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Chest Pain

- **Pleuritic** pain (inflammation of serous surfaces) is characterized by sharp pain that increases with inspiration or cough
 - o Pulmonary embolism, pericarditis, abdominal conditions extending to diaphragm and lower pulmonary serous surfaces
- **Musculoskeletal** pain may feel sharp and occur with inspiration/cough but more POSITIONAL and related to affected msk components
- **Visceral** pain produces poorly localized sensations described as squeezing, pressure, ache, tightness, tearing/ripping or burning rather than pain
 - o MI, aortic dissection, esophageal disease

Risk Factors for CVD

- DM, Smoking, HTN, dyslipidemia, FHx of CHD, CKD, abdominal obesity

History

- Pleuritic Pain:
 - o **Pneumothorax**: acute onset of pleuritic pain with dyspnea. Usually young or sec. to lung disease.
 - o **Pulmonary Embolism**: gradual onset of pleuritic pain, sudden sob
 - o **Pericarditis**: Pleuritic + Positional (relieved sitting forward), substernal pain may radiate to shoulder due to phrenic nerve irritations
 - o **Cholecystitis/Pancreatitis**: Upper abdo conditions that cause secondary pleuritic pain due to diaphragmatic inflammation
- Visceral
 - o **MI**: sensation of squeezing/pressure/burning usually located substernally radiating to ulnar aspect of left arm +/- jaw, shoulder, epigastrium, back
 - o **Stable angina**: brought on by exertion/stress last only minutes and resolves +/- diaphoresis, nausea, dyspnea, palpitations, light-headedness
 - o **Aortic dissection**: abrupt pain MOST INTENSE AT ONSET
 - o **GI disease**: symptoms may relieve with food and worsened in supine position
 - Esophageal spasm difficult to differentiate from angina
- Musculoskeletal pain
 - o Either dull and achy or sharp and pleuritic but localized and worsened with specific movement/position and recreated with palpation
 - o **Neuropathic**: i.e. HZV pain may precede rash but burning in specific dermatome key part of Hx
- Differentiate **nonanginal, atypical**, and **typical** chest pain with 3 important components
 - o *Substernal* location of chest pain
 - o Provocation by physical or emotional stress
 - o Relief with rest/nitro
 - **CHD = 3/3, ATYPICAL = 2/3, NONANGINAL = 1/3**

Physical Exam

- A patient with ischemia often present with normal physical exam
- *Unequal BP in arms*: important but uncommon in **aortic dissection**
- *Hypotension/Irregular rhythm*: life-threatening vascular etiology (**PE/pneumothorax**)
- *Tachypnea* is nonspecific
- *Reproduction of pain* by palpation implies msk (not possible in angina, PE, aortic dissection)

- *Cardiac findings:* S4 (ischemia), apical holosystolic murmur (aortic regurge), pericardial rub (pericarditis)
- *Pulmonary findings:*
 - o hyperresonance to percussion, decreased fremitus, tracheal deviation to contralateral side suggest ~~PE~~ PTX
 - o Pleural rub = pulmonary infarction or pneumonia
 - o Rales and biliar dullness = CHD
- *Abdominal findings:*
 - o pulsatile mass, tender abdominal aorta, aortovascular bruits (vascular)
 - o Right upper quadrant tenderness suggests hepatic/gall bladder inflammation
 - o Midepigastric tenderness suspect wider spectrum GI disease

Diagnostic Evaluation

- ECG in suspected cardiac causes of chest pain
- If stable angina suspected: exercise stress test
- CXR for pleuritic pain and dyspnea
- Chest CT for patients with Hx for aortic dissection or PE (sensitive test)
- Transesophageal echo for detecting aortic dissection at bedside
- V/Q scan for pleuritic pain and normal CXR
- Esophageal pH monitoring or empirical trial of antacids for GERD
- NSAID for MSK/pericarditis problems

TABLE 1-1 Electrocardiogram

- | |
|--|
| <ul style="list-style-type: none"> • Q waves in two or more leads: previous myocardial infarction |
| <ul style="list-style-type: none"> • ST depression >1 mm: ischemia |
| <ul style="list-style-type: none"> • ST elevation: acute myocardial infarction or pericarditis (the latter often has involvement of all leads and associated PR depression) |
| <ul style="list-style-type: none"> • Left bundle branch block: suggests underlying heart disease (ischemic, hypertensive) |
| <ul style="list-style-type: none"> • Right bundle branch block: may be indicative of right heart strain (as in pulmonary embolus) |
| <ul style="list-style-type: none"> • T-wave inversions and nonspecific ST changes: seen both in healthy individuals and in many diseases (therefore, not useful) |

Treatment

- Early emergent interventions are oxygen/ASA
- Nitroglycerin for MI but assess risk for aortic dissection or aortic stenosis before

AHD – Approach to Chest Pain

Background

- Chest pain is the 2nd most common complaint in ER (5-8%) and common in office (1-2%) visits.
- Separated into Cardiac vs. non-cardiac causes; DDx should go common->uncommon and consider life threatening before non-life threatening conditions first
- Anatomical Approach: Anterior chest wall -> back or by organ systems, mnemonic **KITTENDIVP**:
 - o **K(C)ongenital, Infectious, Trauma, Toxin, Endocrine, Neoplastic, Degenerative, Inflammatory, Vascular, Psychogenic**
 - o Heart, Lungs, Chest (esophagus), Abdomen (stomach, pancreas, gall bladder), MSK (thorax, neck, shoulder), psychogenic
- Detailed Hx of chest pain important:
 - o Onset (acute/gradual); provocation/alleviation, Quality of pain, radiation, sites of pain
 - o Timing: constant or episodic, duration, B-symptoms, co-morbidities, habits

Type	Location	Radiation	Character	Precipitation	Relieving	Other
Ischemic	Central, Diffuse	Jaw, neck, back shoulder	Tight, choke, Squeeze,	Exertion, Emotion	Rest, nitro	SOB
Non-Cardio	Peripheral, localized	None	Sharp, burn, stab	Spontaneous, postural, not exert.	Not rest, not nitro	Resp/GI Sx, Psycholog.

- Thoracic organs share the same afferent nerves so difficult to know what organ is involved
- Atypical presentation for ACS:
 - o Diaphoresis, nausea, vomit; Elderly: weak, dizzy, AMS, syncope; women: SOB, weakness, fatigue

DDx

- Common causes: ACS, Stable angina, pneumonia, viral pleuritic, GERD, anxiety/panic disorder
- Uncommon: PE, pericarditis, cardiac tamponade, aortic dissection, aortic stenosis, mitral valve prolapse, pneumothorax, pulmonary HTN, PUD, esophageal spasm, cholecystitis, pancreatitis, HZV

Investigations

- Initial: VS, ECG (within first 10 min then q 30min), CXR, Troponin, CBC, Cr, D-dimer, ABG
- Further work-up: Coronary angiography +/- PCI, Echo (TTE, TEE), CT chest, endoscopy, abdo imaging

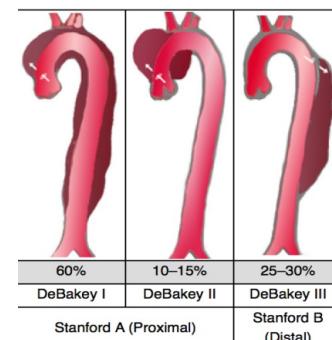
Acute Coronary Syndrome (Unstable angina, NSTEMI, STEMI)

- 2 of: chest pain, dynamic ECG changes, Positive biomarkers
- Pathogenesis: atherosclerosis -> rupture -> thrombus formation/platelet aggregation-> ischemia
 - o If **incomplete** occlusion: unstable angina or NSTEMI
 - o If **complete** occlusion: STEMI
- ACS is life threatening, 28-day mortality = 10%
 - o Myocardial Ischemia with no damage = unstable angina (< 20-30 min of chest pain)
 - o Myocardial ischemia with damage = infarction (> 20-30 min of chest pain)
- RF: male, 65+, FHx in 1^o relative < 55 (M) or < 65 (F), HTN, smoking, DLD, DM
- ECG: obtain within 10 minutes of arrival (repeat q 15-30min in first hour prn)
 - o Can detect ACS (ST changes, Q waves, LBBB); needs to be compared with previous ECG(s)
 - o **Low sensitivity for MI (<50%)**
- Cardiac biomarkers: **TROPONIN** (elevates within 3-4h, peaks at 12h, stays elevated x 7-10d)
 - o Get troponin levels at onset and 3 hours after chest pain
- B-natriuretic peptide (BNP): > 100 is **sensitive** for HF; < 50 has high NPV for HF
 - o Useful to exclude acute CHF as a cause of dyspnea and chest pain

- CBC: ↓ Hb + chest pain THINK ISCHEMIA; CXR may be non-diagnostic in ACS or show CHF
- Echocardiography: TTE or TEE
 - o TTE for pericardial/pleural effusion, diastolic dysfunction, valvular disease
 - o TEE to rule out aortic dissection, intracardiac thrombus, valvulopathies, endocarditis, shunts
- Coronary CT useful in patients with **LOW** pretest probability for CAD (99% NPV for exclusion)
- Coronary CT limited if patient has **HIGH** pretest probability
- **Coronary Angiography (CA)** is the **gold standard** to diagnose CAD
 - o Want primary PCI within 90 min for STEMI or LBBB with chest pain
 - o Urgent PCI for NSTEMI with high risk
 - o Consider CA if ongoing chest pain, new CHF, ventricular arrhythmia, hypoTN, ECG changes

Aortic Dissection

- Tear in intima of aorta: blood tracks between intima and media of aorta
 - o Pulsatile blood flow propagates dissection
 - o Pain described as tearing, ripping in chest or back
 - o Can dissect into ACS
- PE: absent upper extremity pulse or carotid pulse, **BP discrepancy between arms > 20 mmHg** +/- neuro findings
- ECG can be normal or mimic acute MI (often affects the RCA)
- CXR: 90% have **abnormal** CXR, get CT, MRI, or TEE to follow up
 - o CT 98% sensitive (need iodine contrast so CKD/allergy are contraindications)
 - o MRI 98% sensitive (high detail, can localize tear and ID branch)
 - o TEE 94% sensitive but blind spot at the arch



Pericarditis/Pericardial Tamponade

- Acute inflammatory pericarditis has 2 of the following 4 Sx:
 - o (1) Pericarditic chest pain (worse supine, better sitting, +/- pleuritic)
 - o (2) pericardial rubs
 - o (3) new ST elevation/PR depression
 - o (4) pericardial effusion
- Tamponade: impaired filling caused by increased pericardial pressure from fluid, pus, blood, or gas
- Labs: CBC has ↑WBC, ↑ CRP, ↑ ESR, ↑ Cr, TSH/T₄ shows hypothyroidism sometimes

Pulmonary Embolism

- Dx often missed, need high index of suspicion, early Dx decreases mortality
- Signs: Pulmonary HTN, RV dysfunction, low O₂ Sat, chest pain, dyspnea +/- pleuritic, sharp or dull
- ECG may show tachycardia, rightward axis, incomplete RBBB, simultaneous T-wave inversions
- **D-Dimer useful if NEGATIVE** Rules out PE in low risk patients
 - o Can be elevated in cancer, sepsis, trauma, pregnancy so not specific to PE
- CXR can be normal or have:
 - o **Westermark sign:** dilation of pulmonary arteries proximal to embolus and collapse of the distal vasculature creating the appearance of a sharp cut off (low sensitivity **high specificity**)
 - o **Hamptons Hump:** Wedge-shaped infarct (low sens, **high specificity**)
- Other imaging: CT, VQ scan, angiography, venous duplex to R/O DVT



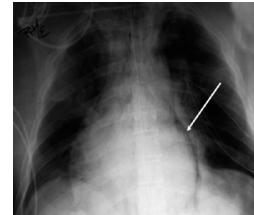
Pneumothorax

- Usually spontaneous: 1^o = no lung disease, 2^o to COPD, CF, asthma, trauma

- Tension pneumothorax is air trapped in pleural space, mediastinal compression and is EMERGENCY
- Pulmonary/Pleural causes
 - o Resp infections (with B symptoms): pneumonia, tracheitis, bronchitis
 - o Pleuritis (inflamm of pleura +/- ↑ lymphocytes): Dx of exclusion, pleuritic chest pain
 - o Pleural effusion (transudative vs. exudative): heaviness in chest, usually need to tap fluid
- CXR in PA and lateral positions ideal; shows infiltrate, air bronchograms, +/- pleural effusion

Other Causes

- **Pneumonia:** test blood and sputum for ↑ neutrophils, and + cultures (to help guide abx choice)
- **Viral Pleuritis:** CXR may be normal or effusion; blood show WBC with ↑ lymphocytes
- **Mediatstinitis:** usually from esophageal rupture; violent vomit, cancer, abnormal CXR showing pneumomediastinum (right), effusion, pneumothorax
- GI causes: GERD, spasm, esophageal inflammation/rupture, gastritis, PUD, hiatal hernia, pancreatitis, cholecystitis
- Image GI with endoscopy, barium swallow, US, CT
- Blood tests: CBC, LFT, liver enzymes, amylase/lipase, H. pylori breath test
- MSK causes: usually sharp and well-localized and reproducible; rib fractures, intercostal muscle strains
- Psychiatric: panic attacks (Dx of exclusion)
- Also consider: HZV, referred pain, autoimmune inflammatory conditions



Shock

- Shock is a clinical syndrome defined by the effect of **reduced perfusion on organ systems** due to a decrease in mean arterial pressures
- $\text{MAP} = \text{P}_{\text{Diastolic}} + 0.3 * \text{P}_{\text{Pulse}}$
- Shock with decreased MAP is from either decreased CO or decreased SVR
 - o $\text{MAP} = \text{CO} * \text{SVR} = \text{HR} * \text{SV} * \text{SV}$
 - o SV determined by contractility and available blood volume
 - o When compensatory responses cannot sufficiently maintain MAP the body presents with shock
- Three main shock syndromes: **Hypovolemic, cardiogenic, distributive**

Shock Syndrome	CO	SVR	JVP/PCWP
Hypovolemic	Decrease	Increase	Decrease
Cardiogenic	Decrease	Increase	Increase
Distributive	Increase	Decrease	Decrease

- The low vascular resistance seen in distributive shock is commonly seen in sepsis but may be mimicked by adrenal crisis or anaphylaxis
- Shock can occur when **systolic BP is < 90 or the MAP is < 70**
- Manifestations of inadequate perfusion:
 - o Renal dysfunction (decreased or no urine output)
 - o CNS dysfunction (worsening mental status)
 - o Tissue hypoxia (lactic acidosis)

History

- Usually not helpful due to patient being delirious due to decreased perfusion, but important features:
 - o Recent use/discontinued use of corticosteroids (adrenal crisis)
 - o Ingestion of certain foods or drugs or the occurrence of bee sting (anaphylaxis)
 - o History of chest pain (pleuritic: PE or tension pneumothorax; nonpleuritic: ischemia)
 - o Recent urinary tract or other infection (sepsis)
 - o Recent bleeding or gastrointestinal volume loss (esophageal varices, cholera)

Physical Exam

- Low BP, compensatory tachycardia
- Pulsus paradoxus: cardiac tamponade (decrease of systolic BP > 10 mmHg on inspiration)
- JVP provides rough estimate of central venous pressure and shock type (table above)
- **No breath sounds** on one side and tracheal deviation on **opposite** side = **tension pneumothorax**

DDx

- Cardiogenic
 - o Pump failure from MI, cardiomyopathy, tamponade, arrhythmia, valvular, obstruction (PE etc.)
- Hypovolemic
 - o Hemorrhage, diarrhea or heat stroke, third spacing
- Distributive
 - o Sepsis, anaphylaxis, adrenal crisis, myxedema coma

Diagnostic Evaluation and Treatment

- Start by treating hypotension and determine etiology of shock starting with JVP
 - o Decreased JVP => start with fluids (IV NS/Ringers)
- *Adrenal insufficiency* supported by: HypoNa, HyperK, HypoGlyc, Abdo pain, Eosinophilia, HyperCa

- Confirmed after suboptimal response to ACTH
- Treat with immediate IV steroids (**4 mg dexamethasone**)
- *Sepsis* suspicion should have blood and urine cultures +/- CSF culture. Start empiric abx
- *Myxedema* presents as “hyposyndrome” of severe HYPOThyroidism
 - Hypothermia, hypoglycemia, hypoventilation
 - TSH, T4, T3, and TH
 - Risk of coexistent adrenal crisis and pituitary failure so treat empirically for those as well
- *Cardiogenic Obstructive Shock*
 - If JVP **increased** IV fluids are **harmful**, do CXR first to look for pulmonary edema/cardiac silhouette or a pneumothorax with mediastinal shift
- *Pneumothorax*: CXR can confirm diagnosis but immediate treatment needed. **Insert chest tube is optimal treatment**. If not available use large-gauge needle in 2nd intercostal space (midclavicular)
- In hypotension and **increased** JVP, echocardiogram to look for effusion (*Tamponade*), RA/RV collapse, or other cardiogenic issues
- In patient with unclear etiology place a **pulmonary artery catheter**
 - Can measure PCWP (proxy for LA filling pressure)
 - Can measure CO (increased in early [warm] sepsis, decreased in late [cold] sepsis)
- If no improvement after initial fluid infusion use **vasopressors** and **inotropic agents**
 - **Norepinephrine** has alpha and beta1 effects (both vasopressor and inotropic effects) and useful in *Distributive* and *cardiogenic* shock
 - **Dobutamine** is selective beta1 agonist for increasing contractility. Use in *cardiogenic* shock
 - **Phenylephrine** is alpha1 agonist that can be used with NE in early (warm) sepsis
 - **Vasopressin** for *Distributive* shock

Coronary Heart Disease and Chronic Angina

- CHD is leading cause of death in people > 45
- CHD is from complex interplay between endothelial dysfunction, DLD, and inflammation
 - o **Atherosclerotic** plaque has several stages
 - o Stage 1 – fatty streak (second decade of life)
 - o Stage 2 – LDL enters endothelium in fatty streak and becomes oxidized attracting macrophages that become “foam cells” that recruit more macrophages and other inflammatory cells
 - o Stage 3 – proliferating SM and connective tissue etc. create a **fibrous cap**
- Ischemia occurs with decreased blood flow due to plaques narrowing lumen
- RF include DM, Smoking, DLD, obesity, low activity level, psychosocial stress.
- CRP is usually elevated but rarely changes management

History

- Symptomatic CHD commonly manifested as **angina pectoris** reported as substernal pressure, heaviness, burning, squeezing that is rarely well localized and can radiate to jaw/back/shoulder/arm
- **Stable angina** brought on by predictable levels of emotional/physical stress and ends quickly
- **Unstable angina** occurs at rest
- Patients with **silent ischemia** may be asymptomatic
- Compromised ventricle function can have CHF symptoms (dyspnea/orthopnea)

Physical Exam

- CHD patients often have normal exam but can have findings of other predisposing conditions:
 - o Retinal vascular changes (changes caused by hypertension)
 - o Third heart sound or displaced point of maxima impulse (congestive heart failure)
 - o Fourth heart sound (hypertension)
 - o Arterial bruits (peripheral atherosclerosis)
 - o Absent or diminished peripheral pulses (peripheral atherosclerosis)
 - o Xanthomas (hyperlipidemia)
- Examining during angina attack may reveal S4 (decreased compliance) or signs of LV failure

DDx

- See DDx for chest pain from earlier

Diagnostic Evaluation

- Framingham prediction model best for identifying patients of high risk
- Resting ECG is normal in 50% of angina patients
- Typical ECG finding during ischemia is **ST segment depression** > 1mm in TWO leads
- Suspected diagnosis of CHD can be confirmed with **exercise stress test**
 - o Increase exercise intensity until 85% of Max HR (220-age)
 - o Stop if chest pain, dyspnea, dizziness or >2mm ST depression
 - o Positive test = ST depression > 1 mm
 - o Sensitivity of test (>70% stenosis in one artery) is 60%, specificity is 77-90%
 - o Low specificity => low pretest probability patients not tested with this to avoid false positive
 - o Sensitivity and specificity can be improved with radiolabeled tracers
 - o Patients who complete exercise study with no symptoms have low CHD mortality (<1%)
- Patients unable to do exercise stress test do pharma stress with **dipyridamole** or **adenosine**
- Echocardiography + exercise is less sensitive than perfusion imaging but more specific

- **Coronary angiography is gold standard for diagnosis CHD**
 - o Indicated when noninvasive tests are inconclusive or clinical parameters suggest
 - o i.e. Stage 3/4 angina, CHF, ejection fraction < 35%, large perfusion defect on stress testing

Treatment

- Goals of treatment are to prevent MI, decrease angina, improve QOL. Use **ABCDE** mnemonic
 - o A: Aspirin, ACEi, and antianginals (nitrates and calcium channel blockers [CCBs])
 - o B: β -Blocker and BP
 - o C: Cholesterol and cigarettes
 - o D: Diet and diabetes
 - o E: Education and exercise

Prevention of MI and Death from CAD

- ASA (75-325 mg daily) limits platelet aggregation and reduces risk of subsequent MI in CHD/post-MI
- If allergic to ASA use **clopidogrel** (75 mg daily)
- ASA + clopidogrel used together following recent MI or stent placement
- Statins reduce all cause mortality for CHD
- ACEi recommended for patients with CHD, DM, or LV dysfunction but strongly consider for all angina

Antiangular Treatment

- Cadioselective B-adrenergic blocking agents reduce myocardial workload
- B-blockers relieve angina symptoms
 - o Contraindication are baseline bradycardia, High degree AV block, decompensated HF
 - o Side effects: fatigue, impotence, bradycardia, worsening HF
- CCB decrease heart contractility and increase coronary blood flow (equivalent antianginals to BB)
 - o Preferred for vasospastic angina or contraindications to BB or side effects of BB
 - o Contraindications are same as BB
 - o Side effects: peripheral edema, reflex tachycardia, constipation
- Nitrates are vasodilators used in sublingual (acute) or transdermal (long-acting)
 - o Side effects (most prominent with sublingual): hypotension, lightheaded, headache
 - o Constant use leads to tolerance which is prevented by 8h free nitrate interval

Revascularization

- *Percutaneous coronary intervention* for patients with persistent angina improves stable angina symptoms
- *Coronary artery bypass grafting (CABG)* reserved for good baseline surgical candidates with complicated left main disease or multivessel disease with reduced ejection fraction

Acute Coronary Syndromes

- Include **unstable angina (UA)** and **Acute Myocardial infarction (AMI)**
 - o AMI divided into NSTEMI and STEMI
- Most AMI occur in underlying CHD spontaneous fissuring and rupture of a coronary plaque
- If the thrombus causes complete occlusion of coronary artery this results in STEMI that creates necrosis of myocardial muscle and results in **pathologic Q waves** on ECG
 - o In NSTEMI, Q waves are absent
- Other causes of AMI:
 - o "Demand ischemia" (tachycardia, hypotension, and/or severe hypoxia in existing fixed CAD)
 - o Coronary artery dissection (often in the setting of a dissecting aortic aneurysm)
 - o Coronary vasospasm (idiopathic Prinzmetal angina or drug induced, e.g., cocaine)
 - o In situ thrombus formation (in the setting of a hypercoagulable state)
 - o Coronary embolism
 - o Vasculitis (e.g., Kawasaki disease)
 - o Carbon monoxide poisoning
- Complications of AMI resulting in early death (within 1 month)
 - o Arrhythmias (ventricular fibrillation/tachycardia, complete heart block)
 - o Heart failure (cardiogenic shock)
 - o Ventricular rupture (peak incidence within 3 to 5 days of AMI)
 - o Other mechanical complications (ventricular septal defect, mitral papillary rupture)
- Death > 1 month post AMI usually from reinfarct, heart failure or sudden arrhythmia

History

- **RETROSTERNAL CHEST PAIN** is common complaint for AMI
 - o Pain often reaches max over ~min and then prolonged and persistent
 - o Radiate to arms, neck, jaw
 - o Nitrates do not resolve the pain but provide some relief
 - o B symptoms sometimes present
- UA present with rest pain or increasing severity of established angina at lower threshold
- Some patients are asymptomatic (especially DM patients)

Physical Exam

- Can be entirely normal in an AMI
- Vitals important for prognosis and hypotension indicative of **cardiogenic shock**
- S4 common (decreased compliance)
- S3 may be present and ischemia of papillary muscle leads to mitral regurgitation murmur (systolic)
- PE should focus on signs of peripheral vascular disease (bruits, pulsatile abdo mass, decrease pulse)

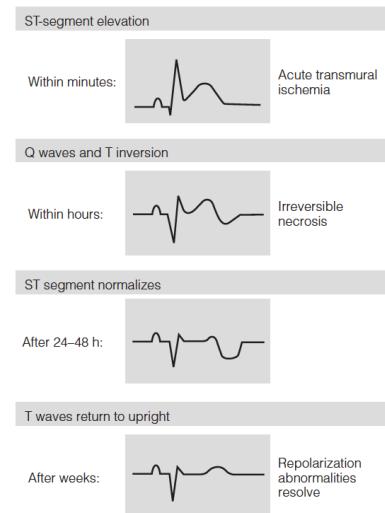
DDx

- See Chest pain DDX
- In patient with chest pain + ST Elevations ddx includes: AMI, Acute pericarditis, prinzmetal angina
- In a patient with known CHD and chronic angina it is difficult to distinguish between AMI and UA

Diagnostic Evaluation and Risk Stratification

- ECG early in evaluation and rechecked frequently during workup
- New **left bundle branch block** is treated as STEMI
- Typical evolution of ECG in the setting of STEMI is:

- Increase in amplitude of the T wave (first minutes after occlusion)
- ST-segment elevation (minutes to hours)
- Development of Q waves (hours to days)
- Resolution of ST-segment elevation (hours to days)
- Hours after an NSTEMI, stable T-wave inversions in affected region may develop
 - **Wellens sign:** deep inverted T-waves in V1-V4 = left anterior descending artery
- MI confirmed with **cardiac specific troponin** which rises 6-9h after symptoms and peaks at 20h
 - Elevated troponins are diagnostic and prognostic (lower = better)
- **Creatine Kinase -MB** is not as sensitive as troponins but rises (3h) and leaves (48h) earlier
- For patients with UA and NSTEMI assess risk with TIMI score (/7):
 - Age >65
 - At least three risk factors for coronary artery disease
 - Known coronary artery disease with at least 50% coronary stenosis
 - ST-segment changes
 - At least two episodes of angina in the past 24 hours
 - Aspirin use in the past week
 - Elevated CK-MB or troponin
- TIMI score: 5+ - high risk for death, 3/4 - intermediate risk, 3+ - early intervention, >3 conservative
- Cardia echocardiography and CXR for imaging studies of heart and lung involvement
- Gold standard for STEMI or UA/NSTEMI with high TIMI is **coronary angiography**



Treatment

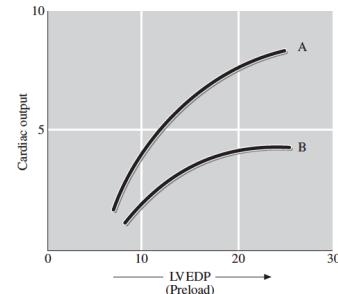
- Acute coronary syndrome is a medical emergency. Goals of therapy:
 - Reduction of myocardial oxygen demand (heart rate, blood pressure)
 - Improvement/restoration of myocardial perfusion
 - Pain relief
 - Recognition and treatment of complications
- If possible AMI immediate treatment are the following steps:
 - Rapid clinical assessment with VS, Hx, PE, and 12-lead ECG within the first 10 minutes.
 - Adminsiter O2 + aspirin + Sublingual Nitro
 - B-blocker + Statin
- **STEMI:** assumed complete occlusion of affected artery
 - **Thrombolytic therapy or primary percutaneous intervention** (PCI best when within 90min)
 - Contraindications to thrombolytic therapy: brain hemorrhage/neoplasm, aortic dissection/bleeding, stroke
 - Patients with cardiogenic shock should be immediately catheterized (best within 90 min)
 - When PCI is performed additional antiplatelet and anticoagulant is given in addition to ASA
- Treat with oral ACEi within 24h to reduce morbidity (Contraindicated in hypotension)
- **NSTEMI:** both NSTEMI and UA where initial cardiac markers insufficient to diagnose
 - All patients can have ASA, B-blockers, antianginal meds and statin (unless contraindicated)
 - **Low risk NSTEMI** (TIMI < 3) administer antiplatelets therapy early with ASA
 - **Intermediate risk NSTEMI** (TIMI 3-7): antiplatelet + anticoagulant (unfractionated IV heparin for those who will get PCI or low-molecular weight heparin for those who won't)
 - Angiography with PCI in patients at intermediate – high risk is recommended

Heart Failure

- Clinical syndrome where heart has reduced ability to pump blood. Classified different ways:
 - o **Hemodynamic** state of CV system (congestive vs. high output)
 - o Predominance of affected ventricle and dysfunction (L v R and systolic vs. diastolic)
 - o Time course (acute/chronic)
- Major predisposing conditions of CHF: CHD, HTN, DM, valvular disease, obesity, cardiomyopathy

Pathophysiology

- Preload = pressure required to distend ventricle to a give volume
- Contractility = work (CO) that the heart generates at a given preload
- Relationship between these two is Frank-Starling law (right A = normal heart B = heart with decreased contractility)
- Afterload = dynamic resistance against which the heart contracts
- **Systolic HF** is the most common form cause by **decreased** contractility
 - o Also known as **HF with Reduced Ejection Fraction (HFrEF)**
 - o As CO drops renin-angiotensin and SNS are stimulated causing systemic vasoconstriction, salt and water retention, increased afterload and myocardial hypertrophy
 - o Cardiac ventricles produce **brain natriuretic peptide (BNP)** to decrease systemic resistance
 - o The balance of neurohormonal response leads to ventricular failure and progressive dilatation
- **Diastolic HF** has **decreased** compliance of the ventricle impairing filling
 - o Also known as **HF with Preserved ejection fraction (HFpEF)**
 - o Conditions that cause diastolic HF: HTN, Amyloidosis, hemochromatosis, Myocardial ischemia
 - o Decreased compliance results in high LV end diastolic pressure that causes pulmonary edema
 - o Differes from HFrEF (normal CO, no Na/H₂O retention)
- HF almost always results in high LV EDP that pushes water into lungs.
- Starling Law: fluid filtration across a capillary is determined by a balance of hydrostatic and oncotic pressures.
 - o Pulmonary edema = $P_{\text{capillary, Hydrostatic}} > P_{\text{capillary, oncotic}}$



History

- Most symptoms caused by HF are pulmonary due to high LVEDP causing capillary congestion:
 - o Dyspnea, Orthopnea, Paroxysmal nocturnal dyspnea, cough, wheezing
- Symptoms in CHF often described according to the New York Hear Association:
 - o **Class I:** Asymptomatic; no limitations in ordinary activity
 - o **Class II:** Slight limitation; ordinary activity causes symptoms
 - o **Class III:** Marked limitation; less than ordinary (IIIa) or minimal (IIIb) activity causes symptoms
 - o **Class IV:** Symptoms at rest; any activity causes symptoms
- History should explore precipitating factors for worsening CHF (diet, medication, fever, angina)

Physical Exam

- PE findings usually come once compensatory mechanisms begin to fail.
- CV findings:
 - o Laterally displaced/enlarged point of maximal cardiac impulse (more in systolic dysfunction)
 - o Sinus tachycardia or hypotension
 - o Loud S2 (caused by pulmonary hypertension), S3 (systolic dysfn), S4 (HTN/Diastolic dysfn)
 - o Murmurs (commonly from mitral/tricuspid regurgitation or from aortic stenosis)
 - o Jugular venous distention and elevated jugular venous pressure (JVP)

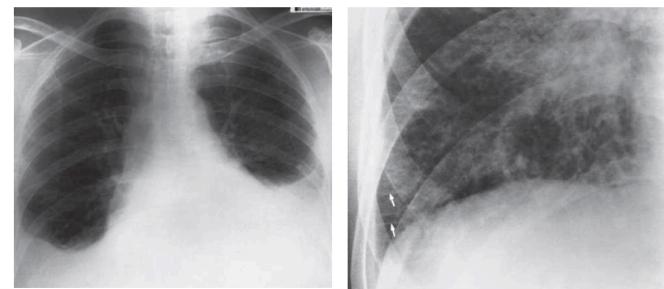
- Pulmonary findings include:
 - o Fine-pitched inspiratory crackles (rales)
 - o Dullness at bases (because of the presence of pleural effusions)
- Peripheral findings:
 - o Pitting edema, Ascites, Hepatomegaly, Hepatojugular reflux

DDx

- DDx includes everything from dyspnea along with etiologies from:
 - o Ischemic (from old myocardial infarctions)
 - o Hypertension
 - o Valvular disease
 - o Toxic (alcohol, cocaine, chemotherapy such as doxorubicin)
 - o Viral infection (especially Coxsackievirus)
 - o Hemochromatosis (initially a restrictive cardiomyopathy, often dilated by time of presentation)
 - o Hypothyroidism

Diagnostic Evaluation

- CXR in CHF may show:
 - o Alveolar infiltrates (central “bat wing” pattern)
 - o Pulmonary venous redistribution
 - o Kerley B lines (arrow right)
 - o Peribronchial cuffing
 - o Pleural effusion
 - o Cardiomegaly (Heart/thorax ratio > 50%)
- ECG important and can help with etiology (normal makes **systolic dysfunction unlikely**)
- BNP diagnostic for unexplained dyspnea
 - o High levels suggest CHF, normal levels make CHF unlikely. Levels also correlate with severity
 - o Does not help distinguish between systolic vs. diastolic HF
 - o High levels can be seen in patients with renal failure and do not exclude pulmonary conditions
- Other blood tests: CBC, lytes, glucose, renal function, LFT
- Echocardiography helpful to determine HFrEF vs HFpEF and valvular causes

**Treatment**

- Treatment for CHF usually focused on HFrEF divided into acute pulmonary edema symptom relief treatment vs. chronic neurohormonal response inhibition treatment.
- **Acute** Pulmonary edema treatment use mnemonic **LMNO**
 - o Lasix, Morphine sulfate, Nitroglycerin, Oxygen
 - o Additional measures include positive pressure ventilation, and inotropic agents (dobutamine)
- **Chronic** treatment of systolic dysfunction and is focused on:

Class	Example	NYHA	Mortality Benefit	Other Benefits	Side Effects
ACEi/ARB	Enalapril, Lisinopril	All	Yes	Fewer ischemic events/hospitalizations	HyperK, cough, Kidney failure
B-Blocker	Bisopropolol, metopropolol	All	Yes	AF ventricular rate control, antiarrhythmia	Fatigue, dyspnea
Vasodilator	hydralazine	3/4	Yes	Added benefit for black people using ACEi/ARB	Headache, dizziness
Aldosterone antagonist	Spironolactone, eplerenone	3/4	Yes	N/A	HyperK, gynecomastia

- Reducing cardiac workload and blocking neurohormonal activation (ACEi, B-Blockers)
- Control accumulation of Na/H₂O (diuretics, fluid/Na restriction)
- Increase contractility (inotropes, digoxin)
 - Note digoxin does not improve mortality
- Therapy for **diastolic** dysfunction is based on therapeutic principles (poor evidence in clinic trials)
 - Treatment aimed at improving BP and HR, with diuretics as needed
 - B-blockers, ACEi, and ARBs often used
 - Inotropic agents are NOT helpful

Advanced HF

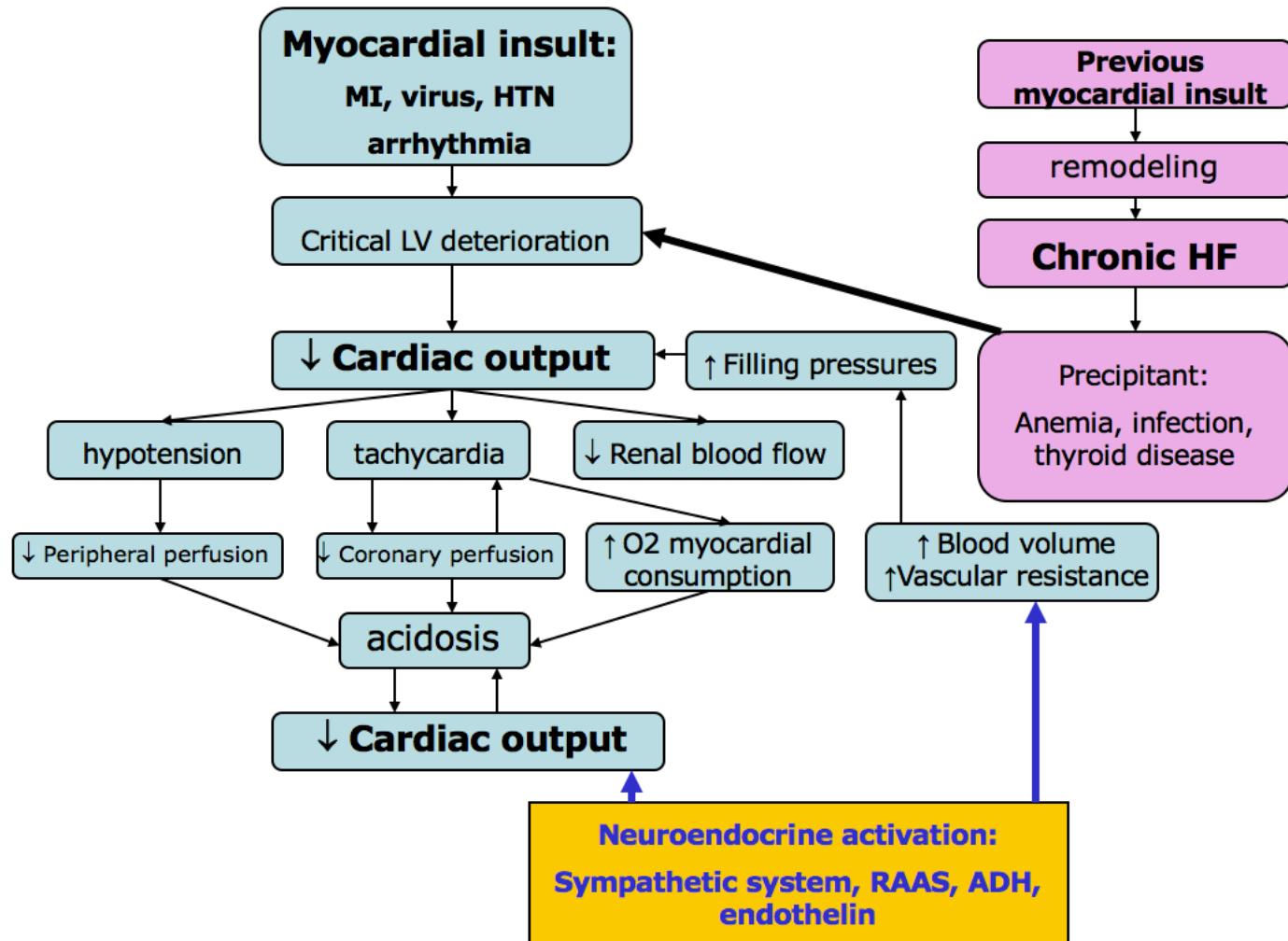
- Automatic implantable cardiac defibrillators are used in patients who have experienced ventricular fibrillation, ventricular tachycardia or cardiac arrest
 - AICD reduce mortality with ischemic or nonischemic cardiomyopathy, NYHA 2-3 HF
 - Should only be used in patients without life-limiting comorbidities and life expectancy > 1 yr
- Biventricular pacemaker for patients with low EF and left bundle branch block with long QRS
- Cardiac transplantation limited due to organ availability

AHD – Heart Failure

Definition of Acute Heart Failure

- A serious condition requiring **urgent** medical attention; presents a rapid onset of signs and symptoms secondary to cardiac dysfunction, such as reduced cardiac output, decreased tissue **perfusion** and increased pulmonary/peripheral **congestion**, with or without previous disease
- Classifications
 - o Systolic (HFrEF) or Diastolic (HFpEF)
 - o Primary vs. Secondary; De novo or acute on chronic; Right vs. Left
- **Primary Cardiac**
 - o Myocardial ischemia, decompensation of preexisting CHF, acute cardiomyopathy, acute arrhythmias, valvular dysfunction, pericardial syndrome (tamponade)
- **Primary non-cardiac**
 - o Hypertensive crisis, aortic dissection, renal failure, high-output syndromes, volume load
- States that can be confused with pulmonary edema:
 - o COPD/asthma exacerbation, PE, pneumonia, tamponade, non-cardiogenic pulmonary edema, pulmonary hemorrhage

Pathophysiology



Diagnosis

- Hx: cough, dyspnea, orthopnea, fatigue, perspiration, comorbidities
- PE: VS, assessment of congestion, assessment of perfusion
- Assessment of hemodynamic profile:

		Increasing Congestion →	
Increasing Perfusion ↑	Dry and Warm (A)	Wet and Warm (B)	
	Dry and Cold (D)	Wet and Cold (C)	

- Important Sx/Signs of **increased Congestion**:
 - o Orthopnea, high JVP, positive hepatojugular reflex, S3, loud P2, edema, Ascites, rales
- Important Sx/Signs of **decreased Perfusion**
 - o Narrow pulse pressure, cool extremities, obtunded, ACEi hypoTN, low Na, poor renal function
- ECG needs to be done and interpreted within 10 minutes of arrival
- CXR: stages of pulmonary edema
 - o (1): redistribution; (2): interstitial edema; (3): alveolar edema; (4): hemosiderosis + ossification
- Echocardiogram:
 - o Ejection fraction: systolic vs. diastolic HF; RV function; Valvular disease; RA/Pulmonary Pressure
 - o Diastolic function can estimate filling pressures in normal and lo EF HF

Treatment

- Goals of Treatment of acute HF:
 - o ABC: Pulse oximetry, O₂ sat > 90%, ABG, seated posture, intubation, BP, continuous cardiac monitoring, IV access, foley catheter
 - o Correct obvious underlying factors: MI, HTN, arrhythmias
 - o Improve hemodynamics + symptoms: diuretics, vasodilators, inotropes
 - o Long-term therapy with neurohormone antagonists when euvoemic
 - o Specific Tx according to hemodynamic profile as well
- **Profile A (Dry and Warm)**: Adjust long-term therapy
- **Profile B (Wet and warm)**: dry out (diuretics + vasodilators)
- **Profile C (Wet and cold)**: warm up to dry out (inotropes)
- **Profile D (Dry and cold)**: Give fluids
- Diuretics are cornerstone of therapy to relieve congestion:
 - o Early pulmonary vasodilatation, give IV, dosing depends on previous PO dose, monitor volume status, weight, ins and outs, electrolytes, renal function; restrict Na and fluids
- Vasodilators: use early even if normotensive, added to diuretics, decrease preload and afterload
- Morphine: early stage of Tx in 1-3 mg boluses; actions:
 - o Venodilatation, mild arterial dilatation, reduces HR, decreases air hunger
- Nitrates
 - o Dose dependent: low dose = venodilatation; high dose = arterial/coronary vasodilatation
 - o Tolerance after 16-24h; 5-200 ug/min with BP monitoring; careful with inferior MI
- Inotropic therapy: Use as bridge to other therapies; Severe LV dysfunction and low output syndrome
 - o Cardiogenic shock, inadequate response to diuretics and vasodilators
 - o **Vasodilating inotropes**: dobutamine, milrinone; for acute HF unresponsive to other therapy
 - o **Vasopressor inotropes**: dopamine, NE; shock with BP < 80
- Other therapies: ultrafiltration, intra-aortic balloon pump, ventricular assist device, transplants

Bradyarrhythmias

- Normal pacemaker of heart generated 60-100 impulses per minute that can be increased by sympathetic stimulation or decreased by cholinergic stimulation
- **Bradyarrhythmias** are defined by a heart rate < 60 BPM
- Slow HR by itself does not mean pathologic
- Pathologic bradyarrhythmias arise by delays in impulse formation or conduction:
 - o Hypoxia, sleep apnea, increased ICP, hypothermia, hypothyroidism, hyperkalemia, increased vagal tone
- Cardiac diseases with bradyarrhythmias:
 - o **Degenerative disease of the cardiac conduction system** (most common due to aging)
 - o Ischemic heart disease, particularly involving the inferior cardiac wall
 - o Infiltrative heart disease (e.g., sarcoid, amyloid)
 - o Infections of the cardiac tissues (e.g., Lyme disease, Chagas disease)
 - o Rheumatic heart disease
- Some meds also cause bradyarrhythmias: B-blockers, CCB, digoxin

History

- Presence of cardiac or CNS hypoperfusion helps determine clinical significance of bradyarrhythmias:
 - o Syncope, light-headedness, dyspnea due to CHF, angina, exercise intolerance

Physical Exam

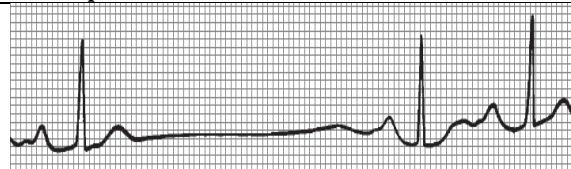
- Vital signs determine severity and help identify cause
- Hypotension (systolic BP < 90) is evidence of hemodynamic instability and needs emerg. Treatment
- Lung exam may reveal evidence of CHF
- Systemic etiology should be assessed (hypothyroid, cardiac murmur, rheumatic heart disease)

DDx

- Classified by regularity of HR
- **REGULAR HR:**
 - o Sinus bradycardia, complete heart block, 2:1 AV block, escape rhythm, "regularized" slow a-fib
- **IRREGULAR HR:**
 - o Sick sinus syndrome (SN dysfunction), 2nd degree AV block (Type 1 or 2), Slow a-fib

Diagnostic Evaluation

- ECG is the main diagnostic test and should be correlated with symptoms
 - o First look for P waves
 - o An irregular bradycardia + no P waves = **slow atrial fibrillation**
 - o **Regularized atrial fibrillation** has complete heart block at the AV node and a lower escape pacemaker that begins to fire
 - Often seen in Digoxin toxicity

Diagnosis	Findings	Example ECG
Sick Sinus Syndrome	<ul style="list-style-type: none"> - Absence of P-waves - Failure of SA node to fire (sinus arrest) - Failure of the SA node to excite the atria - Absence of entire PQRST complex if advanced 	

2 nd degree AV block (1)	<ul style="list-style-type: none"> - PR prolongation leads to a blocked beat so QRS complex fails to follow a P wave - Type 1: PR intervals progressively lengthen before the dropped beat 	
2 nd degree AV block (2)	<ul style="list-style-type: none"> - Dropped beat occurs suddenly - Higher risk of progression to full block vs. 1 	
3 rd degree AV block	<ul style="list-style-type: none"> - No relationship between P waves and QRS - P-waves firing at certain rate, fail to conduct to ventricles so a slower pacemaker begins to fire 	

Treatment

- Acute treatment is of underlying cause
 - o i.e. drugs that increase AV nodal block should be discontinued and digoxin level obtained
 - o if hemodynamically stable they may be observed until resolution
- Emergent treatment with **ATROPINE** for:
 - o Bradycardia causing hypotension, significant CHF, syncope
- Pacemakers used when symptomatic bradycardia fails to resolve on its own or with atropine
- Permanent pacemaker indications
 - o Complete heart block with symptoms
 - o Sinus node dysfunction with symptoms
 - o Bifascicular block with intermittent type 2 second degree AV block

Tachyarrhythmias

- Tachyarrhythmias are HR > 100 bpm
- Sinus tachycardia is a common response to certain stimuli, nonsinus tachycardia are divided into:
 - o Narrow complex tachycardia (QRS <0.12s) => supraventricular origin
 - o Wide complex tachycardias which are either supraventricular or ventricular
- Tachyarrhythmias arrive by either **abnormal impulse formation** or **abnormal pulse propagation**
 - o Enhanced **automaticity** = increased inherent rate of depolarization
- Reentry is the most common cause of tachyarrhythmias that occur when there are two conduction pathways (fast and slow) and continuously loops between them.
- Supraventricular tachycardias (SVT) arise from the atria, ventricles, or AV node
- Ventricular tachycardias (VT) occur below the AV node
- RF for SVT
 - o Hyperthyroidism (atrial fibrillation [AF], ectopic atrial tachycardia)
 - o Hypertension (AF and atrial flutter)
 - o Mitral valve disease (AF)
 - o Chronic obstructive lung disease (multifocal atrial tachycardia)
 - o Postcardiac surgery (nonparoxysmal junctional tachycardia)
- RF for VT
 - o Prior myocardial infarction (MI) (monomorphic VT)
 - o Ischemia (polymorphic VT, ventricular fibrillation)
 - o Long QT syndrome (polymorphic VT/torsade de pointes)
 - o Drugs (digoxin especially)
 - o Hypomagnesemia, hypo- or hyperkalemia (polymorphic VT, ventricular fibrillation)

History

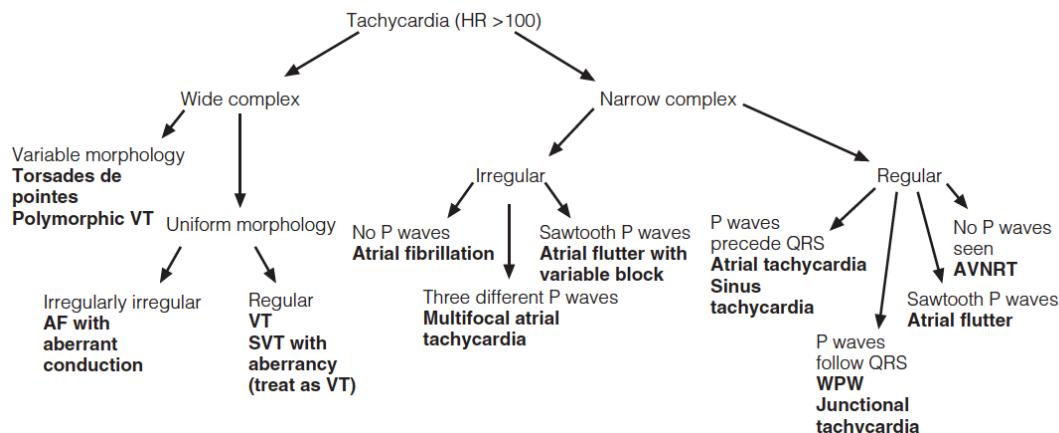
- Often patient is asymptomatic but can frequently present with: presyncope, syncope, dyspnea, palpitations, diaphoresis, chest pain

Physical Exam

- BP should be measured immediately
- Hypotension => hemodynamic arrhythmia that needs immediate therapy
- Signs of AV dissociation (cannon A waves, variability of S1) seen in VT but not SVT

DDx

- Categorize as VT or SVT based on presence of P waves and width and morphology of QRS in ECG



Diagnostic Evaluation

- Electrocardiogram is best tool
 - o Analyze in regard to regularity of rhythm, width and morphology of QRS, presence of P-waves
 - o **Narrow** QRS tachycardia are almost always **SVT**
 - o **Wide** QRS tachycardia may be **SVT or VT**
- Follow flow chart above to narrow your diagnosis
- Underlying exacerbating conditions such as hypokalemia or hypomagnesemia should be excluded
- Obtain digoxin level if patient taking drug
- Obtain TSH in AF to exclude hyperthyroidism

Treatment (General)

- **Synchronized countershock** (cardioversion) is indicated in all patients with hemodynamic instability
 - o Exception to use of defibrillation is in **torsade-de-pointes and digoxin toxicity**
- In hemodynamically stable patients with SVT treatments include:
 - o Vagal maneuvers, Adenosine, B-blockers, CCB, Digoxin (second line)
- For AV node **independent** rhythms (AF, flutter, atrial tachy) above therapies will slow or block conduction through the AV node decreasing ventricular response to SVT and unmasking atrial activity that may have been obscured by rapid ventricular rate
- AV node **dependent** rhythms the above therapies may stop arrhythmia
- Do VAGAL MANEUVERS before pharmacotherapy
- **Adenosine** often diagnostic drug for **narrow complex tachycardias** (short half-life, quick onset)
- **Digoxin** less effective acutely
- **B-blockers** best in situations which adrenergic drive is contributing to arrhythmia

Treatment (Specific)

- *Atrial Fibrillation*
 - o Rate and rhythm control, prevention of emboli
 - o B-blockers, CCB, ablation, CHADS₂ score for anticoagulation (1 point for CHAD, 2 points for S)
 - CHF, HTN, Age > 75, DM, Stroke
 - CHADS₂: 0 – ASA, 1 – ASA or Warfarin, 2+ - Warfarin
- *Atrial Flutter*
 - o Similar treatment to fibrillation but more commonly treated with ablative options
- *Multifocal Atrial Tachycardia*
 - o Focus on underlying pulmonary or cardiac predisposing condition and electrolyte correction
- *Supraventricular Reentrant Tachycardias*
 - o AV node blocking agents, ablation of arm of reentrant loop
- *Ventricular Tachycardia*
 - o Ischemic heart disease usually underlying cause and should be treated
 - o If LV systolic function preserved B-Blockers
 - o If more serious ventricular arrhythmias implantable defibrillator
- *Torsade De Pointes*
 - o Polymorphic VT and usually associated with Long QT interval. Long QTs are caused by:
 - Medications, electrolyte problem, congenital, ischemia
 - o Arrhythmia is usually self-limited but can progress to ventricular fibrillation
 - o Acute treatment with IV magnesium and removal of inciting agent essential

Hypertension

- There is no biologic threshold separating normal from abnormal BP, CV risk increases linearly starting at 115/75. HTN has been defined as the following:
 - o Systolic BP > 140 mmHg or diastolic BP > 90 mmHg on TWO or more occasions
- RF for HTN:
 - o Age, Smoking, Male, Race (black greater than white), Obesity, FHx, High Na, Ethanol, Stress
- Most cases of HTN are **essential hypertension** i.e. idiopathic in nature
- **Secondary hypertension** is when there is a well defined etiology:
 - o Renovascular disease, Kidney disease, primary aldosteronism, pheochromocytoma, Cushing, Hyper/Hypo thyroidism, Obstructive sleep apnea, coarctation of aorta, drugs, polycythemia
 - o Suspect in patients: age 20-50, no FHx, rapid acceleration, HTN with use of 3+ meds
- Poorly controlled HTN can lead to many end-organ complications:
 - o *Cardiac*: MI, CHF, Ventricular hypertrophy
 - o *Cerebrovascular*: Stroke, ischemia, hemorrhage
 - o *Vascular*: Peripheral vascular disease, aortic dissection
 - o *Renal*: AKI, CKD
 - o *Ophthalmologic*: retinopathy, blindness

History

- Most patients are asymptomatic but may report FHx of HTN. History should assess for 2^o causes:
 - o *Thyroid*: changes in skin, hair, heat/cold tolerance
 - o *Obstructive sleep apnea*: morning headache, day time sleepiness, snoring
 - o *Kidney*: Flank pain or urinary changes
 - o *Pheochromocytoma*: spells of "P"s – pounding (headache), perspiration, palpitation, pallor, pyrexia, pressure, postural symptoms
- Symptomatic patients will report:
 - o *Cardiac*: chest pain, dyspnea
 - o *Neurologic*: headache, confusion, numbness, weakness
 - o *Aortic and peripheral vascular*: claudication, erectile dysfunction
 - o *Ocular*: visual changes
 - o Peripheral edema

Physical Exam

- Most important part is accurate BP measurement.
 - o Systole = first sound, Diastole = last sound, patient sitting at least 5 min, arm supported at level of heart and proper cuff size used.
- Rest of PE focus on target-organ damage and clues for 2^o causes:
 - o *Cardiac*: LV heave, S4, pulmonary edema
 - o *Cerebrovascular*: carotid bruits
 - o *Peripheral vascular*: diminished pulses
 - o *Ocular*: AV nicking, papilledema
 - o *Renal*: peripheral edema, renal bruits

Diagnostic Evaluation

- Lab studies to assess target-organ damage: CBC, lytes, GFR, urinalysis, lipids, ECG
- Patients suspected for **primary aldosteronism** should measure renin (suppressed in this condition)
- More specialized test for 2^o causes guided by Hx

Treatment

- Secondary HTN: remediate problem causing HTN
- Essential HTN or uncorrected Secondary HTN goals are:
 - o Systolic BP < 140 for age < 60 or any age with CKD or DM
 - o Systolic BP < 150 for age < 60
 - o Diastolic BP < 90
- Nonpharmacologic therapies: weight loss, smoking cessation, Na restriction, exercise, etc.
- Pharmacotherapy (1st line):

Medication	Mechanism	Example	Side Effects
Thiazide	Increased Na excretion	Hydrochlorothiazide	Urinary frequency
ACEi	Decreased angiotensin II production	Lisinopril, captopril	Cough, angioedema
ARB	Blockade of angiotensin II receptor	Losartan, valsartan	Dizziness
CCB	Direct vasodilation	Amlodipine, Diltiazem	Edema

- Pharmacotherapy (Other):

Medication	Mechanism	Example	Side Effects
B-Blocker	Blocks Beta1 receptors	Atenolol, metoprolol	Bradycardia, ED
α1-antagonist	Block α 1 receptors	Doxazosin, terazosin	Orthostatic hypotension (OH)
Vasodilator	Direct vasodilation	Hydralazine	Hypotension, headache
α2-agonist	Decreased sympathetic output	Clonidine	OH, dry mouth
Dual BB/α1	Blockade of Beta1 and α 1	Carvedilol	OH, bradycardia

- Treatment strategy:
 - o Start meds at low doses and titrate every 2-4 weeks
 - o If inadequate response to a drug either increase dose, substitute, or add another agent
 - o If continued inadequate response add a third agent
- Hypertensive **emergency** is defined as systolic pressure > 180 mmHg or diastolic > 120 mmHg in the absence of end-organ findings.
 - o Can present as: Hypertensive encephalopathy, Intracranial hemorrhage, Acute MI, Acute pulmonary edema, Aortic dissection, Eclampsia
 - o Treat with TWO first line therapy
 - o IV treatment NOT indicated as speed of BP lowering has no proven benefits.

