient- and family-centered goals** to guide treatment plan
- Exercise: inpatient and outpatient PT; exercise programs can reduce **fall risk** (JAMA 2018;319:1705)
- Nutrition: nutrition consult particularly for patients with weight loss
- Cognition training (outpatient OT consult): improve short-term memory, information processing, problem-solving
- Home environment assessment and modifications: consider social work consult, OT consult, iCMP referral
- Referral to OP geriatrics / palliative care for regular review of medications and **reduction in polypharmacy**

POLYPHARMACY AND INAPPROPRIATE MEDICATIONS

Polypharmacy

- No consensus definition; "you know it when you see it." High prevalence: >50% inpts >75yo (BMC Geriatr 2017;17:230)
- Should communicate with PCP about simplifying med list

Inappropriate medications for elderly patients

- **Classes to (usually) AVOID in geriatric patients**:
  - Anticholinergics: delirium, falls, blurred vision, urinary retention, tachycardia. Avoid antihistamines, TCAs, MAOIs, antimuscarinics (oxybutynin), muscle relaxants (cyclobenzaprine), prochlorperazine
  - Benzodiazepines: delirium, falls, cognitive impairment, etc. (also risk w/ non-BZD hypnotics)
  - Antipsychotics: increased mortality with antipsychotics in the elderly (JAMA Psych 2015;72:438)
  - Peripheral alpha blockers and central alpha-agonists: -zosins and clonidine confer risk of orthostasis and falls
  - Long-acting sulfonylureas and rapid/short acting insulin: hypoglycemia
  - PPIs: C. diff, bone loss/fracture (switch to H2 blockers unless clear indication for PPI)
  - NSAIDs: GI bleed and AKI (especially in elderly patients with decreased CrCl)
  - Aspirin for primary cardiac or CRC prevention: bleeding (use with caution and reevaluate at age >70)
- See American Geriatric Society Beer's List and STOPP-START for further details on potentially inappropriate meds
- Parkinson's disease: ondansetron is anti-emetic of choice. *Avoid* metoclopramide, prochlorperazine, antipsychotics
- Dosage adjustments: ensure appropriate renal and weight-based dose adjustment for anticoagulants (enoxaparin, apixaban, rivaroxaban, and dabigatran), antibiotics, etc.
- Ask about OTC medications and herbal/dietary supplements which can be easily missed culprits of drug-drug interactions

Preadmission Medication List (PAML) on admission: especially important for patients with frailty!

- Boston-area 24/7 pharmacies: CVS: 781-894-1600 (dial 2, 2); Walgreens: 617-389-2188 (dial #,0)
- Coordinate discharge Rx planning and education with patient, pharmacy, and PCP → lower risk of readmission with intensive pharmacist intervention (med rec and education) and coordination with PCP (JAMA IM 2018;178:375)

General Approach to Pain Management (NEJM 2015;373:2549, Lancet 2011;377:2236)

- Pain history and etiology can help guide therapy. Goal is to maximize level of functioning and quality of life.
  - Time course, location, radiation, quality, severity, exacerbating/relieving factors, associated symptoms, side effects from prior analgesics, functionality (e.g., ADLs, ambulation)
  - Use adjuvant medications and non-pharmacologics: PT/exercise/activity, heat or ice, CBT, treating comorbid psych dx, addressing existential issues, massage, acupuncture or other integrative therapies
- Step-wise approach to pain management: (WHO Guidelines, CDC guidelines, DFCI Pink Book)
  - Mild to moderate pain: non-opioids and adjuvants
    - Acetaminophen: max dose 3g daily, 2-3g safe in liver disease (Br J Clin Pharmacol. 2016;81:210)
    - NSAIDs: celecoxib if GI risk ↓, naproxen if CV risk ↓, ketorolac if severe pain
  - Moderate to severe pain: ensure non-opioid options ordered as scheduled, then consider short-acting opioids
  - Severe pain requiring around the clock opioids: consider adding extended release (ER) medications
    - Avoid ER opioids if pain source expected to resolve (e.g., bone fracture, hematoma)

Pain Archetypes and Useful Adjuvant Analgesics

*Caution using steroids in cancer patients, may interfere with treatment (e.g immunotherapy)

- 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, methy salicylate-menthol ointment (Bengay); muscle relaxants such as cyclobenzaprine, baclofen, tizanidine (*watch for sedation & delirium*)
- Visceral: deep tisues and internal organs, vague, referred or difficult to localize
  - Visceral distension (e.g., hepatic capsular stretch from liver mets, malignant bowel obstruction): depends on etiology but steroids* can be helpful
- Inflammatory: associated with other signs of inflammation (swelling, erythema, warmth)
  - NSAIDs, steroids*
- Neuropathic: burning, stinging, allodynia (perceiving innocuous stimuli as painful), hyperalgesia
  - Topical camphor/menthol, lidocaine, diclofenac gel (*NB*: short-term benefit, often not covered by insurance as outpatient)
  - Pregabalin, gabapentin, clonidine, SNRIs (duloxetine, venlafaxine), TCAs (amitriptyline, nortriptyline, desipramine)

Opioids

- Opioid-tolerant defined as total daily dose (TDD) x7 days: morphine 60 mg/oxycodone 30 mg/hydromorphone 8 mg/fentanyl 25 mcg/h
- Patients on suboxone or methadone for OUD → consult ACT for assistance with pain management
- No max dose. Goal is to find minimum dose needed to control sx w/ minimal SE
- Avoid using combo pills (limits titration flexibility)
- Treat constipation prophylactically
- Rotate opioids if side effects, dose reduce by 25-50%

Opioid Equianalgesic Doses		
Drug	**PO (mg)**	**IV (mg)**
Morphine	30	10
OxyCODONE	20	n/a
HYDROcodone	20	n/a
HYDROmorphone	7.5	1.5
FentaNYL*	n/a	0.1 (100 mcg)
Fentanyl patch (mcg/hr)	**Morphine PO (mg/day)**	
25	50	

*Use caution converting to Fentanyl (short duration of action)

Converting Opioids

Ex: Pt takes morphine ER 60 mg PO q12h and uses two morphine IR 15 mg PO breakthrough doses per day

Step 1) Calculate total daily opioid requirement

TDD = (60 mg x 2 doses) + (15 mg x 2 doses) = 150 mg morphine per day

Step 2) Convert TDD to equivalent dose of new opioid

$$\frac{30 \text{ mg morphine}}{20 \text{ mg oxycodone}} = \frac{150 \text{ mg morphine}}{x} \qquad x = 100 \text{ mg oxycodone}$$

Reduce dose by 25-50% to account for incomplete cross-tolerance → ~60 mg oxycodone total daily dose

Step 3) Divide TDD by number of doses per day

- If initiating or converting to long-acting opioid, divide TDD into ER doses and add breakthrough dose (10-20% of TDD of ER opioid)

Final dose: oxyocodone ER 30 mg q12h with 10 mg oxycodone q4h prn breakthrough

	Route	Onset (min)	Peak Effect (min)	Duration of Effect (hr)	Clearance/Metabolites
Morphine	IV	5-10	10-30	3-5	AVOID in renal disease
	PO	15-60	90-120	4	
HYDROmorphone	IV	5-20	15-30	3-4	Safer in renal disease
	PO	15-30	90-120	4-6	
OxyCODONE	PO	15-30	30-60	4-6	2nd line for renal disease
HYDROcodone	PO	30	90	3-4	AVOID in renal disease
FentaNYL	IV	<1	5-7	45 min to 2+ hr	Safest in renal and liver disease
Methadone	IV	10-20	60-120	4-6	Safest in renal disease
	PO	30-60	90-120	4-12	

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
  - TID dosing for pain vs daily for OUD
- Fentanyl:
  - Safer in both liver and renal dysfunction
  - Safety concerns: must remove patch if febrile (cutaneous vasodilation → faster transdermal absorption)
  - Requires 18-24h for therapeutic level (patch)

Pain Crisis Management: severe worsening of pain; while treating, pursue reasonable diagnostic workup for etiology (e.g., bowel perforation/peritonitis, procedural complication, bleeding). **Goal is reduction in pain score by >50%.**

1) Opioid-naïve: give morphine IV 2-5 mg or hydromorphone IV 0.2-0.4 mg bolus dose
   Opioid-tolerant: convert usual breakthrough PO dose or 10-20% of total daily ER dose to IV and administer
2) Assess for response after 15 min:
   - No pain relief and no side effects → increase dose by 50-100%
   - Minimal relief and no side effects (<50% reduction in pain score) → repeat the same dose
   - Pain reduced >50% and no side effects → reassess in 2-3 hours, use this dose as new breakthrough dose
   - Side effects with no pain relief → rotate to different IV opioid (no dose reduction if uncontrolled pain)

Uptitration: if pain only moderately controlled with scheduled doses (not in pain crisis), ↑ total daily dose by 30-50%

- If taking ER opioid and needing >3-4 rescue doses daily, ↑ ER dose by 50-100% of total rescue dose used in past 24 hrs

Patient-Controlled Analgesia (PCA): appropriate for patients who are alert & oriented and able to use equipment. Families may NOT use PCA by proxy at MGH.

- Quickest relief if episodes sudden and severe (pain onset to drug administration; don't have to call/wait for RN to pull medication).
- PCA and/or continuous infusion, when implemented safely, reduce burden on nursing for patients who need frequent administration of pain medications (generally q1-2h is the most frequent a PRN can be ordered on the floor)
- Medicine residents can order "General PCA" (for opioid-naïve patients) or "High Risk PCA" (BMI >40, hx OSA, RAAS -2 to -5, age >65). If opioid-tolerant, requiring continuous infusion, or pain difficult to control, consult Palliative Care or Pain.

General Opioid-Naïve PCA Dosing		
	Morphine	**Hydromorphone**
Patient Administered (PCA) Dose	1.5 mg	0.2 mg
Lockout Interval (in minutes)	10 minutes	6 minutes
One-Hour Dose Limit	6 mg	1.4 mg
RN/Clinician Bolus Dose (for breakthrough)	2 mg q30min PRN	0.3 mg q20min PRN
Continuous Infusion Rate	0 mg/hr	0 mg/hr

Adverse Effects of Opioids and Management

- **Respiratory depression**: hold opioid, consider low doses of naloxone but CAUTION if on high dose ER opioids
  - Dilute 0.4 mg **naloxone** (1 ml) in 9 ml saline, give 1-2 ml q2 min until ↑ RR or mental status improves
  - Naloxone half life is shorter than many opioids, watch for recurrence of resp depression
  - All patients being discharged on opioids should also be given a naloxone prescription
- **Constipation**: ALWAYS start standing **senna and miralax** when initiating opioids; lactulose, bisacodyl and other laxatives if needed; methylnaltrexone QOD if failed laxative therapy (but can cause severe nausea and cramping; avoid if concern for GI obstruction)
- Myoclonus: reduce dose or rotate opioid, increase hydration / IVF; can give low dose BZD, baclofen or gabapentin
- Nausea/vomiting: prochlorperazine, metoclopramide, haloperidol; avoid ondansetron (constipating)
- Pruritus: pruritus mediated by mu receptor (not histamine - Benadryl ineffective) unless rash/allergic reaction; treat with nalbuphine 5 mg IV q6h or low dose continuous naloxone infusion
- Sedation: consider CNS stimulants (dextroamphetamine, methylphenidate)
- Delirium: reduce dose or rotate opioid; Haldol 0.5-1 bid-qid or Zyprexa 2.5-5 mg PO QD-BID

Opioid Use and Aberrant Use Definitions

- Addiction: neurobiologic disease with environmental and psychosocial factors, manifested by impaired control over drug use, compulsive use, continued use despite harm, and cravings. *See Psychiatry* section.
- Misuse: use that is contrary to prescriber directions (e.g., not taking as diected, altering route of delivery)
- Diversion: redirection of a drug from its lawful purpose to illicit use
- Tolerance: physiologic adaptation from exposure to a drug resulting in diminished effect from the drug over time
- Physical dependence: withdrawal syndrome in response to abrupt cessation of a drug, rapid dose reduction, or drug antagonist; tolerance/ physical dependence are expected with long-term use and shouldn't be confused with addiction
- Pseudoaddiction: addiction-like behavior that occurs when pain is undertreated; behaviors resolve when pain is adequately treated

Resources: Palliative Care Network of Wisconsin fast facts and concepts for disease specific resources; DFCI "pocket resources": Pink Book for pain, Green Book for nausea/vomiting

Palliation in serious illness and end of life can be challenging and often is helped by a Palliative Care consultation
- "Comfort measures only" is NOT a one-size-fits-all set of orders, be thoughtful about standard CMO orders (foley, discontinuation of scheduled meds such as diuretics, antibiotics) and how they may or may not provide comfort
- For persistent/recurring sx, meds should be made standing, with additional PRNs for breakthrough
- Consider the route of medication to maximize comfort (sublingual, concentrated elixirs); avoid IM

Anxiety: all palliative care patients should be screened for anxiety and depression. See *Psychiatry* section for further details.
- Exacerbated by **meds** (steroids, appetite stimulants), **withdrawal** (opioids, BZDs, nicotine), insomnia, undertreated pain, dyspnea
- Non-pharmacologic strategies: psychotherapy, integrative therapies c/s, SW & spiritual care for coping/support
- For acute anxiolysis: olanzapine 2.5-5mg Q6H PRN, lower doses if elderly. *Use BZDs with caution* due to delirium risk and physiologic dependence. Avoid long acting BZDs and use lowest dose possible for symptomatic relief.
- Longer-term, consider SSRIs and SNRIs. Mirtazapine (15mg QHS) for simultaneous anxiety/depression, insomnia and/or anorexia.

Depression: difficult to distinguish MDD, demoralization, adjustment disorder; clincal depression however is not a normal part of the dying process and should be addressed with nonpharmacological or pharmacological interventions. (Palliative Care Network of Wisconsin.2020)
- Non-pharmacologic strategies: psychotherapy, integrative therapies c/s, SW & spiritual care for coping/support
- If prognosis <4 weeks consider **CNS stimulants** (methylphenidate, dextroamphetamine) over SSRIs due to faster onset of action
- Longer-term, consider **SSRIs**: citalopram and escitalopram are preferred agents as they have have mildest side effect profile, fewer drug interactions and are neither activating nor sedating (Palliat Med. 1999;13:243)
- SNRIs may be helpful for simultaneous anxiety, vasomotor symptoms (hot flashes) or neuropathic pain
- Consider psychiatry consult for pre-existing psychiatric diagnosis, refractory symptoms or polypharmacy

Fatigue: often related to disease progression, medications, other treatments, deconditioning, malnutrition, sleep disturbances, sxs
- Treat uncontrolled sx; for cancer-related fatigue, exercise and psychological interventions >> medications (JAMA Oncol. 2017;3: 961). Consider steroid trial (JCO 2013;31:3076). Psychostimulants (modafinil, methylphenidate) have limited evidence.

Anorexia/Cachexia: common in AIDS, heart failure, COPD, advanced cancer; often highly concerning for family > patient.
- Rule out reversible causes (depression, medication side effects). In general, allow PO for comfort if near end-of-life. Remove NGTs.
- Meds to consider: dexamethasone, megestrol (VTE risk), dronabinol, mirtazapine
- During the dying process, artificial nutrition and hydration are generally not recommended and do not improve QoL or survival

Nausea/Vomiting, Diarrhea, Constipation: see relevant pages in GI section.

Xerostomia: side effect of chemo/XRT, head/neck surgery, or medications
- Oral hygiene, oral hydration, ice chips, sugarless gum, artificial saliva (**Biotene**)

Insomnia (inpatient management):
- Use non-FDA approved treatments on a short-term basis: **melatonin** (3-5mg Q6PM), **trazodone** (12.5-50mg QHS, QTc prolonging), **mirtazapine** (7.5mg QHS)
- Use with caution: quetiapine (12.5-25mg QHS, QTc prolonging); concern for ↑ mortality with antipsychotics in the elderly (JAMA Psych 2015;72:438). Reserve for patients with additional indication (e.g., requiring pharmacologic tx for agitated delirium).
- **Avoid BZDs** and non-BZD hypnotics (e.g. zolpidem, zaleplon, eszopiclone) for inpatient management due to delirium risk. Avoid H_1 blockers (diphenhydramine, hydroxyzine) due to risk of delirium, next-day sedation, anticholinergic side effects.

Delirium: common and often multifactorial. See *Neurology: Delirium* for further details.
- Prevention: remove unnecessary monitoring (tele and pulse ox)/lines/catheters/restraints; family and friends can be more effective at reorientation; use signage to minimize staff/room changes; manage other symptoms. Melatonin 5mg Q6PM.
- No FDA-approved delirium med, but if hallucinations or agitation interfering w/ staff or pt safety consider antipsychotics: **quetiapine** 12.5-25mg if taking PO or **Zydis** ODT 2.5-5mg Q6H PRN. If IV needed, **haloperidol** 0.5-1mg IV Q4H PRN.
- For hyperactive delerium in patients with terminal delirium, consider lorazepam PRN

Dyspnea: exacerbated by deconditioning, cachexia, worsens at EOL, exacerbates anxiety. Does not always correlate w/ hypoxemia.
- Treat contributing causes for comfort: diuresis for volume; nebulizers/steroids for reactive airways; saline nebs for mucous pluging
- For refractory dyspnea, **opioids** are gold standard (often at lower doses than required for pain). BZDs less supported by evidence; can be used for associated anxiety though must weigh risk of delirium.

Secretions: pooled secretions → "death rattle". Disturbing to observers, less bothersome to patient.
- Prepare family, position pt to facilitate postural drainage, stop feeds/fluids, don't deep suction (uncomfortable to pt), continue oral care
- **Glycopyrrolate** 0.2-0.4mg IV Q4H PRN (less deliriogenic). Alternatives: scopolamine patch, atropine (SL, IV), hyoscyamine (PO, SL)

Catastrophic hemoptysis or hemorrhage: impending catastrophic hemorrhage that will likely result in death (hemoptysis in ENT and lung cancer, variceal bleed in ESLD, vaginal bleeding in GYN cancers). Often preceded by "sentinel" small bleed.
- Develop palliative treatment plan with goal of rapid anxiolysis and sedation with medications at bedside (BZDs q5-10 min +/- opioids)
- Prepare room with dark linens/basins (↓ contrast w/ blood), PPE for caregivers, suctioning, warm blankets (hemorrhage → chills)

Serious Illness Conversations

- *When?* Preferred early in disease course as outpatient, but in the inpatient setting some scenarios include:
  - New or progressive serious medical illness such as advanced cancer, ESRD, ESLD, HF, COPD
  - Prognosis trigger: "Would I be surprised if this patient died in the next year?" (J Palliat Med 2010;13:837)
  - Indicator of life expectancy <6 months (calculator, J Palliat Med 2012;15:175)
  - Age > 80 and hospitalized; see *Geriatrics: Frailty*
- *Why?* Ascertain how the patient wants to **live**, what they value; more than just end of life care preferences
- *How?* Often best to plan patient or family meeting (NEJM 2014;370:2506)

Preparation

- Identify time and location to accommodate all meeting participants in an appropriate manner
- Include patient and their preferred participants, primary team, RN, SW, and other providers as appropriate
- If complex decisions/psychosocial issues/family conflict, consider a palliative care consult
- Pre-meet with team to decide meeting leader, discussion goals, unified assessment of clinical scenario, treatment options, and team recommendation

Serious Illness Conversation: suggested outline / prompts (adapted from Ariadne Labs SICG)

Step	Suggested Prompts
Open the conversation	"*I'd like to talk about what is ahead with your illness. Would that be ok?*"
Assess prognostic awareness	"*What is your understanding of your illness?*" "*Looking to the future, what are your hopes about your health?*" "*What are your worries?*"
Share hope and concerns	"*Would it be ok if we talked more about what lies ahead?*" "*I hear you're hoping for ____ and I'm concerned the decline we've seen will continue"* or *"I'm concerned something serious may happen in next (time window: weeks, months, years)*"
Align	"*I wish we didn't have to worry about this*"
Explore what's important	"*If your health worsens, what is most important to you?*" "*How much do your family or friends know about your priorities and wishes?*"
Close the conversation	"*It sounds like ____ is very important to you*" "*Given what's important to you, I would recommend_____*"

**Note: some patients may respond better to being asked about their "health" rather than their illness--especially those who are semi-stable in clinic but have frailty or multimorbidity

Next Steps:

- Debrief with team: **How did that feel?** What went well? What could have gone better?
- Document Serious Illness Conversation in Epic:
  - Patient ID banner (top of chart): click "Code: ___" → "Advance Care Planning Activity" → "Serious Illness Conversation" in left tab; fill out SIC form → "Close"
  - Write ACP note: Within "Advance Care Planning Activity" → "ACP Notes" → "Create ACP Note" → type .ACPSICDOCUMENTATION; write rest of the note if relevant

Advance Care Planning Forms

- Health Care Proxy (**HCP**) / medical power of attorney: an advance directive document that designates a healthcare agent to make future medical decisions if patient loses capacity. Expressly authorized in MA by statute.
  - *If no HCP*: surrogate hierarchy: see Section 3, bullet 6 of MA: An Act Improving Medical Decision Making
- Living Will: an advance directive document in which a competent person specifies future medical treatments in the event of incapacity, usually at end-of-life or if in a persistent vegetative state. Can be used as evidence of a person's wishes, but not considered to have legal authority (no MA statute that expressly authorizes).
- **MOLST** (MA Medical Orders for Life-Sustaining Treatment; hot-pink forms available on all medical units): medical orders for patients with advanced serious illness and limited prognosis that documents preferences for CPR, intubation, hospital transfer, artificial nutrition, and more
  - Transferrable to outside facilities; complete MOLST prior to discharge to rehab/SNF if patient DNR/DNI
  - Remember that you do not have to discuss everything on the back page (clinical discretion)
- **Links to MOLST/HCP** forms are found in banner at the top of a pt's Epic chart or scanned into the Media tab

Code Status Discussions

General Considerations

- Ideally code status should be confirmed in Epic at time of admission
- 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 addressed by outpatient providers
- Code status should reflect a patient's values and preferences and is not equivalent to ACP (it is a specific medical procedure for which harms/benefits should be weighed given clinical context)

Survival Outcomes (Circulation 2019;139:e56)

- *Out-of-hospital cardiac arrest*: survival to hospital discharge 10.4%; survival with good neurologic function 9.9%
- *In-hospital cardiac arrest*: survival to discharge 25.6%; survival with good neurologic function 22%
  - Favorable outcomes: ACS, drug overdose, drug reaction (up to 40% survival)
  - Unfavorable outcomes: age >80 (<10% survival), multiorgan failure, sepsis, advanced cancer, ESRD, ESLD, dementia
  - Post-arrest complications: hypoxic-ischemic brain injury, rib fractures, pulmonary contusion, prolonged ICU care

Conducting Code Status Discussions (JAMA 2012;307:917)

- Initial tips:
  - Suggested framing of CPR for patients: "*CPR is a medical procedure that we would do if you were to die, that is, if your heart were to stop and you were to stop breathing. CPR includes pressing on your chest to pump the heart and the use of a breathing machine to help you breathe*"
  - Do not offer DNI alone, as resuscitation almost always requires intubation
- Two main types of code status discussions:
  1. **Information-gathering** code status discussion
     - *Who*? Patients you would expect and would recommend to be full-code OR when you are meeting the patient for the first time w/ limited rapport (you may need to revisit the conversation later)

Step	Suggested Prompt
Introduce	"*Would it be okay if we did some emergency planning? I want to talk about a procedure called CPR.*"
Assess patient understanding	"*What do you know about CPR*?" "*Do you have any personal or family experience with CPR?*" "*Have you spoken with other doctors about CPR?*"
Share information / confirm goals	Describe CPR as above. If not vocalizing clear desire for DNI or DNR, "*Right now, if your heart were to stop, you would receive CPR. Is this consistent with your goals*?"
Forecast the future	"*In the future, your doctor may no longer recommend CPR because it would be unlikely to help. At that time, your team will talk with you more*."

  2. **Decision-making** code status discussion
     - *Who*? Patients you would recommend being DNI or DNR/DNI as CPR would be unlikely to reverse their underlying chronic illness/frailty
     - Be prepared: know details of your patient's condition and prognosis.
     - Consider if warrants discussion w/ outpatient providers.
     - Often may end up conducting a serious illness conversation within discussion of code status

Step	Suggested Prompts
Introduce/assess	See table above for suggested prompts
Share information	"*Unfortunately, we are in a different place now*." (Discuss medical situation, share concerns using hope/concern statements from serious illness conversation.)
Align	"*I wish we didn't have to worry about this*."
Explore goals/what's important	"*Given where we are, what is most important to you?*"
Close the conversation	"*If something were to happen and you were to die, I would recommend focusing on comfort, allowing a natural death, and not doing CPR. Medical procedures such as CPR cannot reverse your illness and may prolong suffering in the dying process.*"

Practical Steps for Making a Patient CMO

- D/c all unnecessary **lines** and **tubes** (usually maintain IV access but d/c central line if possible; discuss Foley w/ RN)
- D/c **labs**, **routine VS**, and other **interventions** that do not contribute to comfort
- Run order list and d/c **unnecessary medications**. Continue medications that contribute to comfort, that will prevent uncomfortable events (e.g. maintain rate control to avoid AFRVR), or that have a withdrawal syndrome (e.g. SSRIs).
- Generally avoid artificial nutrition and hydration; may cause volume overload without meaningful benefit (JCO 2013;31:111)
- See *Pain Management* and *Non-Pain Symptom Management*. Most often require PRN meds for pain and dyspnea (**opioids,** may require gtt), delirium (e.g. zydis, **haldol**), secretions (e.g. **glycopyrrolate**, scolpolamine patch).

General Inpatient Hospice (GIP)

- Pts with terminal diagnosis and prognosis of < ~2wks, transitioned to CMO, w/ sx management needs requiring inpatient care (e.g. high flow O2, uncontrolled sx requiring IV medications, high RN needs for wound care/suctioning)
- Discuss w/ floor CM team (for insurance benefit screen and coordinate w/ hospice liaison) and Pall Care
- If admitted to GIP, pt transitions off Housestaff team, Pall Care attending becomes AOR, Pall Care clinician becomes RC

Prior to Death

- Involve **family** +/- **chaplaincy** (available 24/7), other care team members (e.g. PCP). Ask about religious/cultural traditions.
- Consider early contact of the New England Organ Bank (**NEOB**) 800-446-6362. The NEOB determines eligibility for donation. They are trained in how to discuss donation with the family; DO NOT discuss this with the family. See *Organ Donation*.
- When passing off a patient who may pass away, prep the "Report of Death" form (at minimum the cause of death section)

Withdrawing Ventilatory Support: palliative extubation or discontinuation of NIPPV

- Prior to extubation: see MGH MICU Policy and ATS Guidelines (AJRCCM 2008;177:912)
  - Allow family time with patient (if desired). Discuss with family the extubation process, expected dying process (e.g. agonal breathing), plans for sx control, and expected timeline (death usually occurs in min to hrs Chest 2010;138:289)
  - Have **PRN meds** ready to address **air hunger and pain (IV opioids)** and **anxiety (IV haldol, IV BZD)** aggressively and discuss w/ RN. May need infusions. **Glycopyrrolate** for secretions. **STOP paralytic agents** (cisatracurium).
  - Do not withhold appropriate sx management because of concern for hastening death (*Principle of Double Effect*: your focus should be on managing sx, including palliative sedation if no other reasonable options). If in doubt, ask for help.
  - Discuss **vent withdrawal plan** with RT (immediate withdrawal vs down-titration of vent support).

DEATH PRONOUNCEMENT

PRONOUNCEMENT. Introduce yourself to the family, explain what you are doing, express condolences

- **FEEL** for pulse, **LISTEN** for heart sounds/breath sounds (> 60 sec), **SHINE** light to determine absence of pupillary light reflex, and **NOTE** time at the end of your exam, which becomes the time of death

QUESTIONS FOR NEXT OF KIN (Not HCP, but **Next of Kin (NOK)**: Husband/Wife > Children > Other Family)

- If no NOK in room, call NOK to notify of patient's death.
- Ask the family if they would like to see a CHAPLAIN or SOCIAL WORK
- Ask if family would want an AUTOPSY?
- If family accepts autopsy, ask about DISPOSITION OF ORGANS. **Consider recommending the option of MGH retaining organs for further testing, education, research (if not, value of/info from autopsy lower)**
- Are there OTHER FAMILY MEMBERS they would like you to inform?
- Will anyone else be COMING TO VIEW THE BODY prior to morgue?
- **What you can tell family**: body is kept at MGH until the funeral home calls MGH (path: 617-726-2967) and arranges for pick-up. Ask family if they plan to contact funeral home or if they have a preferred funeral home they want notified.

AUTOPSIES are **free** and do not delay funerals (can still have open casket). In addition to helping determine cause of death, they can be instrumental in advancing research.

ONCE YOU LEAVE THE ROOM:

- **Notify ATTENDING and PCP**. Email acceptable if death was expected.
- **Obtain "Report of Death" form** from OA. Fill out in **BLACK** ink. If any mistakes, you will need to START OVER.
  - **Log into Epic** before calling the numbers listed on the form.
  - **Call the Medical Examiner** if necessary or in doubt (most cases not necessary; *NB*: alcohol-related deaths, including EtOH-related liver diease, are reportable). Document the first name of the staff member.
  - **Call New England Organ Bank**: 800-446-6362: will need patient's demographics, cause of death. May require: history of cancer, recent infections, recent labs, hx dementia, other PMHx.
  - **Call the Admitting Office (x6-3393) to inform them of the death**. They will ask cause/time of death, Med Examiner, NEOB.
  - **The "Report of Death" goes to admitting with the chart**. Chart/patient cannot leave the floor until the Report of Death is completed.
- **Document a brief "note of patient death"**: SmartPhrase ".MGHDOMDEATHNOTE".
- Complete short **discharge summary** using "Deceased Patient" portion of the Discharge tab in Epic.

Organ Donation after Brain or Circulatory Death

- ~75% of transplanted organs are from deceased donors, including donation after brain death (DBD) and donation after circulatory death (DCD). DCD represents ~8% of organs procured nationally, ~20% in the Boston area (NEJM 2007;357:209). Organs from DCD and DBD donors have similar long-term outcomes (NEJM 2002;347:248).
- DBD = death based on neurologic criteria ("**brain death**," or irreversible loss of all functions of the brain, including the brain stem
- DCD = death based on **cardiopulmonary criteria** (irreversible cessation of circulatory and respiratory function and mechanical ventilatory support is no longer medically indicated, but criteria for brain death are NOT fulfilled)

Eligibility for Organ Donation

- Medical team determines that discontinuation of medical support is appropriate and discusses this with the HCP or legal next-of-kin
- DO NOT broach the topic of potential organ donation with family; New England Organ Bank (NEOB) is specifically trained to do this.
- If family wishes for withdrawal of support, the medical team notifies NEOB (800) 446-6362 who will coordinate the process for consent and donation. This process can take up to **24 hours.**

Care of the Patient Prior to Organ Donation

- Patients with potential for organ donation need to maintain organ viability in response to potentially severe autonomic and inflammatory responses that occur after severe neurologic insult or brain death.
- Interventions often require a delicate balance to preserve multiple organs: (CCM 2015;43:1291, NEJM 2004;351:2730)
  - Continuous temperature monitoring, telemetry, and lab monitoring for renal function, electrolytes, acid-base status
  - Hemodynamics – goal **MAP 60-110** (JAMA Surg 2014;149:969)
    - Hypertensive autonomic storm after brain death. Esmolol to preserve cardiac function. (Am J Transplant 2005;5:684)
    - Fluids and vasopressors for hypotension/vasoplegia. Consider vasopressin before catecholamines (helps w/ DI)
    - Dobutamine for reduced EF
  - Maintenance of **normothermia** via external warming or cooling
  - **Urine output** monitoring: goal 0.5-1.0 cc/kg/hr. Monitor for DI with brain death.
  - Proper ventilatory support and pulmonary toilet; **lung-protective LTVV** as in ARDSNet. Prevent pneumonia with head elevation, etc. (JAMA 2010;304:2620)
  - Maintenance of **eunatremia**, **euvolemia**, and **acid-base** status
  - Consider glucocorticoids for adrenal insufficiency/general inflammation; thyroid hormone for EF <45% or HD instability (poor evidence)
  - Empiric **antibiotics** if concern for infection
- NEOB and transplant team may request additional testing (e.g. TTE, bronchoscopy)

Death Pronouncement in the Operating Room for DCD patients

- Generally, withdrawal of medical support, including extubation, occurs in the OR after pt is prepped by surgical team
- All members of the organ recovery teams must be outside of the room from the time of withdrawal of support to declaration of death; otherwise this poses a conflict of interest. Family may be present in the OR if they wish.
- Medical team (MD and RN) are present to coordinate end of life care from time of withdrawal of support to death, including PRN palliative medications. NEOB staff may not participate in the administration of medications or declaration of death.
- Death must occur and be declared within 2 hours of extubation, otherwise organs are deemed nonviable.
  - "Dead-donor rule" (DDR) = recovery of organs cannot be the cause of death, and organs should be taken only from persons who are already dead (NEJM 2013;369:1287)
- MD declares death based on the irreversible cessation of circulatory and respiratory function (checks carotid artery for pulsations and auscultates for breath sounds using a sterile ultrasound cover over stethoscope)
  - PEA arrest meets criteria for cessation of circulatory function so long as there is no pulsatile flow on arterial line. Death can be declared even if cardiac electrical activity persists.
  - After death is declared, a a 5-minute observation period begins to ensure no ROSC
- Death paperwork should be signed by declaring MD in the OR (i.e. bring prepped death paperwork with you)

Rheumatology — Approach to Rheumatologic Disease

Overview: rheumatologic diseases may be roughly separated into 4 categories:

Category	Inflammatory Arthritis	Connective Tissue Disease	Vasculitis	Other
Diseases	RA, spondyloarthropathies, PMR, crystalline arthritis	SLE, Sjögren's, scleroderma, MCTD, UCTD, myositis (DM, PM)	Small, medium, large (GCA, PAN, GPA, EGPA)	Autoinflammatory diseases, sarcoid, IgG4-related disease
Work-up	RF, anti-CCP, ANA	**ANA first** C3/C4, anti-Sm, anti-dsDNA, anti-Scl70, anti-histone, anti-U1RNP, anti-Ro/La, antiphospholipid Abs	ANCA, cryoglobulins	Limited role for ACE, can send IgG4

Treatment* (Severity ↓)

- *NSAIDS/Glucocorticoids*
- *Hydroxychloroquine*
- *DMARDS (MTX, SSZ)* / *DMARDS (MTX, AZA, MMF)*
- *Most Biologics* / *RTX, belimumab* / *RTX, TCZ*
- *Cyclophosphamide*

*DMARD = disease-modifying antirheumatic drug, MTX = methotrexate, SSZ = sulfasalazine, AZA = azathioprine, MMF = mycophenolate mofetil, RTX = rituximab, TCZ = tocilizumab. Nuances of treatment not encapsulated by this figure.

- **Rheumatologic ROS**: fevers, rashes/photosensitivity, alopecia, nail/nailfold abnormalities, sicca symptoms, conjunctivitis, uveitis, episcleritis, scleritis, Raynaud's, oral/genital ulcers, polychondritis, enthesitis, serositis sx, thromboses, neuropathy, pregnancy loss.
- **Basic labs**: CBC w/ diff, BMP, LFTs, UA, ESR/CRP, TSH
- **Ddx**: Always consider malignancy and infection as alternative diagnoses prior to initiation of immunosuppressants unless at risk of permanent organ damage (i.e. do not withhold glucocorticoids when suspecting GCA, mononeuritis multiplex, RPGN, etc.)

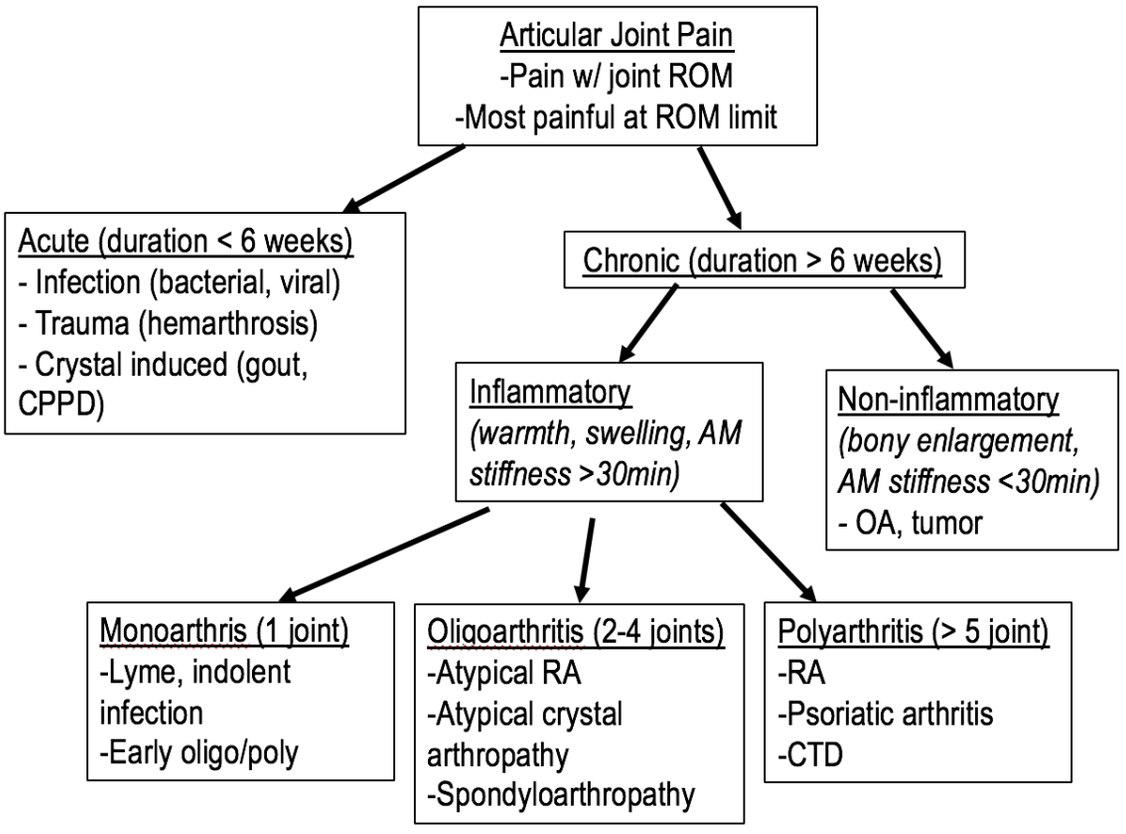
Inpatient Management of Gout
General principle: *Always continue home dose of allopurinol*, send serum uric acid

Diagnosis:
*ACR-EULAR Criteria calculator
- Clinically by symptoms (monoarticular or oligoarticular) Commonly big toe, midfoot, ankles, knees, wrist
- Evidence of tophi
- Joint aspiration with monosodium urate crystals

Monoarticular:
Can consider rheum consult for consideration of steroid injection or dx uncertain. Otherwise treat w/ systemic therapy.

Oligo/polyarticular:
1. NSAID (naproxen 500mg BID)
2. Colchicine (loading dose 1.2mg → 0.6mg 1 hr later → 0.6mg daily for 10-14 days
3. Steroids for 12-14 days (prednisone 40mg daily for 3 days, decrease by 10mg q3days)

Approach to the Patient with Arthritis



Acute Arthritis Syndromes

	Arthritis	Joint pattern	Presentation	Diagnosis	Treatment
ACUTE	**Gout**	- Mono>poly - Podagra (1st sx in 50% pts), hindfoot, fingers, ankle, knee	- Triggers: diuretics, meat, seafood, EtOH, HTN, DM2, CKD - Acute flares→chronic arthropathy (tophi) - Urate nephrolithiasis, chronic nephropathy	- Arthrocentesis: **neg birefringent needle-shaped crystals**, WBC 10k-100k - can co-exist with septic arthritis	- Acute: **colchicine** (1.2mg x1, 0.6mg 1h later, 0.6 mg QD until 2-3d after resolved), **pred** 40mg QD until resolved then taper, **NSAIDs** (approx 5-7d), **intra-articular steroids** - Chronic: **urate lowering tx** if ≥2 attacks/yr, CKD, tophi (uric acid goal<6), diet changes, stop diuretics. Do not stop during acute attack.
	CPPD (pseudogout)	- Mono>poly - Knee>wrist, shoulder, ankle	- Can be asymptomatic - Can coexist with gout, OA	- Arthrocentesis: **small pos birefringent rhomboid crystals,** WBC 10k-100k - chondrocalcinosis	- Acute: if ≤2 joints → **intra-articular steroids** (1st line). 2nd line is same as gout (prefer **colchine** w/in 24h sx onset) - Chronic: consider HCQ, low-dose pred, MTX
	Septic arthritis	- Mono - Knee (50%), >1 joint (20%)	- Hematogenous spread (most common), endocarditis - ↑risk in RA - Staph>strep>GNRs	- Arthrocentesis: positive GS/Cx, **WBC 50k-150k**	- **Antibiotics** for 3-4 weeks - Joint drainage/washout (ortho c/s)
	Reactive arthritis	- Oligo > mono > poly (small joints) - Asymmetric - LE > UE	- 1-4 weeks post-infxn - Enteric: *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C. diff* - GU: *Chlamydia*, *E. coli, Ureaplasma*, *Mycoplasma* - Conjunctivitis, urethritis, cervicitis, oral ulcers, keratoderma, E nodosum	- Presence of preceding infxn - Arthrocentesis: GS/Cx - Stool cx (if diarrhea) - GC/Chlamydia	- If GU infxn, treat. If GI infxn, may not need to treat. - Acute: **NSAIDs** (1st line), intra-articular steroids (2nd line), prednisone (3rd line) - Chronic: if >6 mo, **MTX** or SSZ

Chronic Arthritis Syndromes

	Arthritis	Joint pattern	Presentation	Diagnosis	Treatment
CHRONIC	**Osteoarthritis**	- Poly - Knees, hips, 1st MTP, CMC, PIP, DIP, C-spine, L-spine	- Age >45 - AM stiff <30min, slow progression, no warmth, muscular wasting - Stage 1: pain limits high-impact activity - Stage 2: constant pain, affects ADLs - Stage 3: intense pain	- Clinical dx - Bony swelling, joint deformity, limited ROM	- PT, braces - Topical **NSAIDs**, PRN NSAIDs - Duloxetine 60-120mg QD - **Intra-articular steroids** - If severe, refer to ortho - Not recommended: glucosamine, bisphosphonates (ACR Guideline 2019)
	Rheumatoid Arthritis	- Mono in early stage, then poly - Small peripheral (MCP, PIP, wrists, MTP) - Symmetric	- F>M, age 35-65 - AM stiff >30min - Joint deformity	- **RF, anti-CCP** - Joint XR - Exclude other causes	- Acute: **prednisone** or **NSAIDs**, initiate DMARD if not on - Chronic: **DMARD** (MTX > HCQ > SSZ > lefulomide); if fails monotx, consider combination or transition to **biologic** (infliximab, abatacept, tocilizumab)
	Psoriatic arthritis	- 5 patterns (distal DIP, asymm oligo, symm poly, arthritis mutilans, spondyloarthritis [sacroiliitis]) - axial (spine) involvement (42%)	- 70% with psoriasis - Extra-articular: synovitis, enthesitis, dactylitis, nail pits/onycholysis, uveitis	- Clinical dx - ↑ ESR/CRP (40%) - **HLA-B27** - CASPAR criteria (91% Sn / 99% Sp)	- **NSAIDs** (1st line) - If mod/severe, **MTX** > SSZ, leflunomide - If severe/erosive**, TNFα inhibitor** infliximab, adalimumab, golimumab (ACR Guideline 2018)
	Ankylosing spondylitis	- Spine & SI joints	- Gradual onset - AM stiff >30min - Pain in low back, buttock, ankle, TMJ - Extra-articular: synovitis (mono or oligo), enthesitis, dactylitis, uveitis, psoriasis, IBD	- **Sacroiliitis** (XR or MRI) - Impaired spine mobility - ↑ ESR/CRP - HLA-B27 (90% Sn/Sp)	- **NSAIDs** (1st line) - **No steroids** - DMARDs not effective - **TNFα inhibitor** (2nd line) infliximab, etanercept, adalimumab

Synovial Fluid Analysis

	NORMAL	NON-INFLAMMATORY	INFLAMMATORY	SEPTIC	HEMORRHAGIC
Clarity	Transparent	Transparent	Transparent-opaque	Opaque	Bloody
Color	Clear	Yellow	Yellow to opalescent	Yellow to green	Red to brown
Viscosity	High	High	Low	Variable	Variable
WBC (per mm^3)	< 200	0 - 2,000	2,000 - 100K	50 - 150K	200 - 2,000
PMNs (%)	< 25	< 25	≥ 50	≥ 75	50 - 75

Disease	Clinical Presentation	Work-up	Treatment	Complications
SLE	- F> M, 15-40 y/o - Discoid/malar rash (spares nasolabial fold), photosensitivity, serositis, **nephritis**, oral/nasal ulcers, psychosis, neuro d/o, arthritis, cytopenias, constitutional sx (fever, weight loss, fatigue) - ↑ CK suggests myositis	⊕ ANA (>95%) ⊕ **anti-dsDNA** (~ 70% pts, a/w active dz and lupus nephritis) ⊕ **anti-Sm** (30% pts, specific, remains + in remission) ⊕ **anti-RNP** ⊕ **anti-SS-A/Ro, +anti-SS-B/La** ⊕ antiphospholipid antibodies - C3, C4, ESR, CRP, UPCR (2019 EULAR/ACR Criteria)	- Lupus nephritis: **MMF** (1st line) - Skin, joint, serositis: **prednisone** 20mg and **HCQ** - Other end organ involvement: high dose **prednisone**, **HCQ** + other **DMARD**	- High risk **VTE**/ATE - CNS, Renal dz - 40% w/ **APLAS** - Osteonecrosis (both 2/2 SLE and steroids)
Sjogrens	- F>M, 40-60 y/o - **Sicca sx** (dry mouth/eyes), caries, parotid enlargement, vasculitis, interstitial nephritis, neuropathy, cytopenias, RA/SLE a/w 2° SS	⊕ANA ⊕ **anti-SS-A (Ro),** ⊕ **anti-SS-B (La)** - Schirmer test, parotid gland ultrasound, salivary gland biopsy	- Sicca only: sx mgmt - **Systemic**: **HCQ**/chloroquine, MTX, AZA, RTX, cyclophosphamide, glucocorticoids	- 5-10% lifetime risk of NHL, MALT lymphoma
Myositis (polymyositis, dermatomyositis, inclusion body myositis)	- F:M (2:1), 40-50 y/o - Proximal > distal muscle weakness - Extramuscular: constitutional sx, arthralgias, dysphagia, pulm sx (cough, DOE, ILD), HTN, DM2 - DM skin findings: heliotrope rash, poikiloderma (chest: V-sign; back: shawl sign; thigh: Holster sign), scalp rash, Gottron's papules - DM sine myositis = skin features w/o muscle weakness, a/w severe ILD	⊕ **ANA** (50%), ⊕ **anti-Jo1** (a/w ILD, mechanic hands, arthritis, 20%), ⊕ anti-Mi2 (15-20%, a/w acute onset, shawl sign, good prognosis) ⊕ anti-MDA5 - CK, aldolase, myositis panel, LDH, AST/ALT - Muscle biopsy *DM*: CD4 cells *PM/IBM*: CD8 cells	- Initiation: **prednisone** 1mg/kg x4-6wk then taper - Maintenance: **AZA/MTX** - Resistant/severe: pulse steroids, AZA, MTX, MMF, IVIG, RTX, cyclophosphamide (if ILD)	- Occult **malignancy** in DM (9-32% incidence): commonly ovarian, breast, colon, lung, NHL, nasopharyngeal - ILD in 10% - upper esophageal dz - increased risk of MI
Systemic Sclerosis (scleroderma)	- F:M 4:1, 30-50 y/o - Systemic: may be **limited cutaneous** (67%, skin thickening in hands/face only, commonly with CREST sx, PAH) or **diffuse cutaneous** (33%, diffuse skin thickening, multi-organ dz, less commonly with CREST sx) - CREST: **C**alcific nodules, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias - Other systemic sx: renal crisis, ILD (>70%), PAH (10-40%) - Systemic sclerosis sine scleroderma = pts with scleroderma but *w/o skin findings*	⊕ **ANA** (95%) ⊕ **anti-centromere*** (a/w limited, only seen in 5% pts with diffuse) ⊕ **anti-Scl-70*** (a/w diffuse) ⊕ **RNA-pol-III*** (a/w diffuse and scleroderma renal crisis) - HRCT, PFT, TTE to eval for ILD and pHTN *Ab are >99% specific (Arthritis Rheum 2013;11:2737)	- Skin: MMF, MTX - GI: PPIs, motility agents - Lung: CCBs, endothelin-1 antagonist, PDE inhibitors, prostacyclin agonists - MSK: Low dose prednisone, HCQ, MTX - Raynaud's: **CCBs**	- Increased risk of multiple cancers - **Scleroderma renal crisis** (<20%): AKI, abrupt HTN; a/w anti-RNA-pol III; treat with **ACEi** (captopril) + ***avoid steroids***
MCTD	- 80% F - Overlap of SLE, systemic sclerosis, and polymyositis; Raynaud's; non-erosive arthritis	⊕ ANA (often **speckled**) ⊕ **anti-RNP** (100%) **by definition**	- SLE features: **glucocorticoids**, RTX - Scleroderma features: less responsive to steroids	Main cause of death is **PAH**
UCTD & Overlap syndromes	- Early Raynaud's, incomplete lupus	- Diagnosis of exclusion; does not meet criteria for diagnosis of specific disease	- Managed according to symptoms	- According to dominant clinical presentation

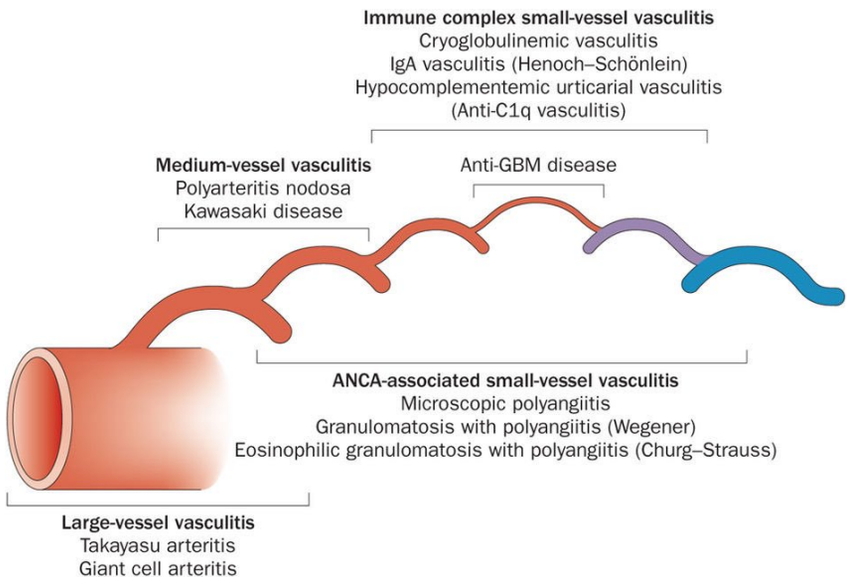
DIAGNOSTIC OVERVIEW (Arthritis Rheum 2013;65:1)

- Classified by size and type of blood vessel involved. Large vessels (aorta and its branches) vs. medium-sized vessels (main visceral arteries = named) vs. small vessels (vessels without names such arterioles, capillaries, venules)

STEP 1 – SUSPECT VASCULITIS

Overview:

- No "typical" presentation but consider in constitutionally ill patient with evidence of multisystem organ involvement and evidence of inflammation
- **LARGE vessel**: aorta/branches, e.g. external carotid, temporal, ophthalmic → limb claudication, bruits, asymmetric BP, absent pulses, HA, visual loss
- **MEDIUM vessel**: renal/hepatic/mesenteric arteries, etc. → cutaneous nodules, "punched out" ulcers, livedo racemosa, digital gangrene, mononeuritis multiplex (e.g. foot/wrist drop), renovascular HTN
- **SMALL vessel**: vessels of skin, small airways, glomeruli → palpable purpura, glomerulonephritis, alveolar hemorrhage, mononeuritis multiplex, scleritis



General testing:

- Inflammation? → CBC w/ diff (ACD, thrombocytosis, neutrophilia, eosinophilia), ESR, CRP
- Organ involvement? → BMP, LFTs, stool guaiac, CXR, brain MRI (if neurologic symptoms), CTA (if GI/claudication)

Presentation-specific testing (i.e. small-vessel s/sx): difficult to discern clinically

- Immune complex formation? → complement levels (C3, C4), ANA, RF/Cryoglobulins
  - ANA/RF are NOT positive in 1° vasculitis; ⊕RF could suggest cryoglobulinemia or endocarditis (in addition to RA)
  - C3/C4 ↓ in cryoglobulinemia, SLE, and 25% of PAN; normal complement levels in all other vasculitides (rarely low in HSP)
- ANCA-associated? → send ANCA for IIF; will reflex to MPO (p-ANCA) and PR3 (c-ANCA) antibody ELISA if positive

STEP 2 – RULE OUT MIMICS: based on suspicion/atypical presentation

- Ddx: infections (**SBE**, HIV, **HBV**, **HCV**, EBV, *Neisseria,* Syphilis), malignancies (leukemia, lymphoma, myeloma, MDS, solid tumors), IgG4-Related Disease (IgG4-RD; NEJM 2012;366:539), cocaine / levamisole, other drug-induced vasculitides, hypercoagulable states (APLAS, TTP)
  - If skin necrosis of lower extremities → consider cholesterol emboli or calciphylaxis
  - If renal artery, internal carotid artery, vertebral artery involvement → consider fibromuscular dysplasia
- Tests: BCx, HBV, HCV, HIV, SPEP/UPEP/SFL/UFL, tox screen, consider IgG4

STEP 3 – CONFIRM DIAGNOSIS

Tissue biopsy: may be required to secure diagnosis

- Skin, sural nerve and muscle (PAN, EGPA, first prove abnormal NCS), temporal artery (GCA), kidney (GPA, MPA), lung (GPA, MPA)
- Less common: testicle (PAN), rectum/gut, liver, heart, brain (1° CNS vasculitis), sinus (GPA)

Conventional angiography: particularly if tissue biopsy is unfeasible

- Celiac/superior mesenteric, renal (PAN), chest (Takayasu, GCA), extremities (Buerger disease), brain (1° CNS vasculitis)

GENERAL TREATMENT APPROACH

- Remove inciting agents (meds, drugs), treat primary conditions (infections)
- Induction: often steroids + cyclophosphamide (CYC) *or* biologic, i.e. rituximab (RTX) for ANCA-associated (RAVE), nephrology at MGH tends to use steroids + CYC + RTX (RITUXVAS)
- Maintenance: less well defined, typically azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), RTX
- Monitoring: disease activity and drug toxicity
- Prevention of treatment complications: PPD, HBV serologies, Pneumovax (and other vaccines), glucocorticoid prophylaxis (consider PPI, TMP-SMX, calcium/vit D)

LARGE–VESSEL VASCULITIS (NEJM 2003;349:160)

GIANT CELL ARTERITIS: inflammation of the aorta & its extracranial branches (i.e. spares ICA), often involves temporal artery (TA), most common primary systemic vasculitis. Age >50, 2:1 M:F. Rare <50 yo = consider alternative diagnoses, mimics.

- **Sx**: constitutional (low grade fevers, fatigue, wt loss, anorexia), new/different HA, abrupt visual disturbance (amaurosis fugax, blindness, diplopia), jaw claudication (most specific sign; fatigue with chewing, NOT PAIN)
- **Exam**: asymmetric BP/pulse; tender, thickened or pulseless TA; jaw claudication (r/o TMJD)
- **Dx**: a combination of **2-3+ symptoms and exam findings** should prompt **doppler U/S** and **rheum consult**. Gold standard = **temporal artery biopsy**. ↑ESR (ESR usually high but <50 in 10%), ↑CRP (correlates with disease activity) ↑IL-6
  - TA biopsy: start w/ unilateral; if ⊖, consider bilateral (↑ yield by 5%); up to 30-45% of bx may be **false neg** due to "skip areas"
  - If concern for large-vessel GCA (e.g. aorta, subclavian): pursue imaging (CTA vs. MRA)
- **Rx**: start **prednisone 1mg/kg/d immediately (up to 60mg)** if high suspicion; **NEVER delay Rx for Bx**
  - Steroid sparing regimens include **tocilizumab**, MTX

POLYMYALGIA RHEUMATICA: seen in 50% of GCA pts; 10% develop GCA, peak age 70-80

- **Sx**: symmetrical AM stiffness/pain (+/- weakness) in neck, shoulders/prox arms, hips/prox thighs
- **Rx**: **prednisone 12.5-20 mg/day** with slow taper, consider addition of MTX if refractory (Ann Rheum Dis 2015;74:1799)

TAKAYASU ARTERITIS: "pulseless disease," inflammation of thoracoabdominal aorta & branches. Age <40, 8:1 M:F, Asians

- **Sx**: inflammation (fever, arthralgias/myalgias, weight loss, night sweats), vessel inflammation (carotidynia, limb claudication), vascular dz (TIA/stroke, HF, CAD, mesenteric ischemia)
- **Exam**: unequal pulses and BPs (lower > upper extremities), ↓ pulses, bruits, formal eye exam
- **Dx**: MRA or CTA; arteriography will show occlusion, stenosis, aneurysms; consider carotid ultrasound/Doppler studies
- **Rx**: **prednisone 1mg/kg/d**; 50% of patients will need 2nd agent for chronic sx (MTX, tocilizumab, TNFi)

MEDIUM–VESSEL VASCULITIS

POLYARTERITIS NODOSA: kidneys, skin, muscles, nerves, GI, joints (almost always spares lung). Age 40-60, **associated with HBV**

- **Sx**: mononeuritis multiplex (in up to 70% of pts), GI distress (mesenteric ischemia), myalgias, AKI (GN suggests alternate etiology), testicular/ovarian pain (>10%), seizures
- **Exam**: HTN, skin lesions (erythematous nodules, purpura, livedo reticularis, ulcers, bullous eruption, palpable purpura), neuropathy
- **Dx**: gold standard = **biopsy**; HBV/HCV serologies, C3/C4, CTA/MRA showing focal stenosis or microaneurysm (renal/mesenteric vessels)
- **Rx**: **prednisone 1mg/kg/d** ± CYC 2 mg/kg/d PO or IV pulse (if mod-severe or steroid-refractory); antivirals if HBV-related

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE): segmental inflammation of small-med arteries and veins of extremities; occlusive intravascular thrombi. Age ≤ 45, 70-90% ♂, strongly associated with **tobacco use**, Raynaud's in 40% of pts

- **Dx**: clinical - 1) age 2) tobacco use 3) distal ischemia 4) arteriographic findings 5) exclusion of autoimmune, thrombophilia, DM, embolism
- **Rx**: **smoking cessation**! Iloprost (PG analog) for pain, CCB (for Raynaud's), intermittent pneumatic compression (painful ulcers)

ANCA–ASSOCIATED SMALL–VESSEL VASCULITIS

c-ANCA = cytoplasmic staining (proteinase 3 [PR3]), p-ANCA = perinuclear staining (myeloperoxidase [MPO])

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S GRANULOMATOSIS): necrotizing vasculitis with granulomatous features by sx (sinusitis, mass lesions [orbital pseudotumor, subglottic stenosis, large pulm nodules]) or on path, usually involving upper and lower airways (90%) and kidney (80%), +/- cutaneous leukocytoclastic vasculitis

- **Dx**: sinus CT (+/- bone erosions), Bx w/ **granulomatous** inflammation of vessel walls, ⊕PR3-ANCA 90%
- **Rx**: limited disease: MTX + prednisone; severe disease: IV pulse steroids x3 days (with oral taper) + RTX *or* CYC

MICROSCOPIC POLYANGIITIS (MPA): necrotizing vasculitis of small vessels **without** granulomas. All ages (mean 50-60), M>F, ↑ in Caucasians; most common cause of pulmonary-renal syndrome (NEJM 2012;367:214)

- **Dx**: ⊕p-ANCA 70%, ⊕c-ANCA rare**,** BAL, gold standard = **skin/renal biopsy;** r/o HIV, cryo, hep B/C
- **Rx:** similar to GPA → methylprednisolone and cyclophosphamide or RTX (NEJM 2010;363:221)

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME): necrotizing granulomatous inflammation of vessels in lungs, skin, nerves; strongly associated with **asthma/allergic rhinitis** (asthma precedes vasculitis)

- **Dx**: ≥4 of following: asthma, >10% peripheral eos, neuropathy, pulm opacities, paranasal sinus disease, consistent bx. 50% ⊕ p-ANCA
- **Rx**: IV pulse steroids x3 days (with oral taper) ± CYC or RTX (if severe disease) or mepolizumab (if not severe)
- Do not delay rx if mononeuritis as can lead to nerve infarction

IMMUNE COMPLEX–ASSOCIATED SMALL–VESSEL VASCULITIS

HENOCH-SCHÖNLEIN PURPURA: 70% in children; ♂>♀; preceding URI, in adults, more severe presentation, med related, a/w malignancy

- **Sx**: classic tetrad of 1) palpable purpura (100%, on LEs/buttocks = dependent areas), 2) colicky abdominal pain (60%), 3) arthritis (75%), 4) renal involvement (40-50%, proteinuria, microscopic hematuria, RPGN)
- **Rx**: children: supportive, usually self-limited; adults may require immunosuppression: steroids, dapsone. NSAIDs if mild GI/ arthralgias

CRYOGLOBULINEMIA: immunoglobulins that precipitate at low temperatures and re-dissolve on rewarming

- **Type 1**: monoclonal (usually IgM or IgG), associated with **Waldenstrom's, MM**
  - **Sx**: peripheral neuropathy, renal impairment, hyperviscosity (Raynaud's, digital ischemia, livedo)
- **Type 2**: "mixed" monoclonal IgM against polyclonal IgG (often IgM with RF activity), associated with **HCV**, HIV, HBV, EBV
- **Type 3**: "mixed" polyclonal Ig (IgM or IgG) against polyclonal Ig (IgM or IgG), associated with **CTDs**, lymphoproliferative disorders, HCV
  - **Sx**: palpable purpura, arthralgias, myalgias, mononeuritis multiplex
- **Rx**: treat underlying cause (e.g. HCV); **prednisone** ± 2nd immunosuppressive agent (RTX, CYC); consider **plasma exchange** for Type 1

Behcet's Disease: autoinflammatory condition characterized by recurrent aphthae, vasculitis, and skin/GI/neuro/joint sx

- **Epi**: F>M, age 20-40, Turkey, Middle East, and Asian countries
- **Sx**: recurrent painful oral ulcers and ≥2 of the following: painful genital ulcers (specific), ocular disease (most commonly uveitis or retinitis), skin lesions (pustules, folliculitis, papules, erythema nodosum),
  - Other manifestations: GI (similar to IBD), neurologic disease (parenchymal, extra-parenchymal), vascular disease (ATE/VTE, **vasculitis**, aneurysms [PA]), arthritis (nonerosive, asymmetric). *Less common*: kidney, heart, lung disease
- **Dx**: clinical dx only, no specific laboratory tests exist; may have ↑ ESR/CRP
- **Rx**: (Ann Rheum Dis. 2018; 77:808)
  - Mild (arthritis, ulcers): **colchicine** 1-2 mg daily, low dose prednisone. Apremilast (PDE-4 inhibitor) for ulcers (NEJM 2019;381:1918)
  - Severe: **prednisone** 1mg/kg/d, may add 2nd line agents: AZA, anti-TNF, IFNα, CYC, CP, MTX
  - If organ failure (esp. ophthalmic involvement): IV pulse steroids x 3d

Familial Mediterranean Fever (FMF): autoinflammatory disorder due to mutations in *MEFV* gene, autosomal recessive inheritance, characterized by recurrent bouts of fever and serosal inflammation

- **Epi**: most common in Jews, Armenians, Turks, and Arabs. Onset <10 yo (65% pts), <20 yo (90% pts)
- **Sx**: recurrent acute attacks (1-3d, resolves spontaneously) of fever associated w/ peritonitis (often mistaken for surgical abdomen), unilateral pleuritis, arthritis (monoarticular, sterile joint), or skin lesions (erysipelas-like).
  - *Other manifestations include*: exertional myalgia, pericarditis, testicular pain, and aseptic meningitis.
  - Long-term complications: secondary (AA) amyloidosis: renal disease (major cause of mortality), SBO, infertility
- **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)
- **Rx**: **colchicine** 1-3 mg/day (to prevent acute attacks and progression to amyloidosis). 5-10% colchicine resistant, add on IL-1 inhibitors (Ann Rheum Dis. 2016;4:644)

Adult Onset Still's Disease (AOSD): systemic inflammatory disorder characterized by fevers, arthritis, and rash. Can present as single episode (wks-mos), multiple flares, or be persistently active.