Valvular Heart Disease

- In **Adults** valvular disease is **acquired**. In **Pediatric** it is usually **congenital**
- Most acquires valvular disease more common in men than women other than mitral stenosis (MS)
- Historically rheumatic fever (RF) was major cause of valvular disease
 - o RF causes chronic inflammation and thickening of valve apparatus and retraction of leaflets leading to regurgitation, scarring and stenosis.
 - o Mitral valve usually most affected

Disease	Etiology	Pathogenesis	History
Aortic Stenosis	<ul style="list-style-type: none"> - Calcific degeneration - Congenitally bicuspid - RF 	<ul style="list-style-type: none"> - Elevated LV sys/dias P - Concentric hypertrophy - LA enlargement - Abnormal LV dias. function - Decreased LV sys. Function 	<ul style="list-style-type: none"> - Exertional angina - Effort-related syncope - Dyspnea
Aortic Regurgitation	<ul style="list-style-type: none"> - Congenitally bicuspid - Infective endocarditis - RF - Aneurysm of aortic root 	<ul style="list-style-type: none"> - LV dilatation - Eccentric LV hypertrophy - Decreased LV sys. function 	<ul style="list-style-type: none"> - Forceful palpitations - Exertional dyspnea - Angina
Mitral Stenosis	<ul style="list-style-type: none"> - RF - Mitral annular calcific. - Iatrogenic (after repair) 	<ul style="list-style-type: none"> - LA enlargement - Pulmonary congestion - Pulmonary HTN - RV hypertrophy/failure 	<ul style="list-style-type: none"> - Exertional dyspnea - Palpitations - Hemoptysis
Mitral Regurgitation	<ul style="list-style-type: none"> - Mitral valve prolapse - MI - Infective endocarditis - RF - LV dilatation 	<ul style="list-style-type: none"> - LA enlargement - Pulmonary congestion - LV volume overload - Eccentric LV hypertrophy - LV failure - Pulmonary HTN - RV failure 	<ul style="list-style-type: none"> - Dyspnea - Pulmonary edema - Palpitations - Fatigue - Chest pain - presyncope

Physical Exam

	Aortic Stenosis	Aortic Regurg.	Mitral stenosis	Mitral Regurg.
Age presenting	<ul style="list-style-type: none"> - 30-40 (RF) - 40-50 (bicuspid) - >60 (degenerative) 	- Variable on etiology	- 20-50	- Variable on etiology
PE findings	<ul style="list-style-type: none"> - Sustained apical impulse - single S2, - pulses parvus/tardus 	- Peripheral signs of increased pulse pressure	- Opening snap, presystolic accentuation of diastolic rumble	- Midsystolic click
Murmur	<ul style="list-style-type: none"> - Midsystolic - Crescendo-decrescendo R upper sternal border 	<ul style="list-style-type: none"> - Decrescendo diastolic "blow" - parasternal 	- Diastolic rumble at LV apex (listen in L lateral decubitus)	- Holo- or late systolic at LV apex
CXR	<ul style="list-style-type: none"> - Dilated aortic root - Calcified AV 	- Dilated LV	<ul style="list-style-type: none"> - LAE - Pulmonary HTN 	- LAE, dilated LV
ECG	- LVH, LAE, LAD	- LVH	- L + RAE, RVH, AF	- LAE, AF

Diagnostic Evaluation

- Principle initial studies are ECG, CXR and echocardiography (typical results above)
 - o Echo highly indicated by **diastolic** or **holosystolic** murmur
 - o Midsystolic murmur is often an ejection murmur in young and aortic sclerosis in elderly
 - o Echo helps determine *presence* and *severity* of disease
- Regurgitant lesions are graded on a scale of 1(mild) to 4(severe)
- Stenotic lesions are grade on associated valve area (less being worse)

Treatment

- Mild-moderate treated conservatively in absence of symptoms
- *Mitral Stenosis*: HR control with B-blockers, CCB, pulmonary congestion with diuretics
- *Mitral Regurgitation*: generally require surgery but stabilized with afterload reduction using nitroprusside or hydrazine + inotropic agents
- Only surgery improves survival for aortic valvular disease
- *Aortic Regurgitation* (medical): afterload reduction with ACEi or CCB
- No effective medical treatment for *Aortic Stenosis* and most meds above may precipitate hemodynamic instability
- Valve replacement is most common surgical approach but valve repair sometimes with MR

Vascular Disease

- Atherosclerosis most common pathogenic mechanism of vascular disease
- Aneurysms are most common in the infrarenal aorta and are prone to tear (**aortic dissection**)
- Arterial occlusions can occur via embolization that come from
 - o LA - in the setting of atrial fibrillation
 - o Aortic/Mitral valves – in the setting of rheumatic or degenerative valvular disease
 - o LV – in the setting of ventricular dysfunction from CHD
- Arterial disease may also rise from nonatherosclerotic disorders:
 - o Marfan, Ehlers-Danlos, bicuspid aortic valve, HTN (**predispose to aortic aneurysm/dissection**)
 - o Takayasu and giant cell arteritis (**vasculitis of aorta and major branches**)
 - o Thromoangiitis obliterans (**vasculitis of small and medium arteries of extremity**)
 - o Infectious diseases (**ascending aortic aneurysms**)
- RF for peripheral artery disease (PAD): smoking, DM, HTN, DLD, Male, FHx

History

- *Acute peripheral arterial occlusion* characterized by six Ps
 - o Pulselessness, Pallor, Poikilothermia, Pain, Paralysis, Paresthesia
- *Acute mesenteric arterial occlusion* characterized by diffuse abdo pain out of proportion to PE finding
- *Chronic occlusive mesenteric disease* can manifest as abdominal angina
- In chronic PAD the most common symptom is **intermittent claudication**
 - o Claudication = muscular pain/aching/numbness that occurs with exercise and relieved with rest
- *Aortic aneurysms* usually asymptomatic until complications
- *Aneurysmal rupture* usually heralded by acute chest or abdo pain
- *Aortic dissection* often described as sudden, sever chest pain that is tearing in quality + diaphoresis

Physical Exam

- Findings depend on anatomic distribution and nature of the vascular disease. Important to examine peripheral pulses and auscultation for bruits
- *PAD*: diminished distal pulses, vascular bruits, smooth shiny hairless skin, ischemic ulceration
- *Acute peripheral arterial Occlusion*: Six Ps from above
- *Aortic Aneurysm*: pulsatile abdominal mass, pulsation in sternal notch, Aortic valve insufficiency
- *Aortic Dissection*: Asymmetric pulses and BP, limb/organ ischemia, aortic insufficiency

Diagnostic Evaluation

- Non-invasive tests to evaluate PAD: Ankle-brachial index, US, MRA
 - o ABI usually first test to assess severity and done sequentially to follow disease progression
 - o Normal ABI > 1.0, ABI < 0.95 = PAD, ABI <0.5 = severe disease
- AAAs assessed with US (most common), CT, or MRA
- Thoracic aneurysms best assessed with CT or MRA
- Aortic dissections diagnosed with transesophageal US, contrast CT, MRA

Treatment

- *Acute Arterial occlusion*
 - o Antiplatelet and antithrombotic agents are started immediately
 - o Definitive restoration of blood flow is essential to avoid tissue necrosis.
 - o Percutaneous balloon angioplasty, stenting, or surgical bypass is usually required, depending on candidacy

- *Aortic Dissection*
 - o Unless in shock, IV Beta blockade to reduce HR and BP
 - o Further treatment depends on location, if in ascending aorta or arch = IMMEDIATE SURGERY, otherwise variable
- *Aortic Aneurysms*
 - o Symptomatic (leaking) need urgent surgical treatment
 - o Asymptomatic can be treated with B-blockers and followed
 - o Indications for aneurysm repair
 - Expansion > 0.5cm/y
 - Thoracic AA > 6 cm
 - AAAs > 5.5 cm
 - AAs in presence of iliac or femoral aneurysms needing treatment
- *Peripheral Arterial Disease*
 - o Pharma: antiplatelets for symptoms
 - o Exercise for 30-45min 3x/week
 - o RF modification especially smoking cessation
 - o Foot care

Syncope

- Syncope is sudden transient LOC and postural tone with quick recovery
- Three main causes, **neural mediated, orthostatic hypotension, primary cardiac**, all caused by a transient decrease in cerebral blood flow
 - o Common cause in chart (right)

History

- Get history from patient AND witness
 - o What were they doing during syncopal episode?
 - o Any preceding symptoms (chest pain, palpitations, nausea etc)?
 - o Medications?
 - o Hx of Heart disease
 - o Seizure activity, incontinence, tongue biting, post-ictal?
 - o Length of unconsciousness
- Vasovagal prodrome (light headed, nausea, weakness) is reassuring
- Following findings on Hx suggest Cardiac syncope
 - o Chest pain, palpitations, exertional syncope, no prodrome or aura

Physical Exam

- Make sure no trauma suffered from fall
- Evaluate for orthostatic BP changes or unequal BPs
- Cardiac exam for murmurs, carotid and subclavian arteries for bruits
- Neuro exam looking for focal deficits

Diagnostic Evaluation

- 12-lead ECG for all patients with syncope

Procedure	Types of Syncope
ECG	Arrhythmia, heart block, conduction disease
Tilt-table testing	Neurocogenic syncope (vasovagal)
Electrophysiologic	VT, some SVT, some bradycardias
24h Holter	Arrhythmias that occur frequently
Evet monitor	Infrequent arrhythmias
EEG, Head CT	Seizure disorder
Carotid Sinus massage	Carotid sinus hypersensitivity

Treatment

- Treatment largely guided by type
- Arrhythmias require specific therapy to type (see notes on arrhythmias)
- Syncope from underlying heart disease requires correction of the structural abnormality, i.e. valve replacement, coronary revascularization
- Syncope from orthostatic hypotension from autonomic dysfunction benefits from nonmedical therapies such as tensing legs or compression stocking.

Neurally Mediated (Reflex)	
Vasovagal (neurocardiogenic)	
Situational	
Micturition	
Tussive	
Valsalva	
Carotid sinus hypersensitivity	
Orthostatic Hypotension	
Volume depletion	
Medications	
Postprandial	
Systemic disease (diabetes, amyloidosis, Parkinson disease)	
Primary Cardiac Causes	
Structural	
Aortic stenosis	
Mitral stenosis	
Hypertrophic cardiomyopathy	
Atrial myxoma	
Arrhythmic	
Supraventricular tachycardia	
Ventricular tachycardia	
Sinus node dysfunction	
AV nodal block	
Decreased cardiac output	
Myocardial infarction	
Pericardial tamponade	
Pulmonary embolism	
Aortic dissection	

Historical Feature	Suggested Cause(s)
Exertional	Aortic or mitral stenosis, HCM, pulmonary hypertension
Associated with chest pain	Myocardial ischemia, pulmonary embolism, aortic dissection
Associated with palpitations	Tachyarrhythmias or bradyarrhythmias
Family history of syncope or sudden death	Hereditary long QT syndrome, HCM
Associated with emotional stress, pain, unpleasant auditory or visual stimuli	Vasovagal episode
Following cough, micturition, or defecation	Situational syncope
After arising from lying or sitting position	Orthostatic hypotension, hypovolemia
After turning head; during shaving	Carotid sinus sensitivity
Associated with certain body positions	Atrial myxoma or "ball valve" thrombus
Diuretic medication use	Hypovolemia
Antiarrhythmic or antipsychotic medication use	Ventricular tachyarrhythmias
Parkinson disease, diabetic neuropathy	Orthostatic hypotension (especially postprandial)
Premonitory aura, tonic-clonic movements, incontinence, or tongue biting	Seizure
History of stroke or head trauma	Seizure
Syncope precipitated by arm movement	Subclavian steal syndrome

AHD - ECG 1 and 2

The electrocardiogram (ECG) is a *voltmeter* that records electric signal at the skin surface generated by the electrical activity of the heart muscle.

Single Cell Model

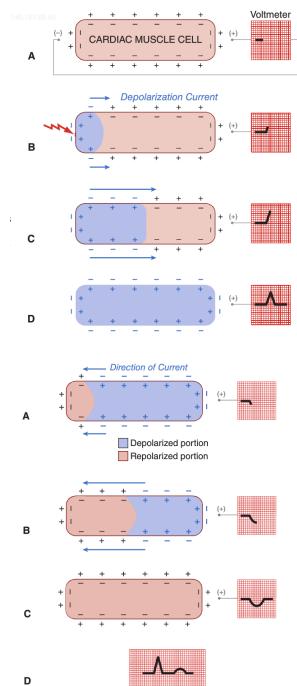
Myocyte Depolarization

- Cardiac Muscle cell is negative inside and positive outside
- (A) 0 voltage because both electrodes are measuring a + signal (no current)
- (B) Left part of cell becomes depolarized as + moves in and – goes to outside. This creates a positive deflection on ECG
- (C) Large depolarization current passes and creates a big ECG deflection
- (D) Entire cell is + inside and – outside so no current again

Myocyte Repolarization

- (A) Left side of cell is repolarizing (- charges flowing in). A small repolarization creates a negative deflection
- (B) A larger repolarization (current) creates a greater amplitude
- (C) Once the entire cell is repolarized there is no more current

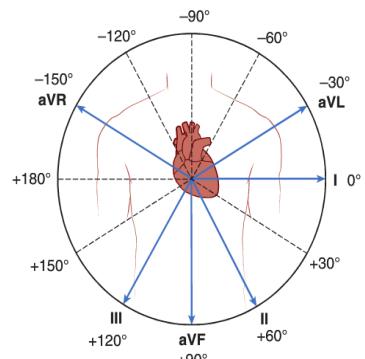
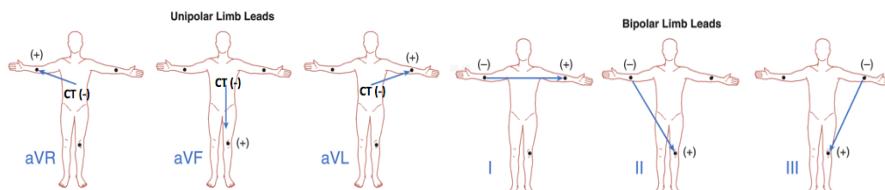
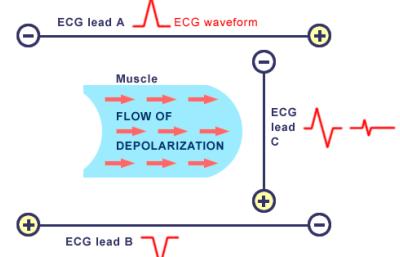
NB: In the heart, the cells that were depolarized *LAST* get repolarized *FIRST* which makes loop in (C) positive instead of negative. Repolarization also takes longer than depolarization.



ECG Recording

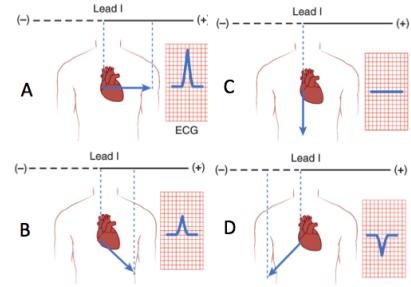
10 wire electrodes are placed directly on the skin on each of the four limbs and 6 on the chest

- **Lead:** Recording of electrical activity between 2 points.
 - o Each lead has a + and – pole
 - o Complete ECG has 12 leads (6 limb + 6 chest)
 - o Snapshot of heart electrical activity in frontal or transverse planes
 - o All leads record same thing but look distinct due to orientation
 - o If depolarization current is *TOWARDS* the +_{electrode} => Positive (A)
 - o If depolarization current is *AWAY* from +_{electrode} => Negative (B)
 - o If depolarization current is *PERPENDICULAR* from +_{electrode} => Biphasic (C)
- 6 limb leads record in the *FRONTAL PLANE*
- 6 chest leads record in the *TRANSVERSE PLANE*
- **augmented, Voltage, Right, Left, Front**
- Right leg is always a ground
- Overlaying all 6 leads creates an axial reference system (right)



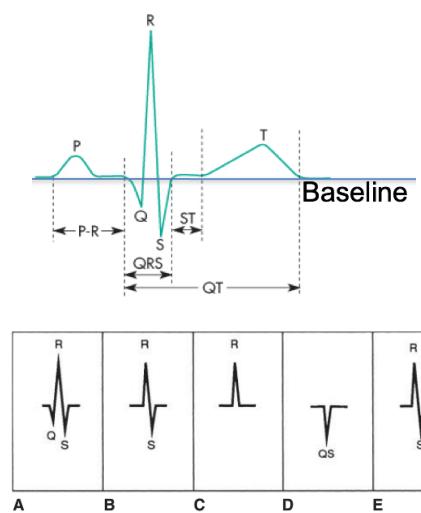
Example ECG

- An electrical force **toward** the $+_{\text{electrode}}$ of a lead results in an **upward** deflection on the ECG (A/B)
- Forces **away** from the $+_{\text{electrode}}$ result in a **downward** deflection (C)
- The more **parallel** the electrical force is to the lead the **greater** the magnitude of the deflection (A vs. B)
- An electrical force **perpendicular** to an ECG lead shows a flat line (D)

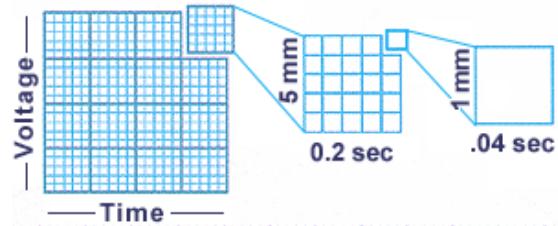
**Sequence of Normal Cardiac Activation**

Each heartbeat is represented by 3 major deflections

- **P-WAVE** = atrial depolarization
 - o Sinus node initiates depolarization of the heart
- **QRS COMPLEX** = ventricular depolarization
 - o Q, R, S waveforms can have many shapes
 - **Q-Wave**: when first deflection is *down* (A/D)
 - **R-Wave**: the *first upward* deflection (A/B/C/E)
 - **S-Wave**: any *downward* deflection after R (A/B/D/E)
 - Additional deflection inscribed with a ' (E)
- **T-WAVE** = ventricular repolarization
- **PR-INTERVAL** = time from **start** of P-wave to **start** of QRS complex
- **QT-INTERVAL** = time from **start** of QRS to **end** of T-wave
- **ST-SEGMENT** = line between **end** of QRS and **start** of T-wave
 - o Normally isoelectric (baseline signal) but may move up or down in response to lack of O₂

**Interpretation of the ECG**

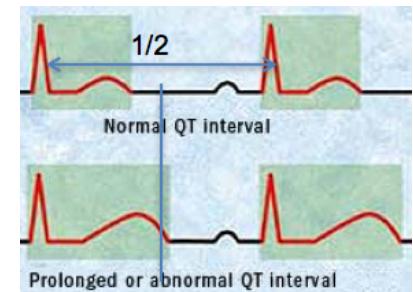
- ECG is recorded on grid divided by 1mm lines. Fifth line is darker to facilitate measurement
- Vertical axis is voltage (mv)
 - o 1mm = 0.1mv
- Horizontal axis is time (ms)
 - o 1 small box = 40ms
 - o 1 large box = 0.2s

**Sequence of Analysis**

1. Calibration
 - o Check height of calibration signal (usually 10mm). If 20mm/5mm means double/half calibration.
2. Heart Rhythm
 - o Normal rhythm initiated by depolarization of the sinus node is "*sinus rhythm*"
 - o Sinus rhythm present when P-waves are **upright** in leads I and II
 - o **NORMAL** sinus rhythm = HR between 60-100 BPM
 - o **SINUS BRADYCARDIA** = HR < 60 BPM
 - o **SINUS TACHYCARDIA** = HR > 100 BPM
3. Heart Rate Determination
 - o **Method 1:** Count #small boxes (each 1mm) between adjacent QRS complexes. Since standard paper speed is 25 mm/s, HR = 1500/#boxes. Useful for FAST HRs
 - o **Method 2:** Count #large boxes between QRS and use sequence 300-150-100-75-60-50
 - o **Method 3:** Count #QRS complexes between 3s markers and multiply by 20 (++ irregular HR)

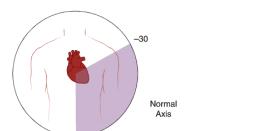
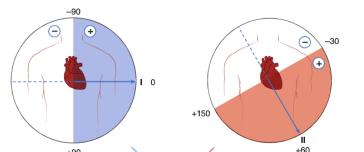
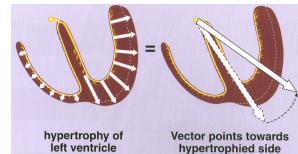
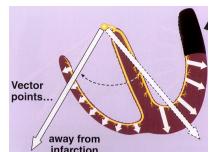
4. Intervals (PR and QT)

- PR interval is time between start of P and start of QRS
 - Normal PR: 0.12 – 0.20s (3-5 small boxes)
 - Decreased PR: Preexcitation syndrome, junctional rhythm
 - Increased PR: First-Degree AV block
- QT Interval is the time between start of QRS and end of T
 - Represents time for ventricular depolarization + repolarization
 - Estimates the duration of the cardiac AP.
 - Any process that prolongs AP will prolong QT
 - Is not a constant interval and will change according to HR.
 - At high HR, heart needs rapid repolarization => shorter QT
 - At low HR, opposite happens
 - Abnormally long QT intervals may predispose patients to lethal cardiac rhythm disturbances
 - Conditions that shorten QT interval: Hypercalcemia, tachyarrhythmia
 - Conditions that lengthen QT interval: Hypocalcemia, Hypokalemia, Hypomagnesemia, myocardial ischemia, toxic drug effects



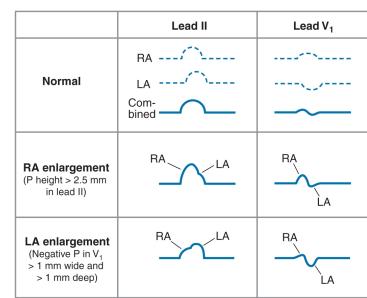
5. Mean QRS axis

- Represents the average of the electrical forces generated during the sequence of **ventricular depolarization** as measured in the **frontal plane**
- Axis may be altered by the heart's orientation in the chest
- Axis may be altered with ventricular hypertrophy
- Axis may be altered with ventricular infarction
- Axis termed Normal or *deviated*
 - Left-deviation caused by inferior wall MI, left anterior fascicular block LV hypertrophy
 - Right-deviation cause by RV hypertrophy, acute heart strain (Pulmonary embolism), left posterior fascicular block
- Determining the axis
 - Lead 1: If QRS + => vector is towards +electrode (between 90° and -90°)
 - Lead 2: If QRS + => vector is towards +electrode (between -30° and 150°)
 - If QRS + in both ½, axis is between -30° and 90° (This is normal)
- Axis Deviation – quick assessment
 - If QRS is not primarily upward in Lead 1 or 2, then the axis is deviated
 - If QRS Lead 1 negative => Right axis deviation
 - If QRS Lead 1 positive, Lead 2 negative => Left axis deviation



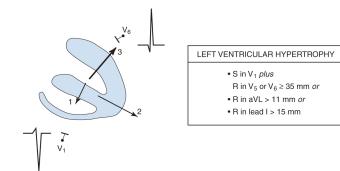
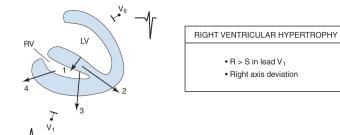
6. Abnormalities of the P-wave

- P-wave represents depolarization of the RA followed by quick depolarization of the LA
- Best seen in Leads 2 and V₁
- Atrial enlargement criteria
 - RA enlargement: P_{height} > 2.5 mm in Lead 2, 3 aVF; >1.5 mm in V₁, V₂
 - LA enlargement: biphasic P wave in V₁ > 1 mm wide and 1 mm deep
- Sawtooth pattern seen in Atrial flutter



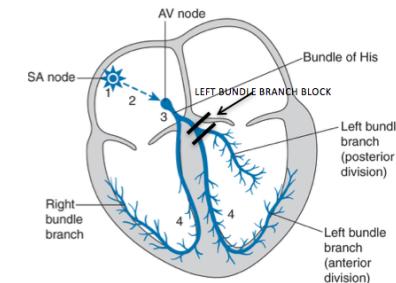
7. Abnormalities of the QRS

- Hypertrophy of LV/RV
 - Causes affected chamber to generate *greater* than normal electrical activity
 - In RV hypertrophy, augmented right-sided forces outweigh left-sided forces
 - Chest leads V1/V2 record greater than normal upward deflections
 - R wave > S wave
 - RA enlargement
 - Increase RV mass deviates the mean axis to right
 - In LV hypertrophy, augmented left-sided forces exaggerate normal left sided predominance
 - Chest leads V5/V6 record greater than normal upward deflections
 - Leads V1/V2 record deeper than normal deflections
 - LA enlargement
 - Increase LV mass deviate mean axis to left



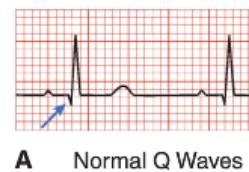
- Bundle Branch blocks

- Interruption of the conduction through the right or left bundle branches
- May develop from ischemic or degenerative damage
- Affected ventricle does not depolarize in the normal sequence
- Cells of that ventricle rely on relatively slow myocyte-to-myocyte spread of electrical activity traveling from the unaffected ventricle
- Prolongs depolarization and widens the QRS complex
- **Normal QRS ≤ 0.10s**
- **Complete bundle branch block: QRS >0.12s**
- **Incomplete bundle branch block: 0.10s < QRS < 0.12s**
- Left bundle branch has 2 main subdivisions: Anterior/Posterior Fascicles
- Fascicular blocks (hemiblocks) occur when conduction is impaired in just one fascicle
- Fascicular blocks markedly alter the mean ECG axis
- **Right bundle branch has “bunny ears” in V1/V2, left bundle branch in V6**

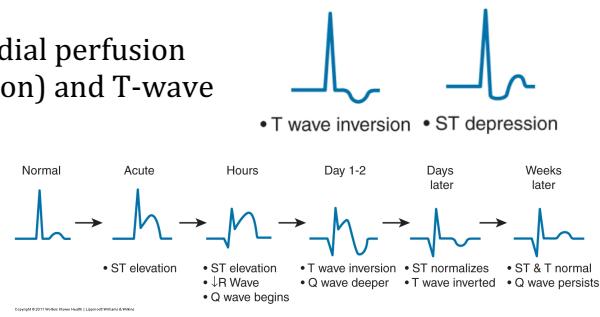


8. Abnormalities of the ST segment and T wave

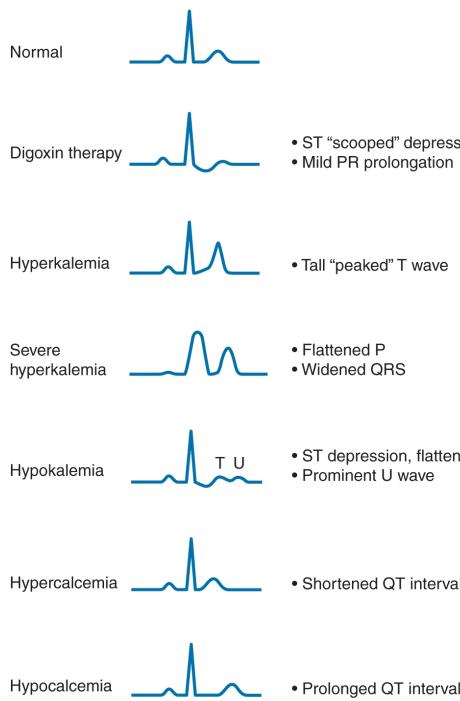
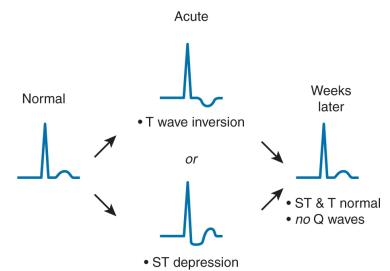
- Physiologic Q waves
 - Normal to have small Q waves in leads V₆ and aVL (septal depolarization)
 - Physiologic Q-waves are short (<0.04s) and shallow (<25% total QRS height)
- Pathological Q waves in MI
 - Sudden occlusion of coronary artery -> Acute MI
 - Without reperfusions, heart will develop irreversible necrosis in zone fed by that vessel
 - Myocardial necrosis is represented by pathologic Q waves in affected zone
 - Necrotic muscle does not generate electrical forces
 - ECG electrode over the necrotic region picks up electrical currents from healthy tissues on the opposite region of the ventricle
 - Q waves are permanent evidence of an old trans-mural infarction
 - Pathologic Q-waves are wide (>1 small square) and deep (>25% QRS height)
 - True pathologic Q-waves appear in specific groupings => a single q wave is non-diagnostic
 - **Anteroseptal:** Q waves in V1/V2
 - **Anteroapical:** Q waves in V3/V4
 - **Aterolateral:** Q waves 1/aVL V5/V6
 - **Inferior:** 2/3/aVF



- Transient Myocardial Ischemia
 - Ventricular repolarization is very sensitive to myocardial perfusion
 - Reversible shifts of the ST segments (usually depression) and T-wave (inversions) are common during ischemia
- Acute ST segment elevation MI
 - Changes are recorded in leads overlying infarction
 - Typically, reciprocal changes are observed in leads opposite of infarction site (i.e. ST depressions)
- Acute Non-ST segment elevation MI
 - In this case, the thrombus is only partially occlusive
 - Causes ST-segment **depressions** and/or T-wave **inversions** in leads overlying affected myocardium
 - Q-waves do not develop as typically only the sub-endocardium is involved
- Not all ST/T abnormalities are caused by ischemia/infarction
- Pericarditis = inflammation of pericardial sac
 - Diffuse ST segment elevation
 - Reflects inflammation of adjacent myocardium
 - Affects most leads except aVR and V1
 - PR segment depression
 - Reflects abnormal atrial repolarization



Unstable Angina/Non-ST-Elevation Myocardial Infarction



Dyspnea

- Awareness and control of respiration by the CNS is influenced by:
 - o Central and peripheral chemoreceptors (measure blood O₂, CO₂, pH)
 - o Mechanical receptors in the pulmonary parenchyma, airways, respiratory muscles, and skin

DDx

- Dyspnea is generally from **pulmonary** or **cardiac** causes that are **acute** or **chronic**
- *Acute Pulmonary:* asthma, bronchitis, pneumonia, pneumothorax, PE, airway irritant or obstruction
- *Acute Cardiac:* CHF, Tamponade
- *Acute Other:* Hemorrhage, hemolysis, Metabolic acidosis, CO poison, Psychogenic, altitude, obesity
- *Chronic Pulmonary:* COPD, Pleural effusion, interstitial disease, pulmonary HTN, kyphoscoliosis
- *Chronic Cardiac:* CHF, Restrictive pericarditis, anemia, severe obesity
- Among **outpatients**, obesity, COPD, asthma, CHF and anxiety are most common

History

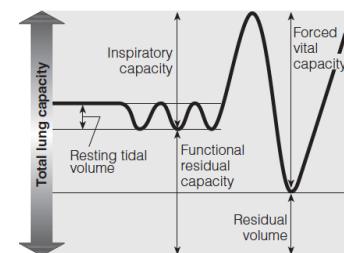
Acute Dyspnea	Chronic Dyspnea
<ul style="list-style-type: none"> - Cough (bronchitis, asthma, pneumonia, irritation) - Sputum (bronchitis, pneumonia) - Pleuritic chest pain (spontaneous pneumothorax, PE, pneumonia) - Visceral chest pain (CHF) - Hemoptysis (PE, bronchitis, pneumonia) 	<ul style="list-style-type: none"> - Smoking (COPD, bronchitis) - Cardiac Hx (CHF) - Occupational/environmental exposures - BASELINE FITNESS (chronic dyspnea usually manifests as exertional so you want to compare)

Physical Exam

Acute Dyspnea	Chronic Dyspnea
<ul style="list-style-type: none"> - Wheezing (asthma CHF) - Stridor (upper airway obstruction) - Consolidation (pneumonia) - Rales, S3, Jugular venous distension (CHF) - Cardiac murmurs (valvular) - Tracheal shift + absent breath sound (PE) - Leg swelling (PE) 	<ul style="list-style-type: none"> - Hyperexpansion (COPD) - Rales (interstitial lung disease) - S3, jugular venous distension (CHF) - Fixed split of S2, right ventricular heave (pulmonary HTN)

Diagnostic Evaluation

- In acute dyspnea get CXR and look for pneumothorax, pneumonia, CHF
 - o Measurement of ABG can help determine degree of respiratory compromise (but not etiology)
 - o Peak expiratory flow -> asthma, BNP ->CHF
 - o If PE suspected -> V/P scan, leg US, helical CT
- Chronic dyspnea should start with CXR, CBC for anemia, more specialized test with pulmonologist
- Pulmonary function tests are commonly used for chronic dyspnea and usually start with spirometry:
 - o **FVC:** forced vital capacity, volume of air exhaled from max inhale-exhale
 - o **FEV₁:** Forced expiratory volume in 1s
 - o **FEV₁/FVC:** ratio of two above
 - o **TLC:** volume of gas contained within lung after max inhale
 - o **RV:** volume of gas remaining in lung after max exhale
 - o **DLCO:** diffusion capacity of CO, ability of gas to diffuse across alveolar-capillary membrane



- Specific patterns of the above spirometry values relate to different diseases:

Disease	FVC	FEV ₁	FEV ₁ /FVC	TLC	RV	DLCO
Emphysema	↓	↓	↓	↑	↑	↓
Chronic Bronchitis	↓	↓	↓	↔	↑	↔
Asthma	↓	↓	↓	↔	↑	↑
Interstitial Lung Disease	↓	↔	↔↑	↓	↓	↓
Extrapulmonary restriction	↓	↓	↔	↓	↔↓	↔
Heart Failure (early)	-	-	-	-	-	↑
Heart failure (late)	-	-	-	-	-	↓
Pulmonary embolus	-	-	-	-	-	↓

- By assessing both cardiac and pulmonary systems, the relative degree of impairment can be used to guide therapy

AHD – Pulmonary Function Tests

- 4 Common PFTs: **Spirometry, Plethysmography, CO diffusing capacity, Max mouth pressure**
- Less common: methacholine challenge (asthma), six-minute walk distance, exercise testing, upright and supine vital capacity, ABG
- Pulmonary disorders detectable with PFTs:
 - o Airway (obstructive): asthma, COPD, bronchiolitis, large airway obstruction
 - o Restrictive: neuromuscular disease, interstitial disease
 - o Vascular: pulmonary HTN
 - o Pulmonary congestion

Indications for PFT

- Diagnosis: to evaluate signs or symptoms or to screen individuals for disease
- Monitoring: assess effect of a therapeutic intervention, or disease severity/progression
- Quantification: evaluate impairment for insurance purposes or medication eligibility

Contraindications

- Unstable angina or MI within 4-6w
- Abdominal, intracranial, or eye surgery or pneumothorax within 4-6w
- Thoracic, abdominal or cerebral aneurysms

Other Considerations

- Infection control
 - o Avoid testing if active hemoptysis or active TB suspected
 - o If testing necessary and a communicable disease suspected, ensure extra attention to cleaning
- Suboptimal conditions: cognitive impairment, mouth, chest, or abdo pain

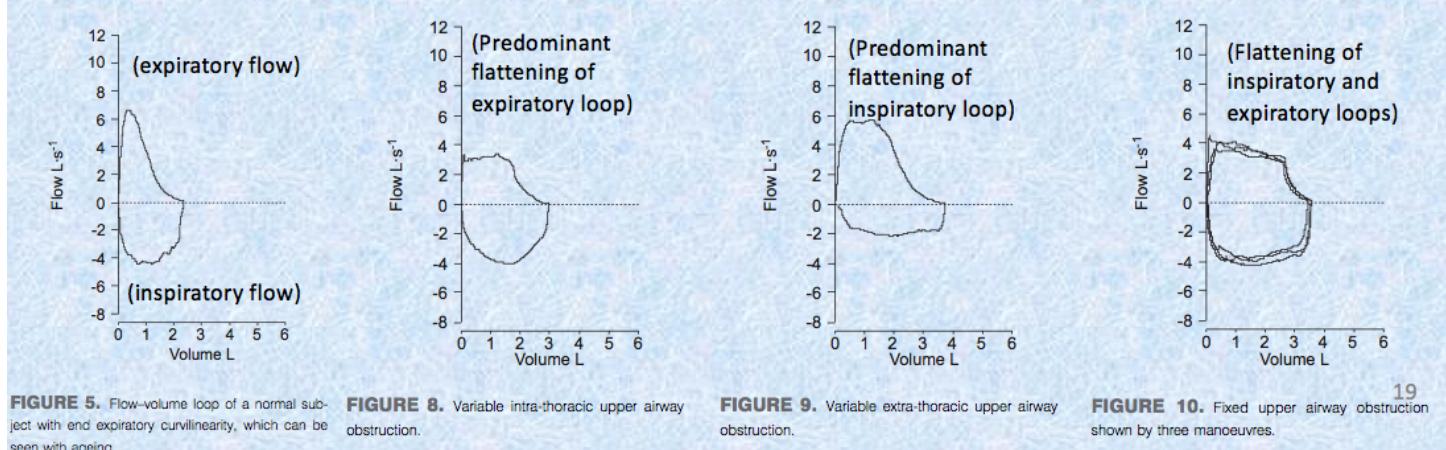
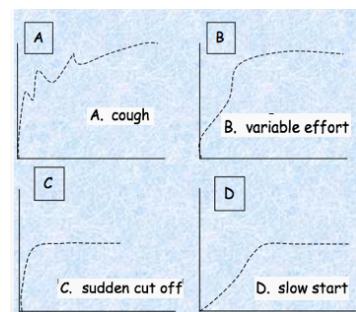
Subject Preparation

- Stopping inhaled therapy before testing
 - o To **Dx a disease**, it is best to have patient **off** treatments that may normalize lung function
 - o To demonstrate **therapeutic effect**, it is best to test **on** therapy
 - o If inhaled therapies being stopped: LABA x 24h, SABA x6h; make sure rescue inhalers handy

Spirometry

- The most common application of spirometry is measurement of the max volume of gas **exhaled** during a forced maneuver
 - o Allows assessment of the lung **size and rate of emptying**
- Common measurements from spirometry
 - o **Forced Expired Volume in first second (FEV₁)**: volume of gas exhaled in the first second of maximal forced exhalation from maximal inspiration
 - o **Forced Vital Capacity (FVC)**: volume of gas exhaled with maximal forced exhalation from prolonged maximal inspiration
 - o **Peak expiratory flow (PEF)**: highest flow rate observed during the maximal forced exhalation from maximal inspiration (more effort dependent than FEV₁)
- FEV₁ and PEF are measurements of expiratory flow, determinants of this include:
 - o Airway resistance (reduced cross-sectional airway lumens i.e. bronchoconstriction)
 - o Driving pressure (elastic recoil of the lung [COPD, fibrosis], effort, neuromuscular disease)
- Determinants of FVC:

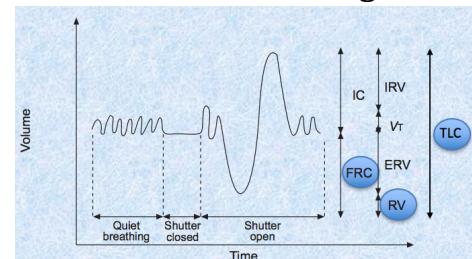
- **TLC determined by:** Inspiratory muscle force (neuromuscular disease, patient effort/cooperation) vs. chest wall and lung recoil forces (kyphoscoliosis, COPD, lung fibrosis)
- **RV determined by:** Expiratory muscle force (neuromuscular disease, patient effort/cooperation) vs. outward recoil of forces of chest wall and airway resistance (COPD, aging)
- Spirometry also provides a V-t curve; shape helps assess quality of the test
- Spirometry also provides a flow-volume loop; appearance can suggest upper airway obstruction (emergency!)



- Post-bronchodilator spirometry: 10-15 min after inhalation looking for **>12% or 200 mL change**

Plethysmography

- Quantification of absolute lung volumes
- Measuring FRC
 - Patient sits in a body box with the mouth attached to a mouthpiece connected to outside
 - The mouthpiece apparatus permits closure of a shutter with measurement of pressure at the mouth while the shutter is closed
 - The body box permits measurement of changes in gas volume within the chest – the change in volume of the body box is the exact opposite of the change in volume of thorax
 - At the end of a quiet breath (FRC), the mouthpiece shutter is temporarily closed and the patient is asked to pant gently against a closed shutter valve
 - The patient's breathing efforts create small pressure and volume changes within the alveolar compartment of the lung
 - The **changes in alveolar pressure** can be measured at the **mouthpiece**
 - The **changes in lung volume** can be measured with the **body box**
- Once FRC is known we can calculate the other lung volumes by simple inspiratory/expiratory maneuvers performed immediately following the FRC measurement
- Determinants of absolute lung volume:
 - **TLC:** equilibrium of outward inspiratory muscle forces (e.g., neuromuscular diseases) versus inward lung and chest wall recoil forces (e.g., emphysema, pulmonary fibrosis, obesity)
 - **FRC:** equilibrium of inward lung elastic recoil forces and outward chest wall recoil forces (e.g., see above); and exhalation time
 - **RV:** equilibrium of inward expiratory muscle forces (plus a small contribution from inward lung recoil forces) versus outward chest wall recoil forces; and dynamic airway closure



Carbon Monoxide Diffusing Capacity (D_{LCO})

- Carbon monoxide has much greater affinity for hemoglobin
- Inhale a known [CO], hold breath for a known time, measure exhaled [CO], calculate difference
- Causes of abnormal D_{LCO} :

Path of CO transfer from environment to Hb	Examples of how this can alter measured D_{LCO}
CO enters the lung during inhalation	Mouthpiece leak during the diffusing capacity maneuver can alter inhaled and/or exhaled [CO], thus affecting D_{LCO}
CO diffuses across the alveolar-capillary membrane	Loss of surface area (e.g., emphysema) or membrane thickening (e.g., fibrosis) decreases diffusion
CO binds to deoxy-hemoglobin to form carboxy-hemoglobin	Pre-existing carboxy-hemoglobin (e.g., a heavy smoker) can reduce number of deoxy-hemoglobin sites available to bind CO. Anemia decreases the capacity of blood to take up CO. Polycythemia increases the capacity of blood to take up CO.
Circulation carries carboxy-hemoglobin away, filling the capillaries with deoxy-hemoglobin	Higher cardiac output exposes more blood to the alveolar-capillary membrane, increasing carbon monoxide uptake

Maximal Mouth Pressures

- A mouthpiece with a pressure gauge measures mouth pressure during a maximal inspiratory and expiratory effort
- MIP: force generated by the diaphragm and accessory **inspiratory** muscles
- MEP: force generated by abdominal muscles and other accessory **expiratory** muscles
- Altered by neuromuscular diseases, patient effort/cooperation

Interpreting PFTs

- PFT reports have predicted values included for a "healthy" person of similar age, gender, and size
- Interpretation involves 10 steps; Steps 1-4 are quality control
 - o Step 5: Is there an **obstructive defect**
 - $FEV_1/FVC < 0.70$ or lower limit of normal = OBSTRUCTIVE
 - If present assess severity and bronchodilator responses (12%/200mL rule = reversible)
 - If present assess severity using % FEV_1/FVC predicted: 30/50/80 = severe/moderate/mild
 - o Step 6: is there a **restrictive defect**
 - Primary diagnostic test is plethysmography ($TLC < 80\%$ predicted = RESTRICTIVE)
 - If present assess severity using % predicted: 30/50/80 = severe/moderate/mild
 - o Step 7: is the D_{LCO} low, normal, or high
 - Low D_{LCO} is defined by the lower limit of normal
 - If present assess severity 40/40-60/60+ = severe/moderate/mild
 - o Step 8: are mouth pressures low or normal
 - Low mouth pressures are defined by the lower limit of normal; if lower limit of normal is not reported then a threshold of 50-60% is commonly used
 - o Step 9: Review prior PFT results and imaging
 - o Step 10: summarize your observations

Case 1

- Pre-dilator: $FEV_1 = 1.36$ (62% predicted), $FVC = 2.36$ (90%); Post-dilator: $FEV_1 = 1.59$ (73%), $FVC = 2.83$ (108%); $TLC = 6.08$ (119%), $RV = 3.55$ (170%), $D_{LCO} = 11.36$ (54%)
- Interpretation: Findings consistent with persistent airflow limitation (COPD)

- **Moderate** (62% predicted) **obstructive** ($\text{FEV}_1/\text{FVC} < 0.70$) defect with significant **bronchodilator response** ($>12\%/200 \text{ mL} \Rightarrow$ Reversible)
- Gas-trapping and **hyperinflation** ($\text{TLC} \sim 20\% >$ Normal, RV greatly increased)
- DLCO is **moderately** (40-60%) reduced.

Case 2

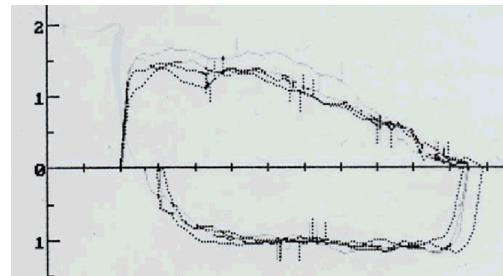
- Pre-dilator: $\text{FEV}_1 = 1.89$ (48% predicted), $\text{FVC} = 4.37$ (87%); Post-dilator: $\text{FEV}_1 = 2.41$, $\text{FVC} = 5.15$; $\text{TLC} = 7.65$ (149%), $\text{DLCO} = 32.2$ (104%)
- Interpretation: Findings consistent with asthma
 - **Moderate** (55% predicted) **obstructive** ($\text{FEV}_1/\text{FVC} < 0.70$) defect with significant **bronchodilator response** ($>12\%/200 \text{ mL} \Rightarrow$ Reversible)
 - Gas trapping and **hyperinflation** ($\text{TLC} > 20\%$ normal); DLCO is **normal** (104%)

Case 3

- $\text{FEV}_1 = 3.13$ (90% predicted), $\text{FVC} = 4.01$ (91%), $\text{TLC} = 5.32$ (75%), $\text{RV} = 1.29$ (54%), $\text{DLCO} = 14.54$ (50%)
- Interpretation:
 - **Moderate** ($\sim 80\%$) **Restrictive** ($\text{TLC} < 80\%$) disease with **moderate** (40-60%) reduced DLCO

Case 4

- Patient with following flow/volume loop
- Interpretation of loop:
 - Blunted inspiration/expiration flows
 - Reproducible rectangular pattern
 - Suggestive of upper airway lesion



Cough

- Cough is a defense mechanism to help clear secretions and foreign particles
- Triggered by receptors located throughout the upper and lower respiratory tract, thus many stimuli
- Cigarette smoking is very common cause of chronic cough

DDx

URTI (viral)	LRTI	Environmental	Mechanical Irritation	Chronic Inflammation	Drugs
- Pharyngitis	- Bronchitis	- Dust	- Tumor	- Asthma	- ACEi
- Sinusitis	- Pneumonia	- Pollen	- Aortic aneurysm	- COPD	- Psychogenic
- Tracheitis	- TB	- Cigarette smoke	- Pulmonary edema	- GERD	- Sarcoidosis

History and Physical Exam

History	Physical exam
<ul style="list-style-type: none"> - Is cough acute (<3w) or chronic - Smoker/history of obstructive airway disease - Sputum – colour +/- blood - Environmental exposures (dust, fumes, animals) - B symptoms (fever, weight loss, night sweats) 	<ul style="list-style-type: none"> - Sinus tenderness (sinusitis) - Rhinitis (URTI) - Tympanic membrane erythema (otitis) - Loose rhonchi (bronchitis/pneumonia) - Consolidation (pneumonia) - Fine crackles (pulmonary edema) - Focal wheezing (tumor/foreign body) - End-expiratory wheezing (COPD)

Diagnostic Evaluation

- Usually etiology is suggested by Hx and PE, if not do CXR
- Gram stain of sputum can help with diagnosis
 - o Purulent sputum with WBCs suggests bronchitis/pneumonia
 - o Eosinophils and mucus casts suggest asthma
 - o RBC may indicate chronic bronchitis, bronchiectasis, or tumor
- Chronic cough can be evaluated with PFTs to look for COPD
- CT chest may reveal lesions

Treatment

- Treatment aimed at etiology
 - o Removal of environmental irritant, smoking sensation, antihistamines or nasal corticosteroids for rhinitis, empirical abx for bacterial causes
- Antitussives suppress cough reflex by anesthetizing peripheral irritant receptor or increasing the threshold of the central cough center
 - o Benzoate (most effective peripheral anesthetic)
 - o Phenol + menthol preparations (peripheral anesthetics)
 - o Codeine (most effective central antitussive)

Chronic Obstructive Pulmonary Disease

- COPD is a condition of **irreversible** chronic airflow limitation that combines 3 major entities
 - o *Chronic obstructive bronchitis*: chronic mucus producing cough > 3 months
 - Hypertrophy+hyperplasia of mucous glands + mucosal/submucosal inflammation (CD8/neu)
 - o *Emphysema*: abnormal dilatation of terminal airspaces with destruction of alveolar septa
 - Centrilobular (smoking) = respiratory bronchioles and alveolar ducts affects
 - Panacinar (α 1-antitrypsin deficiency) = destruction throughout the acinus
 - o *Chronic obstructive asthma*: airway reactivity with fixed obstruction and chronic inflammation
 - Also characterized by inflammation but with CD4 Tcells and eosinophils
- Physiologic COPD changes: V/Q mismatch, Pulmonary HTN, abnormal ventilator response, Right CHF

History

- Hallmark is **cough with sputum**
- Dyspnea not predominant early but onset of exertional dyspnea often triggers medical attention
- Weight gain, lethargy, and cyanosis are late findings

Physical exam

Chronic Obstructive Bronchitis	Emphysema
<ul style="list-style-type: none"> - blue bloaters (cyanosis + obese) - if RHF -> peripheral edema - Lungs are resonant with coarse rhonchi and wheezes - Cardiac -> RV overload - Clubbing rare 	<ul style="list-style-type: none"> - Pink puffer (dyspnea + thin) - Prolonged expiration with pursed lips - Hypertrophy of accessory muscles of respiration - Intercostal retraction - Hyper resonant lungs - Decreased breath sounds - Increased chest diameter - Heart sounds faint

Diagnostic Evaluation

- Spirometry is primary means of quantifying airway outflow (see Dyspnea section)
- A calculated **FEV₁/FVC < 0.7** establishes **airway outflow obstruction**
 - o If post-bronchodilator response is <12% = irreversible = COPD, FEV₁ then gauges stage

Stage	1	2	3	4
Descriptor	Mild	Moderate	Severe	Very Severe
FEV ₁	$\geq 80\%$ predicted	80-50% predicted	50-30% predicted	<30% predicted

- Arterial blood gas for *emphysema*: normal PaCO₂, slightly lowered PaO₂
- Arterial blood gas for *chronic bronchitis*: elevated PaCO₂, depressed PaO₂
- Factors for suspicion of α 1-antitrypsin deficiency: age>45, no smoking Hx, FHx of COPD
- CXR not usually necessary

Treatment (General)

- Key intervention is smoking cessation (does not reverse damage)
- Pharma = *Bronchodilation* (β 2-adrenergic agonists or anticholinergics) and *anti-inflammation* (steroids or phosphodiesterase inhibitors) often used together
- **Ipatropium** (anticholinergic): bronchodilation via vagal stimulation of airways
- **Salmeterol/Formoterol** (β 2 agonists) add further bronchodilation
- *Inhaled corticosteroids* (ICS) used with worse disease and exacerbations
- **Roflumilast** (phosphodiesterase inhib): anti-inflammation during exacerbation but +++side effects

- ICS- β 2 combos effective for patients at risk of frequent exacerbation
- For patients with constant hypoxemia, continuous oxygen is indicated

Treatment (Acute Exacerbation)

- These patients often present with severe dyspnea and increased volume of sputum (Dx with Hx)
- Choice of treatment depends on disease severity and exacerbation severity
 - o Bronchodilator therapy for symptoms, use **SHORT ACTING** (not long acting like in general Tx)
 - o Systemic corticosteroid for 5 days helps reduce length of exacerbation and reduce relapse
 - o Standard respiratory supports (oxygen, noninvasive or invasive ventilation support)

Continued Care

- All COPD should receive flu vaccine and pneumococcal vaccine
- Refer to pulmonary rehab programs

Asthma

- Asthma is a disease of the airways characterized by chronic inflammation to the tracheobronchial tree with **reversible** expiratory airflow obstruction
- Asthmatics have greater degrees of **airway activity** (bronchoconstriction) than non-asthmatics
 - o Stimuli that lead to Chronic inflammation: inhaled allergens, viral infections, industrial chemicals
- Acute asthma is triggered by broncho constricting stimuli: cold air, exercise, NSAIDs, B-blockers, etc.

History

- **Acute** asthma symptoms: dyspnea, wheezing, cough, sputum, sleep disturbance, bronchodilator use
 - o Sx often develop over days to week but can happen more acutely in hours-minutes especially if triggered by NSAID, B-blockers or food additives

Physical Exam

- During acute attack findings include: respiratory distress, tachypnea, wheezing, +/- cough
 - o Lung exam: audible wheeze, scattered rhonchi, prolonged expiratory phase
 - o Chest is hyperinflated in anteroposterior diameter
- VS show tachycardia, and sometimes pulsus paradoxus
- Further signs of respiratory muscle fatigue are accessory muscle use and paradoxical breathing

DDx

- In known asthmatic diagnosis often easy but resp signs mimic: CHF, PE, Pneumonia, Bronchitis

Diagnostic Evaluation

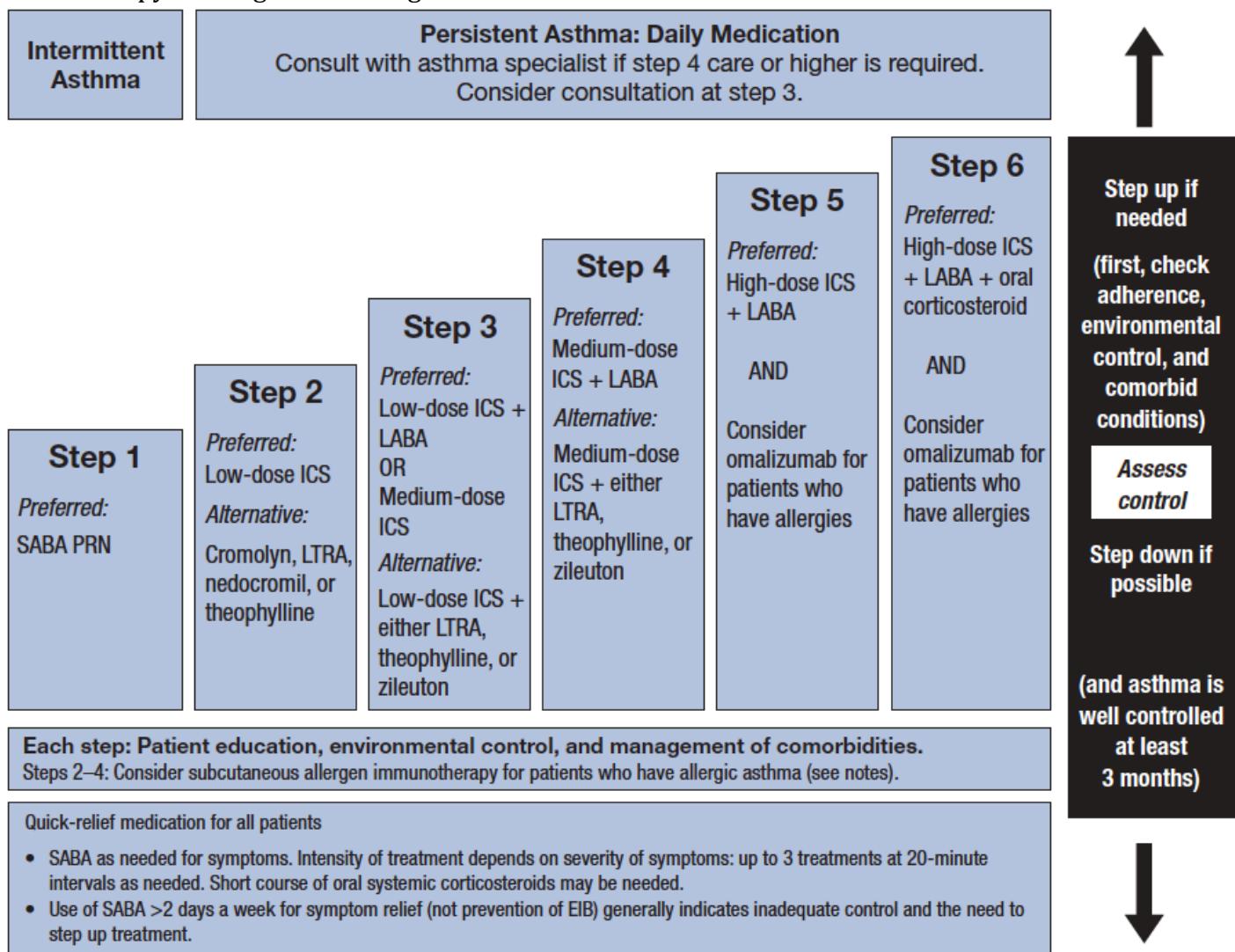
- Peak expiratory Flow (PEF) is primary test to determine severity of acute asthma attack
 - o Results are compared as a % to either normal or patient's best obtainable value
 - o PEF 20-30% = Acute attack, PEF 50% = resolving symptoms, PEF 60-70% = no symptoms
 - o This means signs and Sx can be absent while patient has severe residual airflow limitation
- CXR not usually necessary but may reveal hyperinflation or atelectasis 2^o to mucous plugging
- ABG not recommended in acute attacks
- Classification of severity of asthma in youths > 12 + adults:

Components	Intermittent	Persistent		
		Mild	Moderate	Severe
Symptoms	2d/w	>2d/w not daily	Daily	Continuous
Night waken	2/m	3-4/m	>1/w not nightly	7x/w
SABA use for Sx	2d/w	>2d/w	Daily	Several/day
Daily interference	None	Minor	Some	Extreme
Lung Function	<ul style="list-style-type: none"> - Normal FEV₁ between exacerb. - FEV₁ > 80% norm. - FEV₁/FCC norm. 	<ul style="list-style-type: none"> - FEV₁ > 80% normal - FEV₁/FVC reduced 5% 	<ul style="list-style-type: none"> - FEV₁ > 60% normal - FEV₁/FVC reduced > 5% 	<ul style="list-style-type: none"> - FEV₁ > 60% normal - FEV₁/FVC reduced > 5%
Recommended STEP for initiating treatment	STEP 1	STEP 2	STEP 3 + consider oral sys. steroids	STEP 4-5 + consider oral sys. steroids
2-6 weeks evaluate level of asthma control that is achieved and adjust therapy				

Treatment

- Prevention of acute attack depends on limiting degree of chronic inflammation
- Treatment of acute attack involves anti-inflammatory and bronchodilator agents

- STEP therapy for long-term management of asthma



- Key reasons for **failure** in asthma control are:
 - o improper MDI use (poor patient education)
 - o Failure to recognize acute exacerbation early and institute proper therapy

Pulmonary Embolism

- Most PE come from DVT in lower extremity. Development of DVT increased by 3 things:
- **VIRCHOW TRIAD:** Stasis, Alteration in blood vessels, hypercoagulability

Stasis	Blood vessel injury	Hypercoagulability
- Surgery, CHF, Immobility	- Trauma, Surgery, Fractures	- Postpartum, malignancy, oral contrac.

History

- Most prominent symptom is **sudden onset of unexplained dyspnea**.
- **Pleuritic chest pain** also common, **cough** can also be present, **hemoptysis** is **NOT** normal finding
- Symptoms of lower extremity pain or swelling in context of pulmonary suggest PE
- Other presentations: syncope, SVT, worsening heart failure or lung disease
- Most signs and symptoms not helpful so high level of suspicion important

Physical Exam

- Vital sign abnormalities common in PE: tachycardia/pneumonia, low-grade fever
- Pulmonary exam usually **normal**
- Cardiac exam may reveal signs of right-sided heart strain: Loud P2, Right sided heave + S₃
- Physical exam findings not always seen so lab testing very important

DDx

- For patient who presents with *shortness of breath* and *chest pain*:
 - o Pneumothorax, Myocardial ischemia, pericarditis, asthma, pneumonia
- For patient who presents with *PE + hypotension* and *hemodynamic instability*, also consider:
 - o MI, cardiac tamponade, tension pneumothorax, aortic dissection

Diagnostic Evaluation

- Clinical likelihood of PE using Wells Criteria (right)
- ABG show hypoxia, hypocapnia, and respiratory alkalosis but normal ABG does not r/o PE
- Common CXR findings: atelectasis, increased lung lucency, abrupt vessel cutoff, pleural effusion
- Common ECG findings: "S1-Q3-T3" (wave/lead)
- V/Q scan findings can help with diagnosis:
 - o **Normal** scan **rules out** PE
 - o **High probability** scan is diagnostic if clinical suspicion is high
 - o **Low probability** scan r/o PE in patient with **low pretest probability**
- CT angiography has become better than V/Q at detecting and providing alternative diagnoses
- US can be used to evaluate DVT
- **PULMONARY ANGIOGRAM** remains the gold standard for diagnosis

Criteria	Score
Clinical symptoms of DVT	3.0
Other diagnoses less likely than PE	3.0
Heart rate >100	1.5
Immobilization or surgery in past 4 wk	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability of PE	Score
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0

Treatment

- In high risk patient, heparin started while awaiting workup unless contraindicated
- Patients with DVT also treated with heparin
- In hypotensive patient with massive PE, thrombolytic therapy may be indicated
- Adequate anticoagulation should be achieved in 24h and platelets monitored for heparin users
- Once heparin dose is therapeutic switch to warfarin (INR between 2-3)
- Morbidity from PE avoided by preventing further DVTs. High risk patients treated prophylactically

Interstitial Lung Disease

- ILD is a group of disorders characterized by inflammation and fibrosis of alveolar walls and the perialveolar tissue. All ILD have similar Sx, CXR appearance and change in pulmonary physiology
 - o ↓ transalveolar gas diffusion; Restrictive respiratory pattern; Variable obstructive resp. pattern
- Causes of ILD grouped into 4 main divisions:
 - o **Pneumoconioses:** dusts/gases cause chronic inflammation with by mucous hypersecretions
 - o **Hypersensitivity Pneumonitis:** Immunologically mediated antigen-antibody inflammation
 - o **Drugs:** direct toxicity and immunologic injury
 - o **Other:** ILD can develop in the setting of collagen vascular diseases

Pneumoconioses	Hypersensitivity pneumonitis	Drugs	Other
Dusts: Asbestos, coal, rock, metals, graphite, cotton, grain	Thermophilic actinomycetes, <i>Aspergillus</i> , animal fur dust, wood dust, <i>bacillus subtilis</i> ,	Cytotoxic: bleomycin, vinblastine, alkylating agents, antimetabolites NonCytotoxic: abx, NSAIDs, B-blockers	Lupus, RA, Ankylosing spondylitis, polymyositis, Goodpasture syndrome, Wegener granulomatosis
Gases: acid fumes, NO ₂ , chlorine phosgene			

History

- Usually months-years of gradually progressive dyspnea and a non-productive cough
- Patients with occupational hypersensitivity pneumonitis (HP) may have symptom free weekends
- Important to note environmental and occupation exposures both past and present

Physical Exam

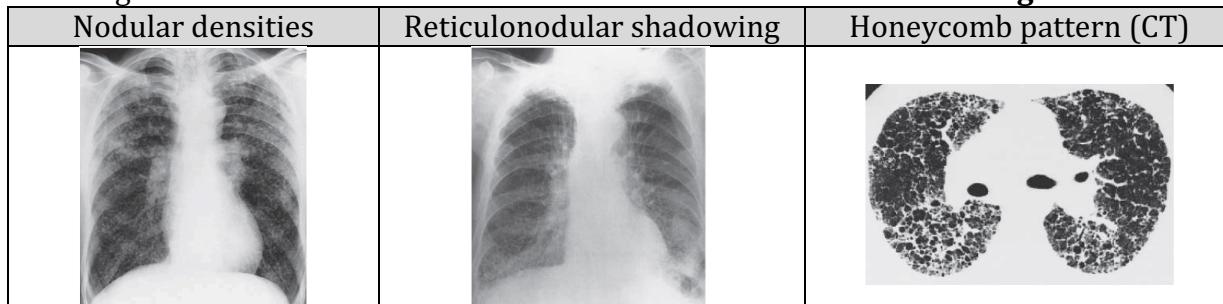
- Initially PE may be unremarkable until disease progresses; Classic finding is **expiratory crackles**
- As fibrosis and pulmonary HTN progress, right heart overload and failure develop

DDx

- Most DDx are of ILD but pulmonary + cough + dyspnea is also seen in: CHD, COPD, asthma

Diagnostic Evaluation

- CXR: looking for **reticular or reticulonodular infiltrates** and **decreased lung volume**



- Anatomic location of lung infiltrates suggests different etiologies:
 - o **Upper:** Sarcoidosis, silicosis, berylliosis, HP; **Lower:** collagen vascular disease, asbestos
- PFTs usually reveal restrictive physiology with ↓ volume; **LUNG BIOPSY:** gold standard for Dx of ILD

Treatment

- In HP, removing/preventing exposure of offending agent is key, often stops respiratory decline
- In cases where removing offending agent is insufficient treatment is limited
 - o High dose corticosteroids followed by tapering can provide some benefit

Pleural Effusions

- A pleural effusion is an accumulation of fluid between the visceral and parietal pleuras.
- The Rate of pleural fluid formation is determined by **starling law** (balance of $P_{\text{hydrostatic}}$ and P_{oncotic})
 - o Normal volume is 0.1-0.2mL/kg
 - o Effusion is either **decrease** (blockage) in removal of fluid or **increase** in production
- Effusion is either **transudate** (more fluid in than out) or **exudate** (blockage +++protein)

Transudate Causes	Exudate Causes
- CHF (increase capillary $P_{\text{hydrostatic}}$)	- Bacterial/Viral pneumonia (pl. membrane damage)
- Cirrhosis (decreased plasma P_{oncotic})	- Metastatic disease (lymphoma blocking nodes)
- Nephrotic syndrome (decreased plasma P_{oncotic})	- PE (pleural membrane damage)
- HYPOalbuminemia (decreased plasma P_{oncotic})	- TB (pleural membrane damage + blocked lymph)
- PE (altered hemodynamics)	- Collagen Vascular disease (pl. membrane damage)
	- Mesothelioma (pleural membrane damage)

History and Physical Exam

History	Physical Exam
<ul style="list-style-type: none"> - Pleuritic Chest pain (bacterial/viral pneumonia, PE, tumour) - Cough (pneumonia, tumor) - Sputum (pneumonia) - Hemoptysis (PE, tumor, TB) - Shortness of breath (CHF, pneumonia) 	<ul style="list-style-type: none"> - Decreased tactile fremitus - Dullness to percussion - Absent or diminished breath sounds - Shift of trachea and heart away from affected side - Adenopathy (malignancy, TB) - Elevated neck veins, peripheral edema (CHF) - Ascites (cirrhosis)

Diagnostic Evaluation

- Large effusions can be seen on CXR, smaller effusions seen better in decubitus films
- Chest CT helpful for small effusions, parenchymal masses and enlarged lymph nodes
- **Diagnostic thoracentesis** for determining transudate from exudate:
 - o pleural fluid/serum albumin ratio > 0.5
 - o pleural fluid lactate dehydrogenase $> 200\text{IU}$
 - o Pleural fluid/serum LDH ratio > 0.6
 - o If any of above limits are exceeded => EXUDATE
- Effusions due to bacterial pneumonia is Dx of **complicated parapneumonic effusion (CPE)** if:
 - o Gross pus present in pleural space
 - o Organisms visible on gram stain of pleural fluid (empyema)
 - o Pleural fluid glucose $> 50\text{mg/dL}$
 - o Pleural fluid pH < 7
- Malignant pleural effusion suspicions: send for cytology followed by biopsy of pleura (mesothelioma)

Treatment

- Transudative effusions managed by correcting underlying pressure problem
 - o Diuretic treatment is mainstay to reduce hydrostatic pressure + rarely thoracentesis for dyspnea
- Exudative effusions require local control of effusion as well as underlying disorder
- CPE need drainage with tube thoracostomy due to poor abx penetration, or surgery in severe cases
- Malignant pleural effusions treatment is often difficult with reaccumulation after thoracentesis
 - o Other options include using sclerosing agents via chest tube, or pleuroperitoneal shunt

AHD – Pleural Effusion

Pleural Effusion

- Abnormal amount of fluid around the lung in the pleural space between visceral and parietal pleura
- Results from excess fluid production or decreased absorption (many causes)
- Imbalance of oncotic and hydrostatic pressures and lymphatic drainage
- Fluid classified as **transudate** or **exudate**
- Diagnosis made with CXR, CT, US, Thoracentesis, Thoracoscopy

History

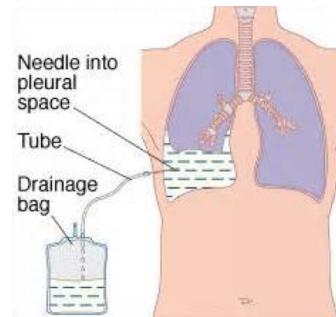
- Sx/Hx of heart failure and heart disease, i.e. peripheral edema, orthopnea, paroxysmal nocturnal dyspnea, chest pain
- Sx/Hx of liver disease, pulmonary embolism, connective tissue disease
- Sx/Hx of infection (i.e. recent pneumonia), constitutional Sx, medication Hx, TB risks, occupational exposures (asbestos)

Physical Exam

- Vital signs including oxygen saturation and temperature
- Look for signs of effusion: diminished air entry, dullness, bronchial breathing, tracheal shift (1000cc), chest wall lesions, friction rub, egophony, decreased fremitus,
- Signs of Dx mentioned under Hx (JVP, peripheral edema, nodes, ascites, adenopathy, skin rash)

Chest Imaging

- **Bilateral** => transudate more likely vs. **unilateral** => exudate especially if large
- Free-flowing vs. loculated (check with lateral decubitus)
- Associated findings (tracheal shift, enlarged cardiac silhouette, edema, consolidation, collapse)
- Pleural plaque, thickening, lung nodules/masses, intrathoracic adenopathy, rib fractures
- Time course (if multiple CXR available important to compare)
- Response to thoracentesis if done before imaging



Diagnostic Thoracentesis

- Usually the next step for unexplained unilateral effusion and for suspected parapneumonic effusions
- When is it safe to tap:
 - o Correct bleed risks (INR > 1.5, Plat < 50,000) and withhold anticoagulants/clopidogrel; ASA is ok
- Fluid analysis:
 - o Protein and LDH in fluid and serum, Glucose, pH, WBC/RBC, cytology, gram stain, TB
 - o Exceptional: triglycerides, amylase, viruses, parasites, RF, ANA, tumour markers
- **Light's Criteria:**
 - o **Exudate:** fluid/serum protein > .5 OR fluid/serum LDH > 0.6 or LDH > 200 OR LDH > 2/3 upper limit of normal serum value
 - o **Transudate** if none of the above are true
- 20-25% of transudates called exudates (potential to misinterpret if you use diuretics before)
- Glucose and pH are correlated; pH < 7.2 => complicated effusion that needs drainage

Transudates

- Caused by imbalance of oncotic and hydrostatic pressures

- Effusions when fluid production exceeds resorption
- **Uncomplicated** = fluid free of infection or inflammation i.e. similar to normal pleural fluid
- Decreased oncotic pressure causes: hypoalbuminemia, cirrhosis, nephrotic syndrome
- Increased capillary hydrostatic pressure causes: LV CHF, fluid from peritoneum via diaphragm

Exudates

- Caused by infection or inflammation of pleura/lung that often don't resolve spontaneously
- Usually parapneumonic or malignancy related; can be PE, infarction, collagen vascular disease also
- Hallmark is excess protein; altered pleural membrane permeability a main feature also
- Causes: pancreatitis, Dressler's syndrome, esophageal perforation, TB, fungal infection, pericardial disease, chylothorax (milky exudate), drugs, asbestos, Meig's syndrome

Urgent Diagnoses that require prompt management

- Transudative:
 - o Hypothyroidism (myxedema coma), CHF in the context of acute coronary syndrome
- Exudative:
 - o PE, empyema, CHF as above, TB, chemo responsive malignancies
- Most other causes of effusion leave you with time to sort out diagnoses and other problems

Parapneumonic Effusions

- Spectrum ranging from reactive pleural inflammation to infection of the pleural space in the context of an underlying pneumonia
- Note that empyema = pus in pleural space
- High propensity for pleural involvement after parenchymal infection with certain pathogens, i.e. anaerobes in context of lung abscess
 - o Note that, aerobic streptococci are the most common cause of CAP infections
- When to tap in context of pneumonia:
 - o Free-flowing effusion > 1 cm on lateral decubitus CXR
 - o Radiographic evidence of complicated effusion (loculation); usually needs US guided tap
- When to drain:
 - o Complicated effusion ($\text{pH} < 7.2$), positive fluid culture, pus
- How to drain:
 - o Theoretical advantages of radiologic guidance but no RCT comparing surgical vs radiology tubes
 - o Small bore tubes may be problematic in terms of blockage, though this has not been observed in prospective studies
 - o Thoracoscopy is the standard of care in most complicated parapneumonic effusions
 - o Monitoring of clinical and radiographic response is crucial (usually by contrast CT)
- Indications for surgery:
 - o Failure to respond clinically and radiologically to closed chest tube drainage
 - o Development of pleural peel with resulting lung function impairment

TB effusions

- Difficult Dx to make (need high suspicion + demographic risk factors)
- Note that lung parenchyma is often normal on CXR in this context
- Pleural fluid AFB/PCR low yield and not sensitive/specific
- High sensitivity and specificity of **fluid adenosine deaminase**

Inflammatory Effusions

- Dressler's syndrome (post MI/post pericardiectomy)
- Connective tissue diseases (RA, SLE)
- Drug-induced (nitrofurantoin, bromocriptine, metronidazole, drug-induced SLE)
- Benign asbestos effusions
- Viral pleuritic (adenovirus, HSV, VZV, EBV)

Chylothorax

- Refers to milky (chyloous) effusions due to chyle with high **triglyceride** level
- Relates to thoracic duct disruption: on **right if below T5-6; on left if higher**
- Most commonly due to non-Hodgkin's lymphoma
- Pseudochylothorax refers to fluid with a high **cholesterol** concentration (not triglycerides)
 - o Usually in longstanding effusions from TB or RA

Most likely Dx from EXUDATES

- Malignancy (mets (breast)> mesothelioma, lymphoma)
 - o Note pleural fluid cytology sensitivity ~60% so negative results DO NOT EXCLUDE MALIGNANCY
- Parapneumonic
- Inflammatory

Management of Effusions

- The presence of respiratory or hemodynamic compromise (tension) **attributable to the effusion** warrants prompt therapeutic drainage
- This can be quickly accomplished by bedside thoracentesis
- A chest tube or pigtail catheter is usually not required immediately, and can hamper subsequent diagnostic efforts e.g. medical thoracoscopy
- Exceptions would be empyema/complicated effusions as previously mentioned, and hemothorax

Management of Malignant Effusions

- Longer-term control of persistent/recurrent malignant effusions is a frequent challenge
- Make sure the patient's Sx truly relate to the effusion (vs. lymphangitic spread, PE, heart failure, etc.)
- If pleurodesis is considered, make sure:
 - o Patient's general condition is suitable, with life expectancy at least 6 months
 - Intermittent taps are very reasonable for symptom control in debilitated patients
 - Consider indwelling pleural catheter when prognosis/function more limited
 - o The lung reexpands and symptoms improve after therapeutic thoracentesis
 - Exclude endobronchial obstruction, lung entrapment due to visceral pleural disease
 - Again, indwelling pleural catheter may be considered when reexpansion is compromised

Thorascopic Talc Pleurodesis

- Most often performed for control of malignant effusions
- Thorascopic talc pleurodesis is preferred approach to control of malignant effusions
 - o Superior to chest tube drainage alone and other sclerosing agents
 - o Thorascopic instillation preferable to bedside chest tube instillation

Indwelling Pleural Catheters

- For relief from Sx of malignant effusions (palliative); no difference between catheter vs. chest tube
 - o lower complication rate with catheter vs. tube, less need for additional interventions

Lung Cancer

- Lung cancer is leading cause of cancer death for both men and women, most often caused by smoking
- If smoking stopped, risk of lung cancer declines and by 10 years, risk only slightly above nonsmoker
- Other risks for developing lung cancer: radon, asbestos, environmental pollutants
- 4 Major types of lung cancers separated into **small cell** (100% smoking) and **non-small cell**
 - o Non-small cell further divided into **squamous cell, large cell, adenocarcinoma**
 - o Rarer subtypes: primary pulmonary lymphoma, carcinoid tumour, mesotheliomas
- Non-small cell cancers: discrete masses within the lung parenchyma and metastasize (TNM staging)
- Small cell cancers: metastasize rapidly to lymph nodes and distant sites (limited/extended staging)
- Lung cancers are more likely to produce active substances that result in **paraneoplastic syndromes**
 - o Hypercalcemia, SIADH, ectopic adrenocorticotrophic hormone secretion, hypercoaguable state

History

- Sx can arise from local mass effect, effects of metastases, paraneoplastic syndromes
- Since most cancers arise in smokers, cough and dyspnea are nonspecific but **change** in previously stable symptoms can suggest underlying malignancy
- Hemoptysis is a commonly seen symptom
- Mass effect symptoms: cough, hoarseness, facial/upper extremity swelling

Physical Examination

- PE doesn't always provide many clues, but some classical findings to specific lung cancers:
 - o Horner syndrome, supraclavicular mass caused by Pancoast tumour, SVC syndrome
 - o Clubbing of fingers are often suggestive of underlying malignancy

DDx

- DDx for lung masses: TB, Fungal infection, metastases, granulomatous disease (sarcoidosis)

Diagnostic Evaluation

- Dx can first be suggested on CXR showing mass and hilar adenopathy
- If mass found on CXR chest CT can help better detect disease
- Sputum cytology can help with diagnosis of malignancy
- Bronchoscopy can help based on location of lesion (scope only goes to second branches of lung)

Treatment

- After Dx of lung cancer histologic type and stage determined to guide therapy
- Sometimes removal of mass by surgery is curative
- Radiotherapy alone is not effective as surgery and is often used for palliative care
- Chemotherapy in non-small cell lung cancer is only used experimentally

Acid-Base Disturbances

- Normal pH of the body is tightly maintained between 7.35 and 7.45
- Lungs (breathing off CO_2) and kidneys (bicarbonate buffer) primarily deal with acid load in the body
 - o Acidemia will stimulate ventilation and alkalemia will suppress it (fast)
 - o Acidemia stimulates H^+ bicarb secretion and alkalemia stimulates bicarb reabsorption (slow)
- Acid-base disturbance can either be metabolic ([bicarb]) or respiratory ($[\text{CO}_2]$) or mixed
- **Acidemia** = pH lower than normal, **alkalemia** = pH greater than normal

	Metabolic Acidosis	Respiratory Acidosis	Metabolic alkalosis	Respiratory alkalosis
pH	↓	↓	↑	↑
CO_2	↓	↑	↑	↓

- Causes:

Metabolic Acidosis	Respiratory Acidosis	Metabolic alkalosis	Respiratory alkalosis
<ul style="list-style-type: none"> - ↑ acid prod. (A-Gap) - ↓ acid excretion - Loss of alkali (GI) 	<ul style="list-style-type: none"> - Failure of respiration and accumulation of CO_2 	<ul style="list-style-type: none"> - ↑ loss of acid (GI) 	<ul style="list-style-type: none"> - hyperventilation and decrease in CO_2
<ul style="list-style-type: none"> - Normally the anion gap (A-gap) is 8-12 mEq/L, calculated as $[\text{Na}^+] - ([\text{HCO}_3^-] + [\text{Cl}^-])$ - The lungs and kidneys will try and compensate for any acid-base disturbances: <ul style="list-style-type: none"> o Metabolic acidosis: 1-1.5 mmHg ↓ PaCO_2 for 1 mEq/L ↓ in HCO_3^- o Respiratory acidosis (acute): 1 mEq/L ↑ HCO_3^- for 10 mmHg ↑ PaCO_2 o Respiratory acidosis (chronic): 3 mEq/L ↑ HCO_3^- for 10 mmHg ↑ PaCO_2 o Metabolic alkalosis: 0.25-1 mmHg ↑ PaCO_2 for 1 mEq/L ↑ in HCO_3^- o Respiratory alkalosis (acute): 2 mEq/L ↓ HCO_3^- for 10 mmHg ↓ PaCO_2 o Respiratory alkalosis (chronic): 4 mEq/L ↓ HCO_3^- for 10 mmHg ↓ PaCO_2 			

DDx

Metabolic Acidosis	Respiratory Acidosis	Metabolic alkalosis	Respiratory alkalosis
Increased anion gap <ul style="list-style-type: none"> - Lactic acidosis - Ketoacidosis - Poison/drugs - Renal failure Normal anion gap <ul style="list-style-type: none"> - Renal tubular issue - Base loss (diarrhea) - Excess acid intake 	<ul style="list-style-type: none"> - Acute respiratory failure (drugs, pneumonia) - Chronic respiratory failure (COPD) 	<ul style="list-style-type: none"> - Volume loss with Cl depletion (vomiting) - Hypermineralcorticoid states (Cushing) - Severe K deficiency - Excess alkali intake 	<ul style="list-style-type: none"> - Hyperventilation (asthma, pulmonary edema, other lung) - Increased respiratory drive (lung issues) - Cirrhosis, pregnant - Excessive mechanical ventilation

Clinical manifestations

- Fatigue and mental status changes are common nonspecific findings. Some specific signs and Sx:
 - o Metabolic acidosis: Deep, labored compensatory breathing (hyperventilation response)
 - o Respiratory acidosis: papilledema (if severe hypercapnia → cerebral edema)
 - o Respiratory alkalosis: paresthesia, cramps, light-headedness

Diagnostic Evaluation

- Diagnosis made with serum electrolytes and ABGs.
 - o Urine pH and plasma creatinine can help assess renal function

- ABG useful but accuracy of measurement can be affected if:
 - o Processing delay, heparin contamination, fail to remove syringe air, *venous blood*

Treatment

- Determine magnitude, direction, and primary abnormality via ABG
- Determine if compensation is appropriate and if not determine if there is a secondary abnormality
- Find and correct underlying abnormality(s)
- Several conditions require specific therapeutic interventions
 - o Metabolic acidosis in CKD may need oral bicarbonate
 - o Severe uncorrectable metabolic acidosis in AKI needs temporary hemodialysis
 - o Metabolic alkalosis from volume and Cl loss needs fluid resuscitation

AHD – Acid Base Problems

Physiology

- pH tightly regulated at 7.35-7.45 by the bicarbonate buffer system
 - (too much acid) $\text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^-$ (too much base)
- Normal daily acid production = 1 mmol H⁺/kg/day
 - Phosphoric acid from phospholipid metabolism
 - H₂SO₄ from sulfur amino acid metabolism (methionine, cysteine, homocysteine, taurine)
 - HCl from metabolism of lysine, arginine

State	pH	HCO ₃ ⁻ (mmol/L)	pCO ₂ (mmHg)
Normal	7.35-7.45	24-28	35-45
Acidemia	<7.35	< 24	< 35 (metabolic) OR > 45 (respiratory)
Alkalemia	>7.45	>28	> 45 (metabolic) OR < 35 (respiratory)

Disorder	Compensation	Acute/Chronic Respiratory Compensation
Metabolic Acidosis	1.3 ↓ pCO ₂ / 1 ↓ HCO ₃ ⁻	
Metabolic Alkalosis	1 ↑ pCO ₂ / 2 ↑ HCO ₃ ⁻	
Respiratory Acidosis (Acute)	1 ↑ HCO ₃ ⁻ / 10 ↑ pCO ₂	
Respiratory Acidosis (Chronic)	3.5 ↑ HCO ₃ ⁻ / 10 ↑ pCO ₂	
Respiratory Alkalosis (Acute)	2 ↓ HCO ₃ ⁻ / 10 ↓ pCO ₂	
Respiratory Alkalosis (Chronic)	4 ↓ HCO ₃ ⁻ / 10 ↓ pCO ₂	

Blood Gas

- Peripheral or central venous vs. arterial blood gas (p/c VBG vs. ABG)
 - pH:** pVBG and cVBG pH is ~ 0.02 – 0.04 units ↓ than ABG pH
 - HCO₃:** pVBG HCO₃ is 1 – 2 mEq/L ↑ than ABG; cVBG ≈ ABG
 - pCO₂:** pVBG is ~ 3 – 8 mmHg ↑ than ABG; cVBG 4-5 mmHg ↑ than ABG
 - If VBG being used for serial monitoring, periodic correlation with ABG is necessary

Urine vs. Serum Testing

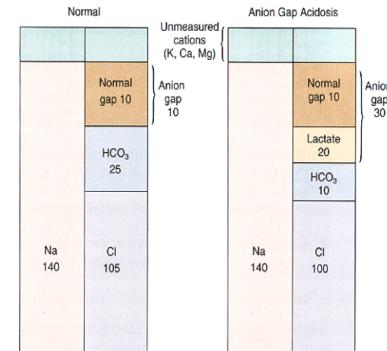
- If **abnormal** kidney function, urine shows wasting or retention of products (K, Mg, PO₄, acid)
- If **normal** kidney function, the urine should represent the serum abnormality
 - HyperK -> ↑ K in urine; metabolic acidosis -> acidic urine; hypoMg -> ↓ Mg in urine

Acid-Base Patient Approach

- Hx: PMHx, surgical Hx, smoking, medications, diarrhea, other ingestions
- PE: variable, cardiac arrest, AMS, signs of renal failure, signs of intoxication
- Investigations: ABG, VBG, electrolytes, albumin, serum osmolarity, urinalysis, lactate, ketones

Metabolic Acidosis (MA)

- Check Anion Gap; AG = Na – (Cl + HCO₃); Normal gap is around 10-12
 - Cations: Na, K, Mg, Ca; Anions: Cl, PO₄, HCO₃, albumin
- ↑ AG MA from loss of HCO₃ or gain of H⁺ **plus anion formation**
 - Mnemonic of causes of HAGMA **GOLDMARK**:
 - Glycols, Oxoproline, L-lactate, D-lactate, Methanol, Aspirin, Renal Failure (uremia), Ketoacidosis
- Normal AG MA is pure loss of HCO₃ or H⁺ (no additional anions added)



Mechanism	Major Causes
Dilutional	Too much IV NaCl
Acid Overproduction	↑ AG masked by hypoalbuminemia; Anion lost in urine (glue sniffing, DKA)
HCO ₃ Loss	GI loss (diarrhea), Ureterosigmoidostomy, Urine loss
Kidney Malfunction	CKD, distal RTA, hyperkalemia RTA, poor parenteral nutrition

Mixed Disorders

- Can have multiple acid-base disturbances at once, look at both change (Δ) in AG and change in HCO₃

$\Delta AG/\Delta HCO_3$	< 0.5	0.5 – 1	1 – 2	> 2
Interpretation	NAGMA	Mixed N/H AGMA	HAGMA (DKA/lactic)	HAGMA + Metabolic alkalosis

Metabolic Alkalosis

- Due to loss of H⁺ or gain of HCO₃
- Chloride **responsive** (urine Cl < 15 mEq/L): vomiting, ↓ Cl intake, pyloric stenosis, diarrhea, CF
- Chloride **resistant** (urine Cl > 20), can have normal BP or low BP
 - o Normal BP: Bartter syndrome, Gitelman syndrome, diuretic therapy, alkali loading
 - o Hypotensive: hyperaldosteronism, renal artery stenosis, renin secreting tumour, Licorice abuse

Respiratory Acidosis

- Can't breathe vs. Won't breathe vs. too much work of breathing leading to exhaustion (COPD, ILD)
- Won't: CNS depression (sedatives), CNS lesion (stroke)
- Can't: Polio, motor neuron disease, phrenic nerve injury, GBS, Myasthenia gravis, kyphoscoliosis

Case 1

- 37 M, Type 1 DM x 11y, presents with 3 day Hx of nausea and vomiting
- Na = 128 K = 5.8 Cl = 87 Urea = 16 Cr = 88 Glucose = 50.2 pH = 7.18 pCO₂ = 12 HCO₃ = 4
- Disorder = **Metabolic Acidosis** (↓ pH, ↓ pCO₂);
- Expected compensation = 1.3 * (24 – 4) = 26 ↓ pCO₂; Observed compensation = 40 – 12 = 28
- AG = 128 – (87 + 4) = 37 => HAGMA; DDx: **GOLDMARK**

Case 2

- 17 F, Type 1 DM, vertigo and vomiting 4-5x/d x3d, unable to retain food/liquid, stopped insulin, AMS
- Na = 121 K = 2.8 Cl = 73 Urea = 12 Cr = 70 Glucose = 37.6 pH = 7.3 pCO₂ = 37.5 HCO₃ = 18
- Disorder = **Mixed Metabolic Acidosis and Alkalosis** (↓ pH, ΔAG/ΔHCO₃ > 2)
- AG = 121 – (73+12) = 36 => HAGMA
- Expected HCO₃ to drop but it is increased so there's also metabolic alkalosis occurring

Case 3

- 26 F, severe weight loss, no nausea, vomiting, abdo pain but has ravenous appetite
- Na = 132 K = 1.7 Cl = 62 HCO₃ = 56 pH = 7.54 pCO₂ = 62 pO₂ = 51 urine: Na = 63, K = 16, Cl = 1, + ketones
- Disorder = **Metabolic Alkalosis** (↑ pH, ↑ pCO₂)
- Expected Compensation = (56-24)/2 = 16 pCO₂; Observed compensation = 62-40 = 22

Case 4

- Elderly man with COPD presents in shock with vomiting and severe abdo pain
- Na = 149 K = 3.2 Cl = 93 Glucose = 4.9 Urea = 10.7 Cr = 141 pH = 7.32 pCO₂ = 70 HCO₃ = 34
- Disorder = **Slight Respiratory Acidosis** (↓ pH, ↑ pCO₂); AG = 149 – (93 + 34) = 22 => **HAGMA!!**
- Compensation difficult to calculate but expected > predicted => **Metabolic alkalosis** as well

Fluids and Electrolytes

- All principle electrolytes are distributed asymmetrically across membranes
 - o Na is main extracellular cation, Cl/bicarb are main extracellular anion
 - o K, Ca, Mg, and organic anions are the main intracellular electrolytes
- Kidneys tightly regulates body Na; Na depletion triggers ↓ excretion, Na overload triggers ↑ excretion
- Peripheral receptors in atria, arteries and juxtaglomerular apparatus sense effective blood volume and regulate Na via the **renin-angiotensin** system and several natriuretic hormones
- Plasma osmolality is regulated via ADH that acts on kidneys to ↓ urine volume and ↑ osmolality
- Ratio of Intracellular/Extracellular K determines membrane excitability in nerve and muscle cells
- Excess K eliminated by kidneys (aldosterone), acidosis favours extracellular K balance shift

Disturbances in Sodium, Potassium, and Water Balance

Disturbance	Causes	Clinical Presentation	Treatment
Volume Depletion	<ul style="list-style-type: none"> - Renal Loss - Excess diuretics - Osmotic diuresis (DM) - Renal disease - Adrenal disease Extrarenal loss: <ul style="list-style-type: none"> - GI losses - Abdo sequestration - Skin (sweat/burn) 	<ul style="list-style-type: none"> - Fatigue, weakness - Orthostatic pre-syncope and syncope - Orthostatic HypoTN - Decreased skin turgor - Dry membranes - Sunken eyes - Oliguria 	<ul style="list-style-type: none"> - Replacement of fluids - Replacement of lytes - PO if possible IV if not - Monitor serum lytes
Hyponatremia	<ul style="list-style-type: none"> - Volume depletion with Na loss - Edematous state (CHF) - Hypo-osmolar states (SIADH, renal failure) - Hyperglycemia - Hyperlipidemia - Hyperproteinemia 	<ul style="list-style-type: none"> - Often asymptomatic As it gets worse (<125 mEq): <ul style="list-style-type: none"> - Lethargy - Confusion - Coma - Hyperexcitability - Seizures 	<ul style="list-style-type: none"> - Treat etiology - IV fluids for dehydration - Free water restriction in edematous states - Raise Na SLOWLY (central pontine myelinolysis)
Hypernatremia	<ul style="list-style-type: none"> - Pure water deficit (insensible losses) - Water loss in excess of Na loss (sweat) - Na overload 	<ul style="list-style-type: none"> - Similar to hypoNa (CNS) - Usually only encountered in rapid/significant [Na] change (>160mEq/L) 	<ul style="list-style-type: none"> - PO or IV water and Na - Free water deficit replaced over 48-72h, only ½ in first 24h
Hypokalemia	K loss <ul style="list-style-type: none"> - GI (diarrhea/vomiting) - Diuretic use - Metabolic alkalosis - Mineralcorticoid excess - Licorice intoxication - Renal tubular disease 	High intra cellular K disturbances <ul style="list-style-type: none"> - Muscle weakness - Smooth muscle dysfunction - Cardiac muscle dysfunction - Peripheral nerve dysfunction 	<ul style="list-style-type: none"> - K replacement PO (KCl) since it changes serum K slowly and is safe - IV K in severe hypoK delivered slowly
Hyperkalemia	<ul style="list-style-type: none"> - Inadequate excretion - Adrenal insufficiency - K-sparing diuretics - Tissue damage - Extracellular K shift - Excess K intake 	Cardiac ECG manifestations <ul style="list-style-type: none"> - Peaking T waves (earliest) - PR prolongation, QRS wide - Complete heart block - Atrial asystole - Ventricular fibrillation 	<ul style="list-style-type: none"> - Calcium (membrane stabilization) - Insulin + glucose, bicarb (intracellular shift) - Diuretics (removal) - Dialysis (removal)