- **Epi**: F=M, bimodal (15-25 yrs old and 36-46 yrs old)
- **Sx**: fever; arthralgias; **evanescent, salmon-colored maculopapular rash** that coincides w/ fever, usually on the trunk, may be precipitated by trauma (Koebner phenomenon); pericarditis; pleural effusions; **macrophage activation syndrome** (rheum-associated HLH; see *Hematology*)
- **Dx**: **Yamaguchi criteria** requires **≥5 features,** including **≥2 major criteria** (J Rheumatol 1992;19:424)
  - Major: fever ≥39ºC for ≥1 week, arthralgias/arthritis ≥2 weeks, salmon-colored rash, ↑ WBC (≥10K + ≥80% PMN)
  - Minor: sore throat, LAD, HSM, ↑AST/ALT, ↑ LDH, negative ANA/RF
  - Other labs (not part of criteria): ↑ ESR/CRP, **ferritin >3000 ng/mL** (if >10,000, consider MAS spectrum), ↑ plt, ↓ Hgb
- **Rx**:
  - Mild: **NSAIDs**
  - Severe: prednisone 0.5-1mg/kg/d (may not respond). If uncontrolled: MTX, anti-TNF, anti-IL6R, anti-IL1

Fibromyalgia: *NOT* a rheumatic disease. Chronic widespread musculoskeletal pain, often w/ fatigue, sleep disturbance, and multiple somatic symptoms.

- **Epi**: F>M, 20-55 yo. Can coexist with other inflammatory diseases like SLE, RA. Often psychiatric comorbidities.
- **Sx**: widespread MSK pain, fatigue, cognitive disturbance (decreased attention & ability to perform complex tasks), psychiatric sx (depression), headache, parasthesias, IBS. Pan-positive ROS not uncommon.
- **Dx**: clinical diagnosis, > 3 months duration of sxs, multiple tender points. Newer criteria involve widespread pain index (WPI) and symptom severity (SS) scale (J Pain 2019;6:611)
  - Labs: normal ESR, CRP, TSH, CBC, BMP
- **Rx**:
  - Initial therapy: patient education, **exercise program**
  - Pharmacologic therapy: 1st line includes **amitriptyline,** duloxetine, or milnacipran; also may consider cyclobenzaprine, gabapentin, and pregabalin (monotherapy > combo therapy). Avoid narcotics.

Antibody	Antigen	ANA pattern	Disease	Comments
Inflammatory polyarthritis				
RF (IgM)	Fc gamma	negative	RA (50-75%), Sjogren's (30%), Cryoglobulinemia (90%), chronic infection	- Nonspecific despite name: RA, CTD, cryoglobulinemia, chronic infxn (e.g. HCV, SBE). - Positive in 10% of healthy patients - RA: "seropositive", a/w erosive and extraarticular manifestations (nodules, scleritis, ILD, pleuritis, rare rheumatoid vasculitis)
CCP	Citrullinated proteins	negative	RA (50-75%)	- Most specific test for RA, positive in 50-75% ("seropositive RA"), a/w erosive dz & extraarticular manifestations - Used for dx only, *NOT* marker of dz activity
Connective tissue diseases (SLE, Sjogren's, SSc, MCTD, UCTD, DM/PM)				
ANA	- ANA = antinuclear antibodies (specific ANA Abs listed below). Low titer ≤1:160 are often false positive. If ⊕, order specific autoantibodies guided by clinical presentation - ⊕ ANA: MCTD (100%), SLE (98%), scleroderma (90%), drug-induced lupus (90%), Sjogren's (60%), PM/DM (50%) - Ddx for ⊕ ANA: *Autoimmune:* autoimmune hepatitis, PBC, IBD, myasthenia gravis, Graves', Hashimoto's; *ID:* malaria, SBE, syphilis, HIV, HSV, EBV, HCV, parvo-B19; *Systemic inflammation:* lymphoproliferative disorders, IPF, asbestosis			
dsDNA	ds/mtDNA	homogeneous	SLE (40-60%)	- Specific for SLE, a/w SLE *activity* and lupus nephritis, consider TNF inhibitor drug-induced lupus
Histone	histones	homogeneous	SLE, drug-induced lupus (90%), Felty's	- Sensitive, but not specific for drug-induced lupus (DIL) - Common meds: procainamide, hydralazine, phenytoin, lithium
RNP	U1-snRNP	speckled	MCTD (100%), SLE (30%)	- MCTD: high-titer anti-U1 RNP
Smith	snRNP	speckled	SLE (30%)	- Specific for SLE, not indicative of dz activity
SS-A/Ro	Ro52, Ro60	speckled	Sjogren's (75%), SLE (40%),	- Can be seen with myositis - In SLE, a/w skin disease and congenital heart block - **2% SLE pts have ⊖ ANA but ⊕ anti-Ro Abs**
SS-B/La	La	speckled	Sjogren's (40%), SLE (10-15%)	- In SLE a/w congenital heart block
ACA	CENP A-F	centromere	lcSSc (15-40%)	- A/w limited systemic sclerosis, ↑ risk of PAH, ↓ risk of ILD, esophageal disease
Scl-70	topo-I	speckled	dcSSc (10-40%)	- A/w diffuse systemic sclerosis; ↑ risk of ILD, scleroderma renal crisis
RNA pol III	RNA pol. III	nucleolar	dcSSc (4-25%)	- A/w scleroderma renal crisis, rapidly progressive skin disease, cancer
Fibrillarin	U3-RNP	nucleolar	dcSSc (<5%)	- A/w PAH, pulmonary fibrosis, and myositis, esp. in African-Americans
PM-Scl	exosome	nucleolar	SSc (5-10%)	- A/w limited systemic sclerosis, ↓ risk of pulmonary and renal dz, ↑ risk inflammatory myositis
Myositis				
Jo-1*	tRNA (His)	cytoplasmic	PM/DM (30%), anti-synthetase syndrome (~20%)	- Antisynthetase syndrome: myositis (DM/PM), ILD (70%), polyarthritis, mechanic's hands, Raynaud's, fever
Mi-2*	Mi-2	homogenous/ speckled	DM (15-20%)	- More likely in acute DM, good prognosis
MDA-5*	MDA-5	negative	DM	- Clinically amyopathic dermatomyositis, rapidly-progressive ILD
TIF1g*	TIF1g	fine speckled	Juvenile DM	- A/w malignancy in adult DM
SRP*	signal recog. particle	cytoplasmic	PM	- Immune-mediated necrotizing myopathy (degenerating, regenerating, and necrotic cells on bx), rapidly progressive disease course
HMGCR	HMG CoA reductase	negative	myositis	- Immune-mediated necrotizing myopathy, 70% with statin exposure (at any time in past), ≠ statin myopathy (does not respond to discontinuation of statin), very high CPK, often steroid-refractory, good response to IVIG
Vasculitis				
PR3 (c-ANCA)	proteinase 3	negative	GPA (90%)	- Poor correlation of titer with disease flare/remission - Antibody frequency lower in GPA without renal involvement
MPO (p-ANCA)	myelo-peroxidase	negative	MPA (70%), EGPA (50%), Renal-Limited, DIV (95%)	- Poor correlation of titer with disease flare/remission - Drug-induced vasculitis (DIV): high-titer positive for MPO (hydral, PTU, minocycline) - Levamisole vasculitis 2/2 cocaine use: MPO or PR3/MPO
Cryo-globulins	Fc gamma	negative	Cryoglobulinemic vasculitis	- HCV > HBV, HIV, CTDs, lymphoproliferative disease - A/w low C4, glomerulonephritis, +RF

* ordered as part of myositis panel

DRUG/CLASS	INDICATIONS	COMMON TOXICITIES
Azathioprine (AZA; Imuran, Azasan) *6-MP is downstream metabolite of AZA*	DM/PM, RA, SLE nephritis, vasculitis	GI, bruising, myelosuppression, lymphoproliferative d/o, hepatotoxicity. **Test for TPMT deficiency as low levels can ↑ toxicity.** (TPMT metabolizes 6-MP to inactive metabolites → deficiency increases circulating 6-MP levels). **Do not give** with xanthine oxidase inhibitors (**allopurinol**, febuxostat)
Cyclophosphamide (CYC; Cytoxan)	SLE (LN), vasculitis (most severe)	Myelosuppression, **hemorrhagic cystitis** (MESNA for ppx), lymphoma, **infertility** (cumulative dose, leuprolide ppx), <1% pneumonitis, teratogen
Hydroxychloroquine (HCQ; Plaquenil)	RA, SLE, Sjogren's	N/V, **retinopathy (q1y retinal exam)**, dizziness, alopecia, myelosuppression
Leflunomide (LFM; Arava)	PsA, RA	N/V, alopecia, rash, diarrhea, HTN, **hepatotoxicity**, URI, dizziness/HA, **teratogen**
Methotrexate (MTX; Rheumatrex, Trexall, Otrexup, Rasuvo, Xatmep)	RA (first line), PsA	**Myelosuppression**, **hepatotoxicity (co-administer folate)**, **pneumonitis**, stomatitis, rash, teratogen
Mycophenolate Mofetil (MMF; CellCept, MyFortic)	AAV, DM/PM, PsA, Scleroderma, SLE	Cardiac (HTN, edema, CP, tachycardia), HA, insomnia, diarrhea, rash, pain, fever, stomatitis, teratogen
Sulfasalazine (5-ASA; Azulfidine)	AS, IBD, JRA, psoriasis, RA	Sore throat, stomatitis, myelosuppression, N/V, rash, HA; check G6PD
Apremilast (Otezla); PDE4 inhibitor	PsA, severe psoriasis	N/D, URI, depression, weight loss
Tofacitinib (Xeljanz); JAK inhibitor	RA, AS, psoriasis	Infection, hepatotoxicity, lymphoma, diarrhea, ↑clotting risk
BIOLOGIC, non-TNF*		
Abatacept (Orencia); CTLA4	PsA, RA	Infection, HA, nausea, HTN, dizziness, dyspesia
Anakinra (Kineret); anti-IL-1R	AOSD/MAS, gout, Schnitzler syndrome	Myelosuppression (neutropenia), rash/injection reactions, HA, arthralgia, fever
Belimumab (Benlysta); anti-BAFF	SLE	**Depression**, HA, infusion reaction, PML, GI
Canakinumab (Ilaris); anti-IL-1b	CAPS, CAD (CANTOS)	Infection, HA, vertigo, GI, MSK pain, nasopharyngitis
Rituximab (Rituxan); anti-CD20	APLAS, GPA/MPA, IgG4-RD, Scl-ILD, (SLE)	Infection, HTN, **infusion reaction (use premeds)**, TLS, PML, fever, rash/pruritus, LE edema, HACA
Tocilizumab (Actemra); anti-IL-6R	GCA, RA	Infection, **hepatotoxicity**, HLD, GI perforation
Secukinumab (Cosentyx); anti-IL17A	AS, PsA, psoriasis	Infection, IBD flare
Ustekinumab (Stelara); anti-IL-12/23	PsA, psoriasis	Infection, RPLS, seizures
IVIG	APLAS, DM/PM, IBM, IMNM, Kawasaki's	**Transfusion reactions/anaphylaxis**, **aseptic meningitis**, **thromboembolism**, HA
BIOLOGIC, TNF inhibition* (all can cause myocardial toxicity)		
Adalimumab (Humira); anti-TNF	AS, IBD, PsA, psoriasis, RA	HA, nausea, rash, infection, **drug-induced lupus**
Infliximab (Remicade); anti-TNF	AS, IBD, PsA, psoriasis, RA	
Golimumab (Simponi); anti-TNF	AS, IBD, PsA, RA	
Certolizumab (Cimzia); anti-TNF	AS (axial), IBD, RA	
Etanercept (Enbrel); sol. TNF-R	AS, PsA, psoriasis, RA	

*Can cause **HBV /TB reactivation (check hepatitis serologies, PPD and/or IGRA prior to starting)**. If positive, start antiviral prophylaxis with entecavir (HBV reactivation) and prophylaxis with INH (latent tuberculosis) as per ID/rheum. TNF-alpha inhibitors are **safe** in **HCV infection**→ may be beneficial (Expert Opin Biol Ther 2012;12:193)

AAV (ANCA-associated vasculitis), AOSD (Adult-onset Still's disease), APLAS (anti-phospholipid antibody syndrome), AS (ankylosing spondylitis), DM (dermatomyositis), EGPA (eosinophilic granulomatosis with polyangiitis), GCA (giant cell arteritis), GPA (ranulomatosis with polyangiitis), IBD (inflammatory bowel disease), IMNM (immune-mediated necrotizing myopathy), JRA (juvenile rheumatoid arthritis), MAS (macrophage activation syndrome), MPA (microscopic polyangiitis), PM (polymyositis), PsA (psoriatic arthritis), RA (rheumatoid arthritis), SLE (systemic lupus erythematosus), UC (ulcerative colitis)

Screening: begin at age ≥45 years *OR* after gestational DM (GDM) *OR* if BMI ≥25 (≥23 in Asian-Americans) + RF (1st degree relative with DM, nonwhite, history of CVD, HTN, HDL<35, triglycerides >250, PCOS, sedentary); screen q3y if normal (ADA Guidelines 2019)

Pre-Diabetes (Diab Care 2019:42:S13)

- Diagnosis: A1c 5.7-6.4%; fasting plasma glucose (FPG) 100-125; or 75g OGTT w/ 2hr glucose 140-199
- Monitoring: A1c at least q1y; if A1c 6-6.4%, screen q6mo *(25-50% 5-year risk of progression to diabetes if A1c 6-6.5%)*
- Treatment: lifestyle interventions most effective; **metformin** also effective, esp. if BMI ≥35, age <45, or GDM hx (Cochrane Rev 2019)

Diabetes (Diab Care 2019:42:S13)

- Diagnosis*:* A1c ≥6.5%; FPG ≥126; 75g OGTT with 2hr glucose ≥200; or random BG ≥200 & symptoms. Unless diagnosis is made by symptoms & random glucose >200, **confirm with repeat or additional test**. For T1DM, check TSH, celiac screen at diagnosis. Use FPG if high RBC turnover: sickle cell disease, 2nd/3rd trimester of pregnancy, ↓G6PD, HD, recent blood loss/transfusion, EPO tx. A1c less reliable post-partum, with certain HIV drugs, and Fe-deficient anemia.
- Treatment*:* goal A1c <7%; liberalize to <8-8.5% if life expectancy ≤10 years or high risk for hypoglycemia.

Healthcare Maintenance for Diabetic Patients	
Every visit	• Review blood sugar log: **goal AM FPG 80-130**, postprandial (1-2h) <180; screen for **hypoglycemia awareness** • Blood pressure: **goal <140/90**; ACEi/ARB first line • Weight, BMI: weight center referral if BMI ≥40 or ≥35 with poor control; nutrition referral for all patients • **Foot exam** (inspect skin, joints, pulses, sensation) esp. if known neuropathy or PVD; ABIs/vascular referral if PVD • Smoking cessation counseling (Advise, Assist, Arrange)
Q3-6mo	• A1c **q6 months** if controlled; q3-6 months if A1c above target
Annually	• Lipids: moderate-intensity **statin** if age 40-75; high-intensity if CVD, mult. risk factors, LDL ≥190, or 10yr ASCVD >20% • Urine mAlb/Cr, BMP; ACEi/ARB if hypertensive w/ proteinuria *or* GFR <60; refer to renal if GFR <30 • Neuropathy exam: 10g monofilament (+ if no sensation at 4/10 sites, see PCOI); pinprick, vibration, or reflexes • Retinopathy screen w/ dilated eye exam or retinal photography; can consider q2-3yr if normal exam(s) • LFTs: consider elastography and/or hepatology referral if elevated to evaluate for NASH
Vaccines	• Influenza annually • Hepatitis B series if age <60 and not immune • PPSV23 x1 age <65; re-dose x1 ≥65 with at least 5 years between doses; PCV13 x1 age ≥65

Basal Insulin Management	
Criteria for initiation	• Consider if **A1c ≥ 9%,** random BG ≥ 300, fasting BG ≥ 250, or symptomatic; suspicion for T1DM; < 65yo on two agents with A1c >8% (or ≥ 65yo and A1c > 8.5%) on two occasions >3 months apart; or A1c rising quickly • Able to perform self-monitoring with glucometer; consider referral to DM educator
Initial dose	• Starting dose: 0.1-0.2U/kg/day or 10U/day (if weight >80kg, may consider starting at 20U/day) • Choice of agent: choose long-acting (glargine, detemir QD) ***or*** intermediate-acting (NPH BID → cheaper!) • Route: pen (easier to use, more expensive) vs. needle/syringe
Titration	• Increase by 2-4U or 10-15% q3 days until AM fasting BS is 80-130; savvy patients can self-titrate • If hypoglycemia occurs or FPG < 80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater

Prandial Insulin Management	
Criteria	• Consider if A1c still not at goal with basal insulin >0.7-1.0U/kg/day and fasting glucose within target range (80-130)
Initial dose	• Strategy 1: add 1 rapid-acting insulin before largest meal → start w/ 4U or 0.1U/kg or 10% basal dose • Strategy 2: change to mixed insulin (e.g. fixed 70/30, NPH + regular) BID (before breakfast and dinner). Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM. Counsel to avoid missing meals to avoid hypoglycemia.
Titration	• Increase dose by 1-2U or 10-15% q3d until target glucose reached (pre-prandial: 80-130; 1-2h post-prandial <180) • If A1c still not controlled: add rapid-acting insulin to another meal and titrate as above • If hypoglycemia occurs or FPG <80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater

Insulin Supplies

- Needles: come as universal pen needles, or attached to syringes, made by many companies. 32G 4mm is less painful (higher gauge = thinner and shorter needle), but obese patients and high insulin doses often require deeper/wider needle.
- Syringes: boxes of 100. Long-acting insulin only = 1 box/3 mo. Basal/bolus insulin = 4 syringes/day (4 boxes/3 mo). Choose smallest syringe that will hold the dose (smaller barrel → clearer scale markings).

Use this barrel size…	With this dose range…
3/10 mL	30 units or less
1/2 mL	31-50 units
1 mL	51-100 units

- Alcohol swabs (or patients can wash hands/skin with soap and water)
- Glucometer & test strips: Many choices (insurance dependent), each with own strip brand. Most test strips come in boxes of 50-100.
- ** All durable medical equipment including test strips and glucometers requires an ICD-10 code on the script itself **

Non-Insulin Agents

Drug/Dose Range	% ↓ A1c	Contraindications	Indications/Benefits	Side Effects/Considerations	Cost
Metformin: 1st line anti-diabetic medication; many effects, primary mechanism is decreasing hepatic glucose production					
Metformin (Glucophage) 500-1000mg BID	1-2	GFR cutoffs: - <45ml/min don't initiate - <30ml/min discontinue - Metabolic acidosis	- **First line therapy** - Weight loss - Improvement in lipids	- **Nausea, bloating, diarrhea** - B12 deficiency - **Lactic acidosis** in severe liver/renal disease or hypoperfusion state	$5 (IR) $10 (ER)
Metformin pearls: to increase adherence, warn patients about GI side effects but remind that side effects usually go away with time. Can be minimized by uptitrating SLOWLY (250-500mg/week), taking WITH food, or switching to ER formulation. Benefits and side-effects are dose-dependent – maintain highest dose tolerated. Can also take a break (e.g. with antibiotics) and re-introduce later.					
SGLT-2 Inhibitors: block renal glucose reabsorption, increase glucosuria					
Canagliflozin (Invokana) 100-300mg QD Empagliflozin (Jardiance) 10-25mg QD Dapagliflozin (Farxiga) 5-10mg QD	0.8-0.9	GFR cutoffs: - <45ml/min new data suggests ok to initiate - <30ml/min discontinue	- **↓ CV events, ASCVD mortality, CHF** hospitalization, and **CKD** progression (NEJM 2019;380:2295) - **Weight loss** - ↓ risk of hypoglycemia - ↓ BP 3-5 mmHg	- **FDA Black Box Warning**: **↑risk of amputation** (canagliflozin); avoid in PAD - UTI & GU **fungal infections** - Small risk of **euglycemic DKA** - Risk of dehydration/HoTN - Risk of fracture (canagliflozin) - May ↑ LDL cholesterol	$475 - $500
SGLT2i pearls: counsel patients on diuretic effect and to replace water losses to avoid euglycemic DKA. Uptitrate to effective dose after 1 month at low dose. For potency, empagliflozin > canagliflozin > dapagliflozin. Benefit is probably not a function of A1c lowering.					
GLP-1 Receptor Agonists: stimulate glucose-dependent insulin release from beta cells					
Liraglutide (Victoza) 0.6-1.8mg QD Dulaglutide (Trulicity) 0.75-1.5mg Qwk Semaglutide (Ozempic) 0.25-1mg Qwk	0.5-1.1	- **FDA Black Box Warning**: ↑ risk **thyroid C-cell tumors**. Avoid if hx thyroid ca/MEN2 - GFR 30-45: avoid exenatide	- **ASCVD** - **Weight loss** - Alternative to basal insulin - ↓ risk of hypoglycemia	- **GI**: **n/v, diarrhea** - **Injection site reactions** - Delayed gastric emptying - ↑ risk of pancreatitis	$600 - $800
GLP-1 RA pearls: for weight loss, semaglutide > dulaglutide > liraglutide > others. Uptitrate to effective dose in 1 month intervals.					
DPP-4 Inhibitors: inhibit degradation of DPP4, increasing glucose-dependent insulin secretion and decreasing glucagon secretion					
Sitagliptin (Januvia) 25mg-100mg QD Linagliptin (Tradjenta) 5mg QD	0.5-0.8	- No contraindications, but very weak	- Safe in **CKD/ESRD** (dose-reduce sitagliptin) - ↓ risk of hypoglycemia - Weight neutral	- Saxagliptin, alogliptin ↑ **hospitalizations for CHF** - Joint pain	$400 - $500
Insulin Secretagogues: stimulate release of insulin from pancreatic beta cells, thus only effective in pts who still have beta cell function					
Sulfonylureas: Glipizide 2.5-20mg QD Glimepiride 1-8mg QD	1-2	- T1DM, DKA - low cross-reactivity in pts with sulfa allergy	- Affordable	- **Weight gain** - **Hypoglycemia** (esp glyburide) - Possible ↑ CV mortality	$5 - $10
Meglinitides: Repaglinide (Prandin) 0.5-4mg QAC	0.5-0.7	- Severe liver disease - Concurrent gemfibrozil therapy	- Use like bolus insulin (short-acting) - **CKD** - ↓ nocturnal hypoglycemia	- **Weight gain** - **Hypoglycemia** - ↑ serum conc. w/ clopidogrel - TID dosing	$15 - $20
Thiazolidinediones: increase insulin sensitivity by acting on adipose, muscle, and liver to ↑ glucose uptake, ↓ ectopic lipid deposition					
Pioglitizone (Actos) 15-30mg QD	1-1.6	- Avoid if hx bladder cancer - NYHA Class III/IV HF	- ↓ risk of hypoglycemia - Possible benefit in NASH	- **FDA Black Box Warning**: **↑risk of CHF** - **Weight gain** - ↑ risk of fracture	$10

* Monthly costs in Boston area pharmacies (GoodRx)

Algorithm for Oral Anti-Diabetic Therapy (Diab Care 2020;43:487)

1. A1c ≥6.5: lifestyle changes +/- metformin. Counsel for whole foods, carbohydrate restriction, and time-restricted eating.
2. Regardless of A1c:
   a. If **ASCVD** or high risk: add GLP-1RA and/or SGLT2i (↓ CV events)
   b. If **HF** (esp. HFrEF) or CKD (eGFR >30 or mAlb/Cr >30): add SGLT2i (↓ CKD progression, ↓ CV events, ↓ HF hospitalizations, ↓CV death), avoid TZD
3. If A1c targets not met with above therapy:
   a. If **weight loss**/neutrality desired: add GLP1RA and/or SGLT2i > DPP4i, avoid sulfonylurea, TZD
   b. If **cost** is a major concern: add sulfonylurea or TZD

INSULIN NOMENCLATURE

Type (Onset)	Formulation	Peak	Duration
Rapid (10 min)	lispro (Humalog) aspart (Novolog) glulisine (Apidra)	0.5-2.5 hr	< 5 hr
Short (30 min)	regular (Humulin R, Novolin R)	2.5-5 hr	4-12 hr
Intermediate (1-2 hr)	NPH (Humulin N, Novolin N)	4-12 hr	12-18 hr
Long (3-4 hr)	glargine (Lantus) QD, detemir (Levemir) BID, degludec (Tresiba) QD	none	24 hr

Basal insulin: fixed intermediate / long-acting for basic metabolic requirements
Prandial insulin: fixed rapid / short-acting to cover meals
Correctional insulin: sliding scale rapid / short-acting to correct hyperglycemia **(not intended to cover meals)**
Pre-Mix (avoid in hospital, but consider for transition to outpatient regimen): combine basal and prandial insulin into one injection
Insulin gtt: use in ICU if BG>180 x 2 and anticipated ICU LOS >3 days; reference MICU Insulin Protocol in Partners Handbook. Ensure an active source of dextrose (e.g. D10W @ 30 cc/hr). Always overlap with SC insulin by 2-3h before stopping insulin gtt.

INPATIENT MANAGEMENT (Diabetes Care 2019;42:S173)

- Glycemic targets: **Floor**: **fasting 100-140** mg/dL, **random <180** mg/dL. **ICU**: **140-180** mg/dL (NOT stricter) (NEJM 2009;360:1283)
- Check **FSBG AC & QHS** (at least for 24-48h) in (1) known diabetics, (2) non-diabetics with BG >140 mg/dL, (3) those receiving therapies a/w hyperglycemia (corticosteroids, octreotide). Check FSBG q6h if on continuous TF or TPN.

Note: FSBGs inaccurate in hypotension (esp. on pressors) and hypothermia due to altered blood flow to skin. Confirm w/ serum glucose.

Admission Orders (NEJM 2006;355:1903)

1. Hold home oral antihyperglycemic agents (***NEVER hold basal insulin for T1DM***). Write for **consistent carbohydrate** diet.
2. **Check A1c** in all patients with hyperglycemia if not done in last 3 months
3. Continue home insulin regimen with dose reduction (~25-50% reduction) given expected change in diet while hospitalized. Hypoglycemia is associated with increased mortality in elderly, so reasonable to be cautious.
4. If **not** on home insulin:
   a. Well-controlled: reasonable to start with **ISS** and soon change to basal-bolus once TDD established
   b. Not well-controlled: start with **basal (0.2 U/kg) & ISS!** Add prandial insulin in 1-2 days.
5. **If NPO**: 50% dose reduction or 0.1 U/kg/day for basal insulin. Be sure to change correctional ISS and FSBG from TID AC to q6h.
6. Correctional insulin sliding scale: use low-dose if insulin-sensitive/ESRD/ESLD/frail, otherwise moderate-dose for most T2DM

Adjusting Insulin Dosing: In general, increase by no more than **20%** of total daily insulin requirement every day

Fasting or AM BG high (w/ other BGs in range)	→	↑ basal insulin dose*
Fasting BG high + HS BG high (w/ other BGs in range)	→	↑ pre-dinner prandial insulin dose
Pre-lunch or dinner BG high (w/ other BGs in range)	→	↑ prandial insulin dose of preceding meal
BG rising steadily over course of day	→	↑ prandial insulin dose at each meal

*Avoid titrating basal insulin more than q2-3d (d/t long half life, requires time to reach steady state) to avoid "stacking" and hypoglycemia

Special Situations:

1. **Glucocorticoids**: NPH 0.1 U/kg/d for every 10 mg pred, up to 0.4U/kg/d (dosed BID); if dexamethasone, use glargine QD instead
2. **Tube feeds**: if not on insulin already, start with regular ISS q6h. Convert to NPH BID based on needs. **If on insulin**, use ½ basal (NPH BID) + ½ bolus (regular insulin q6h) + ISS. **If TF stopped**, give D5W at TF rate until next NPH dose, and ↓ NPH dose by 50% or more based on pre-TF insulin requirements. **TPN**: regular insulin can be added to TPN (discuss w/ nutrition), does not cover basal!
3. **Insulin pumps**: continuous SQ infusion of rapid-acting insulin. Set basal rate (e.g. ~0.01 U/kg/h; can adjust throughout day); carb ratio (units insulin:gram carbs e.g. 1:10); sensitivity factor (units insulin:mg/dl above target - like sliding scale e.g. 1:50); insulin action time (e.g. 4hrs). Complications: site infection, system failure interrupting infusion. Back-up insulin: give 3-4x hourly rate of rapid-acting q3-4h, or give TDD as NPH BID or glargine QD

Disposition: if new home insulin → nutrition c/s + floor RN teaching and arrange outpatient f/u. Using discharge order set, send rx for glucometer, test strips, lancets, syringes/vials or pens/needles to MGH outpatient pharmacy and bring up to floor for RN teaching.

INPATIENT HYPOGLYCEMIA

↑ **Risk**: T1DM, malnutrition, emesis, ↓ body weight, ↓ PO intake, ↓ steroid dose, AKI (↓ insulin clearance), CKD *(esp. dialysis)*

Beware of hypoglycemia unawareness in T1DM and longstanding T2DM

Manifestations: **<70**: shakiness, anxiety, diaphoresis, visual Δ, HA, AMS. **<55**: seizure, coma.
Treatment: PO (15g gel, tabs, juice) > IV (12.5-25g D50) > IM/SQ (1mg glucagon); recheck in 15 min, chase with PO if due to insulin OD
If sulfonylurea OD: 50-75 mcg octreotide SQ. **Review and adjust insulin regimen!**
Ddx: *If ill/medicated*: drugs (insulin [secretagogues], EtOH), sepsis, ESLD, ESRD, HF, adrenal insufficiency, nonislet cell tumor
If well-appearing: insulinoma, post-gastric bypass (late dumping), insulin or insulin receptor antibodies, insulin (secretagogues)

Workup: must meet **Whipple's Triad** to merit eval: sx c/w ↓BG, reliable ↓BG while sx present, sx relief once BG corrected

1. Mixed-meal with postprandial eval (q30min labs for 5h post-meal), or fasting eval with admission for 72-hr fast if no episodes (labs if sx and FSBG <60)
2. Check: serum glucose, insulin level, C-peptide, beta-hydroxybutyrate, proinsulin, sulfonylurea, meglitinide screen

Insulin	Pro-Insulin	C-Peptide	Ddx
↑	↑	↑	Insulinoma, oral hypoglycemic, autoimmune
↑	↓	↓	Exogenous insulin administration
nl	nl	nl	Nonislet cell tumor

DIABETIC KETOACIDOSIS (DKA)

Pathophysiology: think about each element of Diabetic Keto-Acidosis

- *Diabetes*: ↓ insulin & ↑ opposing hormones (glucagon, catechols, cortisol) → hyperglycemia → osmotic diuresis→ hypovolemia
- *Ketones*: ↓ insulin → ↑ lipolysis → ↑ free fatty acids → ↑ ketones (acetoacetate, β-hydroxybutyrate, acetone [fruity breath])
- *Acidosis*: ↑ β-hydroxybutyrate and acetoacetate, and contraction alkalosis with total body HCO_3 deficit (NEJM 2015;372:546)

Precipitants (the "I's"): infection (30-40% of cases), initial presentation of DM (20-25% of cases), insulin non-adherence, inflammation (pancreatitis – but ↑ amylase / lipase in DKA even w/o this), ischemia/infarction (MI, CVA, gut), intoxication (EtOH, cocaine), iatrogenesis (e.g. SGLT2 inhibitors, steroids, thiazides, dobutamine/terbutaline, atypical anti-psychotics), infant (pregnancy)

Presentation: dehydration, polyuria/polydipsia, n/v/abd pain, weakness, AMS, Kussmaul's respirations, fruity breath (acetone)

Dx: BG 250-800, pH <7.3, AG >10, urine/serum ketones. *Consider euglycemic DKA in pt on SGLT2i, EtOH liver dz, pregnancy.*

- Check BMP, CBC w/ diff, UA, Sosm, serum β-hydroxybutyrate, ABG/VBG. Consider hs-trop, EKG, BCx/UCx, CXR, lipase/amylase.
- **Na correction** → *use absolute sodium value* when calculating anion gap. *Use corrected value* to assess for underlying hypotonic hypoNa → add 1.6 mEq/L to Na for every 100 mg/dL of serum glucose >100 mg/dL (e.g. if glucose 300 mg/dL, add 3.2 mEq/L to Na)
- UA ketone **does not** test for β-hydroxybutyrate, which is the predominant ketone in DKA (must measure from **serum**)

Management: **prioritize ABCs, volume status, identifying precipitant → THEN electrolytes (especially K+) → THEN glucose**

Labs: BMP q2h until AG closes, then q4h until normal K^+; VBG, β-hydroxybutyrate q2-4h; FSBG q1h while on insulin gtt

Step 1: **volume resuscitation** (typically 5-8L deficit)

- **Bolus NS** 15-20cc/kg/hr for initial resuscitation in first 1-4 hours (unless CHF, ESLD, ESRD, hypoxemia)
- **Corrected Na** → if **low**, start NS±K^+ at 250-500cc/hr; if **normal/high** or hyperCl **acidosis**, start ½NS±K^+ at 250-500cc/hr
- **Add D5 to IVF once BG<200 (DKA) or <300 (HHS)**

Step 2: **potassium repletion and management**

Potassium	Action
K<3.3	Give 20-40 mEq KCl IV per hour + **hold insulin**!
3.3≤K≤5.3	Add 20 mEq K to IVF
K>5.3	Continue to monitor q2h

K+ may be normal/elevated at presentation, but total body K+ actually low. Multifactorial causes: solute drag of K+ into extraceullar space, osmotic diuresis, ↓ insulin not driving K+ into cells. **Aggressive K+ repletion** is critical: HYPOkalemia will limit your ability to administer the necessary insulin

Step 3: **insulin therapy** (Diab Care 2009;32:1335)

- *The #1 goal of insulin therapy in DKA is to stop ketogenesis and close the AG;* glucose correction is secondary
- Don't start insulin until you have control of K^+
- **Don't stop the insulin gtt** unless true hypoglycemia (<65 mg/dL) or hypokalemia (<3.3 mEq) occurs
- **Initial**: bolus 0.1 U/kg regular insulin, then start 0.1 U/kg/hr IV regular insulin gtt; OR no bolus and start 0.14 U/kg/hr IV gtt
  - Goal is to ↓ BG by 50-75 mg/dL each hour
  - For mild DKA, subcutaneous insulin regimens may be used instead of IV (Cochrane Rev 2016)
- **Titrating insulin drip**: MICU insulin gtt protocol is for general glycemic management, NOT for DKA
  - If BG does not ↓ by 50-75 mg/dL in the first hour, re-bolus (DKA) or double the gtt (HHS)
  - No evidence for hourly titration of the insulin infusion rate in DKA while BG>200
  - Once BG <200 (DKA) or <300 (HHS), ↓ gtt to 0.02-0.05 U/kg/hr and add D5 to fluids
  - Goal is to maintain BG at 150-200 (DKA) or 250-300 (HHS)

For BG < 150	Δ Insulin gtt and glucose source
BG 91-149	↓ gtt by 25% + ↑ D5 gtt by 50 cc/hr
BG 66-90	↓ gtt by 50% + ½ amp D50 + continue D5 gtt
BG ≤ 65	hold insulin + 1 amp D50 + continue D5 gtt

Other electrolytes:

- HCO_3: no proven benefit w/ pH > 6.9. **If pH <6.9**, give 2 amps HCO_3 dissolved in 400mL sterile water w/ 20mEq KCl over 2h
- Phos: total body deficit but serum phos may be ↑ / nml; will ↓ w/ insulin; **only replete if < 1.0** to prevent cardiac dysfunction

Transitioning to SQ insulin: start if BG **< 200** *and* pt is **able to eat** *and* **two** of the following are met: **AG<12, HCO3≥15, pH>7.3.** Start **basal** regimen w/ either: home glargine dose *OR* glargine at 0.25-0.4 U/kg/d *OR* glargine at (# units on IV gtt over past 6h x 4 x 0.7). Start **bolus** regimen w/ either: 0.25-0.4 U/kg/d divided (if T1DM or unknown) *OR* ISS only (if T2DM). **Overlap IV gtt/SQ insulin by 2-4h**.

Ketosis-prone diabetes: characterized by DKA w/ hx T2DM or atypical substrate for T1DM (older age, overweight). Patients should be discharged on insulin and see an endocrinologist for antibody (GAD65, IA2) and β-cell function (C-peptide levels) testing to determine diabetes subtype (antibody +/-, β-cell function +/-). Patients may not require long-term insulin therapy.

HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)

Pathophysiology: hyperglycemia → osmotic diuresis → volume depletion; ketogenesis suppressed by low (but present) insulin levels

Precipitants: same as DKA (note: **pts w/ T2DM and burnt-out pancreas can also present with DKA**)

Presentation: AMS (25-50%), obtundation, seizure, focal neuro def, volume depletion, evolves over **days-weeks** (vs hours-days in DKA)

Dx: glucose >600 mg/dL (frequently >1000), osmolality >320 mOsm/kg, pH >7.3, absent or minimal ketones

Management: as above for DKA w/ modifications: more aggressive IVF (~8-10 L deficit); **goal glucose 250-300 mg/dL** (in DKA, 150-200); transition to SQ insulin when BG<300 *and* mental status improved *and* patient is able to eat. Mortality >> DKA (Diab Care 2014;37:3124)

ETIOLOGY (Lancet 2014;383:2152, NEJM 2009;360:2328)

Primary AI: ↓ **adrenal hormone** → ↑ **ACTH**. Lesion localizes to the **adrenal gland**.

- Causes: autoimmune (80-90% cases in developed countries; anti-21-hydroxylase Ab in 86%, autoimmune polyglandular syndromes) >> infxn (TB, HIV, CMV, histo, meningococcus), bilateral adrenal hemorrhage (infxn, DIC, APLAS), malignancy (mets), genetic (CAH, adrenal leukodystrophy), meds (keto/fluconazole, etomidate, phenobarb, phenytoin, rifampin, opioids)

Secondary AI: ↓ **ACTH** → ↓ **adrenal hormone.** Lesion localizes to **pituitary gland**.

- Causes: chronic glucocorticoids, opioids, medroxyprogesterone and megestrol. Ask about topical, inhaled and intra-articular steroids. Other major etiologic consideration is a pituitary lesion (see *Pituitary Disorders*)

CLINICAL MANIFESTATIONS

Primary AND Secondary:

- Signs/symptoms: weakness, fatigue, anorexia, GI complaints, myalgias, psychiatric sx, wt loss, orthostasis, vasodilatory shock
- Lab abnormalities: hyponatremia, hypoglycemia, hypercalcemia, non-AG acidosis, anemia, eosinophilia, lymphocytosis

Primary only (↓ serum aldosterone): hyperK, salt craving, **hyperpigmentation**; if long-term, nausea/vomiting, abdominal pain

Secondary only (RAAS intact): ± hypopituitarism, hypoglycemia more common than in primary

DIAGNOSIS

- **Diagnostic test**: cosyntropin stimulation test (aka "cort stim") (JCEM 2016;101:364), ↓ **AM cortisol is a late finding in AI.**
- 6-8AM cortisol: definite AI if ≤3 µg/dL (<5 µg/dL highly suggestive); definitely not AI if ≥18 µg/dL
- Cort stim protocol: check serum cortisol and ACTH → give cosyntropin (ACTH) 250 µg IV → serum cortisol 30-60 min later
  - Normal response: serum cortisol at 30-60 min is ≥18µg/dL (*note*: this rules out all cases of 1° AI + *chronic* cases of 2° AI)
    - In acute 2° AI, adrenal glands have *not had time to atrophy*, so cort stim test will be **normal**!
  - Can be performed at any time of day; initial cortisol check will be higher in the morning but stim will always be appropriate
  - If abnormal cort stim, **consult endocrine**
- Falsely low serum cortisol: ↓ **albumin** (e.g. cirrhotics, nephrotic syndrome, malnutrition, critical illness; ↓ bound and total cortisol, but free cortisol may be nl); PM testing (cortisol responses are greatest in morning)
- Falsely high serum cortisol: pregnancy, **estrogen tx** (↑ cortisol binding globulin, ↑ bound/total cortisol, free cortisol may be ↓)
- Additional labs for primary AI: ↑ ACTH >2x ULN, ↓ aldo, plasma renin, 17-OH-prog, 21-OHase Ab, CT A/P
- Additional labs for secondary AI: ↓ ACTH, normal aldo

ADRENAL CRISIS

- Acute-onset AI with distributive shock in s/o major stressor (infxn, trauma, major surgery, critical illness). **Consult endocrine.**
- **No known AI ± not taking chronic steroids**: draw ACTH/cortisol but don't delay empiric treatment; defer cort-stim until stable
- **Known AI or taking chronic steroids**: start treatment; diagnosis can be presumed by history; no role for cort stim test

TREATMENT (JCEM 2016;101:364)

- **Adrenal crisis** → **stress dose steroids** (**hydrocortisone 100 mg IV** or **dexamethasone 4mg IV x1**) and **>2-3L NS.** Follow with hydrocortisone 50mg IV q6h or dexamethasone 4mg IV q24hr ± fludrocortisone 0.1mg QD when off saline infusion if 1° AI.
  - May taper once patient's clinical status improves and *underlying precipitant is adequately addressed*
  - Dexamethasone not detected in cortisol assay; steroid of choice if considering early cort stim dx (Clin Chem 2004;50:2345)
  - Treat AI **BEFORE** treating severe **hypothyroidism**; otherwise can precipitate adrenal crisis
- **Chronic AI** → glucocorticoid: hydrocortisone 15-25 mg PO QD (2/3 AM, 1/3 early PM) or prednisone 3-5 mg PO QAM; Mineralocorticoid (only in 1° AI): fludrocortisone 0.05-0.1 mg PO QD
  - **If minor illness or minor surgery → sick dose:** "3x3 rule" = 3x daily dose for 3 days
  - **If severe illness → stress dose:** hydrocortisone or dexamethasone (as above)
  - Supply patients with **medical alert bracelet** if new diagnosis

STEROID PEARLS

- Taper: **not necessary** if **steroid use <3 wks (independent of dose)** → low risk of HPA suppression. Patients needing to taper off long-term corticosteroids should do so with endocrinology guidance. May need cort-stim before stopping.
- Side effects of supra-physiologic doses: ↑ weight, insomnia, skin thinning, AMS, hyperglycemia, edema, osteoporosis, gastritis
- Prophylaxis: **PJP**: if taking prednisone ≥20mg for ≥4 weeks *plus* second reason for immunocompromise; **PUD**: if also taking aspirin/NSAIDs; **osteoporosis**: start calcium 1200mg/day + vitamin D 800IU/day if on glucocorticoids (any dose) >3 months (consider bisphosphonates for pts at intermediate to high risk of fracture); **DM2**: monitor glucose/A1C, consider NPH dose (0.1U/kg/day up to 0.4U/kg/day) with glucocorticoid if BG/A1C high.

Steroid	Equivalent Anti-inflammatory Dose (mg)	Relative Anti-inflammatory Activity	Relative Na Retention Activity	Duration (hrs)
Hydrocortisone	20	**1**	2	8-12
Predniso(lo)ne	5	4	0.8	12-36
Methylprednisolone	4	5	0.5	12-36
Dexamethasone	0.75	30	0	36-72
Fludrocortisone	n/a	10	125	12-36

HYPOPITUITARISM

Definition: ↓ pituitary hormone production/release resulting from diseases of pituitary (1°) or hypothalamus/stalk (2°)
Causes:

- Surgery, radiation, infection (meningitis), infiltration (sarcoid, hemochromatosis), trauma, tumors (1°: pituitary tumors, mets; 2°: external stalk compression [e.g. craniopharyngioma, meningioma, mets])
- 1° only: **Sheehan's** (infarction), **apoplexy** (hemorrhage), meds (ipilimumab), autoimmune (classically in 3rd trimester/postpartum)

Clinical Manifestations & Diagnosis:

Hormone Deficiency	Signs/Symptoms	Laboratory Tests
Prolactin	Reduced lactation	PRL
ACTH (2° adrenal insufficiency)	Fatigue, weight loss, nausea, orthostatic dizziness, muscle/joint pain, hypotension	8 AM cortisol, cort stim test, ACTH
GH	Fatigue, low energy, central obesity, decreased bone mineral density	IGF-1, insulin tolerance test
TSH (2° hypothyroidism)	Fatigue, weight gain, constipation, bradycardia, hair loss, dry skin, hyporreflexia	TSH, free T4
LH/FSH	Amenorrhea, decreased libido, ED, infertility	LH, FSH, estradiol, AM testosterone

Treatment: replace deficient hormone (JCEM 2016;101:3888) with **endocrine consult**. Most sensitive issue is cortisol/thyroid hormone replacement: if concurrent deficiencies, **treat AI before hypothyroidism** as can otherwise precipitate adrenal crisis.

HYPERPITUITIARISM

Definition: excess of any of the hormones secreted by the anterior pituitary gland (PRL, ACTH, GH, TSH, LH/FSH)
Causes: (1) hyperfunctioning pituitary adenoma, (2) elevated prolactin due to disruption of pituitary stalk, drugs (antipsychotics, antidepressants, antiemetics, verapamil, opioids, cocaine)
Clinical Manifestations: if pituitary adenoma → headaches, visual field deficits

Hormone Excess	Signs/Symptoms
Prolactin (Prolactinoma)	Infertility, amenorrhea, galactorrhea, ED
ACTH (Cushing's disease)	Weight gain, fatigue, irritability, anxiety, depression, insomnia, easy bruising, poor wound healing, central obesity, acne, hirsutism, wide violaceous striae, prox muscle weakness, HTN
GH (Acromegaly)	Arthralgias, fatigue, paresthesias (carpal tunnel syndrome), hyperhidrosis, OSA, CHF, enlarged jaw, hands, feet, coarse facial features, deepening of voice, skin tags, hirsutism, HTN
TSH (2° hyperthyroidism)	Fatigue, exertional intolerance, irritability, palpitations, diarrhea, tachycardia, tremor, hyperreflexia

Diagnosis:

- **Labs**: should be targeted based on **symptoms** – prolactinoma (PRL), Cushing's disease (overnight 1 mg dexamethasone suppression test, late-night salivary cortisol, or 24h urinary free cortisol excretion), acromegaly (IGF-1, confirm with GH level after glucose tolerance test), 2° hyperthyroidism (TSH, free T4, total T3)
- **Imaging**: MRI brain w/ and w/o contrast, pituitary protocol

Management:

- **Prolactinoma**: if >1cm or symptomatic, first-line treatment is a **dopamine agonist** (cabergoline first choice, bromocriptine preferred in preconception setting). If <1cm or asymptomatic, can monitor closely with MRI and prolactin levels (JCEM 2011;96:273)
- For all other hypersecreting pituitary adenomas, treatment is **transsphenoidal pituitary surgery** +/- radiation therapy
- For GH secreting adenomas in patients who are poor surgical candidates, can treat with somatostatin analog (octreotide)

DIABETES INSIPIDUS (DI)

Definition: polyuria (>3L/day) in setting of insufficient amount of ADH (central) *or* insufficient response to ADH (nephrogenic)
Causes: (1) central – trauma, surgery, hemorrhage, infarction, neoplasm, infiltrative (sarcoidosis, histiocytosis), infection, autoimmune, drugs (EtOH, phenytoin); (2) nephrogenic – drugs (**lithium**, cisplatin), hyperCa, infiltrative (sarcoidosis, amyloidosis, MM), sickle cell
Diagnosis:

- **Water restriction test**: *normal physiology*: water restriction → ↑SOsm → ↑ADH → ↑UOsm (JCEM 2012;97:3426)
  - Check Na, SOsm, UOsm, UVol q2hr
    - If UOsm > 800 mEq/kg, stop test due to appropriate vasopressin response (dx: **primary polydipsia**)
    - If (1) **SOsm > 295** mEq/kg, (2) **Na > 145** mEq/L (adequate ADH stimulus) AND (3) **UOsm stable** on several checks despite ↑ SOsm (ADH response plateaued), administer **desmopressin 4 mcg IV**, then check UOsm, UVol q30min x 2hr
      - UOsm < 300 mEq/kg prior to desmopressin suggests **complete DI**; UOsm 300-800 mEq/kg suggests **partial DI**
        - > 50% ↑ UOsm following desmopressin = **central**
        - < 50% ↑ UOsm following desmopressin = **nephrogenic**

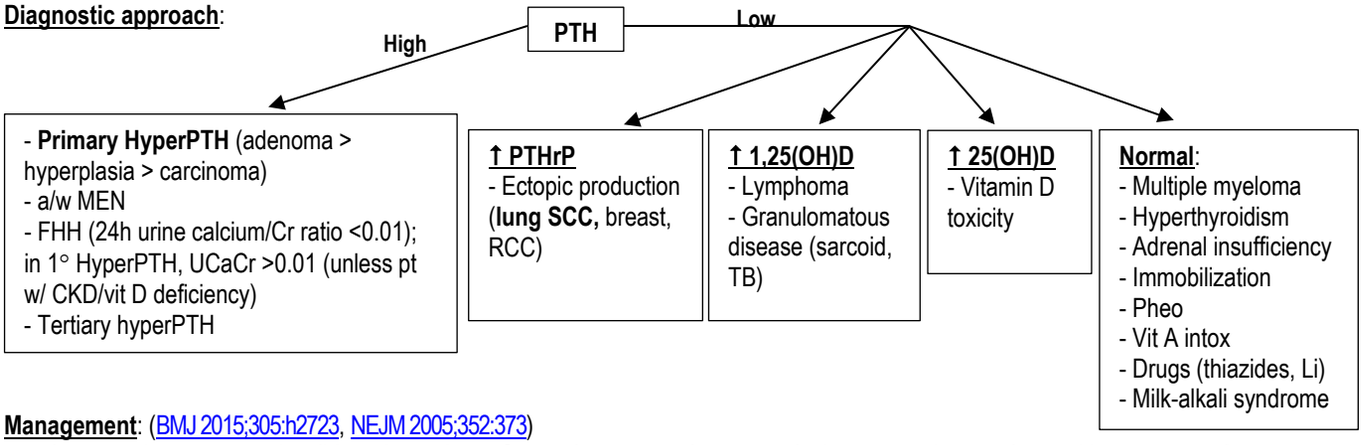
Treatment: correct hypernatremia (see *Sodium Disorders*). Allow patient to drink to thirst. PO preferred to avoid rapid Δ in serum sodium.

- Central: **desmopressin** (exogenous ADH) given intranasally (5mcg qhs + 5mcg QD-TID), can augment with adjunctive meds
- Nephrogenic: if partial, may try desmopressin; if complete, use adjunctive meds
- Salt/protein restriction: low solute intake reduces thirst, thereby reducing free water intake
- Adjunctive meds: **HCTZ** (volume depletion → increases proximal Na/water reabsorption, decreasing distal Na delivery where ADH acts); **amiloride** (mechanism similar to HCTZ, beneficial in Li-induced nephrogenic DI by blocking entry of Li across ENaC), **NSAIDs** (enhance renal response to ADH), **chlorpropamide** (enhances renal response to ADH)

HYPERCALCEMIA

*****MAKE SURE TO CORRECT CALCIUM FOR ALBUMIN: Corrected Ca = Serum Ca + 0.8 x (4-Alb)*****

Definition: mild (corrected Ca < 12); moderate (corrected Ca 12-14); severe (corrected Ca >14)
Clinical signs/symptoms: **MSK ("bones")** → Osteitis fibrosa cystica (1° hyperPTH), arthralgia, osteoporosis, weakness; **renal ("stones")** → polydipsia, polyuria, nephrolithiasis, Type 1 RTA, AKI/CKD; **GI ("groans")** → n/v, anorexia, constipation, ileus, pancreatitis, peptic ulcers; **neuropsych ("overtones")** → fatigue, depression, anxiety, confusion, stupor, coma; **CV** → bradycardia, short QTc, AV block, valve/vessel calcification, HTN
Diagnostic approach:

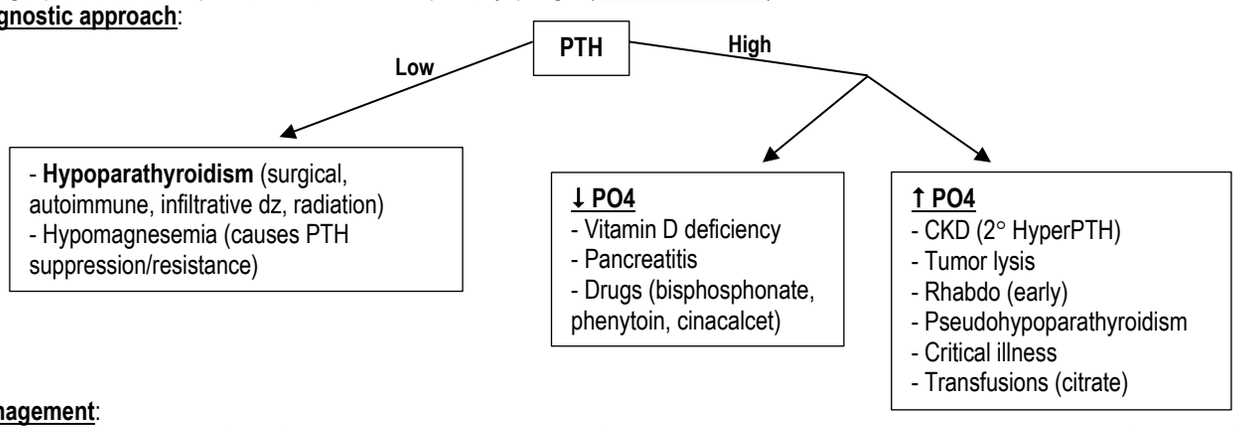


Management: (BMJ 2015;305:h2723, NEJM 2005;352:373)

- In general, asymptomatic mild-moderate hyperCa can be managed conservatively as outpatient; patients with **symptomatic** or severe **hyperCa (>14) should be admitted** for treatment and endocrine consult.
- Conservative measures: avoid contributory meds; oral hydration; oral PO4 repletion to 2.5-3.0 (IV could lead to hypoCa)
- Volume resuscitation: patients are typically very dehydrated; bolus NS then gtt @ 200-300cc/hr with goal UOP 100-150cc/hr
- Loop diuretics: **ONLY** if concurrent HF, CKD (and only once volume replete), elderly; otherwise avoid as they can worsen dehydration
- Bisphophonates: best studied in malignancy; zoledronate >> pamidronate (**except in MM: more ATN**). Takes 2-4d for effect.
  Side effects: hypoCa (check 25(OH)D & replete prior to admin), flu-like illness. Reduce dose if CKD. Avoid if CrCl <30.
- Denosumab: monoclonal Ab against RANKL → blocks pre-osteoclast maturation; good option in patients with CKD
- Calcitonin: 4-8U/kg SC BID for 48 hours (substantial Ca reduction within 12-24 hours). Tachyphylaxis usually occurs within 48-72h.
- Other: glucocorticoids (effective in calcitriol mediated etiologies, takes 2-5 days for effect), HD (if refractory or life-threatening)
- **Special considerations for 1° hyperPTH**: surgery is curative. Indicated if (1) symptomatic *OR* (2) asymptomatic with Ca > 11.5, osteoporosis/vertebral fracture, CCl <60, nephrolithiasis, *or* age <50. If poor surgical candidate, consider **cinacalcet**, bisphosphonate, tamoxifen (JAMA Surg 2017;152:878, JCEM 2014;99:3607)

HYPOCALCEMIA

Clinical signs/symptoms: **neuromuscular** (paresthesias, muscle cramps/spasms, tetany, Trousseau sign [carpal spasm w/ BP cuff inflation 94% Sn, 99% Sp], Chvostek sign [circumoral muscle twitch w/ facial nerve tapping poor Sn / 85% Sp]); **seizures**; **↑ QTc,** laryngospasm, bronchospasm, AMS, abdominal pain, dysphagia (BMJ 2008;336:1298)
Diagnostic approach:



Management:

- **Replete magnesium** (hypoCa can be hard to correct without first correcting hypoMg → causes PTH resistance and ↓ secretion)
- IV Ca repletion: if severe (**corrected Ca < 7.5, iCa < 1**), symptomatic, or prolonged QT
  - 1-2g IV **Ca gluconate** or $CaCl_2$ (in codes: via central line, risk of skin necrosis if extravasates) over 10-20 min
  - IV therapy ↑ serum levels for only 2-3h *(*chase w/ gtt or PO); can do sliding scale repletion in ICU
  - Telemetry recommended as arrhythmias may occur
- PO Ca repletion: if Ca > 7.5 or asymptomatic: 1-2 g elemental Ca QD in divided doses (Ca citrate better absorbed vs CaCO3 esp. if pt on PPI)
- Vitamin D repletion: 800-1000 IU Vit D3 daily (if severely deficient trial 50,000 IU Vit D2 or D3 qweek x 6-8wks and measure 25(OH)D level in 3-4mos). In patients w/ poor conversion of 25(OH)D (e.g. hypoparathyroidism, CKD) use **calcitriol** (start w/ 0.25mcg PO QD)

Definitions:

- **Osteoporosis**: history of fragility fracture or T-score ≤ -2.5 on DXA. **Osteopenia**: T-score -2.4 to -1.
  - T-score: SD compared to mean for normal, healthy young adults
  - Fragility fracture: fracture from a fall from standing height or less or with no trauma, particularly spine, hip, wrist, rib, and pelvis

Etiology:

- Primary osteoporosis is the most common. Risk factors: age ≥65, low body weight (<57.6 kg), FH osteoporosis or fractures, smoking, early menopause, excessive EtOH intake
- Secondary osteoporosis caused by: renal disease, liver disease, hyperthyroidism, hyperPTH, vit D deficiency, hypogonadism, glucocorticoids (≥5mg prednisone for >3mos), myeloma, malabsorption (celiac, IBD), RA, SLE, COPD, drugs (PPI, AED, long-term heparin, leuprolide, aromatase inhib, MTX, GnRH agonists)

Diagnosis:

- Screen women with DXA scan at age 65 or younger if RF or high risk as determined by FRAX (USPSTF guidelines)
- Screen men ≥70 or age 50-69 who have RF (low body weight, prior fracture, smoking) (Endocrine Society Guidelines)
- Labs for secondary causes: CBC, BMP, LFTs, 25(OH)D, TSH, PTH, SPEP

Management:

- **Inpatient following fragility fracture**: assess need for surgical treatment, consult Fracture Liaison Service (p25656), can start medical management (bisphosphonates); zoledronic acid has been shown to decrease mortality post-hip fracture (HORIZON trial)
- **Lifestyle measures**: weight-bearing exercises 3-4x/week, smoking cessation, decrease EtOH intake, RDA 800-1000 IU vitamin D (goal level >30), calcium 1200 mg ideally from diet
- **Pharmacologic therapy**:
  - **Bisphosphonates**: must have normal vit D and calcium levels prior to initiating therapy
    - Indicated for: all patients with osteoporosis, osteopenia in men and postmenopausal women with FRAX 10-yr risk >20% for any fracture, >3% for hip; consider when initiating long-term glucocorticoids in pts with med-high risk of fracture.
    - **PO alendronate** 75mg or PO **risendronate** 35mg weekly for 5-10 yrs. Avoid if GFR <30. Provide strict instructions to prevent pill esophagitis: take on empty stomach w/ full glass of water, sit upright and wait 30 min prior to taking other meds or food.
      - If contraindication to PO bisphosphonate (e.g. GI intolerance, roux-en-Y gastric bypass), **IV zoledronic acid**
    - Re-evaluate q3-5yrs and if low-moderate risk consider a "bisphosphonate holiday" (JCEM 2019;104:1592)
  - **Denosumab** (monoclonal antibody with affinity for RANKL): option for patients with renal dysfunction or other contraindication to bisphosphonates, 60 mg SQ q6mo; treat with teriparatide first if severe osteoporosis. FREEDOM trial showed denosumab improves fracture risk and bone mineral density compared to placebo
  - **Anabolic agents** (teriparatide: recombinant PTH; abaloparatide: PTHrP analog): VERO trial
    - For severe osteoporosis or for patients with contraindications to bisphosphonates, daily SQ injection

INPATIENT TFTs

- If thyroidal illness is suspected, TSH alone is inadequate; should also test for FT4 & T3. TSH will reflect changes within 4-6 wks.
- **Nonthyroidal illness "euthyroid sick"**: alterations in thyroid function due to illness rather than 1° endocrine disorder; may be adaptive (anti-catabolic); no indication to treat; most likely cause of abnormal TFTs among inpatients (Lancet Diab Endo 2015;3:816)
  - **Typical pattern**: (1) acute illness: ↓↓↓T3, ↓T4, ↓/nl FT4, ↓/nl TSH. (2) recovery phase: ↑ TSH → recovery of T4, T3.
  - Sequential FT4 should ↑ in recovering sick euthyroid but remains low in 1° hypothyroid. rT3 can differentiate central hypothyroidism (↓) from sick euthyroid (↑), but rarely needed. FT3 only helpful to dx hyperthyroidism w/ altered TBG.
  - **Undetectable TSH (<0.01)** suggests true hyperthyroidism, and **TSH >20 + low T4** suggests true hypothyroidism.
- Biotin supplementation can interfere with TSH and other assays, ensure pt off biotin x 1wk before testing
- ↓ TSH also seen with glucocorticoids, dopamine, dobutamine, octreotide, ↑ β-HCG levels (pregnancy, trophoblastic disease)

HYPOTHYROIDISM

- **Definition**: elevated TSH with low T4 (primary) or low/normal TSH with low T4 (secondary/central)
- **Signs/symptoms**: general (fatigue, cold intolerance, constipation, dry skin, myalgias), neuro (depression, cognitive dysfunction, carpal tunnel), CV (bradycardia [severe dz], diastolic HTN)
  - Exam: delayed relaxation phase of DTRs, non-pitting edema, lateral eyebrow thinning, macroglossia, froggy voice
- **Labs**: ↑ LDL, ↑ triglycerides, macrocytic anemia, ↓ Na
  - Check other pituitary axes if concern for central hypothyroidism

	TSH	FT4
Primary	↑	↓
Secondary	↓/normal	↓
Subclinical	↑	Normal

- **Workup**: TSH with reflex, anti-TPO ab. No role for thyroglobulin or anti-thyroglobulin ab (only useful for monitoring thyroid Ca)
- **Causes**:
  - **1°: Hashimoto's** (most common, **+TPO Ab**), infiltrative disease (hemochromatosis, sarcoid), transient thyroiditis (lymphocytic, granulomatous, postpartum), drugs (lithium, amio, TKIs, contrast), iatrogenic (thyroidectomy, radiation), iodine deficiency
  - 2°: see *Pituitary Disorders*
  - ↑ **T4 requirement**: pregnancy, estrogen (↑ THBG), weight gain, malabsorptive states (e.g. celiac disease), nephrotic syndrome (↑ excretion), rifampin, phenytoin, carbamazepine, phenobarbital
- **Treatment**: **levothyroxine** (T4) starting dose ~1.6 mcg/kg/d PO (use 25-50 mcg QD for elderly or comorbidities); IV = 50-75% PO
  - Take on an empty stomach 1h before food/meds; several hrs apart from PPI, aluminum hydroxide, iron, cholestyramine
  - Check TSH q6 weeks and adjust by 12-25 mcg until normal TSH

Subclinical hypothyroidism: elevated TSH with normal FT4 (biochemical diagnosis)

- Dx: can check anti-TPO Ab (if ⊕, monitor TFTs regularly because at higher risk for Hashimoto's)
- Treatment: treat if **TSH ≥10**. If TSH <5, consider risk factors (e.g. CV disease, CAD, HLD) to guide tx
- Elderly patients often have higher TSH levels and this can be normal

MYXEDEMA COMA

- Manifestation of severe hypothyroidism, STAT endocrine consult
- Mortality >30%, most common cause of death is hypercarbic respiratory failure
- **Precipitants**: infection, MI, cold exposure, surgery, administration of sedative drugs (esp opioids) in a poorly controlled hypothyroid pt
- **Signs/symptoms**: **AMS** (**lethargy**/obtundation, not always coma), **hypothermia**, **hypotension,** bradycardia, ventricular arrhythmias, hypercarbic resp failure, seizures
  - Exam: puffy hands and face, swollen lips, enlarged tongue
- **Labs**: ↓ Na (be careful with IVF), ↓ Glu, ↓ T4
- **Treatment**: do not wait to start tx for lab confirmation
  - Test and empirically treat **adrenal insufficiency**: give **hydrocortisone** 50-100mg BEFORE **T4** (if concomitant AI, replacing thyroid hormone first will catabolize residual cortisol and cause HoTN/death). Draw serum cortisol before initiating therapy.
  - **Levothyroxine (T4)** 12.5-50mcg IV QD in elderly or at risk for MI, up to 200mcg if sick and young.
  - **Liothyronine** (**T3)** (5-10mcg Q8H) only given if pt is critically ill (T4 conversion to T3 takes several days), give only with endo guidance, can cause rebound hypermetabolism
  - Recheck FT4 in 3-7d; if giving T3, monitor peak levels
  - Patients are **hypometabolic**: use lower drug doses at lower frequency, avoid MS-altering meds.