Acute Kidney Injury

- AKI is a result of impairment of one or more of the kidneys main functions over hours to days
- AKI etiologies are divided into 3 main etiological groups **prerenal, renal, post renal**
- Most common AKI: acute tubular necrosis, prerenal disease, urinary obstruction, glomerular disease
 - o These are associated with surgery, vascular/bladder catheterization, trauma, drugs, sepsis, shock

Prerenal	Renal	Postrenal
- Hypovolemia (blood/fluid loss)	- Vasculitis (hemolytic-uremic, malignant HTN)	- Ureteral obstruction (tumour, kidney stone)
- Decreased CO (acute MI)	- Glomerulonephritis	- Bladder neck obstruction (tumour)
- Renovascular disease	- Acute tubular necrosis (ischemia, nephrotoxic drugs)	- Urethral obstruction (prostate, bladder thrombus)
- Systemic vasodilation (sepsis)	- Interstitial nephritis (abx)	
- Renal vasoconstriction (drugs)	- Tubular obstruction	
- Impairment of renal blood auto-regulation (ACEi, NSAIDS)		

History

- Mild AKI may be asymptomatic. Moderate to severe AKI can reflect some of the following symptoms:
 - o Dyspnea, orthopnea, edema, fatigue, anorexia, nausea/vomiting, pruritus, lethargy, micturition changes (nocturia, hesitancy), hemoptysis, sinusitis, epistaxis, flank/groin/abdo pain (stone)

Physical exam

- Assess fluid status with orthostatic vital signs, skin turgor, JVP
 - o Fluid **depletion** may indicate **prerenal** problem, **overload** can indicate **intrinsic renal** failure
- Presence of abdominal bruits suggest renovascular disease
- Pelvic and DRE may reveal causes of urinary outflow problems (enlarged prostate/pelvic mass)
- Skin changes may indicate vasculitis, atheroemboli or other systemic disease
- **Uremic syndrome** is from accumulating of toxins normally handled by kidneys, can present as:
 - o Pericarditis, uremic frost (urea crystals on skin), asterixis, uremic fetor (pee breath)

DDx and Diagnostic Evaluation

- DDx: Nonspecific AKI abnormalities require ruling out CHF, dehydration, and drug intoxication
- Dx confirmed by finding elevated creatinine level reflecting reduced GFR, then serum lytes measured
- Urine sediment analysis helps Dx: RBC -> glomerular/vascular lesions, WBC -> interstitial nephritis
- Assess degree of proteinuria with 24h urine collection or **urine protein/creatinine ratio**
 - o Nephrotic range proteinuria >3.5g/24h -> glomerular lesion + dysmorphic RBC
- Prerenal AKI is distinguished from acute tubular necrosis with **fractional excretion of Na** (FE_{Na})
 - o $FE_{Na} < 1$ in prerenal conditions as tubules try to preserve intravascular Volume with Na retention
 - o Low FE_{Na} also present in intrinsic renal disease such as glomerulonephritis
- If glomerular process suspected: immune-mediation screened by measuring different antibody levels
- Postrenal obstruction Dx and Tx via bladder catheter-> large post void V-> bladder dysfunct/obstruct
- Renal US imaging can quickly show hydronephrosis, CT can localize obstruction precisely
- In rare cases of uncertain diagnoses kidney biopsy by urologist can be performed

Treatment

- Begins with correction of fluid and electrolyte abnormalities and determining specific etiology
- Etiology important for long-term management, prevention of hypoTN, achieving nonoliguric state
- In all cases nephrotoxic drugs (NSAIDS) should be avoided
- Intrinsic renal diseases like glomerulonephritis and granulomatosis require immunosuppression
- Postrenal injury management = relieving obstruction (For bladder obstruction, catheter is sufficient)
- **HyperK, Lyte disorders, V abnormalities** and **metabolic acidosis** require additional treatment

Chronic Kidney Disease

- CKD is an umbrella term for disorders affecting normal kidney structure, function, and/or filtration
 - o **CKD:** kidney damage > 3mo (based on findings) or GFR < 60 > 3 mo + or - kidney damage
 - Stage (GFR): 1 (>90), 2 (60-89), 3a (45-59), 3b (30-44), 4 (15-29), 5 (<15)
 - o **ESRD:** GFR < 15 or need for kidney replacement therapy (dialysis or transplant)
- CKD can occur following AKI but often gradual due to DM, HTN, glomerulo/interstitial nephritis, PKD
- **Uremia** = syndrome of failure of kidneys to perform proper excretory, metabolic, endocrine function
 - o *Fluid and lytes abnormalities:* fluid overload, metabolic acidosis, Na imbalance, hyper K, P, Ca
 - o *Endocrine abnormalities:* vit D deficiency, hyper- parathyroidism/uricemia/triglyceridemia
 - o *CV disorders (most common cause of death):* HTN, HF, pericarditis, accelerated atherosclerosis
 - o *GI disturbances:* anorexia, nausea/vomiting, peritonitis, ascites, hemorrhage colitis
 - o *Dermatologic abnormalities:* pruritus, uremic frost, hyperpigmentation
 - o *Hematologic abnormalities:* anemia, impaired platelet function
 - o *Neurologic abnormalities:* fatigue, asterixis, headache, myoclonus, seizures, coma

History and Physical exam

- Sx often don't appear until GFR declines to 10-15% normal (biochemical evidence at 30-40%)
- Common Hx and PE findings with advanced CKD are associated with uremia:
 - o Fatigue, shortness of breath, pruritus, headache, peripheral edema, ascites, auscultatory rales, bruising, uremic frost, hyperpigmentation, asterixis, altered mental status

Diagnostic Evaluation

- Determining etiology is important to guide treatment and monitor serum **creatinine** for progression
- GFR can be estimated with 24h urine collection ($\text{Cr}_{\text{urine}} \times V / \text{Cr}_{\text{plasma}}$) or with blood plasma creatinine
- **GFR estimates are not accurate in the setting of rapidly changing renal function**
- CBC monitoring (anemia), urinalysis monitoring (proteinuria -> rapid CKD progression -> ESRD risk)

Treatment

- Tx approach: 1. Determine/control etiology, 2. Monitoring change, 3. Conservative -> Aggressive Tx
- Aggressive control of DM HTN and nephritis syndromes can delay or prevent CKD
- Diet modifications: **fluid and Na restriction** (careful of dehydration), protein reduction
- In patients with **proteinuria:** ACEi or ARB can slow CKD (both with/without DM)
- Follow progression with blood urea nitrogen, Cr, and Cr clearance levels
- Patients stage 4 often need primary care + specialist intervention
- **Stage 5 usually need advanced therapy (hemodialysis, peritoneal dialysis, renal transplantation)**
 - o Hemodialysis needs AV fistula to clean blood with a fixed machine (3/week)
 - o Peritoneal dialysis uses catheter in peritoneum and no machine (patient switches dialysate qid)
 - o Renal transplantation with leukocyte antigen identical (family member usually) if possible
- Peritoneal dialysis can have peritonitis complication which is then treated with abx
- CKD and ESRD have increased risk of CVD
- **Patients need education for nephrotoxic drug avoidance (NSAIDs)**
- CKD lowers immune response so is an indication for vaccination (pneumococcal 13/23, influenza)
- Long-term dialysis can cause psychiatric problems related to self-image, depression and dementia due to aluminum contamination in dialysate

Glomerular Disease

- Glomerulopathies are characterized by **direct** injury to the glomerulus and is suspected when urine shows findings of abnormal filtration: **dysmorphic RBC, RBC casts, proteinuria, lipiduria**
- Two major categories: **Nephritis** and **Nephrosis**

Nephritis

- Characterized by glomerular **inflammation** and or necrosis with **hematuria + proteinuria**
- The immunologic injury is either focal (<50% of glomeruli, less severe) or diffuse
- The most common glomerulonephritic pathology is **IgA nephropathy** (deposition of IgA)
- In **poststreptococcal** glomerulonephritis, deposits of antigen are found in subepithelial region
- **Rapidly progressing glomerulonephritis** (RPGN): extensive capillary crescent formation
- **Antiglomerular BM** disease(Goodpasture): direct damage via inflammation due to antibody to GBM
- **Immune complex** disease: deposition of immune complexes
- **Pauci-immune** (antineutrophil cytosplasmic antibody disease [ANCA]): part of *granulomatosis with polyangiitis* diseases. Immunological mediated but no immunoglobulin show up on fluorescence

Nephrosis

- Characterized by **abnormal permeability** of glomerular membrane with **proteinuria + lipiduria**
- Pathogenesis is much less inflammatory and hematuria and RBC casts are NOT SEEN
- Commonly caused by DM, systemic lupus, amyloidosis
- **Membranous nephropathy**: most common non DM cause with diffuse thickening of GBM due to in situ immune complexed against deposit antigens. Can also be triggered by infection and malignancy
- **Minimal change disease**: little change on fluoroscopy, but MASSIVE PROTEINURIA (8-9g/day)
- **Focal glomerulosclerosis**: focal scarring with scattered glomeruli. Microscopy shows Ig deposits and loss of foot processes

Clinical Manifestations

- Glomerular disease usually manifests as acute nephritis, nephrotic syndrome, or CKD
- **Acute nephritis** manifests with abrupt onset hematuria, HTN, edema, oliguria, and azotemia.
 - o RPGN is acute nephritis that becomes ESRD in days. Anti-GBM disease also often present in RPGN
 - o Rest of acute nephritis is either immune-complex and ANCA diseases
- **Nephrotic syndrome** is proteinuria > 3.5g/day + 2^o hypoalbuminemia and edema, +/- hyperlipidemia
 - o Increased risk for DVT and renal vein thrombosis. Onset can be insidious
 - o Gross hematuria RARE and often no azotemia
- See section before for CKD
- In concurrent presence of **hemoptysis**, ANCA-associated vasculitis/glomerulonephritis suspected
 - o Anti-GBM can also present with pulmonary-renal syndrome; differentiate with biopsy

Diagnostic Evaluation

- Measure electrolytes, creatinine to assess renal insufficiency and electrolyte status
- Urinalysis to detect proteinuria and hematuria
- Microscopic evaluation of urine sediment to look for lipiduria and dysmorphic RBCs and casts
- If suspected RPGN: serology + screen for anti-GBM and ANCA antibody to look for associated disease
- Renal biopsy with examination by light microscopy, fluorescence, and electron microscopy for establishing diagnosis in acute nephritis, RPGN, nephrotic syndrome (usually for serology – patients)

Treatment

- Supportive care with fluid and electrolyte management first and only if disease is self-limited
- For poststreptococcal, suppression of infectious agent with abx needed
- For nephrotic syndromes: control proteinuria with ACEi/ARB
- In DM control BP and glycemia to prevent progression
- Immunosuppressive treatment in diseases like Goodpasture and granulomatosis with polyangiitis
 - o Can also help in lupus, idiopathic RPGN, IgA nephropathy, and amyloidosis if severe
- After normal fluid and electrolyte levels achieved monitor for return of normal renal function

Nephrolithiasis

- Kidney stones form when chemicals in urine exceed their solubility (Ca and oxalate most common)
- Modifiable dietary factors that **increase** risk for nephrolithiasis are:
 - o Low fluid intake, grapefruit juice, high Na intake, high protein intake, low Ca intake
- Hyperparathyroidism, obesity gout, DM and renal tubular acidosis also increase risk
- Nephrolithiasis can be grouped into 4 categories based on stone composition

Calcium	Uric Acid	Struvite	Cystine
<ul style="list-style-type: none"> - 80% of all stones, Calcium oxalate usually <p>Hypercalciuria (Most common)</p> <ul style="list-style-type: none"> - ↑ absorbed Ca or renal leak of Ca - exclude 2^o causes (tumour, hyperpara.) <p>Hypocitruria (deficiency in natural inhibitor)</p> <ul style="list-style-type: none"> - idiopathic, renal tubular acidosis, diarrhea <p>Hyperoxaluria</p> <ul style="list-style-type: none"> - high dietary oxalate, malabsorption, ileal dis. <p>Hyperuricosuria (Nucleating agent for Ca)</p>	<ul style="list-style-type: none"> - Gout - myeloproliferative disease - FHx of stones 	<ul style="list-style-type: none"> - $MgNH_4SO_4$ - Associated with urease-producing bacteria - Can be large 	<ul style="list-style-type: none"> - Uncommon - Cystinuria - Inherited defect of amino acid transport

History, Physical Exam, DDx

History	Physical Exam	DDx
<ul style="list-style-type: none"> - Acute flank pain + hematuria - Gradual pain that escalates - Pain migration = movement through urinary tract - +/- nausea vomiting - pink or grossly bloody urine 	<ul style="list-style-type: none"> - Often unrevealing - +/- tenderness to palpation over flank or costovertebral - peritoneal signs suggest different Dx - Fever NOT typical 	<p>Acute Flank Pain</p> <ul style="list-style-type: none"> - Aortic dissection, Lumbar disk disease - Renal/intestinal infarct/ischemia - Ectopic pregnancy, rupt. ovarian cyst <p>Gross hematuria</p> <ul style="list-style-type: none"> - Renal tumor, pyelo/glomerular nephritis

Diagnostic Evaluation

- Urinalysis is key to diagnosis -> **hematuria** predominant feature
 - o Sediment should have NON-dysmorphic RBC with NO casts (in contrast to glomerulonephritis)
 - o Urine should also be examined for crystals and pH, along with pregnancy test for women
- AXR to look for radiopaque or radiolucent stones, CT is diagnostic test (high sens. and spec.)
- Renal US alternative for non-CT candidates

Stone	Calcium	Uric Acid	Struvite	Cystine
Urine pH (normal 5.5-6)	↑	↓	↑	↓
Crystals	Color Plate 3	Rhomboid	Color Plate 4	Hexagonal
AXR	Radiopaque	Radiolucent	Radiopaque	Radiopaque

Treatment

- Adequate hydration and pain relief, NSAIDs are first line but narcotics if extreme pain or CKD
- Stone retrieval for analysis to determine prevention strategy
- Stones 4-10mm: medical therapy to aid passing (α -Blockers, CCB): Stones > 10 mm: surgical removal
- Struvite stones grow large and complete removal is essential + abx (usually colonized with bacteria)
- 1st time stone formers should have lytes workup, if hyperCa -> test for hyperparathyroidism
- Recurrent stone formers should have 24h urine collection (test: Na, Cr, Ca, uric acid, Citrate, oxalate)
- Recurrent Ca stone formers should have Na restriction and thiazide diuretics
- Hyperoxaluria stone formers should have oral Ca supplements
- Uric acid stone formers should alkalinize urine pH>6 with potassium citrate + protein restriction

Hematuria

- Blood in the urine is common and is classified as **gross** or **microscopic** depending on visibility
- Causes of hematuria are divided based on the anatomic site of blood source, * = most common:

Kidney	Ureter	Bladder	Prostate	Urethra	Systemic
- Infection*	- Stones*	- Infection*	- Infection*	- Urethritis*	- Exercise*
- Stones*	- Tumor	- Calculus*	- BPH	- Stricture	- Coagulopathy
- Tumour	- Endometriosis	- Interstitial cystitis	- Tumor	- Calculus	- Thrombo-cytopenia
- Trauma		- Tumor		- Trauma	- Hemoglobinopathy
- Glomerular disease		- Vascular			
- Cysts		- Endometriosis			
- Ischemia		- drugs			

History

- Often asymptomatic but Some Sx suggest certain etiologies:
 - o Flank Pain (pyelonephritis, nephrolithiasis, neoplasm, ischemia, glomerulonephritis, hemo cyst)
 - o Dysuria (cystitis, pyelonephritis, prostatitis, BPH, urethritis), Urethral discharge (urethritis)
 - o Weight loss (tumor), Fever (pyelon., tumor, tuberculosis), Nocturia (cystitis, BPH, pyelon.)
 - o Recent Strep infection (poststreptococcal glomerulonephritis)
 - o Painless hematuria (bladder cancer), Hx of stones, Travel (parasitic)
- In women, **menstrual Hx** is important for endometriosis
- **FHx** of hematuria suggests PKD, IgA nephropathy, hereditary nephritis (Alport), thin BM disease

Physical Exam

- Skin lesions i.e ecchymoses, petechiae (coagulopathy, vasculitis)
- Costovertebral angle tenderness (pyelon., tumor, glomerulon.)
- Abdominal mass (PKD, renal-cell cancer), urethral discharge
- Urethral discharge (urethritis), suprapubic tenderness (cystitis),
- Enlarged prostate (BPH), tender prostate (prostatitis), prostate nodule (prostate cancer)

Diagnostic Evaluation

- Initial Dx of **microscopic** hematuria is made with urine dipstick or microscopic examination
 - o Dipstick can detect both free and RBC Hb, microscopic can only detect RBC Hb
- Microscope can also reveal bacteria in setting of UTI, RBC casts suggests **renal** origin of hematuria
- RBC morphology can help determine glomerular disease (dysmorphic)
- CBC, platelets, BUN, and Cr should be done in initial evaluation
- **Isolated asymptomatic hematuria** (hematuria with no Sx or source) tested with urine culture
 - o If positive, treat and then repeat culture and urinalysis. If still present evaluate further
 - o Next step is structural examination of the urinary system with CT
 - o Ultrasonography can be used for cystic lesion evaluation or with pregnant women
 - o Other evaluations: PT, PTT, TB screen, malignancy screening, Glomerulonephritis assessment
 - o **Urine cytology** performed on 3 consecutive first void samples (Sensitive for cancer but not UTI)
 - o If bleeding source still unclear refer to urologist for cystoscopy
 - o If still unclear, angiography or renal biopsy can be considered

Treatment

- Determined by causative pathology, if hematuria from exercise this is considered benign (do nothing)

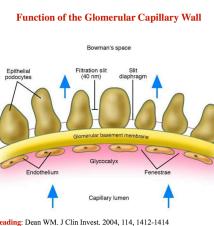
AHD – Approach to Proteinuria

Key things to remember about proteinuria

- Testing to estimate ~24h proteinuria: Dipstick (screening), uACR, uPCR
- Albuminuria: mostly used in DM: >3 mg/mmol is **significant** and associated with **complications**
- Proteinuria
 - o >150 mg/day = **not normal** => search for cause but may be functional proteinuria
 - o >1 g/day = consult nephrology, consider biopsy
 - o >2-3 g/day = urgent nephrology, extensive workup, biopsy stat
 - o Can be a sign of glomerular damage or other disease, can present alone or with hematuria, accelerates AKI via inflammation/fibrosis, level of proteinuria correlates with prognosis.

Physiology of Proteinuria

- Proteinuria is determined by size and charge
- Involves all components of Glomerular basement membrane (GBM) including podocytes, endothelial cells, and the three-layered basement membrane



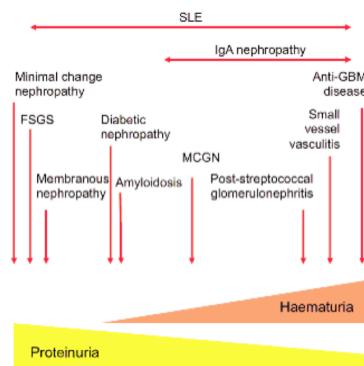
Mechanisms of Proteinuria

- Functional: hemodynamic (fever, exercise), orthostatic (peds), CHF, pregnancy, UTI, tumours
 - o If orthostatic suspected split urine collection: 16h ambulatory + 8h recumbent sleeping
- Overproduction: amyloid, multiple myeloma (MM)
 - o Overproduction of abnormal low weight proteins like light chains (MM), myoglobin (rhabdo) hemoglobin (hemolysis), and lysozyme (AML)
 - o Exceeds reabsorptive capacity of tubules and may be toxic to tubules
- Tubular: impaired tubular function (Fanconi syndrome), HIV, sarcoidosis, medications
 - o Presence of low molecular weight proteins (light chains, macroglobulin, albumin byproducts)
 - o <2 g/day, may not be detected by dipstick
 - o Associated with tubular interstitial diseases and defective absorption in **proximal tubule**
- Glomerular: Podocyte injury (MCD), focal sclerosis, membranous, diabetic
 - o **Most common presentation of proteinuria**
 - o Filtration of macromolecules (albumin) across GBM
 - o Variable amounts of protein including nephrotic range (>3.5 g/day)

Category	Level of Proteinuria	Example
Transient	< 1g/day	Fever, heavy exercise
Orthostatic	1-2 g/day	Pediatrics (uncommon >30)
Overproduction	Variable, nephrotic range	Myeloma, rhabdomyolysis
Glomerular	Variable; nephrotic range (>3.5 g/day)	DM, SLE, Amyloid, IgA nephropathy
Tubular	<2 g/day	Heavy metals, sarcoid, Sjogren's, NSAIDs

Glomerulonephritides

- Nephritic: AKI, HTN, non-nephrotic, dysmorphic RBC with casts, cell cast
- Nephrotic: >3.5 g/d protein, edema, hypoalbuminemia (<30g/L), DLD
- **1^o** is isolated to RENAL with NO EXTRARENAL manifestations
- **2^o** is part of larger disease process
- Overlap of Nephrotic/itc syndromes in SLE, MPGN, IgA, DM2
 - o Diabetic: proteinuria + hematuria; leading cause of NEPHROPATHY; affects 1/3 of DM2 patients; risk for ESRD with microalbuminuria

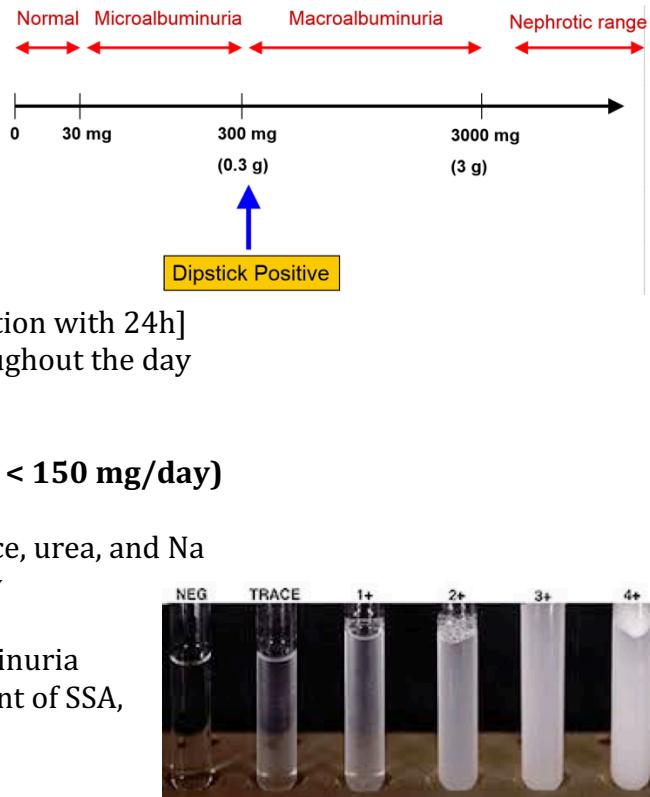


Clinical Significance

- Normal urinary protein excretion =< 150 mg/day
 - o Uromodulin (40), Albumin (30), IgG (3), IgA (4), +trace amounts of low molecular weight protein
- Proteinuria is a marker of kidney disease (more proteinuria the WORSE the kidney outcome)
 - o Increased risk for CV events, progression to CKD (if > 500 mg/day)

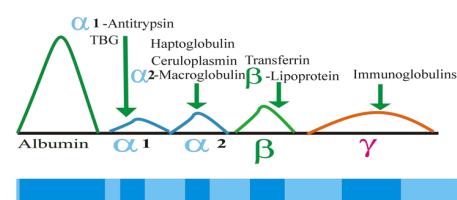
Quantification

- Dipstick
 - o Semiquantitative measurement (graded 0-4)
 - o Measure **primarily ALBUMIN**, not all proteins
 - o Frequently includes blood, glucose, pH, nitrites
- Spot Urine
 - o **Single urine sample sent to lab**
 - o Urine-protein-creatinine ratio (uPCR)
 - o Urine-albumin-creatinine ratio (uACR) [Best correlation with 24h]
 - o Use ratio because protein and Cr vary similarly throughout the day
 - o Careful with units: g/mmol *10 ~ = g/day
- 24h urine collection
 - o **Gold standard for protein measurement (Normal < 150 mg/day)**
 - Test for [Cr], [protein], record total volume
 - o Allows additional determinations such as Cr clearance, urea, and Na
 - o Overcomes variable protein excretion during the day
- SSA test
 - o Use when dipstick negative, but highly suspect proteinuria
 - o Add 0.5-1.0 ml of urine supernatant, add same amount of SSA, shake and look for change



Albuminuria

- Microalbuminuria = **moderately ELEVATED** albumin [not used anymore]
- Albuminuria = **severely ELEVATED** albumin (>300 mg/day) [not used often anymore]
- A1 = Normal/mild elevated < 30 mg/day
- A2 = Moderately elevated 30-300 mg/day
- A3 = severely elevated > 300 mg/day
- Detection of albuminuria
 - o Excretion of 30-300 mg/day (UACR 30-300mg/day)
 - o Day-to-day variation of 40%, 25% higher in day
 - o Values affected by exercise, fever, glycemic control, BP so **repeat x3**
- **Proteinuria vs. Albuminuria**
 - o Albumin is only 1 protein (accounts for 40-50% of proteinuria) but other proteins still present



Measure	A1	A2	A3
AER (mg/24 hr)	< 30	30 - 300	> 300
PER (mg/24 hr)	< 150	150 - 500	> 500
UACR (mg/day)	< 30	30 - 300	> 300
UPCR (mg/day)	< 150	150-500	> 500
Protein reagent strip	- trace	+ trace	+ trace

Clinical Presentations

- Can be incidentally detected with urine dipstick/analysis

- Microalbuminuria: mostly associated with DM
- Persistent proteinuria (+/- hematuria) can present with or without signs of systemic disease
- Nephrotic syndrome can present with or without signs of systemic disease also

Nephrotic Syndrome

- Heavy proteinuria ($>3.5\text{g/day}$), hypoalbuminemia ($<30\text{g/L}$), edema, DLD
- Complications: hypercoaguable, malnutrition, AKI, infections, hormone loss in urine, atherosclerosis
- Non-specific Tx: salt/protein restrictions, BP control, Rx of DLD, ACEi/ARB, diuretic, anticoagulation

Approach

- Need to figure out source of proteinuria
- Hx: onset (rapid/slow), hematuria, foamy urine, recent inf., medication, B symptom, systemic disease
- PE: BMI, CV status, signs of liver disease, volume status, thrush, edema, rash
- Work up: CBC, electrolytes, urinalysis + **microscopy, ultrasound** (assess renal size)
 - o Depending on context: consult nephrology, complements, auto-immune antibodies, blood cultures, CT, biopsy
- Indications for **biopsy**
 - o Many patients with proteinuria $>1\text{g/day}$ (and those with nephrotic syndrome)
 - o Non-nephrotic proteinuria with glomerular hematuria, HTN or reduced GFR
 - o Setting of systemic diseases (SLE, amyloidosis, vasculitis)
- Proteinuria in glomerular disease:
 - o Primary: no evidence of extrarenal disease; Secondary: kidney involvement in systemic disease
 - o **Bland** urinary sediment: oval fat bodies, hyaline, granular casts
 - o **Active** urinary sediment: evidence of inflammation, RBCs, WBCs, RBC/WBC casts

Fever and Rash

- Patient presenting with fever + rash has a long differential of infectious and noninfectious conditions
- Rashes are classified according to their appearance:
 - o *Maculopapular*: outbreak of pigmented bumps
 - o *Petechial/purpuric*: small red or brown spots formed by extravasation of blood into skin
 - o *Vesicular/bullous*: small and large blisters. If the fluid is purulent = *pustule*
 - o *Erythematous*: redness, *Urticular*: hives, flat topped raised area
- DDx for fever and rash is extremely long (chart at bottom)

Clinical manifestations

- Patients presenting with rash are often considered for empiric treatment along with diagnostic tests
- Patient who presents with **petechial rash, fever** and other **systemic** signs likely have serious illness
- **DO NOT MISS** diagnoses: meningococcemia, sepsis, endocarditis, gonococcemia, typhoid fever

History

- Food/water source, drugs, recent travel, animal exposure, sick contacts, Sex Hx, vaccination Hx
- Presence of a prodrome (fatigue, malaise, myalgia) are suggestive of **infectious** disease

Physical Exam

- Determine extent and morphology of rash, examine mucosal surfaces, genitalia, scalp, palms
- Signs of severe systemic illness (hypotension, meningismus) suggest a **DO NOT MISS** Dx

Diagnostic Evaluation

- If Hx and PE narrow DDx to benign illnesses, diagnostic testing unnecessary, otherwise lab tests.
- If patient is systemically ill: **blood cultures**, +/- Lumbar puncture, serology (for vaccination)
- In systemic illness with risk of serious etiology, empiric antibiotics are often started.

Disease	Type of Rash	Epidemiology	Clinical Findings	Disease	Type of Rash	Epidemiology	Clinical Findings				
<i>Infectious</i>											
Endocarditis	P	Abnormal heart valve	Cardiac murmur, mucosal lesions, retinal findings	Herpes simplex virus	VB	Multiple sexual partners, other sexually transmitted diseases	HSV-1 typically oral; HSV-2 typically genital				
Meningococcemia	P, MP, VB	Outbreak of <i>Neisseria</i>	± meningitis, septic shock (hypotension, oliguria), pustules may be present, organisms visible on Gram stain	EBV	U	Outbreaks occur among college students and military recruits	Mononucleosis (fever, adenopathy, pharyngitis, malaise, splenomegaly); 5% incidence of rash in mononucleosis, almost 100% if ampicillin is administered				
Gonococcemia	P, VB	Sexual activity, esp. with prostitutes or multiple partners	± urethritis, joint pain/effusions	Hepatitis	U	IVDU, multiple sexual partners	Urticaria may occur during acute hepatitis, but also during chronic disease				
Typhoid fever	MP ("rose spots")	Poor sanitation (fecal/oral spread), contact with asymptomatic carriers	Prolonged, persistent fever; constipation; relative bradycardia during febrile episodes	<i>Noninfectious</i>							
Staphylococcal sepsis	VB	IVDU, poor skin hygiene	Evidence of dermatologic staphylococcal infection	Allergy	P, MP, VB, E, U	Exposure to various drugs, foods, animals	Manifestations vary greatly				
Vibrio vulnificus	VB	Ingestion of raw seafood, exposure to seawater	Patients with cirrhosis are most susceptible; septic shock; lesions on extremities, legs > arms	Thrombocytopenia	P	Previous viral syndrome, known idiopathic thrombocytopenia	Easy bruising as well as spontaneous petechiae				
Folliculitis	MP, VB	Hot tubs (<i>Pseudomonas</i>), freshwater exposure (swimmer's itch from avian schistosomes)	Diffuse rash, marked pruritus in swimmer's itch	Henoch-Schönlein purpura	P	Mostly in children	Abdominal pain, arthralgias, glomerulonephritis, IgA deposits in skin and kidneys				
Streptococcal infection	E	Outbreaks of scarlet fever	Diffuse erythematous rash with "sandpaper" texture, well-circumscribed cellulitis (erysipelas)	Hypersensitivity vasculitis	P	Antigen exposure (infectious agent, drug)	Biopsy reveals leukocytoclastic vasculitis with antigen/antibody immune complex deposition				
Staphylococcal infection	MP, VB, E	Tampon use (toxic shock), poor skin hygiene	Shock, with diffuse erythema and later palma desquamation (toxic shock), folliculitis, pustules (staphylococcal bacteremia)	Vasculitis (e.g., SLE, polyarteritis nodosum, dermatomyositis)	P, MP	Known history of vasculitis	Manifestations vary as to type of vasculitis				
Ehrlichiosis	E	Endemic area in summer, tick bite, outdoor exposure, liver function test, rash variable	Headache, leukopenia, abnormalities	Erythema multiforme	MP	Drug exposure	Characteristic "target" lesions, can have mucosal involvement (Stevens-Johnson syndrome)				
Rocky Mountain spotted fever	P	Endemic area in summer, tick bite, outdoor exposure	Severe headache, rash starts in extremities and spreads centripetally	Adult-onset Still disease	MP, M	Antecedent infection (bacterial and viral) as "triggers"	Joint pain/swelling (wrists, knees, ankles), sore throat				
Secondary syphilis	MP	Sexual activity, esp. with prostitutes or multiple partners	Involves palms and soles	Plant dermatitis (poison ivy, poison oak)	VB	Known exposure to plants	Weepy, vesicular/bullous lesions in areas of contact, pruritus				
Mycoplasma	MP, U	Younger patients	Bullous myringitis, pneumonia	Vasodilation	E	Shock, vigorous exercise	Blanching, bright erythema				
Lyme disease	MP	Endemic area in summer, tick bite, outdoor exposure	Erythema migrans rash, joint effusions, headache	Psoriasis	E	Known history	Silvery scale present over diffuse erythema, pustular variant seen				
Enteroviral infection	P, MP, VB, E, U	Winter months	Myalgia, diarrhea, headache, meningitis	Lymphoma	E	Peak incidence 55 to 60 years old; 2:1 male:female (cutaneous T-cell lymphoma)	Diffuse erythema can occur in all lymphomas, T-cell lymphoma of skin (mycosis fungoides and Sezary syndrome)				
Rubella	P, MP	No history of immunization	Viral prodrome, rash starts on forehead and spreads downward to feet, adenopathy	Kawasaki disease	E	Generally children	Resembles scarlet fever, but without evidence of streptococcal infection				
Rubeola	MP	No history of immunization	Viral prodrome with conjunctivitis; small, irregular mucosal lesions (Koplik spots); rash starts on forehead and spreads downward to feet								
Adenovirus	MP, U	Year-round occurrence, but greatest in winter months	Upper respiratory illness, conjunctivitis, adenopathy								
Primary HIV infection	MP	Sexual activity, esp. with prostitutes or multiple partners; IVDU	Viral syndrome with fever, malaise, headaches, and myalgia								
HIV (established infection)	VB, U	Sexual activity, esp. with prostitutes or multiple partners; IVDU	Often with no other symptoms								
Varicella-zoster	VB	No history of disease (primary infection)	Reactivation in dermatomal distribution								

Pneumonia

- Pneumonia in otherwise normal individuals is referred as **community acquired pneumonia (CAP)**
- Microbial pneumonia causes range from bacteria, fungi, and viruses. Etiology related to specific RF:
 - o Age, SES, Prior abx, COPD, DM, Chronic liver/renal disease, CHF, immunosuppression, vaccines

History

- Sx usually include: Fever, chills, rigors, cough, sputum, chest pain, shortness of breath
- Additionally make sure to get travel Hx, sick contacts, animal exposure, environmental irritants

Physical Exam

- Physical exam alone lacks sensitivity and specificity for CAP diagnosis.
- Signs of **consolidation**: bronchial breath sounds, egophony, dullness on percussion, ↑ tactile fremitus
- Even if signs of consolidation not present many patients have crackles on lung exam
- **Increased morbidity/mortality** signs: tachypnea, fever, hypotension (90/60), altered mental status

DDx

- **Infectious DDx:** URTI, sinusitis, pharyngitis, bronchitis
- **Noninfectious DDx:** PE, CHF, lung cancer, inflammatory lung disease (Wegener, eosinophilic)

Diagnostic Evaluation

- CXR useful in differentiating pneumonia from bronchitis and detecting abscesses, effusions, masses
- Serum procalcitonin can help differentiate **bacterial vs. nonbacterial** etiology (i.e. if abx indicated)
- Sputum culture, blood culture (aerobic and anaerobic), +/- gram stain
- Urinary antigen test for *Legionella pneumophila* and *S. pneumoniae* is available for quick diagnosis
- Certain lab results predict high morbidity and mortality
 - o WBC<109/L, PaO₂<60mmHg, PaCO₂>50mmHg, pH<7.35, Hematocrit<30%, Cr_{serum}<1.2mg/dL

Treatment

- Two main management questions: 1. Hospital admission required? 2. What abx treatment?
- Severity of illness and social factors determine +/- hospital admission, or CURB-65 risk model:
 - o CURB-65 Risk model: Confusion, BUN > 20mg/dL, RR > 30, BP < 90/60, age > 65
 - o Score 0-1 (outpatient), Score 2 (admission), Score 3+ (ICU)
- If pleural effusion seen on CXR, sample for infection (empyema), if + place chest tube
- Empirical abx should NOT change in first 72h unless lab test indicate resistant/noncovered pathogen
- Many physical signs continue for several days/weeks after treatment (including CXR)
- If initial therapy fails investigate further: bronchoscopy, CT, pulmonary arteriogram (PE), serology

Patient Group	Major Pathogens	Miscellaneous Pathogens	Empirical Therapy
Outpatient (previously healthy and no use of antimicrobials within the previous 3 months)	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> <i>Haemophilus influenzae</i> Respiratory viruses	<i>Legionella</i> spp. <i>Mycobacterium tuberculosis</i> Endemic fungi	Advanced-generation macrolide (e.g., azithromycin or clarithromycin)* or doxycycline
Outpatient (with comorbidities)*	<i>Streptococcus pneumoniae</i> (including DRSP) <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> Mixed infection (bacterial plus atypical pathogen or virus) <i>Haemophilus influenzae</i> Respiratory viruses	<i>Moraxella catarrhalis</i> <i>Legionella</i> spp. <i>Mycobacterium tuberculosis</i> Endemic fungi	Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, levofloxacin) or β-lactam plus a macrolide
Inpatients (non-ICU treatment)	<i>Streptococcus pneumoniae</i> (including DRSP) <i>Haemophilus influenzae</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> Mixed infection (bacteria plus atypical pathogen or virus) Enteric gram-negative organisms Respiratory viruses Aspiration (anaerobes) <i>Legionella</i> spp.	<i>Mycobacterium tuberculosis</i> Endemic fungi <i>Pneumocystis jirovecii</i>	Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) or β-lactam plus a macrolide

Patient Group	Major Pathogens	Miscellaneous Pathogens	Empirical Therapy
Inpatients (ICU treatment)	<i>Streptococcus pneumoniae</i> (including DRSP)	<i>Mycobacterium tuberculosis</i>	A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam: aztreonam for penicillin-allergic patients) plus either azithromycin or respiratory fluoroquinolone
	<i>Haemophilus influenzae</i>	<i>Pneumocystis jirovecii</i>	If <i>Pseudomonas</i> is a concern*: Change β-lactam to an anti-pseudomococcal, antipseudomonal (piperacillin-tazobactam, ceftazidime, imipenem, or meropenem: aztreonam for penicillin-allergic patients) plus either ciprofloxacin or levofloxacin or aminoglycoside and azithromycin
	<i>Chlamydia pneumoniae</i>	Mixed infection (bacteria plus atypical pathogen or virus)	Enteric gram-negative organisms
		Enteric gram-negative organisms	Respiratory viruses
		Respiratory viruses	Aspiration (anaerobes)
		Aspiration (anaerobes)	<i>Legionella</i> spp.

Sexually Transmitted Infections

- STIs are among the most common infections and are influenced by SES, drug use, sexual practice
- Most **nonviral** STIs can induce **inflammation** when the organisms colonize on the mucosa
- Infection of the upper female reproductive tract leads to **pelvic inflammatory disease**
- HPV and HSV infection is lifelong with recurrent episodes, and cervical/penile cancer risk (HPV)

History, Physical Exam and DDx

Clinical Syndromes	History	Physical Exam	DDx
<ul style="list-style-type: none"> - Urethritis - Epididymitis - Vaginitis/cervicitis - Acute PID - Genital ulcers/warts - Hepatitis - Can also be silent 	<ul style="list-style-type: none"> - Dysuria, Discharge - Genital lesions - Abdo pain, fever <p>Sexual Hx</p> <ul style="list-style-type: none"> - Number of partners - Types of sex acts - Condom use - Hx of STI - Hx of Pap smears - Hx of HPV vaccine 	<ul style="list-style-type: none"> - Inspection of genitalia - Speculum + bimanual exam (F) - Testicle and prostate exam (M) - Mucosal surfaces - Look for lymphadenopathy - Skin exam 	<ul style="list-style-type: none"> - Urethritis: UTI, prostatitis - PID: ectopic pregnancy, appendicitis, pyelonephritis, cystitis - Vaginitis/cervicitis: normal menstrual cycle, dysfunctional uterine bleeding

Diagnostic Evaluation

- Diagnosis can be made with culture and nonculture methods: microscopy, fluorescence, serology
 - o Nonculture methods useful for unculturable organisms (*T. pallidum*) or expensive (HSV/HPV)
- Nucleic acid sampling for *Chlamydia* and *Gonorrhea* using a urine sample is common
- In women, urine sample for gonorrhea has **low sensitivity**
- In **urethritis**, r/o cystitis, pyelon., UTI (F), gram stain discharge (M), pelvic exam (F), abx (M/F)
- Because of severe sequelae from PID prompt evaluation and empirical treatment are necessary for women presenting with cervical discharge +/- abdo pain + fever

Treatment

- Usually done as outpatient and simple (single dose) preferable. Hospitalization consideration in PID.
- For nonviral STI, abx (empiric) is mainstay of therapy, Acyclovir used for HSV outbreaks
- Important to screen sexual partners of STI infected individual + education to patient
- Primary prevention: condoms, vaccine for Hep A/B, HPV

Syphilis

- *T. pallidum* infections need special attention due to varied clinical manifestations characterized by periods of active and latency. All patient manifest **primary stage of painless indurated ulcer**
- If untreated, ~50% progress to 2^o stage where organism is systemically dispersed. Signs of 2^o stage:
 - o Generalized maculopapular rash, mucous patches, condylomata, primary chancre, B symptoms
 - o Patients in secondary stage can be asymptomatic with serologic evidence of infection
- **Late syphilis** is marked by end organ damage: CNS, CV, granulomatosis with central necrosis
- Laboratory Dx of syphilis: Dark field microscopy, fluorescence, Serology (VDRL)

Clinical Syndrome	Syndrome Etiologies	Clinical Findings	Laboratory Findings	Treatment
Urethritis (male)	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , Ureaplasma urealyticum	Dysuria, urethral discharge, fever, arthritis, Reiter syndrome	Gram-negative diplococci inside PMNs (<i>N. gonorrhoeae</i>) PMNs without organisms (NGU)*	Third-generation cephalosporin (<i>N. gonorrhoeae</i>); doxycycline or azithromycin (NGU)*
Urethritis (female)	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> <i>Escherichia coli</i>	Dysuria (without frequency and urgency) ± cervicitis	Pyuria	Third-generation cephalosporin (<i>N. gonorrhoeae</i>); doxycycline or azithromycin (NGU)*
Epididymitis	<i>C. trachomatis</i> <i>N. gonorrhoeae</i> Enterobacteriaceae	Testicular pain and tenderness (usually unilateral)	None specific	Third-generation cephalosporin (<i>N. gonorrhoeae</i>), plus doxycycline (<i>C. trachomatis</i>), quinolone (Enterobacteriaceae)
Vulvovaginitis	<i>Trichomonas vaginalis</i> <i>Candida albicans</i>	Vulvar itching, "cottage cheese" discharge (candidiasis); vulvar itching, purulent, malodorous discharge, mucosa visibly inflamed (<i>T. vaginalis</i>)	PMNs, budding yeast on KOH prep or Gram's stain (candidiasis); PMNs with motile organisms seen (trichomoniasis)	Intravaginal azoles (e.g., clotrimazole, miconazole) (candidiasis); metronidazole (trichomoniasis)
Bacteria vaginosis	<i>Gardnerella vaginalis</i> , <i>Mycoplasma hominis</i> , anaerobic bacteria	Malodorous, thin discharge (clear to white)	"Clue cells" on wet prep; replacement of <i>Lactobacilli</i> with mixed organisms of Gram stain, few PMNs	Metronidazole (either orally or intravaginally)
PID	<i>C. trachomatis</i> <i>N. gonorrhoeae</i>	Abdominal pain, purulent vaginal discharge, cervicitis (purulent); nausea/vomiting, fever, cervical motion tenderness	Elevated white blood cells, PMNs in vaginal discharge; gram-negative diplococci seen within PMNs (<i>N. gonorrhoeae</i>)	Inpatient: Third-generation cephalosporin or clindamycin and gentamicin or ampicillin/sulbactam plus doxycycline Outpatient: Third-generation cephalosporin × 1 plus doxycycline or quinolone plus metronidazole
Genital ulcers	HSV; <i>T. pallidum</i> (syphilis); <i>Haemophilus ducreyi</i> (chancre)	Painful ulcers (HSV; chancre); painless ulcers (syphilis); painful ulcers and inguinal adenopathy with overlying erythema (chancre)	Multinucleated giant cells/positive DFA/ viral culture (HSV); spirochetes seen on dark-field microscopy (syphilis); isolation of <i>H. ducreyi</i> from lesion or lymph node aspirate	Acyclovir (HSV); benzathine penicillin G (syphilis). Single IM dose for early disease; three doses for late disease (neurosyphilis requires IV therapy), doxycycline for penicillin allergy; ceftriaxone or azithromycin (chancre)
Genital warts	HPV	Visible papillomas associated with the development of epithelial cancers	Molecular typing is available; but not usually needed to make the diagnosis	Local wart removal (cryosurgery, laser surgery, podophyllin); vaccine is available for prevention
Hepatitis	HBV, possibly hepatitis C virus, hepatitis A (fecal-oral contact)	Fever, hepatomegaly, abdominal pain (see Chapter 41)	Elevated liver transaminases; serologic testing available	See Chapter 41 Vaccines for HAV and HBV

Urinary Tract Infections

- UTIs divided into lower (bladder cystitis), and upper (kidneys + collecting system pyelonephritis)
- Much more prevalent among women than men and majority by **aerobic gram negative bacteria**
 - o *E. Coli* most common pathogen, rest caused by *Enterobacter, Klebsiella, Proteus, Pseudomonas*
- Some UTI organisms have high **virulence factors**: pili/fimbriae, hemolysin, aerobactin, urease
- Risk factors that increase UTI (women): Hx of UTI, Sex activity, using diaphragm, not peeing after sex
- In men, **anatomic abnormalities (BPH)** is major RF, in hospitalized patients, catheters are major RF

History

- Lower tract infections have **Sx of bladder irritation**: Frequency, urgency, dysuria, +/- hematuria
- Upper tract infection distinguishes from lower: fever, flank pain, abdo pain, nausea, vomiting

Physical Exam

- Often does not add much information other than flank pain suggesting upper tract disease
- In women, possible concurrent pelvic examination if evidence of urethritis or vaginitis

DDx

- Other conditions that produce signs and Sx of bacterial UTI:
 - o Vulvovaginitis, urethritis, bladder calculi/tumor, drug-induced cystitis, prostatitis

Diagnostic Evaluation

- Urinalysis and **urine culture** are most important tests to guide diagnosis and treatment
- Microscopy can reveal leukocytes and organisms; presence of WBC casts suggest pyelonephritis
- The presence of **both WBC and nitrites is highly specific for UTI (90%)**
- Urine culture with susceptibility test important for determining empirical abx treatment; indications:
 - o Possible upper tract, known anatomic abnorm., recent abx for UTI, persistent/atypical symptoms

Treatment (WOMEN)

- Most often treatment is done with outpatient PO abx; hospital UTI from catheter -> remove catheter
- Lower tract UTI: **short course abx (7-10d)**; Upper tract UTI use **long course abx** for 10-14d
 - o Standard PO drugs: **Nitrofurantoin, Trimethoprin/sulfamethoxazole, Quinolones, B-lactams**
 - o All have good gram negative activity; **quinolones, B-lactams** reserved for **complicated cystitis**
- Bladder analgesic (phenazopyridine) can be given concurrently
- Most common causes of Tx failure are compliance and resistant organisms
- **Complications of UTI that warrant observation are perinephric abscesses, renal calculi, sepsis**
- If recurrent UTI recommend: voiding after sex, alternative contraception, ↑ fluid intake when Sx start
- In **men**, most common reason for UTI is **urinary tract abnormality**; referral to **urologist plus abx for 10-14 days** is generally treatment approach

Tuberculosis

- TB from *Mycobacterium tuberculosis* creates granulomas via cell-mediated immunity often in the lung
- Spread via inhalation of droplets; When infected bacteria are ingested by macrophages -> granuloma
- Cell-mediated immune response takes 3-9 weeks so will show positive TB skin test
- Granuloma “walls” infection but viable organisms inside so some drugs/conditions can cause escape
- RF for TB: old age (reactivation), low SES, immigrant from endemic area, HIV+

History

- Often asymptomatic and may be seen on CXR; **Sx** are usually **nonspecific** and **constitutional**:
 - o Fever, chills, night sweats, anorexia, weight loss, fatigue, cough, **hemoptysis** (advanced disease)

Physical Exam

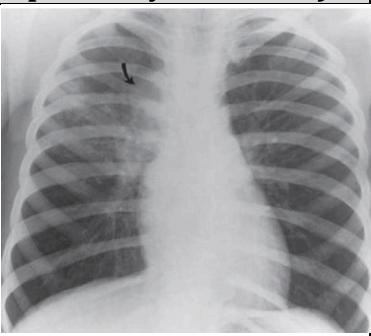
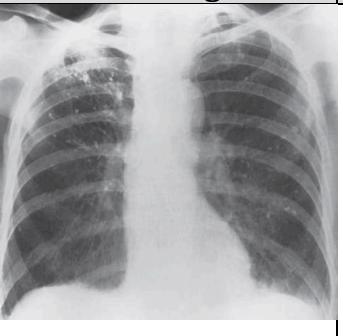
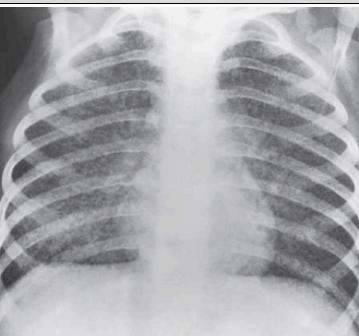
- **Dullness + decreased fremitus** may be present with pleural effusion or thickening
- Signs of consolidation may be present; cavitation may produce hollow breath sounds (**amphora**)
- Extra-pulmonary TB is manifested by signs of the particular organ affected

DDx

- Other disease with similar clinical findings: Fungal (histoplasmosis), Sarcoidosis, malignancy

Diagnostic Evaluation

- CXR is important for presence and extent of disease:

Ghon complex (1 ^o parenchymal lesion)	Apical pleural scarring	Cavitary disease/ Lobar Consolidation	Diffuse (military) disease
			

- Sputum exam with acid fast stain; **POSITIVE** requires heavy organism burden; culture more sensitive
- Skin testing for documenting exposure and infection; **different levels for different populations**:
 - o >15mm in normal host from a low-risk group (don't routinely test)
 - o >10mm in moderate-risk individual (non-HIV, endemic area)
 - o >5mm in HIV-infected individual or close contact with TB (or transplant patients on prednisone)
- New test is *whole-blood interferon gamma assay*; high specificity and sensitivity

Treatment

- Management based on whether active or latent(LTBI) disease; LTBI treated with **chemoprophylaxis**
- 1st line Tx q2m **active TB**: Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA), Ethambutol (EMB)
- Chemoprophylaxis of recent + skin test is INH q9m; cultures reassessed q3m
- Management in HIV+ due to drug interactions; all patients with **active TB** should be tested for **HIV**
- Treatment for MDR TB is difficult and provides a public health challenge
- Compliance usually major problem with treatment (drug side-effects);
- Drug toxicity is usually hepatic so liver function should be monitored during therapy

Gastroenteritis

- Gastroenteritis (GE) is inflammation of stomach and intestines associated with diarrhea
- Acute GE usually follows **ingestion of contaminated food or water, or swimming** in such water
- **Bacteria, Viruses** (Commonly; noro-, rota-, astro-, adeno- viruses), and **protozoans** can cause GE
- Protozoan GE usually from travel exposure to dirty water (*Entamoeba histolytica*, *Giardia lamblia*)
- Enteric pathogens cause GE via several mechanisms:
 - Direct invasion of mucosa (*Entamoeba histolytica*, *EHEC*, *Shigella dysenteriae*)
 - Growth of bacteria in the bowel lumen with toxin release (*ETEC*, *Clostridium difficile*)
 - Adherence of bacteria to mucosal surface preventing water absorption (*EPEC*, *Giardia lamblia*)
 - Production of toxin during bacterial growth (*Staphylococcal aureus*)

History

- Food Hx q48h, Travel Hx, sick contacts, Abx use (*C. diff*), HIV status,
- Once possible exposure suspected, incubation period between onset of symptoms can help identify:
 - 8h (*S. aureus* – food poisoning), 24-48h (*Campylobacter*, *Salmonella*), d-w (*Giardia*)

Physical Exam

- Not usually helpful; fever, abdo pain suggest invasive pathogen + gross/occult blood in stool
- Severity of illness can be indicated by signs of dehydration: orthostatic hypoTN, dry membrane etc.
- See section on diarrhea for DDX

Diagnostic Evaluation

- Often, hydration and watchful waiting sufficient; workup only if septic, bloody stool, recent abx
- **Stool leukocytes** suggest **bacterial** pathogen; gram stain can reveal **gull-wing** (*campylobacter*)
- **Culture** is gold standard for determining pathogen but usually reserved for severe cases
- If **Protozoan** etiology suspected, stool examined for ova and parasites
- In patient with recent abx use, assay for presence of *C. diff* toxin is diagnostic

Treatment

- Primary treatment is supportive with fluid and electrolyte replacement (PO, if severe then IV)
- Antimotility agents (**atropine**) used for Sx; **DO NOT USE** with *C. diff*, *Salmonella EHEC*
- Bulk agents (**kapectate**) give more form to stool but don't decrease fluid and electrolyte loss
- Use of abx controversial; RF for *C. diff* infection, prolongs *Salmonella* infection, worsens *EHEC*

Agent	Pathogenesis	Clinical/Epidemiologic Features	Therapy
<i>Bacillus cereus</i>	Preformed toxin	Generally causes vomiting; may also produce diarrhea; classic association with fried rice	None
<i>Staphylococcus aureus</i>	Preformed toxin	Vomiting with some diarrhea; found in high-protein foods (meats, cream-filled cakes), also in those with high-sugar contents (custards)	None
<i>Clostridium difficile</i>	Toxin production in colon	Fever, abdominal pain, diarrhea, toxic megacolon; association with previous antibiotic use	Metronidazole, vancomycin
<i>Escherichia coli</i>			
Enterotoxigenic	Enterotoxin formation in small intestine	Voluminous watery diarrhea; fever generally absent; fecal/oral transmission	None
Enteropathogenic	Localized adherence to intestinal mucosa	Watery diarrhea; can occur in outbreaks among newborns	Antibiotics
Enteroinvasive	Invasion of the colonic mucosa	Fever, bloody diarrhea; fecal/oral transmission	Antibiotics
Enteroadherent	Adherence to small intestinal mucosa	Diarrhea, can be prolonged; fecal/oral transmission	Antibiotics
Enterohemorrhagic (e.g., <i>E. coli</i> O157:H7)	Production of a cytotoxin (Shiga toxin) in colon	Causes hemorrhagic colitis; colitis can be followed by TTP/HUS; from contaminated meats (especially ground meat)	Diarrhea: none; treatment of TTP/HUS is generally supportive (treatment of diarrhea may increase the risk of TTP/HUS; see text)
<i>Campylobacter jejuni</i>	Colonization (invasion) of large and small bowel	Fever, watery or bloody diarrhea with fecal leukocytes, abdominal pain	Antibiotics
<i>Salmonella typhi</i>	Invasion of small intestine; can then disseminate systemically (via bloodstream)	Protracted illness with fever, headache, malaise, splenomegaly; constipation is more common than diarrhea; fecal/oral transmission	Antibiotics
<i>Salmonella</i> (nontyphi)	Invasion of small and large intestine	Fever, diarrhea with fecal leukocytes; animal reservoirs, also in eggs	Antibiotics (see note in text)
<i>Shigella</i> spp.	Invasion of colon	Fever, bloody diarrhea with fecal leukocytes; fecal/oral spread	Antibiotics
<i>Vibrio cholerae</i>	Enterotoxin	Profuse watery diarrhea; fever is rare; fecal/oral spread (often via water contamination)	Doxycycline
<i>Entamoeba histolytica</i>	Invasion of colonic mucosa	Diarrhea, often bloody; fecal/oral spread	Metronidazole
<i>G. lamblia</i>	Colonization of small intestine	Diarrhea, secondary to malabsorption; abdominal pain; waterborne ("beaver fever")	Metronidazole
Viruses (e.g., norovirus, rotavirus)	Invasion of mucosa	Can occur in outbreaks, generally watery diarrhea	None

Infective Endocarditis

- IE is invasion of endothelial heart lining by microorganisms (bacteria, fungi, rickettsia, chlamydia)
- IE divided into three major groups: **Native Valve** (NVE), **Prosthetic Valve** (PVE), IV drug user IE
- Gold standard for diagnosis is pathology but **Duke criteria** useful for clinical diagnosis:

Major Duke Criteria	Minor Duke Criteria
<ul style="list-style-type: none"> - Persistent +blood culture consistent with IE (2 cultures q 12h or >3 cultures q 1h) - Single + blood culture for <i>Coxiella burnetii</i> - Echocardiographic evidence of endocardial involvement 	<ul style="list-style-type: none"> - Predisposing heart condition - Fever - Vascular (arterial emboli, Janeway lesions) - Immune (Osler nodes, roth spots, Rf, glomerulon.) - +blood culture not meeting Major criteria

- **Definitive diagnosis:** TWO major criteria, ONE major + THREE minor criteria, FIVE minor criteria
- **Possible IE:** ONE major + ONE minor OR THREE minor
- IE often from by streptococci (NVE) or staphylococci (NVE, IV drug) or intraoperative infection (PVE)
- A major RF for IE is **structural heart abnormality**, often valvular disease leading to turbulent flow
 - o Rheumatic, Degenerative, Congenital heart diseases, Hypertrophic cardiomyopathy, foreign body

History

- Patients with IE may present with acute/subacute constitutional Sx (fever, chills, weight loss, etc.)
- Evaluation for IE should include screening of RF, Hx of valvular disease, rheumatic fever, dental work

Physical Exam

- IE often produces destruction/perforation of valve leaflets patients often have **regurgitant murmur**
- New or changing murmur often suggestive of IE; other cardiac manifestations: heart block, CHF
- Skin and peripheral manifestations can be seen due to micro- or macroemboli (not pathognomonic)

DDx

- DDx of a patient fulfilling Duke criteria is limited to IE and other endovascular infections

Diagnostic Evaluation

- Dx often made clinically; confirmation of causative organism via blood culture + **echocardiogram**:
 - o **Vegetations** (abnormal echoes on endothelial valve surface)
 - o **Ring Abscess** (echodense or echolucent area in valve)
 - o New valvular regurgitation or new partial dehiscence of a prosthetic valve
- Lab abnormalities in IE: ↑ ESR, ↑ WBC, anemia, hematuria/proteinuria, +Rf

Treatment

- **Empirical antibiotic therapy** is initial step; indications for early cardiac surgery:
 - o Severe **refractory** CHF due to regurgitation; regurgitation with abnormal hemodynamics
 - o Refractory infection; progressive intracardiac spread of infection
 - o **Prosthetic valve dysfunction**; recurrent systemic emboli; presence of large mobile vegetations
- **Abx goal is vegetation sterilization, usually requires high-dose IV abx** (B-lactam + aminoglycoside)
- In PVE/IV drug users with B-lactam resistance, vancomycin is used instead
- After treatment, monitor patient for late complications of valvular dysfunction (CHF/atrial fib)
- Prophylaxis if significant cardiac abnormalities and undergoing procedures with high bacteremia

Meningitis

- Classically presents with the triad of fever, headache, meningeal irritation; either bacterial or aseptic
- Viral meningitis increases in prevalence in summer, acute bacterial meningitis (ABM) in winter
- *Streptococcus pneumoniae* is most common community-acquired source of ABM
- Most common aseptic cause is nonpolio enteroviruses but can be caused by other viruses and fungi

History

- Classic Hx is severe headache, fever, altered mental status and Sx of meningeal irritation (neck stiff)
 - o One or more of these Sx can be absent but if all 3 absent unlikely to be meningitis
- Ask about photophobia, seizures, rash, travel Hx, sick contacts
- ABM more likely in age < 5 or > 50; AVM more likely in summer and between 5-50

Physical Exam

- Nuchal rigidity/neck stiffness, Kernig/Brudzinski sign (low sensitivity), fundi exam (papilledema), skin rash (meningococcal meningitis), neurologic exam (CN deficits for herniation)

DDx

- Distinguish between ABM and other inflammation sources: brain abscess, IE, septic thrombophlebitis

Diagnostic Evaluation

- Analysis of CSF via LP is main diagnostic test; **CT BEFORE LP** if:
 - o Immunocompromised, Hx of stroke, new seizures, Papilledema, abnormal consciousness
- Blood cultures should be obtained to help in diagnosis of ABM
- **LP analysis:** opening pressure, cell counts, WBC, Glucose, protein, gram stain for bacteria
- Additional CSF tests: acid-fast stain (TB), fungal/viral stain + culture, PCR (HSV), serology for syphilis

CSF Test	ABM	AVM
CSF count (cells/ml)	200-10,000 (<i>polymorphonuclear</i> predom.)	25-100 (<i>lymphocyte</i> predom.)
CSF protein (mg/dL)	100-500	50-100
CSF glucose (mg/dL)	<40	>40
Opening P (mm H ₂ O)	>200	<180
Time of year	Winter	Summer
Age	>5 or >50 (most common)	5-50 (most common)

Treatment

- Potential ABM is a medical emergency and LP followed by empiric abx performed immediately
 - o If CT is to be done before LP **DO NOT DELAY ABX**
- Values in table above are suggestive of ABM vs AVM but have poor PPV/NPV so empiric abx therapy still used if a **definitive** ABM diagnosis has not been made before LP and CSF analysis
- Adult: emp. abx (**Vanco + Ceftriaxone + Ampi**) for *S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*;
- Corticosteroids reduce incidence of complications in ABM in infants and kids
- Once empiric abx are started patient monitored for improvement; if culture results allow, narrow abx
- In cases of probable AVM, once clinical improvement and CSF cultures neg. for 48h abx can stop
- If abx therapy fails, may be due to resistant organisms; CT/MRI + repeat LP may be needed

AHD – Clinical Considerations For Antibiotic Use

HIV: Primary Care of the HIV-Infected Patient

- The **clinical AIDS syndrome**: HIV+ patient with CD4 count < 200/mm³ OR an AIDS defining illness
- HIV is an RNA retrovirus; they bind to CD4 outside cell, enter cell and integrate into DNA and spread
 - o Infects cells with CD4 marker within body; Infection of CD4 lymphocytes results in their death
- HIV transmission via: Unprotected sex, IV drugs, perinatal blood exchange, blood transfusion
- Primary HIV infection linked with **acute retroviral syndrome**: flu-like symptoms, acute CD4 fall
 - o Infection then enters **clinical latency** (asymptomatic); **THERE IS NO VIRAL LATENCY!!**
 - o CD4 lymphocytes continue to fall and disease susceptibility increases; AIDS if untreated in 10y

History

- RF for HIV should be screened; HIV should be suspected in patient with STI; screen pregnant women
- Review of systems for suspected HIV infection:
 - o Constitutional symptoms, Visual disturbances, headache, oral lesions, cough, dyspnea, dysphagia, diarrhea, rectal pain, genital lesions/bleeding, rashes, nodules, lymphadenopathy
 - o ROS important for each visit in known HIV+ patient as it may be only sign of HIV decompensation

Physical Exam

- Baseline and follow-up PE for HIV+ patients should pay attention to signs associated with Sx from Hx
- Women should have pelvic exam + pap smear due to increased risk of cervical cancer in HIV+

Diagnostic Evaluation

- Testing with a screening **ELISA**, if positive, confirmation with **Western blot** for immunoreactivity
 - o Other tests: assay for **p24 antigen**, detection of viral RNA with PCR
- Initial tests for evaluating a newly diagnosed HIV infection to establish stage:
 - o CD4 lymphocytes, HIV RNA quantity (viral load), HIV resistance (genotyping), CBC, CZR, G6PD deficiency, interferon-gamma assay, pap (F), testosterone (M), antibodies (CMV, Hep B/C, toxo)

Treatment (Antivirals)

- 2 parts: **Stall immunologic decline**(antivirals), **prevent/treat opportunistic disease** (prophylaxis)
- **Nucleoside reverse transcriptase inhibitors** (NRTI) are the backbone of treatment regimens
- **Protease inhibitors** (PI) are new modern antivirals that inhibit proper synthesis of viral particles
- **Integrase strand transfer inhibitors** (ISTI) inhibit integration of HIV genome into host genome
- These described therapies (HAART) can ↓ viral loads to below PCR detectability -> ↑ CD4 count
- HAART fallbacks: treatment regimens are complex, many drugs, many times/d, many side effects
- Timing for initiation of HAART is controversial
 - o Consensus: all patients with Hx of AIDS defining illness OR asymptomatic + CD4 < 350 cells/mm³
 - o Most offer treatment to HIV+ asymptomatic + CD count of 350-500 or regardless of CD4
- Before HAART started patient must be aware it is **LIFETIME** treatment; stop/start causes resistance
- Most care involves monitoring (CD4 count/opportunistic diseases) and patient education
- **HIV is NOT** a reportable disease (in Qc); assure patient diagnosis is confidential but encourage to inform partners that may be affected

HIV: Prophylaxis and Treatment of Opportunistic Infections

- Most HIV morbidity/mortality is from OI; **Prophylaxis** important for prevention and ↑ survival
- Specific OI are encountered at different CD4 count levels, and from different types of exposures

History and Physical Exam

Symptoms (DDx)	Physical Exam (Sign)
- Constitutional Symptoms (<i>Mycobacterium</i> , HIV wasting, lymphoma)	- Mucosa (genital lesions, oral candidiasis/ulcers)
- Visual change/eye pain (CMV retinitis, ophthalmic varicella zoster)	- Retina (retinopathy)
- Headache, AMS (toxoplasma encephalitis, CNS lymphoma, meningitis)	- Skin (pigmented lesion, rash)
- Cough, SOB (PCP, TB, recurrent bacterial pneumonia, influenza)	- Lungs (consolidation, crackle)
- Oral lesions (thrush, oral hairy leukoplakia, aphthous ulcers, HSV)	- Lymph nodes (tender, bulky)
- Dysphagia (candida/CMV/HSV esophagitis)	- Liver (hepatomegaly)
- Chronic diarrhea (cryptosporidiosis, isoporiasis)	- Spleen (splenomegaly)
- Genitourinary Sx (recurrent HSV, syphilis, cervical cancer)	
- Skin Lesion (Kposi sarcoma, <i>Bartonella</i> , scabies)	
- Lymphadenopathy (lymphoma, <i>mycobacterium</i> , <i>Bartonella</i>)	

- Once DDx is formulated get CXR (pulmonary Sx) or head CT (neuro Sx)

Treatment

- 3 categories: **1^o Prophylaxis** (lifestyle mod., drugs to prevent OI), **OI treatment**, **2^o prophylaxis**

Pathogen	Prophylaxis indications	Pathogen	Prophylaxis indications
<i>P. jirovecii</i>	CD4 < 200 uL/oral candidiasis	CMV	IgG antibody to CMV + CD4 < 50 uL
<i>M. tuberculosis</i>	TB skin test > 5 mm or + test with contact to active case of TB	HSV	Not recommended
<i>T. gondii</i>	IgG to <i>T. gondii</i> + CD4 < 100 uL	HZV	Exposure to person with acute HZV
<i>M. avium</i>	CD4 < 50 uL	<i>Candida</i>	CD4 < 50 uL
Influenza virus	All patients	<i>C. neoformans</i>	CD4 < 50 uL
Hep A/B virus	All susceptible patients	<i>H. capsulatum</i>	CD4 < 100 uL and endemic area
<i>S. pneumoniae</i>	All patients	<i>C. immitis</i>	CD4 < 50 uL

- Lifestyle recommendations:
 - **Sexual exposure** (condom use for HSV, CMV, STI + spreading)
 - **Environmental exposure** (healthcare, prisons, homeless shelters, animal care, gardening)
 - **Food exposure** (avoid raw/undercooked eggs, meat, seafood, dairy)
 - **Water exposure** (avoid drinking untreated water, and swimming in lakes/rivers)
 - **Travel exposure** (no live vaccines [except MMR], attention to ETEC)

AHD – What a Clerk Needs to Know About HIV

Importance of HIV

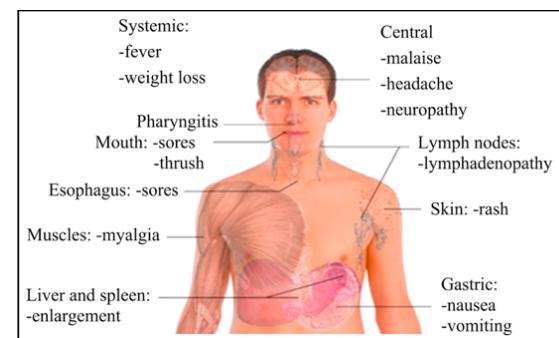
- **1 in 4 people with HIV in Canada don't know they have it.**
 - o Knowing your status and being on treatment is the best way to prevent the spread of HIV to others and avoid any health complications of being diagnosed late.
- There is still a lot of unnecessary **HIV stigma and discrimination.**
 - o This negatively impacts the lives of people living with HIV and discourages people from getting tested, knowing their status and seeking treatment

HIV Infections

- Human: infecting human beings
- Immunodeficiency: Decrease or weakness in the body's ability to fight off infection and illness
- Virus: a pathogen having the ability to replicate only inside a living cell
- HIV Viral load: the amount of HIV in an infected patient's blood
 - o Blood viral load used to monitor the effectiveness of treatment (ARV)
 - o Other bodily fluids not routinely measured; Viral load in the different body fluids are correlated
 - o **As the viral load goes up, the number of CD4 cells goes down** -> weaker immune system
- CD4 Cells are destroyed after HIV uses them to make more HIV
 - o Low CD4 leads to progression of HIV to AIDS

Primary HIV infection

- Symptomatic (50-80 %)
- Early stage of HIV infection 1-4 weeks from initial infection
- Unspecific symptoms (mononucleosis-like):
- HIGHLY infectious because the virus is multiplying rapidly
- HIV test (Antibodies) could be negative
- Very high HIV viral load



Asymptomatic HIV infection

- No symptoms HIV-related, Viral replication mostly in the lymphoid tissue
- CD4 cell count: normal or slightly lower, Lower HIV Viral Load, Gradual evolution over 2-10 years

AIDS

- Because HIV has severely damaged the immune system, body can't fight off opportunistic infections.
- Definition: CD4<200 + Opportunistic infections

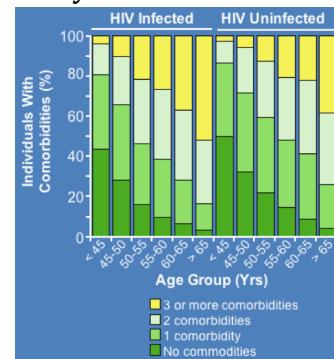
Goals of ARV therapy

- Lower the amount of HIV in the blood; Save CD4 cells and allow the immune system to recover
- After viral load is undetectable, body stops overproduction of CD4 and immune system repairs a bit
- Three Objectives of ARV therapy:
 - o **Biological:** undetectability of HIV in the blood within 3 months
 - o **Personal:**
 - Block the multiplication of HIV in the body
 - Return to symptomless stage
 - Prevent the development of an AIDS stage
 - Prevent the development of other diseases
 - o **Other-focused:** to prevent secondary transmission

- Evolving HIV Treatment landscape
 - o Numerous effective regimens with fewer toxicities, individualized treatment and increased lifespan leading to aging population and increased duration on therapies
 - o Proportion of HIV-positive pts ≥ 50 yrs of age to increase from
 - 28% in 2010 to 50% in 2020 and 73% in 2030
 - o Median age of HIV+ patients on ART will increase from 43.9 yrs in 2010 to 56.6 yrs in 2030

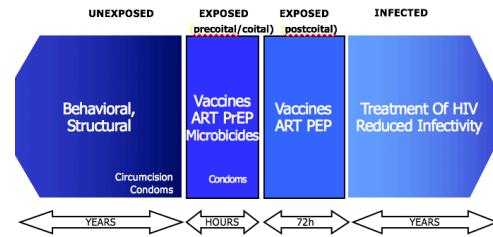
Age and HIV infection

- Comorbidities increase with age and HIV infection
- Age-related non communicable diseases (NCDs):
 - o Cardiovascular diseases (HTN, hypercholesterolaemia, MI and stroke)
 - o Diabetes, Chronic renal Dz, Osteoporosis, Non AIDS-related cancers
- Evolution of the weight of NCDs for HIV + patients:
 - o At least one comorbidity: 29% in 2010 to 84% in 2030
 - o At least 3 comorbidities: 0.3% in 2010 to 28% in 2030
- Increase in polypharmacy in 2030:
 - o 54% of HIV+ pts will be prescribed meds other than ART (increased from 13% in 2010)
 - o 20% will take ≥ 3 meds besides ART, mainly due to CV medications
 - o CV meds + diabetes: 2% in 2010 and 7% in 2030



ART is HIV Prevention

- Four prevention opportunities
 - o Behavioural/structural (unexposed)
 - o Vaccines, ART, PrEP microbicides (exposed precoital/coital)
 - o Vaccines, ART PEP (exposed postcoital)
 - o Treatment of HIV (Infected)
- Blood viral load is associated with the risk of sexual HIV transmission
 - o \uparrow blood viral load \rightarrow \uparrow viral load in semen/vagina/rectum fluids \rightarrow \uparrow risk of sexual transmission
- Early ART led to a **96% reduction of sexual transmission of HIV** in serodiscordant couples
- How do we know that we are at undetectable levels?
 - o With a blood test Being undetectable long term = having an undetectable viral load + taking antiretrovirals daily as prescribed (without forgetting it)
 - o Undetectable = untransmittable
- There is a need for more efficient HIV prevention in men who have sex with men (MSM)
 - o Canada MSM represent 49.1% of new HIV infections annually in Canada
 - o A problem with rectal mucosa: If the transmission probability of receptive anal sex was similar to that associated with unprotected vaginal sex, 5 year cumulative HIV incidence in MSM would be reduced by 80–98%
- PrEP HIV = pre exposure prophylaxis treatment to prevent infection
 - o If HIV enters the body, the antiretrovirals (Truvada®) already present in the body prevents HIV from infecting cells by blocking its replication (multiplication) at a very early stage.
 - o Do not confuse PrEP with post-exposure treatment or prophylaxis (PPE) also known as "emergency treatment" which must be taken within 48 hours after a risk and then every day for a month.
 - o PrEP is for all people > 18 and:
 - Who are not HIV positive, do not use condoms consistently during sexual and are high risk
 - Sex workers
 - People from high prevalence regions (sub-Saharan Africa, etc.) and their partners



- Intravenous drug users
- People with multiple sexual partners
- For serodiscordant couples
- For MSM with at least one of the following criteria:
 - Anal sex without a condom with at least two different sexual partners in the last six months
 - Episodes of ITSS in the last 12 months
 - Use of drugs during sexual intercourse
- Side Effects:
 - 1 in 10 people will have digestive problems (nausea, diarrhea, abdominal pain)
 - 1 in 10 people will have kidney problems with asymptomatic elevated creatinine
 - 1 in 100 people will experience a decrease in bone mineral density

Six statuses from safest to most problematic

- HIV+ Undetectable: 99.99%
- Neg on PrEP: 86-99%
- Neg always safe/ test 3-6 months average: 85%
- Positive and don't know viral load
- Don't know status
- Think negative-proudly assert the status.... Most dangerous and cause high % of epidemic

Abdominal Pain

- Abdo pain can be caused by obstruction, perforation, ischemia, infection, or metabolic disturbances
 - o Abdo pain referred from **viscera** travels via sympathetic nerves (**dull, vague, poorly localized**)
 - o Abdo pain from **parietal** peritoneum produces **sharp, stabbing, well localized** pain

History

- Nause/vomiting common Sx but very nonspecific; Diseases that present with “typical” pain patterns:
 - o **Appendicitis** (vague, cramp-like, moves to RLQ and becomes sharp and intense)
 - o **Biliary Colic** (sever, steady, aching pain in RUQ, pain with meals and often at night)
 - o **Acute Cholecystitis** (persistent abdo pain with fever, can be referred to scapula)
 - o **Pancreatitis** (epigastric/perumbilical location, steady, radiate to back, relieved with sitting)
 - o **Bowel Ischemia** (sudden, severe, Hx of Afib = ++risk arterial embolism)
 - o **Bowel Obstruction** (crampy, midabdo pain in paroxysms, absence of bowel movement/farting, Hx of abdo surger [often caused by adhesions])
 - o **Nephrolithiasis** (gradual and escalating, flank pain radiating to groin or testicles [M])

Physical Exam

- Fever can be seen in both **infectious** and **inflammatory** abdo pain etiologies
- Jaundice suggests hepatitis (absent in cholecystitis unless bile duct blockage)
- Evidence of vascular disease (diminished pulses) should increase suspicion of AAA/ischemia
- Assess **bowel sounds** (absent in pancreatitis/ischemia), **rebound tenderness** (the -itis diseases), **palpable masses** (aortic aneurysms/dilated bowel loop), **DRE** (tenderness, occult blood)
- **Severe pain out of proportion to findings** common in ischemic bowl and pancreatitis

DDx

Diffuse	RUQ	RLQ	LUQ	LLQ	Metabolic
- AAA	- Cholecystitis	- Appendicitis	- Splenic rupture	- Diverticulitis	- Porphyria
- Ischemic bowel	- Biliary colic	- Nephrolithiasis	- Pyelo-nephritis	- -	- Pb toxicity
- Obstruction	- Hepatitis	- Crohn's	-	-	- Withdrawal
- Gastroenteritis	- Pyelo-nephritis	- Pelvic (F)	-	- IBD	- ketoacidosis (DKA)
- Metabolic				- Pelvic (F)	- Mediterr. fever

Diagnostic Evaluation

- Well-appearing patient with signs of gastroenteritis only needs observation
- Acutely ill with peritoneal signs of perforation should go to OR immediately
- AXR may show free air under diaphragm, perforation, bowel obstruction/distension
- Lytes: anion gap acidosis (ischemic bowel, DKA, pancreatitis), HyperK=necrosis (ischemic bowel)
- LFT: elevation in transaminases (Hep), elevation in alkaline phosphatase (cholecystitis)
- Urine sample: hematuria (nephrolithiasis), pyuria (diverticulitis, appendicitis), ketones (DKA)
- Ultrasound: liver/biliary, abdominal (AAA); gall stones from US are not diagnostic of cholecystitis
 - o US cholecystitis finding: gallbladder wall thickening, Murphy sign, pericholecystic fluid
- CT often not needed but sensitive in detecting inflammation (pancreatitis, diverticulitis, appendicitis)
- **Watson-Schwartz** test: elevated levels of porphobilinogen in acute intermittent porphyria

Treatment

- Surgery: appendicitis, ischemic bowel, ruptured AAA, ruptured spleen

Diarrhea

- There are 4 pathophysiological causes of diarrhea that can also be divided into **acute** and **chronic**:
 - o **Increased secretion** (lytes + water), **Increased osmotic load** (more water in intestine), **Inflammation** (protein and fluid exudation), **Altered intestinal motility** (rapid transit times)

History

- Helps best determine if diarrhea is acute or chronic; physical appearance of stool gives clues:
 - o **Watery** (secretory), **Bulky/greasy** (osmotic), **Bloody** (inflammatory)
- Medication Hx important as laxative abuse, drugs, abx, antiHTN, anti-inflammatories cause diarrhea
- Other Hx features: travel, fever, abdo pain, flatulence, extraintestinal Sx, rash, weight loss, edema

Physical Exam

- Degree of hydration, presence of abdominal tenderness, rectal mass, blood, bowel sounds

DDx

Increased Secretion	Increased Osmotic Load	Inflammation	Altered Mobility
- Enterotoxin bacteria	- Sorbitol ingestion	- Ulcerative colitis	- Thyrotoxicosis
- Gastroenteritis	- Bile salt malabsorption	- Crohn's	- IBS
- Carcinoid syndrome	- Pancreatic insufficiency	- Radiation-induced enteritis	- Neurologic disease
- VIPoma	- Lactase deficiency	- Gastroenteritis	
- Cillous adenoma	- Celiac/Gluten intolerant	- Cytotoxic bacteria	
	- Mg-containing laxatives		

Diagnostic Evaluation

- Acute diarrhea is often infectious and if well, tests (culture) may not need to be performed
- Stool exam if: high fever, dehydration, septic, bloody stool, recent abx, immunocompromised, travel
 - o Blood in stool suggests: **SSCYE** organisms, ulcerative colitis, Crohn's; stool should be cultured
- Chronic diarrhea is not usually inflammatory (except IBD); assess change of stool with fasting
 - o **Osmotic** diarrhea **improves** with fasting, **Secretory** diarrhea persists with fasting
- Endoscopy (sigmoidoscopy/colonoscopy) + biopsy can reveal diagnostic findings:
 - o Inflammatory pathology(IBD); *Melanosis coli* (laxative abuse); pseudomembranous colitis (*C. diff*)
- If osmotic diarrhea is suspected, some studies can reveal **malabsorptive** syndromes:
 - o Schilling test/Bile salt breath (ileum), Pancreatic secretions, Lactose challenge, IgA titers (celiac)
- When diagnostic tests fail to find source, IBS should be suspected -> Rome criteria:
 - o Abdo pain for at least 3d/mo x 3mo with 2 or more of:
 - Relieved with defecation, Change in frequency of stool, Change in form of stool

AHD – Dysphagia

Dysphagia

- **Dysphagia** is difficulty with eating
 - o **Deglutition** is the act of swallowing
 - o Cortex -> brainstem (solitary tract nucleus, CN V, VII, IX, X, XII) -> sequence of deglutition)
- Pharynx, soft palate, tongue, epiglottis are the voluntary-striated muscles
- Upper esophageal sphincter (UES) starts peristalsis (involuntary sequence of excitatory and inhibitory nerve pulses) moves food/liquid to body of esophagus to LES
- **Oropharyngeal** dysphagia: coughing/regurgitation, +/- weight loss (problem in voluntary area)
- **Lower Esophageal** dysphagia: Sx overlap with oropharyngeal but patient can't tell where problem is; usually have heartburn, weight loss odynophagia, impaction of food/foreign bodies

Causes of Oropharyngeal Dysphagia

Structural lesions	Cranial Nerve Diseases	Neuromuscular Diseases	Skeletal Muscle Disease (con')
Intrinsic pharyngo-esophageal Lesions	Diabetes mellitus Recurrent laryngeal nerve palsy Transection or injury Diphtheria Rabies Lead poisoning Other neurotoxins	Central Nervous System Diseases Stroke Parkinson's disease Brainstem tumor Amyotrophic lateral sclerosis Other motor neuron diseases Spinal cord injuries Huntington's chorea Tabes dorsalis Poliomyelitis Spinocerebral degeneration Syringobulbia Progressive bulbar paralysis Alzheimer's disease	Muscular dystrophies Oculopharyngeal muscular dystrophy Myotonia dystrophica Other muscular disorders Hyperthyroidism Myxedema Stiff-man syndrome Criopharyngeal Dysfunction Other Disorders Myasthenia gravis Amyloidosis Botulism Mitochondriopathies Miscellaneous Xerostomia Medications
Esophageal carcinoma Benign esophageal lesions Esophageal web Zenker's Diverticulum High esophageal stricture Inflammatory disease Post surgical change Foreign body Cervical lymphadenopathy Vascular anomalies Diffuse idiopathic skeletal hyperostosis	Skeletal Muscle Disease Inflammatory myopathies Polymyositis/dermatomyositis Scleroderma Mixed connective tissue disease		

Lower Esophageal Dysphagia

- Mechanical obstructing lesions
 - o Benign strictures, inflammation, swelling (GERD), cancer, congenital atracia, vascular malformations, bolus/impactions
- Dysmotility: lack of peristalsis (scleroderma), abnormally high LES tone
- Squamous cell Carcinoma: < 50, smokers, EtOH, black, decreasing incidence
- Adenocarcinoma at GE junction: >50, obese, heartburn/reflux, increasing incidence
- Food impaction: sudden onset, painful, drooling, **EMERGENCY**

Approach

- Hx: Meds, surgical Hx, radiation Hx, smoking/EtOH, heartburn, reflux
- PE: ENT for masses/inflammation; Neck for lymph nodes, thyroid; lung for aspiration
- Labs: CBC and LFT to start
- Investigations:
 - o CXR (only helpful in foreign body impaction)
 - o Barium swallow: **useful** in oropharyngeal cases; **DO NOT USE IN IMPACTION**
 - o Endoscopy: diagnostic and therapeutic aspect
 - o Manometry: when Ba swallow/endoscopy fails to identify cause, or confirm motility problem
 - ↓ Peristalsis: presbyesophagus, neuromuscular disease
 - ↑ LES tone: aperistalsis, spontaneous, contractions, achalasia (bird beak)
 - ↓ LES tone: scleroderma
 - ↓ LES tone with normal peristalsis – GERD

- ↑ Esophageal contractions: corkscrew esophagus, nutcracker esophagus (high amplitude)
 - Usually present with non-cardiac/atypical chest pain

Practice MCQ questions

1. What disease is characterized by ↑ LES pressure and lack of peristalsis in body of esophagus
 - a. Diffuse esophageal spasm
 - b. Scleroderma
 - c. Nutcracker/Jackhammer esophagus
 - d. Achalasia
2. What disease is characterized by ↓ LES pressure lack of peristalsis
 - a. GERD
 - b. Scleroderma
 - c. Heller's myotomy, post-operative
3. Radiologic features of Achalasia may include (choose all that apply):
 - a. Tight GE junction
 - b. Dilated Esophagus
 - c. Tortuous "sigmoid-like" esophagus
 - d. Lack of peristalsis
4. Food impaction is treated with which of the following
 - a. Meat tenderizers
 - b. Antispasmodic medications IV
 - c. Barium swallow to localize the bolus
 - d. Urgent esophagoscopy
5. Non-cardiac chest pain is a feature of which of the following (choose all that apply):
 - a. Nutcracker contractions in the esophagus
 - b. Food bolus impaction
 - c. Trauma to chest wall
 - d. Mediastenitis

Answers

d, b, all, d, all

Dyspepsia

- Peptic Ulcer Disease (PUD) and GERD are common and important causes of dyspepsia
- Gastritis is Inflammation of the gastric mucosa, it can be acute or chronic
 - o Acute is commonly due to direct mucosal injury (NSAID, EtOH, steroids, acidic/alkaline agents)
 - o Chronic is characterized by mononuclear infiltrates and lack of mucosal erosion
- **Ulcers** are focal areas of deep erosion through mucosa/submucosa; common in stomach/duodenum
 - o Duodenal ulcer: EXCESS gastric acid; Gastric ulcer: NORMAL gastric acid; *H. pylori* assoc. in both
- **GERD** is from gastric content movement into esophagus; can be from physiologic or pathology
- RF for PUD: *H. pylori*, male, stress, NSAID, steroids, cigarette; Gastritis same RF except *H. pylori*
- RF for GERD: obesity, cigarettes, caffeine, chocolate, alcohol, hiatal hernia
- Functional dyspepsia = dyspepsia with no biochemical or structural causes

History

- Patients usually present with **epigastric** pain
- PUD: gnawing, burning or aching pain; duodenal -> pain **after** food; gastric -> pain **with** food
- GERD: retrosternal pain, sensation of reflux of gastric contents in mouth (acid taste)
- Gastritis: less prominent pain, occult or gross GI bleeding (melena/hematemesis)
- Nonspecific GERD/PUS Sx: nausea, vomiting, emesis +/- blood, melena, back/shoulder pain

Physical Exam

- Epigastric tenderness, sound of air/fluid in distended stomach, rigid abdomen, diminished bowel sounds, rebound tenderness (perforation), occult blood on rectal exam

DDx

- Besides GERD, PUD, gastritis; DDx: pancreatitis, myocardial ischemia, cholecystitis

Diagnostic Evaluation

- Peptic ulcers documented with radiographic studies (barium swallow) and endoscopy
- Gastritis documented with endoscopy;
- GERD by esophageal manometry or pH monitoring; endoscopy in chronic (Barrett esophagus)
- *H. pylori* Dx: culture biopsy (gold standard), serology, direct urease test (biopsy), urease breath test
- Early endoscopy for patients with **alarm Sx**: GI bleed, iron-deficient anemia, unexplained weight loss, dysphagia, recurrent vomiting, epigastric mass

Treatment

- Medical treatment of PUD and gastritis is for symptoms and healing acceleration
- Removal of insulting agent, avoidance of NSAIDs, aspirin, cessation of smoking
- GERD treated symptomatically with antisecretory agents; Empiric treatment often before Dx
 - o **H₂-receptor antagonists** limit basal and stimulated acid secretion (EMPIRIC TREATMENT)
 - o **Antacids** neutralize gastric acid and provide prompt symptom relief (EMPIRIC TREATMENT)
 - o **Proton Pump Inhibitors** are potent acid antisecretory agents
 - o **Sucralfate** protects mucosa without significant antacid effect
- *H. Pylori* common cause of PUD so treated with abx (clarithromycin and amoxicillin)
- If PUD persists after medical treatment, surgery can be performed (rare, usually in malignancy)
- Functional dyspepsia may respond to antisecretory agents, antidepressants (controversial)

Inflammatory Bowel Disease

- IBD is idiopathic, chronic, inflammatory conditions of the bowel; two types have different features

Ulcerative Colitis (UC)	Crohn Disease (CD)
<ul style="list-style-type: none"> - Involves only the colon, 95% rectum also - Disease limited to mucosa (superficial) - Uniform continuous involvement of affected areas 	<ul style="list-style-type: none"> - Any part of GI tract (mouth to anus) - 30% small bowel, 30% large, 40% both, 50% rectum - Disease may involve entire bowel wall (transmural) - Diseased bowel separated by healthy (skip lesion)

- Increased relative risk in first-degree relatives suggests genetic predisposition (*NOD2*) of IBDs
- Pathophysiology (inflammation, granulomas) supports dysregulated immune response in IBD
- Inappropriate inflammation + immune response suggests genetic + microbiota reactions

History

- UC: bloody diarrhea, abdo pain, painful urgency to poo, Travel Hx (ETEC), recent abx (C diff)
- CD: similar but pain more cramp-like + **fever** and **weight loss**; Acute ileitis can mimic appendicitis
- IBS: similar Sx to UC and CD but often prolonged, **no bleeding/weight loss**, Sx relieved by pooping

Physical Exam

- Vital sign abnormalities only in severely ill patients; nonspecific signs: uveitis, arthritis
- Abdo exam: tenderness, if **REBOUND TENDERNESS** consider **appendicitis or perforation**
- CD may have fullness, palpable masses (bowel adherences), rectal fistulas (perirectal abscess)
- Skin: **pyoderma gangrenosum** (trunk ulcer), erythema nodosum (legs), aphthous ulcers (mouth)

DDx

- If lower GI bleed: diverticulosis, colon cancer or polyps, AV malformations, hemorrhoids
- Bloody diarrhea: infectious **SSCYE**; In **Elderly** patient consider these + diverticulitis, ischemic bowel

Diagnostic Evaluation

- Initial: CBC, serum albumin, alkaline phosphatase for inflammation (leukocytosis + ↑ sediment rate)
 - o ↓ albumin -> malabsorption; ↑ alkaline phosphatase -> liver disease (common in IBD)
- Hepatobiliary dis. in IBD: Sclerosing cholangitis(UC), Cholelithiasis(CD), fatty liver, autoimmune Hep.
- **Perinuclear antineutrophil cytosplasmic antibody** -> ulcerative colitis
- **Anti-Saccharomyces Cerevisiae antibody** -> Crohn's disease
- Dx made with sigmoidoscopy/colonoscopy + biopsy showing: **erythematous, friable mucosa** +:
 - o UC: regeneration of mucosa around disease (**pseudopolyps**), **crypt abscesses** (histopathology)
 - o CD: longitudinal ulcerations (**cobblestone**), **granuloma** formation (histopathology)

Treatment

- UC has relatively benign course; CD often relapsing; Medical therapy first (both); surgery indications:
 - o Intractable disease, obstruction, perforation, prophylactic resection to prevent cancer (UC)
 - o Removal of colon cures UC (patient left with colostomy), surgery in CD **never curative**
- **Sulfasalazine** and **5-ASA** 1st line treatment for UC, less effective in CD (no effect in small bowel)
 - o Side effects of Sulfasalazine: Nausea, headache, anaphylaxis, hepatitis, bone marrow suppression
- Prednisone used in moderate-to-severe IBD (not effective at maintaining remission)
- Immunomodulators(methotrexate, cyclosporin A, Azathioprine) maintain remission and ↓steroid use
- **Metronidazole** (abx) can help control mild CD and help heal perianal disease; No abx in UC
- Complications: CD (**enteric fistulas** **bowel obstruction**), UC (**toxic megacolon**, **colon carcinoma**)

AHD – The Liver and Liver Function Tests

Complications of Liver Injury

- Acute: Acute hepatitis, acute liver failure (dysfunction, brain edema, infection)
- Chronic
 - o Chronic Hepatitis
 - o Cirrhosis: hepatoma, portal HTN (ascites, varices, hepatic encephalopathy), ↓ synthetic function (coagulopathy, thrombosis, ↓ opsonisation, hypoglycemia)

Hepatic functions

- Synthesis and secretion of **albumin, cholesterol, alpha1-antitrypsin**
- Excretion of **bilirubin**; drug metabolism
- Main enzymatic functions:
 - o Amino acid/protein synthesis and degradation; carbohydrate and lipid metabolism
 - o Coagulation factors, bilirubin excretion, storage of vitamins and minerals
 - o Hormone production (IGF-1), thrombopoietin production, urea cycle
- Phases of Drug metabolism in the liver:
 - o Phase 1: REDOX reactions, CYP450, Polar products
 - CYP450 enzymes: 1A2, 2C9, 2D6, 2E1 (EtOH/acetaminophen), 3A4
 - o Phase 2: conjugation with glucuronic acid, sulfate, or glutathione
 - o Other: Acetylation

Liver Tests

- Blood tests: markers of injury (enzymes), function (bili, alb, INR, Cr), etiology (serology, molecular)
- Imaging: US, CT, MRI, Nuclear medicine; Procedures: Angiography, ERCP, Biopsy, fibroscan
- **Serum Aminotransferases** (Release of already synthesized enzymes in liver injury)
 - o **Aspartate** (AST): Normal < 35 IU/L; cytosolic/mitochondrial enzyme, also in muscles/kidneys
 - o **Alanine** (ALT): Normal < 45 IU/L; cytosolic enzyme, mostly only in liver
- Classification of abnormal liver enzymes (ULN = upper limit of normal):
 - o $R = (\text{ALT} / \text{ALT_ULN}) / (\text{ALP} / \text{ALP_ULN})$; $R > 5 \rightarrow \text{hepatocellular}$; $R < 2 = \text{cholestatic}$; $2-5 = \text{mixed}$
- **Alkaline Phosphatase** (ALP): Normal < 110 IU/L; present throughout body; Elevation in serum from:
 - o Increased synthesis from hepatocytes and release from canalicular cell membranes
 - o Canaliculus leakage into sinusoid when tight junctions are leaky or bile acid mediation
- **Gamma Glutamyl Transferase** (GGT): Normal < 45 IU/L; Elevation can be ubiquitous, or induced
 - o Often used to confirm elevation of **ALP** to confirm hepatobiliary origin
- **Albumin**: Normal 38 g/L; most important plasma protein, 12-15g/d synth by liver, ↓ concentration in hepatic insufficiency
- **Coagulation factors**: Normal 1.0; Clotting factor proteins made in liver (not VIII); measure PT or INR
 - o Increased PT or INR in hepatic insufficiency

Bilirubin

- **Bilirubin**: end-product of heme metabolism; balance of production/elimination; bili > 50 = jaundice
 - o 2/3 hemoglobin, 1/3 other hemoprotein turnover
 - o Heme \rightarrow biliverdin-IX α (heme oxygenase); Biliverdin \rightarrow bilirubin-IX α (biliverdin reductase)
- Transport:
 - o **Conjugated** bilirubin is **water** soluble, filtered by glomeruli, accounts for **jaundice**
 - o **unconjugated** bilirubin is **lipid** soluble, binds to albumin
- Uptake:

- Carrier mediated, bidirectional for both un- and conjugated bilirubin
- Protein bound intracellularly carried to ER for conjugation
- bilirubin-IX α -> water soluble bilirubin for biliary excretion
- Excretion:
 - Secretion of conjugated bilirubin in canalicular lumen against concentration gradient by membrane carrier MRP2
 - No metabolism in small intestine
 - Bilirubin hydrolyzed -> urobilinogen (bacterial β -glucuronidases)
 - Absorbed urobilinogen excreted by liver into bile, eliminated in stool + small amount in urine
 - **Stercobilin (brown for poo), urobilin (yellow for pee)**
 - Urobilinogen reflects total body catabolism
- Van den Bergh reaction
 - Direct bilirubin (reacts within 30 sec)
 - Total bilirubin (half-life 4 hours)
 - Indirect bilirubin = Total bili – Direct bili
 - Delta bilirubin (measured by liquid chromatography) = bilirubin covalently bound to albumin (half-life 14 to 21 days)

DDx of Liver problems

- Hepatobiliary vs. Other => Biliary vs. Hepatic => Acute vs. Chronic
- Liver Disorders:
 - Viral Hepatitis (Hepatitis A,B,C,D,E); Fatty liver disease (ALD, NAFLD, storage disorder)
 - Autoimmune, metabolic (Wilson's), drug induced

Staging Liver Fibrosis

- Blood tests:
 - Fibrotest: haptoglobin, bili, GGT, apolipoprotein A-1, alpha-2-macroglobulin
 - APRI: AST/platelets
 - FIB4: age, AST, ALT, platelets
 - NAFLD fibrosis score: age, BMI, AST, ALT, platelets, Albumin, DM

Hepatitis

- Hepatitis is inflammation of liver parenchyma; it is acute or chronic (>6 mo); viral most commonly

Virus (type)	Transmission	Chronic %	Lab markers - Acute (bold), Chronic (<i>italics</i>)
HAV (ssRNA)	Fecal-oral	None	HAV antigen, anti-HAV , RNA
HBV (dsDNA)	Parenteral, sex, anal	2-7	HBsAg , HBeAg, anti-HBcAg , anti-HBeAg, HBV DNA
HCV (ssRNA)	Parenteral, sexual	50-70	HC antigen, anti-HCV
HDV (ssRNA)	Parenteral, sexual	5-80	HDV antigen, anti-HDV (HDV needs HBV to work)
HEV (ssRNA)	Fecal-oral	None	HEV Ag, anti-HEV

- Hepatic injury is due to **host immune response** to infected cells, viruses (except hep C) not cytotoxic
- Other non-hepatitis viruses that cause hepatic damage: CMV, HSV, Coxsackie viruses,
- Drugs that cause chronic hep: Acetaminophen, Halothane, Isoniazid, Methyldopa, Azole antifungals
- Alcohol can cause severe hepatitis (**alcoholic fatty liver**) that becomes **cirrhosis**
- Hereditary sources: **autoimmune chronic active hepatitis** (ACAH), Wilson Dz., hemochromatosis

History

- Acute hepatitis presentation: jaundice, dark urine (bilirubin), RUQ abdo pain, fever, nausea/vomiting
- Other Sx: fatigue, malaise, headache, myalgias, arthralgias; mild cases may be asymptomatic
- **Severe fulminant acute hepatitis** have Sx of **liver failure**: encephalopathy, coagulopathy, ascites
- Chronic hepatitis: insidious, Dx suspected with poor LFTs; often has liver cirrhosis/end-stage disease

Physical Exam

- Acute hepatitis: jaundice, hepatomegaly (tender), splenomegaly, adenopathy +/- ascites, asterixis
- Chronic hepatitis: often unrevealing unless significant hepatic impairment

DDx

- Acute: between above sources and toxic: biliary tract disease, drug-induced cholestasis/hepatotoxin
- Chronic: chronic biliary tract disease, non-alcoholic steatohepatitis

Diagnostic Evaluation

- Labs for ↑ **aminotransferases** (AST and ALT), albumin, ammonia, prothrombin time
 - o Viral hepatitis has greater absolute elevation of AST and ALT; aided by serologic tests
 - o In alcoholic hepatitis, serum AST is ↑ out of proportion to ALT ->AST/ALT > 2
- See chart for **acute** and **chronic** viral serology markers; if HBsAg present test for anti-HDV
- Presence of HBsAb indicates **distant resolved infection of HBV** or **successful immunization**
 - o Chronic HBV patients cannot develop this protective measure; anti-HCV is NOT protective
- If ACAH suspected (chronically ↑ AST, ALT + no serology for viruses), perform autoantibody titer:
 - o Antinuclear, antismooth muscle, anti-liver-kidney microsomal, and anti-cytokeratin antibodies
- Percutaneous liver biopsy for histology if above fail to get Dx

Treatment

- No good specific therapies for acute hepatitis, watchful waiting with labs; glucocorticoid for ACAH
- Interferon- α for chronic HBV/HCV (helps since it is due to insufficient immune response)
 - o Side effects: fatigue, nausea, fever; contraindicated in decompensated liver disease
- End-stage liver disease from fulminant acute hepatitis/chronic hepatitis treated with liver transplant
- Prophylaxis: HAV/HBV vaccine, HBV immune globulin (postexposure prophylaxis); **NO HCV vaccine**

Hepatic Cirrhosis

- Cirrhosis is irreversible liver damage with loss of normal function, fibrosis and regenerative nodules
 - o Normal func.: make protein, filter mesenteric blood, metabolise endogenous/exogenous subs.
- Causes: alcohol, chronic HBV/HCV, biliary and cardiac disease, ACAH, genetic, nonalcoholic fatty liver
 - o **Hemochromatosis:** autosomal recessive with ↑ Fe absorption and deposition in organs
 - o **Wilson disease:** autosomal recessive with ↑ Cu excretion and accumulation in liver/brain
 - o **α_1 -Antitrypsin deficiency:** autosomal recessive -> early emphysema, asymptomatic cirrhosis
- **Ascites:** fluid accumulation in peritoneum from portal HTN ($\uparrow P_{\text{Capillary, hydrostatic}}$), \uparrow Na reabsorption, and hypoalbuminemia ($\downarrow P_{\text{plasma, oncotic}}$); predisposes to **spontaneous bacterial peritonitis (SBP)**
- **Esophageal varices (EV)** from portal HTN that is transmitted to veins in gastroesophageal junction; usually present as painless massive hematemesis or melena; confirmed with endoscopy
- **Hepatic Encephalopathy (HE):** \uparrow NH₃ levels, leads to confusion, personality changes, asterixis, coma

History

- End-stage liver disease (ELD) may present without specific complaints besides fatigue and malaise
- Failure of liver function may present with leg edema, easy bruising, \uparrow abdo girth, hematemesis
- Get alcohol Hx, Hx of hepatitis/RF for hepatitis, FHx of inherited diseases (tough since most are AR)

Physical Exam

- Liver can be enlarged, normal, small depending on stage; if palpable, usually firm
- Bulged flanks, shifting dullness (ascites), splenomegaly, in. hemorrhoids, caput medusae (portalHTN)
- Skin: jaundice, spider telangiectases, clubbing, palmar erythema, permanent flexion of metacarpal 3,4

DDx

- In the patient with ascites, consider: abdo malignancy, nephrotic syndrome, cardiac failure

Diagnostic Evaluation

- Lab findings: HypoNa (\downarrow ADH), \downarrow BUN (\downarrow protein production), \downarrow albumin, \uparrow bilirubin (mostly direct)
- Lab (blood): \uparrow PT, macrocytic anemia (\uparrow RBC membrane in liver), thrombocytopenia
- Genetic etiologies test: \uparrow ferritin (hemochromatosis), \downarrow ceruloplasmin (Wilson), \downarrow α_1 -antitrypsin
- New ascites should get **paracentesis** to r/o infection and calculate **serum ascites-albumin gradient**
 - o SAAG < 1.1 mg/dL: malignancy, TB, pancreatitis, Nephrotic syndrome
 - o SAAG > 1.1 mg/dL: cirrhosis (portal HTN), liver metastases, Budd-Chiari syn., cardiac myxedema
- An absolute polymorphonuclear count > 250 cells/ml is consistent with SBP

Treatment

- Alcohol abstinence is most important; prognosis following complications given by Child-Pugh score:

Points	Bilirubin (mg/dL)	Albumin (g/dL)	Ascites	Encephalopathy	PT (s)
1	< 2.3	> 3.5	None	None	< 4 , INR < 7
2	2.3-2.9	3.0-3.5	Easily controlled	Mild	4-6, INR 1.7-2
3	> 3.0	< 3.0	Poor control	Advanced	> 6 , INR > 2

- Model for ELD score (MELD) for prioritizing transplant patients; indicated with severe complications
- Tx **Ascites:** restrict Na, K-sparing diuretic +/- Lasix, large Vol paracentesis, peritoneovenous shunt
 - o Ascites complication: SBP due to \downarrow albumin + protein in fluid; treat empirically (gram - abx)
- Tx **Esophageal varices:** replace blood products, IV vasopressin analogs, ligation of EV
- Tx **Encephalopathy:** Fix precipitating factors, Lactulose (\downarrow NH₃ absorption), Neomycin (broad abx)
- Shunts reserved for refractory cirrhosis or recurrent EV bleeds; Cirrhosis major RF for cancer (HCC)

Cholestatic Liver Disease

- Obstruction of bile flow from liver is **cholestasis**; classified as **intrahepatic** or **extrahepatic**
 - o **Primary biliary cirrhosis** (PBC) [F > 50]; **Primary sclerosing cholangitis** (PSC) [M]
- PBC and PSC have autoimmune etiology; PSC associated with IBS (UC);
- Cholestasis associated drugs: erythromycin, estrogen, anabolic steroids, sulfonamides
- Extrahepatic obstruction is usually mechanical: bile duct stones/stricture, tumours, etc.