HYPERTHYROIDISM

- **Definition**: low TSH with high T4 (primary) or high/normal TSH with high T4 (secondary/central) (Thyroid 2016;26:1343)
- **Signs/symptoms**: general (↓ weight, ↑ appetite, heat intolerance, tremor, weakness), CV (palpitations, AFib, systolic HTN), hyperdefecation, dyspnea, sweating, anxiety, emotional lability, urinary frequency, abnormal menses, osteoporosis
  - Exam: lid lag, exophthalmos and pretibial myxedema (Graves' only), hyperreflexia, thyroid bruit
  - Apathetic thyrotoxicosis: depression, weakness, seen in elderly
- **Labs**: ↑ HDL, ↓ LDL, normocytic anemia, ↑ Ca, ↑ AlkP, ↑ Glu
- **Workup**: 1) TSI and TBII (Graves'), 2) RAIU (not for amio-induced or if recent IV contrast), 3) thyroid US w/ Doppler
- **Causes**:
  - **1°**: **Graves' disease** (most common, **T3:T4 ratio >20**), toxic adenoma, toxic multinodular goiter, transient thyroiditis (lymphocytic, granulomatous, postpartum, viral), drugs (amio, iodine, lithium), iatrogenic (radiation, palpation), exogenous T3 or T4 ingestion (low thyroglobulin), HCG-mediated, struma ovarii
  - 2°: see *Pituitary Disorders*
- **Treatment**: β-blocker for adrenergic symptoms (e.g. metoprolol, propranolol)
  - Graves' disease: thionamides (methimazole > PTU due to hepatotoxicity), radioiodine (risk of opthalmopathy), thyroidectomy (watch for hypoparathyroidism). Monitor total T3 and fT4 q6wks.
  - Toxic adenoma or multinodular goiter: radioiodine, surgery, less commonly thionamides

	TSH	FT4	Total T3
Primary	↓	↑	↑
Secondary	↑/normal	↑	↑
Subclinical	↓	Normal	Normal

THYROID STORM

- Manifestation of severe thyrotoxicosis, STAT endocrine consult
- Mortality rate 10-30%, most common cause of death is cardiovascular collapse
- **Precipitants**: surgery (thyroid or other), trauma, infection, iodine load, irregular use or discontinuation of antithyroid drugs
- **Signs/symptoms**: **AMS** (**agitation**, delirium, psychosis, coma), **hyperthermia**, **tachycardia**, atrial arrhythmias, CHF
  - Exam: goiter, tremor, warm/moist skin, exophthalmos (Graves')
- **Labs**: ↑T4/T3, ↓TSH
- **Dx**: Burch-Wartofsky Point Scale (BWPS) >44 highly suggestive
- **Treatment**:
  - **βB**: only propranolol decreases T4→T3 conversion, may require high doses (2g/day). Titrate to sx and HR (i.e. <80).
  - **Anti-thyroid meds**: only stop formation of new hormone, not release of stored hormone.
    - **Methimazole** (20mg 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 1hr after thionamide; can cause Jod-Basedow in toxic adenoma and Wolff-Chaikoff in Graves.
  - **Hydrocortisone** (300 mg loading dose then 100 mg Q8H) to reduce T4→T3
  - Patients are **hypermetabolic** and will clear drugs quickly

AMIODARONE-INDUCED THYROID DISEASE

Check TSH prior to treatment, q4-6 mo while on amio, and for 1 yr after amio discontinued.

- Typical response to amio acutely: ↑ TSH (2-3x nl), ↑ T4 and FT4, ↓ T3, ↑ rT3 → levels return to normal in 3-6 months
- May cause **hypothyroidism** (due to Wolff-Chaikoff or destructive thyroiditis) ***OR*** **hyperthyroidism**
  - Type 1 (early) → ↑ synthesis due to ↑ iodine
  - Type 2 (late) → direct toxicity of drug causing thyroiditis and stored hormone release without increased synthesis

CLASSIFICATION:

Adverse Drug Reactions (ADRs): (JACI 2010;125:S126)

- **Type A =** predictable (~85-90%): dose-dependent reactions related to drug's known pharmacological action which occur in otherwise healthy patients if given sufficient dose and exposure (e.g. gastritis d/t NSAIDs)
- **Type B =** unpredictable (10-15%): dose-independent, unrelated to pharm action, and occur only in susceptible pts
  - **Drug intolerance**: undesirable pharmacologic effect without abnormalities of metabolism/excretion/bioavailability of drug (e.g. tinnitus after aspirin)
  - **Drug idiosyncrasy**: abnormal effect caused by underlying abnormalities of metabolism/excretion/bioavailability (e.g. hemolysis after antioxidant drug in G6PD deficiency)
  - **Pseudoallergic reaction** (formerly known as anaphylactoid): drug causes direct release of mediators from mast cells/basophils (e.g. flushing during vancomycin infusion, exacerbation of asthma/rhinitis w/ aspirin in AERD)
  - **Drug allergy**: immunologically-mediated hypersensitivity reactions (see table)

Hypersensitivity Reactions (Gell and Coombs Classification): (Clin All 1998;18:515)

Type	Reaction	Mechanism	Presentations
I	Immediate (min-hr)	Ig-E mediated degranulation of mast cells due to antigen binding and cross-linking of IgE	Anaphylaxis, allergic rhinitis, allergic asthma, urticaria, angioedema
II	Antibody	IgM/IgG:antigen interactions on target cell surfaces	Drug-induced cytopenia (incl. AIHA)
III	Immune-complex	Immune complex formation and deposition in tissues →complement activation → local / systemic inflammation	Serum sickness, vasculitis, drug induced lupus
IV	Cell-mediated	Ag activates T cells → Ag later binds to activated T cells → cytokine release → macrophage & cytotoxic T cell accumulation	Contact dermatitis, SJS/TEN, DRESS, AGEP

EVALUATION

- **Key Qs in drug allergy hx**: approximate date, drug, dose and route, doses/days into course, co-administered meds, coincident infections, sx, severity (home/office/ED/hospitalization), how treated, exposures since
- **PLEASE document appropriately** in EPIC allergy section. Document rxn, date, and other meds tolerated (e.g. "hives to penicillin 2015, tolerated ceftriaxone 2019") and distinguish true drug allergies from drug intolerances.

DIAGNOSIS

- **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 number of medications
  - NPV of penicillin skin testing = 95% (Drug Allergy Practice Parameter 2010)
- **Deliberate re-challenge = graded challenge = test dose procedure**
  - Used when there is a **low suspicion for true allergic reaction** to a medication. Does NOT assess cross-reactivity of structurally-related drugs. Contraindication = severe non-IgE mediated HSR (ex: DRESS, SJS, etc.)
  - **How to order**: **Antibiotic Test Dose** in Epic order sets (can also type "penicillin" "allergy" "test dose")
    - Automatically orders the rescue medications, nursing communication orders, and fills in doses of desired med (FYI test dose = 1/10 of rx dose for IV meds and ¼ of rx dose for oral meds)
  - If **negative**: patient is *not* allergic to that agent and can safely receive it
    - If agent was a related agent (e.g. CTX administered in PCN-allergic pt): update "comments"
    - If agent was same agent as recorded allergy (e.g. PCN administered in PCN-allergic pt): remove allergy
  - If **positive**: Epi 1:1000 IM (0.3 mg), Benadryl 50 mg IV/PO. Page allergy fellow (13042) and file incident report

DRUG DESENSITIZATION JACI 2010;125:S126 (used if **true allergy**)

- **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 for advice on dose, administration, and monitoring. Generally, desensitization needs to be done in the ICU (exception: chemo on Lunder, ASA on cardiology floors)
- **If patient stops medication**: procedure must be performed again if pt stops medication for >2-3 half lives

PENICILLIN & CEPHALOSPORIN ALLERGY

- Pathway: Ellucid (or stepwise via Resources → Handbook → EPIC Quick Links → Medication Pathways)
- 10% of pts report a PCN allergy, but **90%** of patients with a h/o PCN allergy can tolerate PCN (JACI 2010;125:S126)
- Patients with a PCN allergy have a **<1% cross reactivity to carbapenems** (CID 2014;59:1113)
- Early studies evaluating the cross-reactivity between PCN and cephalosporins were performed before 1980, when cephalosporins were contaminated with trace amounts of PCN. More recent studies have found that **<2% of patients with skin test-proven sensitivity to PCN will react to cephalosporins** (Annals 2004;141:16)
- PCN allergy is typically mediated by the β-lactam ring, while cephalosporin allergy is due to the R-group side chain. The risk of cross-reactivity is higher with those β-lactams sharing identical R side chains

Groups of common β-lactam antibiotics that share identical R-group side chains				
Amoxicillin Cefadroxil	Ampicillin Cephalexin	Ceftriaxone Cefotaxime Cefpodoxime	Cefoxitin Cephalothin	Ceftazidime Aztreonam

OTHER COMMON DRUG ALLERGIES

- **Taxanes/platinum-based Chemotherapy**
  - Must differentiate *infusion reaction* (SIRS response to chemo agent) from true anaphylaxis (type I HSR)
  - Rates differ between agents: 19.5% with carboplatin, 30% with taxanes (NEJM 1995;332:1004)
  - Increased frequency of infusion reactions occur with subsequent infusions (AAAAI 2009;102:179)
  - Refer patient to Chemotherapy Allergy Clinic for skin testing or desensitization
- **Allopurinol**
  - **Allopurinol hypersensitivity syndrome (AHS)**: rash, fever, hepatitis, and/or renal impairment after exposure. Usually occurs 4-8 wks after initiation (Drug Saf 2013;36:953)
  - In patients of E. Asian descent, unless initiating for TLS, consider sending *HLA-B5801* genotyping (high risk for AHS)
- **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/Immunology
  - **Aspirin-Exacerbated Respiratory Disease (AERD)** (aka Samter's Triad): triad of asthma, rhinosinusitis w/ nasal polyps, and ASA/NSAID sensitivity (nasal congestion, bronchospasm). **Tx**: ASA desensitization

IV RADIOCONTRAST MEDIA (ACR Guidelines 2018)

Type	Pathogenesis	Epidemiology	Presentation	Clinical pearls	Pre-Treatment
Pseudoallergic (Anaphylactoid)	RCM directly stimulates mast cells / basophils *Minority of pts have + skin tests indicating that minority of pts have IgE mediated rxn *Use low/iso-osmolar RCM when possible	1-3% patients with ionic RCM & 0.5% pts w/ non-ionic RCM. Severe rxns occur in 0.22% for ionic RCM, 0.04% for non-ionic RCM Risk Factors: female, asthma, hx of previous rxn to RCM, BB exposure, CV disease	Immediate pruritus, urticaria, angioedema, airway obstruction, HoTN, abdominal pain	**No evidence** that iodine levels in seafood or topical solutions are related to adverse events from RCM. Seafood allergy is **not a contraindication**. **Oral contrast is NOT contraindicated** in a patient with IV contrast allergy, though rarely can cause a reaction.	***Elective*** (13h protocol) 1. Prednisone 50 mg PO at 13, 7, & 1h prior AND 2. Diphenhydramine 50 mg PO 1h prior ***Accelerated*** (4-5h) 1. Methylprednisolone 40 mg IV now & q4h until scan AND 2. Diphenhydramine 50 mg IV 1h prior ***Emergent*** (1h) 1. Methylprednisolone 40 mg IV 1h prior AND 2. Diphenhydramine 50 mg IV 1h prior
Delayed	T cell-mediated	2% of patients	>1h - 1 wk. Usually mild, skin eruption. Rare: SJS/ TEN	**Tx**: Supportive care	

Angioedema (Allergy 2018;73:1393)

- **Definition**: localized non-pitting swelling of the skin or mucosal tissue due to interstitial edema; may affect face, extremities, genitals, bowels. Often asymmetric. Occurs in min-hrs and resolves within 24-48hrs.
- Common triggers include heat, cold, delayed pressure, solar, vibratory, cholinergic, contact, and aquagenic
- **Classification/etiology**:

Type	Urticaria	Triggers
Mast Cell	Usually	ASA, NSAID, CCB, platinum-based chemo, β-lactams, metoprolol, siro/everolimus, risperidone
Histamine	Rarely	Idiopathic / spontaneous
Bradykinin	Never	**ACE/ARB**: 0.1-0.7% pts; may occur any time during therapy and last 6 mo after cessation **Hereditary angioedema**: autosomal dom. C1 esterase deficiency/dysfunction. Screen: ↓C4

- **Treatment**: in ALL: **ABCs, secure airway**
  - **If urticaria**: identify & remove exposure → tx with antihistamines, glucocorticoids, +/- epi if breathing affected
  - **If no urticaria**:
    - On ACE → stop ACE inhibitor → **supportive** care (if severe, consider icatibant)
    - Known hereditary or acquired angioedema → page allergy for C1-inhibitor, **icatibant**. **FFP** is 2nd line.
    - Not on ACE; no known disorder → **diphenhydramine** 50 mg x1 + **prednisone** 40 mg x1

Anaphylaxis (AAAI 2015;115:341; WAO Guidelines: World Allergy Org J 2011;4:13)

- **Definition**: acute, life-threatening, multi-system syndrome due to allergy or hypersensitivity
- **Causes**:

Type	Mechanism	Triggers
Immunologic	IgE mediated	Food (e.g., nuts, shellfish, milk, eggs), insect venom, meds (e.g. NSAIDs, β-lactams, biologics), latex, occupational allergens, aeroallergens, radiocontrast media (RCM)
	Non-IgE mediated	NSAIDs, dextrans (e.g. HMW iron), biologics, RCM
Nonimmunologic	Direct mast cell activation	Physical factors (exercise, heat, cold, sunlight), ethanol, meds (opioids)
Idiopathic	No apparent trigger	Mastocytosis / clonal mast cell disorder, previously unrecognized allergen

- **S/Sx**: skin/mucosal swelling, angioedema, rash/urticaria, bronchospasm/stridor, GI sx (n/v/d/pain), HoTN/shock
  - Associated with **biphasic reaction** in 4-23% pts → return of symptoms 8-72 hrs after initial symptom resolution
- **Diagnostic criteria**: **1 of 3** must be met
  1) **Skin** and/or mucosal involvement AND either **respiratory** compromise *OR* **reduced BP** after exposure to POTENTIAL allergen
  2) **Two** or more of following after exposure to LIKELY allergen: **skin**/mucosa swelling, **respiratory** sx, **HoTN**, **GI** sx
  3) **Low BP** (SBP<90 or >30% drop from baseline) after exposure to **KNOWN allergen** for pt
- **Labs**: consider **histamine** (within 10-30 min of symptom onset) and **tryptase** (within 15 min-3 h of symptom onset and 24h after symptoms resolve to assess baseline). Normal levels do not rule out anaphylaxis!
- **Treatment**:
  - **Establish and maintain airway**, administer oxygen/IVF, remove trigger if possible
  - **Epinephrine**: only medication that reverses airflow obstruction & prevents cardiovascular collapse
    - Dosing: **0.3-0.5mg IM** at **1:1000 dilution** (1mg/mL) *OR* **0.1-0.3mg IV** at **1:10,000 dilution** (0.1mg/mL)
    - May repeat **q5-15 minutes**; if >3 doses required, consider **continuous epi gtt (1-10mcg/min)**
    - If on beta blockers and resistant to epinephrine, administer **glucagon** (1-5mg bolus followed by gtt @ 5-15mcg/min)
  - Adjunctive agents: **albuterol** for bronchospasm (stacked nebs x3), **diphenhydramine 50 mg IV/IM** for hives/pruritis, **methylprednisolone 125 mg IV** QD x2 to prevent biphasic reaction
  - Make sure to **discharge home with EpiPen!**
  - If history of anaphylaxis to stinging **insect**, refer for skin testing. If positive, consider SQ venom immunotherapy, which decreases risk of subsequent anaphylaxis from 50-60% to 2-3% (NNT = 2). False negative skin testing may occur w/in first few weeks after anaphylaxis (NEJM 2014;370:1432)

Mast Cell (MC) Physiology (NEJM 2015;373;163)

- **Activated** by antigens (allergens), anaphylatoxins (C3a/C5a), meds, venoms, physical stimuli (pressure/temperature change), cytokines/neuropeptides. MCs **degranulate** and secrete **vasoactive & pro-inflammatory** mediators including histamine, serotonin, proteases (e.g. tryptase), TNF, cytokines, and chemokines.
- **Serum tryptase** most useful clinically (relatively specific for MCs)

Signs & Symptoms

- Cutaneous: flushing, pruritis, urticaria, angioedema
- GI: heartburn & nausea (histamine → hypersecretion of acid from parietal cells), diarrhea, abdominal cramps
- Respiratory: rhinorrhea, bronchoconstriction, nasal pruritis, throat swelling
- Cardiovascular: **episodic hypotension** associated with compensatory tachycardia, recurrent syncope
- Neuro: Headache, fatigue, mood disorder, insomnia, decreased concentration

Classification of Mast Cell Disorders

- Primary: systemic and cutaneous mastocytosis, monoclonal mast cell activation syndrome (MMAS)
- Secondary: allergic conditions, physical urticarias, chronic inflammatory conditions & neoplastic disorders
- Idiopathic: idiopathic anaphylaxis, idiopathic urticaria, idiopathic histaminergic angioedema, idiopathic mast cell activation

PRIMARY MAST CELL DISORDERS: clonal population of mast cells from affected progenitor (Blood 2017;129:1420)

	Systemic Mastocytosis	Cutaneous Mastocytosis
Epidemiology	Mainly adults. Incidence: 1: 10,000 - 20,000	Mainly **infants and young children**, resolves by adolescence. Incidence < 1:20,000.
Organ systems	Multifocal **infiltration of mast cells** in various internal organs (e.g. GI tract, spleen, liver). **Bone marrow** is involved in virtually **all patients. Skin** more common w/ indolent mastocytosis.	**Skin only,** but mast cell mediators may enter circulation and cause systemic symptoms.
Variants	1. Indolent SM (most common) 2. Smoldering SM 3. SM a/w non-mast cell hematologic neoplasm 4. Mast cell leukemia	1. Urticaria pigmentosa (UP) = maculopapular CM 2. Localized mastocytoma of the skin 3. Diffuse cutaneous mastocytosis
Lab findings	Elevated baseline serum tryptase (>20ng/mL) in non-symptomatic state strongly suggestive of SM	Normal baseline tryptase for most children with UP or mastocytoma; pt with diffuse CM may have elevated baseline tryptase
Diagnostic Criteria	**Diagnosis requires**: major criterion + 1 minor criterion OR 3 minor criteria **Major criterion**: multifocal infiltrates of mast cells in ≥1 visceral organ **Minor criteria**: 1. ≥25% of MCs in infiltrates in extracutaneous biopsies or BM smear spindle-shaped or atypical 2. KIT point mutation in BM or other extracutaneous organ 3. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25 4. Baseline serum tryptase level >20ng/mL	Skin lesions consistent with UP, mastocytomas, or diffuse CM, and typical histologic infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy. **In addition, an absence of features/criteria sufficient to establish the diagnosis of SM.**

Monoclonal Mast Cell Activation Syndrome (MMAS)

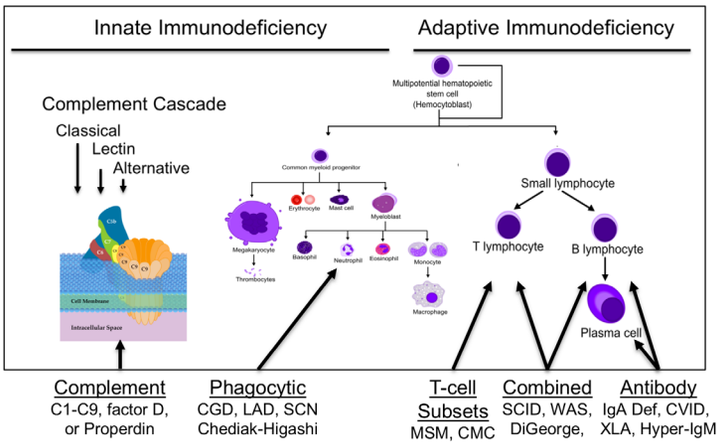
- Adult with **recurrent / episodic symptoms of mast cells** similar to SM (flushing, abdominal cramping, and hypotension) but do **NOT** have UP or characteristic mast cell aggregates in BM
- Baseline serum tryptase normal or mildly increased
- Meets 1-2 minor clonality criteria for SM but does not meet the full diagnosis

SECONDARY MAST CELL DISORDERS

- **Allergic diseases**: IgE-mediated allergies to food, medications, environmental allergens
- **Physical forms of urticaria**: physical factors may activate MCs in susceptible hosts (quick change in temperature, pressure/vibration on skin, exposure to water or UV light, exercise)
- **Chronic inflammatory/autoimmune disorders**: SLE, RA, psoriasis, atopic dermatitis, pulmonary fibrosis
- **Neoplasms**: breast cancer, Hodgkin's, skin and connective tissue tumors

Primary Immunodeficiency Disorders (JACI 2015;136:1186, JCI 2015;35:696)

- Definition: inherited deficits of immune system → increased incidence/severity/frequency of infections
- Prevalence: 1/300 – 1/10,000 pts
- Warning signs in adults: 2 new ear infxn/yr, ≥2 new sinus infxn/yr, recurrent viral infxn (e.g. HSV, VZV), ≥1 PNA/yr x multiple yrs, chronic diarrhea, recurrent deep abscesses, persistent fungal infection, recurrent need for IV abx, infxn w/ benign mycobacteria
- H&P: dev hx, FH, age at onset, frequency & type of infections, syndromic features
- Need to r/o 2º causes (HIV, immunosuppressants, cancer, cirrhosis)
- General principles of management: vaccination, abx ppx, immunoglobulin replacement, HSCT



	Disorder (% Total)	Presentation	Infectious Organisms	Advanced Testing (JACI 2010;125:S297)
INNATE	**Complement** (5%)	Any age - Sinusitis, PNA, meningitis - Lupus-like syndrome - Rheumatoid disorders	Bacteria: encapsulated esp. *Neisseria*	Complement levels CH50 or AH50 (alt pathway)
	Phagocytic (10%)	Infancy/childhood - Oral, anorectal, SSTI - Unusually severe infections - Granulomas, poor wound healing	Bacteria: *S aureus, PsA, Serratia, Klebsiella*, non-TB mycobacteria Fungi: *Candida, Aspergillus*	ANC Oxidative burst via DHR/NBT test for CGD
ADAPTIVE	**T cell subset defects** (5%)	Infancy - Oral thrush	Bacteria: Mycobacteria Fungi: *Candida*	Flow cytometry Anergy/proliferation tests
	B cell / Antibody (65%)	>6 mos, can present in adulthood - Recurrent sinusitis, PNA, viral URI - Chronic GI malabsorption, diarrhea - Autoimmune disease (29% in CVID) (Blood 2012;119:1650) - Post-vaccination paralytic polio with live vaccine - Anaphylaxis to blood products (IgA deficiency)	Bacteria: *H flu,* Strep, Staph, *Moraxella cat, PsA, mycoplasma pneumoniae* Virus: *Enterovirus* (esp with IgA deficiency) Parasites: *Giardia*	SPEP, flow cytometry **Vaccine response** Polysaccharide PPSV23 titers: ≥70% of serotypes ≥1.3 = adequate. If not, give PPSV23 & repeat titers in 4-6 wks Protein: tetanus, diphtheria IgG Conjugated: Hib IgG
	Combined B & T cell (15%)	Infancy - FTT - Oral thrush, viral infections - Diarrhea	Bacteria: *Salmonella*, *Listeria*, non-TB mycobacteria Viruses: CMV, EBV, VZV Fungi: *Candida*, *Aspergillus*, *cryptococcus*, *histoplasmosis* Parasites: *PCP*, *toxoplasmosis*, *Cryptospordium*	As above for B & T cell deficiencies

Immunoglobulin Replacement (JACI 2017;139:S1)

- Manufactured using donor pools of donated human plasma & contains IgG antibodies, administered as IVIG or SQ Ig
- In addition to **antibody replacement**, it also has **anti-inflammatory** and/or **immunomodulatory** effects at higher doses
- Starting doses: 400-600 mg/kg q3-4 wks for trough level >500-600 mg/dL (higher in pregnancy & bronchiectasis)
- Once on IVIG, cannot check serologies for 3-4 months. Can check PCR instead (e.g. HBV PCR)
- **IVIG in infection**: depends on host & infection. If CVID w/ infection, can check SPEP for IgG trough. Beneficial in CMV pneumonitis in solid organ tx recipients, rotaviral enterocolitis & bacterial infections in lymphoproliferative dz (e.g. CLL), Kawasaki disease, ped HIV.

Therapeutic Use of Vaccines in Patients with PID (JACI 2018;141:474)

- **ALL** patients with PID can receive **INACTIVATED** vaccines according to routine schedule. Prioritize yearly influenza vaccine and HPV vaccine. For **LIVE ATTENUATED** vaccine safety/benefit, see UpToDate Table.
- Pts on **immunoglobulin replacement** have adequate titers to measles, mumps, varicella, rubella, pneumococci, Hib, and variable titers to meningococcus. If exposed to an infection in which a "hyperimmune" Ig is recommended (rabies, HBV, tetanus), they should still receive the pathogen-specific Ig.

Causes of AMS: major categories include 1) Metabolic, 2) Infectious, 3) Drugs/Toxins/Medications, 4) Primary CNS, 5) Delirium

- Duration: **Hyperacute** (sec-min): trauma, intracerebral bleed, stroke, seizure, ↑ICP; **Acute** (min-hr): expanding bleed or edema, med/toxin, metabolic; **Subacute** (hr-days): infectious, autoimmune, neoplastic, metabolic; **Chronic** (wks-months): neurodegeneration, nutritional, neoplastic, autoimmune, psychiatric
- **AEIOU TIPS**: **A**lcohol (intox, HE, withdrawal, DTs, Wernicke's)/**A**rrythmia, **E**lectrolyte/**E**ndocrine (gluc, thyroid, adrenal), **I**nfection, **O**xygen (hypoxia, hypercarbia)/**O**verdose (opiate), **U**remia/**U**rine retention, **T**rauma/**T**umor/**T**TP/**T**emp, **I**atrogenic (meds - anticholinergics, BZDs, antidopaminergics, etc), **P**sych/**P**oison**, S**eizure (+post-ictal)/**S**troke/**S**yncope

Approach to Acute AMS

- **ABCs & vitals**:
  - If unresponsive & pulseless call **Code Blue**; if hypoxemic & GCS < 8 call **Rapid Response** & **RICU** for intubation
  - Check **RR** (hypercarbia – opiates, COPD), **BP** (hypertensive encephalopathy), **EKG** (hypoperfusion, arrhythmia)
- **Bedside exam**:
  - Establish **arousal (GCS)**, **command** following, **attention** (days of wk backwards); look for **cranial nerve problems or focal weakness**
  - If not arousable, coma exam off sedation: **pupils** (CN 2/3), **Doll's eyes** (CN 3/4/6/8), **corneals** (CN 5/7), symmetric **grimace** (CN 7), cough/**gag** (CN 9/10); **withdrawal to pain** in extremities, **posturing** (JNNP 2001;71:i13)
  - Pupil clues: **absent light reflex** (brainstem bleed/stroke, sedation, opioid, anoxia, eye drops); **b/l fixed, dilated** (severe anoxia); **u/l fixed, dilated** (herniation w/ CN III compression); **pinpoint** (narcotic, ICH)
  - **Trauma** (c-spine), **asterixis/myoclonus** (toxic, metabolic), **volume** status, **infectious/meningeal** signs, **cherry red discoloration** (CO), findings c/f **toxidromes, tongue bite, incontinence** (sz), **tenderness** (hip fx, fat embolus)
- **STAT orders**:
  - **ALWAYS check fingerstick glucose for acute change in mental status**
  - Consider: ABG; **if c/f stroke,** head CT +/- CTA head & neck
- **Work-up**:
  - **Review meds**: **hypoglycemic** (insulin), **BZD**, **opioid**, **steroid**, **anticholinergic** (TCA), **antihistamine**, antihypertensive (methyldopa, reserpine), antiepileptic, OTC's, anti/dopaminergics, antibiotics (esp w/AKI, incl. **cefepime,** other CSPs, PCN's, FQs (Neurology 2016;86:963)
  - Check **BMP, LFTs, CBC w/diff** (infxn, PV, blast crisis, high/low plts)**, lactate, NH3**, **VBG, UA/UCx/BCx, CXR, bladder scan** (retention)
  - Consider ESR, CRP, drug levels, serum/urine tox screen, CK (rhabdo/NMS), nutritional deficiency (B1, B12), TSH
  - Consider **TTP** (classic: ↓ plts, anemia, renal failure, fever, AMS). Check LDH & STAT smear for schistocytes
  - Consider **substance** use or withdrawal, **serotonin syndrome** (↑T, HR, BP, RR, mydriasis, hyperactive bowels, hypertonia esp in LE's; e.g. SSRI + tramadol, MAOi, linezolid [NEJM 2005;352:1112]), **neuroleptic malignant syndrome** (↑T, HR, BP, RR, rigidity; e.g. antipsychotic), **toxic drug levels** (salicylate, valproate, dig, lithium)

GCS:
Eye Opening:
- Spontaneously (+4)
- To verbal command (+3)
- To pain (+2)
- No eye opening (+1)
- Not assessable (+1)

Verbal:
- Oriented (+5)
- Confused (+4)
- Inappropriate words (+3)
- Incomprehensible sounds (+2)
- No verbal response (+1)
- Intubated (+1),
  +" T" to score ("3T")

Motor:
- Obeys commands (+6)
- Localizes pain (+5)
- Withdrawal from pain (+4)
- Flexion to pain (+3)
- Extension to pain (+2)
- No motor response (+1)

Approach to Subacute AMS: consider neurology consult prior to further extensive work-up

- Consider **EEG with LTM**: eval for intermittent seizures or non-convulsive status if routine EEG shows seizures
- Consider **MRI w/ Gad** (check CrCl first): eval for stroke, malignancy, infxn/inflammatory process, Wernicke's
- Consider **LP**: image to r/o herniation first; eval for cancer, infxn (if c/f infxn, imaging should not delay abx)
  - **Standard studies**: opening pressure, cell count, protein, glucose, Gram stain/Cx
  - **Malignancy**: cytology, flow cytometry, IgH gene rearrangement (for CNS lymphoma), autoimmune encephalopathy panel (d/w Neuro before sending)
  - **Infection**: HSV, VZV, **HIV** (requires consent)**,** cryptococcal Ag, AFB stain/Cx, fungal Cx, whipple PCR
  - **Other**: AI encephalitis panel (d/w neuro first), IgG index and oligoclonal bands (will need SPEP to compare)
- Consider infection (HIV, lyme, syphilis), autoimmune (anti-NMDA, sarcoid), metabolic (thyroid, B1, B3, B12, Wilson's), med (MTX), HTN encephalopathy, PRES (tacro/cyclosporine), Addison's crisis, porphyria (urine PBG)
- Consider neurodegenerative disease if more chronic presentation

Treatment of AMS: treat underlying cause; see disease-specific pages

- **Hypovolemia**: IVF; **Hypoglycemia**: D50 1-2 amps; **Hypoxemia**: O2; **Seizure**: protect airway, IV lorazepam 4mg if GTC > 2 min, then long-term AED; **Trauma**: stabilize C-spine; **Meningitis**: LP, empiric abx; **EtOH toxicity**: thiamine 500 mg IV TID before sugar, then 100 PO QD; **EtOH w/d**: BZD vs. phenobarb; **Opiate toxicity**: naloxone IV/IM/SC bolus q3min (0.04 dilution if mild, 0.4-2 bolus if coding); **BZD toxicity**: consider flumazenil 0.2 mg IV q1min; **Hepatic encephalopathy**: lactulose 30 ml q4h titrate to BM + rifaximin 550 mg BID, consider SBP tx (diag para)
- **Agitation management**: ensure QTc <500. **Haloperidol** (IV/IM/PO; if dystonic rxn, give benadryl 25-50 IM/IV), **olanzapine** (SL/PO/IM), **quetiapine** (PO) (Psych Clin Neurosci 2013;67:323)

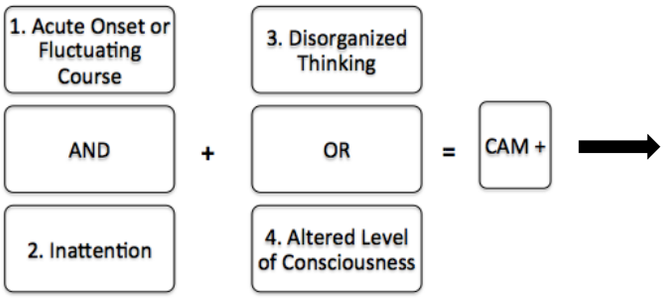
DELIRIUM or "Acute Brain Failure": an acute disturbance of ***attention*** with ***fluctuating*** severity over the course of the day or week & concomitant disturbance in ***cognition***, neither of which are better explained by pre-existing/evolving neuro-cognitive disorder or newly developed reduction in ***arousal***. Presentation is a direct consequence of a medical condition, intoxication, or withdrawal (DSM-5)

- Risk factors: Hx delirium/TIA/CVA/dementia, long hospitalization, EtOH, age >65 (~50% have delirium inpatient), infection, visual/hearing impairment, comorbidity/severe illness, depression, HIV, h/o TBI
- Associated with ↑mortality (JAMA 2010;304:433), ↑institutionalization (Lancet 2014;383:911), ↓cognition (NEJM 2012; 367:30)
- **Both HYPERactive and HYPOactive delirium warrant treatment**

AVOID DELIRIUM BY PREVENTING IT IN VULNERABLE PATIENTS

- **Minimize deliriogenic meds**: anticholinergics, antihistamines, benzodiazepines, opioids **(optimize pain w/ non-opioids)**
- **Precautions**: frequent reorientation, mobilize with PT/OT, OOB to chair, glasses/hearing aids, minimize lines/telemetry/catheters, early volume repletion if c/f dehydration. **Avoid** room changes or physical restraints.
- **Anticipate circadian dysfunction**: standing melatonin 3 mg **q6PM**, **lights on during day and off at night**, schedule rx for earlier in evening, avoid late diuresis, reduce noise.

CAM (Confusion Assessment Method)



Sn 94-100%, Sp 90-95%, high inter-rater reliability (Annals 1990;113:941)

If CAM⊕

- **Do additional mental status exam**
- **Exam for inattention**: reciting months of the year backwards (Sn 84%); days of the week backwards (Sp 82%) (JHM 2018;13:551)
- **Start delirium precautions** (*see above*)
- **Evaluate for precipitating factors**

Management:

- Behavioral management (see top of page)
- Identify & treat **UNDERLYING CAUSE** w/ special attention to life-threatening conditions (see *Altered Mental Status*)
- Daily EKG to monitor QTc (goal <550ms); Daily repletion of K>4 & Mg>2 (in anticipation of pharmacotherapies)

Medical Management (for dangerous behavior ONLY, i.e. if pt is a danger to self or others)
1:1 sitter (re-orients) >> meds >> restraints (deliriogenic)

- **For HYPERactive delirium/AGITATION → start PRN, escalate to scheduled** (Nat Rev Neur. 2009; 5:210)
  - Haloperidol 2-5mg IV q3h PRN vs. 0.5-1mg PO q4h PRN vs. IM q1h PRN (*NB*: *can lead to EPS, acute dystonias in Parkinsonism)*
  - Quetiapine 12.5-50 mg PO q6-12h PRN
  - Olanzapine 2.5-10 mg SL/PO/IM qd-q4h PRN
- **If continued severe agitation → consider Psych/Geri consult**:
  - Haloperidol PRN: double PRN dose q20 min till effective, ~5-20 mg IV, consider standing or gtt (ICU)
  - Quetiapine PRN: standing 25-50 mg TID, extra dose HS
  - Olanzapine PRN: standing 2.5-10 mg BID, extra dose HS
- 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.**

When to Consider Psychiatry/Geri Consultation:

- **Escalating/persistent delirium**, Hx agitated delirium, underlying neurodegen. disorder (esp PD), hx TBI
- **Co-morbid EtOH or other substance use disorders**
- Mult. med co-morbidities (esp CV dz)/critical illness
- At risk for disinhibition/impulsivity

When to Consider Neurology Consultation:

- New focal finding suggesting stroke: Stroke p20202
- Other concerning findings (convulsions, meningismus, e/o elevated ICP, abnl spot EEG/LP): General p20702
- Know last seen well, baseline deficits, anticoag use before calling!

INITIAL EVALUATION: **should almost always be in outpatient setting** where 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 s/e's (e.g. analgesics, anticholinergics, psychotropic medications, sedative-hypnotics)
- Assess cognitive impairment (**MOCA** >> **MMSE**), track score at subsequent visits
- Labs: CBC, TSH, BMP, B12; consider: tox, RPR, Lyme, HIV, UA, metals, ESR, LFT, folate, B1, B6 (Amer Fam Phys 2005;71:1745)
- Neuroimaging: NCHCT or **MRI brain (preferred)** to r/o structural lesion (tumor), assess **atrophy pattern**, eval for vascular dementia and microhemorrhages (CAA). PET can be considered if dx unclear but often unnecessary.
- Formal neuropsych testing: pattern of deficits can suggest particular dementia syndrome; also helpful to r/o comorbid psych disease
- Inpatient evaluation should be considered for any rapidly progressing dementia syndrome or a new dementia diagnosis in pts <55 (consult Neuro for ?LP, consider RT-QuIC >14-3-3 [CJD], ACE [sarcoid], autoimmune encephalitis [only after d/w Neuro]), new focal neurologic deficits (?stroke), fall with head trauma or LOC
- **Outpatient Neurology referral to Memory/Cognitive clinic**

DEMENTIA SYNDROMES (Prog Neurol Psych 2012;16:11, BMJ Neurol, Neurosurg, & Psych 2005;75:v15, Annals of Neurol 2008;64:97)

Syndrome	Presentation	Exam	Imaging	Treatment
Gradually Progressive				
Alzheimer Dementia	• **Amnesia earliest sx**; also language and visuospatial deficits • Apraxia in later stages	• Normal neuro exam (excluding MS) • Neuropsych: amnesia w/ short memory span, alexia, agraphia	**Hippocampal** (+/- global) volume loss; ?microhemorrhages (CAA)	• AChE-inhibitors (mild-severe dz) • NMDA-inhibitors (mod-severe dz)
Lewy Body Dementia	• **Fluctuations** in attention/alertness • **Visual hallucinations** • **REM behavior d/o** • Falls/syncope • Neuroleptic intolerance • Memory problems late	• **Parkinsonism**: resting tremor (can be absent), cogwheel rigidity, bradykinesia, stooped/shuffling gait – named Parkinson's dementia if movement sx present for >1 yr before dementia • Neuropsych: fluctuations w/ intrusions and confabulation, visuospatial impairment	Global volume loss	• AChE-inhibitors (specifically rivastigmine) for memory sx • Carbidopa/levodopa trial for motor deficits • Sx management of autonomic dysfxn
Frontotemporal Dementia	**Behavioral variant** most common: • Changes in personality (disinhibition, apathy) • Stereotyped behaviors • Lack of insight **Primary Progressive Aphasia variant**	• May have **frontal release signs** (non-specific) • 15-20% get motor neuron dz • Neuropsych testing: poor impulse control, difficulty in organization	Atrophy predominantly in **frontal and temporal lobes**	• Management of behavioral sx (low threshold c/s psych) • AChE-inhibitors not helpful • **Avoid** NMDA-inhibitors
Stepwise Progressive				
Vascular Dementia	• **Abrupt focal sx, stepwise progression** • Depression common • Hx: CVA, HTN, HLD, AF	• **Focal deficits** (depending on stroke location), can include: weakness, dysarthria, ataxia, gait changes • Often look older than age	Cortical or subcortical **punctate lesions, white matter disease,** and **volume-loss**	• Secondary stroke prevention and risk factor modification • AChE-inhibitor for memory deficits
Rapidly Progressive				
Prion Diseases (Sporadic, Variant Creutzfeldt-Jacob Disease)	• **Rapidly progressive** sx in memory, concentration, judgment • Mean onset age ~60 for sporadic, 28 for variant • Younger pts: more sig psychiatric sx	• **Myoclonus, exaggerated startle response** • EPS: bradykinesia, nystagmus, ataxia • UMN signs (hyperreflexia, ⊕Babinksi, spasticity) • **LP**: **RT-QuIC>>14-3-3**	**MRI**: **cortical ribboning** on DWI, subcortical hyperintensity on FLAIR **EEG**: 1-Hz periodic epileptiform discharges	• No tx • Death w/in 1 year (median disease duration 6 mo.)
Limbic Encephalitis (Autoimmune, Paraneoplastic)	• Sx evolve days-weeks (more indolent possible) • **Short-term memory sx** • **Psych sx**: agitation, delusions, hallucinations • **Focal seizures**	• Prominent psych features • Dyskinesias, rigidity • Autonomic instability • **LP**: lymphocytic pleocytosis, oligoclonal bands, **autoantibodies** (CSF + serum)	**MRI**: **FLAIR hyperintensity or contrast enhancement** (esp in temporal lobe) **EEG:** extreme delta brush very specific	• Immunotherapy: **steroids, IVIG, PLEX,** rituximab, cyclophosphamide • **Tumor resection**

TREATMENT: treat sx but do not slow the progression of disease

- AChE inhibitors: **donepezil** (first line), rivastigmine (patch), galantamine. Small effect on cognition, ADLs. Major 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 sig behavioral sx)

HEADACHES: distinguish **primary** headaches (tension, migraine, etc.) from **secondary** headaches (tumor, ↑ICP, vessel lesion, etc.)

Tension HA: ~40% population, ♀>♂. **Band-like, radiate forehead to occiput, mild-mod severity, 30m to 7d**. Rarely seek eval. (Am Fam Physician 2002;66:797).

- Abortives: NSAIDs, Tylenol. Can add **caffeine/bultalbital**, antiemetic (metoclopramide, promethazine). Use abortives no more than 2 days/wk.
- Preventatives: amitriptyline, nortriptyline, SSRI, tx OSA, smoking cessation

Red flags for secondary HA evaluation	
Symptoms	**Imaging**
New HA >35 yo, abn neuro exam, acute, severe, positional, worse w/ exertion, immunosuppressed, wakes at night	MRI brain w/ contrast
Vestibular, brainstem, retinal, motor sx	MRA or CTA head & neck

Migraine HA: sx >3/5 criteria POUND (**P**ounding, **P**hoto/phonophobia**, O**nset 4-72hrs, **U**nilat, **N/V**, **D**isabling) (JAMA 2006;296:1274)

- Migraine w/ aura: 1 reversible sx: visual (scintillating scotoma, visual field deficit)**,** sensory (tingling, numbness), speech/lang, motor (wkness, hemiplegic), basilar (dysarthria, vertigo, ataxia, diplopia), vestibular (vertigo), retinal (monocular field deficit). Similar symptoms spread over minutes with each headache (stroke mimic). Aura without migraine headache possible (acephalgic migraine)
- Menstrual migraine: before/during menstruation → tx w/ NSAIDs or sumatriptan (Neurology 2008;70:1555). Consider preventive tx perimenstrually w/ slow triptan (frovatriptan) 2.5mg QD/BID (begin 2d premenstrually, for total 6d/month)
- Abortives: Tx early, escalate stepwise.
  - *Mild/mod pain*: Tylenol, Mg (2g IV), NSAIDs, IVF (Headache 2012;52:467)
  - *Mod/sev pain*: IVF, **triptan**, antiemetics (metoclopramide, prochlorperazine 10mg IV q8h), VPA 500mg IV, **DHE**, steroids (dexameth 10-25mg IV x1) (Headache 2012;52:114).
- Preventatives: if >3 d/mo, long aura, or disability (Neurology 2012;78:1337)
  - **BB/CCB**: *propranolol* 20mg BID, incr to 40-160mg/day. *Metoprolol* 25mg BID, inc to 50-200mg/day. Verapamil 80mg TID, increase gradually.
  - **Antidepressants**: amitryptiline/nortriptyline 10mg qhs, incr to 150mg. Venlafaxine 37.5 mg QD, inc to 75-150 mg.
  - **Anticonvulsants**: topiramate 25mg QD, inc gradually 100mg BID. VPA 500-1500 mg qD (avoid both of these in young ♀).
  - **Supplements**: magnesium 400mg QD, riboflavin 400mg QD, feverfew
  - **Botox**: referral to headache clinic

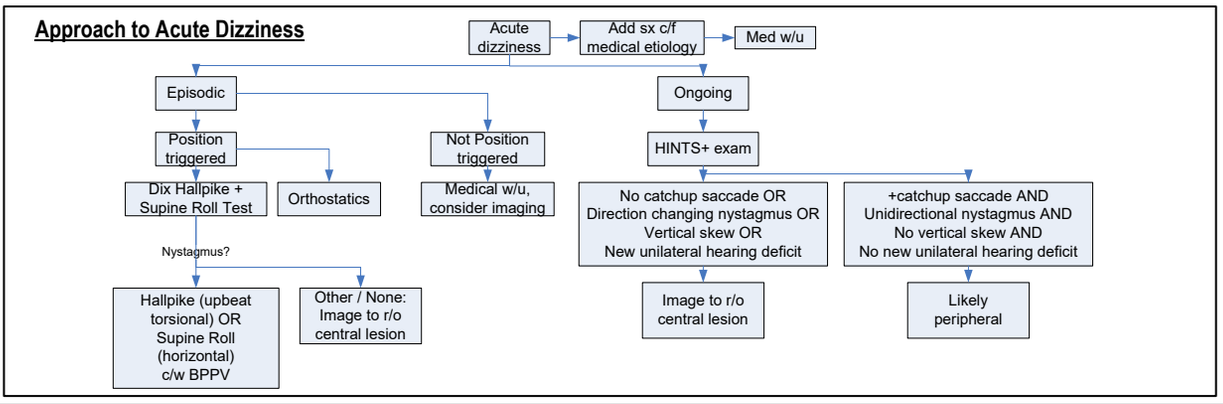
Triptans (max 4x/d, 2x/wk)
Nasal: Sumatriptan 5-20mg q2hrs (max 40mg/day), Zolmitriptan 5mg q2hrs (max 10mg/d) **SC:** Sumatriptan 4-6mg q1hr (max 12mg/d; 70-80% pts w/ sx reduction; 35% resolution) **PO**: Sumatriptan 25-100mg q2hr (max 200mg/day), Zolmitriptan 1.25-2.5 q2hrs (max 10mg/d) **C/I: ischemic CVD/CAD** (vasoconstriction), PVD, liver disease, basilar migraine, MAOIs within 2 wks *Caution w/ SSRIs 2/2 risk of serotonin syndrome
Dihydroergotamine (DHE)
IV: 0.5-1mg IV Q8h x5 days preferred to x1 dose (max 3mg/day) **Nasal:** 1 spray /nostril q15min (max 6 spray/day, 8/week); **SC:** 1mg SC q1hr (max 3mg/day) **Same C/I as Triptans**, do not mix with triptans w/in 24hrs

VERTIGO: illusion of motion of self or world 2/2 vestib dysfxn; a/w n/v, postural/gait instability. **Important to distinguish**: **central vs peripheral** (Am Fam Physician 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). Orthostatics. Dix-Hallpike. **HINTS**.
- HINTS exam: everything *must be c/w peripheral to be reassuring.* In **acute** vertigo, Sn 97% / Sp 85% for stroke (better than MRI!)
  Head **I**mpulse (pt looks at your nose, passively rotate head. No saccade = ambiguous. Catchup saccade = peripheral).
  Nystagmus (unidirectional e.g. always left-beating = peripheral; L-beating in L gaze, R-beating in R gaze, any vertical = central).
  Test of **S**kew (cover one eye then other, any vertical skew/correction = central) (Acad Em Med 2013;20:986)

	Symptoms	Ddx	Imaging
Peripheral	Severe nausea, mild imbalance, hearing loss/tinnitus	Benign positional paroxysmal vertigo (BPPV), infection (labyrinthitis, vestibular neuritis, herpes zoster oticus), Meniere's, vestibular migraine, otosclerosis, trauma (perilymphatic fistula)	If exam reassuring, none
Central	Mild nausea, severe imbalance, rare hearing sx	Cerebral infarction (vertebrobasilar ischemia), TIA, hemorrhage, toxic, cerebellopontine mass (vestib schwannoma, ependymoma, brainstem glioma, medulloblastoma, neurofibromatosis, MS, vestibular migraine	MRI brain w/wo contrast, coronal DWI, MRA head & neck

- Treatment: metoclopramide, prochlorperazine, meclizine (2 wks max, vestib suppression), lorazepam, diazepam AND **vestibular PT**



****Consider stroke for any sudden-onset focal neurologic symptoms****

ACUTE STROKE ACTIVATION

1) If high suspicion and onset of sx within past 24h, page stroke resident p20202. If they agree with stroke diagnosis, activate acute stroke code.
2) **BE AT BEDSIDE. Consider this a code-equivalent.** Ensure 18g PIV is in place and bed is ready for travel with travel monitor in place
3) **ABC/Vitals**: check **VS**, **EKG**, **telemetry**, **glucose, keep NPO** & **HOB >30°**. **Do not treat HTN** unless BP >220/120, ACS, or ICH (see below)
4) Be ready to provide the following information:
   a) **Last seen well (LSW) time** (last time patient confirmed to be normal) – this is NOT the time that sx were noticed by you or patient
   b) AC or antiplatelets, CrCl, allergies, code status, baseline function
   c) Contraindications to tPA - **even if present, call an acute stroke (patient may be candidate for thrombectomy)**
   d) Use **NIH stroke scale** (NIHSS) to quantify severity
   e) Most predictive physical exam findings: facial paresis, arm drift/weakness, and abnormal speech (JAMA 2005;293:239)
5) **STAT CTA Head and Neck** (only need to order CTA; it includes non-con head CT). If unable to receive contrast and/or LSW ≥6 hrs, stroke team will consider STAT MRI +/- MRA.
6) **Labs**: check **BMP**, **LFTs**, **CBC, PT/INR/PTT, Trop, UA/UCx, tox screen, & AED levels (if appropriate)**

IV tPA

Inclusion:
1. Clinical dx w/ measurable deficit, age ≥ 18
2. Time since **last seen well <4.5 hrs** (**may be 9h soon** NEJM 2019; 380:1795)

Exclusion:
History: stroke/head trauma in last 3 mo.; recent head/spine surg; prior ICH; intracranial malignancy, AV malformation, aneurysm; incompressible arterial puncture last 7 days
Clinical: SAH sx; **BP ≥185/≥110 (treat!)**; BG <50; active internal bleeding; bleeding diathesis
Heme: Plt <100K; current AC (warfarin w/ INR >1.7; therapeutic heparin use w/in 48 hrs w/ ↑PTT; DOAC within 48 hours)
Head CT: hemorrhage; multilobar infarct >1/3 involvement of cerebral hemisphere

Intra-arterial therapy

Inclusion:
1. Clinical: **NIHSS ≥ 6, LSW ≤ 24 hrs**, age 18-85, baseline mRS ≤1, life expectancy > 12 mo.
2. Radiological: ICA or MCA M1/2 occlusion, basilar or dominant vert occlusion, small infarct core volume (CT: ASPECTS ≥ 6 + collaterals; MRI: 70 cc by DWI)

Exclusion:
Clinical: **BP ≥185/≥110 (treat!)**, BG<50 or >400
Heme: Plt <40k, INR >3

ACUTE STROKE INITIAL MANAGEMENT

(Stroke team will provide guidance, **but IV tPA may be given by any MD**)

1. ISCHEMIC STROKE: (MGH In House Stroke Protocol)

- **IV (intravenous) thrombolysis (tPA)**:
  - **LSW 0-3 hr**: goal to start IV tPA w/in 60 min of ED arrival (AHA/ASA Guidelines Stroke 2018)
  - **LSW 3-4.5 hr**: IV tPA recommended but w/ relative exclusion criteria including age >80, AC (regardless of INR), NIHSS score >25, ischemia >33% of the MCA territory, h/o both stroke & DM2 (ECASS III NEJM 2008;359:1317) (note: guidelines are actively changing)
  - **Dosing**: 0.9 mg/kg; 10% bolus over 1min, remainder infused over 1hr
- **Intra-arterial therapy (thrombectomy, thrombolysis)**:
  - Patients with disabling deficit & large vessel occlusion with **LSW <6 hours** (MR CLEAN NEJM 2015;372)
  - May extend time to **LSW 6-24 hr** based on imaging criteria (DAWN NEJM 2018;378:11)
- **BP control**: low SBP (<150) a/w poor outcome (Arch Intern Med 2003;163:211)
  - If tPA candidate: goal BP **≤185/110** prior to tPA **(treat STAT if higher!)**; goal BP **≤180/105** after tPA for 24 hours
  - If no tPA: goal BP **≤220/120** (allow auto-regulation) for 1d; lower SBP <20 per day subsequently
  - If anticoagulated: goal SBP **≤180**
  - If active cardiovascular disease (ACS) & requires tighter BP control, discuss w/ neuro
  - **Monitor neuro exam** - sx worse at low BP suggests critical stenosis → **lay bed flat, give IVF bolus, STAT page neuro**

2. HEMORRHAGIC STROKE (see intracerebral hemorrhage section in *CNS Emergencies*)

INPATIENT POST-STROKE CARE

- Frequent **neuro checks** q1-2 hr x 24 hrs if unstable/ICU; q4h if stable/floor pt, **STAT** head CT if change in exam.
- Consult **PT, OT, SLP** (**NPO** until bedside swallow eval). Keep **euthermic** (antipyretics), **euglycemic** (FSG<180), **Mg>2**.
- If received tPA: **NCHCT 24 hrs post-tPA** → if no e/o hemorrhagic transformation, start antiplatelet + DVT ppx.
- If did not receive tPA: **ASA 325 mg x1**, followed by long-term antiplatelet or AC (may delay AC for large ischemic strokes). Start DVT ppx if ischemic stroke (unless large hemorrhagic conversion).
- **Antiplatelet long-term 2° prevention**
  - **ASA** 81mg QD (50-325 mg/d effective; ≤200 mg/d lower risk of major bleed) (Am J Cardiol 2005;95:1218)
  - **Clopidogrel** 75mg QD (may be superior to ASA for atherosclerotic vascular dz) (CAPRIE Lancet 1996;348:1329)
  - **DAPT (ASA + clopidogrel)**
    - **TIA or minor stroke**: consider in patients w/ NIHSS<4 or TIA. ASA+clopidogrel for **3 wks** followed by clopidogrel (or ASA) alone (CHANCE NEJM 2013;369:11). Can consider clopidogrel load (300-600 mg) w/in 24 hrs of symptoms.
    - **Symptomatic intracranial stenosis**: can consider ASA/clopidogrel for **3 mo** (SAMMPRIS NEJM 2011;365:993)
    - **Recurrent stroke on ASA or clopidogrel alone + significant athero**: some use DAPT long-term; no clear evidence & higher bleed risk (CHARISMA NEJM 2006;354:1706 & MATCH Lancet 2004;364:331) – discuss w/ neurology.
- **Anticoagulation long-term 2° prevention** (embolic infarcts from AFib, paradoxical embolus, LV thrombus or hypercoagulable state)
  - **Warfarin or DOAC** for pts w/ AF (hold off x 2-4 wk if hemorrhagic conversion or large hemispheric stroke)
  - **No need** for both antiplatelet & anticoagulation

- Start **Atorvastatin 80 mg** w/ LDL goal < 70 (NEJM 2020;382:9)
- Work up/secondary prevention: (see below)
  - **Labs**: lipids, A1c, TSH, ESR/CRP; if <60 y/o, send tox screen (cocaine), hypercoagulability w/u (if recommended by neuro)
  - **Imaging**: head and neck CTA or MRA (can do TOF if low GFR); carotid U/S as alternative
  - **Cardiac workup**: EKG, TTE (with bubble if <60), inpatient tele then 30-day MCOT vs. LINQ if tele is negative for AFib

CARDIOEMBOLIC STROKE	
SUSPECT WHEN: • ACA/MCA/PCA occlusion w/o sig vascular dz • Infarcts in multiple territories or cerebellar stroke • Known risk factors (LA/LV thrombus, AFib, LVEF<25%, aortic disease, intracardiac shunt) • Hypercoagulability/hyperviscosity (solid organ or heme malignancy, HbSS, cryo, clotting d/o)	**DX WORKUP**: • **TTE (w/ bubble if < 60 yo)** - if PFO, r/o venous thrombus (LENIs/ MRV pelvis), can consider closure (RESPECT NEJM 2017;377:1022) • Inpatient **telemetry followed by 30-day MCOT vs. LINQ** at discharge (unless known AFib) **ACUTE MANAGEMENT CONCERNS**: • **Avoid immediate AC** unless known intracardiac thrombus or mechanical valve. Transition to long-term AC in 2-4 weeks.
SYMPTOMATIC CAROTID STENOSIS	
SUSPECT WHEN: • Carotid stenosis present on ipsilateral side • H/o amaurosis fugax **DIAGNOSTIC WORKUP**: • **CTA** vs. **MRA** head & neck usually sufficient • Alternatives: **carotid US** - typically need carotid U/S prior to carotid endarterectomy (CEA)	**ACUTE MANAGEMENT CONCERNS**: • If **>50% carotid stenosis causing stroke/TIA,** consider **carotid revascularization** (stent/angioplasty/endarterectomy) – ideally w/in 2 weeks of sx (NASCET II NEJM 1998;339:1415) • Consider temporary **anticoagulation** (d/w neurology) • Consider **induced HTN** if symptoms fluctuate with BP
INFECTIVE ENDOCARDITIS	
SUSPECT WHEN: • Unexplained fever w/ stroke or pt with valvular dz **DIAGNOSTIC WORKUP**: • **Blood cultures, TTE** followed by **TEE** if neg • **CTA head** to identify mycotic aneurysms (↑risk bleeding) • If CTA negative, **may need conventional angio** (CTA not as sensitive for mycotic aneurysms)	**ACUTE MANAGEMENT CONCERNS**: • **Immediate antibiotics; caution with tPA** • Early cardiac surgery if small non-hemorrhagic stroke; delayed cardiac surgery (2-4 wk) if large or hemorrhagic stroke • **Avoid anticoagulation or antiplatelet** w/o a separate indication
CAROTID AND VERTEBRAL DISSECTIONS	
SUSPECT WHEN: • <60 yo or posterior circulation stroke in pt w/o RFs • Neck pain, HA, or Horner's syndrome • Trauma (vertebral fx), chiropractor, coughing spells **DIAGNOSTIC WORKUP**: • **CTA** vs. **MRA with T1 fat saturation** • Consider comorbid conditions (Marfan's, FMD)	**ACUTE MANAGEMENT CONCERNS**: • Goal of tx is to prevent stroke: highest risk in first few days • **Anticoagulation** vs antiplatelet. Prefer antiplatelet if: sx onset >3d ago, dissection extends intradurally (no AC due to risk of SAH), large infarct (risk of hemorrhage) (CADISS Lancet Neurol 2015;14:361) • High rate of recanalization → Tx 3 months then re-image vessel
CEREBRAL VENOUS SINUS THROMBOSIS	
SUSPECT WHEN: • Positional HA, vomiting, papilledema, vision Δ • P/w seizure (common, may be difficult to control) **DIAGNOSTIC WORKUP**: • **NCHCT**: hyperdensity in torcula (dense delta sign) • **CTV** vs. **MRV** to assess intracranial venous system • Consider **hypercoagulable workup**	**ACUTE MANAGEMENT CONCERNS:** • **Immediate anticoagulation** even in presence of hemorrhage • AEDs if seizures (not indicated for ppx) • IV fluids, avoid dehydration, modify risk factors (smoking, OCPs)

TRANSIENT ISCHEMIC ATTACK (TIA)

- **Definition**: *transient* neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia w/o acute infarction or end-organ injury as assessed clinically or by imaging
- **Causes**: atherothrombotic stenosis (ICA, vertebral, basilar, small vessel), embolic (arterial, aortic, cardiac, paradoxical), dissection (ICA, vertebral) – identification will guide tx (antiplatelet therapy vs. search for underlying arrhythmia +/- anticoagulation)
- **Imaging**: MRI (w/ DWI/ADC) w/in 24hr of sx onset and vessel imaging of head and neck for large vessel occlusive disease (e.g. MRA (time of flight if low GFR) vs. CTA vs. carotid ultrasound
- **Cardiac w/u**: TTE to excl thrombus & PFO (age <60) & tele/MCOT vs. LINQ monitoring to exclude Afib if suspected embolic TIA
- **ABCD²** score (**A**ge, **B**P, **C**linical features, Sx **D**uration, **D**iabetes): used to identify pts w/ high risk of ischemic stroke w/in 1wk of TIA
- **Management**: immediate intervention reduces the risk of recurrent stroke (1.5-3.5% risk within 48h), *see 2° Prevention* above

Intracranial Hemorrhage (ICH): epidural (EDH), subdural (SDH), subarachnoid (SAH), intraparenchymal hemorrhages (IPH)

- **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 CA's), cortical vein thrombosis, venous sinus thrombosis
- **Presentation**: acute focal neuro deficit, +/- progressive ↓consciousness, n/v. **SAH**: thunderclap HA, N/V, meningismus; **EDH/SDH**: s/p trauma, lucid interval with EDH; **IPH**: focal neuro symptoms (may mimic ischemic stroke clinically); often with HA.
- **Tests**: STAT imaging (NCHCT for all; +CTA head if SAH/IPH), coags/PLTs; need f/u scan at 6h to assess progression
- **STAT management**:
  - STAT Neurosurg (p21111) if SAH/SDH/EDH; otherwise, Neuro (inpatient: p20202; in ED: p20000).
  - Elevate HOB to 30-45° to reduce ICP and prevent aspiration
  - **BP control**: SBP < 140 (studied in SAH or ICH due to ruptured aneurysm/AVM), use **IV labetalol** or **nicardipine drip** (avoid hydralazine if possible), place arterial line (INTERACT Lancet Neurol 2008;7:391, ATACH Crit Care Med 2010;38:637)
  - **Correct coags**: warfarin/**INR**>1.5: tx (vitamin K 10 mg IV x 1) AND (3-5U FFP or Kcentra); **↓Plt** (transfuse, goal >50); Uremia/antiplt use: consider DDAVP 0.3mcg/kg IV; heparin/LMWH: protamine; s/p tPA (check fibrinogen, give cryo, +/- amicar), rivaroxaban/apixaban: give Andexanet Alfa; dosing based on size and timing of last dose (call pharmacy)
  - **Venous sinus thrombosis (VST)**: anticoagulate w/ LMWH/heparin despite hemorrhage (Lancet 1991;338:597). Manage ↑ICP and seizures.
  - Prognosis depends on age, GCS, pre-ICH cognitive impairment and ICH volume/location (FUNC Score) (Stroke 2008;39:2304)
  - Typically acceptable to restart DVT ppx in smaller hemorrhages if stable after 48hrs, but confirm w/ neurology

Elevated Intracranial Pressure (ICP) / Herniation

- **Etiologies**: mass (tumor, abscess, hemorrhage), cerebral edema (infarction, inflammation, hyperammonemia, DKA), hydrocephalus (tumor, intraventricular hemorrhage, leptomeningeal disease, meningitis), PRES. High ICP may cause compression/ischemia. Severe local swelling or CSF drainage with large space-occupying lesions causes herniation (displacement and compression of brain).
- **Signs of herniation**: fixed/dilated/asymmetric pupil (often 1 first) accompanied by nausea, somnolence/confusion, or limited upgaze; flexor/extensor posturing; ipsilateral hemiparesis (uncal herniation); **Cushing's triad (bradycardia, sys HTN, & irreg. breathing)**
- **Tests**: STAT head CT
- **Management**:
  - STAT Neurosurg (p21111) (for ICP monitor/EVD placement/decompressive hemicraniectomy)
  - Secure ABCs, elevate HOB to 30-45˚, keep head midline (to secure venous drainage), treat pain/agitation
  - Neuro-ICU level monitoring (p20202 can help coordinate)
  - Hyperventilate to PaCO2 ~ 30-35 mmHg (if suspect herniation, transiently reduces ICP), only for short-term management
  - IV mannitol therapy 1g/kg q6h (use with caution in pts on HD*)* and/or 23% saline 15cc q6h. Check BMP, Sosm q6h. No mannitol if osm gap >15, Na >160, or serum osm >340. No 23% saline if Na >160
  - **If related to edema from malignancy or bacterial infection**, give 10mg IV dexamethasone x 1, then 8mg BID
  - **Complications during LP**: **if sx of herniation/opening pressures > 40 cm H_2O with space occupying lesion**, consider STAT head CT. Immediately replace stylet into needle, only drain CSF in the manometer, STAT Neurosurg.

Hypertensive Encephalopathy: **PRES (**posterior reversible encephalopathy syndrome)

- **Typically associated with**: severe HTN, but also relative HTN in setting of preeclampsia/eclampsia, cytotoxic/immunosuppressive drugs (cyclosporine, tacrolimus, cisplatin, bevacizumab), acute/chronic renal failure, uremia, sepsis, vasculitides, TTP→ due to impaired cerebral autoregulation and endothelial dysfunction, hypoMg (NEJM 1996;334:494)
- **Symptoms**: HA, confusion, decreased consciousness, visual disturbances, seizures, can result in ICH and ↑ICP
- **Tests**: **Brain MRI w/con**: FLAIR w vasogenic edema w/in white matter in the posterior cerebral hemispheres; DWI/ADC nl (but can have strokes also); add'll regions can be incl including brainstem, cerebellum, basal ganglia, frontal lobes
- **Management**: ICU if severe, strict BP control (reduce 25% daily, if severe use nicardipine or labetalol drip), treat seizures, Mg^{2+} (esp in eclampsia), remove inciting factor
- **Prognosis**: often fully reversible; complications include progressive cerebral edema, ICH, stroke, death

Cord Compression: high level of suspicion in cancer patients with back pain, urinary sx or LE weakness

- **Etiologies**: subacute (tumor/mets, abscesses) vs acute (disc herniation, trauma, hemorrhage)
- **Symptoms**: back pain, motor weakness, hyperreflexia below lesion if chronic (*can be hyporeflexic in acute injury or w/cauda equina), ⊕Babinski, loss of sensation (assess level), bowel/bladder incontinence OR retention, loss of rectal tone, saddle anesthesia
- **Tests**: STAT whole spine MRI w/contrast (cord compression protocol), call ED MRI (x63050) or inpt MRI (x64226)
- **STAT page** NSGY/Ortho spine +/- Rad Onc (x68652) for possible XRT if tumor related
- **Dexamethasone** (10mg IV x1 then 8mg IV BID), esp in malignancy. Solumedrol in acute cord injury 2/2 trauma is controversial

Definitions (Epilepsia 2014;55:475, Epilepsia 2015;56:1515, Continuum 2019;25:306, MGH Status Epilepticus Treatment Protocol)

- **Epilepsy**: ≥2 unprovoked seizures >24h apart or 1 unprovoked seizure + recurrence risk ≥60% over the next 10 yrs
- **Status epilepticus**: at least 5 mins of continuous seizure or 2+ seizures w/ incomplete recovery of consciousness in between
- **Non-convulsive status epilepticus**: non-convulsive electrographic seizure ≥10s or rhythmic EEG responsive to seizure treatment
- **Tonic**: persistent flexion/extension; **Clonic**: limb jerking; **Atonic**: loss of postural tone; **Myoclonic**: sudden brief muscle contraction
- **Psychogenic Non-Epileptic Seizures (PNES)**: important to distinguish from epileptic events. Common features: waxing and waning movements or fluctuating course, long duration of events, eye closure, ictal crying, gradual onset, asynchronous movements, pelvic thrusting, recall during the period of apparent unresponsiveness, and hyperventilation (Ann Neurol 2011;69:997)
- **Classification** (Epilepsia 2017;58:522)
  - *Focal:* unilateral, occuring in one hemisphere **+/- impaired awareness** (formerly simple partial, complex partial)
  - *Generalized:* occuring in and rapidly engaging b/l distributed networks

Etiology: provoked vs not? Primary epilepsy, vascular (stroke/ischemia/hemorrhage), withdrawal (EtOH/BZDs), mass lesions (tumor, abscess), trauma, metabolic (↓ glc, ↑CO2, ↓O2, ↓Ca), meds, infection (systemic, CNS), HTN or HoTN, high fever, eclampsia, PRES

- **Ddx**: syncope, TIA, migraine, PNES (~30% also have epilepsy), myoclonus, dystonia, cataplexy, tremor
- **H&P**: previous sz history, prodrome (palpitation, sweating, N/V, aura), med list (many lower sz threshold), triggers (exertion, pain/fatigue/emotional stress, cough/urination/defecation), tongue biting, incontinence, lateralizing signs, alcohol. GET COLLATERAL.
- **Labs**: **FSBG, Tox, AED levels**, lytes, CBC, LFTs, NH3, VBG, CK, INR, lactate, troponin, blood cx, b-hcg. Prolactin Sn ~50%
- **Monitoring**: tele (↑ risk for fatal cardiac arrhythmias during ictal/post-ictal period; ictal arrhythmias ↑ risk of sudden death)
- **Neuroimaging**: obtain in **all w/ unprovoked 1st sz** (**MRI** w/ con more sens) (Neuro 2015;84:1705) or if **focal neuro exam, h/o trauma, malignancy, HIV, or *focal* seizure** (Neuro 2007;69:1772). Imaging changes management in ~10% (Neuro 2007;69:1996).
- **LP/BCx**: if febrile, HIV/immunocompromised, or if no clear etiology
- **EEG**: within 24h-48h if not seizing, emergent EEG if seizing: **DO NOT wait** to manage. If emergent, contact EEG fellow (p16834)

TREATMENT OF STATUS EPILEPTICUS			
▪ **ABCs**: VS, O2, EKG ▪ **Assess pt safety** ▪ Place **2 PIVs** (BZD + PHT incompatible)	**First 5-10 min (1st line)**: ▪ Ativan 4 mg IV over 2 min → repeat 4 mg x1 PRN in 5min ▪ If no IV, diazepam 20 mg PR or midaz 10 mg IM/nasal/buccal (RAMPART Trial)	▪ **Correct reversible causes**: FSBG (start IV thiamine + D50), lytes, fever, O2	▪ **Concurrently**: call neuro, RICU, continuous EEG ▪ Check AED levels and rebolus if needed → PHT, VPA, PHB 1 hr after load, FOS-PHT 2 hrs after load (correct for albumin)
Persistent SZ (10-30 min, 2nd line): ▪ Levetiracetam, VPA, fosphenytoin/phenytoin, phenobarb, +/- lacosamide (pre/post EKG to check PR)		**Refractory SZ (30-60 min, 3rd line)**: ▪ **Intubate**, continuous EEG Midaz (if HD unstable) +/- propofol gtt	

Seizure PPX: no AED in 1st seizure unless previous brain injury (Level A) OR abnormal EEG (Level A) OR significant abnormal imaging (Level B). Early AED reduces short term recurrence (<2yr), not sustained remission (3+ yrs) (Neuro 2015;84:1705).

- **ETOH seizure**: Ppx not indicated when intoxication or withdrawal is the cause of seizure (Neuro 2006;67:s45)
- **Brain tumor**: no ppx (Cochrane 2008;CD004424). If seizures occur, start AEDs: Keppra > Lacosamide (fewer chemo interactions)
- **Severe TBI**: Keppra 500-750 mg BID x 7 days (Neurosurg Focus 2008;25:E3)
- **ICH**: AED only if clinical seizure or traumatic etiology, Keppra 500mg BID x 7days (Stroke 2016;47:2666)
- **PNES**: treatment with outpatient Cognitive Behavioral Therapy (CBT), psychiatry involvement. In acute setting it may be helpful to educate patients about functional neurologic symptoms (http://www.neurosymptoms.org), and place social work consult.
- In MA, **no driving** for LOC event until 6 mos event free. Counsel pt and include in discharge summary. (Driving laws database)

AED	Loading	Dosing	Goal Level	Side Effects
Levetiracetam (Keppra)	60mg/kg Max 4.5g	1:1 PO:IV	No goal, level to check adherence	**Psychiatric sx** (irritability, anxiety, depression, sedation, psychosis).
Valproic acid (Depakote)	20-40mg/kg	1:1 PO:IV	50-100 mcg/mL (>1h post load)	**Teratogenic. Abnormal LFTs**, **weight gain**, hair loss, N/V, encephalopathy (↑NH3), pancreatitis, thrombocytopenia. **Good for mood disorders.**
Phenytoin (Dilantin), Fosphenytoin	20 pheny equiv/kg	1:1 PO:IV	10-20 mcg/mL, correct for alb, (2h post load)	**Teratogenic.** Gingival hypertrophy, hair growth, rash, AMS, diplopia, ataxia, slurred speech, **hypotension/arrhythmia** (if run faster than 50mg/min; Fosphenytoin is less cardiotoxic).
Lacosamide (Vimpat)	200-400mg	1:1 PO:IV	10-20 mcg/mL	Headache, diplopia, dizziness, nausea, hypotension. Obtain EKG prior and after load, and watch for **PR prolongation.**
Lamotrigine (Lamictal)	No Load	Only PO	3-15 mcg/mL	**Rash**, **SJS**, nausea, somnolence, dizziness, ataxia. **Good in mood disorders.**
Topiramate (Topamax)	No Load	Only PO	N/A	**Weight loss**, **fatigue**, **teratogenic.** Nephrolithiasis, cognitive decline, anxiety, anorexia, tremor
Carbamazepine (Tegretol)	No Load	Only PO	4-12 mcg/mL	**SIADH**, N/V/D, rash, pruritis, fatigue, blurred vision, diplopia, lethargy. **Screening for HLA-B*1502 in Asians.**

APPROACH TO WEAKNESS

- Ask about **functional issues** (getting out of chair, tripping over curbs/stairs)
- **UMN signs**: spasticity, increased tone, hyperreflexia, ⊕Babinski; **LMN signs**: fasciculations, atrophy, decreased tone, hyporeflexia
- **Pattern**: UMN (extensors in UEs, flexors in LEs), proximal (many myopathies), bulbar (dysphagia, dysarthria, diplopia)
- **Associated sensory sx**: reduced sensation, tingling, burning, allodynia, hyperalgesia, decreased temperature sense, imbalance
- **Autonomic sx**: orthostasis, constipation, urinary retention, erectile dysfunction, changes in sweating, hair loss, post-prandial nausea
- **EMG/NCS**: can be helpful with localization, determining fiber type involved, determining if disease is axonal vs demyelinating (which guides tx), and determining injury extent (which guides prognosis). **Often higher yield at least 2-3 weeks into illness and as outpt.**

Localization	Associated Signs/Sx	Diagnostics	Important/Common Causes
Brain	Cortical signs (language/visual field/neglect), cerebellar sx, UMN signs	**MRI Brain** best initial test (+gad if c/f cancer, infxn, demyelinating dz)	**Vascular** (hemorrhage or ischemia)**, tumor, trauma,** demyelinating
Spinal Cord	Sensory level, bowel/bladder dysfxn, UMN signs.	**MRI Spine** (level based on sx, +gad if c/f cancer, infxn, demyelinating dz) **CSF** if c/f inflammatory or infxn	**Transverse myelitis** (MS, NMO, connective tissue dz), infxn (viral myelitis, HTLV), compression (tumor/disc/abscess), vascular**, trauma,** paraneoplastic, toxic, ↓B12/Cu
Anterior Horn Cell	LMN signs. If motor neuron dz: both UMN and LMN signs.	**NCS/EMG** **+/- MRI brain and spine; LP**	**ALS,** SMA, **polio, acute flaccid myelitis** (pediatric)
Radiculopathy	Motor/sensory sx corresponding to nerve root. ⊕Radiating pain.	**MRI Spine** (level based on sx) **LP** if polyradiculopathy **NCS/EMG:** helpful for localization **(sensitivity imperfect → clinical dx)**	Nerve root compression (**disc herniation, spondylosis**) by far most common; polyradiculopathy: **GBS**, iatrogenic (post-op, chemo), ischemic, infxn (**HIV, Lyme**, CMV, EBV), DM (typically thoracic), sarcoid, malig.
Peripheral Neuropathy	Sensory symptoms; autonomic dysfxn if small fibers affected. Often symmetric and length dependent. GBS is ascending.	**Labs**: highest yield = A1c, B12 + MMA, SPEP + immunofixation **Add'l labs** (in select pts): Lyme, RPR, HIV, malnutrition (B1, B6, vit E, B3, Cu), vasculitis (ANCA, ANA, ESR, CRP, RF, C3/C4), celiac, ACE **NCS/EMG**: localization & pattern (NB: nl NCS doesn't exclude small fiber dz)	Symmetric/length-dependent: toxic/metabolic/nutritional (DM, chemo, EtOH, ↓B12, critical illness), paraprotein-related, hereditary (CMT); polyradiculoneuropathy: GBS/CIDP, DM, Lyme; mononeuropathy: compression/trauma; mononeuropathy multiplex: vasculitis, amyloid, sarcoid, HNPP
NMJ	Weakness is fatigable and improves with rest. A/w ptosis, diplopia. No sensory sx.	**Ice pack test**, tensilon (rarely) **Labs**: myasthenia panel (see below) **NCS/EMG**: repetitive stimulation, single fiber EMG **CT chest I+** if above c/w myasthenia	**Myasthenia gravis**, Lambert–Eaton, botulism, tick paralysis
Myopathy	Proximal weakness most common. Pain uncommon.	**Initial labs**: CK, aldolase, LDH, LFTs, TSH/fT4, PTH, ESR/CRP **EMG**: e/o muscle irritability, chronicity **May need muscle biopsy**	**Critical illness**, medication-related (**steroids**, **statins**, colchicine, cyclosporine, NRTI), **inflammatory myopathies** (inclusion body myositis, dermatomyositis, polymyositis)

GUILLAIN-BARRÉ SYNDROME (**A**cute **I**nflammatory **D**emyelinating **P**olyradiculoneuropathy): **symmetric, ascending** numbness & weakness, **absent reflexes** (may be present acutely), facial weakness, autonomic instability, **acute resp failure (30% of patients)**

- Causes: often recent infection (Campylobacter jejuni, HIV, CMV, EBV, Zika) or vaccination (rare)
- Dx: **LP w/** albuminocyt. dissoc. (high protein, norm WBCs). Anti-GQ1B in CMF variant. **NCS/EMG**: highest yield 2-3wks after sx onset
- Tx: IVIG or plasmapheresis (equiv. outcomes); monitor respiratory function with NIF/VC TID (done by RT) - more frequent if crisis
- **Elective intubation w/ 20-30-40 Rule**: VC <20mL/kg, NIF weaker than -30cm H2O, MEF <40 cm H2O, **OR** ≥ 20% decline in ~24 hrs

MYASTHENIA GRAVIS/LAMBERT EATON (MG/LEMS): weakness of voluntary muscles, worse w/ exertion & repetitive movements and in the evening. Typically involves ocular (ptosis, diplopia), bulbar, respiratory, neck and proximal>distal limb muscles.

- Cause: auto-Abs against postsynaptic ACh-R in skeletal muscle (MG) or voltage-gated calcium channels (LEMS)
- Exam: upgaze fatiguability – hold sustained upgaze for 1 min, look for development of ptosis. After observing ptosis, place ice on eyes for 1 min, weakness will improve (Tensilon test rare, requires atropine at the bedside. Only improves MG not LEMS).
- Dx: **Ach-R Ab** (80-90% seropositive, specific); if neg. check anti-MUSK. **EMG/NCS**: order w/ repetitive stim; will show decremental response (MG) or potentiation (LEMS). **Chest CT I+**: r/o thymoma (in 70-80% MG). Find **underlying malignancy** in LEMS.
- Tx: symptomatic (pyridostigmine); immunotherapy: rapid (IVIG, plasmapheresis), chronic (steroids+/-azathioprine/MMF); thymectomy

MYASTHENIC CRISIS: MG exacerbation requiring intubation or delayed extubation post-surgery

- **Triggers**: surgery, infection, IV contrast, pregnancy, certain drugs/meds (antibiotics including fluoroquinolones, aminoglycosides; anticonvulsants; antipsychotics; BBs; CCBs; Mg). AVOID succinylcholine during intubation.
- **Respiratory failure**: bedside exam → follow number counting in single breath, assess cough/swallowing. Trend mechanics with RT: NIFs/VC as above (see *20-30-40 Rule*). Aggressive pulm toilet. HOLD pyridostigmine if bulbar sx and/or intubated (can ↑ secretions).

Neurological prognostication after cardiac arrest is challenging and uncertain (Seminar in Neurology 2017;37:040). The introduction of therapeutic hypothermia alters the timeframe for neurological recovery and the interpretation of prognostic markers. *Studies of neurological prognostication are hampered by heterogenous patient populations and variable definitions of "coma".* We will discuss the clinical predictors of recovery and available diagnostics – clinical exam, electrodiagnostic testing, and neuroimaging.

Cerebral performance category (CPC)

- Good Outcome:
  - CPC 1. Mild deficits. Able to work. May have have mild neurologic/psychologic deficits.
  - CPC 2. Moderate deficits. Capable of independent activities of daily life. Able to work in sheltered environment.
- Poor Outcome:
  - CPC 3. Severe deficits. Conscious but dependent on others. Ranges from ambulatory to severe dementia/paralysis.
  - CPC 4. Coma (no wakefulness) or vegetative state (wakefulness but unawareness).
  - CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

Therapeutic hypothermia: post-cardiac arrest patients are cooled **within 6 hours of return of spontaneous circulation (ROSC)**, **to 32–34°C**, where they are **maintained for 24 hours** via surface or endovascular cooling methods (Nat Rev Neurol 2014;10:190). Targeted temperature management to **36°C, has equivalent efficacy** (NEJM 2013;369:2197). During this period, patients can be paralyzed with neuromuscular blocking agents to prevent shivering, and are commonly maintained on propofol, midazolam, fentanyl and other sedatives. After completion of 24 hours of TH, patients are typically rewarmed in a controlled fashion over 8-12 hours, with discontinuation of paralytics (if used) only once the shivering threshold—estimated at around 36°C—is passed; sedative-hypnotics are continued while patients are paralyzed.

Timeframe post cardiac arrest diagnostics:

- Day 1-2: therapeutic hypothermia and rewarming
  - Electroencephalography (EEG)
    - Timing: started during TH and continued for 24 hours post normothermia.
    - Positive prognosis: continuous background pattern and reactivity at day 3 or later.
    - Poor prognosis: absence of EEG activity, seizures, burst suppression (Neurology 2013;80:339)
  - Clinical exam
    - Poor prognosis: **status myoclonus** at <48 hours post cardiac arrest or normothermia. Defined as spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs and axial musculature. There may be no EEG correlate. **Absent brainstem reflexes:** bilateral pupillary, corneal, and oculocephalic reflexes. Absent brainstem reflexes, along with apnea and other criteria (depending on local guidelines), may signify brain death.
- Day 3-5:
  - Somatosensory evoked potentials (SSEP) – measurement of brain activity in reponse to somatosensory stimulation
    - Timing: 48 hours post cardiac arrest or normothermia.
    - Poor prognosis: Bilateral absence of N20, which reflects the integrity of thalamocortical projections.
  - Neuron specific enolase (NSE) – non-specific marker of neuronal injury (misnomer as it is found in RBC and platelets).
    - Timing: 24-72 hours post cardiac arrest or nomothermia. *Check serially at 24. 48, and 72hrs post-ROSC.*
    - Poor prognosis: >33 ug/l and increasing daily NSE levels (Neurology 2011;77:623). NSE is prognostic in the pre-therapeutic hypothermia era but is not well validated in patients who received therapeutic hypothermia.
  - CT head, 48 hours post cardiac arrest or normothermia
    - Poor prognosis: widespread hypodensity, loss or reversal of grey-white differentiation.
  - Brain MRI, 72 hours post cardiac arrest or normothermia
    - Poor prognosis: DWI and ADC changes suggestive of ischemic injury (Ann Neurol 2009;65:394). Quantitative ADC values may correlate with severity. MRI can be insensitive to lesions if not performed during normothermia.

Combining prognostic indicators (MGH Neuroprognostication Guidelines, 2019):

- Prognostic value of at least **2** of the following findings (measured after completion of re-warming following TH, between 36-72 hours post cardiac arrest)
  - **Bilaterally absent SSEP**
  - **Unreactive EEG background**
  - **Early myoclonus**
  - **Incomplete recovery of brainstem reflexes**
- 79% sensitivity for in-hospital mortality and 62% sensitivity for poor 3-6 mo neurological outcomes (severe disability/dependency, coma, or death). 100% PPV for both in-hospital mortality and poor neurological outcomes.

MENTAL STATUS: document daily if new AMS or worsening psychiatric sx (AFP 2009;80:809)

APPEARANCE/BEHAVIOR: grooming/hygiene, eye contact, attitude/cooperation, abnormal mvmt (fidgeting, tics, TD)
SPEECH/LANGUAGE: mechanics - rate, volume, prosody, articulation, fluency (pt can place 5 words together), paucity of speech, mutism, echolalia (copying provider's speech), verbigeration (repeating meaningless phrases)
THOUGHT PROCESS: presence of disorganization (including derailing/tangentiality); also note vague use of references (common in psychosis); thought blocking (pt appears unable to produce responses to questions)
MOOD/AFFECT: pt's own description, observed affect, future views, self-attitude (worthlessness, grandiosity)
THOUGHT CONTENT/PERCEPTIONS: SI/HI, delusions, hallucinations, overvalued ideas, obsessions, poverty of content
COGNITION: level of consciousness, orientation, MOCA
INSIGHT/JUDGMENT: use examples - insight (pt recognizes sx as pathological/accepts dx); judgment (pt takes meds)

PSYCHOSIS

- Characteristics: delusions, hallucinations (auditory>visual), thought disorganization
- Ddx: schizophrenia, schizoaffective, MDD w/ psychosis, bipolar w/ psychosis, malingering, substance-induced (cocaine, amphetamines, MJ, bath salts, hallucinogens, EtOH), less frequently OCD/PTSD/borderline PD, intellectual disability, dementia, due to another medical condition (**delirium**, epilepsy, AIP, paraneoplastic limbic encephalitis)
  - New onset psychotic disorders in patients >50 is fairly rare. Medical cause of psychotic symptoms in this age group (delirium, CNS pathology, dementia) is more likely unless known psych diagnosis.
- Labs: CBC, BMP, UA, Utox+VPAIN, serum tox including EtOH, UA, med levels, delirium workup (see neuro page)
- Refer to psych: outpatient = always, inpatient = if decompensated (can be associated with fear, agitation, aggression)

Treatment Basics: confirm home antipsychotics/mood stabilizers early in admission, continue only if patient reliably taking; otherwise, dose reduce. Ask if patient on long-acting injectable medication/date of last injection, ask which PRN medications work well for patient. Obtain Depakote, lithium, clozapine levels.

- Antipsychotics:
  - Avoid multiple antipsychotics in 1 patient. If med list includes >1 antipsychotic, confirm before ordering as it's unlikely they're taking all in outpatient setting.
  - Continue home Cogentin (benztropine) if prescribed to reduce EPS sx (common in 1st gen antipsychotics)
  - **If on clozapine, consult psychiatry early to continue medication in house**
- Mood stabilizers:
  - Include lithium, Depakote, lamotrigine, some antipsychotics. Confirm compliance with lamotrigine given risk of SJS.
  - Consider **lithium toxicity** in patients with n/v/d, tremor, ataxia, confusion, agitation → seizures, nonconvulsive status, encephalopathy if severe. Precipitating factors include dehydration, AKI, new medications (NSAID, ACE/ARB, diuretics).

AGITATION IN DELIRIUM: (see *Delirium* in neuro section)

- Safety: #1 priority is patient and staff safety. LISTEN to nursing concerns. Very low threshold to page security.
  - Can always page psychiatry (page APS resident after 6PM on weekdays/5PM on weekends)
  - Offer oral medications early. Consider lorazepam 1st line if strong suspicion for stimulant intoxication or catatonia
  - If patient requires restraints, ensure appropriate sedation as agitated patients are at risk of rhabdo/MSK injury
  - 2nd generation antipsychotics carry a black-box warning for increased all-cause mortality in pts with dementia (who commonly present with superimposed delirium) – goal is lowest effective dose for shortest time possible
- Treat underlying cause:
  - Carefully review pts' medications and assess risk/benefit of continuing anticholinergics & benzodiazepines. If opiates are required, use PO oxycodone or IV hydromorphone if needed
- Management:
  - Use behavioral strategies (including frequent re-orientation & light/physical activity (OOB/PT) cues) as first-line
  - If medication is required for adults with QTc <550ms, can trial **oral quetiapine** (initial doses 12.5-25mg q6 hrs)
  - If requires IV, trial **IV haloperidol** (initial dose 2.5-5mg, 1-2mg in elderly/frail). May be effective and is less associated with dystonia than IM or PO dosing. Prefer early psych consultation for pts requiring higher/more frequent doses.
  - Monitor QTc, replete Mg ≥2 and K ≥4 while using antipsychotics.
  - AVOID antipsychotics in patients with Parkinsonian syndromes, catatonia, NMS
- IM medications: use only as a last resort in case of emergencies. Consult psychiatry for pts requiring IMs.
  - IM haloperidol (5mg) should be co-administered with either IM diphenhydramine (25-50mg) or IM benztropine (0.5-1mg) to reduce risk of dystonia although these medications may temporarily worsen delirium.
  - IM olanzapine or thorazine may be given alone but should be used cautiously in elderly pts given risk of orthostasis
  - IM olanzapine cannot be administered with IM benzos/barbiturates due to risk of cardiorespiratory depression

Three Elements of Valid Informed Consent (Psychosomatics 1997;38:119; NEJM 2007;357:1834)

1. Relevant clinical information: at minimum: diagnosis, proposed intervention, its purpose, its risks/benefits, alternatives, and risks/benefits of alternatives (including no intervention)
2. Voluntary decision: the decision must be voluntary and without coercion from hospital staff or family/friends
3. Capacity: confirm patient has the ability to make a decision about the ***specific question*** being addressed

Exceptions to Informed Consent

1. Emergency: imminent risk of death or serious harm without medical intervention. All attempts should be made to find HCP/other surrogate decision-maker. Always discuss with team attending. Document emergent situation, lack of capacity, lack of available surrogate, need for emergent intervention. Consider 2nd opinion/consulting MGH lawyer-on-call.
2. Lack of capacity or competency: turn to the appropriate HCP/surrogate decision-maker

Capacity Assessment

- **Capacity**: person's ability to make an informed decision about a ***specific question***. It can change over time.
- **Competence**: legal designation made by a judge. Determines a person's ability to make decisions in multiple areas of life.
- **Any physician can make a determination of capacity**. Psychiatry should be consulted **only** for complex cases, such as when neuropsychiatric illness may be impairing decision-making or when the pt, family, and medical team disagree. Inform consultant of pt's expressed decision and risks/benefits of each intervention.
- **The strictness of the capacity test varies as the risk/benefit ratio of a decision changes**: the more favorable the risk/benefit ratio, the lower the standard for capacity to consent and higher the standard to refuse, and vice versa.

Criteria for Determining Capacity (ALL must be met for patient to have capacity) (NEJM 2007;357:1834 NEJM 1988;319:1635)

Criterion	Approach in Physician's Assessment
Communicate a clear and stable choice	Ask patient to indicate a choice. No expression is a presumption of incapacity. Frequent reversals of choice may indicate lack of capacity.
Understand relevant information	Ask patient to describe his/her understanding of the information given by the physician (diagnosis, proposed intervention, purpose of intervention, risks/benefits, risks/benefits of alternatives including no intervention).
Appreciate the situation and its consequences	Ask patient to describe views of diagnosis, interventions, and likely outcomes. Is patient aware of her illness? Its seriousness? Consequences?
Be able to manipulate information provided in a rational fashion	Ask patient to compare treatment options, consequences, and reasons for choice. Does the patient weigh the risks and benefits logically?

Documention: "Based upon my evaluation of the pt, he/she [*does/does not*] express a consistent preference regarding the proposed treatment, [*does/does not*] have a factual understanding of the current situation as evidenced by [*example*], [*does/does not*] appreciate the risks and benefits of treatment and non-treatment, and is [*able/unable*] to rationally manipulate information to make a decision as evidenced by [*example*]. Therefore, in my opinion, this pt [*has/lacks*] capacity to make this medical decision." ***If capacity present*:** "We should respect the patient's right to make this decision to [*details*]." ***If lacks capacity*: "**Surrogate decision-maker needed."

Surrogate Decision-Makers

- Encourage each pt to sign legal HCP form specifying surrogate. Activated (court procedure) when pt lacks capacity.
- Surrogate's job is to make the decision pt would have made for herself if able—**not** what the surrogate wants. If a pt's wishes cannot be known, the surrogate should make the decision in the best interest of the patient.
- HCP may be uncomfirmed (most common) or confirmed. **Court-confirmed HCP is required when pt's surrogate is activated & pt actively objects to surrogate's decision**. If HCP confirmation required, contact Guardianship team.
- Guardianship: legal process by which the MA Probate Court grants a guardian the authority to make decisions on behalf of someone whom a judge has ruled is not competent. **Required when there is no HCP identified & pt is unable to designate a HCP**. *Note: a patient may not have capacity to make a certain medical decision **and** still be able to designate a HCP*. For help: contact 'Guardianship Team' - Lisa Lovett, LICSW & Mary Lussier-Cushing, RN/PC
- Emergency guardianship is not required to provide lifesaving treatment & should not delay care. Can consult MGH lawyer-on-call.

Temporary Involuntary (Psychiatric) Hospitalization (Section 12 in MA - MGL ch.123 §12): Consult psychiatry for all pts on 12a.

- **Section 12a** (the front of the "pink paper"): MD uses this form to apply for involuntary psych hospitalization of a pt who, based on MD's exam & opinion, requires hospitalization to avoid likelihood of serious harm by reason of mental illness
- Authorizes pt's transport to psych facility and, if necessary, the use of restraint of the pt to maintain safety.
- Issued when likelihood of serious harm to self and/or others is imminent (general rule of thumb is within 24-72 hrs) AND
  1. Is the result of a "**serious mental illness**": must be supported in writing with specific evidence. Symptoms caused soley by *alcohol or drug intake, organic brain damage, or intellectual disability* **do not** consistute a serious mental illness.
  2. Meets ≥1 of the following 3 criteria: (1) substantial risk of **physical self-harm**; (2) substantial risk of **physical harm to others**; (3) very substantial risk of **physical self-impairment or injury** as manifested by evidence that the person's judgment is so affected (i.e. by serious mental illness) that he/she is unable to protect him/herself in the community.
- **Section 12b** (reverse side of the "pink paper", "72 hr hold"): completed by evaluating MD at receiving psychiatric facility

Civil Commitment for Substance Use Disorder Treatment (Section 35 in MA - MGL ch.123 §35)

- Process by which the court may involuntarily commit someone to inpatient substance use disorder treatment when there is likelihood of serious harm as a result of the disordered substance use; must be pursued via petition filed at courthouse

CATATONIA: *behavioral syndrome* that occurs in the context of underlying psychiatric or medical diagnosis, marked by inability to move normally despite full physical capacity; pathophysiology incompletely understood

- **Subtypes**: retarded: immobility, mutism, withdrawal; excited: mania, hyperkinesis, stereotypy, disorientation; malignant: accompanied by hyperthermia, autonomic instability, rigidity & delirium (Arch of Gen Psych 2009;66:1173)

Etiology: (Schizophr Bull 2010;36:239, Behav Brain Sci 2002;25:555)

- Psychiatric: mood disorders > thought disorders (schizophrenia, autism) > dissociative disorders
- Medical: seizures (including NCSE), PRES, CNS lesion, infection, TBI, PLE, delirium, anti-NMDAR encephalitis, SLE
- Drug: dopamine-blockers, dopamine withdrawal, sedative/hypnotic withdrawal, hallucinogens, synthetic MJ, opiates

Diagnosis: DSM-V *or* Bush-Francis Catatonia Rating Scale (BFCRS), requires ≥ 2 of 1st 14 (Psych Scand 1996;93:129)

- Most common signs include: (World J Psych 2016;6:391)
  - >80%: immobility, mutism, withdrawal & refusal to eat, staring
  - >50%: negativism (oppose/no response to instruction), posturing/catalepsy (spontaneous maint of posture), rigidity
  - >10%: waxy flexibility (ability to mold limbs with initial resistance), stereotopy (repetitive, purposeless movements), echophenomena (repetition of examiner's words or movements), verbigeration
  - Other signs: automatic obedience, mitgehen, ambitendency (motorically stuck in indecisive movement), grasp reflex
- Exam: observe for 30s outside pt room. Attempt to engage in conversation. Scratch head or gesture in exaggerated manner (echopraxia). Examine for cogwheeling in arms, alternate force, attempt to reposture. Test for mitgehen. Extend hand & say, "Do not shake my hand" (ambitendency, pt will appear stuck). Reach into pocket & say, "Stick out your tongue. I want to put a pin in it" (automatic obedience). Check for grasp reflex.
- **Ddx**: delirium, dementia, stroke, PD, stiff person & locked in syndromes, NCSE, akinetic & elective mutism, anti-NMDAR encephalitis; If *malignant:* NMS, malignant hyperthermia, SS, DTs, CNS infection/vasculitis, anticholinergic toxicity

Treatment: (Schizophr Bull 2010;36:239)

- Hold D2 blockers (e.g., typical/atypical antipsychotics; prochlorperazine, promethazine, metoclopramide)
- Ativan Challenge: **2mg IV x1** (1mg in frail elderly), repeat BFCRS in 30 min. If response, 2mg IV Ativan q6-8h, uptitrate as tolerated. DO NOT HOLD FOR SEDATION (signs of catatonia can be mistaken for sedation → write hold for resp depression). If no response, consider ECT.
- Adjunctive agents: amantadine (100mg QD up to 600 QD), memantine (10-20mg QD), zolpidem, AEDs

NEUROLEPTIC MALIGNANT SYNDROME: (Am J Pysch 2007;164:870)

- **Overview**: abrupt onset of 1) Δ in mental status 2) rigidity 3) fever 4) autonomic dysfunction associated with DA blocking agent or withdrawal of pro-dopamine agent (List of Meds Associated with NMS)
- **Risk factors**: initiation/increase of above agent (typically occurs within hours/days but can be idiosyncratic), hx of NMS/catatonia, withdrawal from EtOH/sedatives, basal ganglia disorders, exhaustion, dehydration, agitation
- **Labs**: ↑ WBC and CK = most common lab abnormalities (↑ CK only seen in 50% of cases). Low serum iron is 92-100 % sensitive for NMS but not specific. May also see mild elevations in LDH, alk phos, AST, ALT, electrolyte abnormalities
- **Ddx**: serotonin syndrome, malignant hyperthermia, malignant catatonia (significant overlap), CNS infection, spinal cord injury, seizure, heat stroke, acute dystonia, CNS vasculitis, thyrotoxicosis, drug intoxication/toxicity, withdrawal states

Stage	Clinical Presentation	Intervention
Early	Mild rigidity, confusion, T<100.4F, HR <100	• Stop offending agent & ?contributors (serotonergics, Li, anticholinergics) • **Lorazepam** 1-2mg IM/IV Q4-6H • Aggressive fluids
Moderate (may require ECT)	Moderate rigidity, T100.4-104F, HR 100-120	• Cooling measures +/- ICU • **Bromocriptine** 2.5-5mg PO Q8H *or* **amantadine** 100mg PO Q8H
Severe (may require ECT)	Severe rigidity, +/- coma, T >104F, HR >120	• ICU level of care (if intubation required, versed>propofol for sedation) • **Dantrolene** 1-2.5 mg/kg IV Q6H x 48hr

SEROTONIN SYNDROME (NEJM 2005;352:1112)

- **Overview**: exposure to serotonergic agent leading to triad of 1) Δ mental status, 2) neuromuscular hyperreactivity (tremor, hyperreflexia, clonus), 3) autonomic instability (tachycardia, tachypnea, diaphoresis, mydriasis, hyperthermia, shivering, sialorrhea, urinary incontinence, diarrhea). *Note:* n/v/d common in SS prodrome but rarely seen in NMS
- **Causative agents**: amphetamines, bupropion, buspirone, carbamazepine, carbidopa-levodopa, cocaine, cyclobenzaprine, diphenhydramine, fentanyl, levodopa, linezolid, lithium, LSD, MAOIs, MDMA, meperidine, methadone, methylene blue, metoclopramide, ondansetron, SNRIs, SSRIs, TCAs, tramadol, trazodone, triptans, tryptophan, VPA
- **Diagnosis**: can use Hunter's criteria for diagnosis of serotonin toxicity if unclear (QJM 2003;96:635)
- **Treatment**: 1) hold offending agent (generally will resolve within 24 hrs), 2) use BZDs if agitation present (**lorazepam** 2 mg IV, repeat PRN), 3) if unsuccessful, can use **cyproheptadine** 12 mg x1 then 2mg Q2h until clinical response seen. Very severe cases with hyperthermia may require ICU level of care with cooling, intubation, sedation, and paralysis.

MAJOR DEPRESSIVE DISORDER (MDD)

Overview:

- Epi: common in general population; estimated U.S. prevalence 9% (CDC Morb Mort Wk Rep 2010;59:1229)
- Screening: USPSTF (2013) recommends **universal screening of adult primary care patients** (Grade B)
  - **PHQ-2**: In last month, have you 1) felt down/depressed/hopeless? 2) had little interest/pleasure in doing things?
    - **≥1** = pos. screen, 97% Sn / 67% Sp for MDD → **PHQ-9** to grade severity. (AFP 2012;85:139)
- DSM-5 criteria: must have depressed mood and/or loss of interest/pleasure + ≥4 of following sx: ↑or ↓ weight/appetite, ↑ or ↓ sleep, psychomotor agitation/slowing, fatigue, worthlessness/guilt, poor concentration, thoughts of death or SI; sx must be present over same **2 wk period** and cause significant **impairment/distress**
  - Ddx: drugs/meds, OSA, hypothyroidism, stroke, TBI, dementia, MS, HIV, bipolar, schizoaffective
- Treatment: drugs + therapy more effective than either alone, but monotherapy of either acceptable (APA 2010). SSRIs generally 1st line (other common options: bupropion, SNRI). Consider **escitalopram** & **sertraline** as 1st line (better efficacy/acceptability profile vs duloxetine, paroxetine) (Lancet 2009;373:746)

Side Effect Profiles of Commonly Prescribed Antidepressants

	Drowsiness	Insomnia/Agitation	GI upset	Weight gain	Sexual dysfxn	Orthostatic HoTN	QTc Prolongation
SSRIs	--/↑	↑/↑↑ (fluox, sert)	↑/↑↑ (sertraline)	↑/↑↑ (paroxetine)	↑↑ ↑ (paroxetine)	↑	↑
SNRIs	--/↑	---/↑	↑↑	---/↑	↑/↑↑ (venlafaxine)	---/↑	---/↑
BupropionΔ	---	↑↑	↑	---/↓	---	---	↑
Mirtazapine	↑↑↑	---	---	↑↑↑	↑	---	↑
Trazodone¶	↑↑↑	---	↑↑↑	↑↑↑	↑	↑↑↑	↑↑

ΔBupropion lowers the seizure threshold; contraindicated in pts w/ seizure disorder, anorexia/bulimia nervosa
¶Trazodone is rarely (1/1,000-1/10,000) associated w/ priapism (i.e. urological emergency)

Dosing of Common Antidepressants

Adequate trial is 6-12 wks at full dose; if poor tolerance/response after 4-6 wks, augment or switch classes.

	Starting Dose	Titration	Usual (Max) Dose	Discontinuation
Citalopram	20mg QD	↑ 20mg Qwk	20-40mg QD (40)	Taper over 2-4 wks
Escitalopram	10mg QD	↑10mg after ≥1wk	10-20mg QD (20)	
Sertraline	50mg QD	↑25-50mg Qwk	50-200mg QD (200)	
Fluoxetine	20mg QD	↑20mg Q3-4wk	20-80mg QD (80)	0-2 wks (long $t_{1/2}$)
Paroxetine – IR	20mg Qam	↑10mg Q ≥1wk	20-50mg QD (50)	3-4 wks (short $t_{1/2}$) withdrawal effects more common/severe
Paroxetine – CR	25mg Qam	↑12.5mg Q≥1wk	25-50mg QD (62.5)	
Duloxetine (SNRI)	40-60mg QD or divided BID; ≥60mg QD w/o additional benefit			2-4 wks
Venlafaxine (SNRI)	37.5 QD or in 2-3 divided doses; ↑75mg Q≥4d, 75-375mg daily or divided			37.5-75mg QD x4wks

Refer to psych: concern for bipolar depression, failure of 2 adequate rx trials, severe MDD w/ SI/HI, psychosis, or catatonia

GENERALIZED ANXIETY DISORDER (GAD)

Overview:

- Epi: US lifetime prevalence is ♀7.7% & ♂4.6% (AFP 2015;91:617). 90% will meet criteria for at least 1 co-morbid psych condition in their lifetime (MDD, dysthymia, AUD, simple phobia, social anxiety) (Arch Gen Psych 1994;51:355)
- Excessive worry associated w/ poor CV health, ↑coronary heart disease, ↑CV mortality (Nat Rev 2012;9:360).
- Screening: **GAD-7**: score ≥5 indicates mild GAD (97% Sn / 57% Sp, LR 2.2); score ≥10 indicates moderate GAD (89% Sn / 82% Sp, LR 5.1) (Arch Intern Med 2006;166:1092). Commonly done annually with PHQ2; no USPSTF recs.
- DSM-5 criteria: A) excessive anxiety/worry occurring most days for ≥ 6 months re: multiple life domains, that is B) difficult to control, and C) associated w/ ≥3 sx: restlessness, fatigue, poor concentration, irritability, muscle tension, sleep disturbance. Must also cause D) significant distress/impairment; and E/F) not better explained by drugs/meds/other psych
- Treatment: 1st line therapy = **SSRIs/SNRIs** and/or CBT, based on availability/pt preference; no head-to-head trials (meta-analyses have found effect sizes ≈ equivalent). No individual SSRI/SNRI shown more effective; select based on side effects and pt treatment history/preference; titrate & adjust as for MDD above.
  - In general, SSRIs have lower risk of insomnia/agitation over SNRIs. Citalopram, escitalopram, paroxetine cause least agitation; sertraline and fluoxetine cause more agitation
- **Refer to psych**: failure of 2 adequate next-step trials or severe GAD w/ recurrent panic

ALCOHOL USE DISORDER (AUD)

Diagnosis and Presentation:

- **Screen** all patients with the Audit C. Risky drinking is >4 drinks per occasion for men and >3 for women OR >14 drinks a week for men and >7 drinks per week for women.
- If the patient screens positive, ask about the **5 Cs**: **C**ontrol, **C**ravings, health and relationship **C**onsequences, **C**ompulsion to drink, and being unable **C**ut back.
- AUD is based on the DSM-5 criteria (11 criteria; 2-3 = mild, 4-5 = moderate, ≥ 6 = severe). Criteria include physiologic dependence, damage to personal life, and compulsion (6). If pt meets criteria can initiate a brief intervention/motivational interviewing at bedside. Consult ACT if concerned.
- Chronic use: cytopenia (low Hb, WBC, Plt) low K/Mg/Ca/Phos/VitD – EtOH toxic to renal tubules, lowers GI absorp; ketoacidosis – EtOH metab → less gluconeogenesis → rel hypoglycemia → low insulin state → FFA to ketones. Lactic acidosis (increase ratio of NADH/NAD) (NEJM 2017;377:1368).

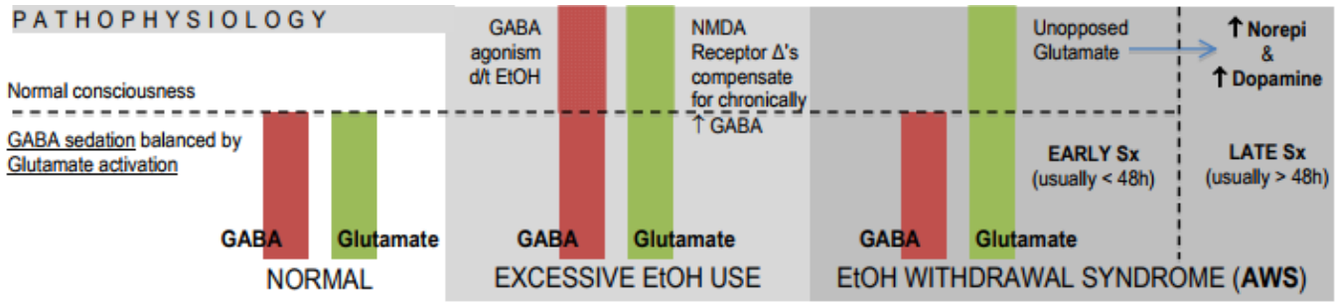
Treatment for Moderate/Severe AUD:

- More successful when combining medications and individual/group therapy. Consider consulting ACT to refer to CSS/TSS/halfway house for those without housing and/or IOP/WestEnd Clinic.
- **1st line**: naltrexone and acamprosate equal in efficacy but data suggest naltrexone>acamprosate (JAMA 2006;295:2003).
  - Naltrexone (MOA: ↓reward/cravings) PO 25mg to start→50mg daily or IM (Vivitrol) 380mg q4wk (CI: acute hepatitis/ALF, current opioid use)
  - Acamprosate (↓cravings) 666mg TID (CI: severe renal impairment CrCl<30, pregnancy).
- **2nd line**: disulfiram, topiramate, gabapentin (can be used for mild alcohol withdrawal and reduces heavy drinkining days (Addiction 2019;114:1547), and baclofen (Am J Psych 2018;175:86).
- Success can range from reducing heavy drinking days to abstinence. Remember to utilize principles of harm reduction.

Wernicke-Korsakoff Syndrome:

- Wernicke encephalopathy: acute
  - Clinical diagnosis w/ ***Caine Criteria*** (85% Sn) requires ≥2: (1) dietary deficiency, (2) oculomotor dysfxn, (3) cerebellar dysfxn (LE ataxia), (4) either AMS *or* poor memory. *Note*: Serum B1 level NOT diagnostic (J Neuro, Nsgy, and Psych 1997;62:51)
  - Tx: thiamine IV 500mg TID x 5d (**1st dose before glucose**) → IV 250mg QD x 3d → PO 100mg TID x1-2wks → then PO 100mg QD.
  - Ppx: IV 250mg QD x3-5d → 100mg TID 1-2wk →100mg QD (Intern Med J 2014;44:911).
- Korsakoff's (chronic): antero+retrograde memory deficits (confabulation), apathy, intact sensorium

ALCOHOL WITHDRAWAL SYNDROME



Pathophysiology: GABA (inhibitory) and glutamate (excitatory) work in balance

- **Chronic EtOH use**: high GABA stim → glutamate upregulation. After chronic stim, GABA receptors are less sensitive & require more EtOH to balance increased glutamate.
- **Abrupt Cessation of EtOH**: decreased GABA → unbalanced excess Glutamate activity → noradrenergic surge → increased dopamine release → complicated withdrawal sxs

Clinical Presentation

- Withdrawal symptoms by timecourse after last drink: (Ind Psych 2013;22:100)
  - **Minor withdrawal**: 6-48h; tremors, sweats, ↑HR, ↑BP headache, anxiety, intact orientation
  - **Alcoholic hallucinosis**: 24h-6d; visual/tactile > auditory hallucinations (patient is typically aware of hallucinations), clear sensorium
  - **Withdrawal seizure**: 6-48h; generalized tonic-clonic, can have multiple in short span
  - **Delirium Tremens (DTs)**: 48h-5d, can last 2wks; tremors, sweats, ↑ HR, HTN, fever, inattention, paranoia, hyperalert, hallucinations, disorientation, agitation. Usually CIWA >20. Death 1-4%.

Initial Evaluation

- H&P: last drink time, hx complex withdrawal (sz, ICU/intubation, DTs), hx of leaving AMA, co-ingestions (including BZD), EtOH use history (drinks per day/week, type of alcohol, binge driking, recent changes in drinking)
- Labs: CMP, CBC, serum osm if HCO2 <15 or AG, CPK if found down, tox screen, serum EtOH (clear ~15-35 mg/dL/hr, chronic= faster metab, higher tolerance) (J Forensic Sci 1993;38:104)
- **Predictors of severe withdrawal**: age, comorbidities, hx of DT/withdrawal, ↑BP, hyponatremia/hypokalemia BUN >26 Plt <150 (JAMA 2018;320:825).

Management

- Initial Tx for all EtOH withdrawal:
  - IV thiamine (if concerned for Wernicke's, see above), D5NS (**after thiamine**) to fix ketoacidosis**,** replete lytes, folate 1mg QD, MVI, place on CIWA, offer ACT c/s for AUD treatment
- **Decide phenobarbital vs. BZD protocol**: no difference in outcome/sedation between the two (Psychosom 2019;60:458)
  - Consider **phenobarbital** if: hx DTs, seizures, BZD-resistance, success w/phenobarb, or prior ICU admissions for w/d; current Sx of DTs; not responding to BZDs; risk of paradoxical response to BZDs (chronic CNS dz)
    - Contraindications: >30mg ativan equivalents; high likelihood of leaving AMA; Hx SJS/TEN; Hx AIP; unstable respiratory status
    - Advantages: auto-taper, long half-life, predictable effect, uniform efficacy, level is accurate if needed, wide therapeutic window, no paradoxical agitation, doesn't require CIWA evaluation.
  - Consider **BZD** if: mild-mod w/d sx, no hx complicated w/d, phenobarb contraindicated

Phenobarbital Protocol: binds GABA-A and glutamate, $t_{1/2}$ = 1-4d

- **NO MORE BZD** after phenobarb started. Total of prior BZD in last 24h must be <30mg Ativan equivalents
- Side effects: apnea, hypoventilation, hypotension, bradycardia, laryngeal spasm
- IM load (80% given initially) + PO taper
  - To calculate doses: use excel sheet and http://stagehandbook.partners.org/pages/4281
  - Input: 1) height (IBW) *2) high-risk withdrawal?*: past DTs +/- sz AND (EtOH use in <2wks OR active w/d sx OR ⊕BAL with labs predictive of severe w/d: low plts, high MCV, low K) *3) high-risk sedation?*: age>65, liver dz, head injury, recent benzos, concurrent sedatives
  - *If cirrhosis: slower excretion/metabolism, max load 8mg/kg, check level and adjust taper, stop taper after 2d
  - *If lung disease: consider max load 8-10mg/kg
  - Serum level not required. Check 5h after load if considering re-load
- ED IV phenobarb load: must stay 1hr in ED after IV load. **NO MORE IM** after IV unless re-load (see below). Start PO 8hrs after IV load, dose per excel sheet.
- Assess frequently! IM loading dose is split to allow monitoring: 40% 0h, 30% 3h, 30% 6h. Peak plasma concentration 30m-4h post-IM dose and 2-8h post-PO. If uncontrolled sx or developing sedation, call for help from pharmacy to change doses.
- Consider reload: for breakthrough sx despite IV or IM load. If 5h level <15, OK to reload, Target level 12-15. Consult psych, ACT, or pharmacy.
  - Options: 1) reload IM, e.g. if serum level 6, give equivalent IM load again to target 12 OR 2) increase taper: jump up to PO doses for higher serum target
- Discharge: phenobarb increases receptor sensitivity to benzos/EtOH; drinking after IV/IM load can be fatal. Will autotaper over days. If exam/VS stable, **ok to d/c patient before all doses complete, no earlier than day 3**. No PO doses on d/c.

Benzodiazepine Protocol:

- Use Epic Alcohol Withdrawal Order Set!
- Route: PO Ativan if able to take POs>IV Ativan>>Valium and Librium (long half-life, delayed toxicity, cleared by the liver)
- **PRN**: use CIWA scale (only if patient can **communicate**), NOT ↑HR, ↑BP alone as poor predictors of DTs (JGIM 1996;11:410). PRN protocol inappropriate if AMS, DTs, or severe w/d. Consider switching to RAAS scoring.
- **Standing**: if likely to have severe w/d
- Beware paradoxical response, resistance (>6mg ativan/hr), or BZD toxicity (similar to DTs) w/ escalating dose
- Consider switch to phenobarb if CIWA consistently >16 and BZD dose <30mg Ativan equivalents

OPIOID USE DISORDER (OUD): chronic, relapsing d/o of opioid use due to dysfunction of brain reward circuits (J Addict Med 2015;9:358)

- Screen all patients with: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" Confirm diagnosis using DSM-5 Criteria for opioid use disorder. Use ≠ addiction.
- Focus on building a therapeutic alliance and performing risk assessment (Med Clin N Am 2018;102:587)
  - Assess risk of withdrawal: current opioids, frequency of use, last use PTA, g/day or $ spent per day, recent withdrawal
  - Assess treatment readiness: treatment 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/join 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" page*).
  - Assess risk of overdose: h/o non-fatal OD, ↓ tolerance from recent incarceration or abstinence-based treatment, access to naloxone, high-dose Rx'd opioids and/or other sedatives (check PDMP), injection use (Addiction 2015;110:996)
- Labs: serum/urine tox, LFTs, HIV, HBV/HCV, TB, RPR, EKG. *NB*: urine fentanyl is separate order, takes days to result
- Pain control: pts w/ OUD and/or chronic opioids likely have developed tolerance and require higher doses of opioids to treat pain
  - If using non-prescribed opioids: can initiate methadone for withdrawal & add short-acting opioids titrated to pain
  - If taking meth_Jadone: give usual dose once confirmed & add short-acting opioids (e.g., oxycodone) titrated to pain
  - If taking buprenorphine: there are several strategies:
    - For pain of short duration, may continue daily bup & add short-acting opioids (may need high doses, consider PCA)
    - Give TDD of bup divided 3-4x daily (e.g. 4-8 mg q6-8h for mod-severe pain)
    - D/c bup & use short-acting opioids to tx acute pain. Blocking effects of bup wear off after 24-72 hrs, so pt must be monitored for OD (b/c initial opioid dose will be higher than ultimately needed). After acute 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, oxygen saturation, and ensure RR>10, **NOT** to achieve normal level of consciousness
  - Dose: 0.04mg IV, if no response increase dose q2 min:→0.5mg→2mg→4mg→10mg→15mg.
  - Administer intranasally or IM if no IV access
  - NB: too much naloxone will precipitate opioid withdrawal. Consider diluting 0.4 mg in 10 ml saline and push 1 ml q2-3min.
  - If failing to respond, consider endotracheal intubation (STAT RICU consult)
- Post-resuscitation: continuous O2 monitoring (naloxone effect shorter than many opioids), CXR (post-OD pulmonary edema does NOT respond to diuretics, may evolve to ARDS), APAP level. Examine skin for fentanyl patch. Consider naloxone gtt.

ACUTE OPIOID WITHDRAWAL: agonist treatment with buprenorphine or methadone is first line treatment for opioid withdrawal and OUD. Should be offered to every patient. Long-term agonist therapy decreases mortality and morbidity (BMJ 2017;357:j1550)

- Sx: dysphoria, restlessness, irritability, yawning, piloerection, mydriasis, rhinorrhea, lacrimation, mylagias/arthralgias, n/v/d, abdominal cramping. Onset: 6-12h after short-acting opioids, 24-48 hours after last methadone use, variable with fentanyl analogs
- Medications:
  - Buprenorphine (Suboxone): high affinity partial agonist with less 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 Suboxone tablet)
    - Second dose: if continued withdrawal sx, give another 4mg/1mg after 45-60 minutes
    - Third dose: if recurrent withdrawal sx, give another 4mg/1mg after 6-12 hours
    - Maximum dose for Day #1 is 12mg buprenorphine
    - Prescribe total from Day 1 for Day 2, then reassess later in the day. Can give additional 4mg/1mg for withdrawal symptoms, but max dose for Day #2 is 16mg buprenorphine
  - Methadone: long-acting full agonist. Check and trend EKG for QTc, use with caution with other QTc-prolonging meds
    - Day 1 Initial dose: 10-20mg x1. COWS q2h: If <6 → observe; if 6-12 → 5mg dose x1; if ≥ 12 → 10mg dose x1. REQUIRED to call ACT if ≥40 mg daily dose.
    - Day 2 Stabilization: day 1 dose if COWS <6, increase by 20% if COWS 6-12.
    - If not planning to transition to methadone maintenance, decrease dose by 20% per day.
  - If unable to initiate suboxone/methadone, offer symptomatic medications and short-acting opioids for pain:
    - Autonomic dysregulation: clonidine 0.1-0.2mg TID PRN (monitor BPs; avoid w/ 1st Suboxone/methadone dose)
    - GI upset: Bentyl 10-20mg Q6H PRN abd cramps; promethazine 25-50mg IM PRN N/V; loperamide 2mg PRN diarrhea
    - Anxiety: hydroxyzine 25mg Q8H PRN or trazodone 50-100mg q8h PRN
- Discharge: ensure pts have insurance, PCP, provider who can prescribe suboxone/methadone, list of shelters/needle exchanges
  - Last dose letter for patients on methadone maintenance (includes date/amount of last methadone dose)
  - Prescribe naloxone and teach OD response. Emphasize that Narcan reverses OD for ~30m. After OD → EMS to the ED.
  - Bridge clinic: Call 617-643-8281 Mon-Fri 8am-4pm to schedule appt or present as walk-in

MGH Tox Screens:

- **Basic serum toxicology screen**: quantitative assays for EtOH, salicylates, acetaminophen; qualitative assay for TCAs
- **Drug screen, prescription/OTC ("full tox")**: send out to Mayo, will take >3 days to return (www.mayomedicallaboratories.com)
  - Common OTCs: caffeine, acetaminophen, salicylates, ibuprofen, naproxen, dextromethorphan, diphenhydramine, guaifenesin
  - Neuro/psych drugs: barbiturates, AEDs (incl. carbamazepine, lamotrigine, levetiracetam, topiramate), propofol, TCAs, SSRIs, SNRIs, bupropion, phenothiazines (incl. chlorpromazine, thioridazine), clozapine, muscle relaxants (cyclobenzaprine, metaxalone), sleep meds (i.e. zolpidem, zaleplon)
  - Others: lidocaine, trazodone, theophylline, some pesticides
  - Limited use for illicit drugs: benzos, some opiates (incl. codeine, meperidine, methadone, oxycodone, fentanyl), amphetamines
  - **Drugs NOT on screen**: cocaine, lithium, digoxin, ethylene glycol, iron, lead (order separately and note some are send-outs)
- **Urine toxicology screen**: amphetamines, barbiturates, benzodiazepines, THC, cocaine, opiates, phencyclidine
- **VPAIN** ("urine pain panel"): buprenorphine, oxycodone, methadone, 6-monoacetyl morphine (heroin metabolite)
  - *NB*: **urine fentanyl** is an **add-on test**—consider sending for suspected opioid OD (esp. with PEA arrest) given prevalence of high prevalence of synthetic fentanyl analogues in the community
- **Oral fluid drug test**: differentiates TYPE of benzo (lorazepam vs diazepam), opiate (codeine vs heroin), amphetamine

Urine Test Characteristics: (Mayo Clin Proc 2008;83:66)

Class	Detection Time (days)	False Positives	False Negatives
Amphetamines	1-2d after use (2-4d for chronic exposure)	Bupropion, labetalol, trazodone, ranitidine, pseudoephedrine, selegiline	Ritalin & atomoxetine won't test ⊕
Barbiturates	2-20d after use	Fioricet (contains butalbital)	
Benzodiazepines	1-5d (most), 2-30d after diazepam	Oxaprozin (NSAID)	Lorazepam, clonazepam <1mg/day
Cannabinoids	1-7d after use, up to 1mo heavy chronic use	Hemp products, Marinol	Synthetic cannabinoids
Opiates (NOT methadone, fentanyl, meperidine)	1-3d after use, 6-8d after heavy use	Poppy seeds (unlikely); At MGH, methadone, naloxone, fluoroquinolones do NOT interfere	Oxycodone, oxymorphone, Suboxone
Cocaine	2-4d after use, 1-3wks after heavy use	NONE	
Phencyclidine (PCP)	7-14d after use	Lamictal, Effexor, Tramadol, dextromethorphan, doxylamine	
Buprenorphine	5-10d	High doses of opiates/methadone/tramadol; quinine, hydroxychloroquine, naltrexone	
Methadone	1-5d	Quetiapine, diphenhydramine, doxylamine	
Oxycodone	2-4d	Substances that change urine color (e.g., Flagyl) will cause refusal	

Cocaine Intoxication/Withdrawal:

- **Intoxication**: grandiosity, euphoria, hyperactivity, anorexia, anxiety, psychotic sx (formication, paranoia, AH/VH), fever, mydriasis. Vasospasm can cause HTN emergency, stroke, MI and seizures. **Tx**: labetalol, phentolamine (**AVOID** unopposed alpha stimulation)
- **Withdrawal**: depression, fatigue, nightmares, cravings,↑ sleep/appetite. **Tx**: *Acute*: propranolol, quetiapine for severe sx; *Chronic*: consider topiramate and/or baclofen for cravings/dependence (consult ACT) (Psychiatry 2005;2:44)

Benzodiazepine Withdrawal: manage withdrawal per protocol (*see "Alcohol Withdrawal" section*). Higher risk for delirium with BZD withdrawal. If possible, initiate taper with same BZD agent (e.g. due to extremely short half-life, alprazolam requires alprazolam taper).

Commonly Used Benzos	Comparative Dosages (approx)	Half-life (hours) (approx)
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)
Triazolam (Halcion)	0.25mg	2-3 (oral peak 0.7-2)

*Most common illicit usage bc most commonly prescribed

Spice/K2/Bath Salt Intoxication: agitation/violence, hallucination/paranoia, anxiety, tachycardia, arrhythmia, myoclonus, diaphoresis.