History

- Sx (**cholestasis**): pruritus, fatigue, steatorrhea, jaundice; fat soluble vitamin malabsorption (A,D,E,K)
- Patients with **pancreatic carcinoma** have triad of **jaundice, weight loss, back/abdo pain**
- Extrahepatic Sx (**ascending cholangitis**): fever, chills, RUQ pain, jaundice, nausea, vomiting

Physical Exam

- In early disease, PE is normal; jaundice and scleral icterus appear later; splenomegaly, ascites, telangiectasia, and lower extremity edema are signs of cirrhosis or advanced PBC/PSC

DDx

Differentiation from Jaundice	Extrahepatic obstruction	Intrahepatic obstruction
<ul style="list-style-type: none"> - Hepatocellular injury - Hemolysis - Acute/chronic pancreatitis - Gilbert Disease 	<ul style="list-style-type: none"> - Pancreatic carcinoma - Cholangiocarcinoma - Parasitic infections - Bile duct strictures - Choledocholithiasis 	<ul style="list-style-type: none"> - PBC (also extrahepatic) - PSC (also extrahepatic) - Drug reaction - Viral hepatitis - Nonalcoholic steatohepatitis

Diagnostic Evaluation

- ↑ alkaline phosphatase (can be from bone disease so confirmed with GGT for hepatic source)
- ↑ (direct, conjugated) bilirubin -> suggests advanced obstruction; mild ↑ AST, ALT (not in viral Hep)
- With evidence of cholestasis determine extrahepatic vs. intrahepatic; start with ultrasound (US)
 - o Bile duct dilatation suggests extrahepatic obstruction but may not occur for 24h+
- Extrahepatic: cholangiogram (localization), **endoscopic retrograde cholangiopancreatography**
- Abdo CT: visualize bile ducts if US inadequate, pancreatic masses, bile duct stones, stage cancer
- With no bile duct dilation, blood tests +/- biopsy for diagnosis:
 - o **Antimitochondrial antibody** (PBC), **perinuclear, antineutrophil cytoplasmic antibody** (PSC)

Treatment

- In general, intrahepatic is medical, extrahepatic requires intervention
- **Intrahepatic:** Remove toxic agent (drugs); **ursodiol** (PBC), ↓ LFT problems and delays transplant
- **Extrahepatic:**
 - o ERCP preferred method of stone extraction; sometimes surgery needed
 - o **Cholestyramine** used for Sx control of pruritis in long standing cholestasis
 - o Treat vitamin deficiency to prevent complications: Vitamin D (osteoporosis, hypoCa), Vitamin A (night blindness), Vitamin K (increased Prothrombin time), Vitamin E (ataxia, neuropathy)
- Since PSC occurs young and progresses, patients with ELD should consider transplantation

Pancreatitis

- Consequence of inappropriate activation of enzymatic precursors causing organ autodigestion
- **Alcohol and gallstones** are common causes; direct injury, viral infection, metabolic are less common
- **Pancreas divisum**: congenital abnormality where dorsal/ventral buds don't fuse so the main pancreatic duct drains through the minor papilla; role in pancreatitis heavily debated

History

- Sx: **severe abdominal pain** (epigastric), steady, boring, radiates to back, nausea, vomiting

Physical Exam

- Abdo exam is usually less impressive than pain but tenderness and rebound are present
- VS abnormalities (hypoTN, tachycardia) suggest volume depletion; high fever suggests infection
- Other findings: Erythematous skin nodules, dullness to percussion, ↓ breath sounds, blue periumbilical discoloration (Cullen sign), bruising on flanks (Grey-Turner sign)

DDx

- Distinguish from other diseases associated with abdo pain especially those with ↑ amylase (*)
 - o Perforated Viscus*, Cholecystitis*, bowel obstruction*, mesenteric ischemia*, ectopic pregnancy*
 - o Dissecting aneurysm, renal colic, diabetic ketoacidosis,

Diagnostic Evaluation

- ↑ **Serum amylase** is most **sensitive** test (↑ 6-12 hours of Sx); ↑ **Serum lipase** ↑ accuracy of diagnosis
 - o Amylase levels do not predict severity but higher levels are more **specific** to pancreatitis
- Amylase is NOT used to monitor disease; other findings that are helpful:
 - o ↑ hematocrit, ↑ WBC (nonspecific), hypoCa, ALT > 3x normal, Hyperbilirubinemia, Hypoxemia,
 - o High triglycerides may make amylase levels falsely normal in acute pancreatitis
- AXR can rule out other causes such as perforation or obstruction; dilated ileus (nonspecific AXR sign)
- Abdominal US useful for cholelithiasis and to rule out biliary obstruction
- Abdominal CT + contrast or MRI has high sensitivity for disease; usually reserved for complex cases

Treatment

- Pancreatitis ranges from self-limited fulminant organ failure/death; assess with Ranson criteria:
 - o **Admission:** Age >55, WBC >16,000, LDH >350 IU/mL, SGOT >250 IU/mL, Glucose >200mg/dL
 - o **Within 48h:** Hct >10% ↓, BUN ↑ >5 mg/dL, PaO₂ < 60mmHg, Ca < 8 mg/dL, Base deficit >4
 - o Patients with < 3 Ranson criteria have low mortality; 6 or 7 have extremely high mortality
- After establishing Dx treatment plan:
 - o Correction of underlying causes/factors (discontinue suspected drugs, ERCP if from gallstones)
 - o IV fluids with monitoring of vitals; analgesics (NOT MORPHINE); food restriction (no food x 3d)
- Use of prophylactic abx not suggested in current guidelines
- Mortality from pancreatitis usually from infection or multiorgan system failure; other causes:
 - o **Pancreatic abscess/infected necrosis:** suspect if fever continues, Dx with CT; Tx: aspiration
 - o **Pancreatic pseudocyst:** suspect if palpable mass + abdo pain stays, Dx with CT, Tx: self-limited
 - o **Chronic Pancreatitis:** from alcohol-induced pancreatitis; Dx with ERCP, Tx: symptomatic

Colorectal Cancer

- Colorectal is third in incidence and second in mortality -> important to screen, Dx, and Treat
- Current hypothesis: colorectal cancers (CRC) arise from pre-existing benign adenomatous polyps
 - o **Adenomas** are neoplastic lesions; classified as **tubular** (80%), **tubulovillous**, or **villous**
 - o **Adenomatous polyps** are premalignant lesions; RF for malignancy: ↑ size, villous histology
- Neoplastic transformation believed to be DNA damage from endogenous and exogenous agents
- RF: Hx of adenomatous polyps, IBD (UC > CD), familial disorders, Hx of cancer, FHx of CRC
- Dietary RF: red meat, low fiber, obesity, ethanol, refined sugar, cigarettes

History

- Often asymptomatic until metastatic disease; when present main symptoms of CRC:
 - o GI bleeding, change in bowel habits, abdominal pain, anorexia/weight loss

Physical Exam

- Often insignificant findings, mass may be found on abdominal palpation or on DRE (uncommon)

Diagnostic Evaluation

Test	Characteristics	Advantages	Disadvantages
FOBT	<ul style="list-style-type: none"> - 50% sensitivity/specificity - Certain foods give false + - Can have false - 	<ul style="list-style-type: none"> - Inexpensive, easy 	<ul style="list-style-type: none"> - Not great sens/spec - Does not localize upper vs. lower GI
FIT	<ul style="list-style-type: none"> - Detect Hb directly - More specific than FOBT 	<ul style="list-style-type: none"> - Inexpensive, easy, more spec than FOBT 	<ul style="list-style-type: none"> - Less sens. for early adenomas than imag.
Sigmoidoscopy	<ul style="list-style-type: none"> - Imaging up to sigmoid colon 	<ul style="list-style-type: none"> - Direct visualization - Safer than colonoscopy 	<ul style="list-style-type: none"> - Inability to show lesions in prox. colon - Lower sens than BE/colono.
Barium enema	<ul style="list-style-type: none"> - Sens of 80-90% for lesions > 1 cm, 50-75% if < 1cm 	<ul style="list-style-type: none"> - Visualization of prox. and distal colon 	<ul style="list-style-type: none"> - No ability to remove lesion
Colonoscopy	<ul style="list-style-type: none"> - Gold standard for Dx - Sens of 95% + 	<ul style="list-style-type: none"> - Visualization of prox/distal colon + biopsy 	<ul style="list-style-type: none"> - High cost, ↑ risk to patient, uncomfortable
CT colonoscopy	<ul style="list-style-type: none"> - CT reconstruction of colon 	<ul style="list-style-type: none"> - Noninvasive 	<ul style="list-style-type: none"> - less sens. than colonoscopy for small lesions
Fecal DNA	<ul style="list-style-type: none"> - Detect characteristic mutations for CRC 	<ul style="list-style-type: none"> - Noninvasive 	<ul style="list-style-type: none"> - Precise role in screening unclear

Treatment

- Large focus on primary prevention (screening); If neoplasms treated, monitoring recurrence is key
- If polyps or carcinoma in situ are detected they are removed with excisional biopsy
- Colectomy is Tx for invasive cancer + chemotherapy/radiotherapy

Risk Factor	Recommendation
None	Start age 50; annual FIT, DRE; sigmoidoscopy q 3-5y OR colonoscopy q 10y
Ulcerative Colitis	Colonoscopy after 8-10y of disease; colonoscopy q 1-2y
Adenomatous polyp	Colonoscopy q 3-5y after removal, 1-3 if multiple or villous polyps
Familial polyp disorder	Genetic counselling +/- screening; sigmoidoscopy age 20
Familial nonpolyp disorder	Genetic counselling; colonoscopy age 35-40 (or 10y before Dx of relative)
Positive FHx	Screening as average risk; consider BE or colonoscopy

Weight Loss

- Pathologic weight loss is due to alterations of the balance of dietary intake and metabolic output
 - o Intake is linked to appetite, controlled by hypothalamus; GI peptides, Leptin suppresses appetite;
 - o Metabolic output is linked to basal metabolic needs (temperature, physical activity, digestion)
- Causes of involuntary weight loss categorized based on effect of intake or output:
 - o **Decreased Intake:** "Five Ds" in the elderly, depression, dementia, dentition, dysgeusia, drugs; malignancy, CHF, CKD, advanced HIV can also cause anorexia; anorexia nervosa (psychiatric)
 - o **Decreased Absorption:** amyloidosis, pancreatic insufficiency, celiac, parasite, cholestasis
 - o **Accelerated Metabolism:** hyperthyroid, chronic infection, malignancy, pheochromocytoma
 - o **Accelerated Caloric Loss:** nonmetabolic losses i.e. vomiting, diarrhea, diabetic glucosuria

History

- Loss of appetite and dietary Hx important in all patients; Travel Hx in all patients (parasites)
- Patients with weight loss from ↑ metabolic demand usually describe ↑ appetite and consumption
- Medications should be reviewed to look for those that affect appetite
- GI and lung cancer are common malignancies associated with decreased appetite so screen for Sx
- Patient with malabsorption report increase flatulence, steatorrhea, abdo pain after meals
- Sx of depression should be screened especially in the elderly patient;

Physical Exam

- Document weight and compare with previous values; oral thrush indicated immune deficiency
- Examine thyroid for enlargement or nodularity; **clubbing +++ pulmonary malignancy**
- Exam for possible malignancy includes: lymph node, DRE, breast, abdo, pelvis, and skin

Diagnostic Evaluation

- If specific cause not evident from Hx and PE the following initial screening tests indicated:
 - o CBC, ESR, CRP, Albumin, LFT, lactate, Ca, TSH, Urinalysis, CXR, Fasting glucose
- HIV antibody testing in a patient that presents with risk factors
- Patient with Hx of malabsorption test feces for fat, ova, parasite, TTg (celiac), B₁₂
- Abdominal CT considered given high frequency of GI etiologies; endoscopy for cancer screening
- In general, extensive work up not indicated; follow closely 1-3m for new Sx

Treatment

- If a specific cause identified, correct underlying etiology
- Calorie supplementation to promote restoration of the body mass while correcting abnormality
- Pharmacologic agents can be used to improve appetite

Hyperthyroidism

- Hyperthyroidism characterized by excessive T₄/T₃ and TSH suppression; more prevalent in women
- **Grave's disease** (diffuse T₄ overproduction) primary cause of hyperthyroidism in young (20-50)
 - o Autoimmune thyroid disease caused by production of antibodies to thyroid TSH receptors
 - o Thyroid stimulating Ig (TSI) stimulate the thyroid leading to increased hormone production
- In **multinodular goiter**, autonomously secreting nodules produce thyroid hormone without TSH
- **Subacute thyroiditis**: follicle destruction, release of T₄; healing results in acute HYPOTHYROIDISM
 - o Hashimoto's is chronic autoimmune thyroiditis causing chronic HYPOTHYROIDISM
- Ectopic T₄ production is rare(struma ovarii, pitu. cancer); pituitary diseases with excess TSH is rare

History

- Sx: Heat intolerance, palpitations, weight loss, nervous, fatigue, weakness, oligomenorrhea, diarrhea
- Elderly may present with apathetic hyperthyroidism characterized by weight loss, anorexia, fatigue
- Investigate ingestion of exogenous thyroid hormone (over replacement with levothyroxine)
- Recent iodine exposure may precipitate hyperthyroidism with autonomous nodule or Grave's
- Amiodarone is an antiarrhythmic that can cause hyperthyroidism

Physical Exam

- Tachycardia present in most patients; irregular pulse may be a sign of afib; fever in thyroiditis
- Other signs: warm and moist skin, eye lid lag, tremor
- Thyroid exam reveals enlarged painless thyroid (Graves) or painful thyroid (thyroiditis); nodule(s) may be palpable in adenoma (1), multinodular goiter (2+)
- Patients with excessive exogenous or ectopic hormone have nonpalpable glands
- Two findings exclusive to **graves: exophthalmos** (bug eye), **Pretibial myxedema** (brawny/thick)

DDx

- Divided physiologically by iodine uptake on thyroid scan:
 - o **High uptake:** Grave's, Toxic multinodular goiter, solitary adenoma, TSH pituitary tumor (rare)
 - o **Low Uptake:** thyroiditis, exogenous, struma ovarii, metastatic thyroid cancer

Diagnostic Evaluation

- 1st step is presence of ↑ free T₄ and **DECREASE TSH** (primary hyperthyroidism); if ↑ TSH, secondary
- If free T₄ is normal and TSH low consider T₃ thyrotoxicosis or subclinical hyperthyroidism
- **Thyroid scan** with radioactive iodine (RAI) used to evaluate uptake (¹²³I for scan, ¹³¹I for ablation)
- **Antithyroid peroxidase antibody** and TSIs present in autoimmune Grave's disease
- ECG can show tachycardia or atrial fibrillation

Treatment

- Non-Hashimoto **thyroiditis** is self-limited to a few weeks; B-blockers for cardiac Sx during episode
- Diseases with over-production of T₄ (Graves, nodules): ¹³¹I ablation, anithyroid drugs, Surgery
 - o Ablation is effective but requires lifelong T₄ therapy; ablation contraindicated in pregnancy
 - o Anithyroid drugs (thionamides) stop production of T₄ [methimazole or propylthiouracil]
 - Side effects include agranulocytosis (Sx: fever/sore throat) and hepatitis
 - o Surgery reserved for failed thionamides or massive goiters or Grave's disease
- Patients with Grave's treated with ablation need hypothyroid monitoring

Hypothyroidism

- Hypothyroidism is characterized by ↓ levels of T₃/T₄ and **increased** TSH; subclinical = asymptomatic
- 2^o hypothyroidism: ↓TSH and ↓T₃/T₄ (rare pituitary problem); **myxedema coma** = Extreme hypothy.
- Causes: Iodine deficiency, autoimmune (**Hashimoto's**), iatrogenic (ablation for hyperthyroidism)
- RF: Hx of other autoimmune disease (Hashimoto's), FHx of thyroid disease, neck irradiation

History

- Sx: cold intolerance, weight gain, fatigue, constipation, hoarseness, memory loss, menstrual changes, decreased libido, dry skin; patient may also present with carpal tunnel syndrome or anemia
- Assess prior radioactive iodine therapy or head and neck irradiation
- Medication Hx for amiodarone (inhibits T₄ → T₃ conversion) and lithium (inhibit T₄ release) use

Physical Exam

- Diastolic BP often mildly elevated, bradycardia, hypothermia, dry skin, coarse hair, slow nail growth
- **Goiter in Hashimoto thyroiditis:** firm, lobulated
- Neuro exam may show delayed deep tendon reflexes, carpal tunnel syndrome
- Patients with myxedema have edematous face, periorbital edema, nonpitting pretibial edema

DDx

- Primary: Hashimoto, I deficiency, recovery from acute thyroiditis, Lithium/Amiodarone, iatrogenic
- Secondary: Panhypopituitarism, Hypothalamic disease

Diagnostic Evaluation

- Characteristic lab findings (1^o): **Low Free T₄** and **INCREASED** TSH; TSH is low in 2^o hypothyroidism
- Nonthyroid studies: hyper-cholesterolemia/triglyceridemia, ↑ creatine phosphokinase, anemia
- Thyroid autoantibodies (**thyroid peroxidase, thyroglobulin**) present in Hashimoto's

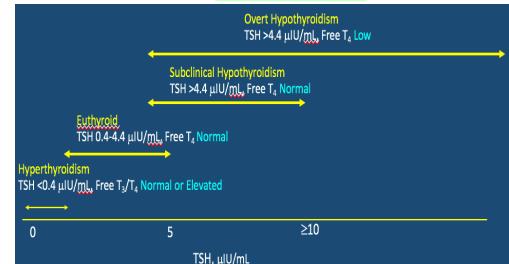
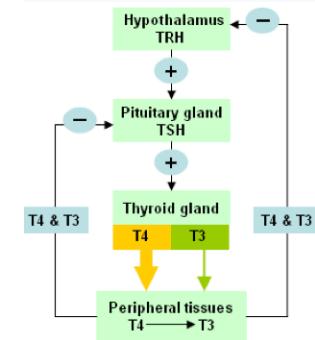
Treatment

- Subclinical hypothyroidism: watchful waiting until symptomatic or extremely low T₄
- **Levothyroxine (T₄)** is medical treatment of choice; speed of replacement depends on age/severity
- **Myxedema Coma** use IV levothyroxine
- Patients with suspected 2^o hypothyroidism or myxedema coma may have adrenal insufficiency so exogenous T₄ could use up remaining cortisol and cause **adrenal crisis** -> add **hydrocortisone** to Tx
- Follow serum TSH when using levothyroxine for 4-6 weeks
- Patients with Hx of radiation exposure have ↑ risk for thyroid cancer so do a routine thyroid exam

AHD – Thyroid Disorders

Physiology

- Thyroid hormones (T_3 and T_4) regulate overall body metabolism
- $T_3 \uparrow$ BMR, $\uparrow O_2$ consumption by peripheral tissues, and \uparrow heat production
 - o T_3 stimulates lipolysis and release of free fatty acids and glycerol
 - o Induces expression of lipogenic enzymes and stimulates carbohydrate, protein, and cholesterol (LDL) metabolism
- T_4/T_3 regulated by Hypothalamic-Pituitary-Thyroid axis
- Thyroid disease spectrum
 - o **Hyperthyroidism** is characterized by sustained \uparrow in T_4/T_3 biosynthesis and secretion.
 - o **Hypothyroidism** is associated with \downarrow in T_4/T_3 production.
 - o **Overt hypothyroidism** is defined as the triad of classical signs and symptoms of hypothyroidism, \uparrow serum TSH, and \downarrow free T_4



Hypothyroidism

- Clinical Manifestations (think \downarrow function):
 - o \downarrow Psychomotor, fatigue, cold, coarse hair, weight gain, hoarseness, constipation, depression, hyporeflexia, edema, bradycardia
- Workup: TSH, free T_4 , Auto-Antibodies (Hashimoto's), free T_3 is expensive so not usually done
 - o **Primary hypothyroidism:** \uparrow TSH and \downarrow T_4 (90% of cases)
 - o **Subclinical hypothyroidism:** \uparrow TSH and NORMAL T_4
 - o **Secondary hypothyroidism:** \downarrow TSH and \downarrow T_4 (Rare pituitary or hypothalamic disorder)
- Further workup includes: CBC (anemia), \downarrow Na (SIADH), CK, Glucose, Cortisol (adrenal insufficiency)
- Causes of Primary Hypothyroidism:
 - o **Hashimoto's:** autoimmune (TPO ab +), goiter, FHx
 - o **Iatrogenic:** Post ablation from hyperthyroidism/nodule
 - o **Thyroiditis:** Silent (painless), De Quervain's (painful)
 - o **Iodine deficiency:** not too common in 1st world anymore but in nutrition poor countries
 - o **Medication** (lithium, amiodarone), **infiltrative diseases**
- Goal of Tx is to replace thyroxine to mimic normal physiologic levels; use **Levothyroxine** (synthroid)

Hyperthyroidism

- Clinical Manifestations (think \uparrow function):
 - o Palpitations, Tremor, anxiety, apathy (elderly), \uparrow sweating, weight loss, overheated, diarrhea, \uparrow reflexes, atrial fibrillation, \uparrow Bowel sounds, exophthalmos + pretibial myxedema (Grave's)
- Workup: TSH, free T_4 , TSI ab (Grave's), radioactive iodine uptake (RAIU) scan, CBC, lipids, LFT
 - o **Primary hyperthyroidism:** \downarrow TSH and \uparrow T_4 (90% of cases)
 - o **Subclinical hypothyroidism:** \downarrow TSH and NORMAL T_4
 - o **Secondary hypothyroidism:** \uparrow TSH and \uparrow T_4 (Rare pituitary or hypothalamic disorder)
- Causes of Primary Hyperthyroidism:
 - o **Grave's:** autoimmune, young adults present with goiter, exophthalmos, and pretibial myxedema
 - o **Toxic adenoma/Toxic multinodular goiter:** T_4 producing nodule(s) on thyroid
 - o **Thyroiditis** (see above); **Medication** (Lithium, amiodarone); **Ectopic:** struma ovarii; **exogenous**
- Tx: **Thionamides** (inhibit synthesis), **radioactive iodine ablation**, **surgical resection**
- Adjunctive therapy: B-Blockers (slow heart), Steroids (prevent $T_4 \rightarrow T_3$ conversion)
- **Thyroid Storm** is severe hyperthyroidism and is a medical emergency

Diabetes Mellitus

- DM is a chronic metabolic disorder characterized by abnormal glucose regulation (hyperglycemia)
 - o Type 1 DM (DM1) is from autoimmune destruction of the pancreas causing insulin deficiency
 - o Type 2 DM (DM2) is from peripheral resistance to insulin; hyperglycemia despite normal levels
- DM1 begins with autoimmune destruction of pancreatic islet β -cells after an environmental trigger
 - o Without insulin, these patients are prone to **diabetic ketoacidosis** (DKA)
- DM2 insulin resistance comes from a combination of genetic predisposition and weight gain
- Hyperglycemia causes **microvascular** complications: retinopathy, nephropathy, neuropathy
- Patients with DM are also at risk for **macrovascular** complications: CAD, stroke, PVD

History

- DM1 presenting with DKA look ill with vomiting, nausea, polyuria; DM2 often asymptomatic initially
- DM2: Positive FHx, obesity; presenting Sx: polyuria, polydipsia, polyphagia, fatigue, blurred vision
- Minority of patients initially present with micro or macrovascular complications

Physical Exam

- PE focuses on organ complications: fundoscopy (retinopathy), vibration/light touch (neuropathy), increased JVP (CAD), S4 (CAD), displaced max impulse (CAD), decreased peripheral pulses (PVD)
 - o If sensation is severely impaired, foot ulcers can appear

DDx

- Other hyperglycemia causes: Drugs, IV dextrose, Stress, excess counter regulatory hormones
- Disorders causing DM secondarily: Hemochromatosis, pancreatic insufficiency

Diagnostic Evaluation

- Criteria for diagnosis of DM (FG = fasting glucose, G = glucose, 2hPG = 2h after glucose challenge):
 - o FG \geq 7 mmol/L **OR** HbA1c \geq 6.5% **OR** random G \geq 11.1 mmol/L **OR** 2hPG \geq 11.1 mmol/L
- Once Dx is made, glucose control is monitored with HbA1c (gives indication of G over last 3 months)
- DM patients should be assessed for complications: nephropathy (albuminuria)
 - o **Urine microalbumin** and creatinine should be measured daily in all diabetic patients

Treatment

- Management has two goals: **restore glycemic control** and **monitor/treat complications**
- DM2: healthy diet + exercise/weight loss often adequate for glucose control; also important in DM1
- Patients with DM2 who are unable to control glucose with diet/exercise can use oral hypoglycemic
 - o **Metformin** is the first line; **no risk of hypoglycemia** when used as monotherapy
- **Sulfonylureas** stimulate insulin release and often chosen as first line in **non-obese** patients
 - o Side effects are weight gain and potential hypoglycemia
- **Thiazolidinediones** increase insulin sensitivity in the liver and muscle; increase risk of CHF, MI
 - o Due to potential complications, these are saved for patients who fail other therapies
- **α -glucosidase inhibitors** inhibit carbohydrate absorption in small intestine;
 - o Side effects of bloating, diarrhea, flatulence; not very effective as monotherapy
- Subcutaneous insulin is required for all DM1 patients and often DM2
- DM1 approach: long-acting insulin once daily with short-acting insulin at mealtimes
- DM2 approach: Metformin, if fails add sulfonylurea, if fails change sulfonylurea to long-acting insulin

Complications

- **DKA** is generally seen in DM1 precipitated by infections, vascular events or cessation of insulin
 - o Patient presents with nausea, vomiting, +/- diffuse abdo pain, confusion if severe
 - o Labs show anion gap acidosis, hyperglycemia, positive ketones in urine and blood
 - o Tx with volume repletion (IV NS) and insulin replacement (IV bolus then continuous infusion)
 - o Glucose monitored every hour; if it drops too low (before ion gap normalizes) -> IV dextrose
 - o Patients with DKA should have K fluid replacement as soon as urine output is established
- **Hyperosmolar nonketotic coma** usually seen in DM2 with osmotic diuresis and dehydration
 - o Usually precipitated by vascular event or infection that limits ability to stay hydrated
 - o Acidosis may be present but usually related to starvation ketosis and lactic acidosis not DKA
 - o Tx involves hydration and treatment of precipitant factor
- **Hypoglycemia** is a risk with more chronic and complex medical treatment
 - o Adrenergic Sx: tachycardia, diaphoresis, tremulousness, palpitations, anxiety
 - o Neuroglycopenic Sx: headache, blurred vision, confusion, seizures, LOC
 - o Patients at risk of hypoglycemia should have sugar pills and glucagon injections readily available
- **Retinopathy** occurs in majority of patients with DM > 15y
- **Nephropathy** can be detected by screening for microalbuminuria
 - o If microalbuminuria develops Tx with ACEi or ARB to decrease progression
 - o Glucose control is the only way to delay sensory neuropathy
- All diabetics are at increased risk for **macrovascular** complications and should be counseled on smoking cessation, BP control, lipid-lowering therapy
 - o Prophylactic aspirin and statin therapy should be given to diabetics > 40y
 - o Metformin may reduce CV risk and should be considered in early hypoglycemic therapy

AHD – What You need to know about Diabetes

Definition of Diabetes Mellitus (DM)

- DM is a syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/relative deficiency of insulin or a reduction of biological effectiveness of insulin or both

Type	Definition
DM1	Autoimmune destruction of pancreatic beta cells causing lack of production of insulin
DM2	Insulin resistance or relative deficiency to predominant secretory defect with insulin resistance
Gestational	Glucose intolerance with onset or first recognition in pregnancy

- Diagnosis of Diabetes
 - o FPG $\geq 7.0 \text{ mM/L}$ OR HbA1C $\geq 6.5\%$ OR 2hPG OGTT $\geq 11.1 \text{ mM/L}$ OR random PG $\geq 11.1 \text{ mM/L}$

Evaluation of the Diabetic Patient

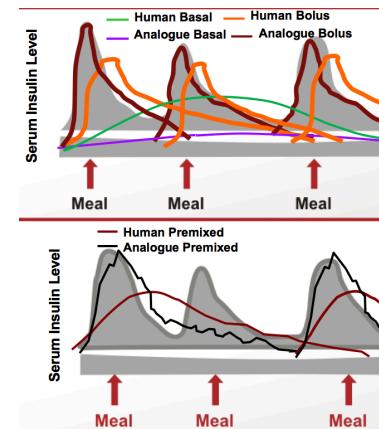
- PMHx (years Dx, following physician), Insulin for how many years
- Macrovascular complications (CAD, CVA, PVD)
- Microvascular complications (retinopathy, nephropathy, neuropathy)
- Autonomic dysfunction (orthostatic hypoTN, dysregulated GI motility, erectile dysfunction)
- Hypoglycemia unawareness

Diabetes Targets

- HbA1C $\leq 7.0\%$ for MOST DM2; HbA1C $\leq 6.5\%$ (young); HbA1C of 7.1 – 8.5% (in some really old)
- A1C targets individualized based on age, comorbidities, functional dependence and complications

Diabetes Outpatient Management

- Lifestyle modifications (exercise, diet) always first
- Pharmacotherapy based on glycemia; start with **metformin**, then individualize after 3 mo follow-up
 - o Initial A1C $< 8.5\%$: start with metformin, reassess in 3 mo
 - o Initial A1C $\geq 8.5\%$: start with metformin and consider combo therapy to reach target
 - o If Sx and glycemia both bad and concern about insulin deficiency **metformin + insulin**
 - o Lots of different second agents but make sure to check renal function
- Types of Insulin:
 - o Long acting: take at night to increase basal level of insulin
 - o Short acting: take with meals to increase pre-meal insulin
 - o Mixed is combined short and long so that it can be taken less times
- Multifaceted management for DM2 essential:
 - o ↑ risk of MI, need to control glucose, lipids, HTN, and use vascular protective medications, along with lifestyle changes
 - o **ABCDEs:** A1C <7 , BP $<130/80$, Cholesterol $<2.0 \text{ mM/L}$, Drugs for heart, Exercise and healthy eating, Smoking cessation



Diabetes Inpatient Management

- Hyperglycemia common in hospital, leads to ↓ immune function, ↓ wound healing, ↑ oxidative stress
 - o These cause ↑ risk of postop infection, prolonged stays, ↑ renal dysfunction
- **Insulin** is the Tx of choice in hospital, NEVER USE SLIDING SCALE ALONE, use with basal bolus
- **Avoid HYPOGLYCEMIA**, start LOW, go SLOW
 - o Remember: high blood glucose means more insulin is needed at PREVIOUS meal
 - o ↑ AM sugar: more bedtime (long acting insulin), ↑ lunch sugar: more AM (rapid insulin), etc.
- **DKA**: aggressive IV NS, IV insulin + KCl, monitoring of anion gap (switch NS -> D5W when sugar N)

Hypercalcemia

- Normally, serum Ca tightly regulated by **parathyroid** hormone (PTH), **calcitonin**, and **Vitamin D**
 - o PTH ↑ serum Ca through ↑ bone, renal tubular, and GI (↑ vitamin D activation) resorption of Ca
 - o **Calcitonin** ↓ serum Ca by inhibiting bone resorption;
- Two most common causes of HyperCa are **primary hyperparathyroidism** (HPTH) and **malignancy**
 - o HPTH is from ↑ PTH secretion, overactive parathyroid, and loss of normal inhibitory feedback
 - HPTH etiologies: solitary parathyroid adenoma, parathyroid hyperplasia, carcinomas (rare)
 - o Malignancy HyperCa mechanisms: **direct bone destruction**, **humoral hyperCa of malignancy**
 - Direct Bone destruction: breast cancer, nonsmall cell lung cancer, multiple myeloma
- Less common causes of HyperCa:
 - o **Vitamin D**: ↑ Vit. D ingestion, granulomatous disease, Hodgkin/non-hodgkin lymphoma
 - o **↑ Bone turnover**: Hyperthyroidism, immobilization, Vit. A intoxication
 - o **Decreased Renal Ca excretion**: Thiazide diuretics, Milk-alkali syndrome (excessive antacids)
- Lithium use and familial hypocalciuric hypercalcemia (FHH) and other causes with ↑ PTH
 - o Both causes a decreased activity in the calcium-sensing receptor leading to ↑ Ca levels

History

- Sx are usually nonspecific: fatigue, anorexia, drowsiness; confusion and stupor if severe hyperCa
- GI complaints: nephrolithiasis, nausea, vomiting, constipation, polyuria ("Stones, bones & Groans")
- Medication Hx for diuretics, diet for vitamin ingestion, FHx of FHH

Physical Exam

- Usually unrevealing but should include a search for findings suggestive of malignancy, such as adenopathy or abnormal masses; volume depletion may also be present

Diagnostic Evaluation

- **Ionized Calcium** (free form), is the biologically active form and can be directly measured
- Acidemia ↓ Ca binding to albumin thus ↑ ionized Ca; Hypophosphatemia seen in HPTH
- **Intact PTH assay** most helpful test for determining cause of hypercalcemia
 - o If ↑ ->HPTH (90%) or FHH; if ↓, malignancy most likely, measure Humoral HyperCa (HHM) for Dx
- Cancer suspicion: CXR (lung cancer), Urine for red cells (Renal cancer), Mammogram (breast cancer)
 - o If these tests still unrevealing chest/abdo CT; metastases/myeloma appear as lytic lesions on film
- Long standing HPTH may have the following bone manifestations:
 - o Osteitis fibrosa cystica, supperiosteal resorption in phalanges, chondrocalcinosis + pseudogout
- Cardiac manifestations present as **shortened QT interval** on ECG

Treatment

- Goal is to normalize calcium; IV NS is first treatment for volume depletion and ↑ renal Ca excretion
- Loop diuretics (furosemide) only indicated when volume overload is a concern
- Next goal is to maintain normal Ca by preventing bone resorption (bisphosphonates, corticosteroids)
- Surgery indicated in symptomatic HPTH; single adenoma-> remove; hyperplasia-> remove 3.5 glands
- For asymptomatic HPTH surgery is recommend for age <50; indications for older patients:
 - o Ca > 1.0mg/dL above normal, Hx of life-threatening hyperCa, Nephrolithiasis, ↓ Cr clearance
- If surgery performed, monitoring for hypocalcemia: muscle twitching, spasm

Adrenal Insufficiency

- **Adrenal cortex** is responsible for synthesis of three major steroid hormones:
 - o Glucocorticoids (cortisol), mineralcorticoids (aldosterone), androgens
- **Adrenal medulla** produces catecholamines (Epi/NE); main stimulus for secretion is SNS
- Adrenal **insufficiency** (AI) is from failure of the adrenal glands (1°) or hypothalamus/pituitary (2°)
- Primary AI (**Addison disease**) is rare; secondary AI is more common (therapeutic glucocorticoids)
- 1° AI usually related to **autoimmune source (polyglandular autoimmune syndrome Type 2)**
 - o Other causes of Addison: TB, HIV, carcinoma metastases

History

- Often nonspecific Sx: fatigue, weight loss, nausea, anorexia, abdominal pain, salt craving (1° AI)
- Acute AI can occur with poor adrenal reserve after surgery, infection, or injury (hemorrhage)

Physical Exam

- **Orthostatic hypotension** is associated with AI and **overt shock** with acute AI
- **Hyperpigmentation** due to ACTH precursor is unique to primary AI

DDx

- Difficult to differentiate from other things but suspect when constitutional symptoms are accompanied by GI distress, weight loss, or gradual increase in skin pigmentation

Diagnostic Evaluation

- Primary AI has characteristic HyperK and HypoNa; NO hyperK in secondary AI +/- HypoNa (SIADH)
- Other labs: HyperCa, eosinophilia, normochromic normocytic anemia, acidosis, autoantibodies
- Morning cortisol < 3mcg/dL is suggestive of AI (poor sensitivity)
- Synthetic ACTH test helps confirm 1° AI: ACTH > 52pg/mL or high plasma renin/low aldosterone
 - o In patients with recent ACTH deficiency this test may be falsely normal

Treatment

- Chronic AI treatment involves hydrocortisone with monitoring of appetite
 - o Excess replacement avoided to avoid side effects
- Primary AI uses **fludrocortisone** for mineralcorticoid replacement; monitor orthostatic VS and lytes
- Acute AI treated with IV NS and IV glucocorticoid therapy

Cushing Syndrome

- Cushing Syndrome (CS) is caused by excess cortisol; Iatrogenic CS from glucocorticoids is common
- CS cortisol excess is either ACTH **dependent** or **independent**; Source of ACTH overproduction:
 - o Pituitary adenoma (Cushing disease), Ectopic ACTH production (Small cell lung cancer)
 - o In ACTH independent CS, cortisol is autonomously produced by adrenal glands (tumour)
- Effects of Cortisol:
 - o Glucose metabolism: ↑ gluconeogenesis + ↓ peripheral glucose uptake -> **hyperglycemia**
 - o Adipose tissue: ↑ lipolysis; Connective tissue: inhibition of fibroblasts -> **skin atrophy/bruising**
 - o Bone: ↑ bone resorption, ↑ urinary Ca excretion, ↓ GI Ca absorption; Kidney: ↑ Na retention
 - o Immune: ↓ prostaglandin synthesis and neutrophil migration

History

- CS complaints: weight gain (central obesity), muscle weakness, easy bruising, depression, irregular menses, impotence, decreased libido

Physical Exam

- Central obesity is common in CS, round/moon face, excess fat deposition on cervical spine
- Skin: wide **purple striae** on abdomen, axillae, internal thighs; muscle atrophy; HTN

DDx

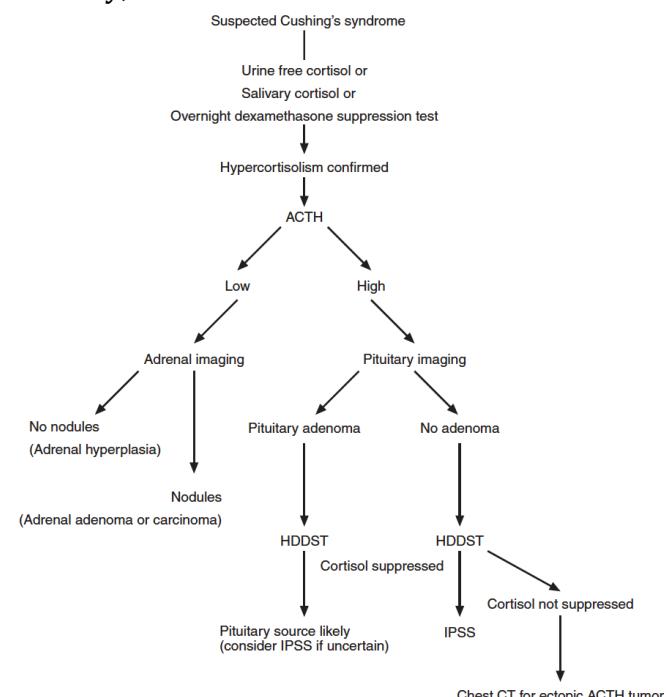
- Excess cortisol also seen in alcoholism, obesity, severe depression

Diagnostic Evaluation

- **Urine free-cortisol** usually 3-4 times higher than normal
- Overnight **dexamethasone suppression test**: administration of 1 mg at midnight should suppress next morning's cortisol to < 5 µg/dL, failure to suppress cortisol -> Cushing; False + in DDx disorders
- **Late night salivary cortisol**: sample saliva at night when cortisol production should be low
- Once hypercortisolism confirmed **serum ACTH** determine primary (adrenal) vs. secondary
 - o ACTH is suppressed in primary causes and high in secondary;
 - o High doses dexamethasone suppression test can differentiate between secondary causes
- In ACTH-dependent CS localization may require inferior petrosal sinus sampling
 - o A blood ACTH ratio of 2+ (sinus/peripheral) is diagnostic for pituitary source of ACTH
- Abdo CT can locate masses in adrenal adenomas; Head MRI for pituitary adenomas

Treatment

- Surgical resection is treatment of choice for CS
- If localized adrenal nodule: unilateral adrenalectomy
- Ectopic CS often have unresectable tumours
- If surgery fails, bilateral adrenalectomy will eliminate CS but lifelong gluco- and mineralcorticoids necessary
- Adrenal blocking drugs are temporary Tx while waiting for surgery



Pituitary Disease

- Diseases of the pituitary are classified as diseases of **oversecretion** (adenoma) or **undersecretion**
 - o **Prolactinoma** most common adenoma; non-functioning adenomas create hormone subunits
 - o Undersecretion of ALL hormones in **panhypopituitarism**; Vasopressin in **diabetes insipidus**
- Pituitary adenomas occur in association with **multiple endocrine neoplasia Type 1 (MEN1)**

History

- **Hypogonadism** (amenorrhea/impotence F/M) and **galactorrhea** (F) in prolactin adenomas
- Acromegaly complaints are nonspecific: fatigue, arthralgias, headache, hypersomnolence, sweating
- Nonfunctioning adenomas usually produce local, NOT SYSTEMIC, Sx: visual defects, headaches
- TSH-producing adenomas are rare and mimic hyperthyroidism
- Sx of **hypopituitarism**: loss of axillary/pubic hair, impotence, fatigue, weight loss or gain
- Polyuria and polydipsia suggest DI

Physical Exam

- HTN often seen in acromegaly and Cushing disease; orthostatic hypotension in panhypopituitarism
- Skin: hirsutism (cushing, acromegaly), tags, moist, doughy (acromegaly), purple striae (cushing)
- **Bitemporal hemianopsia** may be related to compression of optic chiasm in acromegaly

DDx

- **Hypopituitarism**: large pituitary adenoma, pituitary apoplexy, sellar tumor, granulomatous disease, postpartum necrosis, radiation
- **Amenorrhea/hirsutism**: PREGNANCY, Cushing, acromegaly, PCOS, congenital adrenal hyperplasia

Diagnostic Evaluation

- Measure prolactin levels for suspected prolactinomas; GH is measured by ↑ **insulin growth factor 1**
- TSH, LH, FSH should all be measured
- MRI with gadolinium is imaging of choice for pituitary abnormalities
- Lab studies for panhypopituitarism: Low free T₄/T₃ with normal/low TSH, low testosterone, low estrogen with low FSH and LH
- DI suggested by **low urine osmolality** in the setting of **high serum osmolality**; improvement with vasopressin and not fluid restriction suggests central etiology (pituitary or hypothalamus)

Treatment

- Management of adenomas aimed at correcting oversecretion of hormone and mass effect of pituitary
 - o Non-functioning adenomas, asymptomatic prolactin microadenomas don't need immediate Tx
 - o Symptomatic prolactin adenomas respond well to **dopamine antagonists**
 - o In Non-prolactin adenomas, surgery is often indicated (transsphenoidal)
 - o GH -secreting tumours that recur after surgery need medical treatment
- Panhypopituitarism treatment usually involves hormone replacement therapy
 - o Testosterone (M) and Estrogen (F) relieves hypogonadism; GH not routinely replaced
 - o Cortisone usually first hormone replaced with additional stress doses
 - o Levels of TSH, ACTH, LH, and FSH are **not** useful for monitoring efficacy of replacement
- DI and hypernatremia need replacement of free water either PO or with IV D5W
 - o **Desmopressin acetate** (synthetic vasopressin) used for polyuria in central DI

Nutritional Disorders

- **Vitamins** are organic compounds serving as cofactors for enzymes or as functional molecule (Vit A)
- **Minerals** are inorganic compounds that are important components of enzymes and proteins
- **Trace elements** are minerals present in body fluid at concentrations < 1ug/g
- **Recommended daily allowance (RDA)** is minimum amount needed to prevent deficiency

Vitamin	Deficiency	Excess/Toxicity	Therapeutic Use
B ₁	Beriberi, Wernicke-Korsakoff	None	None
B ₆	Dermatitis, peripheral neurop.	Sensory neuropathy	Lowers homocysteine
Folate	Megaloblastic anemia	None	Reduce neural tube defects, lowers homocysteine
Niacin	Diarrhea, dementia, dermatitis	Flushing, GI Sx, hyperuric.	Large dose lowers chol.
C	Scurvy	GI discomfort	None
A	Night blindness, corneal ulcer	CNS effect, hepatosplenom.	None
E	Ataxia, ophthalmoplegia	Bleeding (warfarin)	Antioxidant effect (CAD)
D	Osteomalacia, hypoCa	HyperCa	Prevents fractures/falls
K	Bleeding	None	None

Vitamin A

- Forms the prosthetic group of carotenoid proteins in the retina for retinoid excitation
- Obtained directly from food or synthesised from B-carotene; excess B-carotene turns skin orange
- Deficiency manifests as night blindness, corneal ulceration, xerosis +/- scaling
- Excessive intake causes hepatosplenomegaly, ataxia, joint pain, alopecia

Vitamin D

- Important in calcium absorption and bone formation; can be synthesized in skin with UV exposure
- Vit D deficiency is the **most common vitamin deficiency**, manifests as hypoCa and osteomalacia
- Since formation of active form of Vit D is regulated internally toxicity requires massive ingestion

Vitamin E

- Consists of a group of compounds known as tocopherols; serves as an antioxidant
- Deficiency is rare but can manifest as hemolytic anemia; genetic condition causing Vit E deficiency associated with ataxia, posterior column neuropathy, and ophthalmoplegia
- Toxicity is not seen but patients may have risk of bleeding with Warfarin use, easy bleeding

Vitamin K

- Important co-factor for blood clotting factors; found in green vegetables and made by GI flora
- Deficiency manifests as a bleeding disorder (iatrogenic - warfarin)

Vitamin B₁ (Thiamine)

- Thiamine pyrophosphate is the active form of thiamine and is a cofactor in carb/protein catabolism
- Deficiency often in alcoholics due to malnutrition; CV problems (Beriberi), CNS problems (Wernicke)

Vitamin B₆ (Pyridoxine)

- Important cofactor in amino acid catabolism, heme synthesis, and glycogen breakdown
- Deficiency results in angular stomatitis, glossitis, dermatitis, ↑ homocysteine (subclinical)
- Over ingestion can lead to sensory neuropathy

Niacin

- Essential component of nicotinamide and adenine dinucleotide for RedOx reactions
- **Pellagra** Is the classic niacin deficiency syndrome with diarrhea, dementia, dermatitis
- Large doses of niacin cause flushing, hyperuricemia, and liver dysfunction

Folate

- Folate is important for purine and pyrimidine synthesis as well as methionine production
- Deficiency results in megaloblastic anemia and is also implicated in neural tube defects

Vitamin C

- Important for collagen synthesis and acts as an antioxidant
- Deficiency leads to scurvy: bleeding gums, loose teeth, easy bruising, poor wound healing

Iron

- Iron deficiency is usually secondary to blood loss but can be seen in poor dietary intake
- Excessive intake can lead to poisoning (pediatrics) with diarrhea vomiting, seizures

Zinc

- Integral to the function of numerous proteins and enzymes within the body
- Deficiency can result from malabsorption and manifests as diarrhea, dermatitis, growth retardation

Copper

- Important for function of enzymes in connective tissue synthesis, iron transport, energy production
- Deficiency is rare but can be caused by excess zinc supplementation decreasing Cu absorption
- Copper excess is seen in Wilson disease

Therapeutic Use

- Vitamin D appears effective in slowing osteoporosis in postmenopausal women
- Folate decreases neural tube defects if taken in first trimester of pregnancy
- Homocysteine can be lowered with folate, B₁₂, B₆ but no decrease in CV events has been demonstrated.

Dyslipidemia

- Serum lipids in blood: low-density lipoproteins (LDL), high-density lipoprotein (HDL), triglycerides
- Dyslipidemia (DLD) consists primarily of **elevated LDL**, **elevated triglycerides**, or **low HDL**
- Genetic factors play a role in DLD through polygenic mechanisms:
 - o **Familial hypercholesterolemia:** defective hepatic LDL receptor $\rightarrow \uparrow$ LDL
 - o **Familial combined hyperlipidemia:** \uparrow cholesterol, \uparrow triglycerides, or both
- Alcohol \uparrow triglycerides by inhibiting their metabolism; DLD evaluation involves assessing CHD RF:
 - o M/F > 45/55, FHx of early CAD, Smoking, HTN, DM, low HDL (High HDL is PROTECTIVE)

History

- Hx should concentrate on RF for CHD as listed above and comorbid factors (alcohol, diet), medication

Physical Exam

- Almost always normal in DLD except in extreme cases of \uparrow cholesterol (in hereditary disorders):
 - o **Tendinous xanthomas** (painless nodules), **eruptive xanthomas** (papules), **Xanthelasmas**

DDx

- Once DDx of DLD is made consider: hypothyroidism, nephrotic syndrome, renal failure DM2, cholestatic liver disease, drugs (thiazides, B-blockers, oral contraception), Alcohol

Diagnostic Evaluation

- Initial screening test is a fasting lipid profile; $LDL = Total - HDL - triG/5$; Normal: Total < 200, HDL > 40
- Lab tests to rule out DDx causes: TSH, fasting glucose, creatinine, LFT, urinalysis for protein
- Usually a CV risk assessment is done (Framington calculator)

Treatment

- Main reason to treat DLD is to lower CV risk; intensity of treatment varies by individual
- Dietary therapy recommended to all: limiting cholesterol, saturated/trans fats, \uparrow fruit/vegetables
 - o **Mediterranean** diet has strong evidence of CV event reduction
- All patients with CV disease are similar risk are placed on **statins**; following people are HIGH risk:
 - o CHD, Cerebrovascular disease, peripheral artery disease, 10-year CV risk > 20%
- Primary prevention statin therapy can be given to individuals without CV disease
 - o For those > 40 with DM it is recommended; for others guidelines differ in recommendations
- Important side effect of statins is myopathy (at high doses); baseline creatine kinase levels should be obtained for those at risk of myopathy and compared if it presents
- Patients should have fasting lipid analysis and LFTs 1-3 months after starting therapy
- \uparrow Triglycerides in normal LDL can be seen; no evidence lowering triglycerides affects CV outcomes

Drug	Mechanism	LDL	HDL	TriG	Side Effects
Statin	Block HMG-CoA reductase	↓	↑	-	Myalgias, hepatitis, rhabdomyolysis
Niacin	Inhibit LDL production and HDL clearance	↓	↑↑	↓	Flushing, gout, hyperglycemia
Bile resin	Bind bile acid	↓	-	↑	Constipation, Drug int.
Fibric acid	Stimulate lipase	↑↓	↑	↓↓	myopathy
Ezetimibe	Impair GI choles. absorption	↓	-	-	↑ LFT when with statin

Acute Monoarticular Arthritis

- Inflammatory process that develops in a single joint; bacteremia needs quick Dx and Tx

History

- Duration of Sx helps differentiate the cause of joint inflammation
 - o Rapid onset with a “pop” or “snap” implies torn menisci or ligament
 - o Gout and bacterial infections develop over hours to days; pseudogout takes several days
 - o Rheumatologic causes are often more subacute over weeks
- Previous Hx of monoarticular arthritis may suggest crystalline or rheumatologic disease
- RF for gout: DM, HTN, obesity, DLD, alcohol, thiazide use
- Bacterial infection more common in DM and IV drug users
- Patients on anticoagulation or inherited coagulation defect are at increased risk for hemarthrosis

Physical Exam

- Fever is an important sign for bacterial etiology; gout and rheumatologic source may also have fever
- Skin: rash (gonococcal [GC] found on extremities), **erythema migrans** (lyme disease), needle marks
- Joints: warm and tender, painful limitation of motion
 - o Knee most common in bacterial infection, lyme, pseudogout, trauma
 - o Gout primarily in big toe or ankle but may be knee; **tenosynovitis** usually in hand tendons (GC)

DDx

Infection	Crystalline	Trauma	Rheumatologic Disease
- Gonococcal (GC)	- Gout	- ACL, MCL or meniscus	- Rheumatoid arthritis
- Non-GC (S. aureus)	- Pseudogout	- Osteoarthritis	- Seronegative spondyloarthropathy
- Lyme disease		- Hemarthrosis	- Systemic lupus erythematosus (SLE)

Diagnostic Evaluation

- Arthrocentesis is definitive Dx procedure; aspiration of some joints (hip) requires image-guidance
- Fluid appearance: blood confirms hemarthrosis; cloudy/turbulent likely 2^o to infection or crystalline
- Leukocyte count to determine inflammatory nature of effusion; Culture and gram stain for infection

WBC count	<200	<2,000	2,000-50,000	50,000-100,000	>100,000
Interpretation	Normal	Noninflammatory (osteoarthritis)	Mild-moderate (rheum/crystalline)	Severe inflammation (sepsis/gout)	sepsis

- **Crystal examination** to r/o gout (needle-shape), or pseudogout (rhomboid); does not r/o infection
- Urethral, pharyngeal, cervical (F), and rectal specimens sent for culture if suspected GC infection
- X-rays of affected joints may show chondrocalcinosis (pseudogout) or fracture (trauma)
- Uric acid level **IS NOT** useful in acute gouty arthritis;
- Lyme antibody can't distinguish active from inactive infection but negative result r/o Lyme arthritis

Treatment

- Infection: Abx therapy when cultures sent; **Vancomycin** (S. Aureus); DM need gram – coverage too
 - o Repeat drainage for all patients with non-GC septic arthritis to avoid damage
 - o If suspected GC infection: **Ceftriaxone**; Lyme infection: doxycycline, if severe use IV ceftriaxone
- Crystalline: gout and pseudogout treated with NSAID; intra-articular steroid injection if infection r/o
- Traumatic: rest, ice, elevation, and anti-inflammatories; osteoarthritis with acetaminophen/NSAID

Low Back Pain

History

- Back pain without **sciatica** (pain radiating from nerve below knee) unlikely to be disk herniation
- Hx of back pain with morning stiffness in young person -> suspect **ankylosing spondylitis**
- Pain that worsens with walking and prolonged standing -> **spinal stenosis**
- **RED FLAGS:** Hx of malignancy, fever, weight loss, bladder/bowel dysfunction, "saddle anesthesia"
- Back pain with malignancy is usually 2° to malignancy; pain usually not relieved in supine position
- **Fever** with back pain raises suspicion of osteomyelitis or epidural abscess

Physical Exam

- Focused on elucidating signs of **nerve root compression**; disk herniation commonly L4-L5 or L5-S1
 - o Weakness of dorsiflexion (L5 root), weakness of plantar flexion (S1 root)
- **Cauda equina:** rare but "must-not-miss" Dx, saddle anesthesia due to compression of sacral nerves

Location	Root	Pain Radiation	Neuro Deficits	Other Features
L4-L5	L5	Anterolateral leg, big toe	Dorsiflexion	
L5-S1	S1	Posterior leg and lateral toes	Plantar flexion	↓ ankle reflex
Midline disk	Cauda equina	Bilateral leg numbness	Saddle anesthesia	Urinary retention

- Focal vertebral tenderness often seen in osteomyelitis or epidural abscess but not specific
- Overreaction during exam and superficial tenderness suggest a psychological component

DDx

Musculoskeletal Cause	Systemic Cause	Referred Pain
<ul style="list-style-type: none"> - Musculoligamentous injury - Herniated disk - Spinal stenosis - Vertebral compression fracture - Spondylosis 	<ul style="list-style-type: none"> - Malignancy (metastases) - Vertebral osteomyelitis - Epidural abscess - Spondyloarthropathy 	<ul style="list-style-type: none"> - Aortic dissection or aneurysm - Pyelonephritis - Nephrolithiasis - Prostatitis - Pancreatitis or carcinoma

Diagnostic Evaluation

- If no worrisome clinical features, then Hx and PE sufficient (watchful waiting)
 - o Radiologic findings may mislead by showing asymptomatic disk protrusions
- Patients > 50, Hx of weight loss, trauma, malignancy or chronic steroid use need **lumbar spine film**
- ESR (not sens/spec) may be elevated in infectious or malignant causes
- Early MRI for patient with known malignancy that develops new back pain (spine compression)
- Hx or PE worrisome for malignancy: do tests for common metastatic sources (lung, breast, prostate)
- New compression fracture should raise suspicion for multiple myeloma; serum and urine immunoelectrophoresis to r/o this Dx

Treatment

- Non-worrisome pain: NSAIDs, continue normal activity (avoid bed rest), ice + warm compress
- MRI/surgical referral for sciatica that doesn't improve, progressive neuro deficit, suspicion of epidural abscess, and bilateral neurologic deficits or urinary retention (cauda equina)

Rheumatoid Arthritis

- RA is a **symmetric** inflammatory polyarthritis with lymphocytic infiltration of synovial joints
- Appears to be a genetic predisposition (HLA-DR); first-degree relatives have 4x risk of RA
- Pathogenesis unclear other than synovial T cells become activated and cause inflammatory cascade
 - o Synovial tissue in RA reveals high levels of TNF- α and IL-1 (these upregulate metalloproteinases)

History

- Patients often present with gradual onset of **pain** and **swelling** in peripheral joints; Sx are usually polyarticular and symmetric; **MORNING STIFFNESS** is a key feature; +/- constitutional symptoms

Physical Exam

- Proximal interphalangeal, metacarpophalangeal, and wrist most common joints
- Knee joints may be involved (Baker cyst); exam of joints reveals warmth, tenderness, swelling; axial joints uncommon but C-spine if so
- Late presentations: reduced grip, joint deformities, vasculitis (finger infarct)
- Subcutaneous nontender **rheumatoid nodules** (forearm, elbow, Achilles)
- **Felty syndrome:** triad of Splenomegaly, RA, leukopenia

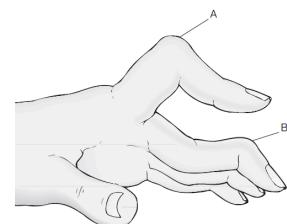


Figure 58-1 • (A) Boutonnière deformity. (B) Swan neck.

DDx

- DDx involves other etiologies of arthritis or joint pain (see previous notes for details):
 - o Osteoarthritis, psoriatic arthritis, gout, pseudogout, lupus, infectious/septic/reactive arthritis

Diagnostic Evaluation

Numbers/site of involved joints	Serologic abnormality	Acute phase response	Sx Duration
- 2-10 large joints (1 point)	- Low positive RF/anti-CCP (2 points)	- Elevated ESR or CRP (1 point)	- 6+ weeks (1 point)
- 1-3 small joint (2 points)	- High positive RF/anti-CCP (3 points)		
- 4-10 small joints (3 points)			
- 10+ joints (5 points)			

- Score of 6+ needed for definite Dx of RA; RF = **rheumatoid factor**: autoimmune antibody to IgG
- Anti-CCP and RF positivity are **sensitive** tests for RA (80%); RF is **NOT** specific, anti-CCP **IS** specific
- Other conditions with RF+: Old, autoimmune diseases, infective endocarditis, Hep C, chronic infection
- Other labs: ↑ ESR, ↑ CRP, antinuclear antibody negative; joint aspiration done to r/o other causes
- CXR: rheumatoid nodules, interstitial lung disease, pleural effusions

Treatment

- Goal of treatment is complete remission of RA (asymptomatic, progression free, normal ESR/CRP)
- When remission cannot be achieved with monotherapy, combination therapy is indicated
- Sx relief with analgesics (NSAIDs); Corticosteroids used **sparingly** in RA (Sx relief but bad side effect)
- **Disease modifying antirheumatic drugs** (DMARD): use early in all RA patients; Drugs +side effects:
 - o **Methotrexate**: bone marrow toxicity, hepatic fibrosis, pneumonitis, stomatitis (**FIRST LINE**)
 - o **Sulfasalazine**: rash; **Leflunomide**: diarrhea, rash; **Minocycline**: hyperpigmentation;
 - o **Azathioprine**: immunosuppression; **Cyclosporin**: kidney failure, HTN
- If DMARDs above don't control disease, **biologic anticytokine agents** (against TNF- α and IL-1)
- **Rituximab** is a biologic against CD20 that has demonstrated effectiveness for RA
- Monitoring RA consists of following patients Sx, functional status, and joint examinations
 - o ESR/CRP levels for inflammation monitoring; hand/foot films for disease progression
 - o Patients should be maintained on Ca and Vitamin D; routine bone density scan for osteoporosis

Seronegative Spondyloarthropathies

- Group of inflammatory disorders affecting spine joints and periarthritis structures including:
 - o **Ankylosing spondylitis (AS)**, Psoriatic arthritis, Reactive arthritis, enteropathic arthritis

Feature	AS	Reactive (SSCYE/Chlamydia)	Psoriatic	Enteropathic
Spine	Always	Occasional	Occasional	Infrequent
HLAB27	90%	70%	20%	10% (sacroiliac dz.)
Skin	None	Keratoderma, circinate balanitis	Psoriasis, nail pitting	Erythema nodosum
Eye	Uveitis	Uveitis, conjunctivitis	Uveitis (bilateral)	Uveitis (bilateral)
Natural Hx.	Chronic	Self-limiting	Chronic	Flares with IBD

History

- Chronic low back pain with morning stiffness in young adults is worrying for AS; Improvement with exercise further and nocturnal awakening due to pain enhances AS suspicion
- **Enthesopathy** (inflammation of ligaments and tendons) is a key feature of spondyloarthropathies
- Eye involvement: conjunctivitis (reactive), uveitis can present as pain, photophobia, ↓ vision

Physical Exam

- Sacroiliac involvement in AS may show pain on pelvic compression, limitation of lumbar spine flexion, extension, loss of normal lumbar lordosis, tenderness to palpation
- Inflammation in reactive/psoriatic causes digit swelling “sausage digit”
- Peripheral arthritis is often asymmetric, localized to lower extremities;
- Peripheral enteropathic arthritis flares with IBD, spinal locations do not flare with IBD
- Skin (not always present): **keratoderma blennorrhagica** (reactive) on soles of feet

DDx

- Low back pain: lumbar strain, herniated disk, spinal stenosis, malignancy
- Inflammatory Peripheral Arthritis: septic arthritis, RA, Gout, lyme disease, lupus, sarcoidosis

Diagnostic Evaluation

- Blood labs: ↑ ESR, ↑ CRP, ↑ IgA (AS) seronegative for rheumatoid factor and antinuclear antibody
- HLAB27 is **NOT** specific, not recommended for screening; useful in atypical cases
- Spinal and pelvic XR often normal early but good for monitoring; XR features of AS:
 - o Sacroiliitis (erosion of bone with pseudowidening); vertebrae squaring, ossification of ligaments
- Reactive arth.: Stool culture; **urethral chlamydial DNA probe** (urethritis); urinalysis (sterile pyuria)

Treatment

- AS is lifelong and may remain localized or ascend thoracic and vertebral spine
- Reactive: usually self-limited, can become chronic; if active chlamydia: azithromycin/doxycycline
- Abx do not have a role in enteric reactive arthritis
- Psoriatic and enteropathic arthritis may regress with Tx of underlying disease
 - o Removal of diseased bowel (enteropathic); Skin treatment (psoriatic)
- Anti-inflammatory meds are effective; back extension exercise help maintain mobility (sacroiliitis)
- **NSAIDs are first line therapy**
- Chronic disease (AS, chronic reactive) have ↑ risk for **spinal fractures**, cardiac complications (AS)

Connective Tissue Diseases

- CTD are characterized by alterations in immune function leading to **autoantibodies**
- CTD are most common in women (40-50y); genetic predisposition with certain MHC-II genes
- Pathology in CTD is diverse: Immune complex depositions (lupus), vascular damage, overproduction and accumulation of extracellular matrix components, altered immune responses

History

- Diffuse complaints consistent in systemic disease; Lupus: myalgia, arthralgia, fever, rash; Sjögren: dry mouth + eyes; polymyositis(PM): proximal muscle weakness; Scleroderma(SSc): Raynaud phenom.
- **Raynaud phenomenon:** vasospasm of small blood vessels, hand/foot color changes with cold/stress

Physical Exam

Disease	MSK findings	Derm findings	Other organs
SLE	Symmetric small joint arthritis	Malar rash, alopecia photosensitivity	Oral ulcers, pericarditis, interstitial lung disease, nephritis, cerebritis
SSc	Small/large joint arthralgia/swelling, Raynaud	Thick skin, calcinosis, telangiectasia	Esophageal hypomotility, pulmonary fibrosis/HTN
PM/DM	Proximal limb muscle weakness	Rash, telangiectasia	CHF, arrhythmia, lung dis.
Sjögren	Polyarthralgias, Raynaud	None specific	Dry eyes+mouth, corneal ulcers, thyroiditis, interstitial lung/renal

- Malar (butterfly) rash spares nasolabial folds; heliotrope rash of dermatomyositis (DM) is purple
- SSc mnemonic **CREST** (calcinosis, Raynaud, esophageal dysmotility, sclerodactyl, telangiectasia)

DDx

- Main DDx consists of the other CTD including RA and spondyloarthropathies
- Viral illness (Epstein-Barr, HIV) can mimic CTDs with arthritis, pericarditis, fever, myalgias
- Parotid and lacrimal involvement of sarcoidosis may be confused with Sjögren syndrome
- Distinguish PM from metabolic (glycogen storage disease) and neuromuscular (myasthenia gravis)

Diagnostic Evaluation

- Dx relies on clinical exam and systemic physical findings; Lab studies show nonspecific inflammation
- Certain antibodies may assist in Dx: **antinuclear antibody (ANA)** is most common (sens not spec)
- Active SLE lab abnormalities: immune complex glomerulonephritis (RBC casts/dysmorphic in urine), decreased complement, **leukopenia, autoimmune hemolytic anemia**

Treatment

- SLE: Goal is remission; mild disease with NSAIDs; visceral organ involvement requires prednisone
- SSc: Methotrexate if early/diffuse; IV epoprostanol for pulmonary HTN; ACEi for renal crisis
- PM/DM: high dose prednisone; worsening myopathy with improved lab markers is 2° to prednisone
- Sjögren: Artificial tears/saliva for dry mucosa; thyroid disease treatment; steroids for lung/renal dis.
- ↑ risk of malignancy in PM/DM/Sjögren; ↑ risk of atherosclerosis in SLE -> aggressive prevention

Vasculitis

- Vasculitides involve inflammation of blood vessels; classified by the size of vessels/organs involved:

Large Vessel Vasculitis	Medium Vessel Vasculitis	Small Vessel Vasculitis
- Takayasu arteritis	- Polyarteritis nodosa (PAN)	- ANCA associated vasculitis (MPA, GPA, EGPA)
- Giant cell arteritis	- Kawasaki disease	- Hypersensitivity vasculitis

- Many vasculitides associated with immune complex deposition or granulomatous involvement

History

- Nonspecific findings: fever, weight loss, malaise, arthralgias; organ-specific findings in some diseases:
 - o PAN: visceral arteries with **abdo pain**; Eosinophilic granulomatosis with polyangiitis (EGPA): **recurrent asthma**; GPA:**sinusitis, cough, dyspnea**; Temp arteritis: **headache, jaw claudication**

Physical Exam

- Skin: **palpable purpura** (raised red/purple lesions that do not blanch), often in hypersensitivity vas.
- HTN in renal vasculature (PAN, MPA, GPA); Diminished peripheral pulses (Takayasu);
- Eyes: episcleritis, uveitis; saddle-nose; CHF if cardiac involvement (EGPA)

DDx

- Vasculitis with fever, skin lesions and weight loss needs differentiating from **bacterial endocarditis**
- Palpable purpura also seen in **meningococcal, gonococcal** infections
- Eosinophilia (EGPA) seen in: **allergic bronchopulmonary aspergillosis, eosinophilic pneumonia**

Diagnostic Evaluation

- Inflammation: ↑ ESR, normochromic normocytic anemia, thrombocytosis, leukocytosis (infection)
- CXR: pulmonary infiltrates (GPA/EGPA), cavitary lesions (GPA), widened aorta (Takayasu/giant cell)
- Blood cultures with initial evaluation (infection); C-ANCA diagnostic for GPA; P-ANCA in MPA/EGPA
- ↑ RF may be seen in rheumatoid vasculitis; HCV antibody (cryoglobulinemia); HBsAg (PAN)
- Renal disease occurs most notably in GPA/MPA
- Biopsy is definitive test for inflammation and destruction; If biopsy not possible -> angiography

Vasculitis	Vessels Involved	Appearance
Hypersensitivity	Arterioles and venules	Leukocytoclastic vasculitis
EGPA	Various sizes including venules	Granulomas with eosinophils
MPA	Small arteries and veins	Mono/poly nuclear lymphocytes, necrotizing
GPA	Small arteries and veins	Granulomas
PAN	Small to medium size arteries	Mono/poly nuclear lymphocytes, necrotizing
Giant cell	Medium size arteries (temporal)	Granulomas
Takayasu	Large arteries (aorta, subclavian)	Usually not biopsied

Treatment

- If removal of offending agent not possible then immunosuppression is mainstay of Tx
- **Prednisone** and **cyclophosphamide** are first line therapy for GPA, MPA, and PAN
 - o Prednisone for several months then tapering; cyclophosphamide until remission
 - o To avoid cyclophosphamide complications (bladder cancer, infertility) **rituximab** used (GPA)
- Plasma exchange is used for life-threatening GPA and active renal disease
- Prednisone used for temporal arteritis and EGPA; Takayasu treated with steroids or methotrexate
- Complicated cases can have surgical repair with grafting of affected arteries

Amyloidosis

- Disorder characterized by extracellular deposition of fibrous protein (amyloid) in the body
- Amyloid histology: amorphous, eosinophilic, β -pleated sheet, green birefringence with polarized light
- Can be 1^o or 2^o; **AL amyloidosis** (immunoglobulin light-chain), **AA amyloidosis** (Serum Amyloid-A)
 - o AL: 1^o amyloidosis, multiple myeloma; AA: RA, chronic infection/inflammation, Mediterranean Fever
- Patients usually present with impairment to organs affected by AL or AA (kidney, heart, liver)

History

- Nonspecific Sx: fatigue, weight loss (usually quite high); organ specific symptoms more helpful:
 - o **Neuro:** autonomic dysfunction, carpal tunnel, distal polyneuropathy
 - o **Cardiac:** restrictive cardiomyopathy, conduction disturbance
 - o **Renal:** nephrotic syndrome, renal tubular acidosis
 - o **GI:** malabsorption, motility disorders, macroglossia; **Heme:** acquired factor X deficiency (AXD)
 - o **Hepatic:** intrahepatic cholestasis; **rheumatologic:** symmetric arthritis;

Physical Exam

- VS: bradycardia (conduction) or orthostatic hypoTN (autonomic)
- Fever suggests infectious (osteomyelitis with 2^o amyloidosis);
- ↑ JVP + Kussmaul sign (JVP rises instead of descends during inspiration) OR rapid descent of JVP (see picture on right)

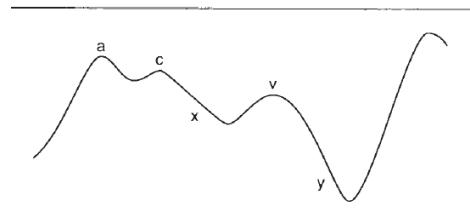


Figure 62-1 • Rapid y descent in the JVP seen in restrictive cardiomyopathy.

DDx

- Amyloidosis often considered in context of chronic wasting illness (fatigue, weight loss)
- Other etiologies such as malignancy may resemble or cause amyloidosis

Diagnostic Evaluation

- ECG: heart infiltration shown with conduction disturbance (AV block) and low voltage QRS
- Echocardiogram: myocardium “sparkling”, thickened ventricle wall; ↑ troponin/BNP has ↓ prognosis
- Urinalysis: proteinuria (nephrotic syndrome); light-chain excretion **NOT** detected by dipstick
- Urine Immunoelectrophoresis: monoclonal light-chain spike (1^o amyloidosis/multiple myeloma)
- Nonspecific lab findings: ↑ alkaline phosphatase (cholestasis), ↓ albumin (nephrotic), ↑ PT (AXD)
- Dx made with biopsy that shows green birefringence with polarized light after Congo red staining
 - o Risk of bleeding in affected organs makes biopsy dangerous; Dx alternative: **abdominal fat pad aspiration** (sensitivity = 70%) or **rectal biopsy**
- Amyloidosis is also detected in bone marrow biopsies that are done to r/o multiple myeloma

Treatment

- Focused on supportive care, no effective Tx for amyloidosis independently
- Diuretics for Sx relief of CHF, edema; AVOID digoxin (cardiotoxicity); dialysis in ESRD
- Tx of underlying etiology may prolong survival; Mediterranean fever treated with colchicine; autologous stem cell transplantation for young AL patients with limited organ involvement

Anemia

- Anemia is the reduction in total RBC mass, hemoglobin level, or percentage of hematocrit
- Anemia is a result of either: ↓ RBC production, ↑ RBC destruction (hemolysis), or blood loss

History

- Often asymptomatic unless ↓ hematocrit level is sudden or severe; general Sx: fatigue, dyspnea, dizzy
- Folate deficiency, liver disease, and alcohol consumption all can cause macrocytic anemias
- Assess for potential sites of blood loss; vaginal bleeding common source for premenopausal women
- GI bleed may have Hx of dark, tarry stools or bright red blood from rectum

Physical Exam

- Mild anemia usually has normal PE; if Hb < 11: pallor of nail beds, palmar creases, conjunctivae
- Fever suspicious of hemolytic anemia; glossitis and peripheral neuropathy suggests B₁₂ deficiency
- **Iron deficient anemia:** atrophic glossitis, angular cheilitis (mouth scaling), Koilonychia (spoon nails)

DDx

- Classified by mechanism/size of RBC; **microcytosis:** MCV < 80μm³; **macrocytosis:** MCV > 100μm³

↑ Reticulocyte	↓ Reticulocyte - Micro	↓ Reticulocyte - Macro	↓ Reticulocyte - Normocytic
<ul style="list-style-type: none"> - Acute blood loss (trauma) - Hemolysis 	<ul style="list-style-type: none"> - Iron deficiency (FeD) - Thalassemia - Anemia of Chronic Disease (ACD) - Sideroblastic anemia 	<ul style="list-style-type: none"> - B₁₂/folate deficiency - Excessive alcohol - Liver disease - Severe hypothyroidism - Myelodysplastic syndr. - Sideroblastic anemia 	<ul style="list-style-type: none"> - ACD - Renal failure - Multiple myeloma - Aplastic anemia - Hypothyroidism - Myelophthisis

- ACD is caused by iron trapping in reticuloendothelial system and suppression of erythropoiesis
 - o ACD categories: infection, malignancy, and inflammatory disease
- **Sideroblastic anemia:** ringed sideroblasts in bone marrow and iron accumulation in mitochondria
- **Myelodysplastic syndrome:** stem cell disorder with arrest in blood cell maturation (pancytopenia)
- **Myelophthisis:** extensive marrow infiltration inhibiting function (pancytopenia)
- **Thalassemia:** inherited defect in α- or β-globin gene resulting in ↓ production (often asymptomatic)

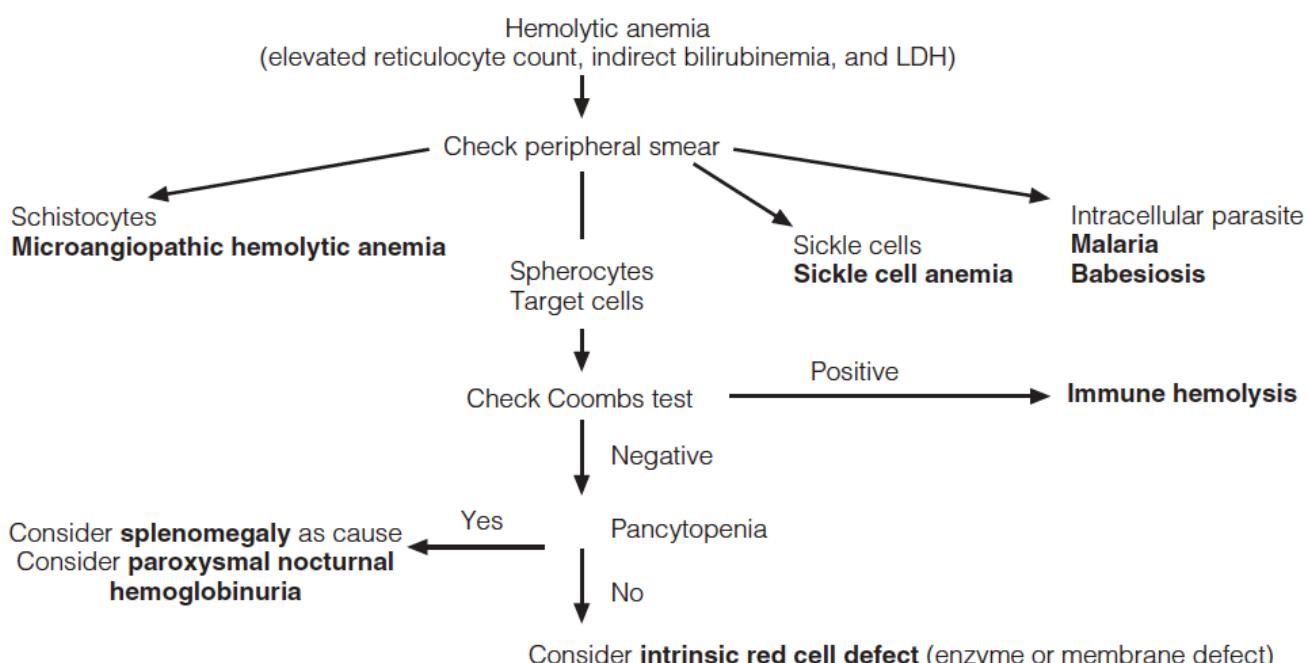
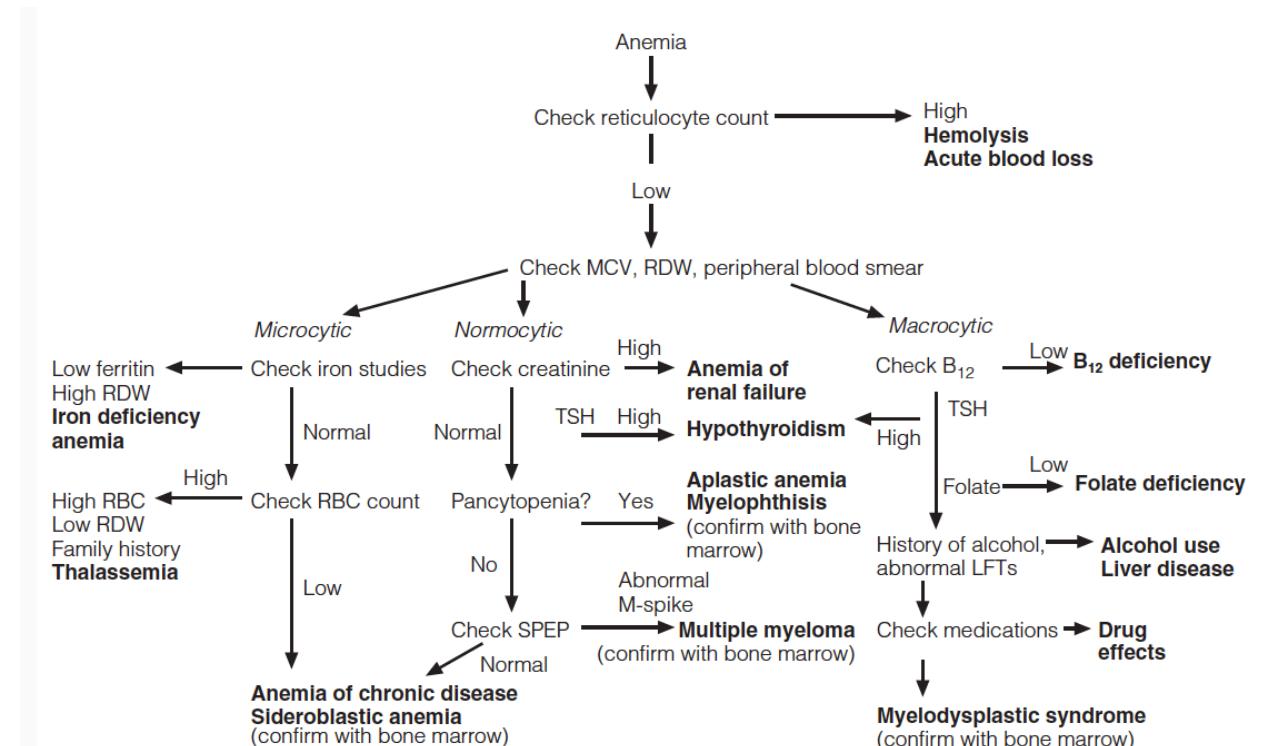
Diagnostic Evaluation

- Classify anemia by RBC index and RC; $RC_c = RC \times (Hc/Hc_{ex})$; <2%: ↓ RBC prod.; >3%: hemolysis/loss
- Examine peripheral smear for **RBC distribution width:** ↓RDW (thalassemia); ↑RDW (FeD anemia)
- **Microcytic Anemia:** all pure microcytic anemias associated with low reticulocytes (RC)
 - o Iron studies are useful initial tests; Difficult to distinguish ACD, FeD (both ↓ Fe)
 - o An ↑ RBC count suggestive thalassemia; β-thalassemia confirmed with β Hb A2

Disease	Iron	Total Iron Binding Capacity	Ferritin
FeD	↓	↑	↓
Thalassemia	Normal	Normal	Normal
ACD	↓	↓	↑
Sideroblastic	↑	Normal	Normal/↑

- **Macrocytic Anemia:** r/o ↑ RC first then subclassify as with/without DNA synthesis impairment:
 - o Megaloblastic anemias include B₁₂ and folate deficiencies (check levels) along with drug effects
 - o ↑ B₁₂ in myelodysplasia, ↑ lactate dehydrogenase in megaloblastic anemias; get LFTs and TSH

- **Normocytic Anemia:** r/o ↑ RC first; ACD is most common cause; aplastic has pancytopenia and 0 RC
 - o Serum protein electrophoresis and serum free light chains checked for multiple myeloma
 - o Bone marrow biopsy to r/o myelophthisis or other bone marrow process if chronic
- **FeD Anemia:** Empiric therapy for pregnant/menstruating women; GI bleed is most concerning cause
 - o Evaluate for GI bleed with endoscopy; FeD with no clear source may have malabsorption (celiac)
- **B₁₂ Deficiency:** Lack of intrinsic factor (pernicious anem.); bacterial overgrowth (**blind loop syndr.**)
- **Bone marrow biopsy indications:** pancytopenia (aplastic or marrow infiltration), macrocytic anemia of unknown etiology (suspected myelodysplasia), sideroblastic anemia, myelophthisis



Hemolytic Anemia

- Hemolytic anemia is characterized by ↓ Hb and ↑ RC count; can be mimic by acute blood loss
- Hemolysis cause by **extraerythrocytic** factors (acquired disease) or **intrinsic** RBC defect (inherited)
- **Intravascular** hemolysis: Hb binds to **haptoglobin** -> filtered by kidneys -> **urine hemosiderin** -> **hemoglobinuria** (positive occult blood on dipstick but no RBC [severe hemolysis only])
- **Extravascular** hemolysis: RBC removed by spleen-> little/no blood Hb-> no hemosiderin/globinuria

History

- No specific symptoms are associated with hemolytic anemia; Travel Hx may increase risk of malaria
- FHx of hemolytic anemia may be found in inherited RBC defects
- Drugs associated to warm-antibody hemolytic anemia: methyldopa, quinine, sulfonamides, penicillin
- G6PD deficiency + oxidative stress causes hemolysis: fava beans, sulfonamides, nitro, methylene blue

Physical Exam

- Fever suggests infectious or microangiopathic etiology; scleral icterus may be seen; **splenomegaly** may BE the cause of hemolysis or a CONSEQUENCE of hemolysis (not helpful in etiologic distinction)

DDx

Extraerythrocytic Factors				RBC Defects	
Microangiopathic (MAHA)	Immune-mediated	Infection	Splenomegaly	Hemoglobinopathies	Enzyme
- Hemolytic Uremic (HUS) - Thrombotic thrombocytopenic purpura (TTP) - Cardiac valve hemolysis - Disseminated intravascular coagulation (DIC)	- Warm antibody - Cold antibody	- Malaria - Babesiosis - Clostridial Toxin	- Infiltrative diseases - Portal hypertension	- Sickle Cell Disease (mutation in β-Hb)	- Pyruvate kinase deficiency - G6PD deficiency (X-linked)

- Membrane: Heredit. spherocytosis (HS), elliptocytosis, paroxysmal nocturnal hemoglobinuria (PNH)
 - o PNH results in lack of GPI anchor in RBC and complement-mediated hemolysis

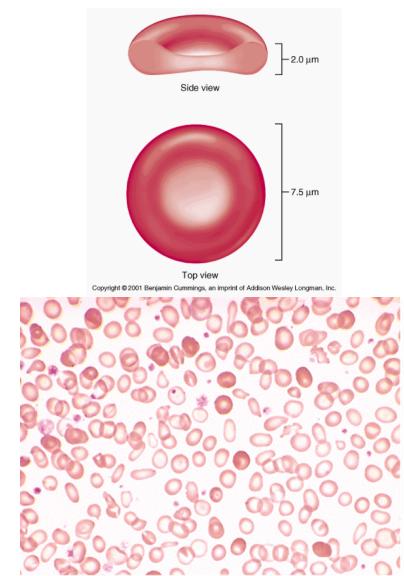
Diagnostic Evaluation

- Key labs: ↑ indirect bilirubin, ↑ lactate dehydrogenase (LDH), ↑ RC count, ↓ haptoglobin
 - o ↑LDH and ↑ bilirubin also seen in ineffective hematopoiesis (B₁₂ deficiency) **BUT ↓ RC count**
- **Thrombocytopenia** most prominent in TTP, HUS, DIC; PT is ↑ in DIC, normal in TTP, HUS
- **Peripheral Smear** next to look for abnormal RBC in hemolysis (target cells and spherocytes)
 - o Large numbers of spherocytes are limited to HS and warm-antibody hemolysis
 - o Elliptocytes are seen in elliptocytosis and severe iron deficiency; schistocytes confirms MAHA Dx
- If smear eliminates MAHA, **Coombs test** performed to evaluate for **immune mediated** hemolysis
 - o **Indirect** Coombs test looks for antibody in the patient's serum that agglutinate normal RBC
 - o **Direct** Coombs test is the definitive test for immune-mediated hemolysis (antibody on own RBC)
 - **Warm-antibody** hemolysis is IgG mediated (Direct Coombs + for C3 on RBC surface)
 - **Cold-antibody** hemolysis is IgM mediated (Direct Coombs + for C3 on cell surface)
- **Osmotic fragility test** used to look for membrane defects such as HS; **Flow cytometry** for Dx of PNH
- **Sickle Cell** may be confirmed by **hemoglobin electrophoresis** showing hemoglobin S
- **Fluorescent Spot Test** is reliable measure for G6PD deficiency

AHD – Approach To Anemia

Approach

- Morphological (MCV): Microcytic vs. Macrocytic vs. Normocytic
- Kinetic (reticulocyte counts): hypoproliferative vs. hyperproliferative
- Tools: Hx, CBC, peripheral blood smear, imaging and special tests
- RBC have a Hb filled periphery (dark red) and a Hb **free** center (pale)



Microcytic Anemia

- Iron-deficiency anemia (IDA)
 - o Hx: chronic blood loss
 - o ↓ Ferritin, Serum Fe, saturation; ↑ TIBC
 - o Not all RBC round (poikilocytosis), not all same size (anisocytosis)
- Anemia of chronic disease or inflammation
 - o Decreased RBC production
 - o ↓ Serum Fe, TIBC, Saturation; ↑/normal ferritin
- Hemoglobinopathies (thalassemias, sickle cells)
 - o Hx: ethnic origin, familial, splenomegaly
 - o CBC shows microcytic picture, Hemoglobin electrophoresis helps make Dx
 - Nucleated RBCs, codocytes (target cells), sickled cells
 - o Types of hemoglobin in blood helps differentiate between alpha and beta thalassemia
 - Beta thalassemia (problem with beta subunit) shows variety of weird hemoglobin
 - Alpha thalassemia has normal hemoglobin since beta can only bind to specific alpha subunits
- Sideroblastic anemias

Macrocytic Anemia

- Ineffective erythropoiesis
 - o B12/folate deficiency: lack of building blocks, diseased marrow, or drug interference
 - Hx: neuro symptoms, clues to etiology of nutritional deficiency
 - Tests: B12/folate, homocysteine, methylmalonic acid
 - Etiology: strict vegan, antacids, anti-parietal cell/intrinsic factor antibody, partial gastrectomy, pancreatic insufficiency, Ileal disease, celiac disease
 - o Myelodysplastic syndrome: clonal disorder of marrow
 - Hx: B symptoms (fever, weight loss, night sweats)
 - Dx: marrow biopsy (hyposegmented neutrophils)
 - o Drugs (AZT, hydroxyurea)
 - o Marrow replacement: leukemia/lymphoma
- Effective erythropoiesis: Reticulocytosis vs. Liver Dz vs. Alcohol abuse vs. Hypothyroidism

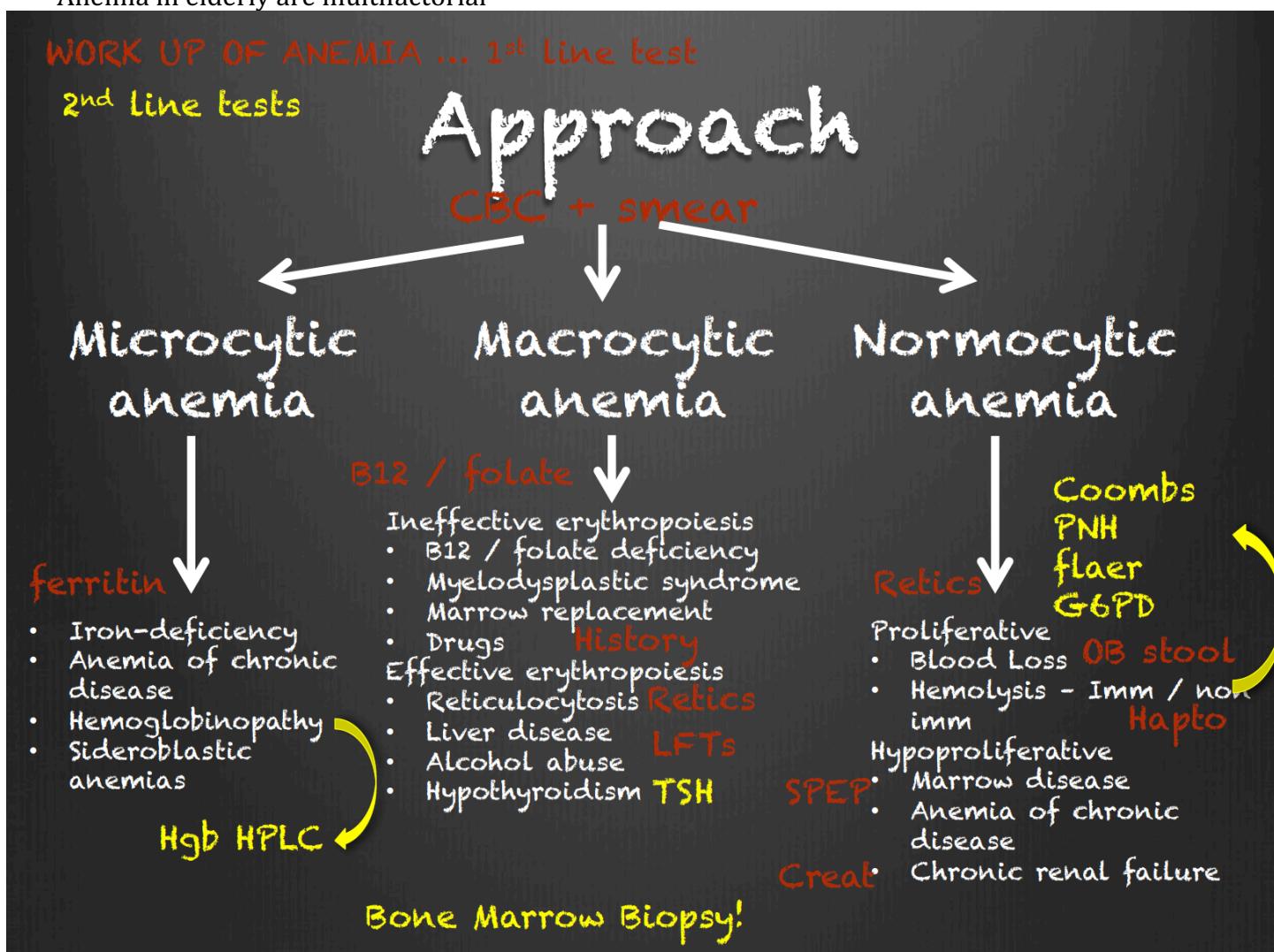
Normocytic Anemia

- Proliferative (↑ reticulocytes)
 - o Blood loss (usually from GI)
 - o Hemolysis (immune vs. non-immune): in vivo RBC destruction
 - ↓ **haptoglobin**, ↑ indirect bili, ↑ LDH, ↑ reticulocytes
 - Clues to etiology: B-symptoms (malignancy), autoimmune diseases, drugs, transfusion hx
 - Tests: coombs test (+ in immune)
 - Non-immune: mingroangiopathic hemolytic anemia (MAHA), HUS/TTP, DIC, frag RBCs, hereditary spherocytosis/other membrane defects, G6PD deficiencies, hemoglobinopathies

- Test for spherocytes with osmotic fragility test
- Paroxysmal Nocturnal Hemoglobinuria
 - Clonal stem cell disorder caused by mutation in the PIG A gene
 - Intravascular hemolysis, cytopenias, thrombosis
 - Dx with flow cytometry (FLAER test)
- Hypoproliferative (\downarrow reticulocytes)
 - Marrow disease: multiple myeloma, leukemia, lymphoma
 - Anemia of chronic disease/inflammation
 - Chronic renal failure

Important Messages

- Worrisome features
 - Rapidly progressive anemia -> hemolysis/bleeding/advanced marrow disease
 - Associated cytopenias -> marrow disease
 - B-symptoms -> hematologic malignancy
 - IDA in male or postmenopausal females
- Anemia in elderly are multifactorial



Adenopathy

- Adenopathy is enlargement of the lymph nodes

History

- Adenopathy lasting more than a week is less likely to be infectious in origin; Sx (etiologies):
 - o Weight loss, night sweats (lymphoma, metastatic cancer, TB); pets (cat-scratch disease, toxo.)
 - o Sore throat (mononucleosis, pharyngitis); genital lesion (syphilis, chancroid)
 - o Hx of travel to southwestern USA (coccidioidomycosis) or Midwestern USA (histoplasmosis)
 - o Hx of IV drug use or high-risk sexual behaviour (HIV)
- Age > 50 more likely to be malignant etiology; Age < 30 benign 80% of the time
- Ask about phenytoin (Dilantin) use as it can cause pseudo-lymphoma syndrome