- **Tx**: low stimulation environment, IVF, consider IV BZDs to reduce agitation and prevent seizure (Curr Psychiatry Rep 2016;18:52)

THC Intoxication: euphoria followed by relaxation; tachycardia; hallucinations (especially w/ high potency THC, e.g., wax/dab)

- **Cannabinoid hyperemesis syndrome**: chronic user with recurrent n/v, abd pain; **sx relief w/ hot showers**; mild leukocytosis. **Tx**: IVF, antiemetic, and THC cessation; consider BZD, followed by antipsychotic and capsaicin (J Med Toxicol 2017;13:71)

GENERAL SCREENING GUIDELINES [Evidence Grade] ([a]USPSTF, [b]ADA, [c]AACE, [d]ACC/AHA, [e]ACCP, [f]CDC, [g]ACS)

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+
Cardiovascular Screening / Preventative Health Recommendations															
CVD Risk	Assess RFs q4-6y [B][d] (age, sex, total chol/HDL, SBP, DM, smoking, FHx)							Estimate risk w/ ASCVD calculator q4-6y [B][d] If ASCVD risk ≥20% consider high intensity statin* [B][a]							
ASA for 1° ppx$^{\Delta}$								Low dose ASA in adults 40-70 with higher ASCVD risk but not higher bleeding risk$^{\delta}$ [A][d]						Not recommended for adults > 70 [B][d]	
Diabetes	If HTN or BMI ≥25 (≥23 Asian) w/ ≥1 DM RF^ [B][b]								A1c Q3y. ↑interval if abnl result, ✓ annually in pre-DM[b]						
HTN	Q3-5y; Q1y if BP >135/90, obese, AA [A][a]							Q1y [A][a]							
HLD	One-time screening age <20		Men 20-45, women 20-55: screen Q5yr, ↑ if RF [C][c] Q 3-5y in DM if wnl at dx							Men >45, women >55 Q1-2y if no RF* [A][c], Q1y in DM [B][c]			Screen Q1y [A][c]		
Obesity	Annual BMI → refer for or offer comprehensive lifestyle program if ≥25 (overweight) [B][d]														
Diet	Intensive behavioral counseling if CVD RF* [B][a]														
Exercise	150 min/wk mod exercise or 75 min/wk intense exercise & 2 days of muscle strengthening activity[f]														
Universal Cancer Screening															
Colorectal CA	Start 10 years prior to age of affected family member at dx***									Colo Q10y, flex sig q5y, FIT q1y [A][a]					+/-***
Lung CA											Q1y low-dose CT if 30 pack-yrs & current smoker or quit w/in last 15y [B][a]				
Skin CA	Insufficient evidence for routine skin exams by clinicians [I][a]														
Infectious Disease Screening															
HIV	Screen at least once; repeat based on risk assessment [A][a]														
HCV	Screen all 18-79 at least once; repeat based on risk assessment [B][a]														
HBV	Born in endemic region, getting HD, or immunosuppression, HIV+, IVDU, MSM, close contact w/ HBV+ person [B][a]														
Latent TB	Screen if born or lived in high risk country (see CDC website) or high risk setting (homeless, jail) in last 2 years [B][a]														
Psych/SUD/Social Risk Factor Screening															
Depression	Q1y [B][a]; PHQ-2: in 2 wk how often (a) little interest/pleasure doing things & (b) down/depressed/hopeless														
EtOH Misuse	Screen regularly with AUDIT-C [B][a]														
Tobacco	Every encounter [A][a]. **A**dvise to quit, **A**ssist doing so (plan, quit date, QuitWorks, meds), **A**rrange f/u.														
Intimate Partner Violence	Screen regularly in women of reproductive age [B][a]. HITS screen well-validated. Assess immediate safety & consider HAVEN referral.									No data but consider ongoing IPV, elder abuse screening					
Fall Risk													PT, Vit D [B][a]		

* If ASCVD borderline risk (5%-7.5%) or intermediate risk (7.5%-20%) use risk-enhancing factors (i.e. FHx, metabolic syndrome, CKD, race/ethnicity, CKD, chronic inflammatory disease) or CA calcium scanning to guide decision about preventative interventions

$^{\delta}$ 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, NOACs, Warfarin)

^DM RFs: prior abnl testing (A1c≥5.7), FHx, AA/Latinx/Asian/NA ancestry, Hx GDM, PCOS, CVD, HDL<35 or TG>250, physical inactivity

***Age 40: ≥1st degree relative dx<65; Age 45: AA/ 1st degree relative dx<65; Age 50: expected to live >10y; 75+: based on life expectancy

ADDITIONAL SCREENING GUIDELINES FOR MEN [Evidence grade] ([a]USPSTF, [g]ACS)

Age	18-40	40	45	50	55	60	65	70	75+
AAA							If +tobacco hx [B][a]		
Prostate CA*		FHx** Q2y[g]	FHx, AA Q2y[g]	Screen all men Q2y if life expectancy ≥ 10-15 yrs[g]					
					PSA 55-69yo if pt preference [C][a], *recommend against* if >70yo [D][a]				
Testicular CA	*Recommend against* routine screening in all men[D][a]								

* All patients should be informed of the uncertainties, risks, and potential prior to deciding if they would like to be screened

** >1 first-degree relative with history of prostate cancer

ADDITIONAL SCREENING GUIDELINES FOR NON-PREGNANT WOMEN [Evidence grade] ([a]USPSTF)

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+
Breast CA	Consider BRCA counseling if +FHx. Screening tools available. [B][a]							Individualized screen by risk (Gail Model)		Q2y mammography age 50-74. Stop if <10yrs life expectancy. [B][a]					
Cervical CA				Q3y [A][a]		Q3y or Q5y + HPV co-testing [A][a]								Stop$^{\Sigma}$	
STIs	≤24: GC/CT annually [B][a]					Screen based on risk assessment									
Contraception	Discuss with everyone. Start folic acid at reproductive age if planning/capable of pregnancy [A][a]														
Osteoporosis	Consider earlier screening based on FRAX assessment [B][a]												DEXA [B][a]		

$^{\Sigma}$ Stop if 3 consecutive neg paps or 2 consecutive neg co-tests within 10 years w/ most recent test within 5 years. Continue x20 yrs s/p dx pre-cancerous lesion regardless of age. Do not resume age ≥65 for new sexual partner only.

ADDITIONAL SCREENING GUIDELINES FOR SPECIAL POPULATIONS

- MSM (men who have sex with men) and SMW (sexual minority women): see *LGBTQ Health*
- Immigrants and refugees: see *Immigrant & Refugee Health*

Note that there is considerable discrepancy between societal guidelines created using the same evidence.
Ex: Breast Cancer – USPSTF: biannual screening age 50-74 [B]; discussion of risks/benefits age 40-49 [C]; no recommendation for women ≥75 [I]. ACS: annual mammography age 45-55; discuss transitioning to biennial screening at 55 until life expectancy <10 years; discuss initiation of annual screening at age 40. ACOG: offer mammography at 40; start screening at 50; discuss cessation at 75; screen Q1-2 years.

MANAGEMENT OF ABNORMAL PAP SMEAR (ASCCP Consensus Guidelines, 2012)

Abnormal Pap Cytology Results				
	ASCUS	**LSIL**	**HSIL**	**AGC**
Age 21-24	Preferred: mgmt as per LSIL (annual cytology) Alternative: **HPV reflex**. If HPV⊖, resume regular screening; if HPV⊕, manage as LSIL	**Repeat cytology** at 1 & 2 yrs: *Yr 1*: ⊖, ASC-US, or LSIL → repeat in 12 months; if >LSIL → colpo *Yr 2*: if ⊖ x2 resume regular screening; if ≥ ASC-US → colpo	**Colpo** w/ endocervical curettage. May also choose monitoring w/ colpo & cytology q6mos for up to 24 mos before tx	For AGC-NOS, AGC-endocervical, or adenocarcinoma in situ (AIS) → will need **gyn follow up** for **colpo w/ biopsy** & endocervical sampling, w/ additional sampling if ≥ 35yo or younger w/ endometrial neoplasia RFs (unopposed estrogen, tamoxifen, early menarche, late menopause, PCOS, DM, obesity) For AGC-endometrial → endometrial & endocervical sampling
Age 25-menopause	Preferred: **HPV reflex**; if HPV⊕ → colpo. If HPV⊖ repeat co-testing in 3 years. Alternative: **Repeat cytology** in 1 year. If ⊖, resume routine screening. If ≥ ASC-US → colpo	**Colposcopy**, even if have HPV-result	Option 1: **colpo** w/ endocervical curettage Option 2: immediate **LEEP** (not if pregnant or desiring pregnancy)	
Post-menopausal		3 options: - **HPV reflex**: if ⊕ →colpo; if HPV⊖, repeat pap in 1 yr *OR* - **Repeat pap** in 6 & 12 months: ≥ ASC-US → colpo *OR* - Refer for **colpo**		

VACCINES (CDC)

Standard Immunizations	**19-21**	**22-26**	**27-49**	**50-64**	**≥65**
Influenza	1 dose annually				
Tdap/Td	1 dose Tdap then Td booster every 10 years				
MMR	1-2 doses based on indication (if born in 1957 or later)				
Varicella	2 doses (if born in 1980 or later)				
Zoster					2 doses (recombinant)
HPV	3 doses				
PCV13/PPSV23	Based on indication (see below)				1 dose PPSV23. Shared decision making re PCV13. If both, give 1yr apart

Vaccine	**Special Indications**
Influenza	No live vaccine (intranasal) if immunocompromised or pregnant
TDaP / Td	Extra dose of Tdap during each pregnancy
PCV13/ PPSV23	Special pops: CSF leak, cochlear implant, functional asplenia, immunocompromised, HIV, CKD, nephrotic syndrome, malignancy, solid organ transplant, full list at CDC): - Age >18: give PCV13 x1 followed by PPSV23 8 wks later followed by PPSV23 re-dose x1 at 5 yrs & again at age 65 (if >5yrs from most recent) - Age 19-64 w/ chronic heart, lung, or liver disease, diabetes, alcoholism, or cigarette smoking: 1 dose PPSV23
Varicella*	Consider 2 doses in pts with HIV w/ CD4≥200
Zoster*	2 doses RZV 2-6 mo apart if >50yo (if received ZVL, at least 2 mo after dose). If >60, give RZV (preferred) or ZVL.
HPV	If MSM, transgender persons, or M with HIV vaccinate through age 26; Not recommended during pregnancy
MMR*	1 dose in women of childbearing age; 2 doses if HIV & CD4≥200 OR health care personnel born in 1957 or later.
Hep A	2 doses for travel to endemic countries, MSM, **any** drug use (not just IVDU), liver dz, clotting disorder, undomiciled, contacts of those at risk
Hep B	3 doses for those w/ HCV, sexual exposure risk, IVDU, DM, ESRD, any chronic liver dz, HIV, health worker/occupational exposure, travel to endemic country, household contacts, incarcerated persons
Meningococcus (MenACWY/ MenB)	1-3 doses depending on type for living in dorms, asplenia, HIV, MSM, complement def, military, occupational exposure, travel in endemic country
Hib	1 dose if not immune for asplenia, 3 doses after HSCT regardless of vaccination history

* Hold in pregnancy, malignancy, immunocompromised (i.e. CD4 < 200)

VULVAR/VAGINAL COMPLAINTS (Obstet Gynecol 2008;5:1243)

Vaginal discharge: ask about amount, color, odor, pain, pruritus; infectious vaginitis is more likely to present acutely

- **Bacterial vaginosis (BV)**: malodorous discharge, most common, most pts asymptomatic, high prevalence in WSW
  - Dx: Amsel criteria (≥3): 1) homogenous, thin, **grey-white discharge** smoothly coating vaginal walls; 2) **clue cells**; 3) **fishy smell** on **KOH**; 4) **pH >4.5** (less reliable if post-menopause)
    - Order "Genital culture female", collected with rayon swab. GS assesses for clue cells (7-10 = BV)
  - Tx: **Metronidazole** 500mg BID x7d, clinda 300mg BID x7d (vaginal gels also available w/less systemic effects), or secnidazole 2gm x 1; can opt not to tx if not pregnant
- **Candida**: curd-like discharge, pruritus, physical signs (vulvar erythema, edema may occur)
  - Dx: pH normal, order "Genital culture female", add on anti-fungal sens. if recurrent
  - Complicated infxn: recurrent (≥4x/yr, severe symptoms, non-C. albicans, comorbid dz (DM, immunosuppression)
  - Tx: miconazole 2% x 7d (pregnancy) or **fluconazole** 150mg PO x1; longer PO course for complicated infxn
- **Trichomonas**: purulent, malodorous, thin discharge, inflammation on exam, postcoital bleeding (DDx gonorrhea/chlamydia)
  - Dx: if ⊕ pear-shapes on **wet mount**, don't need NAAT test. If ⊖, order "Trichomonas vaginalis antigen"
  - Tx: **metronidazole** 2g x1 for patient **and** sexual partners (tinidazole is better tolerated but more expensive)

Dermatoses: more likely to present chronically, often require GYN referral and vulvar punch biopsy to confirm diagnosis

- **Contact dermatitis**: erythema, swelling, fissures, erosions → r/o Candida, remove offending agent
- **Vulvar atrophy**: 50% postmenopausal ♀ 2/2 less secretions, Δ flora → lubricants, topical estradiol
- **Lichen simplex chronicus**: intense pruritis + lichenified plaque in pt w/ atopic dermatitis hx → antihistamines, steroids
- **Lichen sclerosus**: onset 50-60s, cigarette paper skin + porcelain white papules in pt w/ autoimmune dz. May lead to labia minora fusion, clitoral hood phimosis, fissures, perianal dz. 5% incidence of malignancy → high potency steroids x4 wks
- **Lichen planus**: "purple, papular, pruritic," white lacy striae, also involves vagina → high potency steroids, monitor for SCC

URINARY INCONTINENCE: very common (25% young women, 75% of older women); most women do not seek help

- Types: **stress** (leakage w/ coughing, laughing w/out bladder contraction), **urge** (urination preceded/accompanied by urge), **mixed** (stress + urge), **overflow** (incomplete emptying), & **functional** (impaired mobility/cognition/neurologic); **other** (UTI, vaginal atrophy)
- History: systemic sx (fevers, dysuria, pain), **meds** (anticholinergics, diuretics, etc.), bowel habits, **caffeine**/EtOH use, voiding diary.
- Exam: check for prolapse, fistula, diverticulum; cough stress test (can be supine, but standing w/ full bladder ↑sensitivity); urethral mobility; rectal exam (fecal impaction, sphincter tone); neuro exam.
- Dx: UA/Cx, **PVR** (abnl >150cc), **bladder stress test**; urodynamic studies not indicated in initial eval of uncomplicated UI.
- Tx: **bladder training** (timed voiding; use PCOI handout), **lifestyle interventions** (e.g. wt loss, ↓fluid/caffeine intake), **pelvic floor muscle exercises** (e.g. Kegels; use PCOI handout, can refer to pelvic floor PT). *Stress/mixed*: **pessaries** (best if wish to avoid therapy, refer to urogyn for fitting), **vaginal estrogen** (post-menopausal w/ vaginal atrophy), and **procedures** (midurethral sling, urethral bulking agents). *Urgency:* **antimuscarinics** (numerous side effects), **β-agonists** (e.g. mirabegron, avoid w/uncontrolled HTN, ESRD, liver disease), and **intravesicular botox**

AMENORRHEA (AFP 2013;187:781)

- Initial labs: HCG, FSH, LH, TSH, PRL
- In adults, most commonly 2° amenorrhea: cessation of regular menses for 3 mos **or** cessation of irregular menses for 6 mos
- Ddx: functional hypothalamic hypogonadism (weight Δ, eating disorder, excessive exercise, stress, prolonged illness), pituitary dysfunction (hyperprolactinemia, mass effect from non-functioning adenoma, apoplexy), 1° ovarian insufficiency, PCOS, hypo/hyperthyroidism, poorly controlled DM, exogenous androgen use, h/o uterine instrumentation (Asherman Syndrome)
- **Progestin challenge**: medroxyprogesterone acetate 10 mg x10 days. If ⊕ withdrawal bleeding → anovulation
  - If ∅ withdrawal bleeding → E/P challenge → ⊕ bleeding = hypoestrogen state (nml/↓FSH = hypothalamic; ↑FSH = ovarian failure). ∅ bleeding = outflow tract obstruction (hysterosalpingogram/hysteroscopy)

POLYCYSTIC OVARY SYNDROME (PCOS) (J Clin Endo Met 2013;98:4565; NEJM 2016;375:54)

- Affects 5-10% of women of reproductive age
- **Rotterdam Criteria** 2/3: 1) oligo/anovulation, 2) clinical/ biochemical hyperandrogenism, 3) polycystic ovaries on pelvic U/S
- Workup: **testosterone**; exclude other dx (hCG, FSH, 17-OHP [pre-8AM], prolactin, TSH), metabolic d/o, OSA, mood d/o (depression)
- Tx: weight loss, exercise, **OCP** (1st line), spironolactone, metformin (if insulin resistant), fertility referral for pregnancy (clomiphene)

INFERTILITY (Fertil Steril 2015;103:e44)

- Evaluate after **12 mo** unprotected intercourse in <35 yo, **6 mo** in >35 yo
- DDx: ovulatory dysfunction, fallopian tube or uterine abnormalities, cervical factors, endometriosis
- Hx: duration of infertility, prior OB/GYN hx (menstrual hx, pregnancies, PID, fibroids, cervical dysplasia, endometriosis, contraceptive use, DTE exposure), sexual hx (timing, frequency, lubrication, dyspareunia), meds, prior chemo/XRT, substance use, FHx
- Dx: 1) **Test ovulation**: mid-luteal progesterone (day 21, 1wk before expected menses, goal >3), home kit to check for LH surge.
  2) **Test ovarian reserve**: FSH/estradiol (day 3, goal FSH <10, estradiol <80), clomiphene challenge test
  3) **Additional workup**: chlamydia PCR, hysterosalpinogram & saline infusion sonohysterography (tubal patency), pelvic U/S (uterine myomas/ovarian cysts), TSH, semen analysis of partner, laparoscopy if strong suspicion of endometriosis
- Tx: correct reversible etiologies, refer to **reproductive endocrinology** for aggressive induction of ovulation, IVF, or donor oocytes

MENOPAUSE

- Amenorrhea x12 mo w/o alt etiology (no need to ✓labs), avg onset at 51, suspect 1° ovarian insuff if <40 (Obstet Gyn 2014;123:202)
- **Vasomotor sx** (hot flashes):
  - Systemic hormone tx (estrogen + progestin, estrogen mono tx if hysterectomy) most effective tx but *only recommended if* <60 yo & for <5 yrs duration (don't use if CVD >10% or high risk for breast CA) (J Clin Endocrinol Metab 2015;100:3975). Side effects: breast tenderness, vaginal bleeding; ↓CRC, fracture risk; ↑breast CA, CVD, VTE; Ø ↑risk of mortality after 5-7 yrs (JAMA 2017;318:927).
  - **Try alternatives first**: paroxetine, venlafaxine, gabapentin, clonidine
- **Vaginal sx**: dryness, burning, pain w/ intercourse
  - Lubricants (KY): prior to intercourse; moisturizers (Replens) = longer-term relief
  - Topical estrogen therapy: ring, tablet, cream; start at 0.3 mg/day; Ø ↑ risk of endometrial hyperplasia
  - SERM (ospemifene): for sx atrophy not relieved by non-pharm tx or not amenable to topical tx; side effects incl ↑hot flashes

CONTRACEPTION (Quick Start Algorithm, CDC USMEC 2016, CDC 2020 Update)

- 45% of pregnancies are unplanned → rule out pregnancy before initiating contraception → LARCs (IUD, implant) are first line
- Hormonal methods take ~1 wk to work → use backup method for 7 days

	Use	1yr Failure Rate*	Pros/Cons	Contraindications
Estrogen-progestin				
Pill	Daily	9% (0.3%)	- Pros: ↓menses, PMS, cramps, acne, endometrial/ovarian CA - Cons: n/v, breast tenderness, can ↑HTN/TGs, ↓libido, spotting for first few months, cannot start if < 21 days post-partum (VTE risk), **requires patient adherence**	- VTE, thrombogenic mutation - Active breast or liver CA - Migraine w/ aura, >35 yo + any migraine - Uncontrolled HTN, DM w/ vasc complications, CVD, valvular dz - >35 yo + >15 cig/day - ESLD
Ring (Nuva-Ring)	3 wks in, 1 wk out	9% (0.3%)		
Patch (Xulane)	Weekly x3 wks, 1 wk off; apply to arm, torso, or buttock	9% (0.3%)		
Progestin-only				
IUD (hormone content Mirena > Kyleena > Skyla)	Mirena Q7Y Kyleena Q5Y Skyla Q3Y	0.2%	- Pros: effective, long-acting, lighter periods, may reduce cramping - Cons: **irregular bleeding**, physical complications (rare)	- Abnl uterine cavity, G/C at time of insertion, PID, endometrial/cervical/ breast/liver Ca, APLAS, pregnancy, ESLD
Implant (Nexplanon)	Q3Y to upper inner arm	0.05%		- Unexplained vaginal bleeding - Breast/liver CA, APLAS, ESLD
Injection (Depot-Provera)	Q3mo IM/SQ to buttock	4% (0.2%)	- Pros: long-acting - Cons: **irregular bleeding**, weight gain (<5 lb), ↓BMD, prolonged return to fertility (1 yr)	- Unexplained vaginal bleeding - Breast/liver CA, APLAS, ESLD - CV risk factors, uncontrolled HTN, DM w/ vasc comp, iCMP, CVA, vasc disease
Pill (Micronor)	Daily	8% (0.3%)	- Pros: few contraindications - Cons: **irregular bleeding**, must take at same time daily	- Bariatric surgery - Breast/liver CA, APLAS, ESLD
Hormone-free				
Copper IUD (Paraguard)	Q12Y	0.8%	- Pros: effective, long-acting, safe in ESLD, **emergency contraceptive** - Cons: heavier bleeding, cramping	- Abnl uterine cavity, endometrial/cervical CA - G/C at time of insertion, PID, - Pregnancy
Male condom	Every encounter	13% (2%)	- Pros: STI prevention - Cons: **require patient adherence**	- Oil based lubricant w/ latex condom
Sterilization	Permanent	0.5%	- Pros: effective, long-acting - Cons: irreversible	- Surgical risk, patient unsure of decision

* Typical use – i.e. % women who will have unplanned pregnancy in 1 year on this method; (perfect use not realistic for most)

Oral Contraceptives (OCPs) (CDC MMWR 2013;62:1)

- **Types**: monophasic vs multiphasic/ triphasic; combined (estrogen + progestin) vs progestin-only
- **OCP selection**: 2nd gen progestin-containing (levonorgestrel, norethindrone): ↓ VTE risk. 3rd gen progestin-containing (norgestimate, desogestrel): ↓ androgenic SE, higher VTE risk. Progestin-only (norethindrone 0.35 mg): if breastfeeding or if contraind. to estrogen

Emergency Contraception (Obstet Gynecol 2010;115:1100)

- **Plan B** (levonorgestrel 1.5mg x1 or 0.75mg x2): OTC, use <72 hrs, less reliable if BMI >30. Ella (ulipristal acetate 30 mg): requires Tx, use <120 hrs, more reliable in higher BMI. **Paragard** (copper IUD): ideally placed within 120 hrs (okay up to 160hrs), **most effective**
- In cases of **sexual assault**: refer pt to the ED for an exam by a trained SANE RN. If IPV: ask if partner has access to online medical records prior to detailed documentation and prepare safety plan. **MGH HAVEN referral: 617-724-0054**

ABORTION (Guttmacher Institute Fact Sheet; Am J Public Health 2017;107:1904; Obstet Gynecol 2014;123:676)

- See PCOI for list of providers in MA. Avg cost ~$500, 50% pay out of pocket. Counseling: **1-866-4-EXHALE**
- Workup: confirm pregnancy with LMP and pelvic U/S, check CBC/Rh, offer STI testing and immediate post-abortion contraception
- Medical abortion (<10 wks gestation, 92% effective): mifepristone x1 → buccal misoprostal in 24-48 hr → pt passes pregnancy at home over hrs. A/w cramping and bleeding. Tx with NSAIDs. F/u bHCG or pelvic U/S usually in 14d
- Surgical abortion (<24 wks gestation, 99% effective): same-day office procedure → no f/u unless complications

General Considerations
LGBTQ individuals are at higher risk of depression, anxiety, suicide attempts, medical mistreatment, and lacking health insurance compared to cisgender heterosexual individuals (Am J Prev Med 2018;55:336, BMC Psych 2008;18:70)

- **When in doubt, ask your patient!** Use open ended questions, ask for pronouns, focus on patient's health behavior rather than assumptions about orientation/identity, provide anatomy-based screenings, learn from your patients' lived experiences
- Gender Terminology
  - **Sex assigned at birth**: based on external anatomy vs **gender identity**: internal sense of one's gender
  - **Transgender/trans**: when one's assigned sex at birth and gender are not congruent
  - **Cisgender**: when one's assigned sex at birth and gender identity are congruent
  - **Non-binary, gender non-conforming, genderqueer**: gender identity not w/in society's M/F binary

Preventive Health Care for MSM (NEJM 2015;373:854)

- Health Inequities:
  - **HIV/AIDS** (In U.S. 63% of all new HIV infxn, 50% of all persons living with HIV), **STIs**, **cancer screening**, **immunizations**, substance & tobacco use, mental health, childhood sexual abuse, domestic violence (IOM 2011) (CDC 2018)
- Recommendations:
  - **Annual STI Screening**: HIV; TrepAb for syphilis; site-specific GC/CT NAAT based on sexual history (urine, rectal, pharyngeal); urine NAAT as sensitive as urethral; **self-collected rectal swabs** as sensitive as provider-collected rectal swabs; testing pharyngeal swabs for CT not recommended
    - Screen q3-6mo if multiple/anonymous partners, sex in conjunction w/ drug use
  - **Immunizations:**
    - **HAV vaccine** (fecal-oral transmission, don't need to check immunity); **HBV** SAg & SAb once, vaccinate if non-immune; **HCV** Ab once if born 1945-1965 & check HCV Ab q1y if high risk
    - **Meningococcal** vaccine, **HPV** vaccine if <27 (NEJM 2011;364:401)
  - Anal Pap: if HIV- consider q2-3y; if HIV+, perform q1y (high-grade AIN 29%) (Lancet Oncol 2012;12:487)
  - **PrEP**: Consider if high-risk sexual activity, HIV-, nml Cr, able to take daily. TDF-FTC or TAF-FTC QD are both FDA approved options that have been studied in MSM populations (CDC 2019); see *HIV* section.
  - Educate on how to access **PEP within 72h of high-risk exposure** – can page 36222 at MGH

Guidelines for Sexual Minority Women (SMW) (ACOG 2012;119:1077)

- Higher prevalence of **obesity**, **EtOH** use, and **tobacco** use → Increased risk of cardiovascular disease and DM
- Still at risk for **HPV** infection although lower rates of screening reported (Arch Fam Med 2000;9:843).
- Discuss conception options, intimate partner violence (using gender neutral language), and substance abuse

Transgender Medicine: 0.6% of adults in the U.S. identify as transgender or gender non-conforming (NEJM 2019;381:2451)

- Health inequities**:** mental illness (**suicide attempts**, depression, anxiety) **cervical cancer** (counsel that less likely to obtain adequate sample), **HIV** (trans women w/ 22% HIV infection rate vs 10% of MSM in the US) (J Adolesc Health 2015;56:274; JGIM 2014;29:778; Lancet Infect Dis 2012;13:214)
- **Gender-affirming care**: see WPATH Standards of Care, UCSF Center for Excellence in Transgender Health, Fenway Guide
  - Informed consent and well documented gender dysphoria/incongruence is needed to initiate hormone therapy
  - Discuss fertility preservation needs prior to starting hormones
  - **Feminizing hormone therapy cornerstones:** estradiol + concomitant androgen blocker
    - **Estradiols**: oral/sublingual, transdermal patch, estradiol valerate/estradiol cypionate IM
    - **Androgen blockers**: spironolactone, GnRH agonist; can decrease required estrogen dose
  - **Masculinizing hormone therapy cornerstones**:
    - **Testosterone (T)** (testosterone cypionate/enanthate IM/SQ or testosterone topical gel/transdermal patch)

(J Clin Endo Metab 2017;102:3869)	Potential Risks	Irreversible changes	Reversible changes	Monitoring
Masculinizing Therapy (testosterone)	- Breast or uterine cancer - Erythrocytosis - HTN, HLD - Sleep apnea	- Deepening of voice - Facial and body hair - Possible male pattern baldness - Clitoromegaly	- Cessation of menses - ↑ sex drive - ↑ muscle mass - Possible acne, mood changes	- CBC, lipids, BP q3mos first year then q6-12 mos - **Regular pap tests if cervical tissue present** - Serum T q3 mos until in normal physiologic M range
Feminizing Therapy (estrogen, spironolactone)	- Infertility, erectile dysfunction - Breast cancer - Blood clots (DVT, PE) - Increased risk of CAD, HTN, stroke, liver dz - Migraines	- Breast growth - Testicular atrophy - Redistribution of fat mass - Infertility	- ↓ muscle mass - Weight gain - Hair/skin softens - ↓ sex drive - ↓ libido, erections	- If on spironolactone, BUN/Cr and K q3mos first year then annually - Yearly prolactin - Serum T and estradiol levels q3 mos

- **Pregnancy prevention for transmasculine pts**: T suppresses period but may not prevent pregnancy
- **Additional practices to alter appearance**: binding, tucking, hair removal, silicone injections

Interpreter Services:
- In-person MGH Interpreter Services: x66966 or pager 27403 (Mon-Fri 6a-8p; Sat/Sun 8a-6:30p)
- CyraCom Phone Interpreter: 617-643-3344 Pin #1050

Medical Examination (CDC checklist)
History: obtain prior medical records if possible
- Country of origin, transit countries, residence in refugee camps or detention centers, amount of time living in US
- Family structure, food security, housing stability, safety in home/neighborhood
- Chronic diseases: HTN, DM, tobacco/substance use, kidney disease, chronic pain, age-appropriate cancer screening
- Mental health: PTSD, anxiety, depression; RHS-15 (screen at 2nd visit to minimize effect of re-traumatization)

Physical Exam:
- Vision, dental, hearing, BMI, BP screenings. See PCOI for low-cost referral options "Patient Education" → "Health Care Access"
- Complete skin exam: rashes, signs of trauma, signs of micronutrient deficiencies.

Vaccinations: if no vaccine documentation, assume pt not vaccinated (CDC Adult Schedule). For varicella and HBV, check titers first

Screening and Labs: (see CDC regional profiles)
- General screening: CBC/diff (eos, anemia), U/A (hematuria), BMP (glucose, renal dz), ♀ hCG
- Tuberculosis: ask every year about sx, recent travel, sick contacts; IGRA preferred to PPD (see *TB* section) → CXR → induced sputum
- STIs: syphilis (Trep Ab at MGH, VDRL/RPR elsewhere); HIV; GC/CT if ♀ ≤25 & sexually active or ♀ > 25 + risk factor
- HBV serologies: if from Asia, Africa, Middle East
- Malaria: treat if from SSA and did not receive pre-departure Tx, or from endemic country +sx. If pregnant or breastfeeding, test first (do not treat empirically). Obtain thick/thin blood smears or PCR (more sensitive if no sx)
- Intestinal and tissue invasive parasites: depends on country of origin and pre-departure treatment. See CDC guidelines for details on diagnosis and treatment. Do not give empiric ivermectin if pt from *Loa loa*-endemic country.
- Micronutrients (Fe, D, B12, etc): if malnutrition, anemia, h/o food insecurity

Infection	Signs and Symptoms
Strongyloidiasis, filariasis, schistosomiasis	Peripheral eosinophilia
Schistosomiasis	Hematuria, ♀ infertility, chronic pelvic pain
Malaria, schistosomiasis	Splenomegaly
Mycetoma, onchocerciasis, other filarial diseases	Chronic rash or itching
Chagas disease	Esophageal dysmotility, HF, conduction dz
Neurocysticercosis	Seizures, CNS sxs

Legal Considerations
- **Do not** document immigration status in EMR.
- In MA, MassHealth eligibility is NOT contingent on immigration status. Refer all pts to PFS; PCOI page "Patient Education" → "Health Care Access" → "Help Uninsured Patients Access Medical Care." Videos for patients on the ACA
- Know your Rights: handouts re: ICE (English) (Spanish); Red Cards (rights cards in different languages)
- Legal services available for patients in the Boston area; consider referral to LINC at MGH Chelsea
- For the latest on public charge and other legal changes that may affect immigrant patients, refer to:
  - Protecting Immigrant Families (PIF)
  - Massachusetts Immigrant and Refugee Advocacy Coalition (MIRA)
- Asylum screening questions:
  - What led you to leave your home country?
  - Were you ever a victim of violence or abuse there? (verbal, sexual, physical)
  - If so, was it due to your religion, race, political beliefs, nationality, or particular social group (including gender, sexual identity)?
  - If so, did you face violence from anyone working for the government, military, or police?
  - If yes→refer to legal org above, to PAIR, or to the MGH asylum clinic (mgartland1@partners.org)
- Resources on conducting asylum evaluations and working with asylum seekers

Type	Details
LPR	Lawful Permanent Resident: **Green card** recipient; pathway to citizenship. Family members 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.
TPS	Temporary Protected Status: Short list of countries, where conditions preclude safe return. Cannot be deported while country of origin on list.
Cancellation of Removal	Based on exception hardship to self or LPR/citizen spouse, parent, child if deported; ineligible with certain criminal convictions.
Asylum	Well-founded fear of being persecuted based on race, religion, nationality, membership in social group or political opinion. Application due within 1yr date of entry. If granted, may also apply to spouse and children if in United States.
Refugee	Same legal standard as Asylum, based on persecution or well-founded fear, but granted prior to arrival in US. Maximum set annually by President (no limit to Asylum).
Medical Deferred Action	Temporary reprieve from deportation for immigrants facing life-threatening medical conditions and other humanitarian circumstances
Withholding of Removal	Asylum/CAT/Withholding all part of same application. No 1yr rule; may apply at any time. Ineligible with certain criminal convictions.
CAT	Convention Against Torture: similar to Withholding, but still eligible with criminal convictions.
Undocumented	Patients should seek legal counsel to ensure no options to apply for alternative statuses.

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.

Location	Traumatic	Related to Activity	Atrauamatic
Anterior	Quadriceps or patellar injury	Patellofemoral syndrome, Osgood-Schlatter Bursitis, Quadriceps/patellar tendinopathy	RA, gout, pseudogout, septic joint
Lateral	Lateral meniscal tear, LCL injury	Iliotibial band syndrome	Lateral OA
Medial	Medial meniscal tear, MCL injury, tibial plateau fracture	Anserine bursitis	Medial OA, Saphenous nerve entrapment
Popliteal	PCL injury	Popliteal artery entrapment, Baker cyst	Popliteal artery aneurysm, DVT

Knee Exam		
Test	**Maneuver**	**Positive in**
Lachman (sim. to anterior drawer)	Pt supine with knee flexed, one hand on pt's femur, just above knee. Other hand on pt's tibia. Apply slight flexion and pull sharply towards your abdomen. If tibia feels less restrained, ⊕ test	**ACL** injury
Posterior drawer	Pt supine with knee flexed, can stabilize foot by sitting on it. Place hands around tibia, apply pressure backward in place parallel to femur. If less restrained motion, ⊕ test.	**PCL** injury
McMurray	One hand over medial joint line with knee fully flexed. Externally rotate foot/tibia, apply valgus stress and gently flex/extend knee. If clicking around medial joint line, ⊕ test.	**Meniscal** injury

- **XR imaging**: if trauma <1wk old & c/f fracture, follow **Ottawa** Rules (Sn 98%, Sp 49%; Annals 2004;140:121)
  - Obtain if any of the following: >55yo, isolated patellar tenderness, tenderness at head of fibula, cannot flex to 90°, or cannot bear weight for 4 steps (limp doesn't count).
  - If eval of chronic OA, get weightbearing views of both knees; patellar view for patellar problems.
- **Reserve MRI** until 4 weeks conservative care *unless* suspect fracture, infection, or internal derangement (e.g. ACL, meniscal tear in younger patients). *Asymptomatic meniscal tears:* 13% <45 yo, 36% >45 yo (Clin Ortho Rel Res 1992;282:177)
- **Meniscal tear treatment**: limited benefit of arthroscopy, esp. in degenerative meniscal tears in >45, pts with OA (BMJ 2017;357:j1982). Start with NSAIDs, PT, wt loss. Consider glucosamine+chondroitin or platelet-rich-plasma (AHRQ 2017)

Shoulder Pain

- **Rule out neck etiology**: neck pain, pain radiation beyond elbow, numbness, tingling
- History: trauma, acute vs chronic, constitutional sx, orthopedic history, day/night, provoking activity, loss of ROM, weakness
  - Get precise pain location

Etiology	History & Physical Exam Findings
Subacromial Bursitis	Ref. pain to deltoid. Pain w/ arc 60°-120° abduction +/- impingement. Overuse, heavy lifting. No imaging.
Rotator Cuff	Acute=trauma. Chronic=age, acromial spurring, overuse. Can be tendonopathy, partial or full thickness tears. Pain & weakness, ↓ ROM, ⊕ **internal/external lag test,** painful arc, impingement. Ortho referral, MRI if tear.
Glenohumeral OA / Adhesive Capsulitis	Aching, stiff; chronic loss of active and passive motion in all planes. OA: crepitus, age >60 yo. Capsulitis: ↑ risk with diabetes, thyroid disease, immobilization, often 40-60 yo. Plain films for OA
Labral Tears & Instability	Young athletes. "Click, pop, catch." Ant inferior→*shot-blocking arm pulled back.* Posterior→*push-up.* SLAP (Superior Labrum Anterior Posterior) →*baseball pitching, swimming.* Crepitus/catching w/ ROM. MRI
AC Joint Pain	Young: traumatic sprain, fall with separation. Older: AC evolves into OA (can contribute to impingment) Pain, tenderness, swelling over AC joint, ⊕ cross arm test. Plain films (w/ "stress views" for trauma)

Shoulder Exam	
Test	**Maneuver**
Drop Arm (RTC)	Ask patient to abduct arm at 90°. ⊕ if cannot smoothly adduct shoulder to waist-level.
Internal Lag Test (RTC)	Bring dorsum of patient's hand against lumbar region of back. Take forearm and hand away from the back (~20°). Ask pt to maintain position while supporting elbow. ⊕ if not maintained.
External Lag Test (RTC)	Externally rotate shoulder 90°, flex elbow 90°. Ask pt to maintain position. ⊕ if not maintained.
Neer (subacromial/RTC)	Fully pronate forearm (thumbs point backwards), bring shoulder to full forward flexion. ⊕ if pain.
Hawkins (subacromial/RTC)	Forward flex shoulder to 90°, flex elbow to 90°, and internally rotate the shoulder. ⊕ if pain.
Ext. Rotation (teres minor & infraspin.)	Flex elbow 90°. Pt externally rotates shoulder while examiner provides resistance. ⊕ if pain.
Empty Can (supraspinatus)	Flex shoulder 90°, internally rotated forearm. ⊕ if pain w/ resistance of downward push

- **Imaging**: x-ray if h/o trauma c/f fracture or dislocation, gross deformity, exam concerning for RTC tear or joint involvement; true AP of glenohumeral joint, axillary lateral, & "Y view" of AC joint. MRI w/o contrast in pts with ⊕ internal/external lag tests, r/o full thickness RTC tear, previous abnormal radiograph, persistent pain despite 2-3 mos of conservative therapy (see below)
- **Treatment**: bursitis/capsulitis/tendinopathy/impingement/OA/partial thickness RTC tear: conservative therapy (e.g. activity avoidance, NSAIDs, PT/home exercises +/- steroid injections short-term); surgery for refractory instability, labral/full RC tear, AC joint seperation

Low Back Pain:

- 84% lifetime acute back pain, 50% sciatica (Mayo Clin Proc 2015;90:1699); 75-90% improve over 4 weeks

	Definition	Signs and Symptoms	Etiologies
Axial	Originates from muscles, discs, endplates, facet joints, SI joints.	**85% of acute low back pain in primary care is nonspecific** *Disc*: young & ↑ w/ spine loading (i.e. sitting) *Facet*: > 40 yo, ↑ in extension and ↓ by sitting. *SI pain*: MVA/falls, rheum *Compression fx*: older, trauma, osteopenia, steroids *Cancer*: PMH, weight loss, night pain *Inflammatory back pain*: AM stiffness, night pain *Infection*: fever, night sweats, immunosuppression, IVDU	Muscle/ligament injury, facet, DJD, vertebral compression fx, cancer, spondyloarthropathies, discitis/osteo/epidural abscess
Radicular	Originates from disc herniation w/ nerve compression (90% L4-S1), spinal stenosis	*Sciatica* is 95% Sn / 88% Sp for herniation Leg > back pain w/ dermatomal distrib. of lancinating/burning pain Straight leg raise ⊕ L4-5: foot dorsiflex. L5-S1: foot plantarflex and ankle reflex.	Disk herniation, spinal/foraminal stenosis, can't miss cauda equina (bladder/bowel involv.)

- **Physical exam**: palpation of midline, ROM spine/hip, strength/reflexes of LEs, rectal tone (if c/f cauda equina), SLR
- **Imaging**
  - **Early MRI** / x-rays if **RED FLAGS**:
    - Focal severe/progressive neuro deficits, cauda equina sx; trauma; suspect fracture, osteopenia risk (age >50 or <20, PMH, steroids); major risk factors/hx of cancer; fevers/wt loss/IVDU (Spine 1996;21:2885)
  - Otherwise, defer imaging until after initial 4-6wk tx (Annals 2007;147:478; Choosing Wisely guidelines) as herniated disks, disc bulging, and degenerative discs are common findings (Am J Neuroradiol 2015;36:811)
  - Always explore potential poor coping, fear/avoidance, social/psychological stressors. Tx: depression, anxiety, SUD
  - See STarT Back Screening tool for further guidance
- **Possibly effective and lower-risk therapies**:
  - Avoid bed rest! Activity as tolerated.
  - **PT & exercise** w/ progressive home exercise (no demonstrated benefit in acute LBP, modest benefit for subacute/chronic)
  - **Non-pharmacologic therapies**: acute LBP → heat/cold, massage, manipulation, acupuncture; chronic LBP → yoga, cognitive behavioral therapy, mindfulness, multidisciplinary rehabilitation (Annals 2017;166:514)
  - **NSAIDs** (ibuprofen 400-800 TID or naproxen 200 to 400 BID) are first line for limited duration if no contraindication
  - *Muscle relaxants*: combo tx w/ NSAIDs may give add'l benefit acutely if NSAIDs alone ineffective (JAMA 2015;314:1572)
  - *Duloxetine and tramadol* for **chronic** LBP (no benefit in acute); second line after NSAIDs (Annals 2017;166:480)
  - *Radicular pain:* if no improvement despite 6+wks of non-invasive tx, consider referral to Pain Med or PM&R for trial of epidural steroids (limited evidence, benefits likely limited and short-term). Not recommended for acute or nonradicular pain.
- **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:* limited evidence of effectiveness, & higher risk of harm (JAMA 2018;319:872). Before prescribing, review potential benefits vs. risks. MA law: *Must check PMP and limit 7 days for initial opioid prescription.* Plan to d/c in 6-8 weeks if no benefit

LONG-TERM OPIOIDS FOR MSK PAIN

- Limited evidence for chronic MSK pain. High risks of hyperalgesia, tolerance, dependence, addiction.
- **Before prescribing longer-term opioids**:
  - Exhaust non-opioid options. *Avoid benzodiazepines, hypnotics*. Screen for sleep apnea, SUD, mental health. Stress that pain control is a mutual goal, **complete pain relief is unlikely**, set functional goals.
  - Perform a risk assessment (Screener & Opioid Assessment for Patients with Pain (SOAPP)-Revised). Check MassPAT (also linked in Epic). Obtain prior records & speak to prior prescribers. Agree that *single prescriber* will provide scripts.
  - Create a **pain agreement** with the patient: discuss **6-8 week initial trial,** safe use, secure storage and disposal of opioids. Educate that random UTox and toxicology, random pill counts are for pt safety. Rx on 28-day cycle ending on weekday to facilitate refills. Prescribe the patient *naloxone* to be used in case of overdose risks.
  - **Discontinue opioids if no significant benefit at 6-8 wks**, significant side effects, risk > benefit, non-adherence.
  - **C*aution prescribing > 50 mg/day morphine equivalents (MME), avoid > 90 MME (obtain pain consult).***
- **Follow-up for longer-term opioids**:
  - See patients in office at least q1-3 months to review pain, function, side effects, compliance, and re-evaluate plan.
  - Early refill requests should trigger an appointment to assess reason, obtain tox screen, discuss use.

CHRONIC COUGH (Am Fam Phys 2017;96:575, NEJM 2016;375:1544)

- Acute (≤3 weeks) vs. subacute (3-8 weeks) vs. chronic (>8 weeks)
- **Most common causes**: **upper airway cough syndrome (UACS), asthma, GERD**; 18-62% pts have combo
  - Other causes: post-infxn (self-limiting; can last up to 3+ months, treat sxs), nonasthmatic eosinophilic bronchitis, chemical irritant (eg. cigarette smoke), laryngopharyngeal bronchitis, psychogenic/habitual cough, bronchiectasis, CA, TB, sarcoid.
  - Normal CXR usually excludes bronchiectasis, persistent PNA, sarcoidosis, TB.
- **General approach**: 1) obtain good history (smoking status, URI hx, ACE-i use); consider CXR if no ACE-i or irritant exposure (except smoking) and ↓ suspicion for UACS/asthma/GERD; consider spirometry; 2) remove possible offending agent; 3) start empiric tx for UACS/asthma/GERD sequentially until resolution → tx should be *added* to initial regimen; 4) consider PFTs, esophageal pH monitoring, chest CT, sputum tests, cardiac studies if sxs 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. Exam of throat/nose may reveal cobblestoning. Can be absent of symptoms other than cough. Common causes: allergic/non-allergic rhinitis, sinusitis.	Avoid environmental triggers of allergic rhinitis. Intranasal steroids, antihistamine nasal spray, oral antihistamine, oral decongestants, or saline nasal rinse can be used for symptom relief
Asthma	Typically w/ episodic wheezing & dyspnea. Cough variant asthma p/w only cough. Pt may have h/o atopy. Exam: may have nasal polyps. Need spirometry w/ bronchodilator response & bronchoprovocation (e.g. metacholine challenge) for dx.	PRN bronchodilators +/- inhaled corticosteroids. Some pts may use only seasonally. See "Asthma" in *Pulmonology* section for stepwise therapy.
GERD	30-40% of chronic cough. Epigastric burning sensation, sour taste in mouth, but sxs absent in >40% of patients.	Lifestyle modifications, moderate dose PPI/H2 blocker. Consider H pylori testing.
Respiratory tract infection	H/o recent viral illness. 2/2 postnasal drip/UACS or direct effect of virus on bronchial reactivity/cough receptors. Pts have been shown to experience transient bronchial hyperreactivity as well.	UACS tx as above. 2nd gen (cetirizine) or 3rd gen (fexofenadine) antihistamine. If bronchial hyperreactivity, tx w/ usual asthma care.
ACE Inhibitor	Produces cough in 3-20% of pts. 2/2 ACEi mediated increase in bradykinin. Sxs can occur 1 wk to 6 mos after starting.	Withdraw ACEi (resolves within 1-4 weeks), change to ARB (**not** associated with cough).

RHINOSINUSITIS (Otolaryngol Head Neck Surg 2015;152:598, NEJM 2016;375:962)

- Acute (<1mo) vs. subacute (1-3mo) vs. chronic (>3mo, usually w/ anaerobes); recurrent (4 or more annual episodes)
- **Dx**: rhinorrhea (viral=clear, bact=purulent) + nasal obstruction or facial pressure/pain/fullness. A/w anosmia, ear fullness, cough, H/A
- Acute rhinosinusitis is *infectious* while chronic is *inflammatory* (atopy, asthma, granulomatous disease, immunodeficiency, CF)

Etiology	Time Frame	Treatment	
Bacterial: only 0.5-2% of acute rhinosinusitis S. pneumo (41%), H. flu (35%)	>10 days, or worsening within 10d after initial improvement	Watchful waiting in pts w/ follow-up vs. Augmentin 875mg BID** or Doxy 100mg BID x 5-7d	• NSAIDs/Tylenol for pain • Saline irrigation/Netipot • Topical nasal steroids, decongestant, expectorants
Viral: most common cause	7-10 days	Symptom control, oral decongestant	
Fungal: mucor (invasive) in DM, immunocompromised	Acute (invasive) to more chronic (>3mo)	Surgical removal of fungal mucin or "fungal ball" (mycetoma). ENT emergency if invasive (destruction of sinus, erosion into orbit or brain)	

** 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 of absence of nasal polyps
  - W/out 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 headache; AMS; meningeal signs

PHARYNGITIS (JAMA 2012;308:1307, NEJM 2011;364:648)

- Most cases are **viral** (suspect if + conjunctivitis, coryza, cough, diarrhea, hoarseness, discrete ulcerative stomatitis, viral exanthema). Only 5-15% of adult sore throat visits are Group A Strep (GAS).
- **Exclude dangerous etiologies**: epiglottitis, peritonsillar abscesses, infx in submandibular or retropharyngeal space, primary HIV
- **Identify & treat GAS** 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 pt for each: tonsillar exudates, tender ant. cervical LAD, fever, ∅ cough; (-1pt if age ≥45)
    - 0-2: no testing, treat sx. 3-4: send Rapid Strep antigen detection test (Sn 70-90% / Sp 95%) + throat culture (if neg rapid but ↑ clinical suspicion; not indicated for routine use in adults w/ neg rapid)
  - **Tx**: PO Penicillin V 250mg QID vs 500mg BIDx10d; amoxicillin 500mg BIDx10d; IM Pencillin G benzathine 1.2 mill Ux1
    - PCN-allergic: cephalexin 500mg BIDx10d
    - β-lactam sensitivity: clinda 300mg TIDx10d; azithromycin 500 mg QDx1d, then 250 mg QDx4d
- **Symptomatic Tx**: OTC lozenges (e.g. Sucrets, Cepacol), throat sprays, NSAIDs/Tylenol for pain relief. No PO steroids.
- **Follow-up**: if no improvement in sx in 5-7 days, evaluate for other infectious causes (e.g. mono, primary HIV, GC/chlamydia) or suppurative complications such as tonsillopharyngeal cellulitis or abscess or otitis acute media.

Red Eye (Am Fam Physician 2010;81:137):
- **DDx**: ⊕ **discomfort**: conjunctivitis, corneal abrasion, acute angle closure glaucoma, iritis/uveitis, scleritis, endophthalmitis, dry eye. ⊖ **discomfort**: subconjunctival hemorrhage, episcleritis, mild dry eye syndrome
- **H&P**: assess for **red flags**: recent eye surgery, trauma, severe foreign body sensation, severe HA/nausea, chemical injury, immunocompromise, decreased vision, colored haloes, mod-severe pain, proptosis, ciliary flush, corneal opacity, fixed pupil → **urgent ophtho referral**

Conjunctivitis (JAMA 2013;310:1721)
- **Viral**: most common cause (80%), higher prevalence in summer, most commonly **adenovirus**, **highly contagious**
  - Presentation: **sero-mucoid** discharge (more watery than bacterial), gritty sensation, intense and diffuse injection, +/- itching, +/- periauricular lymphadenopathy (more prevalent in viral cases)
  - Dx: **clinical**, PCR/culture rarely needed
  - Tx: supportive, cool compress, artificial tears, strict hand hygiene, refrain from work as long as discharge present; self-limiting course 1-2 weeks; HSV (1.3-4.8% cases)/VZV require topical/oral therapy/ophtho referral
- **Bacterial**: common pathogens include *S.aureus* in adults vs. *S.*pneumo/h.influ in children; **highly contagious**
  - Presentation: **mucopurulent** discharge, diffuse injection, eyelid edema, pain/stinging, foreign body sensation (bilateral discharge, eyelids adhering, lack of itching, or prior episodes strong predictor of bacterial conjunctivitis)
  - Dx: GS/Cx if pt immunocompromised, wears contacts, fails tx, severe purulence, c/f gonococcal/chlamydial infection; If gonococcal ⊕: warrants systemic abx and ophtho referral
  - Tx: no single abx class superior; **trimethoprim-polymixin B** 1-2 drops QID or **erythromycin ointment** 0.5" QID for 5-7d; tx decreases recovery time but observation reasonable; usual course 7-10d
- **Allergic**: chronic or seasonal (90% of cases), hx of atopy
  - Presentation: bilateral, intense itching, painless tearing
  - Tx: cold compress, artificial tears; try **antihistamine/mast-cell stabilizer drops** like olopatadine/ketotifen BID; limit OTC vasoconstrictor/anti-H1 combos (e.g. Visine-A), as can cause rebound hyperemia; +/- PO anti-H1

In general, pts should NOT wear contacts for duration of symptoms; avoid topical corticosteroids, vasoconstrictors, analgesics

Cellulitis: also see *Viral Respiratory & Head & Neck Infections* (Am Fam Physician 2016;93:991, Am Fam Physician 2015;92:106)

Orbital Cellulitis	Preseptal/Periorbital Cellulitis
Infection of soft tissues of orbit, a/w paranasal sinusitis; red/swollen eyelid, ⊕ **orbital pain** w/ EOM, restricted mobility, **vision changes**/ diplopia, can have subtle proptosis **Requires admission and ophtho consult*	Infection of preseptal tissues, often a/w local skin deficit; **red/swollen eyelid**, **NO pain** w/ EOM, **NO vision changes** *CT w/ contrast can help distinguish from orbital if hx/exam concerning
Tx: empiric **vanc/CTX**; add flagyl if cannot r/o CNS involvement or if a/w sinus/dental source	**Tx**: **Bactrim** or clindamycin PLUS **amoxicillin** or amox-clav or cefpodoxime or cefdinir

Ear Pain (Am Fam Physician 2018;97:20)
- **History**: previous episodes, smoking status, alcohol abuse, hearing loss, otorrhea, TM fullness, vertigo suggest 1°otalgia; pain w/ chewing, sinusitis, dental work, GERD suggest 2° otalgia
- **1° causes**: otitis media and externa, foreign object, eustachian tube dysfunction, barotrauma; less common causes include auricular cellulitis, cholesteatoma, mastoiditis, Ramsay Hunt Syndrome (HSV)

	Otitis Media	Otitis Externa
History & Exam	Recent URI, smoking, hx eustachian tube dysfunction, conductive HL, bulging TM w/ reduced mobility	Water exposure, DM2, discharge, itching, erythematous canal, ⊕ pain with retraction of pinna
Tx	**Amox-clav** or 3G cephalosporins for 5-7d for mild-mod case *If ruptured TM, can add antibiotic drops, but NO steroids, refer to ENT if does not close in 6 weeks	Cleanse w/ water + hydrogen peroxide or acetic acid; topical tx: **abx-steroid drops** (like cipro-hydrocort) + **acetic acid drops**; if c/f fungal, clotrimazole drops

- **2° causes**: TMJ syndrome, dental/sinus infxn, GERD, neuralgias, Bell's Palsy, zoster (Ramsay Hunt), tumor; less common but **emergent** causes include temporal arteritis, MI, thoracic aneurysms

Tinnitus (NEJM 2018;378:1224 Am Fam Physician 2014;89:106)
- **History**: ask about dizziness/vertigo (suggests Meniere's), hearing loss and laterality (can suggest schwannoma), meds (ASA, loops, abx), hx trauma, CVA, HA, depression/anxiety
- **Dx**: audiometry (esp if unilateral, >6mo), imaging if unilateral, pulsatile, asymmetric hearing loss, focal neuro deficits
- **Sensorineural hearing loss**: most common cause of persistent tinnitus; **Tx**: hearing aids**,** acoustic stimulation, CBT**,** patient education**,** noise cancelling devices; no meds/supplements have been shown to significantly reduce tinnitus

Adrenal Nodules (>1cm) (Endocr Pract 2009;15:450, Eur J Endocr 2016;175:G1)

- Is it malignant? (<5% primary, <2.5% mets): ↑risk: diameter >4 cm, >20 HU, heterogeneous, irregular shape, calcification, high T2 signal on MRI, delayed contrast washout
- Is it functionally active? (10-15%): clinical exam & lab testing for all nodules >1cm (unless obvious myelolipoma) to r/o pheo & Cushing's (see table). Also test for hyperaldo if HTN, hypokalemia. Only test for production of excess sex hormones if clinical stigmata. **AVOID** testing inpatients due to high false positive rates.

Diagnosis	Suggestive Clinical Features	Laboratory Tests
Cushing's syndrome (~6-10%)	HTN, metabolic syndrome, central obesity, prox muscle weakness, facial plethora	1mg o/n dex suppression test, serum DHEAS (if ⊕ send ACTH, 24H urine cort, 8mg o/n DST)
Pheochromocytoma (~3-5%)	HTN, palpitations, headache, diaphoresis; CT: ≥10 HU, vascularity, cystic changes	Serum fractionated metanephrines, 24H urine fractionated metanephrines and catecholamines
Hyperaldosteronism (~1%)	HTN, hypokalemia	Plasma aldo & renin activity (d/c aldo antagonists before testing). May req. adrenal vein sampling
Hyperandrogenism	Virilization, hirsutism, irregular periods	DHEAS, total testosterone, 17-OHP

- Consider adrenalectomy: if ↑ risk characteristics, >4cm, malignant, or hormonally active; surgery after hormonal eval
- Consider FNA: if c/f adrenal met from another primary without known metastatic disease (**only** after excluding pheo)
- Follow up: repeat CT scan in 12 mos. Consider annual DHEAS/1mg DST x4-5y (unknown effectiveness, EJE guidelines don't recommend). Adrenalectomy if nodule grows >1 cm, reaches 4cm, or becomes functional

Thyroid Nodules (Thyroid 2016;26:1, Endocr Pract 2016;22:622)

- Is it malignant? ↑ risk: h/o irradiation to head/neck, +family hx, or h/o thyroid cancer syndromes (i.e. MEN 2), age <30
- Workup: obtain **thyroid ultrasound** and check **TSH** (↑ TSH = more likely CA)
  - Low TSH: measure FT4 and FT3, obtain Thyroid radionuclide (^{123}I) scan
    - If "hot nodule," consider Tx for hyperthyroidism if symptomatic. No biopsy necessary.
    - If "cold nodule," refer for U/S-guided FNA if U/S criteria met
  - If normal or high TSH, r/o hypothyroid (FT4, TPO antibody) and refer for U/S-guided FNA if U/S criteria met
- FNA: any nodule w/ extrathyroidal extension, extrusion through rim calcs, abnormal cervical LNs, adjacent to laryngeal nerve/trachea OR >1cm w/ irregular margins with microcalcs, rim calc, or solid/hypoechoic. No FNA for purely cystic nodules.
- Follow up (benign): based on U/S characteristics. If highly suspicious U/S findings, repeat US and FNA within 12 mo. If low-moderate suspicious U/S findings, repeat U/S 12-24 mo., consider FNA if >1-2cm change. Stop f/u after 2 neg FNAs.

Incidental Pulmonary Nodules (<3cm) (Radiology 2017;284:228, Chest 2013;143:e93S, Thorax 2015;70 Suppl 2:ii1)
*NB: these guidelines are for **incidental findings**; recommendations for f/u of nodules found on LDCT for lung cancer screening are different as that population is high risk (see Lung-RADS classification tables online)*

- 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 if it is stable on CT for a defined period of time (>2 years for solid and >5 years 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 6-12 months, then CT every 2 yrs until 5 yrs. *Part solid*: if <6mm, no routine f/u. If >6 mm, CT at 3-6 mos, then annual CT for 5 yrs if unchanged and solid component <6 mm. *Solid nodules*: see below.

Nodule type	< 6 mm	6-8 mm	> 8 mm
Single solid nodule			
Low risk	No routine follow up	CT at 6-12 months, then consider CT at 18-24 months	Consider CT at 3 months, PET/CT, or tissue sampling
High risk	Optional CT at 12 months	CT at 6-12 months, then CT at 18-24 months	Consider CT at 3 months, PET/CT, or tissue sampling
Multiple solid nodules			
Low risk	No routine follow up	CT at 3-6 months, then consider CT at 18-24 months	CT at 3-6 months, then consider CT at 18-24 months
High risk	Optional CT at 12 months	CT at 3-6 months, then at 18-24 months	CT at 3-6 months, then at 18-24 months

- Consider referral to the Pulmonary Nodule Clinic: refer in Epic or call x38728 for appointment

TIPS FOR CALLING CONSULTS

- **To do BEFORE you call**:
  - Place **order** in Epic for consult
  - **Know your patient**: you may be asked to provide additional information (current status, **exam**, workup). Review the H&P/chart and *briefly see/examine the patient* if you have not done so previously.
    - **GI**: melena/hematochezia, current/prior Hct, plts, coags, transfusions, past EGD/colo, vitals, IV access, NSAID/ASA use
    - **Cards**: EKG/tele, prior stress/echo/cath (know anatomy), dry weight, biomarkers, current cardiac meds, outpt cardiologist
    - **Renal**: baseline Cr, CKD stage, on/off HD, dialysis access, electrolyte mgmt, current UOP, nephrotoxins, outpt nephrologist
    - **Onc**: known cancers w/ stage/tx history, biopsy results (for new dx), current anticoagulants, special slide, outpt oncologist
    - **ID**: current/past micro data, possible sources, current/prior abx (incl # of days), fever curve, hardware, travel, exposures
  - **Know your question** – Bigelow JAR should specify consult question in task list. *If not there, ASK. It is always OK to clarify.*
- **To do DURING the page/call**:
  - Call as early in the day as possible (ideally before noon), find out how to page using the paging directory
  - In your **page** to consulting team, include: **pt name, MRN, location, call back #, brief consult question +/- level of urgency**
  - Avoid "curbside" questions. If there is a specific question about management, call a formal consult.
  - Tell the consultant a **brief HPI,** a clear **explanation of the team's thinking,** and a **clear and specific question**
- **To do AFTER the call**:
  - Invite the consultant to find you to relay their recommendations or tell them who will be covering for you

CALLING EMERGENT CONSULTS

- **Surgery**: STAT to surgeon means life-threatening emergency (e.g. hemorrhage, lost airway, perforated or ischemic bowel). Include reason for consult in your page to help surgeon triage urgency
  - 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
- **Ophtho**: page p21004 for all consults. Backup/emergency number is 617-573-4063 (MEEI ED back desk).
- **Toxicology (ingestions/overdoses/exposures/interactions)**: call Poison Control Massachusetts (617-355-6607 or 800-222-1222).
- **Cardiac Surgery**: call "*In-House fellow*"

CALLING SURGICAL CONSULTS AT MGH

- All surgical consults are considered urgent. For a non-urgent consult overnight, wait to page until AM.
- **In the ED**: speak directly to (do not page) the surgery team that sits in Acute. Once patient on the floor, page intern on the *consulting team*. Do NOT page the ED Surgery resident who placed initial consult note. Do NOT page surgery attending.
- **New ward consult** → page "***Senior** Resident on call"* under Emergency Surgery/Trauma (Churchill) Team.
  - Existing ward consults, page the intern for that Churchill service, not the team on call that day
- **New private consult** (patient had prior operation by MGH surgeon) → page "***Senior** Resident on call"* for new consult on **Baker** surgery services; team depends on which surgery attending is requested.
- **Thoracic Surgery consult** → page "*Consult **resident**"* under "Thoracic Surgery" or "Surgery"
- **Vascular Surgery consult** → page *"Consult **resident"*** under "Vascular Surgery" or "Surgery"
- **Cardiac Surgery consult** → if non-emergent (8:30am-5pm) place order and call referral coordinator 617-724-4833. Can page NP at 30010. All other times (5pm-8:30am, weekends) call "*In-House fellow"*
- **Ortho consult** → page *"Floor resident"* at 20296 under "Orthopedics" or if ED consult, page 22566
- **Transplant Surgery consult** → page *"Intern"* (6a-6p) or *"House officer on call* (6p-6a)" under "Transplant Surgery"

CALLING OTHER SUBSPECIALTY CONSULTS

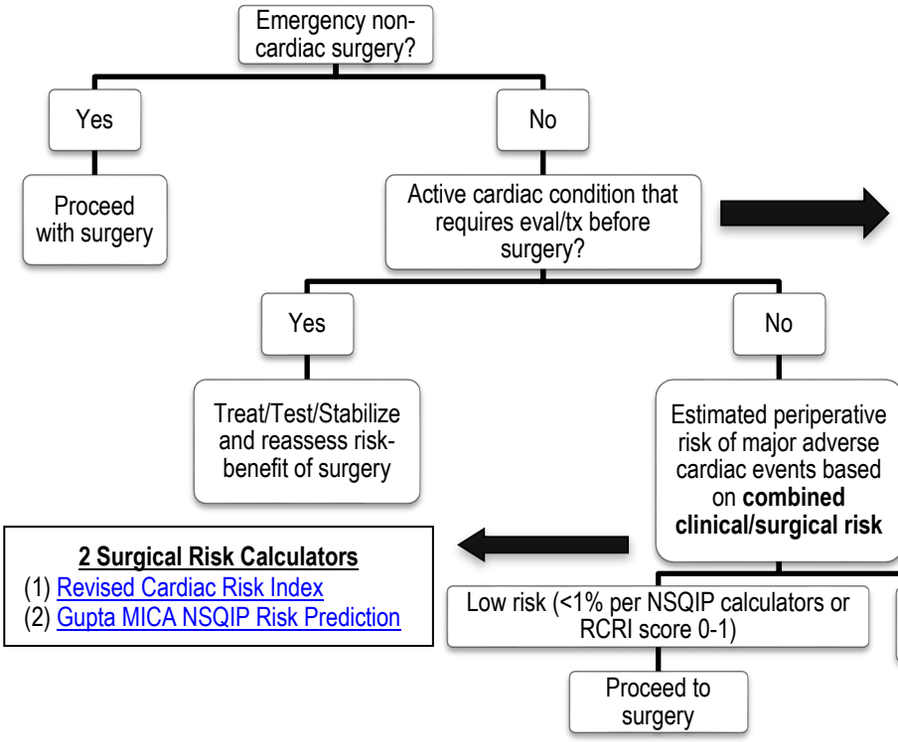
- **ACT (Addiction Consult Team)**: place consult in Epic (no need to call), for EtOH or other substance use disorders, suboxone, etc.
- **AMS (Anticoagulation Management Service)**: for established pts: p30104, or click AMS icon in Epic to determine existing AMS RN. For discharge – place Epic consult; if urgent or questions, page Discharge Pathway Service: p30103
- **Cardiology**: login to Amion under "mghcardiology" to identify appropriate fellow (link also in paging directory)
- **Chronic pain (cancer pain, pain in addiction)**: p17246
- **Acute pain service (epidurals and periop pain)**: p27246
- **Diabetes nurse educator**: service NP p20737; MD p14364
- **ENT**: page 22220. Backup/emergency number is 617-523-7900 (MEEI operator) and ask them to page ENT resident on call.
- **Optimum Care Committee ("OCC," Ethics)**: page ethics support pager: p32097 (Mon-Fri, 8am-4pm, except holidays)
- **Ophtho**: for all consults p21004. Backup/emergency number is 617-573-4063 (MEEI ED back desk). *Determine whether patient can **travel to MEEI** for an exam and if **ok to dilate** prior to calling consult.*
- **Psychiatry**: for non-emergent floor consult: order psych consult in Epic
  - *Weekday, Weekend Night, Holiday Night:* Call CL coordinators (6-2984). These consults will be seen within 24 hours.
  - *Weekend or Holiday 8am-5pm***:** p17911 (weekend rounding psychiatrist)
- **Transfusion reactions**: page blood bank resident at 21829

Peri-Operative Cardiac Risk Stratification and Risk Reduction

GOAL: to **estimate** and **optimize risk** of peri-operative cardiac events, ***NOT to "clear for surgery"***

- Peri-op cardiac events: **MI** (usually clinically silent, NSTEMI>STEMI, POD#0-3, not intraop), **CHF**, **VT/VF**, **cardiac arrest, death**
  - Major determinants include: (1) condition of patient (2) risk of procedure (3) functional capacity
- Emphasis on risk stratification. **Very few patients need non-invasive/invasive testing** unless testing would change management in the absence of surgery.