Physical Exam

- Location of lymphadenopathy often helps Dx; tender, erythematous nodes consistent with infection
- Rubbery adenopathy found in lymphoma; metastatic disease tends to present as hard, fixed nodes
- Erythema nodosum with hilar adenopathy is suggestive of **sarcoidosis**
- Maculopapular rash involving palms and soles seen in **syphilis**
- Splenomegaly seen in infectious mononucleosis or hematologic malignancy

DDx

- Evaluation is best categorized by location

Generalized	Cervical	Inguinal	Supraclavicular	Hilar
- HIV	- Mononucleosis	- Syphilis	- Mediastinal or pulmonary malignancy (right)	- Sarcoidosis (bilateral)
- Lymphoma	- Malignancy	- HSV	- Abdominal malignancy (left)	- Lymphoma
- Hypersensitivity	- Pharyngitis	- Chancroid		- TB
- SLE	- Toxoplasmosis	- Malignancy		- Bronchogenic Carcinoma (unilateral)
- Secondary Syphilis	- Sarcoidosis			- Fungal (bilateral)
- TB	- TB			

Diagnostic Evaluation

- In young patient with cervical adenopathy, mononucleosis is the primary consideration
 - o CBC shows lymphocytosis with atypia; **heterophile antibody** confirms mononucleosis Dx
 - o If heterophile negative, consider CMV, HIV, and toxoplasmosis
- Inguinal adenopathy: urethral or cervical cultures to rule out STI
- Older patient with supraclavicular adenopathy: CXR to r/o bronchogenic carcinoma or lymphoma
 - o These patients are likely to get biopsy due to concern of malignancy
- Mammogram for all women with axillary adenopathy (+ biopsy if infection ruled out)
- Asymptomatic hilar adenopathy: follow if TB/fungal r/o
- **Lymph node biopsy** is the definitive diagnostic test for any adenopathy; Early biopsy considered in:
 - o Node >2-3cm without suspicion of mono.; adenopathy + abnormal CXR; supraclavicular + old;
- Other tests: TB skin test, toxoplasma titers, HIV antibody testing, Rapid plasma (r/o syphilis)

Bleeding Disorders

- Defects in coagulation or thrombolysis can lead to either **hypercoaguability** or **bleeding disorders**
- **Bleeding disorders** are classified by the defect in the clotting cascade:
 - o ↓ clotting factors (inherited, ↓ production), thrombocytopenia, abnormal platelet function, drugs
- Most common hemorrhagic disorders are **acquired**:
 - o Vit K deficiency: ↓ in coagulation factors II, VII, IX, X; Warfarin interferes with Vit K(similar effect)
 - o Liver Failure: liver produces/metabolizes coagulation factors; failure causes bleeding tendency
 - o DIC: diseases trigger accelerated unregulated activation of coagulation cascades
- **Inherited** bleeding disorders: von Wilebrand disease (vWD) and hemophilia

History

- Bleeding disorders may present with **epistaxis** or **easy bruising**, otherwise asymptomatic
- **Inherited disorders** present with abnormal bleeding young or during times of hemostatic stress
 - o Lack of bleeding after surgery argues AGAINST inherited disorder; FHx important clue FOR
- Meds Hx: anticoagulants (warfarin, aspirin); some Abx cause immune-mediated platelet destruction

Physical Exam

- **Platelet** disorders usually manifest as **superficial** bleeding (skin, mucous membranes, GI, urinary)
 - o Skin: petechiae, ecchymosis; bleeds occurs **immediately** after trauma (can't make platelet plug)
- **Coagulation Factor** defects manifest as **deeper** bleeding (joints, peritoneum, other cavities)
 - o Platelet function intact so bleeding **does not** occur immediately after trauma (delay hours -days)
- Physical exam should look for signs of liver disease and presence of splenomegaly

DDx

Platelet Disorders	Coagulation Factor Disorders	Fibrinolytic Pathway
- Abnormal function (vWD, aspirin/NSAID)	- Defective factors (hemophilia) - Consumption of factors (DIC) - Vit K deficiency (diet, malabsorption, liver dis.) - Vit K interference (warfarin) - Coagulation factor interference (heparin)	- Exogenous plasminogen activator (Tx for MI/stroke) - Abnormal regulation (plasmin inhibitor deficiency)
- Thrombocytopenia (DIC, marrow failure, immune)		

Diagnostic Evaluation

- Initial workup: CBC, Prothrombin time (PT), activated partial thromboplastin time (aPTT)
 - o CBC for WBC, RBC, platelets; aPTT assess **intrinsic limb** of coagulation; PT assess **extrinsic limb**

Disease	Platelets	PT	aPTT	Thrombin Time	Fibrinogen
Thrombocytopenia	↓	Normal	Normal	Normal	Normal
DIC	↓	↑	↑	↑	↓
Hemophilia A (VIII deficiency)	Normal	Normal	↑	Normal	Normal
vWD	Normal	Normal	Normal/↑	Normal	Normal
Vit K deficiency (diet/warfarin)	Normal	↑	Normal	Normal	Normal
Dysfibrinogenemia	Normal	↑	↑	↑	Normal

- Thrombocytopenia may be caused by ↑destruction, ↓production, or sequestration
 - o ↑ destruction: HUS, TTP, DIC; **Idiopathic TP**: immune mediated destruction of platelets

Treatment

- Transfusion of blood products (NOT in DIC, TTP, HUS, heparin); **Frozen plasma**: rapid coagulation factor replacement; **platelet** transfusion (thrombocytopenia); **prednisone** (ITP); **splenectomy** if thrombocytopenia occurs after prednisone removal in ITP; **Oral vitamin K** (vitamin K deficiency)

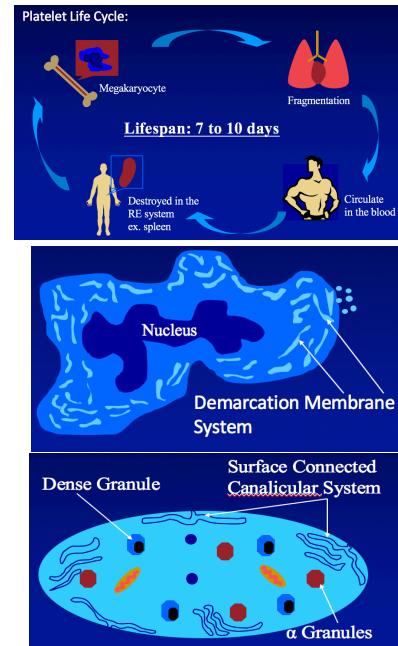
AHD – Platelets and Platelet Problems

Definitions

- Platelets: anuclear cells which circulate in the blood and participate in coagulation
- Megakaryocytes: precursors of platelets found in the bone marrow
- Thrombocytopenia: peripheral blood platelet count **below** the lower limits of normal
- Thrombocytosis: peripheral blood platelet count **higher** than normal

Platelet Life Cycle

- Lifespan is 7 – 10 days
- Megakaryocytes from marrow go to lungs for fragmentations, circulate in the blood, and then destroyed in the RE system by the spleen



Megakaryocytes

- Multilobed, nucleated, and polyploidy (4N to 64N)
- Demarcation membrane system from invagination of plasma membrane system and demarcates areas of cytoplasm that will form platelets

Platelet Structure

- Dense Granules: ADP, Calcium, Serotonin
- Surface connected canicular system: membrane bound channels for endocytosis and secretion
- α granules: adhesive proteins, coagulation factors, growth modulators
- Platelet adhesion receptors for Collagen, fibrinogen and von Willebrand factor (vWF)

Platelet function during injury (Platelet Activation)

- Adhesion
 - o Vascular injury exposes collagen vWF, Tissue factor and fibronectin
- Spreading or shape change
 - o Platelets adhere to and spread over exposed collagen and lose discoid shape/filopodial projections
- Secretion
 - o Platelet agonists: collagen, thrombin, ADP, TxA₂
 - o Platelet secretion: α granules (fibrinogen), Dense granules (ADP), platelet membrane (TxA₂)
 - o Results in recruitment and activation; Changes vascular tone, smooth muscle
- Aggregation
 - o Occurs when fibrinogen binds to its platelet receptor (GPIIb/IIIa)
 - o Aggregates of platelets form a plug

Thrombocytopenia

- Platelet abnormalities lead to defects in primary hemostasis
- Skin or mucosal bleeding: bruising, petechiae, gum bleeding, epistaxis, menorrhagia
- Symptoms often not seen until platelet counts extremely low
 - o 150-400 (normal); 50-150 (rare bleeding); 20-50 (bleeding with trauma/surgery); **10-20 (bruising, gum bleeding); < 10 (greater chance of spontaneous bleeding)**
- Classification of thrombocytopenia:
 - o Decreased Production of platelets

- Empty bone marrow (aplastic anemia, chemotherapy)
- Replaced bone marrow (leukemia, cancer)
- Dysfunctional bone marrow (myelodysplasia)
- Sequestration (pooling) of platelets in the spleen
 - Up to a third of the circulating platelet pool is normally found in the spleen
 - Any condition which may cause enlargement of the spleen can cause pooling
- Increased Destruction of platelets
 - Some disease lead to a shortened lifespan of platelets
 - Increased consumption (in coagulation)
 - Increased destruction (immune mediated)

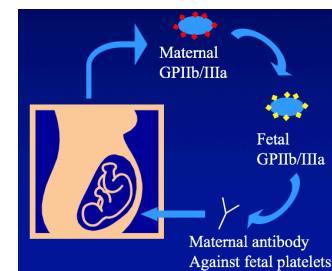
Non-Immune Platelet Consumption	Immune Thrombocytopenia
<ul style="list-style-type: none"> - Disseminated Intra-Vascular Coagulation (DIC) - Thrombotic Thrombocytopenic Purpura (TTP) - Hemolytic Uremic Syndrome (HUS) 	<ul style="list-style-type: none"> - Idiopathic Thrombocytopenic Purpura (ITP) - Neonatal Alloimmune Thrombocytopenia (NAIT) - Post-Transfusion Purpura (PTP)

Idiopathic Thrombocytopenic Purpura

- Common cause of thrombocytopenia
- ITP is an autoimmune process: antibodies are made against self-antigens
- Antibody coated platelets are destroyed by cells of the RE system in the spleen

Neonatal Alloimmune Thrombocytopenia

- Rare cause of neonatal thrombocytopenia
- NAIT is an alloimmune process: mom makes antibodies to an antigen which is foreign to her



Thrombocytosis (Platelet > 450)

- Primary: a form of myeloproliferative disease
- Secondary: inflammation, surgery, hyposplenism, asplenia, hemorrhage/iron deficiency
- Over-medication with drugs that treat thrombocytopenia may also cause this

Qualitative Platelet Disorders

- Disorders in which the platelet count is normal but the function is abnormal
- Congenital:
 - Bernard Soulier Syndrome: abnormal or absent vWF receptor
 - Glanzmann thrombasthenia: abnormal or absent fibrinogen receptor
 - Gray Platelet Syndrome: absent alpha granules
- Acquired
 - Aspirin: inhibits cyclo-oxygenase and prevents conversion of arachidonic acid to prostaglandins and eventual formation of TxA₂
 - Ticlopidine: impairs binding of fibrinogen to GP IIb/IIIa and ADP induced platelet aggregation
 - Systemic diseases that affect platelet function (renal, cardiopulmonary bypass, myelodysplasia)

Investigations for Platelet Disorders

- CBC, Liver/renal function, PT/PTT (coagulation), bone marrow aspirate
- Bleeding time (normal 6-9 minutes)
- Platelet aggregation studies, electron microscopy (alpha/dense granules), platelet glycoprotein analysis
- Platelet antibody testing

Breast Cancer

- Most common type (F) and 2nd most common cancer death (F); ↑ Risk with FHx, BRCA 1/2 genes
- Other RF are related to hormones: Early menarche, late menopause, nulliparity, late pregnancy
 - o Combined hormone therapy (Estrogen and progesterone) ↑ risk; Diet (fat/alcohol) do NOT ↑ risk

History

- Asymptomatic **breast mass** is the most common complaint; Important Hx about mass:
 - o Associated RF, duration of mass, change in size, menstrual Hx, **nipple discharge**
 - o **Unilateral BLOODY** discharge ↑ concern/risk for malignancy

Physical Exam

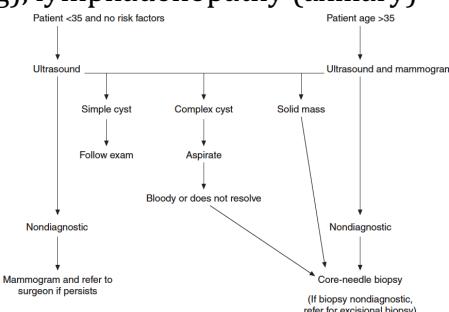
- Focused on finding mass; benign are often mobile, soft, cystic (criteria are not specific to r/o cancer)
- Examine breasts for asymmetry, skin changes (thickening/dimpling), lymphadenopathy (axillary)

DDx

- Non-malignant: Cyst, fibroadenoma, fibrocystic changes
- **Nipple discharge:** ductal papilloma, ductal ectasia, prolactinoma

Diagnostic Evaluation

- Ultrasound: differentiate cystic from solid mass (young patient)
- **Mammography** for suspicious/non-palpable lesions;
- Irregular speculated mass/cluster of microcalcifications suggests carcinoma; HIGH false negative rate so normal does **NOT** r/o cancer
- Fine needle aspiration or core needle biopsy help with Dx; if suspicious result, do **excisional biopsy**
- Mammograms used to screen women 50-74; Breast MRI screening in women with BRCA



Breast Cancer Staging

- Number of lymph nodes involved strongly correlated with prognosis; Other ↑ prognosis factors:
 - o Tumour < 2cm; steroid receptors (ER/PR) on tumor; no HER-2/neu oncogenes; low grade
- Stage 0: in situ; Stage 1: 1-3 nodes + 2-5 cm; Stage 3: 3+ nodes + >5cm; Stage 4: metastatic disease

Treatment

- **Lumpectomy + radiation** (breast conserving surgery) OR **modified radical mastectomy** with +Dx
- **Sentinel lymph node mapping** to locate/remove 1^o draining node (if negative, leave axillary nodes)
- Adjuvant therapy (early stage): chemo/hormonal therapy; ↑ benefit in + nodes, less for - nodes
- **Tamoxifen** used in **premenopausal** women with steroid receptor positive tumours
- **Aromatase inhibitors** for **postmenopausal** women with steroid receptor positive tumours
- **Ovarian ablation:** only beneficial as hormone treatment in premenopausal women
- **Chemotherapy** is the mainstay of treatment in high-risk disease (+ lymph nodes)
- **HER-2/neu** monoclonal antibody can be used for tumours where this growth factor is overexpressed
- Stage 4 is not curable; Aromatase inhibitors (1st line Tx); oophorectomy in premenopausal women
- Follow-up involves screening and monitoring for recurrence (5x ↑ risk in contralateral breast)

Prostate Cancer

- Most common cancer (M) and second most common cause of cancer deaths (M).
- Risk ↑ with age, FHx, black ethnicity, red meat, animal fats; ↓ Risk with lycopene (tomato products)

History

- Prostate cancer often detected by screening prostate specific antigen (PSA) test and is asymptomatic
- Symptoms of obstruction (urinary frequency, urgency, nocturia) not distinguishable from BPH

Physical Exam

- DRE Often normal or diffusely enlarged prostate consistent with BPH
- Sometimes presents as a prostate nodule but many detected this way are locally advanced

DDx

- In a patient with ↑ PSA other prostate diseases considered: BPH, prostatitis
 - o Acute urinary retention, transurethral resection of prostate and prostate biopsy can all ↑ PSA

Diagnostic Evaluation

- PSA is 90% sensitive and 85% specific to prostate cancer; <4 ug/mL: normal, > 10 ug/mL: high risk
 - o **Age-specific PSA** changes range of normal PSA (higher for >70, lower for < 50)
 - o **Free PSA** values usually lower in patients with prostate cancer
- **Transrectal biopsy:** definitive Dx test
- Screening is controversial due to unclear effects on mortality (high false positive, unnecessary Tx)
 - o A normal PSA does not definitely rule out prostate cancer; Screen patients 50+
- Gleason score (GS) used for grading; Gleason score = sum 2 most common patterns in biopsy (2-10)
 - o Well differentiated (GS 2-4), moderately (GS 5-6), moderate-poor (GS 7), poor (GS 8-10)
 - o Score of 6 or less is considered low risk for prostate cancer related death
- Staging: nonpalpable (T1), palpable (T3), advanced (T3-T4); lymph node involvement (N0, N1)
- MRI scan can help identify extracapsular disease in certain individuals

Treatment

- Tx involves Surgery, radiation therapy, +/- androgen deprivation therapy (ADT)
- Tx regimen depends on GS, advanced disease status, comorbidities, patient preference
- In low grade cancers (GS < 7) **active surveillance**; Serial PSA, DRE and repeat biopsy for progression
- **Radical prostatectomy** in prostate-confined disease with few comorbidities; impotence side-effect
- **Radiation** (external beam or brachytherapy) comparable to surgery for survival; add ADT in T3/T4
- **Androgen Deprivation Therapy** for locally (T3/T4) or regionally advanced (N1) or metastases(M1)
 - o **Orchiectomy** (castration): gold standard but psychological morbidity is high
 - o **Lutenizing hormone-releasing hormone** (LHRH) agonist: suppress LH by stimulating LH receptor; side effects of osteoporosis, muscle wasting, hot flashes;
 - o Most patients respond to ADT but hormone-resistance eventually develops so chemo is added
- Follow up involves monitoring for recurrence usually with PSA test
 - o PSA should be <0.1 ng/ml after surgery; specific level varies with radiation but still low
 - o A steady ↑ in PSA is biochemical recurrence, +/- ADT (not everyone develops metastases)
 - o Any new onset back pain should be evaluated for bone metastases (XR or bone scan)

Leukemia

- Leukemias are neoplasms of the **bone marrow** that spread to peripheral blood and body; Subtypes:
 - o Acute Lymphoblastic Leukemia (ALL); Acute myelogenous Leukemia (AML), Chronic lymphocytic Leukemia (CLL), chronic myelogenous Leukemia (CML)
 - o ALL is mainly a disease of kids; CLL (most common, age > 50); CML/AML in age > 65
- Associated environmental exposures: **radiation exposure** (CML, AML), **chemotherapy** (AML), **chemical toxins** (*Benzene* – AML, *Agent Orange* – CLL), myelodysplastic syndrome (AML) [MDS]
- **Philadelphia chromosome** (translocation 9;22) associated with CML; t(15;17) in AML
- CLL characterized by a mature B-cell line (CD19+) that also expressed CD5

History

- **ALL/AML:** Constitutional symptoms (fever, malaise, dyspnea, fatigue), bleeding (thrombocytopenia), infection (sepsis), bone pain, neuro symptoms (headache, seizure, cranial nerve palsies)
- **CLL/CML:** usually silent; **CML** characterized by mild then blast phase; **CLL** may mimic lymphoma

Physical Exam

- Ecchymosis + petechiae (thrombocytopenia), lymphadenopathy (CLL), hepatosplenomegaly (CML), gingival hypertrophy (AML),

DDx

- Patient with ↑ WBC: leukemia, leukemoid reaction (infection/paraneoplastic), demargination of neutrophils (physiologic stress, corticosteroids)

Diagnostic Evaluation

- **Elevated WBC** is hallmark of leukemia (>15,000 – 100,000);
- **AML:** Peripheral smear shows myeloblasts + thrombocytopenia; blasts have prominent nucleoli with ↑ nuclear-to-cytoplasm ratio and lack of granules; **AUER ROD** key feature pathognomonic for AML
- **CML:** Leukocytosis + thrombocytosis; Lack of alkaline phosphatase (not seen in leukemoid reactions)
- **CLL:** lymphocyte predominance (absolute > 5000); fragile lymphocyte are flattened (**smudge cells**)
- **Bone marrow biopsy:** definitive for **AML** Dx (>20% blast cells); **CML** shows hypercellular marrow + ↑ myeloid cells and Philadelphia Chromosome (genetic testing)
- **Flow cytometry:** shows typical clonal phenotype in **CLL**; biopsy often not needed
- Other labs: hemolytic anemia, ITP, hypogammaglobulinemia (CLL); DIC (APL), Hyperuricemia (AML)

Treatment

- **AML:** remission induction with chemotherapy; Patients who don't remiss often respond to other Tx
 - o Relapse common in AML; Stem cell transplant (SCT) can be performed at 1st relapse
 - o Acute promyelocytic leukemia (AML class) Tx with chemo + **all trans retinoic acid**
- **CML:** Inhibition of the tyrosine kinase produced; effective in chronic, accelerated, and blast phases
- **CLL:** relatively benign course so not treated unless complications arise (organomegaly, systemic Sx)
 - o No standard regimen for treatment, often combinations of: **purine analogue, alkylating agents, and monoclonal antibody** against CD20
 - o Disease can transform to more aggressive disease and is then treated like lymphoma (suspect this if patient develops B symptoms or rapid enlargement of lymph nodes)

Lymphoma

- Lymphomas are neoplasms of hematopoietic cells that arise in **peripheral lymphoid tissue**
 - o Separated into **Hodgkin lymphoma** (HL) and **non-Hodgkin lymphoma** (NHL) [most common]

Hodgkin	Indolent NHL	Aggressive NHL	Highly Aggressive NHL
- Nodular sclerosis	- Follicular	- Diffuse large B-cell	- Burkitt lymphoma
- Mixed cellularity	- Small lymphocytic	- Mantle cell	- Precursor lymphoblastic
- Lymphocyte rich	- Marginal zone	- Anaplastic large cell	
- Lymphocyte poor			

- Etiology often unknown; Evidence of viral infection role; HIV and immunosuppression ↑ risk of NHL
- *H. pylori* associated with gastric mucosal-associated lymphoma; abx usually leads to remission
- Genetic translocations for lymphomas: Follicular t(14;18); Mantle cell t(11;14); Burkitt t(8:14)

History

- Painless lymphadenopathy +/- mass; common locations: axillary, supraclavicular, and cervical nodes
- Mediastinal adenopathy can cause cough/respiratory compromise; B symptoms may also be present
- Unusual Sx is ↑ pain with alcohol ingestion (HL)

Physical Exam

- Lymph nodes are usually firm, freely mobile, and non-tender; splenomegaly may be present

DDx

- DDx involves conditions related to lymphadenopathy (see few chapters back)

Diagnostic Evaluation

- Dx made with biopsy of suspicious nodes/masses; Excisional biopsy necessary for architectural info
- **HL:** presence of **Reed-Sternberg cell**, large cell with bilobulated nucleus and "owl's eye" nucleoli
- **CT** and **bone marrow biopsy** are done in the workup to determine stage of disease
- **PET** scan for indication of splenic involvement and suspicious lymph nodes and bone marrow
- **Ann arbor staging classification:** 1 (1 node/group); 2 (2+ nodes/group same side of diaphragm); 3 (nodal involvement on both sides of diaphragm); 4 (disseminated, extralymphatic involvement)
- Prognosis: ↑ lactate dehydrogenase has worse outcomes; all NHL patients need HIV testing

Treatment

- **Limited stage HL:** chemo + radio therapy; **ABVD** (Adriamycin, bleomycin, vinblastine, dacarbazine)
 - o Bleomycin can cause long-term pulmonary toxicity; doxorubicin can cause cardiomyopathy
- **Advanced HL:** Also treated with ABVD
- Initial Tx for **indolent lymphoma** is like leukemia; **rituximab** (anti-CD20) +/- **bendamustine**
- **Follicular lymphomas** are treated like aggressive lymphomas; potentially curable with chemo
- **Aggressive NHL:** chemo **R-CHOP** (rituximab, cyclophosphamide, doxorubicin, oncovin, prednisone)
 - o Patients who don't respond may be considered for additional multidrug regimens or stem cell transplantation
- Follow-up for remission done with PET-CT scans every 6 months; Radiation to head and neck ↑ risk for other cancers (breast, lung, thyroid); Also have risk of premature CAD and hypothyroidism

Headache

- Headache is common and separated into primary (migraine, cluster, tension) and secondary types:
 - o **Vascular:** Subarachnoid hemorrhage, subdural hematoma, carotid dissection, AVM, temporal arteritis
 - o **Intracranial masses:** primary brain tumours, metastases; **Infection:** meningitis, sinusitis
 - o **Severe HTN; Pseudotumor cerebri**
- Most have primary headaches; tension (most common prevalence), migraine (most common for Tx)
 - o Migraine often 20-40y (F:M 3:1); Cluster 30-40y (F:M 1:5); Temporal arteritis in age > 50

History

Characteristic	Migraine	Tension	Cluster
Quality	Pounding, pulsatile	Nonpulsatile, mild-mod.	Sharp, stabbing
Location	Uni or bilateral	Bilateral	Unilateral
Associated Sx	Nausea, vomit, photo/phono phobia	Myofascial sensitivity	Lacrimation, congestion
Activity	Disabling, rest in dark room	Rest or inactive	Restless, agitated
Acute Tx	Triptans, NSAIDs	NSAIDs, ASA, Tylenol	O ₂ , Triptans

- **Secondary headaches** that present with worrisome features on Hx:
 - o Worst headache of life/Thunderclap (SAH); First exertional headache (SAH, carotid dissection); new headache/ > 50 (tumour, temp. arteritis, stroke); stiff neck (meningitis, SAH); focal neuro deficit (brain tumour); personal Hx of cancer (metastases); pregnant (venous sinus thrombosis)
- **Medication induced headaches:** headache relief med overuse, caffeine, or birth control (estrogen)
- Patient who complains of **morning** headaches should be evaluated for **obstructive sleep apnea**
- **Temporal arteritis** presents as general headache in older patient +/- jaw claudication

Physical Exam

- Primary headaches have few findings, PE should focus on secondary sources:
 - o BP (HTN emergency); neuro exam for nuchal rigidity/AMS (meningitis); fundoscopy for papilledema; temporal artery tenderness; myofascial tenderness

Diagnostic Evaluation

- Main decision is +/- need for imaging; Hx and PE indicative of 1⁰ headache, usually not required; Imaging indicated for patients with focal neuro deficit, AMS, or worrisome Hx features
- If sudden onset headache: CT quick, can detect SAH; MRI has higher yield for aneurysm/neoplasm
- Lab tests not required for most headaches; ESR/CRP may be ↑ in temporal arteritis if suspected
- LP to diagnose meningitis; CT sensitivity decreases over time for SAH

Treatment

- **Migraine:** mild -> NSAID +/- **prochlorperazine** (nausea); moderate+ -> **Triptans** (vasoconstriction)
- **Preventative Tx** for migraines indicated if frequent and poor response to meds
 - o Goal of prophylaxis is decrease number by ½: **B-blockers, ACEi, antiepileptics**
- **Tension:** often responds to NSAID, Aspirin, acetaminophen; combine med with caffeine
 - o May exist with migraine (Tx like migraine); Prophylaxis with tricyclic antidepressants if severe
- **Cluster:** respond to high-flow oxygen; triptans also effective in acute attacks
- Other: regular sleep, exercise, regular meals, avoidance of too much med to prevent **rebound** headache

Delirium

- Delirium is a state of impaired consciousness and cognition developing over hours to days
- Pathogenesis is multifactorial; conditions that ↑ **baseline susceptibility to delirium**:
 - o Stroke, Dementia, organic brain disease (i.e. PD), old age, sensory impairment, depression
- **Precipitating factors:** medications (interactions, abuse, withdrawal), sleep deprivation, infection, dehydration, pain, immobilization, metabolic (lytes, hypoxemia), organ failure, hyper/hypothermia

History

- **Acute onset of confusion and inattention;** unable to focus/follow commands during interview
- **Disorganized thinking** (incoherence, rambling, tangential) and **altered consciousness** (lethargic)
- May demonstrate **psychomotor** agitation or retardation, hallucination, sleep-wake cycle changes
- Assess MHx and try to get indication of baseline state; **Timeline** of changes is of primary importance
- Identify: med changes/nonadherence/abuse, decompensation of chronic illness, acute illness

Physical Exam

- Vital signs, oxygenation, hydration status (mucous membranes, skin turgor), signs of cranial trauma, skin (cyanosis, IV drug use), neuro exam (focused deficit), survey for infection, mental status exam

DDx

- **Dementia** also presents with impaired cognition but NOT impaired level of consciousness;
- **Psychotic disorders** present with disorganized thinking but less often attention deficits
- Behaviour changes that only occur at night is NOT delirium but rather a circadian rhythm disorder

Diagnostic Evaluation

- First step often involves r/o **medication effect** (interaction, abuse, nonadherence, withdrawal)
- Lab testing based on patient Hx: Electrolytes, CBC (infection), ABG (acid-base), TSH, toxicology, NH₃ level + LFT (renal), thiamine level (Wernicke), B₁₂ (if decline is semi-chronic), bacteria culture
- **Lumbar puncture** for meningitis indicated if infectious suspicion with no clear etiology
 - o Elderly patients may present WITHOUT fever or classic Sx in meningitis so do LP if suspicious
- Imaging (CT/MRI) done only if unclear etiology and **BEFORE LP** (signs of ↑ intracranial pressure)
- **Electroencephalography** (EEG) in patients with Hx of head trauma, stroke, seizures, brain lesions

Treatment

- **Acute Management:** remove offending drugs, Tx of infections, Tx of other abnormalities from labs
- **Supportive care:** Hydration, orienting stimuli (clocks, calendars, hearing aids), bedside sitters
- **Neuroleptics** (sedative) used in severe agitation that interferes with patient or health care safety
- **Benzodiazepines** used mostly in acute alcohol/drug withdrawal (can cause delirium themselves)
- For elderly, preventative measures after Tx should be taken (medication review, orienting stimuli)

Dizziness

- Dizziness is a nonspecific term for symptoms of vertigo, presyncope, confusion, and weakness

Vertigo	Presyncope	Disequilibrium	Other
Peripheral (ears) - BPPV, otitis media, ear wax, labyrinthitis, Meniere	- Dehydration - Vasovagal - Medications - Arrhythmia - CHF	- P. neuropathy - Neuromuscular - Stroke/TIA - PD - Medication	- Psychological - Medications - Metabolic disturbances
Central (CNS) - Ischemia (brain stem, cerebellum), vertebrobasilar insufficiency			

History

- Key component: determine what Sx patient is using to describe dizziness; Med review also important
- **Vertigo:** sensation of movement, spinning, exacerbated by head motion; **Peripheral** is often acute onset with significant severity lasting s-min; **Central** more gradual, less intense, and chronic (w-mo)
 - o Peripheral more common with movement; Central more common to be random
 - o Peripheral also associated with tinnitus, hearing loss, fullness feeling in ear
 - o Central associated with other neuro Sx: visual changes, headache, ataxia, gait disturbances
- **Presyncope:** usually FULL BODY MOTION (not just head like in vertigo) required as trigger
- **Disequilibrium:** usually in setting of peripheral neuropathy or neuromuscular disease
- **Psychogenic:** often long duration without specific features

Physical Exam

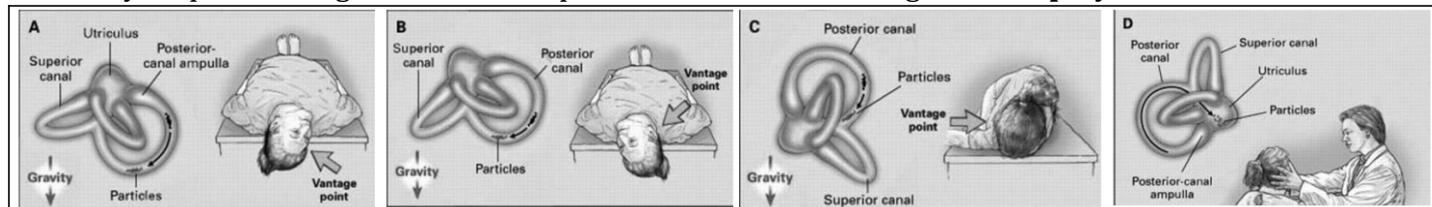
- Neuro exam is the focus, cardiovascular supplementary for predisposing signs to CV disease
- **Neuro exam:** sensation, proprioception, gait, motor function, CN, fundoscopy (\uparrow ICP), otoscopy (ear)
- If suspected BPPV: **Dix-Halpike test:** eyes remained open during test to look for nystagmus
 - o Positive Dix-Halpike: induced vertigo + mixed torsional and vertical nystagmus of affected side
- **Pure torsional or vertical nystagmus** is suggestive of **central** vertigo

Diagnostic Evaluation

- Usually Hx and PE will narrow cause; if a brain lesion is suspected urgent brain imaging is indicated
 - o MR angio for vasculature or CT for gross imaging
- Electrocardiography used to assess arrhythmia or ischemia if Hx is suggestive; labs not indicated

Treatment

- Presyncope is managed with fluid replacement; BPPV is managed with **Epley manoeuvre:**



Dementia

- Dementia is defined as the decline of memory along with at least one other cognitive domain that causes ↓ function and is not exclusively present with delirium or better explained by something else

Dementia	Pathology	Clinical Findings
Alzheimer (AD)	β-Amyloid plaques, neurofibrillary tangles hippocampal atrophy	Short-term memory loss insidiously progressing to severe deficits
Vascular	Infarcts	Stepwise/insidious progression, focal neuro deficits
Lewy Body	Intraneuronal α-synuclein aggregation	Cognitive fluctuation, visual hallucin., parkinsonism
Frontotemporal	Focal frontotemporal atrophy	Executive, behavioural, and language dysfunction
Hydrocephalus	Enlargement of ventricles	Gait abnormality, incontinence

- All dementia syndromes share common risk factor of advancing age; other factors that ↑ risk:
 - o Heredity (AD), renal failure (Vascular dementia), Down syndrome (AD), Female (AD)
- **Mild cognitive impairment (MCI)**: diffuse conditions with cognitive changes (↓) but normal function
- ↓ Risk of dementia if: social, physical activity, cognitive activity, higher education

History (features listed in table above not listed here)

- Relevant Hx of cognitive decline usually provided by family and other friends/caretakers
- Frontotemporal dementia (FTD): memory loss is prominent/early; **REDUCED INSIGHT** into deficits
- For all dementias, **neuropsychiatric Sx** may be prominent: depression, agitation, hallucination

Physical Exam

- Neuro exam important; focal neuro deficits (vascular); gait abnormalities (Normal pressure hydrocephalus [NPH]); parkinsonism (Lewy body/PD), psychomotor retardation (depression)

DDx

- Dementias, depression, delirium, medication, B₁₂ deficiency, syphilis, hypothyroidism

Diagnostic Evaluation

- Cognitive assessment can be done with MoCA or MMSE for screening (not sensitive enough for Dx)
- Potentially reversible dementias are NPH and **chronic subdural hematoma** (detect with CT)
 - o NPH triad: dementia, gait disturbance, incontinence (Dx: clinical + imaging + ↑ P on LP)
- Imaging can help with primary dementias but sensitivity and specificity are imperfect
 - o CT: vascular pathology (does not r/o AD); MRI: hippocampal atrophy (AD), FT atrophy (FTD)

Treatment

- **Cholinesterase inhibitors (CI)** are mainstay for AD (modest effect in mild-moderate AD)
- High dose **Vitamin E** for moderate-severe AD (not useful for prevention in MCI)
- Vascular dementia that overlaps with AD has Sx relief from CI
- FTD may respond to **trazodone** (improved behaviour, depression) but reduced insight remains
- Lewy body dementia responds to CI; Use before neuroleptic drugs (hallucination relief)
- Avoidance of adverse meds is important for therapy in all dementia (no anticholinergics)
- NPH patients may benefit from ventriculoperitoneal shunts; subdural hematoma needs surgery

Stroke

- Acute stroke is the sudden onset of focal neurologic injury related to ischemia (85%) or hemorrhage
- Ischemia may be caused by intravascular thrombosis, embolism, or general hypoperfusion
 - o Since atherosclerotic thrombosis is a major cause of stroke, stroke risk is correlated with CV risk
 - o **Emolic** stroke results from cardiac, aortic, or other arterial sources
 - o Cerebral **hypoperfusion** can occur in any hypotensive state (cardiogenic shock, GI bleed)
- **Hemorrhagic** stroke (intracerebral [ICH], or subarachnoid [SAH]) result from HTN, drug abuse or rupture of an arterial aneurysm (SAH)

History

- Patients presenting with focal neuro deficit must be assessed for brain injury; TIME OF ONSET key
- Usually a quick Hx and PE to differentiate from migraine or seizure and then an urgent CT
- Med Hx important as drug intoxication can mimic stroke

Stroke Etiology	Characteristic History	Characteristic Findings
Atherothrombosis	Stuttering/fluctuating course	PVD, infarct at small arteries
Embolism	Sudden onset of severe deficits	Afib, retinal cholesterol crystals
Hypoperfusion	Shock or other low-flow state	HypoTN, "watershed" infarct (CT)
ICH	Gradual deficit progression	Hemorrhage on CT
SAH	Sudden, severe, headache, AMS, nausea, vomit	Menigismus, RBC on LP

Physical Exam

- Vital signs usually show HTN; HTN can be **causative** or a **physiologic response** => nonspecific
- Other findings: Hypotension (hypoperfusion); poor peripheral pulses (atherosclerotic); carotid bruit (atherosclerotic); Afib (cardiac enlargement); retinal cholesterol crystals (embolism); meningismus or AMS (SAH); cardiac murmur (endocarditis)
- Neuro exam can reveal location of injury; **Posterior cerebral circulation** dysfunction needs MRI
 - o Basilar a. (oculomotor deficits, cerebellar ataxia); vertebral a. (dysphagia, dysarthria, ataxia)
 - o Crossed findings (opposite side of face and body affected) suggests posterior circulation problem

DDx

- In a benign CT: seizure, migraine, tumour, conversion disorder, stroke not detected by CT

Diagnostic Evaluation

- URGENT CT should be performed in any suspected stroke; CT highly sensitive for ICH (less for SAH)
- LP performed to assess for SAH (presence of RBC) but takes more time
- Hypoglycemia, hypoxia can also mimic stroke so blood glucose and O₂ saturation obtained

Treatment

- **Thrombolysis (tPa)**: Can be used for **ischemic** stroke within **4.5 hours of onset** (<3h ideal)
 - o **Contraindications for bleed risk**: trauma/stroke last 3 mo., Hx of ICH/ICH on CT, ischemic damage >1/3 of brain, suspected SAH, active bleeding (↑ PT), warfarin use, HTN (185/100 +)
 - o **Clinical contraindications**: rapid improvement, major surgery/trauma last 2 weeks, GI bleed last 3 weeks, MI last 3 months, pregnancy/lactation, seizure at onset of Sx
- Secondary prevention: **aspirin** 24h after tPa but within 48h of onset; **statins** also recommended
- Supportive therapy: supine q 24h, glucose control, DVT prophylaxis, HTN control (<220/120 if NO tPa, < 180/105 if tPa used), evaluation/treatment of fever
- Following stroke, patients are monitored for function recovery and often spend time in rehab facility

Seizures

- **Epileptic** seizures are from abnormal synchronous neuron firing; Epilepsy = 2+ unprovoked seizures
- Seizures can be caused by trauma, tumours, ischemia, metabolic disturbances, psychologic stress
 - o **Psychogenic nonepileptic** seizures are called **pseudoseizures** and may exist with epilepsy
- Seizures may be **partial** (focal) or **generalized** (diffuse); automatisms key to partial seizures

Seizure Subtype	Clinical Presentation	Comments
Partial Simple	Preserved LOC, focal abnormality	"aura" prior to complex partial or generalized
Complex partial	Impaired LOC, focal abnormality	Appears awake but doesn't respond
Generalized absence	Impaired LOC, staring	Generally limited to pediatrics
Generalized tonic-clonic	"yell" at onset, tonic back arching, clonic rhythmic motor movement	Cyanosis, tongue biting, incontinence

- **Status epilepticus:** prolonged (>10 min) of seizure or multiple seizures without full recovery

History

- Focus is on confirming seizure-like activity, differentiating subtype, and determining etiology
- Get Hx of behaviour before, during (witness), and after (witness/patient); FHx seizures (generalized)
- Presence of simple partial aura symptoms is suggestive of **epileptic** rather than nonepileptic activity
- Seizure auras (partial simple) usually a warning sign related to specific part of brain involved
- Level of consciousness (LOC) and activity (automatism, tonic/clonic) help classify the seizure
- **Postictal** period is the brain recovery period after an epileptic seizure (confusion, amnesia)
- Triggers: flashing lights, loud music, strong emotions, exercise, fever, menses, sleep deprivation
- History of medications important to r/o drug induced causes

Physical Examination

- Ictal state: focus on LOC, and behaviours; Difficult to differentiate past seizure subtypes with PE
- Neuro exam for neuro deficits; **lateralized** finding in postictal state suggests **contralateral** lesion

DDx

- Epileptic seizures must be differentiated from other disorders that may cause seizures: syncope, paroxysmal movement disorders, TIA, migraines, pseudoseizure

Diagnostic Evaluation

- Labs: glucose, Na, Ca, Mg, BUN, Toxicology, thyroid function tests; LP if suspected CNS infection
- **Prolactin** is ↑ acutely after a seizure; caution for Dx use (nonspecific to seizure type, insensitive)
- Urgent CT if suspected intracranial hemorrhage, stroke, or mass effect from lesion; MRI if non-urgent
- EEG is most definitive test for seizure activity; epileptiform activity is specific for seizure

Treatment

- Avoidance of triggers; Antiepileptic drugs avoided if 1st seizure or if unlikely to recur; indicated in:
 - o 2nd/frequent seizures, structural brain abnormality, abnormal EEG, cognitive retardation
 - o Choice of drug depends on patient, tolerable side effects and drug-drug interaction avoidance
- **Status epilepticus:** benzodiazepines are first line followed by a long-acting antiepileptic
- Focal epilepsy that continues with therapy may benefit from focal surgery to remove focal lesion

AHD – The Last Hours of Life

Premises underlying end-of-life care

- The ethical imperative to provide adequate relief of suffering
- That dying patients should not be subjected to ineffective therapies or investigations that would cause further distress
- All patients have the right to care that enables them to have the best possible life given the constraints of their prevailing circumstances

Terminal phase of life

- The period of inexorable and irreversible decline in functional status prior to death
- Terminal phase can last from a few hours to weeks unfolding gradually or precipitously
- Common Features:
 - o Profound weakness (progressive): essentially bed-bound, total care for ADLs
 - o Diminished intake/interest in food and fluids
 - o Difficulty swallowing medicine
 - o Drowsy or reduced cognition for extended periods with decreased interactions
 - o Severely limited attention span
 - o Mottling, cyanosis, cool limbs, tachypnea, shallow breathing, Cheyne-Stokes breathing
- Prevalence of Sx in last **week of life**: Confusion (39%), Dyspnea (46%), Nausea (71%), Pain (99%)
- Anticipate needs
 - o Rx: pain, agitation, rales, nausea, vomiting, fever
 - o Document at home clarifying DNR order

Goals of Care

- Ensure the best QOL for the patient with Sx control and safe environment
- Make end-of-life peaceful and dignified
- Support both patient and family
- Reassess Tx: redundant PO meds, Routine VS, IV/fluids, O₂ (if patient finds this uncomfortable)
- Food intake:
 - o The patient isn't eating because they are dying, they aren't dying because they aren't eating
 - o Neither TPN nor tube feeding are recommended for nutritional support in terminal phase
 - o Discussion around this is complex and rooted in sense of frustration, helplessness, desperation

Pronouncement and Certification of Death

- Present yourself to family and tell them why you're there; Death often expected and explainable
- Do not ask them to leave the room while you examine the patient, ask if they want to stay
- If uncertain about religious rituals ask a family member to guide you
- Confirm absence: pulse, heart sounds, lung sounds; confirm dilatation of pupils; **document findings**
- Death certificate has cause of death (primary and secondary), list other possibilities linked to death
 - o DO NOT WRITE "cardiopulmonary arrest" (this is how everyone dies), write cause i.e. pneumonia
- Common errors in writing death certificates:
 - o Choosing conditions with nonspecific diagnoses (i.e. cirrhosis)
 - o Reporting mechanism instead of cause (cardiac arrest vs. pneumonia)

AHD – Impact of End-Stage Illness on Families

How do families respond to life limiting illness

- Cancer affects the entire family system, it is the first line support for the patient, they can be directly affected by the cancer experience, and family often knows the patient better than clinicians ever will.
- Cancer:
 - o Creates anxiety, uncertainty, tension, and irritability, disrupts life plans, changes interpersonal communication patterns, and alters household functioning and member roles
- Families are at increased risk of depression, general anxiety, panic attacks, cardiac events, suicide
 - o People in bereavement report increased use of medication and increased visiting of health centers (80%) compared to the general population
- **Anticipatory Grief** is a normal mourning reaction to **an expected death** that allows emotional preparation for loss; families begin grieving immediately following cancer Dx
- **Disorganization**
 - o Anxiety and feelings of helplessness, guilt, keeping busy with activities as to not feel the pain, denial, absence of affect, depression, feelings of resentment, Broken promises, state of shock, denial of death.
- **Loss**
 - o Of daily routine, of ability to complete usual tasks, sleep, fatigue, of confidence in the ability to do all that is needed, of financial security, of employment, of intimacy/sexuality, of companionship, of meaning in life
- **Anger**
 - o Conflict within the family or between patient and family
 - o Dysfunctional family system, lack of trust in health care system, disagreement among team members as to what should be done results in inconsistent messages
 - o Verbal threats, physical acts, passive aggression, anger towards the self/another person, trying to split up the treating team
- Families tend towards more conflict in end of life care that lead to high rates of psychosocial morbidity.

Identify At Risk Families

- Factors that influence risk:
 - o Psychological well-being, expectations for the future, risk taking behaviour, social support system, parenting, relationship with the dying family member, loss history
- Assess expectation: prognostic awareness (do you understand?), problematic expectations (cure)
- Practical issues: is there a will, funeral arrangements, settling the estate

The role of the family meeting within a multidisciplinary team

- Family meetings facilitate planning of disposition and continuing care and provide opportunity to patient and families to meet the treating team and vice versa
- Triggers for setting a family meeting:
 - o Change in medical status, poor advanced care planning, decision making, late comers to the medical scene, resolving/repairing a conflict
 - o Can provide a safe setting to address questions and for families to express themselves
 - o Give information to the family at the same time and can help calm a situation
- Gather info about the family: watch dynamic, discrepancies, power struggles, who remains silent
- Pre-planning of family meeting, before and after:

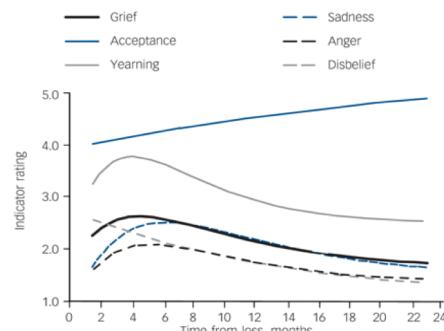
- Attending usually calls meeting, should have a brief meeting before the family arrives to discuss who attends, where, when, **how long**
- Determine who will write the summary of the family meeting in the chart
- Getting started: don't arrive late, postpone if necessary, everybody should introduce themselves and the goals of the staff and family should be made explicit and aligned
- Don't expect the meeting to solve everything, don't rush, make sure family understands info
- Identify marginalized members and try to involve silent members; attend to cultural variations
- Acknowledge where family is doing **well**, acknowledge suffering as well
- Involving Children
 - Parental fear tends to manifest the desire to protect and thus exclude children
 - Children should be offered the opportunity to join
- End the family meeting well
 - A poor ending can undo the good of the meeting, let the family know at the beginning how long they can expect the meeting to go
 - Assess impact (clarity, agreement); Family satisfaction associated with assurance that the patient would not be abandoned, is comfortable and pain is under control and that they feel implicated in the end of life decision making.
- Document all the details of the meeting (goals, discussions, outcomes, new plans)

Identify strategies to provide appropriate psychosocial support to families

- Be aware of your anxiety
 - Conversations about cancer/death can be stressful, our effort can seem clumsy, superficial or insufficient
 - Acting on our anxiety can lead us to assume undue control of a conversation or influence decisions that are not ours to make
 - Find ways to reflect on the role anxiety is playing in your role as a physician
- Make sure to listen, approaching someone with a respectful curiosity can be a welcome source of support; ask open questions that encourage gentle elaboration
- Learn to be comfortable with silence especially during emotional moments

The phenomenon of bereavement

- Uncomplicated bereavement (first 6-12 months):
 - Profound sadness interspersed with moments of reprieve, vivid images and thoughts, strides to accept death, low levels of anger, diverse types of somatic distress, social isolation, yearning
 - Many will cope fine without the need for intervention
 - Others will seek out professional support; motivation is key
 - **STUG:** sudden temporary upsurges of grief
- Between 15-20% of the population will have complicated grief:
 - Prolonged grief disorder vs. complicated grief vs. **persistent complex bereavement disorder**
- Persistent complex bereavement disorder (from DSM-V)
 - Individual has experienced the death of someone close
 - At least 1 of the following has persisted > 12 months: intense yearning, intense sorrow, preoccupation with the deceased, preoccupation with the events of the death
 - At least 6 of the following: difficulty accepting death, emotional numbness, difficulty with positive reminiscing, bitterness and anger, self blame, excessive avoidance of reminders, desire to be reunited, trust issues, feeling alone, meaninglessness, loss of purpose, no plans for future



- A vicious cycle between unsuccessful coping efforts that leads to **anguished search for meaning**, social marginalization, suicidal ideations
- Grief is different from depression but the early stages of bereavement can mimic depression
 - This acute period of grief is often transitory and shouldn't persist more than 3 months

<u>Clinical Depression:</u>	<u>Persistent Complex Bereavement Disorder:</u>
Loss of pleasure	Intense yearning
Flat emotional presentation	Intense sorrow
Suicidal ideation	Preoccupation with the deceased
Difficulties concentrating	Preoccupation with the events of the death
Psychomotor agitation or retardation	Difficulty accepting the death
Sleeping a lot more or a lot less	Disbelief/emotional numbness
Guilt and self-criticalness	Difficulty with positive reminiscing
Feeling punished	Bitterness and anger
Loss of Interest in Sex	Self blame
	Excessive avoidance of reminders of the deceased
	A desire to die to be reunited
	Difficulty trusting
	Feeling alone
	Meaninglessness/emptiness
	Loss of role, purpose in life
	Difficulty making plans for the future

Referral procedures for professional psychosocial services

- Psychosocial oncology, CLSC or family doctor, bereavement groups
- Psychosocial oncology referral needs to come from physician
 - Assessment of mood, coping, support, family issues, bereavement
 - Make sure patient wants referral, be clear about the reason for referral
 - Patient, family, or both?