Peri-Operative Cardiovascular Evaluation for Non-Cardiac Surgery (JACC 2014;64:e77)

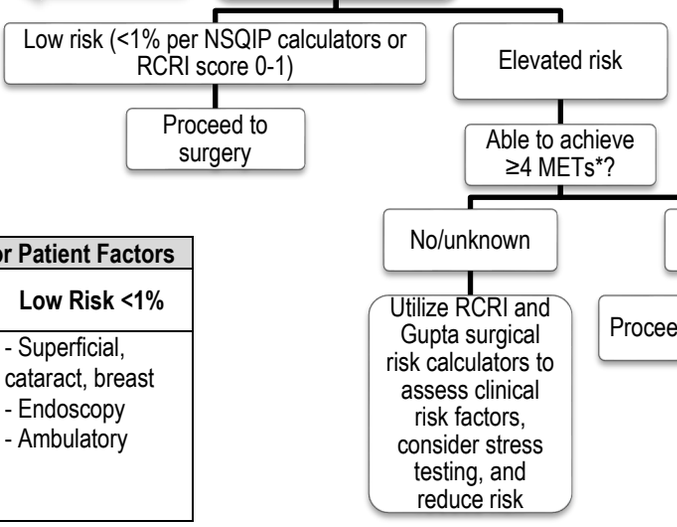


Active Cardiac Conditions

- **Unstable Coronary Syndromes**: unstable/severe angina, acute (<7d) or recent (<30d) MI
- **Decompensated HF**
- **Significant Arrhythmias**: symptomatic/new ventricular arrhythmias, SVT with HR >100 at rest, symptomatic bradycardia, high-grade AVB
- **Severe Valvular Disease**: severe sx AS (mean grad >40, AVA < 1.0 cm^2), sx MS (progressive DOE, presyncope, HF)

2 Surgical Risk Calculators

(1) Revised Cardiac Risk Index
(2) Gupta MICA NSQIP Risk Prediction



***4+ METs:**
↑2 flights stairs; walk 4 blocks; golf, bowl, dance

Operative Risk without Adjustment for Patient Factors		
High Risk >5%	**Intermediate Risk 1-5%**	**Low Risk <1%**
- Emergent major surgery, especially in elderly - Aortic, peripheral, or major vascular	- HEENT, CEA - Intrathoracic, intraperitoneal, prostate - Orthopedic	- Superficial, cataract, breast - Endoscopy - Ambulatory

Revised Goldman Cardiac Risk Index (RCRI) (Circ 1999;100:1043)

- **Six independent predictors (risk factors) of major cardiac complications**
  1. High-risk noncardiac surgery (not a clinical RF but incorporated elsewhere in algorithm): *OR 2.6*
  2. CAD (MI, PCI, CABG, angina, nitrate use, EKG with pathologic Q waves, or ⊕ exercise stress test: *OR 3.8*
  3. HF (CHF, pulm edema, bilateral rales, or S3): *OR 4.3*
  4. Cerebrovascular disease (stroke or TIA): *OR 3.0*
  5. Diabetes mellitus with preop insulin therapy: ***OR 1.0!***
  6. Renal insufficiency with preop Cr >2.0 mg/dL: ***OR 0.9!***

Rate of cardiac death, MI, pulm edema, CHB, cardiac arrest/VF according to # predictors (data from cohorts in RCRI)		
#RCRI Predictors	Rates of event	(95% CI)
0	0.4-0.5% or ~0.5%	(0.05-1.5)
1	0.9-1.3% or ~1%	(0.3-2.1)
2	3.6-6.6% or ~5%	(2.1-10.3)
≥3	**9.1-11.0% or ~10%**	(**5.5-18.4**)

Alternative Cardiac Risk Assessment: Gupta Perioperative Cardiac Risk (Circ 2011;124:381)

- Identified 5 risk factors predictive of *risk of STEMI or cardiac arrest* w/in 30 days of surgery:
  1) Type of surgery/procedure, 2) preoperative functional status, 3) serum Cr >1.5, 4) ASA class, 5) increasing age
- Compared to RCRI, **better** discriminative predictive value
- **Limitations**: likely underestimates actual risk because MI was defined in the study based on only ECG changes: STEMI or new LBBB; biomarkers were NOT monitored post-op, which is necessary to detect more than 50% of perioperative MIs.

Preoperative Coronary Revascularization (NEJM 2004;351:2795)

- **CARP**: multicenter RCT of 510 high-risk vascular surgery patients, showed prophylactic revascularization w/ BMS/CABG conferred no survival benefit; data extrapolated to lower risk non-vascular/non-cardiac surgeries.
  - Exclusion criteria: EF<20%, unstable angina, LMCA disease >50%, severe AS

Peri-operative β-Blockade and Other Cardiac Drugs

- **Evaluate for peri-operative β-blockade** (Circ 2009;120:e169)
  - **Continue β-blocker**: if already taking for other indication (e.g. CAD, arrhythmia, HTN) for goal HR 55-65 (Class I, LOE C)
  - **Initiate β-blocker**: ≥3 RCRI risk factors or if pt has indication for βB otherwise (Class IIa, LOE B). *Never start on day of surgery!*
  - **Uncertain role of β-blocker**: if no known CAD but either ⊕stress test or significant risk factors
- **Anti-platelet**: (POISE-2 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 → delay elective surgery. If urgent, continue ASA, hold P2Y12i x5d.
- **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 ↑ 30d mortality (Anesthes 2015;123:288).
- **Other**: all other anti-hypertensives should be continued perioperatively to goal BP <180/100 to avoid bleeding
- **Anticoagulation**: recommendations for bridging in patients using VKAs stratified by risk (Chest 2012;141:e152S, JACC 2017;69:871)
  - **BRIDGE**: notably ~90% were low-risk/outpatient surgeries. Exclusion criteria included: mechanical valves, stroke/TIA w/in 12 weeks, major bleeding w/in 6 weeks, CrCl <30, Plt <100k (NEJM 2015;373:823)
  - More data needed on DOACs but generally do not bridge; see ACC guidelines re: timing of interruption and re-initiation

Risk Levels	Risk Factors for Thromboembolism	Recommendations
Low	- AF w/ CHA_2DS_2-VASc ≤ 4, no prior embolism - VTE >1 year ago and no additional risk factors - Bileaflet AVR w/ out risks for stroke and no history of AF	- No bridging recommended due to increased risk of bleeding from BRIDGE trial (note exclusion criteria)
Moderate	- AF w/ CHA_2DS_2-VASc 5-6 or prior embolism (≥ 3 mo. ago) - VTE w/in 3-12 months, recurrent VTE, non-severe thrombophilia, active malignancy - Bileaflet AVR w/ risk factors for stroke	- Consider bridging based on individualized patient bleeding/embolism risk and procedure
High	- AF w/ **CHA_2DS_2-VASc ≥ 7**, recent embolism**, valvular AF** - **VTE w/in 3mos**, or **antiphospholipid antibody** syndrome - All **mitral valves**, caged ball/tilt disc AVR, or any mechanical valve w/ CVA ≤ 6 months	- **Bridge** with LMWH or UFH - Enoxaparin should be stopped ~24h prior to surgery - UFH should be stopped 4-6h prior to surgery - Ideal to resume ≤ 24 h post-op if bleeding stabilized

See *Hematology: Anticoagulation Management* for more details.

VTE Prophylaxis (Mayo Clin Proc 2014;89:394)

- Postop VTE risk assessment: Caparini Score
- Non-orthopedic surgeries: those undergoing **general** or **abdominal/pelvic surgery** are at highest risk
- Orthopedic surgeries: **all pts at high VTE risk** 2/2 tourniquet time + immobilization; minimum duration 10-14d (35d if higher risk)

Peri-operative Monitoring and Considerations (NEJM 2015;373:2258)

- **ACS**: most MIs occur w/in 48h while patients are on analgesics that mask pain → some data show benefit of troponin monitoring (JAMA 2012;307:2295). Elevated post-op NT-proBNP can be used as a predictor of post-op MI and death (JACC 2014;63:170)
- **AF**: may be a more important risk factor than CAD for 30d post-op mortality (Circ 2011;124:289)
- **Post-operative PNA**: ~20% mortality; pre-op CXR or PFTs not recommended because rarely change management
  - Risk factors: COPD, age >60, ASA class ≥II, albumin <3.5, poor functional dependence, weight loss >10% over previous 6 months (Annals 2006;144:575)
- **Renal dysfunction**: increased risk of complications in ESRD; AKI also a/w high morbidity and mortality (Ann Surg 2009;249:851)
- **ESLD**: high risk of peri-op death; MELD predicts survival (>15 median survival ~2 months); Child-Pugh C very high risk (>60% in-hospital mortality) (J Gastroenterol Hepatol 2012;27:1569)
- **Low albumin**: independent predictor of 30d post-op morbidity and mortality (Arch Surg 1999;134:36)

Before Consulting Dermatology: *Upload photo of rash* *(ideally pretreatment) to media tab of EPIC using Haiku*

- If consulting for drug rash, note exact timing of rash development and administration of suspect medications

Quick Steroid Guide
• Face/intertriginous areas: hydrocort. 2.5% cream, hydrocort. valerate 0.2% cream • Body: fluocinolone 0.025% cream if mild, clobetasol 0.05% ointment if severe → mid strength to super potent depending on severity • Scalp: 0.01% fluocinolone scalp solution or oil (dermasmoothe); oil better for dry scalp ***Counsel patients:*** Use daily x2 wks then 1 wk "off", avoid face (risk = skin thinning)

MGH topical steroid formulary by level of potency	
Super-potent	clobetasol 0.05%, betamethasone dipropionate 0.05%
Potent	fluocinonide-emollient 0.05%
Upper-mid strength	betamethasone valerate ointment 0.1%
Mid-strength	fluocinolone ointment 0.025%
Lower mid-strength	fluocinolone cream 0.025%, betamethasone valerate cream 0.1%
Mild	hydrocortisone valerate 0.2%, fluocinolone scalp oil 0.01%
Least potent	hydrocortisone 2.5%, hydrocortisone ointment 1.0%
Over the counter	hydrocortisone cream 0.5%, 1.0%

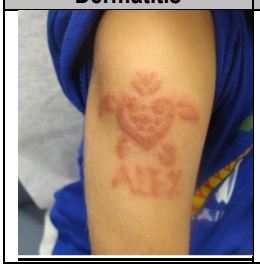
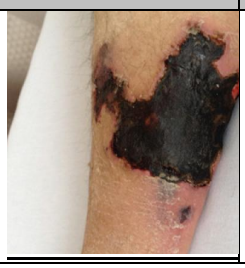
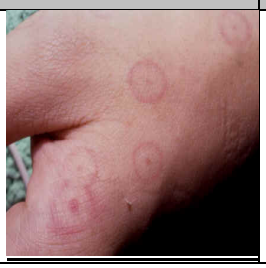
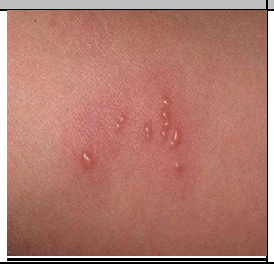
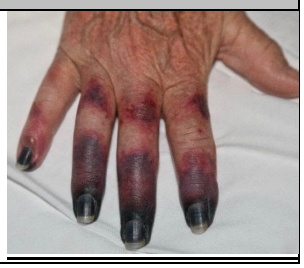
Common Dermatologic Conditions

- **Allergic contact dermatitis**: localized, but may generalize 2/2 autoeczematization (a.k.a. "id reaction", may also occur 2/2 tinea anywhere on the body). Identify and remove suspected trigger. Tx w/ high potency topical steroid for limited BSA (low to mid potency for face). Pred taper (>1wk) for more extensive BSA involvement
- **Eczema/atopic dermatitis**: tx depends on severity. Intense BID/TID moisturization (plain hydrated petrolatum, Cetaphil®, CeraVe®). For affected areas, use mid-strength to super-potent topical steroids BID x 2wks. For face, use least potent to lower mid-strength steroids BID x 1-2wks. Scalp: mid- to high-potency steroid in solution, foam, or oil vehicles. Erosions/fissures: petrolatum or mupirocin ointment BID x 1-2wks
- **Cellulitis**: consider **derm consult if not improved in 48h** to distinguish cellulitis mimickers (30% of cases).
  - Calculate ALT-70. 5-7 = 82.2% likely cellulitis; 3-4 = consider derm c/s if no improvement by 48h with abx. Consult reduces abx use + duration (JAAD 2017;76:618, JAMA Derm 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
  - **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 collab) for: acute wound issues such as limb ischemia, wet gangrene, any wound requiring OR debridement. Consider derm c/s to confirm etiology.

Other Dermatologic Conditions

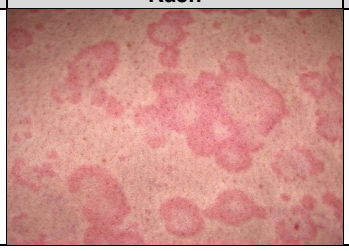
- **Calciphylaxis**: extreme pain (may precede lesion), violaceous retiform patch/plaque → necrosis, ulcer, eschar.
  - Risk Factors: ESRD on dialysis (most common), warfarin, 1° hyperPTH, malignancy.
  - Dx: skin biopsy (gold standard, not always needed); Ca^{2+} x phos product, PTH; bone scan w/ increased uptake
  - Tx: Normalize serum Ca^{2+}, phos, PTH via non-calcium based phos binders (i.e. sevelamer) and cinacalcet; IV sodium thiosulfate; treat 2° infections (death from sepsis), pain control, wound care (Medihoney). D/c warfarin if possible; consider AC if appropriate. Calciphylaxis = indication for HD in CKD pts
- **Cutaneous GVHD**: skin pain/pruritus can precede eruption, acral → central; acute vs. chronic based on morphology, *not* time course.
  - Acute: follicular erythematous papules. Chronic: asteatotic, LP-like, eczematous, sclerodermoid, poikilodermatous.
  - Stage 1: <25% BSA, stage 2: 25-50% BSA, stage 3: >50% BSA, stage 4: erythroderma w/ bullae (TEN-like).
  - Tx: immunosuppression with corticosteroids +/- cyclosporine or tacrolimus, supportive care
- **Herpes simplex virus 1/2**: always confirm w/ DFA or PCR from vesicle base; cx possible but takes long to result
  - Uncomplicated orolabial: primary is usually gingivostomatitis → acyclovir 400mg TID x7-10d; if recurrent → valacyclovir 2000 mg PO q12h x 1d or famiciclovir 1500mg PO x1 at sx onset; periocular skin involvement warrants ophtho c/s to r/o herpetic keratitis
  - Uncomplicated genital (immunocompetent): 1° episode (<72 hr after onset) → valacyclovir 1000mg PO BID x 10d, acyclovir 400mg PO TID x10d, or famciclovir 250mg TID; recurrent episodes (<24hr onset) → valacyclovir 500mg PO BID x 3-5d or acyclovir 400mg PO TID x 5d.
  - Complications: sacral radiculitis (acute urinary retention), proctitis (MSM).
- **Herpes zoster (shingles)**:
  - Uncomplicated, <72 hr (immunocompetent): valacyclovir 1000mg PO Q8H x7d or acyclovir 800 mg PO 5x/d x7-10d.
  - Disseminated: >20 vesicles outside two 1° (non-adjacent) dermatomes; acyclovir 10mg/kg IV q8h; consider immunodeficiency w/u; droplet precautions.
  - Immunosuppressed: acyclovir 10 mg/kg IV q8h; IVFs if hypovolemic/CKD to decrease risk of crystalline nephropathy; obtain DFA/viral culture; monitor for complications (PNA, encephalitis, aseptic meningitis, hepatitis).

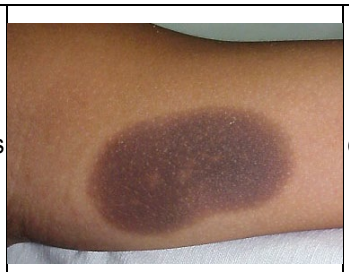
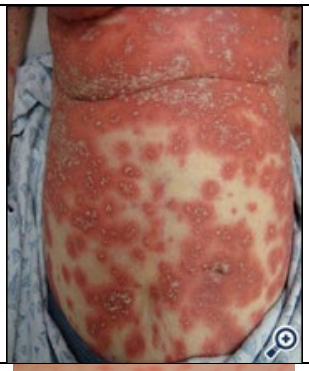
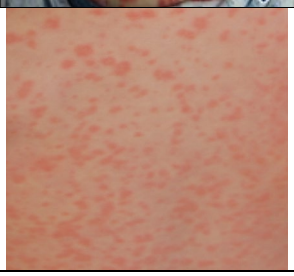
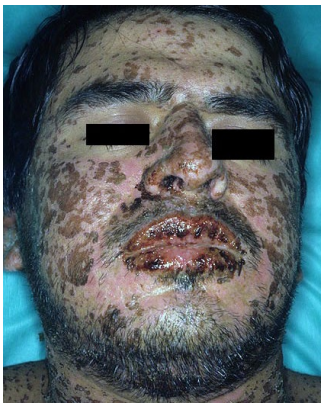
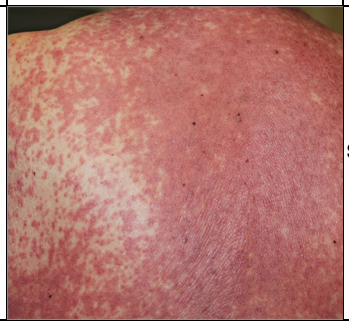
  - Zoster ophthalmicus: urgent ophtho consult if c/f ocular involvement ("Hutchinson sign" = vesicle on nasal tip).
  - Post-herpetic neuralgia: risk ↓ w/ early antiviral treatment (<72 hr); if higher risk (≥50yo w/ mod-to-severe acute pain) consider preventive tx w/ gabapentin 300mg PO QD, titrate up to 3600mg QD, divided TID as tolerated.
  - Consider high lysine, low arginine diet + post-episode vaccination to prevent HSV recurrence.
- **Erythema multiforme**: target lesions (well-defined, circular erythematous macules/papules w/ 3 distinct color zones + central bulla or crust) on palms/soles +/- mucosal involvement occurs within 24-72 hours; persist for 2wks;
  - 90% triggered by infection (HSV, mycoplasma, GAS, EBV); less commonly drug rxn
  - Tx: treat underlying infxn, NSAIDs, cool compresses, topical steroids, antihistamines; systemic steroids only if severe
- **Erythroderma**: diffuse redness >90% BSA.
  - Causes: psoriasis, atopic 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 2º 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); can be unilateral or bilateral
- **Psoriasis**: depends on severity; Short-term tx includes topical steroids, calcipotriene, intense moisturization +/- occlusion w/ plastic wrap; Long-term tx includes phototherapy, acitretin, MTX, biologics w/ outpt derm f/u (JAAD 2011;65:137)
- **Seborrheic dermatitis**: Face: least potent to lower mid-strength topical steroid BID x 1wk and/or ketoconazole 2% cream BID x4wks, then 1-2x/wk for maintenance; 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

Allergic Contact Dermatitis	Calciphylaxis	Erythema Multiforme	HSV	Purpura fulminans
				

Drug Eruptions

- Step 1: Make timeline to determine time course of drug initiation and development of rash
- Step 2: **Discontinue** offending agent. Common drugs for each eruption listed, but **any** drug can be a culprit at any time

	Time Course	Rash	Signs/Sx	Common Drugs	Treatment
Urticaria/ Anaphylaxis	Immediate (min-hr) – delayed (days)		Pruritic, well-circumscribed, erythematous papules/plaques with central pallor. +/- 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 **same location** each time drug ingested. Can evolve to bullae. Oral/anogenital mucosa common sites but can occur anywhere. Usually asx.	Abx (sulfa, TMP, FQs, TCNs), NSAIDs, barbiturates	-Topical steroids if symptomatic
Acute Generalized Exanthematous Pustulosis (AGEP)	2-14 days		Small non-follic. pustules on erythem./edematous plaques, begin on face or intertriginous areas then widespread. Usually w/in 24-48hrs of med exposure. Burning, pruritus common. Fever, marked neutrophilia +/- oral mucosal erosions, facial edema	Abx (PCN, macrolides) **Can occur after only one exposure**	-Anti-pyretic -Topical steroids
Exanthematous/ Morbilliform	4-14d (if prev. exposed to the drug, could be sooner)		Pruritic, erythematous macules/papules. Start on trunk, spread centrifugally to symmetric extremities. May lead to erythroderma. +/- low grade fever	Abx (PCN, sulfa), allopurinol, phenytoin, **requires repeat exposures**	-Topical steroids, antihistamines (Note: may take 7-14d after stopping drug to resolve)
SJS/TEN	4-21 days		Fevers, malaise, myalgias, arthralgias. Pruritic atypical targetoid (amorphous, 2 color zones) macules→ bullae→ desquamation; <10% = SJS, 10-30% = SJS/TEN overlap, >30% = TEN. Mucosal bullae, erosions & crusting, conjunctivitis. + Nikolsky. Complications: 2° infection, resp. compromise, GIB, visual impairment	Abx (esp. sulfa), AED, NSAIDs, allopurinol, phenobarb.	-Cyclosporine (preferred at MGH) -Steroids possible mortality benefit (JAMA Derm 2017;153:514) but controversial -IVIG, anti-TNF **-Burn level care if >30% BSA**
DRESS	3-6 wks		Morbilliform; spreads down symmetric. from face; can see SJS/TEN-like lesions & mucosal involv. Face often swollen/painful (can help diff. from morbilliform drug) Fever, arthralgias, eos, internal organ involv. (liver, kidney; rarely lung, heart), LAD	Abx, AEDs, carbamazepine, ARTs (nevirapine, abacavir)	-Supportive care -IV Solumedrol (decreased risk of bowel edema vs. PO), SLOW taper (3-6 wks)

See *Calling Consults* for details on how to call the appropriate surgical service.

Small Bowel Obstruction: (J Trauma Acute Care Surg 2015;79:661)

- Causes: adhesions from any previous abd surgery, hernias, cancer >> intussusception, volvulus, foreign bodies, stricture
- Dx: abd distension, vomiting, obstipation. Labs normal or hypoK/hypoCl metabolic alkalosis from repeated emesis. Examine for evidence of hernias and **prior abdominal scars**. If severe pain, consider ischemia from strangulation (lactate, leukocytosis).
- Imaging: KUB - air-fluid levels; **CT A/P + PO contrast** - dilated bowel proximal to & decompressed bowel distal to obstruction
- Tx: **NPO**, large bore **NGT** (18Fr) to continuous low wall suction; consider surgical exploration if signs of strangulation/bowel ischemia, s/p gastric bypass (high risk of internal hernia), closed loop obstructions, or if no improvement in 72 hours

Necrotizing Fasciitis: (CID 2007;44:705, Front Surg 2014;1:36)

- Definition: progressive, rapidly spreading infection in deep fascia with secondary necrosis of skin and subcutaneous tissues
- Microbiology: 70-90% of cases are polymicrobial (anaerobes, group A strep, *S. Aureus, Clostridium*, *Peptostreptococcus*, *Enterobacteriaceae, Proteus*, *Pseudomonas*, *Klebsiella*, *Vibrios* spp.), less commonly mono-microbial.
- Clinical signs: **rapidly spreading erythema** (hrs to days) → evidence of soft tissue necrosis; pain disproportionate to exam.
  - Suggestive features: rapid expansion of erythema on serial exams, pain extending beyond border(s) of erythema, dusky/violaceous skin, undermining of skin and subcutaneous tissues, turbid ("dishwater") discharge, palpable crepitus
- Dx: CT + contrast helpful, has a ~95-100% NPV. Labs for **LRINEC** (CRP, WBC, Hg, Na, Cr, Gluc) – score ≥ 6 has a 96% NPV.
- Tx: **IV abx** ([Vanc or Linezolid] + [Pip/Tazo or meropenem] + Clinda to inhibit toxin production) + **urgent surgical consultation**

Ischemic Limb: (NEJM 2012; 366:2198)

- **6 P's P**ain, **P**oikilothermia (cool), **P**aresthesia, **P**allor, **P**ulselessness, **P**aralysis suggest arterial thrombotic/embolic occlusion

Stage	Description	Sensory Loss	Motor Loss	Arterial Doppler	Venous Doppler
I	Viable	None	None	Audible	Audible
II (a/b)	Threatened	Minimal, painful	None or Mild	Variably inaudible	Audible
III	Irreversible	Profound	Profound	Inaudible	Inaudible

- Dx: check and document pulses and/or Doppler signals
  - Obtain ankle-brachial indices, Dopplers at bedside—if stage I, non-urgent, obtain formal studies
- Tx: consider IV heparin; surgical emergency: **consult Vascular Surgery immediately**

Compartment Syndrome (Extremity): (Lancet 2015;386:1299, Musc Lig Tend J 2015;5:18)

- Definition: excessive pressure within a muscle compartment, impairing perfusion
- Etiology: crush injury, ischemia → edema, bleed, etc.
- Clinical signs: tight, tender skin; pain out of proportion to known injuries; **pain with passive ROM**; ↑ lactate or CPK
- Dx: measurement of compartment pressures at bedside using Stryker transducer needle (call Churchill Service for assistance)
  - Arterial flow diminished once compartment pressure within 30 mmHg of DBP, 20 mmHg in hypotensive patients
  - Nevertheless, compartment syndrome is a **clinical diagnosis**, regardless of measured compartment pressure(s)
- Tx: surgical emergency (fasciotomy/decompression); **consult Churchill Surgery immediately**

Abdominal Compartment Syndrome and Intra-Abdominal Hypertension (IAH): (Intens Care Med 2013;39:1190)

- Definition: IAH = IAP >12. Abdominal Compartment Syndrome = IAP > 20 AND clinical evidence of organ dysfunction (e.g. high airway pressures, decreased venous return, elevated CVP/PCWP, ↓UOP/AKI, elevated lactate, acidemia). IAP measured via bladder pressure (most reliable if paralyzed, only done in ICU)
- Typically occurs after massive resuscitation in ICU patients with trauma, burns, s/p liver tx, severe ascites, pancreatitis, sepsis
- Tx: True Abdominal Compartment Syndrome (IAP >20, organ dysfunction despite medical management): **surgical decompression** provides definitive management
  - If IAP 12-20 w/o clinical instability:
    - Evacuate lumenal contents (NGT/rectal tube/enema)
    - Increase pain control/sedation (to level of paralysis if necessary)
    - Head of bed tilted up
    - LVP if ascites
    - Decrease tidal volume, permissive hypercapnia
    - Avoid over-resuscitation

Symptomatic Urolithiasis (kidney stones)

- **Evaluation/management**:
  - Imaging: CT Stone Protocol non-con **(I^-, O^-)**: evaluates position, hydronephrosis, hints at composition
    - Alternative is KUB *and* ultrasound (requires both), with non-diagnostic studies prompting CT
  - UA/UCx: in all patients except those with urostomies. If positive Cx, need decompression with stent by urology or percutaneous nephrostomy (PCN) by IR
  - Rehydration: **NS** @ 150 mL/hr if tolerated → ↑ ureteral peristalsis
  - Alpha-Blockers: **tamsulosin** 0.4mg PO QD (hold for SBP < 90) → ureteral relaxation
  - Analgesia: **opioids** preferred. NSAIDs/Ketorolac more effective but risk of bleeding and AKI
  - Preoperative workup if requiring intervention: NPOpMN, EKG, Coags, T&S
- **Consider urology consult**: solitary or transplanted kidney, DM, immunosuppression, AKI, +UA/UCx, sepsis, inadequate pain control
- **Urosepsis management**: image ASAP, BCx/UCx, urgent Urology consult; IV abx to cover GNRs + enterococcus
- *Clinical Pearl: patients with an acute abdomen lie still, pts with renal colic writhe in pain*

Hematuria / Obstructed Catheter

- DDx: UTI, INR>3, traumatic catheter placement, bladder CA (5th most common neoplasm), upper urinary tract CA, prostate CA
- Workup: "The three C's": 1) **hematuria protocol CT** (3-phase: non-con, arterial phase, delays to assess ureters); 2) urine **cytology** once hematuria clears (blood interferes with test); 3) outpatient **cystoscopy**
- Tx: If obstructed (can't void or catheter not draining / "clot retention") or significant hematuria: **irrigate bladder** via Whistle-Tip catheter using a 60 cc catheter-tipped syringe – flush in and out with saline to remove clots until urine is clear. Then place 3-Way foley on **continuous bladder irrigation** (CBI, AKA Murphy drip)
  - Start CBI after clot extraction; titrate to keep urine cranberry juice color or lighter

Urinary Retention

- **Urethral/bladder pathology**:
  - Etiology: BPH, UTI, constipation, neurogenic (MS, SC injury), DM, immobility, anticholinergics, opioids, benzos, pelvic surg
  - Treatment (improvement may take 3-12 months):
    - Aggressive bowel regimen, treat UTI, minimize narcotics and anticholinergics, encourage ambulation
    - Alpha blockers (finasteride does not help acute retention, takes 4-6 months to work)
    - Clean intermittent catheterization (CIC) with bladder scans to ensure low residual volume vs chronic Foley/SPT
- **Ureteral pathology**: typically external compression on ureter by mass or LN → hydronephrosis. Often due to underlying malignancy, portends poor prognosis. Management depends on GOC, prognosis, GFR, need for nephrotoxic chemo. Options: PCN, ureteral stent.

Urinary Incontinence

- **Classifications**: stress (leakage w/ coughing, etc.), urge (proceeded by urgency), mixed (most common), overflow (PVR >150), functional (neurologic, impaired mobility/cognition)
- **Treatment**:
  - All types: lifestyle interventions, bladder training (timed voiding), Kegel pelvic floor exercises
  - Stress: vaginal estrogen (post-menopausal women w/ vaginal atrophy), pessaries (mixed data), surgery (midurethral sling)
  - Urge: antimuscarinics (oxybutynin, tolerodine, beware of side effects), beta agonists (mirabegron, avoid w/ uncontrolled HTN, ESRD, liver disease), intravesicular botox

Tubes and Drains: see *Tube Management* for placement and management

- **Foley catheter**: *externally placed tube which travels through urethra and into bladder*
  - Call urology if difficulty with placement
  - Foley size: Hx instrumentation or urethral stricture → small Foley (14 Fr or smaller). If elderly man/BPH or difficulty placement → large Foley (18 Fr Coudé or larger). **Coudé catheter** has a gentle upward curve to pass through the prostate
  - Urethral trauma: leave catheter in for at least 5 days to allow for urethral healing
- **Suprapubic tubes (SPT)**: *externally placed tube which travels through the overlying skin and directly into the bladder*
  - Placed by GU IR. Once tract formed (after 1-2 changes by IR), change q6-12wks similar to Foley
  - Staph aureus becomes a more common organism involved in infections
- **Percutaneous nephrostomy tube (PCN)**: *externally placed tube which travels through the overlying skin directly into the renal pelvis*
  - Placed by GU IR usually under local anesthesia. Cannot be coagulopathic, thrombocytopenic, or on ASA/Plavix
  - Urine collects in external bag. If low UOP into bags, passage of blood or concern for malposition - obtain CT A/P, call GU IR
- **Ureteral stent**: *internally placed stent which maintains ureteral patency from level of renal pelvis to bladder*
  - Placed by Urology in OR with general anesthesia, requires change every 3-6 months. May cause urinary urgency. Is NOT changed in setting of infection
- Note: If stents/PCNs/Chronic Foley or SPT/ileal conduit or neobladder – UTIs should be treated only if symptomatic, NOT based on UA/UCx

Consultants ENT

To call an ENT consult: page the ENT consult resident p22220. **To transfer a patient to MEEI**: call MEEI ED at 617-573-3431.

Epistaxis (nosebleed)

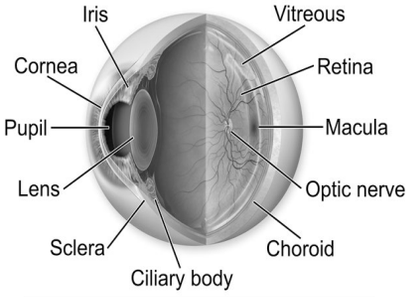
- **Acute management**:
  - Have pt **lean forward**, **pinch nostrils**, hold **pressure for 20 min**
    - Do not lean head back or hold bony part of nose
    - Hold over basin, measure blood loss as possible
    - **Do NOT "peek"** – hold continuous pressure for 20 min
    - Usually a patient will not pinch hard enough – best for RN/MD to do so
  - **Afrin (oxymetazoline 0.025%)** nasal spray (after gently clearing clots)
  - Control SBP (goal < 120) if much > baseline
  - Correct coagulopathy if present
  - **Consult ENT if continued bleed**
    - If bleed visualized, silver nitrate cauterization, nasal packing, or Neuro IR embolization
    - Nasal packing: risk of Toxic Shock very low but may prescribe prophylactic cephalexin or clindamycin; packing typically removed after 5d by ENT (whether inpt or outpt)
- Location: most are anterior bleeds; posterior are more rare/serious/difficult to manage
- Hx: side, duration, EBL, prior episodes (and txs), trauma (fingers, fists, foreign body, etc), prior nasal surgery, nasal trauma hx, FHx or PMHx coagulopathy, nasal tumors, HTN, anticoagulant meds, nasal steroid spray use
- Exam: rapidity of bleeding, inspect nasal septum and oropharynx for originating site; suction clots from OP to protect airway
- Tests: coags, CBC, type & screen; crossmatch pRBC if brisk bleed
- Epistaxis prevention: after resolution, x 2 weeks: **petroleum jelly** (or bactroban if cautery used) inside rims; **no nose blowing/touching**, no exercise, keep head higher than heart (use pillows), sneeze with mouth open, use humidification (**saline nasal spray BID**), **oxymetazoline spray PRN** if re-bleeding

Stridor

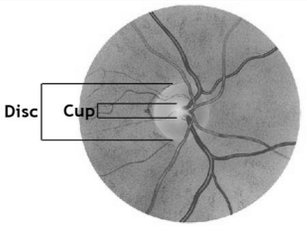
- **Acute management**:
  - **IV access, 100% O2 by non-rebreather**
  - **Racemic epinephrine neb x1 STAT** if concern for supraglottic source**, 10 mg dexamethasone IV x1 STAT**
  - Consider **IM/IV epinephrine** and **Benadryl** if allergy suspected (see *Angioedema & Anaphylaxis*), consider **Heliox**
  - **If unstable → Call RICU & trauma surgery (x6-3333) for possible surgical airway**
  - **If stable → Call ENT for airway evaluation**
- Epinephrine dosing: if allergic reaction suspected: **0.3mg IM (1:1,000 solution)** or 0.1mg IV (1:10,000 solution)
- Hx: timing/evolution, inspiratory/expiratory/biphasic, inciting events, prior episodes, evidence of infection, allergy, hx EtOH/tobacco (cancer risks), hx of known cancer of head and neck, radiation
- DDx (in adults): iatrogenic/post-intubation (laryngeal/vocal cord edema/praxis of the recurrent laryngeal nerve from ET tube); infectious (epiglottitis, laryngitis, laryngotracheitis [croup], bacterial tracheitis, Ludwig's angina); allergic; tumor/mass of larynx or trachea; neurological (vocal cord spasm or immobility); foreign body/trauma
- Imaging: if stable, **CT** with contrast of head/neck/chest to localize source

Acute Sinusitis (Otolaryngol Head Neck Surg 2007;137:S1)

- See *Respiratory Complaints* for outpatient management
- Primarily a **clinical diagnosis**: CT usually not necessary, and CT findings alone (usually) not sufficient as 40% of asymptomatic people have CT abnormalities of sinuses (Otolaryngol Head Neck Surg 1991;104:480)
- Signs/symptoms:
  - Uncomplicated (confined to sinuses): *Major Sx*: facial pressure/pain, purulent nasal discharge, nasal obstruction; *Minor Sx*: fever, cough, malaise, anosmia, dental pain, ear fullness.
  - Complicated (extra-sinus extension): vision changes, proptosis, mental status changes, severe HA, facial soft tissue changes on exam. In immunocompromised or critically ill, consider invasive fungal sinusitis, a surgical emergency. (*See Invasive Fungal Infections*)
- Workup: uncomplicated → no testing required; complicated → CT w/ contrast +/- nasal endoscopy to look for evidence of purulence
  - If needing to rule out invasive fungal sinusitis, nasal biopsy with STAT pathology required
- Inpatient treatment:
  - If requires hospitalization, use levofloxacin or **amp/sulbactam IV** +/- surgery if complicated / drainable extra-sinus collection
  - Invasive fungal sinusitis: **liposomal amphotericin**, surgical debridement, ID consultation



Uvea = iris + ciliary body + choroid



Basic Eye Exam: "Ocular Vital Signs"

- Visual Acuity (e.g. 20/200, CF)
- Pupils (4mm → 2mm OD, No APD)
- Visual Fields
- Extra Ocular Movements
- Intraocular pressure
- Color vision testing (Ishihara cards)

Common Abbreviations:

APD	Afferent pupillary defect	NLP	No light perception (VA)
AT	Artificial tears	NPDR	Non-prolif. diabetic retinopathy
cc/sc	With/without refractive corr.	NS	Nuclear sclerosis (i.e. cataract)
CE	Cataract extraction	OD/OS	Right eye, left eye
CF	Count fingers (VA)	OU	Both eyes
CWS	Cotton wool spot	PDR	Prolif. diabetic retinopathy
DES	Dry eye syndrome	PF	Pred Forte gtt (prednisolone)
EOM	Extraocular movement	PFAT	Preservative-free artificial tears
HM	Hand motion (VA)	PVD	Posterior vitreous detachment
IOL	Intraocular lens	RD	Retinal detachment
IOP	Intraocular pressure	SLE	Slit lamp exam
LP	Light perception (VA)	SPK	Superficial punctate keratitis/dry eye
MGD	Meibomian gland dysfunction	VA, VF	Visual acuity, fields

To call an Ophtho consult: **check vision using vision card and pupils *prior* to calling consult!**
General inpatient consult: **page 21004;** can also call MEEI ED back desk **617-573-4063**

High-Yield Pearls for the Wards

- **Vision loss**: acute (requires urgent evaluation) vs. chronic (outpt referral) – assess patient with their glasses on!!
- **Glaucoma drops**: prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, or alpha 2 agonists – all lower IOP
  - *If brand-name drops unavailable, fractionate combo meds, ask pharm for substitution advice, or have pt bring in home meds*
- **Ophthalmoscope**: available on most floors. Tropicamide (dilating drop) is available to order. Can make pt light-sensitive for 4 hours.
- **Dilating drops**: 0.5% tropicamide (parasympathetic antagonist), 1-2 drops placed 15-20 minutes before exam
- **Finding the retina:** dilate the eye and use the ophthalmoscope as in http://stanfordmedicine25.stanford.edu/the25/fundoscopic.html

Common Eye Pathology

- **Red Eye**: typically benign; **refer to ophtho** if no improvement or any "ocular vital sign" changes (see above)
  - **Viral conjunctivitis**: eyes "stuck shut" in AM, itchy, crusty discharge, ± URI symptoms, ± pre-auricular nodes, winter time
    - Tx: supportive/isolation (typically adenovirus, highly infectious). Wash hands thoroughly if you suspect this!
  - **Allergic conjunctivitis**: olopatadine 0.1% gtt bid x 5d. Clear Eyes/Visine not rec'd (rebound redness 2/2 alpha agonism)
  - **Anterior uveitis**: pain and true photophobia **must** be present ± eye injection. **Refer to MEEI ED**.
  - **Contact lens keratitis**: have patients remove contact lens when admitted! Use glasses. P/w red/uncomfortable eye; infection until proven otherwise. **Refer to MEEI ED**.
- **Blepharitis** (inflammation of eyelids): p/w crusting/red eye/gritty feeling
  - Tx: baby shampoo, warm compresses, abx ointments x 2 weeks, then daily lid hygiene. Tx for **hordeolum ("stye")** is same.
- **Dry Eye Syndrome (DES)**: p/w eye pain or "grit"/paradoxical tearing ± vague "blurriness."
  - Tx: artificial tears q1h prn first line tx, refer if no improvement
- **Corneal abrasion/exposure keratopathy**: unilateral, redness, mild light sensitivity, common after sedation
  - 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 24 hrs.
- **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**. Will likely require vitreoretinal surgery.
- **Subconjunctival hemorrhage**: blood between conjunctiva and sclera from ruptured vessel. No vision changes, not painful. Can be 2/2 associated blood dyscrasia, valsalva, trauma, spontaneous. Will resolve spontaneously. No need to consult ophtho.
- **Endophthalmitis**: infection within globe. Can be 2/2 trauma, surgery, or endogenous source (bacteremia/fungemia).
  - Tx: Ophtho c/s, antibiotics/antifungals that will penetrate blood-brain barrier. May require vitrectomy (surgery).

How to Consult

- **Obstetrics**: if pt has pregnancy >20wk or has established MGH OB provider. If hCG⊕ but no confirmed intrauterine pregnancy, should be followed on **ectopic list**
- **GYN Onc**: if pt has biopsy confirmed GYN malignancy or established GYN onc provider
- **GYN**: everyone else (e.g. pregnancy <20wk, undifferentiated ovarian mass)

Abnormal Uterine Bleeding

- Postmenopausal bleeding is never normal. If premenopausal, rule out pregnancy and its complications (e.g. ectopic, miscarriage)
- **History**: verify source of bleeding is vaginal, duration and quantity (#soaked pads), associated sx (pain, dizziness), triggers (e.g. postcoital), trauma hx
  - LMP/menstrual hx, full pregnancy hx, known GYN conditions (e.g. fibroids), meds (hormones, AC), h/o coagulopathy
  - **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.

Differential Diagnosis for Abnormal Uterine Bleeding	
Pregnant	**Ectopic pregnancy**, miscarriage, implantation of pregnancy, subchorionic hematoma, placental abruption, placenta previa/accreta, vasa previa, trophoblastic disease, cervical/vaginal/uterine pathology (e.g. polyp)
Not pregnant	Endometrial/cervical polyp, adenomyosis, fibroids, **endometrial hyperplasia/cancer**, coagulopathy, ovulatory dysfunction, cervical cancer, thyroid disease, vaginal/vulvar etiologies (e.g. laceration, atrophy)

- **Workup**:
  - CBC, T&S, coags, pad count (Epic order, monitors bleeding quantity)
  - If premenopausal, first step is **urine hCG**
    - If ⊕, obtain **serum quant. hCG** (more sensitive for early pregnancy) and **pelvic U/S** (must **rule out ectopic pregnancy** in all pregnant women with bleeding)
    - If U/S nondiagnostic (i.e. intrauterine pregnancy not confirmed), measure serial **serum hCG q48h** (should increase 35-50% in 48h) and repeat pelvic U/S
  - If postmenopausal, **endometrial biopsy** (difficult to do inpatient) or **pelvic U/S** (biopsy if endometrial lining >4mm)

Pregnancy and Its Complications

- Nomenclature: gravida/para (GP), G= #pregnancies, P= #births; TPAL (T=term births, P=preterm births, A=abortions, L=living children)
- **Preeclampsia**: **new onset HTN** + significant end-organ dysfunction +/- **proteinuria** after **20 wks gestation**
  - Preeclampsia with severe features: BP >160/110 *OR* BP >140/90 with one of following: 1) new onset cerebral/visual sx (**photophobia**, **severe HA**, **AMS**), 2) RUQ/**epigastric pain**, 3) plt <100k, 4) Cr >1.1, 5) **pulmonary edema**
  - **Eclampsia** = preeclampsia + grand mal **seizures**
  - **Labs**: BMP, LFTs, CBC with diff, LDH, smear, urine protein/Cr ratio or 24hr urine protein
  - Can develop **postpartum** (2 days - 6 weeks)
  - **Stroke** is the most serious complication (most commonly hemorrhagic stroke)
  - **Treatment**: **delivery** = definitive; antihypertensives only if BP >150/100 (IV labetalol, hydralazine)
    - **Magnesium sulfate** for seizure prophylaxis (Lancet 2002;359:1877) initiated at onset of labor
      - Contraindicated in myasthenia gravis, use cautiously in pulm edema
      - 6g load + 2g/hr gtt (goal 4.8-8.4), reduce maintenance dose if renal insufficiency
      - Monitor for **Mg toxicity** q1-2h (loss of reflexes, ↓RR, somnolence, HoTN, bradycardia, ECG changes); antidote = **calcium gluconate**
- **HELLP syndrome**:
  - **Symptoms**: rapid onset abdominal pain (epigastric, RUQ), n/v, HA in pt >28 weeks gestation
  - Many patients also have HTN and proteinuria
  - **Labs**: BMP, LFTs, CBC with diff, LDH, haptoglobin, smear, urine protein/Cr ratio, coags
  - **Dx**: **hemolysis** (at least 2: smear w/ schistos and burr cells, bilirubin >1.2, low hapto or ↑ LDH 2x ULN, severe anemia not related to blood loss), **elevated liver enzymes** (AST or ALT >2x ULN), **low platelets** (<100k)
  - **Treatment**: **delivery** = definitive; **magnesium** (as above) for seizure prophylaxis; blood/plt transfusion if bleeding

Radiology Contact Information

Main Number
617 – (643 / 724 / 726) – XXXX

Reading Rooms	
Dodd Reception	44212
Teleradiology	44270
Cardiac CT	47132
Cardiac MRI	66947
Chest CT	33899
CXR Inpatient	42051
CXR Outpatient	62197
ED	41533
ED Neuro	68188
GI CT	65162
GI Fluoro/KUB	32605
GI MR	49919
GI US White 2	60595
GI US Yawkey 6	31577
IR (GI & VIR)	34723
Mammography	40228
MSK	40516
Neuroradiology	41931
Nuclear Cardiology	43600
Nuclear Medicine	61404
Pediatrics	42119
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
Pediatrics	61367
PET	64209
Scheduling	4XRAY
US White 2	53074

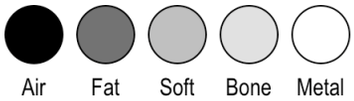
On Call Pagers	
Cardiac CT	22122
Cardiac MRI	33133
IR GI/GU	34071
IR Neuro Spine	33722
IR Neuro Vascular	21154
IR Vascular	38553
Mammography	20022
MSK/MSK IR	36321
Neuro ED	39991
Neuro Inpatient	32535
Nuclear Medicine Resident	On call
Pediatrics	On call

Consults – Weekdays	8am	12pm	5pm	7pm	8am
Cardiac CT	Dodd				XXXXXXXXXXXXXXXXXXXXX
Chest	Dodd				ED
GI	Dodd				ED
Neuro	Neuro Consult (730am – 430pm)			Neuro ED	
Vascular	Dodd			ED	
Other	Reading Room			ED	

Consults – Weekends & Holidays	8am	12pm	5pm	7pm	8am
Cardiovascular	Dodd		ED		
Chest	Dodd			ED	
GI	Dodd			ED	
Neuro	Neuro ED				
Other	ED				

- **Life Images**
  - Upload images to lifeIMAGE and Epic: Partners Applications → utilities → MGH Upload Image to Radiology (LifeImage) → Access LifeImage → find exam on CD/DVD → upload images
  - Send images to MGH PACS: upload to MGH → request read
  - Retrieve images from The Cloud: ISDrequests.partners.org → file an urgent ticket
  - Additional information:
    - Urgent reads: contact ISD **(p34188, x30003)**
    - Multiple body parts: interpretations only given for selected body parts
    - Multiple LifeImages of the same body part: upload all images → request a read only on the most recent
    - Exams will not be read if: requisition was for a different body part than the uploaded images; study >6 months old; a more recent LifeImage is available; US, fluoroscopy, or mammography

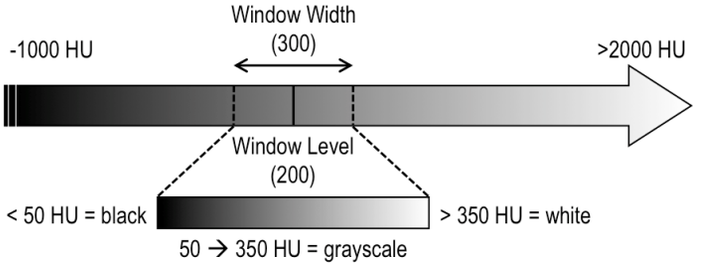
- **X-ray**:

5 Radiographic Densities

Air Fat Soft Tissue Bone Metal

Silhouette Sign: loss of the margin between two opposing structures of the same radiographic density	
• RUL – right paratracheal stripe	• LUL – aortic arch
• RML – right heart border	• Lingula – left heart border
• RLL – right hemidiaphragm	• LLL – left hemidiaphragm

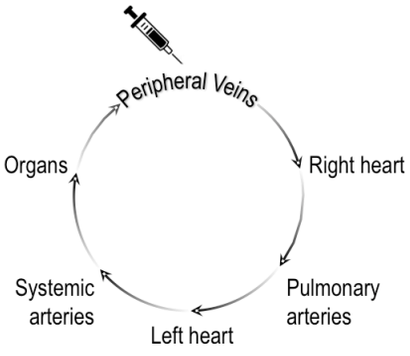
- **Computed Tomography (CT)**:
  - Hounsfield Units (HU): measurement of CT attenuation
  - Windowing and leveling: adjusting contrast and brightness to highlight structures
    - Window (contrast): range of Hounsfield units displayed across the grayscale
      - Wide window – best for large differences in attenuation
      - Narrow window – best for subtle differences in attenuation
    - Level (brightness): HU that corresponds to mid-gray
      - High level – best for structures with high attenuation
      - Low level – best for structures with low attenuation

Substance	HU
Air	-1000
Fat	-100
Water	0
Blood	50
Soft tissue	100
Bone	1000
Metal	>2000

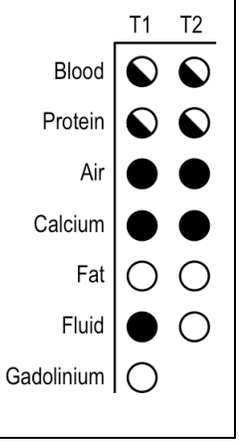


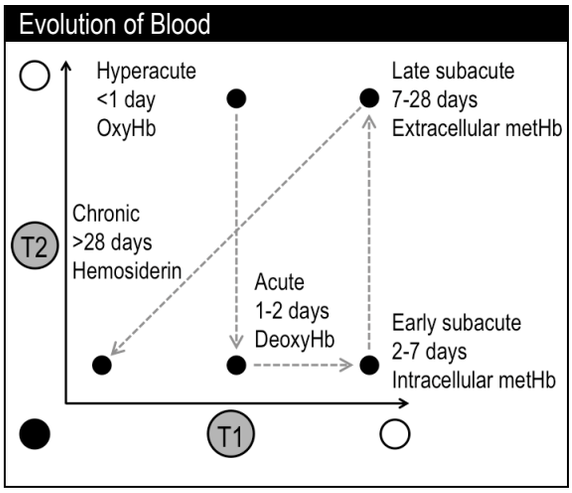
  - Phases of contrast:

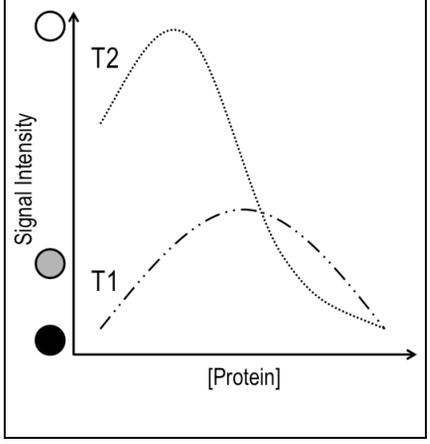
Phase	Time After Injection	Structures Evaluated
CTPE	15 s	Pulmonary arteries
Arterial (CTA)	30 s	Aorta, systemic arteries, renal cortices
Late arterial	60 s	Routine chest
Portal Venous	70 s	Routine abdomen
Nephrographic	100 s	Renal medulla
Venous	120 s	Peripheral veins
Delayed (Urogram)	10-15 min	Ureters, bladder



- **Magnetic Resonance Imaging (MRI)**:

T1 & T2 Signal

T1 T2 Blood Protein Air Calcium Fat Fluid Gadolinium

Evolution of Blood

Hyperacute <1 day OxyHb; Late subacute 7-28 days Extracellular metHb; Chronic >28 days Hemosiderin; Acute 1-2 days DeoxyHb; Early subacute 2-7 days Intracellular metHb; T2; T1

Protein Signal

T2 T1 Signal Intensity [Protein]

  - MRI safety:
    - Device compatibility: www.mrisafety.com

- **Indications**:
  - IV: whenever possible, particularly for **infection, tumors, and vessel imaging**
  - PO positive (hyperdense): bowel obstruction, bowel wall pathology, differentiate bowel from other abd. structures
  - PO negative (hypodense): inflammatory bowel disease, GI bleed, mesenteric ischemia
  - Rectal: appendicitis, penetrating abdominal trauma
- **Pregnancy and breast feeding**: (ACR 2020)
  - Pregnancy:
    - *Iodinated*: no need to withhold contrast (no data to suggest potential harm to fetus)
    - *Gadolinium*: unknown risk to fetus → consider noncontrast or alternative study
  - Breast feeding: mother's informed decision to "pump and dump" for 12-24 h after scan
- **Renal function**: (ACR 2020, MGPO 2020)

	Contrast Induced Nephropathy	Nephrogenic Systemic Fibrosis
Risk factors	Age >60 years, dialysis, kidney transplant, single kidney, renal cancer, renal surgery, HTN on medication, DM, metformin	Dialysis, kidney transplant, single kidney, renal cancer, renal surgery, HTN on medication, DM
Screening (At risk pts only)	Outpatient: GFR within 30 d Inpatient: GFR within 24 h	Outpatient: • GFR 45-59: GFR within 6 wks • GFR <45: GFR within 2 d Inpatient: GFR within 2 d
Prevention	**GFR ≥ 30: contrast per protocol (NO PREHYDRATION RECOMMENDED)** GFR < 30: non-contrast or alternative study • If necessary → consult radiology	**GFR ≥ 30: gadolinium per protocol** GFR < 30: non-contrast or alternative study • If necessary → consult radiology and nephrology, obtain informed consent
Dialysis pts	HD within 72 h after scan	Prompt post-scan HD (PD inadequate)
Repeat studies	Decision is clinical and subjective Insufficient evidence to hold contrast for 24 h	No risk factors: proceed At risk pts: consult radiology
Metformin	GFR ≥ 30: continue metformin GFR < 30 or AKI: hold for 48 h after scan	No need to hold metformin

- **MGH prehydration protocol** (*prophylaxis only indicated when GFR < 30*): (MGPO 2020)
  - PO (preferred): 1-2 L PO non-caffeinated beverage 12-24 h prior to scan
  - IV (outpatient): NS 250 mL IV bolus @ 1 h prior to scan
  - IV (inpatient): NS 100 mL/h IV 6-12 h before and 4-12 h after scan (ACR 2020)
- **Contrast reactions**: (ACR 2020)

	Allergic	Physiologic
Mild	Limited urticaria Itchy throat Nasal congestion URI symptoms	N/V, flushing/warmth HA/dizziness Mild HTN Transient vasovagal reaction
Moderate	Diffuse urticaria Facial/laryngeal edema w/o dyspnea or hoarseness Bronchospasm w/o hypoxia	Protracted N/V HTN urgency Isolated CP Vasovagal reaction requiring tx
Severe	Anaphylaxis Facial/laryngeal edema w/ dyspnea or hoarseness Bronchospasm w/ hypoxemia	HTN emergency Arrhythmia Seizure Protracted vasovagal reaction

Indications for Premedication
• **Prior mild-moderate allergic reaction**
• None for prior physiologic reactions
• None for shellfish allergies
• No cross-reactivity between iodinated contrast and gadolinium

- **Adult premedication protocol**: (ACR 2020)
  - Elective (13 h protocol)
    - **Prednisone 50 mg PO @ 13, 7, and 1 h prior,** *AND*
    - **Diphenhydramine 50 mg PO @ 1 h prior**
  - Accelerated (4-5 h protocol)
    - Methylprednisolone 40 mg IV now and q4h until scan, *AND*
    - Diphenhydramine 50 mg IV @ 1 h prior
  - Emergent (1 h protocol) – no evidence of efficacy, only if no alternatives
    - Methylprednisolone 40 mg IV @ 1 h prior, *AND*
    - Diphenhydramine 50 mg IV @ 1 h prior

Corticosteroid Dose Equivalents
Prednisone 50 mg PO
Hydrocortisone 200 mg
Methylprednisolone 40 mg
Dexamethasone 7.5 mg
PO:IV 1:1

Ordering Studies:
- **All cross-sectional studies are protocoled by radiology** – simply provide the necessary information:
  - Body part and modality
  - Indication: clinical history relevant to the study (GOOD HISTORIES IMPROVE INTERPRETATIONS)
  - Contrast: "per radiology discretion" unless *specific* reason otherwise
  - Contraindications for contrast: kidney injury or prior allergic reaction (see *Contrast*)
  - Questions: call the appropriate division or page the appropriate on-call radiologist (see *Contact Information*)
- **Level of Urgency**:
  - Routine: order of interpretation depends on acquisition time
  - Urgent: takes priority over routine studies
  - STAT: **means NOW, high acuity/life threatening emergencies**
    - Patient must be ready for immediate transport
    - Patient must be accompanied by a responding clinician capable of providing emergency care
    - Responding clinician must be present for the entire exam
    - Radiology will provide preliminary read: phone call for XR/US, at the scanner for cross-sectionals

Overnight Reads:
- Studies with full interpretations overnight: all ED studies, STAT studies, and acute CT PEs
- Verbal preliminary reads:
  - Typically done for **ICU studies only**
    - **Inpatient studies** are only reviewed overnight if there is an **urgent clinical question** (i.e. one that would alter overnight management). Consider face-to-face consult in ED.
  - After communication w/ the primary team, all verbalized prelim reads will be documented in the chart
  - A full interpretation will be generated the following morning for all prelim reads

ED Protocols:
- Trauma: I+, single phase (arterial for chest, portal venous for abdomen/pelvis – images checked at the scanner by radiology for possible delays)
  - Blunt trauma: includes bone kernel reformats for improved visualization of bones
  - Penetrating trauma: O+R+ for increased sensitivity of bowel injury
- Cervical spine: I-, need for CTA determined by radiology, bone kernel reformats in all 3 planes
  - Images checked at the scanner by radiology only if IV contrast is required for another body part
- Appendicitis: I+ and O+/R+ (please specify PO or PR), kidneys through pelvis only
- Neuro ED: call reading desk @ x68188

Cardiovascular Protocols:
- DVT imaging: U/S (LENI) is initial test of choice (Cardiovascular Diagnosis and Therapy 2016;6:493)
  - CTV/MRV: primarily used for central venous thrombosis when initial U/S is equivocal or non-diagnostic
- Arterial imaging:
  - CTA: three phases (noncontrast, arterial, delays) → stenosis, dissection, aneurysm
  - Requisition: specify vessel of interest, field of view, and indication
- Coronary CTA:
  - ECG-gated study of the heart → only performed by CV CT on-call radiologist during normal hours
  - Specify if body parts other than the heart should be imaged (thoracic aorta, CABG grafts, etc.)
- Other EKG-gated CTAs:
  - Indications: any evaluation of the heart or ascending aorta
  - EKG-gating is unnecessary for the descending thoracic aorta, abdominal aorta, and pulmonary arteries
- Noncontrast vascular studies:
  - RP hematoma, pre-op aortic calcifications, coronary calcium score, follow-up aortic size

Thoracic Protocols:
- All chest CTs are high resolution – traditional "high res chest CT" is now the diffuse lung disease CT (see below)
- Routine chest vs CT PE vs CTA chest:
  - Routine chest: single phase (late arterial) → workhorse protocol
  - CT PE: single phase (pulmonary arterial) → pulmonary arteries
  - CTA chest: three phases (noncontrast, arterial, delays) → systemic arteries
- Double rule out studies:
  - Clinical concern for PE and aortic dissection
  - Contrast can only be optimized for one (must pick CT PE or CTA)

- Diffuse lung disease (a.k.a. misnomer "high res CT"):
  - Indications: ILD, lung transplant, air trapping
  - Inspiratory and expiratory images, plus prone images to differentiate between atelectasis and fibrosis
- Nodule follow-up: (Radiology 2017;284:228)
  - Indications: incidental nodule on prior CT, age >35 y, AND no history of malignancy or recent infection
  - Fleischner Society 2017 Guidelines

GI/GU Protocols:

- Stone protocol: I-O-, low dose
  - Order contrast-enhanced CT if there is concern for ANYTHING else (stones may still be visualized)
- Routine abdomen/pelvis vs renal mass vs bladder cancer vs hematuria:
  - Routine abdomen/pelvis: I+O+, single phase (portal venous) → workhorse protocol
  - Renal mass: I+O+, two phases (noncontrast, nephrographic), abdomen only → renal masses or cysts
  - Bladder cancer: I+O+, two phases (portal venous, delayed) → workup or monitoring of GU malignancy
  - Hematuria: I+O-, "three" phases (noncontrast, nephrographic, urogram) → hematuria, hydronephrosis
- CT urogram vs CT cystogram:
  - Urogram: antegrade filling of ureters and bladder with IV contrast (delayed phase)
  - Cystogram: retrograde filling of bladder with contrast via Foley catheter → evaluation of bladder rupture
- Arterially-enhancing tumors:
  - MR CHIT: melanoma, RCC, choriocarcinoma, HCC, islet cell (neuroendocrine) tumors, thyroid
- Does my patient need to be NPO?
  - IV contrast CT: 2 h Abdomen/pelvis CT: 8 h Non-contrast CT: no NPO
- Fluoroscopy protocols:
  - Requisition: specify indication, h/o surgery or aspiration
  - Barium swallow vs modified barium swallow vs UGI series vs SB follow-through:
    - Barium swallow: esophagus, GE junction, proximal stomach → dysphagia, GERD
    - Modified barium swallow: mouth, pharynx, upper esophagus → dysphagia, aspiration
    - UGI series: barium swallow plus stomach, pylorus, and duodenal bulb → bariatric surgery
    - SB follow-through: small bowel, terminal ileum, and proximal LB +/- UGI series beforehand

Neuroradiology Protocols:

- Inpatients: page Neuro IP on-call radiologist @ p32535
- Acute stroke:
  - Inpatients/ICU: page acute stroke consult fellow @ p21723
  - ED: activate ED2CT via the group pager
- Head CT: typically noncontrast
  - Indications for contrast-enhanced head CT: infection and/or tumor AND contraindication for brain MRI
- Spine MRI: for more than 1 segment, please order total spine and specify indication
  - Separate MRIs should not be ordered prior to neurology/NSGY consult
- Fluoroscopy-guided LPs: performed by neuroradiology fellows, NOT neuro IR
  - Indications: difficult anatomy, and only after LP is attempted on floor
    - Not to be used as an anesthesia service for unruly patients (typically performed without conscious sedation, although this can be arranged if required for patient safety)

Musculoskeletal Protocols: if questions: page MSK IR on-call radiologist @ p36321

Nuclear Medicine Protocols:

- Overnight studies:
  - Tagged RBC study: BRBPR (NOT guaiac positive stools, melena, or massive bleeding)
    - Requirements: consult IR first for possible angiogram if study is positive
  - VQ scan: acute PE (NOT chronic PE), ONLY if results will alter management (i.e. AC tonight)
    - Requirements: CXR within 24 h, patient stable for duration of scan (~4 h)
  - HIDA scan: acute cholecystitis, ONLY if results will alter management (i.e. OR tonight)
    - Requirements: NPO 4-24 h prior to study, no opiates 12-24 h prior to study, bilirubin <10
- PET:
  - Fasting: hold everything but meds and water
    - Overnight is ideal, but AT LEAST 6 hours for non-DM patients
    - AT LEAST 4 hours for DM patients
      - Continue long-acting insulin, hold short-acting insulin 4 h prior to scan
  - Blood sugar thresholds: FDG-PET brain < 175 mg/dL, FDG-PET whole body < 250 mg/dL

Chest X-Ray

1. **Line placement:**
   - SVC: between right tracheobronchial angle and right heart border (Chest 1998;114:820)
   - Cavoatrial junction: two vertebral bodies below the carina (JVIR 2008;19:359)
   - Line positioning:
     - Central line: tip in the SVC or at the cavoatrial junction
     - HD catheter: tip in the right atrium
   - Post placement: check for pneumothorax (see below)
2. **Pneumothorax**:
   - Sensitivities:

Imaging Position	Detectable PTX Size	Imaging Findings
Supine/Portable	500 cc	Deep sulcus sign, lucency along mediastinal border
Upright	50 cc	Sharp visceral pleural line, absence of distal lung vessels
Lateral decubitus	5 cc	Nondependent collection of air

   - Tension: contralateral mediastinal shift, collapse of ipsilateral lung, flattening of ipsilateral hemidiaphragm, widening of ipsilateral rib spaces
   - Artifacts that mimic visceral pleural lines: (BMJ 2005;330:1493)
     - Medial border of scapula: in continuity with rest of bone
     - Skin folds: form an interface (not a line), extension beyond rib cage, presence of distal lung vessels
3. **Pulmonary edema**:
   - Vascular redistribution (first sign): increased caliber of pulmonary vessels in upper lobes (cephalization)
   - Interstitial edema: increased interstitial opacities, indistinctness of pulmonary vasculature, Kerley B lines, peribronchial cuffing
   - Alveolar edema: perihilar/central opacities, pleural effusions, cardiomegaly
   - Pearls: typically bilateral and symmetric, rapid appearance/resolution of radiographic findings
   - Pitfalls: low lung volumes can mimic increased interstitial opacities

Abdominal X-Ray (KUB)

1. **Line placement:** (Pediatric Radiology 2011;41:1266)
   - GE junction: within 1 vertebral body of the T10-T11 disc space, <16 mm from left spine border
   - Pylorus: C-loop of duodenum is only reliable indicator of post-pyloric placement
     - Right side of spine is unreliable
   - Line positioning:
     - Decompression: gastric fundus or dependent portion of stomach
     - Feeding: distal duodenum or proximal jejunum
   - Post placement: check for endobronchial placement
2. **Small bowel obstruction:** (RadioGraphics 2009;29:423)
   - **KUB**: preferred initial examination
     - Assess for: small bowel dilatation >3 cm, air-fluid levels, stacked loops of bowel, transition point
   - **CT**: equivocal cases or for further evaluation
     - Assess for: SB dilatation, collapse of distal bowel loops, transition point
     - Severity:
       - Partial: passage or air or contrast beyond the obstruction
       - High grade partial: 50% difference in caliber between dilated and collapsed SB loops
       - Complete: no passage of air or contrast beyond the obstruction
     - Transition point: look for small-bowel feces sign (fecal material mixed with gas bubbles in small bowel)
     - Cause: adhesions, Crohn's, malignancy, hernias
     - Complicated SBO:
       - Closed loop obstruction: radially oriented bowel loops, engorged mesentery, whirl sign
       - Strangulation: bowel wall thickening, lack of bowel wall enhancement, pneumatosis intestinalis, portal venous gas
4. **Pneumoperitoneum**: (AJEM 2009;27:320)
   - Upright: air beneath the diaphragm
   - Left lateral decubitus: air over the liver
   - Supine (insensitive):
     - Anterior superior oval sign: gas bubbles projecting over liver
     - Hyperlucent liver sign: free air overlying liver
     - Rigler's sign: air on both sides of the bowel wall

- Falciform ligament sign: linear density projecting over liver

Ultrasound

1. **Cholecystitis**: (AJR 2011;196:W367)
   - U/S is preferred initial examination
   - Gallstones: echogenic foci with posterior shadowing
   - Common findings: gallbladder wall thickening >3 mm, gallbladder distension >40 mm, peri-cholecystic fluid
   - Sonographic Murphy's sign: 92% sensitivity (analgesics reduce sensitivity)
   - Gallstones and gallbladder wall thickening: 95% positive predictive value for acute cholecystitis
2. **Deep venous thrombosis**: (Cardiovascular Diagnosis and Therapy 2016;6:493)
   - Compression U/S: noncompressibility of vein, echogenic thrombus within vein, venous distension
   - Venous duplex U/S: absence of color Doppler signal within vein, loss of flow phasicity, loss of response to augmentation maneuvers
   - CT venogram:
     - Alternative to U/S in critically ill patients who have undergone CT PE
     - Pros: evaluation of pelvic veins and IVC, which are difficult to assess on U/S
     - Cons: invasive, requires contrast, radiation, possible streak or mixing artifacts

Cross sectional imaging: For anatomy, http://www.radiologyassistant.nl/.

CT Head
1. Brain parenchyma a. Mass lesion: brain windows b. Intracranial hemorrhage: brain and subdural windows c. Infarction: stroke windows 2. Vessels 3. CSF spaces: ventricles, sulci, cisterns 4. Midline shift or herniation 5. Soft tissues (great place to start for trauma head CTs) 6. Bones/sinuses

MRI Brain
1. Brain parenchyma a. Mass lesion: T1, T2, FLAIR b. Intracranial hemorrhage: SWI, T1, T2 c. Infarction: DWI, ADC 2. Vessels: T2 for flow voids, T1 post-contrast, TOF if noncontrast MRA 3. CSF spaces: T2 4. Midline shift or herniation: coronals helpful 5. Soft tissues 6. Bones/sinuses

CT Chest
1. Lines and tubes (scout can be very helpful) 2. Abdomen 3. Soft tissues 4. Bones 5. Heart and mediastinum: thyroid, lymph nodes, heart and pericardium, major vessels, esophagus 6. Pleura: pleural effusion, pneumothorax 7. Lungs: secondary pulmonary lobule is the key a. Radiology Assistant → Lung HRCT Basics

MRCP
1. Choledocholithiasis: hypointense filling defect within CBD surrounded by hyperintense bile

CT Abdomen/Pelvis
1. Lung bases 2. Liver/gallbladder: focal lesions, biliary ductal dilatation 3. Spleen 4. Pancreas: focal lesions, pancreatic ductal dilatation 5. Adrenals 6. Kidneys/ureters: hydronephrosis, stones, focal lesions 7. Bladder/pelvic organs 8. Peritoneum: free air or fluid 9. Lymph nodes 10. Vessels 11. GI tract: bowel distension, bowel wall thickening 12. Soft tissues 13. Bones

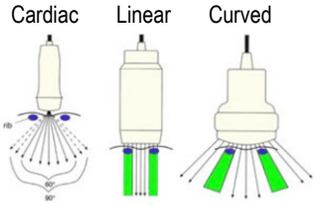
Equipment (NEJM 2011;364:749)

Basic Terminology:

- Frequency: 1Hz = 1cycle/sec; medical U/S typically between 2-15MHz (derm U/S up to 100MHz)
  - High frequency (>5MHz): ↑ resolution, shallow tissue penetration. **Ideal for vascular, skin, breast, thyroid**.
  - Low frequency (2–5MHz): ↓ resolution, deeper tissue penetration. **Ideal for abdominal, OB/GYN, cardiac**.
- Gain: signal amplification; similar to brightness control
- Depth: depth of field of view (FOV). Excessively large FOV ↓ spatial resolution; tight FOV limits view of nearby structures.
- Attenuation: reduced signal transduction through a medium = ↓ signal intensity behind it (bone/air have high attenuation)

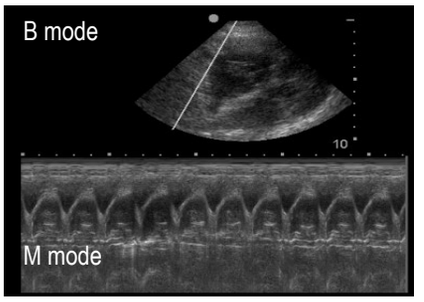
Transducer (**probe**): converts electricity into sound waves → transmits sound wave into tissue → receives sound waves echoed back from tissue**.** Indicator (denoted by light or notch on probe) displays on **left of the screen**. *Exception*: echocardiography → indicator displays on **right side**. Ensure have probe positioned appropriately.

- PHASED-ARRAY (cardiac) probe: good for looking in small windows (i.e. between intercostal spaces for cardiac or pulm imaging); low resolution, produces fan-like image.
- LINEAR (vascular) probe: good for shallow structures (i.e. vascular, soft tissue). Uses high frequency with good resolution, produces rectangular image.
- CURVED (abdominal) probe: good for deeper structures (i.e. intra-abdominal). Uses lower frequency; combines linear and sector probe image qualities.



Commonly Used Modes

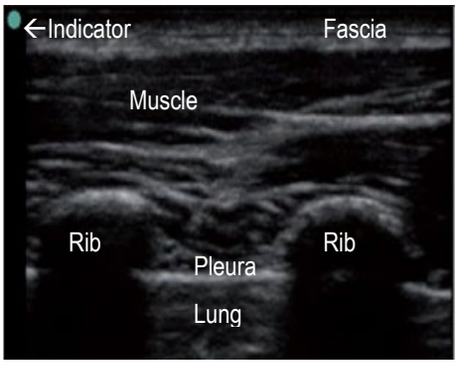
- B-mode (brightness mode): standard 2D gray-scale image.
- D-mode (doppler): detects flow to or away from transducer. Useful to find and define vessels, flow across valves
  - Color → direction and velocity are color coded and superimposed on B-mode image. "BART" (Blue is Away from probe, Red is Towards)
  - Power → detects very low flow but not direction, useful in vascular compromise
  - Spectral → velocity presented graphically on a timeline
- M-mode (motion mode): takes a slice of a B-mode image over time. Often used in TTE. Useful to assess lung sliding for pneumothorax.



General Imaging Concepts

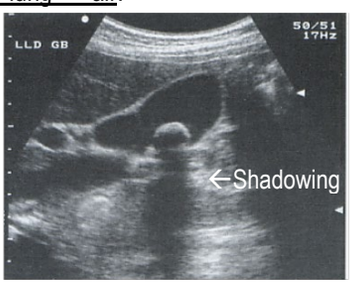
Typical Appearance of Normal Tissue:

- Skin and pleura are smooth and brighter than surrounding tissue (echogenic or hyperechoic)
- Fat and muscle are dark, though varies depending on the tissue (hypoechoic)
- Fluid (e.g. blood, effusion) appears black on ultrasound (anechoic), though thick fluids (pus) can be brighter than typical fluid
- Tendons and nerves are bright / hyperechoic when perpendicular to probe, but dark / hypoechoic when angle is changed (anisotropy)
- Bone has a bright hyperechoic rim (due to reflection) around a black / anechoic image with a shadow beyond it

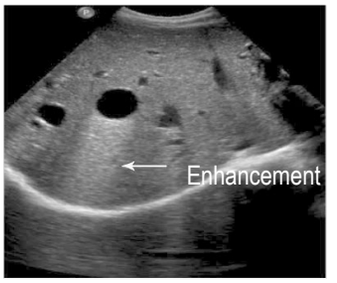


Artifacts: elements seen on ultrasound image that do not exist in reality

- Reflection: proportional to the difference in acoustic impedance between two tissues (↑ difference = ↑ reflection)
  Relative acoustic impedance: bone >> solid organ > fat >> lung >> air.
- Shadowing: ↓ signal beyond a strongly attenuating OR reflecting structure (e.g. stones, bone)
- Enhancement: ↑ signal posterior to weakly attenuating (hypo or anechoic) structure (e.g., cysts)
- Mirror image: structures in front of strong reflector (e.g. diaphragm) appear to lie behind it as well
- Reverberation: evenly spaced lines at various depths beyond a strong reflector (e.g. A lines beyond pleura)
- Comet tail: tiny, narrow reverberations beyond very strong reflector (e.g. metal pellet) blending into a line



Acoustic Shadowing (gallstone)

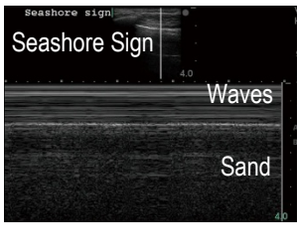


Acoustic Enhancement (liver cyst)

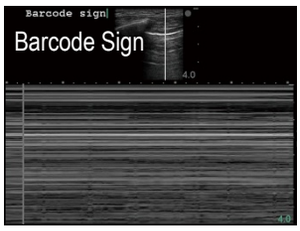
Imaging and Tips

Diagnostic Use:

- **Pneumothorax**: use LINEAR (vascular) probe. With patient supine, look in the 3rd intercostal space on the anterior chest. Identify the hyperechoic rims of the ribs with posterior shadowing; within the intercostal space identify the hyperechoic stripe that is the pleura. A normal lung will slide along the pleural line with respiration, a pneumothorax will not. If ambiguous, use M mode to confirm. A lack of lung sliding will change the normal 'seashore' sign to a static 'barcode' sign. Sn 91% / Sp 98%, superior to CXR. A lung point is not sensitive but is 100% specific (J Emerg Trauma Shock 2012;5:76, Ann Emerg Med 2013;61:207)

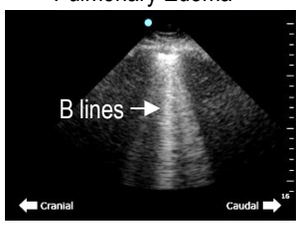


Pneumothorax



- **Pulmonary embolism**: use PHASED-ARRAY (cardiac) probe. Bedside ultrasound can be used to identify right heart strain. Look for RV size ≥ LV size, septal bowing, though note Sn/Sp for PE 53%/83%. RV/LV ratio is most easily visualized in the apical 4 chamber view but can be misleading based upon slight changes in plane. Assess with septum vertical in line with midpoint of probe. Combine with the parasternal axes for better reliability (J Am Soc Echocardiogr 2017;30:714)

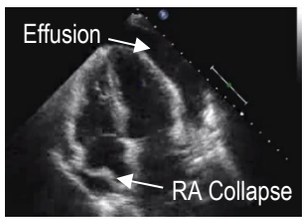
Pulmonary Edema



- **Pulmonary edema**: use PHASED-ARRAY (cardiac) or CURVED (abdominal) probe to evaluate the lung between rib spaces as above, across lung fields as for auscultation. Look for B-lines: comet like artifacts that shine perpendicular from the pleural line and obliterate A-lines. ≥3 in one interspace is consistent with interstitial fluid, and bilaterally suggests pulmonary edema. Operator dependent but can outperform CXR. (Am J Emerg Med 2015;33:620)

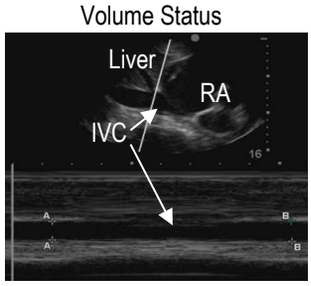
- **Pericardial effusion**: use PHASED-ARRAY (cardiac) probe. Look for an anechoic stripe between the heart and the hyperechoic pericardium, though hemorrhagic or purulent effusions can appear more complex. On parasternal long axis this will be anterior to the descending aorta, while a pleural effusion would be posterior. All four views are important, but often only subxiphoid used in emergencies. Look for chamber collapse indicating tamponade: RA is more sensitive; RV is more specific (Resuscitation 2011;82:671)

Pericardial Effusion



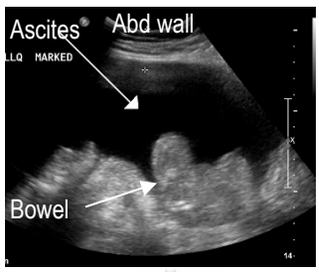
- **Volume status**: use the PHASED-ARRAY (cardiac) probe. IVC collapsibility has been proposed as a proxy for CVP and fluid responsiveness, though data is mixed and there are no consensus guidelines. Start with subcostal view of RA/RV, then rotate probe to the sagittal plane to find the IVC draining into RA and abutting the liver. Look at IVC 2cm from RA: fluid responsiveness or an underfilled IVC is suggested by 1) IVC diameter ≤2.1cm and 2) IVC collapses ≥½ its diameter. Can use M mode to track variation, cycles are inverted if spontaneously breathing vs mechanical ventilation, more accurate in the latter. (Crit Care 2012;16:R188, CCM 2013;41:833, Shock 2017;47:550)

Volume Status

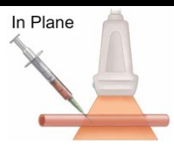


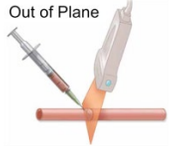
Procedural Use: *refer to pages on specific procedures for more details*

- **Paracentesis**: use CURVED (abdominal) probe. Locate largest fluid collection, often in LLQ. Try rolling patient to side to increase pocket size. LINEAR (vascular) probe can help identify any overlying vessels to your approach, particularly the inferior epigastrics. Bowel appears as hyperechoic finger-like projections within the anechoic ascites. Measure the depth of the abd wall and compare to your needle to determine when to expect flash, though with tenting this will be a slight underestimation.



- **Central venous access**: use LINEAR (vascular) probe. Reduces complications and quality of placement compared to landmark approach (Crit Care 2017;21:225)
  - In-plane (long axis): can view entire tip, but harder to keep needle in view
  - Out-of-plane (short axis): easier to center needle, may underestimate depth





- **Peripheral IV**: use LINEAR (vascular) probe. Most of your time should be spent finding the best vein to go for, often in the medial groove between biceps/triceps or anterior forearm. Track along vessel length to determine trajectory, look for large, superficial, compressible vessels that are not adjacent to pulsatile, non-compressible arterial vessels.

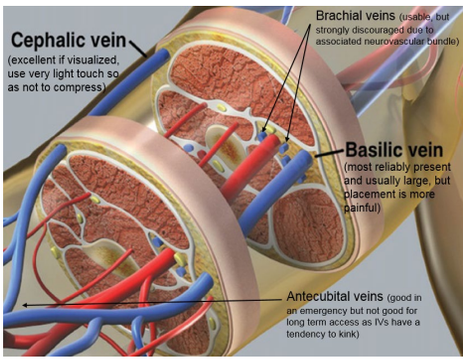
General Considerations

Indications: non-emergent access in a patient with difficult access. *If emergent, obtain IO or central access.*
Locations: AC, basilic, brachial, cephalic; larger veins offer higher chance of success than smaller veins
Contraindications: relative: sensory/motor deficits (clot risk), HD fistula, hx of LN dissection
Materials: angiocath (18 or 20G best; small IVs not well visualized on U/S), vascular probe, gel/sterile lubricant, tourniquet, alcohol wipe/chlorhexidine, tegaderm, extension tubing, saline flush, +/- vacutainer adapter and tubes (for labs)

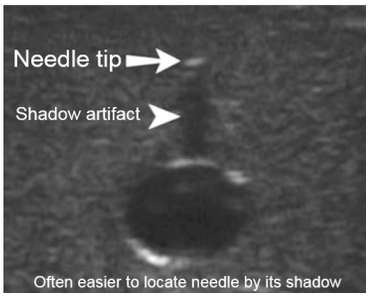
- Angiocath selection: standard length (30mm) good for vein <0.8cm deep; long needle (48mm) preferred for ≥0.8 cm (48mm 18G [green] stocked in most supply rooms, but 48mm 20G [pink] more difficult to find)

Transverse Technique

NEJM 2012;366:e38: choosing a vein (8:45), transverse (10:05), longitudinal (12:28)

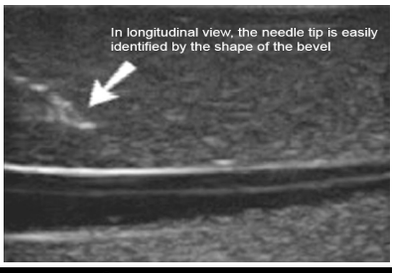


1) Setup: positioning is *very* important. Place U/S on opposite side of pts bed, adjust bet to appropriate height, obtain seat if needed, abduct & externally rotate pts arm.
2) Place tourniquet: place tourniquet as proximal as possible, near axilla if possible. Can stack two tourniquets for extra compression.
3) Confirm anatomy: use vascular probe on U/S at minimum depth to locate adequate superficial veins.
   - *Find vessels*: start at AC and move proximal and distal. Key is to find LARGE vessels (>0.4cm) that are CLOSE to the surface (depth between 0.3cm – 1.5cm) (J Emerg Med 2010;39:70). Common veins: basilic, cephalic > deep brachial
   - *Confirm venous circulation*: gentle pressure differentiates veins (fully compressible, non-pulsatile) and arteries (pulsatile); color doppler can confirm
   - *Trace vessel course*: follow the vessel course proximally and distally; recognize and avoid branch points, diving veins, and irregular coursing veins
4) Sterility: use alcohol pad or chlorhexidine swabs to sterilize proposed venipuncture site; clean U/S probe then cover with tegaderm; use sterile lubrication (or sterile U/S gel) as conduction medium for probe
5) Orient ultrasound: center target vein on U/S 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 U/S probe* – this will be directly over the vein if vein is centered on screen
   - Insertion site at skin is *distal* to the planned site of insertion into vein
   - At insertion, eyes should be on the *site of venipuncture*, not on the U/S screen, though after puncture, should be watching screen and not hand
7) Find tip and advance: as insert, needle tip (and shadow) should appear on screen → advance PROBE until you lose needle tip → advance NEEDLE tip until it reappears on U/S 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.
10) Slide off catheter: once 3-5mm into vein, can slide catheter off needle into vein and hub, and retract needle.
    Optional: continue to advance needle until angiocath is hubbed to skin
11) Flush: attach extension tubing, REMOVE TOURNIQUET, pull back on saline flush (ensure drawback), THEN FLUSH with saline
12) Secure: secure catheter and tubing with tegaderm; floor and ICU nurses may redress IV



Longitudinal Technique: use the following adjustments to the above technique

1) Identify target vein in the transverse view
2) **Rotate the probe to obtain a longitudinal view with the indicator towards your needle**
3) Align needle in the plane of the probe; puncture skin at 45 degrees, visualize needle tip
4) Advance needle until you can see that the tip of the catheter itself is fully within the vein
5) Do not to go through the back wall. Advance the catheter under direct visualization.



Technique	Pros	Cons
Transverse (short axis)	- Faster, requires less finesse with U/S probe - Allows visualization of adjacent structures	- Harder to visualize the needle tip - Risk of "through and through"
Longitudinal (long axis)	- Improved visualization of the needle tip - Can advance catheter under direct visualization	- Challenging to maintain probe/vein/needle in plane - Cannot see adjacent structures.

Troubleshooting (Transverse Video; Longitudinal Video; written guide: West J Emerg Med 2017;18:1047)

- *Can't see needle:* gently bounce the needle tip to generate artifact
- *Too much loose tissue:* use tape or have someone assist by putting tension on the tissue w/o applying pressure over target vein
- *Vein rolls:* reposition directly over the middle of vein, use a slightly steeper angle to take advantage of the sharp edge of the needle
- *Trouble finding any veins:* try using a blood pressure cuff high in the axilla instead of a tourniquet, but give the patient frequent breaks

General Considerations

Indications: hemodynamic monitoring (CVP, CVO_2); admin. of noxious meds (pressors, chemo, hypertonic solution, TPN); rapid large volume resuscitation; inadequate peripheral access; HD/CVVH/pheresis); to introduce other devices (PA line, temp wire)
Contraindications: vein thrombosis or stenosis should prompt another site. Coagulopathy/thrombocytopenia are relative contraindications, if severe coagulopathy, avoid subclavian (not a compressible site + difficult to effectively monitor for bleed)
Site selection: general preference at MGH is RIJ > LIJ > subclavian, femoral due to historical concern for infection. However, more recent data suggests no difference between these sites with proper attention to sterile technique
Catheter selection: select based on number of lumens and speed of infusion; if rapid infusion required → large bore, short length Cordis
Alternatives: PICC (if no concern for bacteremia) or IO (should not be used for > 24h, but in extreme circumstances OK for 48h)

Scheduled exchange of catheters without evidence of infection is **NOT** indicated
Cultures drawn from indwelling catheter have **↑ false ⊕ rate**; generally not done aside from time of sterile placement (NEJM 2003;348:1123)

Internal Jugular Vein

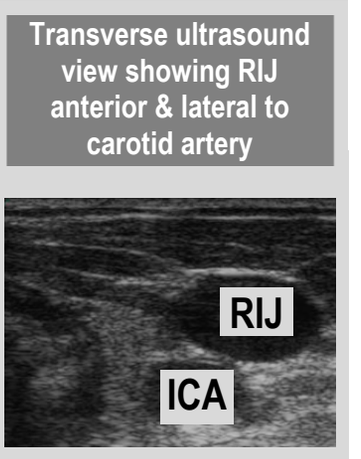
Video https://www.nejm.org/doi/full/10.1056/NEJMvcm0810156

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 U/S guidance @ MGH: ↓ first attempt failure, procedure time, and failure / complication rate.
Positioning: supine + Trendelenburg to engorge veins, maximize target, ↓ risk of air embolus
Site selection:

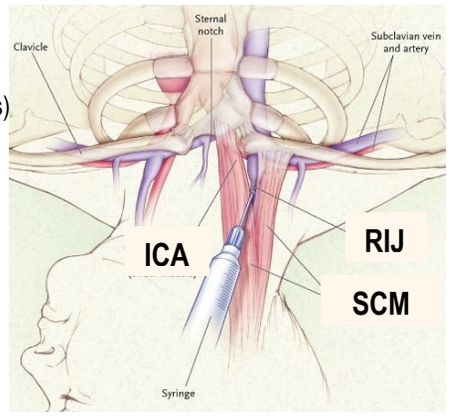
- Locate triangle formed by medial and lateral portions of SCM with the clavicle as base
- Find IJ → superficial and lateral to carotid, compressible, larger, thinner
- RIJ generally preferred (direct course to SVC; LIJ ↑ risk of PTX and thoracic duct injury)

Entry: bevel up at the apex of SCM / clavicle triangle, about 4-5 cm above suprasternal notch
Target: aim at ipsilateral nipple, 45 degrees (map out trajectory of vessel using ultrasound)



Transverse ultrasound view showing RIJ anterior & lateral to carotid artery

1) Preparation and positioning are essential; ensure someone is always available to help
2) Obtain consent; perform TIME-OUT; complete checklist (usually RN)
3) Use 2% chlorhexidine solution to prep (in the kit); drape the entire patient in sterile field
4) Place caps on CVC, flush all lines with sterile saline, remove cap from brown port; ensure guide wire advances easily and syringe comes off needle easily
5) Locate IJ vein & carotid artery using ultrasound
6) Anesthetize with lidocaine; can make wheal & inject along tract (aspirate before injecting!)
7) Insert and advance the large bore needle bevel up, 45°, towards ipsilateral nipple, visualizing tip with US; apply negative pressure. Once flash of blood is obtained → stop advancing the needle, continue to draw back venous flow (dark, non-pulsatile)
   - If arterial flow seen, remove needle and compress ~10 min
   - If air drawn back, suspect PTX → STAT CXR, 100% FiO_2, decompress if tension
8) Once flow obtained, stabilize needle with your non-dominant hand, remove syringe from locator (occlude hub with thumb to minimize risk of air embolism in non-ventilated patients)
9) Feed the curved end of the wire into the needle (*never* feed the opposite end) **NEVER LET GO OF THE WIRE**.
   - If any resistance, remove wire, assess for flow w/ syringe; If good blood flow, try twisting wire or flattening angle of needle
   - For R-sided IJ → feed ~25cm of wire (between two and three dark lines) → watch for ectopy (suggests wire in RV → withdraw)
     NB: catheter length = 14cm (usually), so need at least this distance of wire in vessel.
10) Remove needle
11) Confirm wire is in vein using U/S in transverse and longitudinal planes
12) Perform manometry confirmation → advance angiocath from kit over wire, remove wire, connect manometer tubing → venous blood should be non-pulsatile, dark, and rise < 20cm (can directly visualize fill in tubing or connect tubing to manometer) → replace wire through angiocath, remove angiocath
13) Extend puncture site with scalpel by inserting along path of wire (face cutting edge away from wire to prevent cutting wire)
14) Thread dilator over wire (using twisting motion) until about 1/3 is inserted, then remove; goal is to dilate skin/subcutaneous tissue, NOT the vessel itself (increased bleeding); ensure the wire moves back and forth freely while dilating (may otherwise be kinked)
15) Advance catheter over wire (wire comes out brown port, which is why it must be uncapped); remove wire
16) Draw back off all ports through caps using saline flush (only need to see small amount of flash), flush all lines clean, clamp ports
17) Secure with sutures; place Biopatch prior to securing with dressing
18) Order CXR (ASAP) to assess position, rule out PTX and hemothorax; **look at the CXR yourself**; 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."



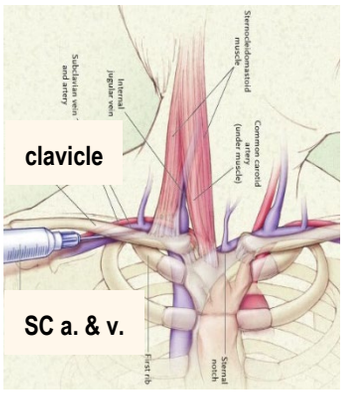
Subclavian Vein

Video: http://www.nejm.org/doi/full/10.1056/NEJMvcm074357

Advantages	Disadvantages
Anatomy is more reproducible, even in obese patients, given bony landmarks	Risk of PTX (**1-8%**), L side slightly > R due to higher dome of L pleura
Improved patient comfort; easier to dress and maintain	**Not easily compressible**; more risk a/w bleed if coagulopathic
	Risk of subclavian artery puncture / hemothorax (0.5-1%)

Positioning: some place a roll of towels between scapula to expose subclavicular area… others say this distorts anatomy; place in Trendelenberg to engorge vein
Entry: @ MGH → infraclavicular approach (as opposed to supraclavicular); puncture skin 1cm caudal to junction of medial 1/3 and middle 1/3 of clavicle (where vein flows just under the bone)
Target: bevel up and aim toward sternal notch, 30° to the skin; needle should advance just on the underside of the clavicle (~3-5cm depending on anatomy); some people "walk down" the clavicle to ensure this, but may lead to dulling or bending of needle as well as 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

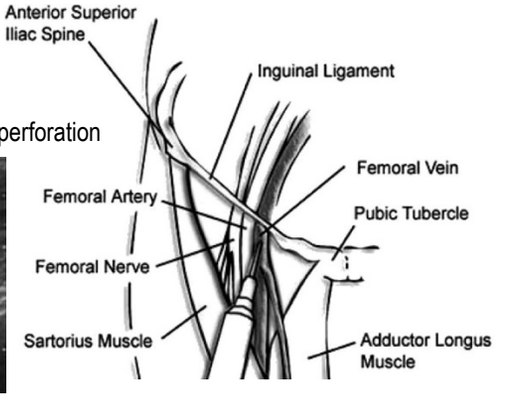
Video: http://www.nejm.org/doi/full/10.1056/NEJMvcm0801006

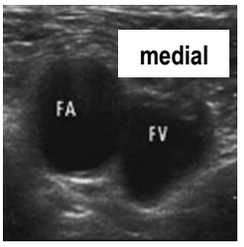
Advantages	Disadvantages
Compressible	Femoral artery puncture 5-10%
No risk of PTX	Risk of development of deep venous thrombosis
Can be cannulated more easily during CPR	Less patient comfort in hip flexion, requires immobility
Large caliber vein technically easier to cannulate	May occlude flow if patient is obese
	Caution in patients with inferior vena cava filters

Positioning: head of bed flat; abduct lower extremity and externally rotate the hip
Entry: bevel up, 2-3 cm below inguinal ligament, 1cm medial to palpated pulse → femoral vein lies medial & inferior to the femoral artery

- If non-urgent use ultrasound to visualize
- "**NAVEL toward the NAVEL**" → Nerve, Artery, Vein, Empty, Lymphatics (alternative: venous→penis)
- Two fingerbreadths lateral to pubic tubercle if pulse not palpable
- DO NOT approach vein above inguinal ligament → risk for RP bleed & peritoneal perforation

Target: directly superior at 30-45°.





Cordis (aka venous introducer sheath)

Combined dilator and sheath w/ side port for IV access
Indications:

- Rapid resuscitation (shorter length, wider diameter)
- Introducer sheath for PA catheter
- Introducer for temp wire placement.

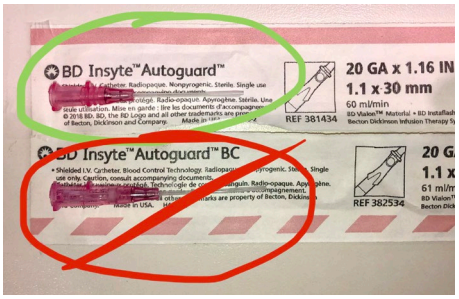
Sites: IJ (R preferred for PA line), subclavian vein, femoral vein
Placement technique: uses Seldinger technique (advance catheter over a wire) but dilator and sheath are advanced over wire together as unit; dilator and wire then removed together; side port aspirated and irrigated prior to use.

CVC Complications

Arterial puncture: hold pressure x 10 mins; compress 1 inch inferior (IJ) or 2 inches superior (femoral) to puncture mark
Dilation / line placement in an artery: consult vascular surgery BEFORE removing line; consider CT if pt stable
Pneumothorax (IJ & subclavian): suspect if hypoxemia, hypoTN, difficult stick; obtain STAT CXR → thoracic surgery consult if PTX or hemoTX; if tension physiology (shock) → immediate decompression with 16G angiocath @ 5th ICS, mid-axillary line (enter above the rib)
Retroperitoneal bleed (femoral): suspect if hematoma or hypotension; STAT CT → vascular medicine consult
Loss of wire or wire stuck in vessel: DO NOT use excessive force to pull out wire if it is stuck → leave in place, hold pressure to prevent exsanguination → STAT KUB / CXR if wire loss → vascular medicine consult

General Considerations

Indications: real-time BP monitoring (pressors, HTN emergency, CVA); frequent ABGs, lab draws (≥3 per day)
Locations: radial > femoral > dorsalis pedis > axillary; brachial not recommended given lack of collaterals unless placed by anesthesia
Contraindications: lack of collaterals (abnormal Allen test), h/o arterial grafts/stents, Raynaud's/scleroderma
Risks: pain, infection, bleeding, ischemia, vasospasm, arterial dissection, embolization, necrosis, loss of limb
Materials: arm board, tape, Chux, chlorhex prep, 4 x 4 sterile gauze, pack of sterile towels, sterile gloves, mask, eye protection, bouffant, 20G angiocaths, guide wire, Tegaderm, U/S probe cover (if needed)

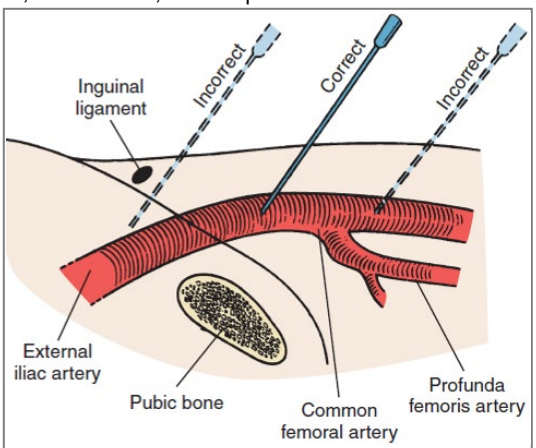


- If pt awake → consider lidocaine (w/o epi), small syringe and 25G needle
- Use PINK SOLID STRIPE angiocath; do NOT use pink interrupted stripes, which has a one-way valve so can't pass wire
- Alt: use Arrow arterial line kit; the kit's longer catheter is preferable for femoral site

Radial Technique

Video: http://www.nejm.org/doi/full/10.1056/NEJMvcm044149

1) Obtain consent and perform TIME-OUT; ask RN to prepare for A line
2) Confirm anatomy by palpating pulses or with U/S. Test for collateral circulation of the hand:
   - **Allen test**: make fist for ~30 sec, then occlude ulnar & radial arteries; pt opens hand (palm should be blanched); then release pressure from ulnar artery → palm should regain color within ~5 sec
   - **Modified Allen test**: place sat probe on index finger or thumb; occlude radial and ulnar arteries until wave form lost; release ulnar artery → should get arterial tracing if good collateral flow.
3) Proper positioning is key to successful placemen: adjust bed to appropriate height
   - 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; mark course of artery w/ pen or indent with top of pen or use U/S / doppler PRN
4) Sterilize wrist widely with 2% chlorhexidine swabs; open towel packet to create sterile field
5) Prepare field: drop angiocath & guide wire on sterile field; don sterile gloves and drape widely w/ sterile towels
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 with non-dominant hand; plan to puncture distal to the pulse you palpate, aim towards that pulse
8) Insert angiocath: with *bevel up*, advance angiocath needle at a 45° angle toward pulse until flash is obtained (similar to ABG)
9) Once flash obtained, go *"through-and-through"*: advance ~0.5cm through artery; hold the top of the plastic catheter with non-dominant hand; push button to retract needle, while steadying the catheter **(should be no blood flow)**
10) Hold guide wire close to head of angiocath w/ dominant hand
11) Pull back slowly: lower angiocath as parallel to skin as possible and SLOWLY pull it back until pulsatile blood flow is obtained
12) Advance wire: inset 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.



Proper femoral puncture site (*Interventional Cardiac Catheterization Handbook*, 3rd Ed. 2013)

Daily ✓ for ischemia (cool, white, purple) & infection (need for removal)

Troubleshooting and Alternatives

- If using Doppler, mark out course of artery with marking pen or indentations.
- If using U/S, can try advance needle/catheter under U/S guidance and once firmly in vessel, advance catheter over wire (no guide wire; similar to PIV).
- If unable to thread guide wire AFTER ATTEMPTING TO SPIN during insertion, consider micropuncture wire (cardiac cath lab or MICU med room). May help with atherosclerotic arteries at the price of ↑ risk of perforation
- After multiple attempts, the artery may spasm. Pursue alternative site.
- Femoral artery access can be considered in difficult cases. Use the long catheter in the Arrow arterial line kit. Puncture must occur distal to the inguinal ligament to prevent RP bleed. Too distal, however, and the femoral artery will bifurcate into superficial and deep femoral vessels. The femoral artery usually transverses the inguinal ligament ~1/3 distance from pubic symphysis to the ASIS. Optimal point of skin puncture is 1-2 cm below the inguinal ligament at point where pulse is palpated (*see above*)

Procedures — Intraosseous Line

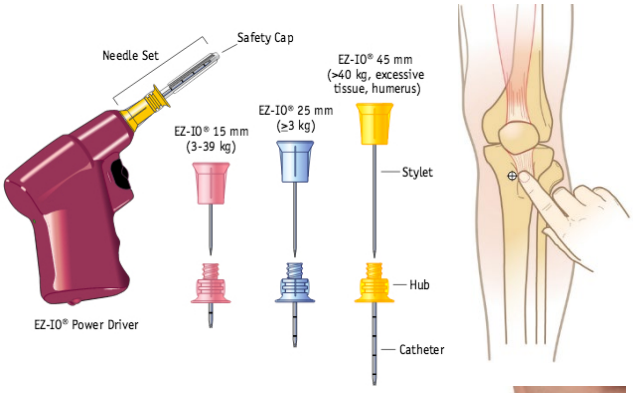
General Considerations

Video: If you have 15 min; If you have 1 min

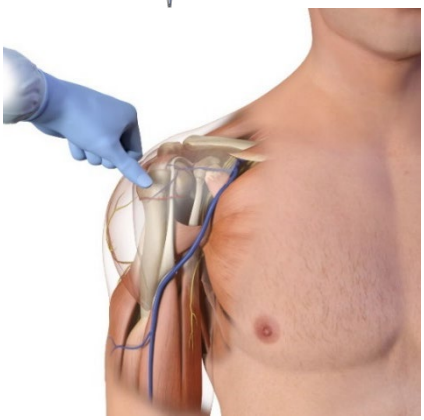
- **Anatomy**: veins that drain medullary sinuses of bones; veins supported by bones do not collapse in patients in shock.
- **Indication**: patients without available IV access with urgent need (arrest, shock, status epilepticus, trauma, etc). Used for delivery of fluids/medications; labs (but tenuous – 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)
- **Note**:
  - Infusion rate roughly 160mL/min at tibia or humerus with use of pressure bag, half of that rate without
  - IO samples only accurate for some studies (Hgb, T&S, drugs, Cx). NOT for PaO2, WBC, K, AST/ALT, iCal, after drug admin

Set-Up

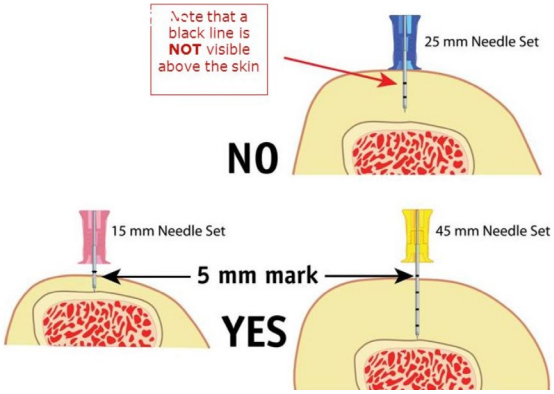
- **Materials**: ALL IN KIT → EZ-IO Power Driver, IO needle-set, connector tubing, 10 cc syringe with saline flush, chlorhexidine/povidone iodine, sterile gloves. If awake, 3cc syringe with 1% lidocaine via 25G needle
- **Location:**
  - Proximal tibia (preferred): find the flat surface 2cm below tibial tuberosity, 1-2cm medial along tibia
  - Proximal humerus: position pt palm on abdomen (elbow flexed, shoulder internally rotated) greater tubercle 2cm below acromion process
  - Other sites: distal tibia, distal femur, iliac crest



Procedure (Crit Care 2016; 20:102)



1. Don surgical mask, eye protection, sterile gloves
2. Flush connector tubing with NS or cardiac lidocaine if patient is awake
3. Identify injection site
4. Clean injection site with antiseptic (chlorhexidine or iodine)
5. If patient is awake, create wheal with 1% lidocaine
6. Choose proper needle size: generally blue (25mm); yellow (45mm) is for excess tissue or for humerus approach
7. Magnetic pole holds the needle in place on the drill; turn the safety cap clockwise for removal
8. Hold drill perpendicular to bone; manually press the needle through the skin until it touches the bone
9. Confirm you see one black line on the needle (5mm mark); if not, use a longer needle
10. Apply gentle, steady, downward pressure while holding the trigger; allow drill to do the work
11. Release trigger when 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 dressing for other size
17. Administer rapid NS bolus, blood product, pressor, etc. with a pressure bag or syringe
18. Always return the IO kit to the CCU resource nurse to refill



Removal

- Remove **within 24 hours** of insertion once other access is obtained, or if signs of erythema, swelling or extravasation

Indications: **Video:** http://www.nejm.org/doi/full/10.1056/NEJMvcm062234

- **Diagnostic**: new-onset ascites, unknown etiology of ascites, rule out SBP. Low threshold for inpatients with cirrhosis and often helpful to obtain concurrent RUQUS with Doppler to rule out hepatic or portal vein thrombosis
- **Therapeutic**: large volume paracentesis (>5L) → performed for abdominal pain/discomfort, diuretic-refractory ascites, respiratory compromise, abdominal compartment syndrome, adjunctive treatment of esophageal variceal bleeding (can lower portal pressures)

Contraindications: overlying infection (i.e. cellulitis), inability to demonstrate ascitic fluid on U/S, bowel obstruction/distention, acute surgical abdomen, 2nd or 3rd trimester pregnancy

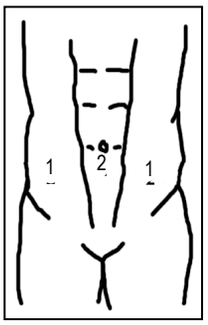
- ↑ INR / ↓ plts are **NOT** contraindications (INR in patients with cirrhosis is NOT reflective of the risk of bleeding). There is no need to correct coagulopathy w/ FFP or platelets unless severe DIC (Hepatology 2013;57:1651)

Materials: sterile gloves, bouffant, face shield, chlorhex, sterile towels, ultrasound, 1% lidocaine (10cc syringe, SQ 25G needle, 1.5 inch 20-22G needle), two 18G needles, 60cc syringe, diagnostic assay tubes as below, gauze, bandage or Tegaderm dressing

- Diagnostic: **20G two-way (pink box) angiocath** or 18–22G 1.5-inch needle. In obese pts, may use angiocath from femoral art line kit. Purple and green top tube, black top tube (for micro). Technically DO NOT need to inoculate blood culture bottles at the bedside.
- Therapeutic: **safe-T-Centesis kit** (preferred, pigtail minimizes perforation risk) or paracentesis kit (straight rigid needle), 1L vacuum bottles, 25% albumin dosed 6-8g per liter of fluid removed if >5L (Hepatology 2013;57:1651)

Site Selection/Positioning:

- Position patient supine, turned slightly toward the side of the paracentesis, and angled upright at 30°
- Use abdominal probe to **identify fluid pocket at least 2-3cm in all dimensions** by rotating/fanning probe and ensure **absence of bowel loops**
- Avoid superficial veins or prior surgical incisions and **use vascular probe with Doppler to avoid SQ vessels**
- **Approaches**:
  - LLQ (1): **more commonly used**; LLQ ↓ risk of bowel perf, use caution if pt with splenomegaly; **avoid inferior epigastric vessels** that run along lateral borders of rectus muscles
  - Infraumbilical (2): midline, 2cm below umbilicus; lowest risk of bleeding but **must ensure bladder empty**



Approaches

Instructions:

1. Identify best site with abdominal U/S probe and mark site with pen or round base of needle
2. Open sterile OR towels package and use light blue covering as sterile field to drop sterile supplies. Don sterile protective equipment (technically only need gloves, mask, bouffant cap) and clean skin vigorously with chlorhexidine. Create sterile field over patient with OR towels or open kit and use dressing provided
3. Anesthetize overlying skin using ~0.5cc lidocaine (SQ 25G needle) to make a wheal. For LVP, use 1.5 inch 20-22G to anesthetize deeper tissues with lidocaine in 10cc syringe. Use **Z-line technique** (below) and aspirate while advancing needle. Once ascitic fluid begins to fill syringe, stop advancing the needle & inject remainder of lidocaine to anesthetize the highly sensitive parietal peritoneum

Z-line technique: reduces risk of ascites leak. With non-dominant hand, pull skin ~2cm caudad to deep abdominal wall while para needle is being slowly inserted

Diagnostic paracentesis instructions:
a) Insert **20G two-way (pink) angiocath** through wheal at same angle as U/S probe and advance until slightly past when flash seen
b) Advance the catheter without moving the needle
c) Retract needle, attach 60cc syringe, and fill syringe
d) Withdraw the catheter and apply pressure with sterile gauze
e) Apply dressing using folded gauze under Tegaderm
f) Attach 18G needle to 60cc syringe and fill diagnostic tubes

Therapeutic paracentesis instructions:
a) Prepare Safe-T-Centesis kit: place catheter on needle, attach syringe, and prep tubing
b) Use scalpel to make small superficial incision (enlarge PRN)
c) Advance needle/catheter while pulling back on syringe until ascitic fluid return is visualized, then advance 0.5 cm
d) Advance catheter until hubbed (only with Safe-T Centesis kit!), hold rigid needle in place
e) Retract needle, attach 60cc syringe for dx sample PRN
f) Connect tubing to catheter and puncture vacuum bottles
g) Withdraw catheter and apply gauze/Tegaderm dressing
h) Give **25% albumin (6-8g/L removed) if >5L removed**

Diagnostic Assays:

Tube	Lab	Tests
Green top	Chem	Fluid albumin (send serum albumin to calculate SAAG), fluid total protein (to determine need for SBP ppx)
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 epigastrics → stop, assess for hematoma w/ U/S, IR or surgery consult if HD unstable
- Hypotension: likely vasovagal or fluid shift (>1500cc tap) → Trendelenburg, hydrate, and consider 25% albumin
- Bowel perforation: may lead to polymicrobial bacterascites/sepsis → surgery consult for potential laparotomy
- Fluid leak: prevent with Z-line technique → apply pressure dressing, seal w/ Dermabond or single stitch (4-0 non-absorbable suture)

Indications

Diagnostic: evaluation of inflammatory mono/oligoarthritis or uncharacterized joint effusion. A single inflamed joint should always have diagnostic aspiration to differentiate septic arthritis, crystalline arthopathy, inflammatory arthritis, and hemarthrosis

- **Avoid if overlying cellulitis or periarticular infection**; prosthetic joints should prompt Ortho/Rheum consult; safe to perform if on warfarin (Am J Med 2012;125:265) or DOAC (Mayo Clin Proc 2017;92:1223) but consider smaller needle
- Ultrasound may be used to guide needle insertion and can also offer diagnostic information with complexity of fluid
- Hip joint aspiration should be performed by interventional radiology

Therapeutic: injection of corticosteroid/anesthetic in autoimmune arthritis (RA/JIA, spondyloarthropathies) or single-joint gout flare (especially when systemic therapy is contraindicated); drainage of large effusion, pus, or blood

- Avoid if overlying cellulitis, periarticular infection, septic arthritis, periarticular fracture, joint instability
- Use of intra-articular steroids in OA is falling out of favor due to progressive cartilage damage (JAMA 2017;317:1967)

Complications: iatrogenic infection (1/3500, >48h after procedure, may see systemic signs of infection), post-injection flare (mirrors infection and occurs within 24-48h of procedure), hemarthrosis, leakage of joint fluid, local or systemic steroid effects

Technique: Knee

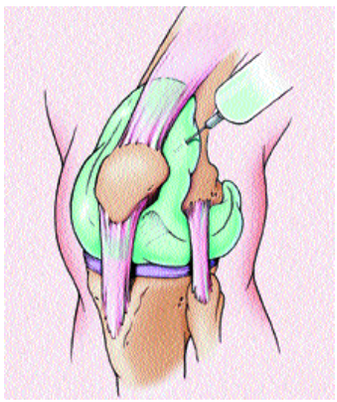
NEJM Video: http://www.nejm.org/doi/full/10.1056/NEJMvcm051914

Materials: sterile gloves, chlorhexidine/iodine, 5cc 1-2% lidocaine 5cc w/o Epi (25G needle, 5cc syringe) or ethyl chloride spray, 18-22G needle, 20-60 mL syringe, diagnostic tubes (purple/green top, aerobic/anaerobic bottles), sterile towels/sheet, bandage

Positioning/Approach: position the knee in extension or 15-20° flexion. Approaches described below:

- **Lateral** (see image): 1cm lateral and 1cm superior to the superior 1/3 of the lateral patella. Angle the needle approximately 45° toward the feet and insert behind the patella at a 45° angle to the skin. **More likely to yield fluid in difficult cases**
- **Medial**: 1cm medial to the superior 1/3 of the medial patella. Angle the needle perpendicular to the leg and at a 45° angle to the skin

Lateral Approach



Protocol:

- Identify landmarks as above and mark point of entry with the base of a needle cap or pen. Sterilize the site. A sterile field is not technically required but may drape the area w/ a sterile sheet or towels. Prep needles and syringes.
- Anesthetize overlying skin using ~0.5cc lidocaine (SQ 25G needle, 5cc syringe) to make a wheal. May use remaining lidocaine along procedure tract.
- Attach 18-20G needle to 30cc syringe and position needle according to approach. Advance needle slowly (avg 1-1.5 in) and aspirate while advancing.
- Once fluid is visualized, aspirate joint fluid to fill syringe. May attach a 2nd 30cc syringe to drain additional fluid for sx relief pending size of effusion.
- Withdraw needle and apply bandage. Fill diagnostic tubes (purple top for cell count/diff and crystal eval, aerobic/anaerobic cx bottles).

Diagnostic Assays: cell count/diff, crystal analysis, gram stain/culture **AND** blood cultures (Am Fam Physician;2003;68:1)

- **Septic arthritis**: most common locations: knee > hip > shoulder > elbow
  - If patient HDS, **hold antibiotics prior to tap**; 70% *Staph*, 17% *Strep*, 8% GNR (*H. flu* child > adult)
  - WBC count usually 50-150K but can be lower (e.g. <20K in disseminated gonorrhea); ↑WBC = ↑ risk of infection
  - **Presence of crystals does not rule out septic arthritis** (up to 5% of pts with crystals also have septic joint)
  - Gram stain: sens 75% for *Staphylococcus*, 50% for GNR, < 25% for *Gonococcus*
  - Joint cx usually positive but only 50% sensitive in gonococcal arthritis (swab genitalia & pharynx for diagnosis)
- **Gout**: negatively birefingent needle-shaped urate crystals (yellow) on polarized microscopy (Sn 63-78% / Sp 93-100%)
- **Pseudogout**: positively birefringent CPPD rhomboid crystals (blue) on polarized microscopy (Sn 12-83% / Sp 78-96%)

Indications

Diagnostic: suspicion for CNS infection (most common), CNS malignancy/mets, SAH, or CNS demyelinating/inflammatory process
Therapeutic: idiopathic intracranial hypertension, NPH, ↑ICP in cryptococcal meningitis, intrathecal meds/chemotherapy/anesthesia
Contraindications: no absolute contraindications; high risk if skin infection over puncture site, epidural abscess, ↑ICP 2/2 mass lesion or obstruction (risk of brain herniation), spinal cord tumor or AVM, thrombocytopenia (<50K) or coagulopathy (INR > 1.5)
Preparation:

- **Hold AC**: time frame needed to hold AC prior to procedure: IV heparin (4hrs, PTT<35), LMWH therapeutic (24hrs), LMWH ppx (12hrs), Plavix (5-7 days), DOAC (3 days), warfarin (3 days, 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), DOM policy can be found in Ellucid.
- **Head CT**: only obtain head CT if **≥1 of the following**: age > 60, hx CNS disease, seizure in last 7d, immunocompromised, AMS, aphasia, cranial nerve deficit; if none of these, then 97% NPV for no mass lesion (NEJM 2001; 345:1727)

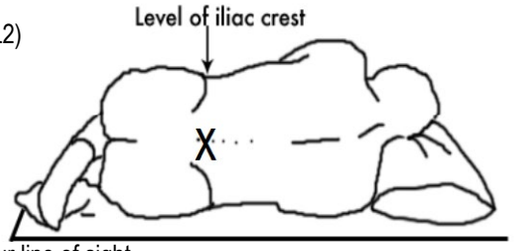
Technique (NEJM 2006;355:e12)

NEJM video: http://www.nejm.org/doi/full/10.1056/NEJMvcm054952

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 measuring opening pressure): place pt in fetal position (maximize neck and hip flexion), no hip / shoulder rotation; keep back parallel to edge of bed
- Upright (easier if obese): sit on bed, head / arms rest on table, spine flexed
- To identify target, place a hand firmly on each iliac crest and mark where your thumbs meet at the midline or draw a line between the iliac crests. Before inserting the needle, place your thumb and pointer finger on either side of the spine to ensure needle is midline
- Sitting while performing the procedure is often easier than standing, as the needle is in your line of sight

Protocol: (JAMA 2006;296:2012)

1) Prep: sterilize and drape widely. Re-identify target. Make lidocaine wheal w/ 25G, then inject track (aspiration before injecting, goal is **not** spinal anesthesia). Keep CSF collection tubes in order nearby. If checking pressure, have manometer connected and ready.
2) Tap: check needle / stylet mobility. Bevel should face ceiling when pt is lateral. Needle angles slightly toward the head (as if aiming to umbilicus), straight at the back. Stabilize with your hand against the skin and advance with your dominant hand. Remove stylet frequently to check for CSF flow but **always keep stylet in place when advancing**.
3) Troubleshoot: if hitting bone, partially withdraw, adjust angle, and re-advance. Try another space below if no luck. If patient has pain, DO NOT withdraw → ASK "where?" If pain is shooting down the left side, withdraw slightly and go slightly more to the right. If hitting bone early, more likely to be superior or inferior; if hitting bone late, more likely to be too lateral.
4) Measure OP: once flow is established, remove stylet and connect manometer to measure opening pressure (must be in lateral decubitus position). Pt must **extend legs** to obtain accurate pressure. If performing therapeutic LP, drain until pressure normal.
5) Collect: collect CSF tubes 1 to 4; if flow slows, try rotating needle or minimally advancing or withdrawing with stylet in place.
6) Finish: re-insert stylet prior to needle removal (associated w/ ↓ post-LP headache).

Diagnostic Assays		
Tube	**Lab**	**Tests**
1 (1 mL)	Heme	CSF cell count
2 (1 mL)	Chem	Total protein, glucose
3 (3-5+ mL, depending on number of tests)	Micro	Gram stain/culture. Consider HSV PCR, VZV PCR, cryptococcal antigen, viral culture, AFB stain, VDRL. Ask lab to save extra CSF. **If you may need flow cytometry, DO NOT FREEZE CSF!**
4 (1 ml)	Heme	CSF cell count (should have fewer RBCs than tube 1 unless hemorrhage)
Additional tests: cytology & flow cytometry (meningeal carcinomatosis), oligoclonal bands (multiple sclerosis), paraneoplastic antibodies, 14–3–3 & RT-QuIC (prion disease); may want to collect extra black top tubes for these purposes; if c/f prion disease, contact materials management for instruction on special disposal of materials (highly contagious!)		

Complications	
Cerebral herniation (acute AMS, fixed pupils, ↑ BP, brady, arrest)	Immediately replace stylet and do not drain more CSF beyond what is in manometer. STAT consult neurosurgery and treat with ICP-lowering agents (e.g. mannitol)
Nerve root injury	Shooting pains during procedure usually transient. Withdraw slightly and adjust position away from direction of pain. Consider dexamethasone if pain is persistent.
Post-LP headache (10-30% incidence; likely 2/2 dural leak)	Onset 72h, lasts 3-14 days. Give pain meds that do not affect plt. No evidence for bed rest. If persistent, c/s anesthesia for epidural blood patch (65-98% success, usually immediate relief).
Spinal hematoma	Suspect if on AC w/ persistent back pain or neuro sx → urgent MRI → IV dexamethasone + NSGY c/s

Indications

Diagnostic: to establish etiology of ≥1cm pleural effusion visualized by U/S (not necessary for small effusions w/ probable alternative dx)
- *NB*: pleural effusions are visible on CXR when > 200mL of fluid is present

Therapeutic: large effusions → resp compromise or sx (e.g., dyspnea), hemothorax, empyema, complicated parapneumonic effusion

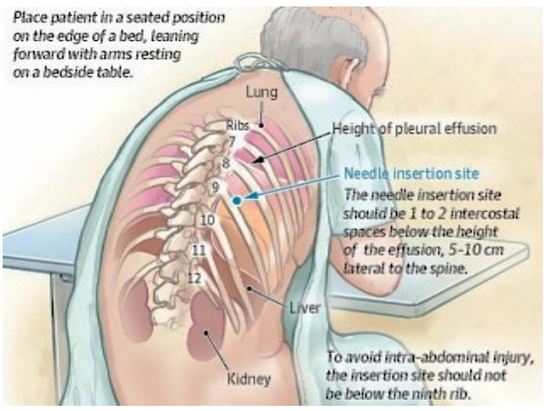
Contraindications (relative, not absolute) (Chest 2013;144:456)
- Consider reversing coagulopathy (INR >1.5, recent LMWH) or thrombocytopenia (plt < 50k), but no data to support
- Skin infection (cellulitis or herpes zoster) over site of entry ↑ risk of pleural space infection
- Positive pressure ventilation ↑ risk of PTX by 1-7% but is not a contraindication (Crit Care 2011;15:R46)

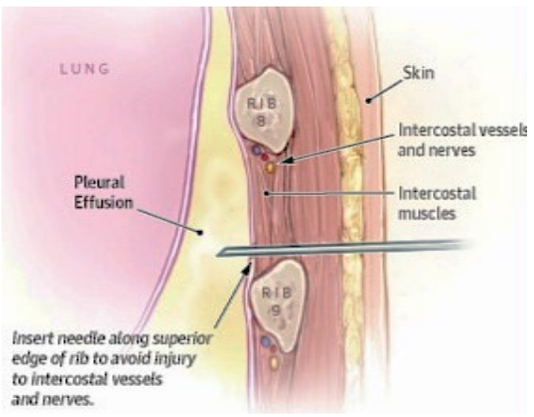
Preparation

- Materials: skin cleansing agent, gauze, sterile gloves/drape, hemostat, 1-2% lidocaine, 10mL syringe with 22 & 25 gauge needle, thoracentesis kit with 18-20g over-the-needle catheter, 60cc syringe, 3way stopcock, drainage tubing, specimen tube, evacuation container, occlusive dressing
- Attending **MUST** be present for thoracentesis: page IP (p23710), pulm, or call MICU x68048 to see who is on service

Technique (NEJM 2006;355:e16), Video

- 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 ultrasound to confirm location of effusion.
  - Mark 5-10 cm lateral to spine & 1-2 ICS below effusion. Lowest level recommended is 8th ICS (above diaphragm)
  - In patients who cannot sit upright → mid-axillary approach (patient supine) or posterior axillary with patient lateral decubitus
- Prep & drape: set up thoracentesis kit, put on sterile gown and gloves, sterilize patient w/ chlorhexidine, then drape
- Using 25G needle, place wheel 1% lidocaine over superior edge of the rib
- Using 22G needle, walk the 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) with 2-3cc of lidocaine. Note penetration depth.
- Attach 18G over-the-needle catheter to syringe & advance over superior aspect of the rib, pulling back while advancing
- When fluid aspirated, stop advancing & guide plastic catheter over needle
  Catheter has valve preventing fluid or air from entering the pleural space, so may use both hands to prepare for your next step
- Attach 60 cc 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

- Send fluid for: TP, LDH, chol, glucose, pH, cell count, culture and Gram stain, anaerobic culture, fungal wet prep with culture.
- Consider: TG (chylothorax), Cr (urinothorax), amylase (pancreatitis, esophageal rupture), ADA (TB), AFB culture, modified AFB culture, cytology

Complications

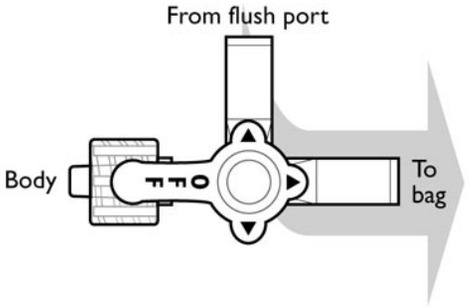
1. **Hemothorax/intercostal vessel injury**: ↑ risk if inferior approach to rib or elderly (tortuous vessels). CXR, H&H. Consider chest tube.
2. **PTX**: 5-20% risk; most can be monitored with serial CXR; monitor for signs of tension PTX and obtain STAT expiratory CXR; if PTX is large / patient is symptomatic and/or in distress → needle decompression with 16G angiocath at **5th ICS mid-axillary line** (always above nipple); chest tube indicated in 20% of cases → consult IP (p23710) or thoracic surgery
3. **Vasovagal syncope/pleural shock**: caused by needle penetrating parietal pleura; supportive care
4. **Re-expansion pulmonary edema**: to avoid, stop thoracentesis if cough, CP, or dyspnea, limit volume removal (<1.5L). Do not attach to vacuum, remove fluid slowly without excessive negative pressure; treat w/ O2, diuretics, BiPAP.

Indications:
- Pericardial effusion with tamponade physiology (or if at high risk for development of tamponade physiology)
- Diagnostic or palliative drain of stable pericardial effusion

Relative Contraindications: *no absolute contraindications*
- Coagulopathy: INR>1.7, platelets<20, PTT>60 or on heparin gtt. Consider FFP/platelets when on call for procedure
- Effusion associated with aortic dissection or myocardial rupture, as decompression could lead to extension of injury
- Effusion associated with severe pHTN (controversial), as decompression could lead to RV dilation and acute RV failure (Pulm Circ 2013;3:467)

Management Overview: *if in doubt about management, page the cardiology team that placed the drain*
- Pericardiocentesis does not completely evacuate a pericardial effusion. A pericardial pigtail catheter is often left in for 24-72h to allow for serial drainage, preventing re-accumulation and repeated procedures.
- Frequency of drainage depends on chronicity and size of the effusion, usually q6-q12h. Recommendations are often found in the report from the cath lab when the drain was initially placed.
- **Give cefazolin 1g q8h** (or vancomycin if PCN allergy) for prophylaxis while drain is in place.
- Monitor effusion resolution and recurrent tamponade. Check serial hemodynamics/pulsus paradoxus.
- If >100cc output/day for 3 days s/p drain placement, aggressive therapy may be indicated (i.e. pericardial window, sclerosing agents, etc.)
- Consider removal of pericardial drain if <50cc output over 24 hours. Obtain approval from cardiology prior.

Materials:
- Sterile technique: gloves, mask, hat
- Sterile towels
- Chlorhexidine swabs (at least 3)
- 60cc Leur lock (screw-on) syringe (x2-3 if high output)
- New blue cap for 3-way stopcock
- Heparin (10U/mL) pre-mixed syringe (in MICU/CCU med rooms)



Technique:
1. Put on, gloves, mask and hat (gown is optional). Open supplies onto sterile field.
2. Ask RN/assistant to lift catheter off skin by flush port. Sterilize distal exposed catheter and stopcock with chlorhex swab. Holding the sterilized area, take catheter from RN and sterilize remaining portion
3. Place sterile towels around and underneath distal catheter and stopcock, and lay the now-sterilized catheter down
4. Ensure the stopcock is turned towards the catheter. This means the catheter line is closed.
5. Remove and throw away one blue cap (doesn't matter which).
6. Sterilize open stopcock tip with iodine or chlorhex swab.
7. Hold up flush port; RN will connect heparin syringe (syringe itself is not sterile) to open/sterilized tip. Turn stopcock toward the remaining capped valve (opens flush port/catheter), and infuse 2cc heparin.
8. Turn stopcock back towards catheter, remove (do not discard) heparin syringe, and connect 60cc Luer lock syringe.
9. Turn stopcock to the remaining capped valve and slowly withdraw pericardial fluid. This may require significant negative pressure. Consider different patient positions (Trendelenberg, lateral decubitus, etc.) to mobilize pericardial effusion. Patient may experience chest discomfort. Monitor hemodynamics
10. Save/transfer pericardial fluid if needed for analysis. Otherwise discard.
11. Can stop draining once fluid flow diminishes/ceases. Turn stopcock back towards catheter and remove syringe.
12. Ask RN to re-attach heparin syringe and infuse another 2cc heparin. Again close stopcock to the patient.
13. Remove heparin syringe and attach new blue cap to open flush port.
14. Consider re-sterilizing distal exposed catheter and stopcock with chlorhex swab.
15. Write procedure note. Be sure to deduct the 2-4cc infused heparin when calculating amount of fluid removed.

Fluid Studies:
- Gram stain and bacterial/fungal culture
- Specific viral studies/PCR
- Cytology
- AFB stain, mycobacterial culture, adenosine deaminase, IFN-gamma, or lysozyme (if considering TB pericarditis)
- Protein, LDH, glucose, red/white cell count are **not** helpful for fluid characterization

LUMBAR PUNCTURE INTERPRETATION

Condition	Pressure (cm H2O)	WBC per 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	Culture, Gram stain
Viral meningitis (Enteroviruses, HSV, VZV, arboviruses)	9–20	50–1000	Lymph; early echovirus / HSV can have 80% PMN	>45; low in LCM and mumps	<200	HSV/VZV PCR, consider further viral PCR or Ab if clinical suspicion; d/w ID
Lyme meningitis	9–20	10–300	Lymph	Normal	50–100	Ab testing paired with serum ab (though poor sensitivity)
TB meningitis	18–30	50-300	Lymph	< 50	50-300 >2000 if subarach block	MTb Cx < 60% sensitive, Nucleic acid test not approved by FDA
Fungal meningitis	18–30	< 300	Lymph	< 50	40–300	Fungal wet prep + Cx, discuss other testing with ID
Cryptococcal meningitis	18–30+	5–500	Lymph	< 40	>45	Fungal wet prep + culture, cryptococcal antigen
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

	⊕ **Ascites culture**	⊖ **Ascites culture**
PMN ≥ 250/μL	**S**pontaneous **B**acterial **P**eritonitis (SBP) (Secondary Peritonitis → polymicrobial)	**C**ulture **N**egative **N**eutrocytic **A**scites (CNNA)
PMN < 250/μL	**N**on-**n**eutrocytic **B**acter**a**scites (NNBA)	Normal

CNNA: has similar clinical presentation and prognosis as SBP, thus treat for suspected SBP after diagnostic PMN count without waiting for Cx (*ddx*: peritoneal carcinomatosis, tuberculosis, pancreatitis)

Calculations: # of PMNs = Total nucleated cells x % of PMNs
Correction for RBCs (RBC count > 50,000/mm^3, seen in "traumatic tap") = measured PMN – (measured RBC / 250)

Clues in Fluid Analysis for SBP vs. Secondary Peritonitis:
- If ≥2 present, increased suspicion for secondary peritonitis: 1) serum total protein >1 2) serum glucose < 50 3) serum LDH > upper limit of normal
- Consider **repeat paracentesis after 48hrs of antibiotic treatment:** if PMN ↓ *and* only 1 org. on prior culture, likely SBP; if PMN ↑ *and* multiple org. on prior culture, then likely secondary peritonitis

	SAAG ≥ 1.1 g/dL (etiology related to portal HTN)	**SAAG < 1.1 g/dL (etiology NOT related to portal HTN)**
Fluid total protein < 2.5 g/dL	Cirrhosis	Nephrotic syndrome
Fluid total protein ≥ 2.5 g/dL	Heart failure Budd-Chiari syndrome	Pancreatitis Peritoneal carcinomatosis TB

SAAG = Serum Albumin – Ascites Albumin (from samples obtained on the same day)

PLEURAL FLUID INTERPRETATION

Transudate (due to Starling forces) vs. Exudate (due to increased capillary leak) (NEJM 2002;346:1971)

Light's Criteria: exudate if ≥ 1 criteria present (98% Sn / 83% Sp)*
1. **Pleural fluid protein / serum protein > 0.5**
2. **Pleural fluid LDH / serum LDH > 0.6**
3. **Pleural fluid LDH > 2/3 ULN of serum LDH (i.e. > 140)**

*Diuretics cause ~25% of transudates to be misclassified as exudates

If ≥ 1 of these, it's an exudate with 98% Sn / 70% Sp:
- Pleural fluid protein > 2.9, LDH > 95, cholesterol > 45

More specific criteria for confirming exudate:
- Pleural fluid cholesterol > 60 (54% Sn / 92% Sp)
- Serum albumin – pleural albumin ≤ 1.2 (87% Sn / 92% Sp)
- Pleural NT-proBNP < 2,300pg/mL (>80% Sn / >70% Sp)

- Other tests: adenosine deaminase, amylase, triglyceride, cholesterol, Gram stain/culture, 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

NASOGASTRIC TUBES

Indications:
- Decompression of SBO or minimize vomiting in ileus
- Enteral feeding / med administration; charcoal admin (ODs), oral contrast or colonoscopy prep
- Lactulose (hepatic encephalopathy)

Contraindications:
- Head / maxillofacial trauma, basilar skull fracture, or recent neurosurgical intervention
- Esophageal stricture or ≥ grade 2 varices / recent banding (discuss w/ GI if uncertainty regarding varices / banding)

Supplies:
- NGT, lubricant/viscous lidocaine ("UroJet"), Chux, emesis basin, cup of water with ice and straw, 60mL syringe, tape
- If NGT needed for decompression: use 14 to 16 Fr Salem sump NGT (larger diameter, ↓ clogging)

NGT Placement:

TYPES OF NGTs & USES
• Dobhoff: PO formula, meds • 14, 16 Fr: Decompression

- Assess patency and symmetry of nares by direct visualization
- Consider topical anesthetic (e.g. 4% lidocaine) pre-treatment
- Position patient in upright "sniffing" position with neck flexed and chin to chest
- Estimate distance of NGT insertion by measuring from xiphoid process→earlobe→nose tip
- Apply lubricant / ice to tip of NGT and/or apply viscous lidocaine directly into the nares
- Insert NGT into nares along floor & apply pressure posterior & slightly inferiomedial, not upward
- After passage of NGT into oropharynx (will feel curve & ↓ resistance), have patient swallow water via straw while advancing rapidly
  - If patient excessively coughs, gags, has change in voice or dyspnea, or increased resistance, **STOP** (never force) and suspect improper location (in airway or coiled) and immediately withdraw. Look in posterior oropharynx for coiling.
- Advance to predetermined depth. 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).

Dobhoff tube / Enteroflex: thinner, more flexible; more comfortable but ↑ **risk of placement into lung**

- Requires 2-step 2-CXR placement method
  1. Measure from nose to earlobe to mid-sternum → insert tube this distance → secure → obtain CXR
  2. If CXR shows tip (1) past carina & (2) midline → advance into stomach → repeat CXR → remove stylette once confirmed

General Troubleshooting:
- If tube coiling repeatedly in oropharynx on insertion, soak tip in ice water to make tube more rigid prior to insertion.
- NGT to suction should "sump" – air should audibly enter blue port and exit main port; if not: (1) flush blue port with air (never fluids), (2) flush main port with water (not NS, does not need to be sterile), (3) aspirate from main port → if not able to withdraw flush, NGT needs to be advanced vs. withdrawn (KUB can guide)
- To prevent clogging or adherence to gastric wall, NGTs should be flushed with 30cc water & air Q8hr. If clogged, can try methods to unclog tube as below in "Gastrostomy Tubes"

Complications (↑ with longer duration):
- GI: malposition, coiling, knotting anywhere along course of tube, nasal/GI tract perforation. ↑ risk acid/stomach content reflux and aspiration → consider PPI. Chronic suction → gastritis/pressure necrosis: consider removal if grossly bloody
- Pulm: intubation of lung → inadvertent med, contrast, TF administration → PNA, pulm abscess, tracheal perforation, PTX, death
- HEENT: nasal irritation, epistaxis, intracranial placement, skin erosion, sinusitis, alar necrosis, tracheoesophageal fistula/perf

Removal:
- If for ileus/SBO, consider removal when passing flatus or resolved n/v. Alternatively, may remove when NGT output <1L over 24 hours. Consider clamp trial before removing (clamp 4 hours, then check residual. Remove if <150 cc)
- Remove tape. Flush tube w/ 10mL air or NS. Turn OFF suction & clamp. Fold Chux around tube insertion site. Gently remove tube

GASTROSTOMY TUBES

Description:

- Clear, soft, graduated tubing held in place w/ plastic mushroom-shaped ring/balloon in stomach (~3 cm deeper in obese pts)
- May be replaced at bedside after epithelialized track forms (~2-4 wks; delayed by malnutrition, steroids, immunosuppression)
- Gastrojejunostomy (GJ) tubes have 3 access ports: G tube port, J tube port and balloon port
- Secured with vertical Hollister device
- Venting means access port is attached to a foley bag so contents/gas can flow out as needed

Troubleshooting

- Clogging: **only tube feeds and elixir meds should be given through J tube**
  - Attach 3cc syringe w/ warm H_2O to female Leur adaptor. Push or pulse plunger to force through debris. Flush w/ 30cc warm H_2O to ensure not clogged.
  - Can also try Seltzer, ginger ale, Coca-Cola. If persistent, can try pancrealipase (Viokase) with sodium bicarb
- Leaking: retract balloon or mushroom back to skin level; do NOT insert larger size tube (can cause stoma to enlarge), call service who placed G tube if persistent
- Migration: can cause n/v (w/ or w/o feeds), dumping syndrome. Confirm placement w/ *tube injection study* (30-60 mL 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 to protect)

FOLEY CATHETER

Choosing Catheter: (order from Central Supply, ED, or Ellison 6 if not on floor)

- **Many contain Latex**, use silicone if allergy; silicone also ↓risk CAUTI
- 2-way Foleys (drainage & balloon ports):
  16F (stock), 12F if stricture or device, **18F/20F Coudé if BPH** or high bladder neck → insert curve up / nub on hub pointed toward umbilicus
- 3-way Foleys (drainage, balloon, irrigation ports): 20F/22F used for **continuous bladder irrigation (CBI) in gross hematuria**

Placement:

1. Lay patient flat, prep, hold penis upright (keep on stretch while advancing)
2. Instill 10cc 2% viscous lidocaine (“**UroJet”)** into urethra
3. Insert Foley catheter to the hub
4. As catheter reaches bladder neck, keeping penis on stretch, point phallus down towards toes (to mimic natural curve urethra).
5. After urine return AND catheter hubbed, fill balloon w/ 10cc sterile H_2O
6. Gently withdraw catheter to bladder neck
7. Verify position by flushing with 60cc fluid (catheter in bladder) and withdraw. Inability to withdraw suggests:
   a. Bladder empty and sucking against bladder mucosa (instill 60 cc)
   b. Catheter in urethra or false passage
   c. Catheter outside bladder (undermined bladder neck in pt s/p prostatectomy/TURP)
8. Don’t forget to reduce foreskin (if not, may cause paraphimosis = **urologic emergency**)

Continuous Bladder Irrigation (CBI): consult urology to initiate

- Indications: gross hematuria (when you cannot see your hand through the foley due to presence of blood) +/- with clots
- Titrate flow to “fruit punch” colored urine (should be able to see through)
- When d/c’ing, usually start with clamp trial to ensure resolution before removal

Bladder Pressure: only done in the ICU

Indications: concern for intra-abdominal hypertension (≥12mmHg) or frank abdominal compartment syndrome (>20mmHg)

1. Ensure patient position correlates between measurements (head position as flat as possible) and pressure transducer set-up is arranged
2. Drain bladder and clamp drainage tube of foley
3. Inject 25cc of NS into aspiration port, wait 30-60s (allows detrusor muscle relax.)
4. Connect pressure transducer to aspiration port of foley and measure pressure at end-expiration

Special Circumstances:

- **Artificial Urinary Sphincter (AUS)**: men s/p prostatectomy c/b sig. urinary incontinence. DEACTIVATE device prior to placing foley. Place smallest catheter possible (12F) and remove ASAP.

Troubleshooting:

- **Difficulty in female patient**: likely poor positioning. Place sheets under hips & place pt in Trendelenburg
- **Urethral trauma**: blood at meatus. Leave catheter ≥3-5d
- **Foley is leaking**:
  - Bladder spasms 2/2 infection, mucosal irritation, overactive bladder. Start anticholinergic (oxybutynin 5mg TID PRN)
  - Foley obstructed 2/2 sediment, kinked, dome of bladder, clot. Flush catheter & bladder US
  - Urethra patulous (women w/ chronic indwelling catheters)

Suprapubic Tubes:

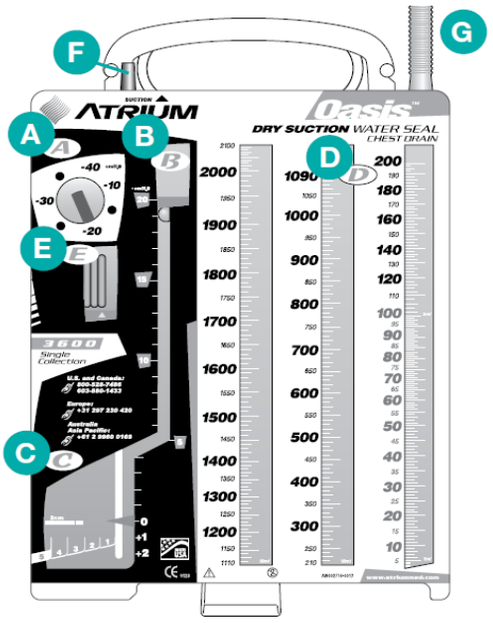
- Many types, usually standard Foley catheter
- Know type & size catheter, who exchanges, how exchanged, how frequently
- Is this a new tract (<7d, ask urology to replace) or established (years, you can try and replace)?
- If need to reinsert, decompress balloon and remove indwelling SPT tube. Use foley kit, prep area, apply lubricant to new tube, insert through tract (may have to use some force) until urine return, inflate balloon and ensure tube is mobile, attach to foley bag

CHEST TUBES

Indications: drainage of air (PTX), blood (hemothorax), pus (empyema), or lymph (chylothorax)

Chest Tube Logistics:

- Drainage: measured by gradations in 3 columns; if significant drainage, watch for re-expansion pulmonary edema
- Suction control: adjusts negative pressure applied to pleural space
  - Suction determined by setting on the device **[A]**, NOT at the wall; if working properly, suction verification window **[E]** orange bellows will be at triangle marker
  - **"Suction"** vs. **"water seal"**: if disconnected from wall suction, it is on water seal (i.e. "to gravity") and will allow for one-way flow of air out of chest, **[E]** orange bellows not expanded



A Dry suction control
B Water seal chamber
C Air leak monitor
D Collection chamber
E Suction monitor bellows
F Tube to suction
G Tube from patient

Troubleshooting:

- Air leaks: if bubbles present in the water seal chamber **[C]**, indicates air in pleural space. Higher level in chamber, greater leak. Ask patient to cough to assess for leak if bubbles are not continuous.
  - Ddx: air in pleural space (parenchymal lung injury or BPF) vs. leak in chest tube (check tubing and connections to Pleur-evac)
  - Note: "Tidaling" (movement w/ respiratory variation in water seal chamber) **[C]**) is normal – i.e. *not* an air leak
- Clogging: look for debris in tube, lack of tidaling, can try "stripping the tube" by compressing it with your fingers while pulling TOWARDS the drainage system, helpful to have an alcohol prep pad for lubrication, might require tPA (alteplase) for clot or Pulmozyme (dornase) for fibrinolysis → involve IP / surgery (whoever placed tube)

Removal:

- General criteria: no active air leak, pt off positive pressure ventilation, <150cc of drainage over 24h
- Steps to removal: place on suction (-40 mm Hg to -10 mm Hg) → place on water seal → clamp trial (clamp tube with hemostat)
  - With each step, wait 4 hours, then obtain CXR to ensure stable or improving PTX
- After stable on clamp trial, tube should be removed during exhalation (patient humming). Large chest tubes often require surgical knot to close hole covered by occlusive dressing (xeroform, 4x4 gauze, large tegaderm) for 48 hrs.

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)
   - Outside of normal business hours, page the on-call occupational health provider at p21272
   - **Have the following information available** for the OHS staff member at the time of your call:
     - Source patient: name, MRN, DOB, location, MD, diagnosis, known Hx, exposure to HBV/HCV/HIV meds
     - Needle: brand, size, gauge, specific device, device manufacturer, safety design type, part of a kit?
4. **Test the patient for HBV, HCV, and HIV**
   - **HBV/HCV: one gold top tube**
     - Order HBsAg and HCV qualitative Ab; if patient known HCV+, also send HCV RNA
     - If using paper form (available from OA), mark with BILLING NUMBER CL00009 so pt not charged
   - **HIV: another gold top tube**
     - **By law in Massachusetts** (MGL Part I Title XVI Chapter 111 Section 70F [M.G.L. c. 111, §70F])
     - *Written consent* is required to release HIV results to a third party. In the event of an exposure, since HIV status is being released to the exposed individual, *written consent* is assumed to be required.
   - **Send HIV tube to STAT lab** (results ~60 min once received), send HBV/HCV tube to standard core lab

If the patient is CONSENTABLE	If the patient is NOT CONSENTABLE
1. Obtain a special HIV occupational exposure consent form/lab requisition from the OA 2. Write STAT result in the comment section 3. Have the patient sign and then sign it yourself 4. Ensure the form is marked with BILLING NUMBER CL00009 so the patient is not charged	1. A valid and invoked health care proxy (you need paperwork!) can sign the occupational exposure consent form **OR** 2. Facility legal staff can assume temporary guardianship If the exposure occurs to a member of the *primary team*, the implication of the law is unclear, as that person is not technically a third party. Be conservative and obtain written consent anyway. If this is not possible, consider contacting Kimon Zachary (infectious disease), the Chiefs, the program director, or the chief medical officer.

5. **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)

PATHOGEN	EXPOSURE RISK (IF PATIENT IS POSITIVE)	POST-EXPOSURE PROPHYLAXIS (PEP)

HIV	Percutaneous (blood): 0.3%
	Mucocutaneous (blood): 0.09%
	
	There has only been 1 confirmed case of occupational transmission since 1999 (CDC)
		PEP can vary but usually includes 3 anti-retroviral drugs:
		• 2 NRTI **tenofovir PLUS emtricitabine** (or lamivudine) **AND** INSTI **dolutegravir** (or raltegravir)
		  ○ *INSTI can be substituted with a PI (darunavir) boosted by ritonavir*
		• 28 days of treatment recommended but optimal length unknown
		• Regimen usually well-tolerated, side effects include:
		  ○ Common but mild: n/v/d, fatigue, HA
		  ○ Rare: hepatitis, hyperglycemia, fevers, rash, pancytopenia
		• Serial testing at 6wk, 12wk, and 6mo if patient positive

HCV	Percutaneous: 1-2%	No PEP; serial testing at 4wk, 12wk, and 6mo if patient positive
AHBV	Percutaneous: 30%	Positive immune titers usually are an employment requirement Vaccine non-responders should be seen in occupational health

6. **File a safety report!**

Cardiac Monitoring (MGH Clinical Guidelines for Cardiac Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	- Cardiac monitoring for diagnostic purposes only	- Continuous cardiac monitoring - May be off monitor ONLY in presence of licensed clinical personnel	- Continuous cardiac monitoring
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	- No cardiac monitor - Unaccompanied	- With cardiac monitor - Accomp. by MD, PA, NP, or RN	- With cardiac monitor - Accomp. by MD, PA, NP, or RN
Example indications*	- Indicated to make dx or guide treatment - Post-op AF - Post-stroke AF - Routine syncope eval. - Low risk chest pain syndrome - Uncomplicated EtOH withdrawal	- Typical chest pain syndrome - Acute decompensated HF - Uncontrolled AF - 24 hrs s/p PPM/ICD placement and not PPM-dependent - Suspected cardiogenic syncope - Actual or risk for QTc prolongation - Complicated ETOH withdrawal	- Early ACS - S/p cardiac arrest - Critical care patients - Temporary PPM/pacing pads - s/p PPM/ICD and PPM-dependent - Mobitz II AVB, advanced 2nd deg. HB, complete HB - Unstable arrhythmias

*Refer to 2017 AHA guidelines on ECG monitoring for more detailed indications and monitoring duration (Circ 2017;136:e273)

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

O2 Saturation Monitoring (MGH Clinical Guidelines for O2 Saturation Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	- Spot check O2 sats as frequently as clinically indicated	- Continuous O2 sat monitoring - May be off monitor ONLY in presence of licensed clinical personnel	- Continuous O2 sat monitoring
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	- No O2 sat monitor - Unaccompanied	- With O2 sat monitor - Accomp. by MD, PA, NP, RN, or RRT	- With O2 sat monitor - Accomp. by MD, PA, NP, RN, or RRT
Example Indications	- Stable chronic respiratory disease - Post-procedure - Opioid naïve patients receiving PO narcotics	- COPD exacerbation - OSA not on CPAP - PCA use	- Acute respiratory distress - High-risk airway - NIPPV - Intubation - Continuous narcotic infusion

DVT Prophylaxis (MGH Anticoagulation Management Stewardship Committee VTE Prophylaxis Guidelines)

	Low Risk	Moderate Risk	High Risk
Risk factors	- Ambulatory - Estimated LOS <48 hr - Not meeting moderate- or high-risk criteria	- Major surgery (>45 min, not craniotomy, ortho, spine, or for cancer) - Acute illness; immobility w/ est. LOS >48h - H/o VTE, thrombophilia (incl. hormone tx) - Active malignancy	- Major surgery (craniotomy, ortho, spine, or for cancer) - Critical illness in ICU - 2+ moderate risk factors
Prophylaxis	Ambulation	Pharmacologic OR mechanical	Pharmacologic AND mechanical

- **30 / 30 / 30 Rule**
  - Pharmacologic prophylaxis: can be administered if platelets >**30**K
  - Mechanical prophylaxis: SCD boots should not be off the pt for >**30**% of the day
  - Ambulation: pts should ambulate **30** min/shift (60 min/day)
- **Pharmacologic prophylaxis options**:
  - Enoxaparin (Lovenox): 40 mg SC q24h; default in patients with CrCl >30 and BMI <40
  - Heparin (UFH): 5,000 units SC Q8h-Q12h; preferred in patients with CrCl <30 or BMI >40; Q8h pref. in cancer patients
  - Fondaparinux: 2.5 mg SC q24h (can be used if concern for HIT)
  - Alternatives to UFH during shortage: apixaban 2.5mg PO q12h, rivaroxaban 10mg PO q24h (avoid if CrCl <30)
    - Do not use if critically ill (ICU), trauma/spinal cord injury; avoid if recent/high risk for bleeding, anticipated invasive procedure, GI/GU CA and active intraluminal lesions, Childs B/C cirrhosis or any liver disease w/ coagulopathy

GI Prophylaxis

- Indications (Crit Care Med 2016;44:1395):
  - Admitted to ICU AND one of the following: 1) mechanically ventilated >48 hr, 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 >6 days, steroids >60 mg prednisone daily, ICU LOS >7 days
- Prophylaxis options (PO unless contraindicated): **PPI** (omeprazole, esomeprazole, pantoprazole) or **H2 blocker** (famotidine)

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 *Hematology* section 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)

	High Bleed Risk		Low Bleed Risk	
	CrCl >50	**CrCl <50**	**CrCl >50**	**CrCl <50**
Dabigatran	≥48hrs (4 doses)	≥96hrs (8 doses)	≥24hrs (2 doses)	≥48hrs (4 doses)
Rivaroxaban	≥48hrs (2 doses)	≥48hrs (2 doses)	≥24hrs (1 dose)	≥24hrs (1 dose)
Apixaban	≥48hrs (4 doses)	≥48hrs (4 doses)	≥24hrs (2 doses)	≥24hrs (2 doses)
Edoxaban	≥48hrs (2 doses)	≥48hrs (2 doses)	≥24hrs (1 dose)	≥24hrs (1 dose)

Cardiac Cath Lab Anticoagulation Guidelines

Medication	Hold Pre-Procedure*	Resume Post-Procedure
Heparin	**Therapeutic** (>15k U/d): 1hr or on call to CCL **Prophylactic**: continue	4hrs after sheath removal; no bolus
Enoxaparin (Lovenox)	**Therapeutic** (1mg/kg): 24hrs; **Prophylactic** (≤60 mg/d): 12hrs	Next morning
Bivalirudin	1hr or on call to CCL	4hrs after sheath removal; no bolus
Argatroban	1hr or on call to CCL	4hrs after sheath removal; no bolus
Dalteparin	**Therapeutic**: 24hrs; **Prophylactic** (≤5000 U/d): 12hrs	Next morning
Warfarin	5 days or INR ≤1.8	Night of cath
Apixaban, rivaroxaban, edoxaban	CrCl ≥30: ≥2 days; CrCl <30: ≥3 days	Next morning
Dabigatran	CrCl ≥50: ≥2 days; CrCl <50: ≥5 days	Next morning
Fondaparinux	CrCl ≥50: ≥4 days; CrCl <50: ≥7 days	Next morning

*Guidelines for endomyocardial biopsy differ. See "MGH Cardiac Cath Lab Anticoagulation Guidelines" on 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 *Cardiology: 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 1-6hrs pre-procedure.

IR Procedures

- **NPO guidance**: NPO (no solid food; ok to take medications with sip of water) for 8hrs if will receive sedation (e.g. port placement, biopsies, tube placement) or if a patient-specific need for sedation.
- **Low bleeding risk procedures**: para., thora., chest tube, PleurX, PICC, non-tunneled central catheter, transjugular liver biopsy, IVC filter placement & simple removal, catheter/tube exchange, dialysis access interventions, superficial bx/aspiration (thyroid, LN, breast, superficial bone), embolization for bleeding control
  - AC goals: INR <3, plt >20k; if cirrhosis: INR <3, plt >20k, fibrinogen >100 (if cirrhosis). **No need to hold AC.**
- **High bleeding risk procedures**: tunneled central access catheter placement/removal, G- or J-tube placement, nephrostomy tube placement, biliary interventions, TIPS, solid organ/deep tissue biopsies, LP/spine procedures, arterial interventions/angiography, intrathoracic venous interventions (SVC/IVC), portal vein interventions, catheter-directed lysis, complex IVC filter removal
  - AC goals: INR <1.8, plt >50k; if cirrhosis: INR <2.5, plt >30k, fibrinogen >100. AC management per table below.

Medication	Hold Pre-Procedure**	Resume Post-Procedure
Heparin	**Therapeutic**: 4-6hrs; **Prophylactic**: 6hrs	6-8hrs
Enoxaparin (Lovenox)	**Therapeutic**: 24hrs / 2 doses; **Prophylactic**: 12hrs / 1 dose	12hrs
Dalteparin	24hrs / 1 dose	12hrs
Fondaparinux	CrCl ≥50: 2-3 days; CrCl <50: 3-5 days	24hrs
Bivalirudin	2-4hrs	4-6hrs
Argatroban	2-4hrs	4-6hrs
Warfarin	5 days or INR ≤1.8	Day after procedure; bridge if high-risk
Apixaban, edoxaban	CrCl ≥50: ≥2 days / 4 doses; CrCl <50: ≥3 days / 6 doses	24hrs
Rivaroxaban	CrCl ≥30: ≥2 days / 2 doses; CrCl <30: ≥3 days / 3 doses	24hrs
Dabigatran	CrCl ≥50: ≥2 days / 4 doses; CrCl <50: ≥3-4 days / 6-8 doses	24hrs

**See "MGH Interventional Radiology Periprocedural Management" guidelines on Ellucid for further details.

CODES

A-Access
B-Backboard
C-Code Status
D-Defib
D-Drips
E-Epi
E-Electricity (150-200J; tele)
F-Fluids
F-Family
G-Glucose

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

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

H's and T's:

CAUSE	MANAGEMENT
Hypoxemia	Intubate, ECMO
Hypovolemia	Access, crystalloid, product
H+ (Acidemia)	Bicarb
Hypo/hyperK	Tx hypoK (D50W 1-2 amp + insulin 10 units IV), calcium gluconate 1-2g IV
Hypothermia	Warming
Hypoglycemia	D50
Tamponade	Pericardiocentesis
Tension PTX	Needle decompression
Thrombosis – MI	PCI, ECMO
Thrombosis – PE	tPA, ECMO
Toxin / Drugs	Stop drugs, reversal agents (narcan)

Others:

CAUSE	MANAGEMENT
Septic Shock	Abx, source control
Mucus Plug	Suction/Chest PT
Auto-PEEP	Disconnect vent
Anaphylaxis	Crystalloid, epi

Code/Rapid Data to Obtain

[ ] Preceding events
[ ] Vitals
[ ] Exam
[ ] FSBG
[ ] PMH
[ ] Recent procedures
[ ] Cardiopulm. history
[ ] Last TTE
[ ] Med list
[ ] PRN meds received
[ ] Infusions
[ ] EKG
[ ] Tele if arrhythmia
[ ] Last Hgb
[ ] Last K
[ ] Last Bicarb
[ ] ABG

If Intubating:
[ ] Prior intubations
[ ] Difficult airway?
[ ] Hemodynamics/Heart
[ ] Aspiration Risk?
[ ] Labs

ACS

ASA 325, heparin, statin, TNG, BB.
CCL if HD unstable, refractory CP, VT

STEMI: x6-8282
Interventional attending; decides on CCL

Bradycardia

Conduction disease, R sided MI, vagal, med effect, ↑ICP, hypothyroidism, hypoxemia

Atropine 0.5-1mg q3-5m, max 3mg
Dopamine 2-20mcg/kg/min
Epinephrine 2-10mcg/min
Isproterenol 2-10mcg/min
Transcutaneous pacing (midaz/fentanyl or ativan/dilaudid)
Transvenous pacing

Tachycardia

Narrow: AVRT/AVNRT, AF/AFlutter, AT, MAT
Wide: MMVT, PMVT, SVT w/aberrancy, PM mediated/tracked
Synchronized Cardioversion
Narrow/regular: 50-100J
Narrow/irregular: 120-200J
Wide/regular: 100J
Wide/irregular: 150-200J
Medications
Narrow/reg: **adenosine** (6, 12, 12)
Wide/reg:
- **Amio**: 150mg→1mg/min
- **Lido**: 100mg→50mg q5 x3 →1-2 mg/min
- **Procainamide**: 20-50mg/min until hypoTN or QRS ↑50%→1-4 /min
- consider adenosine unless WPW

Wide/irreg:
- **PMVT**: amio, lido; tx ischemia
- **Torsades**: Mg 2mg, ↑HR (Isuprel)
- **AF+WPW**: proc, ibutilide (1mg) (⊘adenosine, BB/CCB, dig)

GIB

2 large bore IV, T&S, IVF, pRBC, IV PPI 40mg. Octreotide 50mcg + CTX if portal HTN. Correct coagulopathy. RICU if hematemesis.

Hypotension

Cardiogenic: MI, ADHF, BB/CCB toxicity, acute myocarditis, valvular disease (AS)
Distributive:
S-Sepsis **A**-Adrenal Insuff
A-Anaphylax **S**-Spinal Shock
L-Liver dz **S**-Sleeping
T-Toxin
Hypovolemic: blood, over diuresis / removal w/ HD, insensible losses
Obstructive: PE, tamponade

Acute Hypoxemia

Aspiration
Mucus plug
Pneumonia
Pulm edema (vol., MI, HTN, tachy)
PE
PTX
Pleural effusion

Hypercarbia

↓RR: sedatives, central sleep apnea, OHS, brainstem stroke, tumor, infection, hypothyroidism
↓V_T: OSA, pleural effusion/fibrosis, obesity, kyphosis/scoliosis, abd dist, PTX, neuropathy, NMJ disorder, myopathy,
↑V_D and/or ↓V_T: COPD, asthma, OSA, ILD, CHF, PNA, PE

AMS

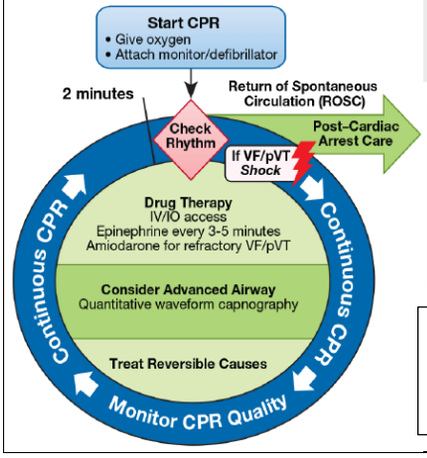
CNS: CVA, ICH, sz, infxn, PRES
Metabolic toxins: NH3, CO2, BUN, Na
Exogenous toxins: meds, drugs, w/d
Vitals: hypoTN, hypoglycemia
Misc: TTP, AI, hypothyroid

PE

Large PE? PE w/ abnormal VS (tachycardia, hypotension), evidence of R heart strain (TTE, EKG, or +biomarkers), central or saddle PE → **PERT x4-7378**
Order: TTE, EKG, CBC w diff, PT/PTT, BMP, LFTs, lactate, D-dimer, Trop, NT-proBNP, T&S, LENIs
tPA: Pulseless→50mg/2m, 50mg in 30m | Pulse→100mg/2h | Follow w/ heparin gtt
Contraindications: prior ICH, ischemic CVA <3mo., active bleeding, CNS surgery/trauma (<2-3mo.)

ACLS

Non-shockable rhythm: Epi as soon as feasible
Shockable rhythm (VT/VF): Epi after initial defib attempts are unsuccessful



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

Post Arrest:
Pressors:
if brady→levophed
if tachy→neo
BRING EPI (can give 100mcg)

Epi: 1mg IV/IO q3-5m
Amiodarone (VT/VF): 300→150 mg

Seizure

Ativan 2-4mg IV x2, diazepam 20mg PR, or Keppra 20mg/kg

Anaphylaxis

Epi 0.3-0.5 IM (1:1000; 1mg/mL); alt: 0.1-0.3mg IV (1:10,000; 0.1mg/mL) → repeat q5-15min; start gtt if >3 required
Other agents: diphenhydramine 50mg, methylpred 125mg IV, albuterol nebs, IV fluids

NUMBERS

ICU Resource RN	x6-6718	p25213
Cardiac Access RN	x4-2677	p31951
MICU Intensivist	c857-331-0741	p26955
HCICU Intensivist		p29151
ECMO	c857-310-0335	p29151
STEMI	x6-8282	
PERT	x4-7378	
Rapid Response, RICU, Stroke	x6-2333	

Post-Acute Care: post-hospital care of patients to help them return to baseline

- Largest source of Medicare regional variation. High cost growth (NEJM 2014;370:689) and risk of readmission (Health Aff 2010;29:57).
- 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 scanners), procedures, or significant acute issues (hypoxemia, hypotension)

Setting (most to least intensive)	Description	Patients / Diagnoses	Avg LOS	MD	Therapy / Ancillary Services
Long Term Acute Care Hospital (LTAC)	High intensity hospital-level care	- Tracheostomy - Chemotherapy **≥ 3-day ICU stay** required to qualify	20+ days	Daily MD visits	- RT - PT/OT PRN - HD
Inpatient Rehabilitation Facility (IRF, "acute rehab")	Intensive therapy for recovery of function	- Post-stroke - Spinal cord injury - Note: Specific dx codes required to qualify	7-21 days	2-4x/week MD visits; PM&R presence	- 3+ hours of therapy/day (pt must be able to participate)
Skilled Nursing Facility (SNF)	"Sub-acute" rehabilitation; looks/feels like nursing home; must have 3-night hospital stay to qualify under Medicare	- CHF, PNA, UTI - Generally older patients with functional decline / unsafe at home	3-21 days	~1x/week MD visits; very limited capacity for management changes	- 1-2 hours of therapy/day (pt must be able to progress)
Home Health	Home-based services post-hospitalization or via PCP referral	- Wound care - IV antibiotics - Post-hospital functional decline - Home safety eval	N/A	Managed by PCP or prescribing outpatient clinician	- 4-8 PT/OT visits - RN visits as needed

Special Cases

- **Hospice**:
  - Criteria: pt must have a terminal illness with prognosis of ≤6 months as certified by a physician. Depending on the hospice agency, pt may need to forego curative treatments (i.e., chemo, expensive antibiotics, etc.)
  - Home hospice: fully funded by Medicare. RNs visit, but patients need full-time caregiver support in the home, which can be a barrier to home hospice discharge
  - Inpatient hospice (SNF or dedicated inpatient hospice facility): room & board (~$400 per day) only covered by MassHealth, but not other insurers
  - GIP (in-hospital hospice care): fully funded by Medicare, patient must quality → discuss with Pall Care
- **Long-term care**:
  - Patients residing in nursing homes with stably poor functional status and who require assistance with ADLs/IADLs, but do not require post-acute level care
  - Private pay or covered by MassHealth, but not funded by Medicare
- **Patient/family refusal of SNF/rehab**: recommend higher-quality SNFs in Partners Skilled Nursing Facility Network
- **Alternative programs**: if patient is in Partners ACO, discuss additional home-based care options with case manager

Recommended websites for formulas:
www.mdcalc.com
www.nephromatic.com

Drug Dosing and Body Weights

Actual Body Weight (ABW): actual weight recorded on admission (most commonly used weight for dosing)

Ideal Body Weight (IBW):
Male: 50.0kg + 2.3kg for every inch over 5 feet
Female: 45.5kg + 2.3kg per inch over 5 feet

Adjusted Body Weight (AdjBW):
AdjBW = IBW + 0.4 x (ABW – IBW);
use for obese pts (i.e., if ABW>1.3x IBW)

Electrolytes and Fluids

[Na^+] in fluids (mEq/L): NS = 154, ½NS = 77, 3% = 514, LR = 130

Total Body Water (TBW):
TBW = F x weight; F = 0.6 ♂, 0.5 ♀ (or 0.5 and 0.45 if elderly)
Intracellular fluid (ICF) = 2/3 TBW
Extracellular fluid (ECF) = 1/3 TBW
ECF = 3/4 interstitial, 1/4 intravascular

Free Water Deficit in Hypernatremia:

$$\text{water deficit (L)} = \text{TBW} \times \left(\frac{\text{measured Na}}{140} - 1 \right)$$

ΔNa based on Infusate Sodium (per 1L infusion) [use for hypoNa *or* hyperNa]:

$$\text{change in serum Na} = \frac{\text{infusate Na} - \text{serum Na}}{\text{TBW (in liters)} + 1}$$

Sodium Correction in Hyperglycemia:
corrected Na = measured Na + (2.4/100 mg/dL) x (glucose–100)
Needed for routine chemistries; not required for ABG specimen

Calcium Correction for Hypoalbuminemia:
Corrected Ca = Ca (mg/dL) + 0.8 x (4.0 − measured alb (mg/dL))

Transtubular Potassium Gradient:

$$\text{TTKG} = \frac{\text{KUrine / Kserum}}{\text{UOsm / SOsm}}$$ accurate if UNa > 25, UOsm>SOsm

Normal TTKG = 8-9, but >11 with K load
Hyperkalemia: <6-7 suggests hypoaldosteronism
Hypokalemia: <2 suggests extrarenal loss; >7 suggests renal loss

Fractional Excretion of Sodium and Urea:

$$\text{FeNa} = \frac{\text{UNa} \times \text{PCr}}{\text{PNa} \times \text{UCr}} \quad \text{FeUrea} = \frac{\text{UUN} \times \text{PCr}}{\text{BUN} \times \text{UCr}}$$

Osmolality

Plasma Osmolality:

$$\text{calc osm} = 2 \times \text{Na (mEq/L)} + \frac{\text{glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8} + \frac{\text{EtOH (mg/dL)}}{4.6}$$

Osmolar Gap:
OG = P_{osm} – calc osm (normal: < 10)

Stool Osmol Gap:
SOG = Osm_{stool} – 2 × (Na_{stool} +K_{stool})
>125: suggests osmotic diarrhea; <50: suggests secretory diarrhea

Urine Osmol Gap:
U_{osm} = 2(U_{Na} + U_K) + U_{urea} / 2.8 + $U_{glucose}$ / 18 (normal: 10-100)
<150: shows impaired NH_4^+ excretion (type I/IV RTA)
>400: shows increased NH_4^+ excretion (type II RTA/diarrhea)

Acid/Base Physiology

Primary metabolic acidosis (Winter's formula):
compensated pCO_2 = 1.5 × HCO_3 + 8 ± 2

Primary metabolic alkalosis:
compensated pCO_2 = 0.7 × HCO_3 + 20 ± 5

Primary respiratory acidosis:
Acute: ΔpH 0.08 for each Δ$PaCO_2$ 10 mmHg; ΔHCO_3 1 for each Δ$PaCO_2$ 10 mmHg
Chronic: ΔpH 0.03 for each Δ$PaCO_2$ 10 mmHg; ΔHCO_3 4 for each Δ$PaCO_2$ 10 mmHg

Primary respiratory alkalosis:
Acute: ΔpH 0.08 for each Δ$PaCO_2$ 10 mmHg; ΔHCO_3 2 for each Δ$PaCO_2$ 10 mmHg
Chronic: ΔpH 0.03 for each Δ$PaCO_2$ 10 mmHg; ΔHCO_3 4-5 for each Δ$PaCO_2$ 10 mmHg

Anion Gap:
AG = Na – (Cl + HCO3) [normal ~12]
Corrected AG = AG + 2.5 x (4 – measured alb (mg/dL))

Delta-Delta Gap:
ΔΔG = ΔAG* / ΔHCO_3 = (AG - 12) / (24-HCO_3):
<1 mixed hyperchloremic and anion gap acidosis;
1-2 anion gap acidosis
>2 anion gap acidosis and metabolic alkalosis
*In lactic acidosis, use 0.6*ΔAG (due to ↓ renal clearance of lactate compared to other anions)

Urine Anion Gap:
UAG = U_{Na} + U_K – U_{Cl} (normal: -20 to +20)
>20: Type I/IV RTA; <20: diarrhea/Type II RTA

Cardiovascular Physiology

SaO_2 and PaO_2 Correlation:

SaO_2	99	98	95	**90**	88	80	73	60	50	40	30
PaO_2	149	100	80	**60**	55	48	40	30	26	23	18

Arterial Oxygen Content (C_aO_2):
C_aO_2 = (1.34 x Hb x S_aO_2) + (0.003 x P_aO_2)

Cardiac Output: CO = HR x SV

Cardiac Output (Fick): CO = VO_2 / (C_aO_2 – C_vO_2)
→ $VO_2 \approx$ 3 x wt (kg) *or* 125 x BSA (roughly 250 ml/min; use metabolic cart to measure precise value)

Systemic Vascular Resistance (normal 800-1200):

$$SVR\,(dynes \cdot sec \cdot cm^{-5}) = \frac{MAP\,(mmHg) - CVP\,(mmHg)}{CO\,(L/min)} \times 80$$

Pulmonary Vascular Resistance (normal 150-250):

$$PVR\,(dynes \cdot sec \cdot cm^{-5}) = \frac{mPAP\,(mmHg) - PCWP\,(mmHg)}{CO\,(L/min)} \times 80$$

Law of LaPlace: σ (wall stress) = P × r / 2h
P = intraventricular pressure, r = radius, h = wall thickness

Pouiselle Equation: $\Delta P = 8\mu \times L \times Q / \pi r^4$
μ = dynamic viscosity, L = length, Q = flow, r = radius

Bazett Formula: QTc = QT / √RR (♀ < 460 ms; ♂ < 440 ms)

Friedewald Formula: LDL = TC – HDL – (TG / 5)

Maximum Heart Rate: Max HR = 220 – age (if unable to achieve ≥85% max HR, suggests chronotropic incompetence)

Pulmonary Physiology

Transpulmonary and Diastolic Pulmonary Gradient:
TPG = mPAP – PCWP; >12-15 suggests pre-cap pulm HTN
DPG = PAd – PCWP; >7 mmHg suggests pre-cap pulm HTN

Alveolar-arterial (A-a) Oxygen Gradient:
Calculated A-a gradient = $PAO_2 - PaO_2$

$$\text{where } PAO2 = FiO2 \times (Patm - PH2O) - \frac{PaCO2}{R} \approx FiO2 \times 713 - \frac{PaCO2}{0.8}$$

FiO_2 = 0.21 on RA; add 0.03 for each extra L O_2/min cannula
P_{atm} = atmospheric pressure (mmHg) = 760
P_{H2O} = alveolar pressure of water (mmHg) = 47
R = respiratory quotient = $V_{CO2}/V_{O2} \approx 0.8$

Normal A-a gradient = 2.5 + (0.21 x age)

Shunt Fraction (normal: 3-8%, but ↑ 5% for every 100 mmHg drop in PaO_2 below 600 mmHg):

$$\frac{Qs}{Qt} = \frac{0.0031 \times (PAO2 - PaO2)}{[0.0031 \times (PAO2 - PaO2)] + (Ca - vO2)}$$

where Qs = shunt flow, Qt = total flow, $C_{a\text{-}v}O_2$ assumed 5%.
FiO_2 must be 1.0 in this calculation
R becomes 1.0 after breathing 100% O_2 for 20 minutes because of N_2 wash-out
> 15% = pathologic shunt

Minute Ventilation (V_E) (volume per unit time): V_E = RR x V_t

Bohr Equation (i.e., dead space fraction) (normal: 0.2 – 0.4):

$$\frac{Vd}{Vt} = \frac{PaCO2 - PetCO2}{PaCO2}$$

Gastroenterology and Hepatology

Maddrey's Discriminant Function for Alcoholic Hepatitis
MDF = 4.6 x (PT – control PT) + total bilirubin
>32: consider treatment with glucocorticoids

MELD (Model for End-Stage Liver Disease): use online calc

Correction of Ascitic PMN for Ascitic RBC
Corrected $PMN_{ascites}$ = $PMN_{ascites}$ – ($RBC_{ascites}$ / 250)

Neurology

Correction of CSF WBC for CSF RBC:
Corrected WBC_{CSF} = WBC_{CSF} – (WBC_{serum} x [RBC_{CSF} / RBC_{serum}])

Nephrology

Creatinine Clearance from Timed Urine Collection

$$CrCl = \frac{UCr\,(mg/dl) \times Uvolume\,(ml/min)}{serum\ Cr\,(mg/dL)}$$

eGFR: use CKD-EPI equation (if black, multiply by 1.159)

Hematology

Absolute Neutrophil Count: ANC = WBC x (% PMN + % bands)

Reticulocyte Production Index (RI) (normal: 2-3):

$$RI = \%retic \times \left(\frac{Hct}{patient's\ normal\ Hct}\right) / \text{maturation factor (MF)}$$

MF: 1.0 (Hct > 36), 1.5 (Hct 26-35), 2.0 (Hct 16-25), 2.5 (Hct < 15)

RI: <2 in hypoproliferative state; >3 in hyperproliferative state

Statistics and Epidemiology

Sensitivity = TP / (TP + FN)

Specificity = TN / (FP + TN)

Positive Predictive Value = TP / (TP + FP)

Negative Predictive Value = TN / (FN + TN)

Positive Likelihood Ratio = Sensitivity / (1 – Specificity)

Negative Likelihood Ratio = (1 – Sensitivity) / Specificity

Number Needed to Treat = 1/absolute risk reduction (ARR)

Main Number		
617-726-2000 (MGH prefix: -724, -726, -643)		
857-238-XXXX (Lunder), 617-523-XXXX (MEEI)		
See Partners Paging Directory for consult pagers		
Emergency Numbers		
Senior On (Med Sr)/Bauer Room	3-1388, p22337	
ED Triage Sr (ED Sr)	6-2333: x75360	
Med Consult Pager (Code Backup)	p13480	
RICU Team (intubation)	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	
Pharmacy (on call)	6-4276	
RT (on call)	p24225	
Acute Stroke (neurology)	6-3333	
ICU Nursing Supervisor	6-6718, p25213	
Hospital Floors	**Phone**	**Fax**
ED – Front desk	4-4100	6-7415
Acute	4-4170	
Urgent	4-4190	
Fast Track	4-4134	
APS	6-2994	p27792
ED Obs Bigelow 12	6-3800	
Bigelow/Gray 3 – OR	6-8910	
Bigelow 7 – Medicine	6-3496	6-0997
Bigelow 9 – HMU	4-9000	4-9999
Bigelow 10 – Dialysis	6-3700	6-5876
Bigelow 11 – Medicine	4-1500	6-4202
Bigelow 13 – RACU	8-1300	8-1320
Bigelow 14 – HMU	6-6100	6-7562
Blake 4 – Endoscopy Suite	6-8074	4-6832
Blake 6 – Transplant Surgery	4-8610	4-8650
Blake 7 – MICU	6-8048	4-0102
Blake 8 – Cardiac SICU	4-4410	4-4450
Blake 11 – Psychiatry	4-9110	4-9150
Blake 12 – ICU	6-8071	6-7560
Blake 14 – Labor & Delivery	4-9310	4-9450
Ellison 4 – SICU	4-5100	6-7566
Ellison 6 – Ortho / Urology	4-4610	4-4650
Ellison 7 – Surgery	4-4710	4-4750
Ellison 8 – Cardiac Surgery	4-4810	4-4850
Ellison 9 – CICU	4-4910	4-4950
Ellison 10 – Step Down Unit	4-5010	4-5050
Ellison 11 – Cardiac Access	4-5110	4-5150
Ellison 12 – HMU	4-5210	4-5603
Ellison 13 – Obstetrics	4-5310	4-5350
Ellison 14 – Plast/Burn/OMFS	4-5410	6-7561
Ellison 16 – HMU / Onc	4-5610	3-5082
Ellison 19 – Thoracic Surgery	4-5910	4-5950
Phillips 20 – HMU	4-6010	4-6050
Phillips 21 – HMU	4-6110	4-6150
Phillips 22 – GYN / Surgery	4-6210	4-3497
White 3 – PACU	6-2835	4-8422
White 6 – Ortho	6-6106	6-7555
White 7 – Surgery	6-3336	6-7550
White 8 – Medicine	6-3339	6-7551
White 9 – Medicine	6-3342	6-7557
White 10 – Medicine	6-3345	6-7564
White 11 – Medicine	6-3348	6-7558
Lunder 6 – Neuro ICU	8-5600	8-5701
Lunder 7 – Neuro / NSGY	8-5700	8-5701
Lunder 8 – Neuro / NSGY	8-5800	8-5899
Lunder 9 – Oncology	8-5900	8-5999
Lunder 10 – Oncology/BMT	8-1000	8-1089
Pharmacy		
Outpatient pharmacy (fax: 6-3789)	4-3100	
Outpatient pharmacy (private line)	6-2354	
Pharmacy – White 8	p17648	
Pharmacy – White 9	p24382	
Pharmacy – White 10	p22527	
Pharmacy – White 11	p17718	
Pharmacy – Bigelow 7	p24406	
Pharmacy – Bigelow 11	p27604	
Pharmacy – Blake 7	p27614	
Pharmacy – Ellison 9	p28333	
Pharmacy – Ellison 10	p28334	
Pharmacy – Lunder 9	p28337	
Pharmacy – Lunder 10 (BMT)	p17905	
Pharmacy – Lunder 10 (Leuk)	p28338	
Laboratories		
General lab info	4-LABS	
Chemistry/Hematology	6-2345	
STAT Chemistry/Hematology	4-7617/4-4734	
Serology	4-7645	
Special coagulation	6-3900	
Blood gas / STAT lab – Bigelow 5	6-3856	
Blood bank – Bigelow 2	6-3623	
Blood bank – Lunder	8-5280	
Microbiology – Bigelow 5	6-3613	
After hours (blood culture room)	6-7919	
Parasitology	6-3861	
Virology	6-3820	
Pathology lab – Blake 3	4-1449	
Immunopath (Flow, ANCA, EM)	6-8487	
Cytology / Cytopathology – Warren 1	6-3980	
Toxicology (blood/urine)	4-7618/4-7615	
CCU Fellow Back-Up – see Partners Paging Directory		
Overnight Issues / Echo	Overnight fellow	
Access (hematoma, sheath, IABP)	Access fellow	
Cardiology Studies		
Cath Lab	6-7400	
Echo Lab	6-8871	
Stress Lab	4-3600	
Holter Lab	6-7737	
EP Lab	6-5036	
Pacer Interrogation (PPM)	p16939	
Vascular Studies		
Vascular Lab – Warren 9 (PVR/ABI)	6-2034	
Pulmonary Studies		
PFTs – Cox 2	6-1200/3-9680	
Sleep Study (inpatient/outpatient)	4-7426	
GI Studies		
Endoscopy Lab – Blake 4	6-8074/6-3732	
Neurology Studies		
EEG – Blake 12	6-3640	
EMG/NCS – Blake 12	6-3644	
Medical Records		
Record requests	6-2470/6-2477	

Administration	
Administrator on-call	p26501
Admitting (fax: 4-8409)	6-3390/6-3384
Finance Department	6-2171
MD Connect (OSH Transfer Requests)	6-3384
Physician Referral Line	6-5800
Registration	866-211-6588
Registrar's office	6-2119
Security	6-2121
IT Help Desk	6-5085
Primary Care Clinics	
Bulfinch Medical Group	617-724-6610
IMA 1A	617-726-2370
IMA 1B	617-726-2374
IMA 2	617-726-7930
IMA 3	617-724-8400
IMA 4A	617-724-6200
IMA 4B	617-726-2674
IMA 5	617-726-7939
IMA 6	617-726-2375
IMA 7	617-724-2700
IMA 8	617-726-2368
IMA 9	617-726-8157
IMA 10	617-724-4600
Massachusetts General Medical Group	617-724-8059
Medical Walk-In Unit	617-726-2707
MGH Back Bay	617-267-7171
MGH Beacon Hill Health Associates	617-726-4900
MGH Charlestown	617-724-8315
MGH Chelsea 100 Everett Avenue	617-887-4600
MGH Chelsea 151 Everett Avenue	617-889-8580
MGH Downtown	617-728-6000
MGH Everett Family Care	617-394-7500
MGH Primary Care Associates Waltham	781-487-4040
MGH Revere 300 Broadway	781-485-1000
MGH Revere 300 Ocean Avenue	781-485-6303
MGH Senior Health	617-726-4600
MGH West (Waltham)	781-487-4300
MGH Women's Health Associates	617-724-6700
North End Waterfront Health	617-643-8000
Subspecialties	
Allergy / Immunology	6-3850
Anesthesia Pre-Op Inpt Evaluation	6-3382
Anticoagulation (AMS)	6-2768
Boston Healthcare for the Homeless	781-221-6565
Brace Shop (White 10)	6-3248
Breast Center	6-9200
Cardiology	6-1335
Dental	6-1076
Oral and Maxillofacial Surgery	6-2740
Dermatology	6-2914
Endocrine	6-8720
Gastroenterology (Fellows)	4-6113
General Surgery	6-2760
Gynecology	4-6850
Gyn Onc	4-4800
Hematology	4-4000
Infectious Disease	6-3906
Infection Control	6-2036

Interventional Radiology	
GU/GI	6-8073
Neuro	6-8320
Vascular	6-8315
Nephrology	6-5050
Neurology	
Acute stroke consults	6-2333 / p34282
Non-acute stroke & ICU consults	p20202
Non-stroke floor consults	p20702
Non-stroke EW consults	p20000
Neurosurgery	6-1002
Obstetrics	6-2229
Oncology	4-4000
Optimum Care Committee (Ethics)	p32097
Orthopedics	6-2784
Pain Service (Acute) – peri-op/trauma	6-8810
Pain Service (Chronic)	p17246
Palliative Care	4-4000
Pathology (FNA service)	6-3980
Physical Therapy	6-2961
Podiatry	6-3487
Poison Control (ingestion)	617-232-2120
Psychiatry	4-5600
Psychiatry intake (for patients)	4-7792
Pulmonary	6-1721
Radiation Oncology	6-8650
Rheumatology	6-7938
Thyroid Clinic	6-3872
Travel Clinic	4-6454
Urology	6-2797
Mass Eye and Ear Infirmary	
Page Operator	617-523-7900
Direct Dial to MGH from MEEI	87 + last 5 digits of MGH #
Emergency Room	617-523-7900 x3240
11th floor (Inpatient)	617-523-7900 x2480
ENT Consult (MEEI ED)	617-573-3431
ENT Clinic	617-573-4101
Ophthalmology Clinic	617-573-3202
Ophthalmology Consult	p23555 or 617-573-3412 opt 3
iPOP (Translation Service)	
IPOP	6-6966
IPOP Access Code	017616
IPOP Pin – Blake 7	1054
IPOP Pin – Ellison 9	8043
IPOP Pin – Ellison 10	8034
IPOP Pin – Bigelow 7	1056
IPOP Pin – Bigelow 11	8059
IPOP Pin – White 8	7934
IPOP Pin – White 9	1050
IPOP Pin – White 10	7930
IPOP Pin – White 11	7931
IPOP Pin – Lunder 9	8081
IPOP Pin – Lunder 10	8077

See "Radiology" Section for Radiology contact information.

Main Number
617-243-6000

Key Pagers	
4 Usen Admitting SAR/NF	p56789
4 West Admitting SAR/NF	p56788
Locum Tenens/Covering Intensivist	p57651
Hospitalist	p51253

Hospital Floors	
ED	6193 / 6194
ICU (2nd floor)	6587
3 West	6363
4 Usen	6459
4 West	6400
6 Usen	6307
6 East	1670

Laboratories	
Main Lab (for add-ons)	6300
Hematology	6095
Blood Bank	6091
Chemistry	8389
Urine Studies	6090
Microbiology	6096
Pathology	6140

Radiology	
Main Number	6600 / 6076
Radiology Reading Room	6162
ED Radiology	6185
Ultrasound	6581
CT (main)	6725
CT (ED and after hours)	6505
MRI	6217
PET	6334
Nuclear Medicine	6087
Interventional Radiology	6800 / 3761
Night Watch	617-732-5657

Cardiac Studies	
ECG	6229
Echo	6231 / 2665
ETT or Nuclear Stress	5375 / 6229 / 6087

Ancillary Staff	
Nursing Supervisor	p57711
Pharmacy	6012
Respiratory Therapy	6213
Phlebotomy	5903
Speech Language Pathology	6548
Infection Control	6282
Case Management/Social Work	6695
Chaplain	6634
Interpreter Services	6698

Miscellaneous	
OR	6289
PACU	6295
GI Unit	6151
Dialysis	6203
Pulmonary Lab	6127
EEG/EMG	6624
Anticoagulation Clinic	6147
Cancer Center	1230
Cardiovascular Health Center	7100
Infusion Clinic	6350
Occupational Health	6168
Admissions	5500
CareFinder (new NWH PCP)	6566
MDConnect (transfer to MGH)	877-637-3337
DOM Office (6 South)	6467
Chief Medical Resident	6470
Outside Calls	617-243-6841

Getting to NWH (2014 Washington St, Newton, MA)

- You will receive transportation information prior to your NWH rotation
- Note that all transportation stipends are taxed
- MGH Uber Account
  - Use Uber for Business → MGH DOM Internal Medicine Residency Program account
- Driving
  - Stipend covers gas and tolls
  - On day 1, park in patient garage for ~$10
  - Pay $15 cash/check at parking/security office for pass to park in employee garage behind West Entrance
- Public transportation
  - Take MBTA Green Line D outbound train to Riverside -> Woodland stop -> NWH is 2 blocks to the left